PECULIARITIES OF THE THREE-DIMENSIONAL STRUCTURES OF ISOMERS OF 1,2,5-TRIMETHYL-4-AMINO(AMIDO)PIPERIDINES FROM THE ^1H AND ^{13}C NMR SPECTRA

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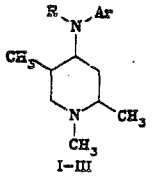
The three-dimensional structures of seven 1,2,5-trimethyl-4-amino(amido)piperidines were studied by means of the ^1H and ^{13}C NMR spectra. The $^3J_{HH}$ values and the ^{13}C chemical shifts indicate that the substituents in the piperidine ring of all of the 2c,5c,4r isomers have a 2e,4e,5a orientation, while those in the piperidine ring of all of the 2c,5t,4r isomers have a 2e,4e,5e orientation. The conformational change (as a result of ring conversion) 2e,4a,5e → 2a,4e,5a was observed for the 2t,5c,4r isomers on passing from the corresponding amine to the amide; this change is associated with striving of the more bulky amide substituent to become equatorially oriented. Retarded rotation about the $C_{(4)}$–N bond was observed in the 2c,5t,4r isomer of the 4-(N-phenylbenzamido) derivative; this is explained by steric hindrance due to the 5e-CH_3 group.

It has been previously established that one of the two configurational isomers of 1,2,5-trimethyl-4-phenylaminopiperidine is the 2c,5c,4r isomer (IA) and that the other is the 2c,5t,4r isomer (IB) [1]. It was shown that isomer IA has a 2e,4e,5a orientation of the substituents and that isomer IB has a 2e,4e,5e orientation of the substituents vis-à-vis a chair form of the piperidine ring [1]. Yet another series of analogous compounds was recently synthesized, and their individual isomers were isolated chromatographically [2].

In the present paper we present an analysis of the NMR spectra of seven individual isomers of N-substituted 1,2,5-trimethyl-4-aminopiperidines I-III, on the basis of which conclusions regarding their three-dimensional structures were drawn.



I-III

I R=H, Ar=C_6H_5; II R=H, Ar=2-pyridyl; III R=C_6H_5CO, Ar=C_6H_5

The previously obtained data [1] for isomers IA and IB were used as basis data for the interpretation of the spectral data for the new compounds (Tables 1-3).

Recording of the ^1H NMR spectra at 400 MHz made it possible to interpret the spectra of the protons of the piperidine ring, which are usually extremely complex because of the close first-order chemical shifts. Preliminary examination of the ^1H and ^{13}C chemical shifts and the J_{HH} spin-spin coupling constants (SSCC) showed that each of the even investigated compounds is one of three configurational isomers: 2c, 5c, 4r (A), 2c, 5t, 4r (B), or 2t, 5c, 4r (C). It must be noted that the fourth possible isomer [2t, 4r (D)] could not be isolated in a single case; if it is formed, it is evidently produced in extremely small amounts.

The similarity between the chemical shifts of the protons of the piperidine ring, their SSCC, and the chemical shifts of the carbon atoms of this ring in the isomers of 4-amino derivatives IIA and IIB and the corresponding parameters of isomers IA and IB (Tables 1-3) indicates the identical three-dimensional structures of these isomers: isomer IIA has a 2c,5c, 4r configuration, and isomer IIB has a 2c,5t,4r configuration with, respectively, 2e,4e,5a

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TABLE 1. Chemical Shifts of the Protons of the Isomers of I-III ($CDCl_3$)

Compound	2e	2a	3a	3e	5a	5e	6a	6e	4a	4e	NCH_3	2-CH_3	5-CH_3
IA [1]	—	1,95	1,39	1,68	—	2,20	2,28	2,74	3,50	—	2,22	1,10	1,01
IB [1]	—	1,97	1,08	2,07	1,64	—	1,89	2,86	2,92	—	2,25	1,07	0,97
IC	—	2,1	1,46	1,89	—	2,15	2,02	2,62	—	3,59	2,27	1,04	0,92
IIA	—	1,72	1,19	1,38	—	2,21	2,11	2,48	3,91	—	2,02	0,93	1,00
IIB	—	1,78	1,09	1,73	1,55	—	1,67	2,60	3,51	—	2,05	0,96	0,88
IIC	—	1,89	1,43	1,73	1,96	—	1,72	2,30	—	3,88	2,04	0,90	0,80
IIIA	—	1,92	1,43	1,07	—	2,78	2,75	2,47	4,65	—	2,20	0,98	1,28
IIIB*	—	1,87	1,46	1,87	2,2	—	2,66	3,04	4,22	—	2,22	1,02	1,02
IIIC	2,48	—	1,92	1,27	—	2,65	2,31	2,74	5,07	—	2,18	0,94	1,31

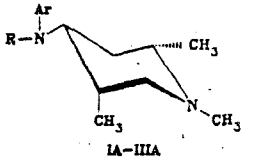
*From the spectrum at 80 MHz (d_6-DMSO, 120°C).

TABLE 2. Spin-Spin Coupling Constants (SSCC) of the Protons of the Piperidine Ring in the Isomers of 4-Amino(amido)piperidines I-III (Hz)

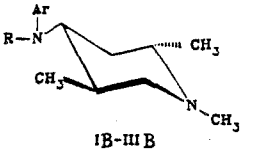
Compound	Coupling protons										
	2,3a	2,3e	3a,4	3e,4	4,5	5,6a	5,6e	3a,3e	6a,6e	2a,2-CH_3	5a,5-CH_3	4a(e)NH
IA	12	3	12,5	4	4	3	2,5	−13	−11,5	6	7	
IB	12	2,5	12	4	12	11,5	4	−12	−12	6	6,5	8
IIC	11,5	2,5	3,5	2,5	3,5	11,5	3,7	−13	−11,7	6,2	6,8	7
IA	10,5	2,7	11,5	4,2	4,2	2,9	2,5	−12,3	−11,5	6,4	7,1	7
IIB	11,0	2,5	11	4	11	11	4	−12,5	−11,5	6	6,7	8
IIC	11,2	3	3,5	3	4	11,5	3,5	−13,2	−11,5	6	6,8	9
IIIA	11	2,5	13,5	4	4	3	2,5	−13,5	−11,5			
IIIB*	11	4	11	4,4	11	11	4	−12,5	−11	6,3	6,5	—
IIIB**	4,8	4	9,8	4,8	4,8	5,5	4	−12,5	−11,5	6,5	7,0	
IIIC ***	4,7	4,2	11,2	4,2	4,2	4	3,2	−12,5	−11,5	6,6	7,1	

*The SSCC of the protons of the piperidine ring were evaluated by calculation of the spectrum at 80 MHz by means of the PANIC program.
**In $CDCl_3$.
***In C_6D_6.

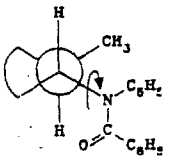
and 2e,4e,5e orientations of the substituents in the chair form of the piperidine ring. The differences in the ^1H and ^{13}C chemical shifts in isomeric amides IIIA and IIIB from the corresponding amines can be explained by the different effect of the substituent attached to the $C_{(4)}$ atom; however, the similarity of the vicinal SSCC of the ring protons in IIIA and IA and IIA and in IIIB and IB and IIB indicates identical configurations and conformations of these isomers.



IA–IIIA



IB–IIIB



Regarding isomer IIIB, its PMR spectra at both 400 and 80 MHz and room temperature were found to be so broadened that even spin-spin splitting of the signals from the 2- and 5-CH_3 protons did not appear, and assignment of the broad signals of the protons of the piperidine ring was not possible. Broadening of the $C_{(3)}$, $C_{(4)}$, and $C_{(5)}$ signals in the ^{13}C NMR spectrum (100 MHz) was also observed. The ^1H NMR spectrum without exchange broadening could be obtained only at 80 MHz with heating of the sample to 120°C (solution in d_6-DMSO). The vicinal SSCC found (Table 2) and the ^{13}C chemical shifts (Table 3) correspond to a 2e,4e,5e orientation of the substituents in isomer IIIB vis-à-vis a chair form of the piperidine ring. The fact that broadening of the signals was not observed in the spectra of isomers IIIA and IIIC of the same amide is evidently associated with retarded rotation about the $C_{(4)}$—N bond rather than the N—CO bond of the amide substituent because of steric hindrance on the part of the

TABLE 3. ^{13}C Chemical Shifts of the Piperidine Ring and Methyl Substituents (ppm) in the Isomers of 4-Substituted 1,2,5-Trimethylpiperidines I-III

Compound	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	NCH_3	2-CH_3	5-CH_3
IA [1]	59,4	36,1	52,9	31,5	62,7	43,2	20,6	11,7
IB [1]	58,6	41,7	56,9	38,5	64,4	42,6	20,5	16,3
IC	53,2	39,0	50,8	34,7	58,7	43,0	19,8	15,7
IIA	59,3	36,2	51,6	32,1	62,7	43,1	20,6	12,0
IIB	58,5	41,7	54,8	38,2	64,1	42,4	20,3	16,1
IIC	49,4	39,5	53,3	34,6	58,8	42,9	19,9	15,6
IIIA	59,6	34,5	58,5	31,3	63,0	42,9	20,7	14,1
IIIB	58,7	39,1	58,0	34,9	64,2	42,3	20,6	16,2
IIIC	53,8	34,3	52,9	32,7	55,7	42,7	14,5	12,3

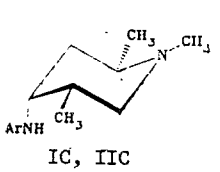
5-CH_3 group, which is particularly great in the case of an ee orientation of this group and the amide substituent.

Thus, according to the ^1H NMR data, the three-dimensional structures of all isomers IA-IIIA, as well as all isomers IB-IIIB, prove to be identical. The starting point in the establishment of their structures was the SSCC of the 4-H proton, the signals of which lie at weaker field than the signals of the remaining protons of the piperidine ring (2.9-4.6 ppm, Table 1). Thus, for example, the presence of only one large SSCC (12.5-13.5 Hz) for this proton in the spectra of isomers IA-IIIA indicates, first, an equatorial orientation of the substituent attached to the $C_{(4)}$ atom and, second, an axial orientation of the 5-CH_3 group. In the spectra of isomers IB-IIIB the two large vicinal SSCC of the 4-H proton (11-12 Hz), in turn, indicate an equatorial orientation of both the subtituent attached to the $C_{(4)}$ atom and the 5-CH_3 group.

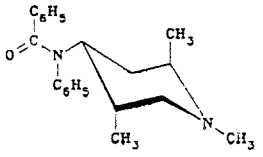
Taking into account all of the remaining values of the vicinal SSCC the configurations and conformations of these isomers are determined completely unequivocally only from ^1H NMR data. However, the carbon-13 chemical shifts also give additional confirmation (Table 3). Characteristic here is the strong-field shift of the signals of the $C_{(3)}$ atom (4.5-5.5 ppm, Table 3) on passing from isomers B to isomers A, which is associated with the so-called "γ effect" in the case of an axial orientation of the 5-CH_3 group. A strong-field shift is also characteristic for the carbon atom of the 5-CH_3 group (2-4 ppm); this shift can be explained by 1,3- and 1,4-steric cross coupling in the case of an axial orientation of this group.

For the amine isomers IC and IIC, which were studied for the first time in this research, the small SSCC of the proton attached to the $C_{(4)}$ atom constitute evidence for an axial orientation of the substituent attached to this carbon atom. The combined examination of all of the J_{HH} values (Table 2) in these isomers determines a 2e,4a,5e orientation of the substituents vis-à-vis a chair form of the piperidine ring.

Regarding isomeric amide IIIC, obtained from amine IC [2], the situation here differs markedly from that for IC and IIC. The single large SSCC of the proton attached to the $C_{(4)}$ atom indicates an equatorial orientation of the substituent attached to this carbon atom, and the small values of the vicinal SSCC of the 2- and 5-H protons (Table 2) indicate an axial orientation of the two methyl groups. Thus the piperidine ring in isomer IIIC proves to be converted with respect to identical configurational isomers IC and IIC, i.e., the methyl groups here have a less favorable diaxial conformation.



IC, IIC



IIIC

The bulky amide substituent attached to the $C_{(4)}$ atom, which strives to assume an equatorial orientation, which leads to ring interconversion, serves as the reason for this phenomenon. The ^{13}C NMR data (Table 3) serve as graphical evidence for an axial orientation of the methyl group attached to the $C_{(2)}$ atom, as well as to the $C_{(5)}$ atom. An exceptionally

large strong-field increment for 2-CH_3 was observed here, and the chemical shift for this carbon atom is 14.5 ppm, whereas it was more than 19.8 ppm in all other cases. A "γ effect" in this case is clearly observed not only for $C_{(3)}$ but also for $C_{(4)}$ and $C_{(6)}$ (Table 3).

The substantial dependence of the vicinal SSCC on the solvent in isomer IIIC (Table 2) nevertheless indicates that, despite the clear preponderance of the 2a,4e,5a conformation, equilibrium 2a4e5a $\rightleftarrows$ 2e4a5e exists and is shifted to favor the diequatorial form on passing from C_6D_6 to the polar solvent $CDCl_3$.

In principle, the low barrier to inversion of the pyramidal ring nitrogen atom in N-alkylpiperidines [3] makes it possible to consider both equatorial and axial orientations of the N-methyl group as possible in all of the investigated configurational isomers. However, in no case did we obtain NMR data that would enable us to reliably establish the orientation, although, as we have previously pointed out [1], its equatorial orientation in isomers A and B finds confirmation in the ^1H chemical shifts of the protons of the piperidine ring.

EXPERIMENTAL

The ^1H NMR spectra of 5% solutions in $CDCl_3$ or C_6H_6 (with tetramethylsilane as the internal standard) were obtained with a WM-400 spectrometer (400 MHz). The method of double homonuclear resonance was used for assignment of the signals. The ^1H NMR spectra of isomer IIIB on heating to 120°C in d_6-DMSO were recorded with a WP-80 spectrometer. The ^{13}C NMR spectra of isomer IIIB were obtained at 100.6 MHz with a WM-400 spectrometer. The ^{13}C NMR spectra of the remaining compounds were recorded with a WP-80 spectrometer (20 MHz).

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ELECTRONIC STRUCTURES AND REACTIVITIES OF DERIVATIVES OF 1,4-DIHYDROPYRIDINES.

2.* 1-METHYL-3-CARBOXYAMIDO-1,4-DIHYDROPYRIDINE AND ITS CATION RADICAL

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The three-dimensional and electronic structures of 1-methyl-1,4-dihydronicotinamide and its cation radical were calculated within the MINDO/3 approximation. The results are compared with the physicochemical properties of 1,4-dihydropyridine derivatives.

The redox transformations of the coenzymes NADH and NADPH lie at the foundation of the most important biochemical processes [1]. The corresponding 1,4-dihydropyridines are structural models of these coenzymes [2]; inasmuch as they have high physiological activity, they

*See [22] for Communication 1.

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