^1H AND ^{13}C NMR SPECTRA AND THREE-DIMENSIONAL STRUCTURES OF 1,2,5-TRIMETHYL-4-PHENYLAMINOPIPERIDINE ISOMERS

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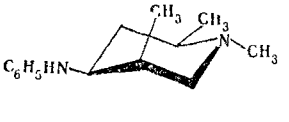
The three-dimensional structures of two isomers of 1,2,5-trimethyl-4-phenylaminopiperidine were established on the basis of an analysis of their ^1H and ^{13}C NMR spectra. The piperidine ring has a chair conformation in both isomers. The δ isomer has the 1,2e,5a,trimethyl-4e-phenylaminopiperidine structure, while the γ isomer has the 1,2e,5e-trimethyl-4e-phenylaminopiperidine structure.

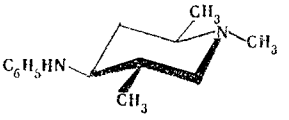
Secondary amines of the piperidine series are of interest in the synthesis of physiologically active compounds, the action of which [among which are included the similarly constructed well-known analgesics promedol (γ) and its isomers (α- and β-promedols)] depends to a considerable degree on their three-dimensional structures [1]. The establishment of the configurations and conformations of such compounds is therefore important. Nuclear magnetic resonance spectroscopy has been used most successfully for this purpose. Thus the stereochemistry of isomeric "promedol" alcohols (1,2,5-trimethyl-4-phenyl-4-piperidols) has been previously studied by means of the PMR spectra [2].

In the present paper we present the results of a study of the three-dimensional structures of the δ and γ isomers of 1,2,5-trimethyl-4-phenylaminopiperidine. This piperidine amine was obtained by reduction of N-(1,2,5-trimethyl-4-piperidylidene)aniline with sodium borohydride [3], and its isomers were separated by chromatography. The designations of the isomers correspond to those adopted for isomeric 1,2,5-trimethyl-4-phenyl-4-piperidols [the γ isomer is 1,2e,5e-trimethyl-4e-phenyl-4-piperidol, while the δ isomer (which is unknown) is 1,2e-5a-trimethyl-4e-phenyl-4-piperidol].

In order to establish the configurations and conformations of these isomers we made a detailed comparative analysis of the ^1H NMR spectra at 360 MHz and the ^{13}C NMR spectra at 20.1 MHz (see Tables 1-3). The analysis of the PMR spectra of piperidines at 80 or 100 MHz is a very complex problem because of the small difference in the chemical shifts of the signals of the ring protons and their overlapping with the signals of the methyl protons of the substituents. We found that the piperidine ring in both isomers has a chair conformation; the δ isomer is 1,2e,5a-trimethyl-4e-phenylaminopiperidine (cis orientation of the t-methyl and 4-phenylamino groups and cis orientation of the 2- and 5-methyl groups), while the γ isomer is 1,2e,5e-trimethyl-4e-phenylaminopiperidine (trans orientation of the t-methyl and 4-phenylamino groups and trans orientation of the 2- and 5-methyl groups). Thus these isomers differ only with respect to the orientation of the methyl group attached to the C_5 atom. The most favorable equatorial orientation of all of the substituents is realized in the γ isomer.



δ-isomer



γ-isomer

In contrast to the analogous tertiary 4-piperidols [2, 4], the vicinal constants of the protons of the piperidine ring in the δ and γ isomers (Table 2), with allowance for the Karplus dependence, do not make it possible to assume an appreciable contribution of conformations other than the chair conformation. As in cyclohexane systems, in the spectra of both isomers the signals of the axial protons are shifted to strong field as compared with the corresponding equatorial protons (Figs. 1 and 2). For example, in the case of the δ isomer

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TABLE 1. ^1H Chemical Shifts in Parts Per Million

Isomer	Piperidine ring protons								Methyl protons			NH	Phenyl			
	2a	3a	3e	4a	5a	5e	6a	6e	NCH_3	2-CH_3	5-CH_3		ortho	meta	para	
δ	1,95	1,39	1,68	3,50	—	2,20	2,28	2,74	2,22	1,10	1,01	3,42	6,61	7,17	6,68	
γ	1,97	1,08	2,07	2,92	1,64	—	1,89	2,86	2,25	1,07	0,97	3,29	6,68	7,17	6,88	
Δσ*	+0,02	−0,31	+0,39	−0,58	—	—	−0,39	+0,12	+0,03	−0,03	−0,04	−0,13	+0,07	0	+0,20	

*This is the change in the shielding of the protons (in parts per million) on passing from the equatorial (γ) to the axial δ isomer.

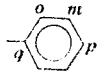
TABLE 2. Spin–Spin Coupling Constants in Hertz

Isomer	2a		3a		3e		4a		5a		5e		6a		6e	
δ	2a2CH_3	−6	3a3e	−13	3e3a	−13	4a3a	12,5			5e5CH_3	7	6a6e	−11,5	6e6a	−11,5
	2a3a	12	3a4a	12,5	3e2a	3	4a3e	4			5e6a	3	6a5e	3	6e5e	2,5
	2a3e	3	3a2a	12	3e4a	4	4a5e	4			5e4a	4				
											5e6e	2,5				
γ	2a2CH_3	6	3a3e	−12	3e3a	−12	4a3a	12	5a5CH_3	6,5			6a6e	−12	6e6a	−12
	2a3a	12	3a2a	12	3e2a	2,5	4a3e	4	5a6e	4			6a5a	11,5	6e5a	4
	2a3e	2,5	3a4a	12	3e4a	4	4a5a	12	5a6a	11,5						
									5a4a	12						

TABLE 3. ^{13}C Chemical Shifts in Parts Per Million

Isomer	Piperidine ring					Methyl substituents			Phenyl†			
	C_2	C_3	C_4	C_5	C_6	N—CH_3	2-CH_3	5-CH_3	*q*	*o*	*m*	*p*
δ	59,4	36,1	52,9	31,5	62,7	43,2	20,6	11,7	147,3	129,4	113,7	117,4
γ	58,6	41,7	56,9	38,5	64,4	42,6	20,5	16,3	147,8	129,4	113,2	117,1
Δσ*	−0,8	+5,6	+4,0	+7,0	+1,7	−0,6	−0,1	+4,6	+0,5	0,0	−0,5	−0,3

*This is the change in the shielding of the carbon atoms in parts per million) on passing from the equatorial (γ) to the axial δ isomer.

† 

the signals of the 3a and 6a protons are shifted 0.29 and 0.46 ppm, respectively, to strong field relative to the 3e and 6e protons. In the case of the γ isomer the analogous shifts to the same protons are 0.99 and 0.97 ppm, respectively. The change in the orientation of the 5-CH_3 group on passing from the δ isomer to the γ isomer is followed most clearly from the spin–spin coupling constants (SSCC) and the chemical shifts of the protons attached to C_4, C_5, and C_6 (Tables 1 and 2). For example, the proton attached to the C_5 atom of the γ isomer does not have even one significantly large SSCC that could be ascribed to axial–axial coupling ($^3J_{aa}$), while in the case of the γ isomer, in which it has an axial orientation, there are two such constants (5_a6_a 11.5 and 5_a4_a 12 Hz). A change in the chemical shift in this proton to strong field (0.56 ppm) in the case of the 5e → 5a change in orientation is also characteristic. These changes are also reflected in the SSCC of the protons attached to the C_4 and C_6 atoms (Table 2).

Broadening of the signals from the 4a protons was observed in the PMR spectra of both isomers; broadening of the signal from the 3e proton was also observed in the spectrum of the δ isomer. The broadening of the signal from the 4a proton, which disappeared upon heating, is associated either with retarded rotation of the phenylamino fragment or with residual coupling of HCNH under conditions of slow NH exchange and with quadrupole broadening from the ^{14}N nucleus.

It has been shown [5] that the parameters of the ^{13}C spectra are associated with the stereochemistry of the similarly constructed isomers of 1,2,5-trimethyl-4-phenylpiperidine. We therefore analyzed the ^{13}C spectra of both isomers. The chemical shifts thus found are presented in Table 3. A comparison of the ^{13}C chemical shifts of the methyl groups and the carbon atoms of the piperidine ring in both isomers confirms the axial orientation of the 5-CH_3 group in the δ isomer. Just as in the case of the axial conformers of methylcyclohexanes

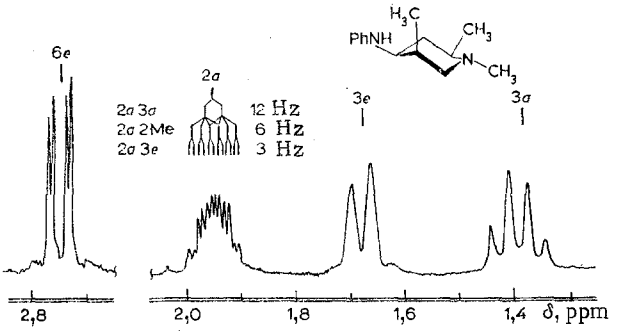


Fig. 1. Spectrum of the 2a, 3e, 3a, and 6e protons of the piperidine ring of the δ isomer.

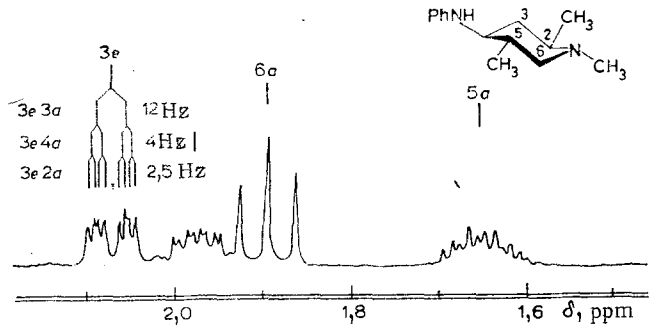


Fig. 2. Spectrum of the 3a, 3e, 5a, and 6a protons of the piperidine ring of the γ isomer.

[6], the signals of the C_2, C_4, C_5, and C_6 atoms of the δ isomer are shifted to strong field as compared with the equatorial (C_5) γ isomer. A characteristic "γ effect" for the C_3 atom (5.6 ppm) and a strong-field shift of the signal of the 5-methyl group (4.6 ppm) are noted. On the basis of the chemical shifts of the carbon atoms (Table 3) and the chemical shifts of the protons (Table 1) it may be concluded that the N-methyl groups in the δ and γ isomers have identical orientations and that it is most likely that the equatorial orientation is the energetically more favorable one.

EXPERIMENTAL

The PMR spectra of saturated solutions of the compounds in $CDCl_3$ were obtained with a Brucker WH-360 spectrometer with a superconducting solenoid and a Tesla BS-497 spectrometer (100 MHz).* The ^{13}C spectra of saturated solutions of the investigated compounds in $CDCl_3$ were obtained with a Brucker WP-80 Fourier NMR spectrometer. For the assignment of the signals we carried out experiments with selective decoupling of the protons. The ^1H and ^{13}C chemical shifts were measured relative to tetramethylsilane. The ^1H chemical shifts are presented with an accuracy of up to 0.01 ppm, while the SSCC are presented with an accuracy of up to 0.1 Hz. The ^{13}C chemical shifts are presented with an accuracy of up to 0.1 ppm. To refine the assignment of the signals we carried out experiments involving homonuclear double resonance. A Lorentzian–Gaussian filter was used to contract the lines and to make more accurate measurements of the SSCC prior to Fourier transformation.

1,2,5-Trimethyl-4-phenylaminopiperidine. A solution of 43.2 g (0.2 mole) of N-(1,2,5-trimethyl-4-piperidylidene)aniline in 200 ml of ethanol was added with stirring to 38 g (1 mole) of sodium borohydride, and the mixture was refluxed for 7 h. Water (500 ml) was then added at room temperature, and the mixture was heated until hydrogen evolution ceased. The alcohol and part of the water were removed by distillation, and the reaction products were extracted with ether. The extract was dried with sodium sulfate, the ether was removed, and the residue (41 g) was distilled to give 39.4 g (90%) of a mixture of isomers of 1,2,5-trimethyl-4-phenylaminopiperidine as a colorless liquid with bp 132-134°C (2 mm) and n_D^{23} 1.5460.

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A 1-g sample of the base obtained was taken for chromatography on activity II Al_2O_3 [h = 50 cm, d = 2.3 cm, elution with hexane–ethyl acetate (5:1)]. Initially, 0.34 g (34%) of the δ isomer was eluted in the form of a viscous colorless liquid with R_f 0.6 [activity II Al_2O_3, elution with ethyl acetate–hexane (1:2)]. At the end of the chromatographic process we isolated 0.6 g (53%) of the γ isomer as a viscous yellowish liquid with R_f 0.3 (the same system). Found: C 76.9; H 10.4; N 12.5%; M^+ 218. $C_{14}H_{22}N_2$. Calculated: C 77.1; H 10.1; N 12.8%; M 218.

A 1-g sample of the mixture of isomers was dissolved in 30 ml of ethanol. A solvate (0.2 g) of the δ isomer with one molecule of alcohol precipitated at room temperature in the form of colorless crystals with mp 73-82°C. Found: C 73.4; H 10.6; N 10.5%; M^+ 218. $C_{14}H_{22}N_2 \cdot C_2H_5OH$. Calculated: 73.7; H 10.6; N 10.6%.

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AMINO DERIVATIVES OF 9,9-DIORGANO-9,10-DIHYDRO-9-SILA-3-AZAANTHRACENE

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Derivatives of 9,9-disubstituted 9,10-dihydro-9-sila-3-azaanthracene (compounds with possible biological activity) were synthesized by means of two methods. 10-β-Cyanoethyl derivatives were obtained by condensation of dihydrosilaazaanthracenes with acrylonitrole in the presence of Triton B. One of these products was reduced with lithium aluminum hydride to 9,9-dimethyl-10-(γ-aminopropyl)-9,10-dihydro-9-sila-3-azaanthracene. The second method involves conversion of dihydrosilaazaanthrones (obtained by oxidation of dihydrosilaazaanthracenes) to oximes followed by reduction of the latter with hydrazine hydrate in the presence of Raney nickel to give 10-amino derivatives. The latter were subjected to acylation.

We have previously described the synthesis of 9,10-dihydro-9-sila-3-azaanthracene derivatives [1, 2]. It seems of interest to study their properties in order to search for physiologically active substances. Considering the fact that many biologically active compounds contain an amine function, we addressed ourselves to the synthesis of amino derivatives of dihydrosilaazaanthracenes, which were obtained by two methods, viz., by reduction of 10-β-cyanoethyl dihydrosilaazaanthracenes and also by reduction of oximes of silaazaanthrones.

The starting compounds in the cyanoethylation reactions were 2-methyl-9,9-diphenyl(I)- and 9,9-dimethyl(II)[9-methyl-9-phenyl(III)]-9,10-dihydro-9-sila-3-azaanthracenes. The reactions were carried out in the presence of Triton B. The principal products of the Michael reaction were products of monocyanoethylation at C_{10}, viz., IV-VI, the yields of which varied in the order V > VI > IV this is evidently due to the different degree of shielding of the methyl group by the substituents attached to the silicon atom of the starting dihydrosilaazaanthracenes.

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