^1H and ^{13}C NMR SPECTRA, ISOMERS, AND IMINE-ENAMINE TAUTOMERS OF N-(1,2,5-TRIMETHYL-4-PIPERIDYLIDENE)ANILINE

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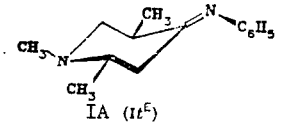
The product of condensing 1,2,5-trimethylpiperidin-4-one with aniline has been investigated by NMR spectroscopy. Three isomers of N-(1,2,5-trimethyl-4-piperidylidene)aniline have been identified differing in the configuration of the methyl groups at C_2 and C_5 of the piperidine ring and the Z,E isomerism about the C=N bond. Traces of the enamine tautomeric form of the imine were also detected. $^3J_{HH}$, $^1J_{CH}$, and $^1J_{CC}$ spin-spin couplings were used to determine the structural configuration of the isomers.

There is interest in the stereochemistry and isomeric composition of azomethines obtained from 1,2,5-trimethypiperidin-4-one since they are starting materials for the synthesis of compounds showing promising biological activity.

We have previously reported the reduction products [1] of N-(1,2,5-trimethyl-4-piperidylidene)aniline (I) and its reaction with acetylenedicarboxylic ester [2] together with their steric structures. Up to now the isomers and conformers of imine I have not been reported in the literature due both to its instability and to the complex isomeric composition of I.

For imine I there are four possible isomers — two cis (Ic^Z and Ic^E) and two trans (It^Z and It^E) isomers with Z and E configurations about the C=N bond. However there were only three ^{13}C NMR signals in the region 172-176 ppm corresponding to the chemical shift (CS) of a quaternary imine carbon atom [3], i.e., there were three imine forms in the ratio IA:IB:IC = 3.5:1.6:1. In order to determine the configuration of these isomers the ^1H and ^{13}C NMR spectra were analyzed and the NMR parameters measured (Tables 1-4) using the INADEQUATE [4] and 2D heteronuclear correlation (^1H, ^{13}C COSY [5]) spectroscopic methods.

Comparison of the direct $^1J(C_3, C_4)$ and $^1J(C_4, C_5)$ spin-spin couplings (SSC) with respect to the stereospecificity of these SSC related to the unshared electron pair of the nitrogen atom in the imines [6] points to an E-configuration about the C=N bond in isomers IA and IB and the Z-configuration in IC. The vicinal $^3J_{HH}$ SSC of azomethine IA (Table 2) differ little from the analogous constants in the trans-isomer of 1,2,5-trimethylpiperidin-4-one and point to a chair conformation of the piperidine ring with an equatorial orientation of the methyl substituents.



IA (It^E)

Supporting evidence comes from the ^{13}C CS for the C_2' and C_5' atoms which also differ little from the ^{13}C CS of the starting piperidone. As was to be expected the direct $^1J_{CH}$ SSC was stereospecifically related to the unshared electron pair of the amine nitrogen atom and to the π-orbital of the C=N bond: $^1J(C_6, H_{6a}) < {}^1J(C_6, H_{6e})$, $^1J(C_3, H_{3a}) < {}^1J(C_3, H_{3e})$. The $^1J(C_2, H_2)$ and $^1J(C_5, H_5)$ SSC data for IC point to an equatorial and axial orientation, respectively, for the methyl groups at C_2 and C_5.

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TABLE 1. Proton Chemical Shifts for the Azomethine I Isomers (400 MHz, TMS) (δ, ppm)

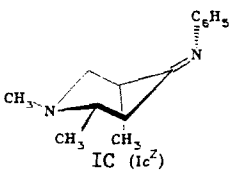
Isomer	Protons									
	2	3a	3e	5	6a	6e	2-CH_3	5-CH_3	N—CH_3	C_6H_5
IA	2,04	1,87	2,42	2,74	2,10	3,09	1,03	1,15	2,31	6,67...7,27
IB	2,50	2,17	2,32	2,72	*	2,67	0,94	1,28	2,33	6,57...7,27
IC	2,16	2,59	2,28	2,62	2,24	2,65	1,20	1,24	2,26	6,57...7,30

*Signal could not be assigned.

TABLE 2. Spin-Spin Coupling of Protons in Isomers IA, IB, IC in Hz

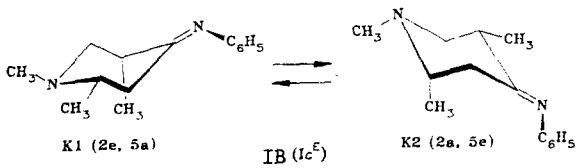
Isomer	Ring spin-spin couplings						Methyl spin-spin couplings	
	geminal		vicinal				vicinal	
	3a,3e	6a,6e	2,3-cis	2,3-trans	5,6-cis	5,6-trans	2,2-CH_3	5,5-CH_3
IA	−13,7	−11,3	2,8	11,6	5,0	11,5	6,1	6,6
IB	−14,0	*	4,3	7,2	*	*	6,5	*
IC	−14,0	*	2,9	11,8	3,5	1,7	6,1	7,1

*Could not be measured.



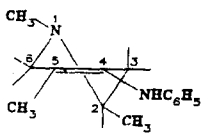
IC (Ic^Z)

Comparison of the $^1J(C_5, C_5')$ for isomers IA and IC shows the following orientational dependence: $^1J(C_5, C_5'_a) < {}^1J(C_5, C_5'_e)$. The analogous values for IB occupy an intermediate position and point to a conformational equilibrium.



The conformational heterogeneity of isomer IB was also confirmed by the $^1J(C_2, H_2)$ and $^1J(C_5, H_5)$ values, the ^{13}C CS of atoms C_2' and C_5', and the $^3J^{trans}_{2,3}$ vicinal SSC. Assuming as limiting values $^1J(C_5, C_5'_e)$ = 37.5 Hz (IA) and $^1J(C_5, C_5'_a)$ = 33.9 Hz (IC) it is possible to estimate the conformational population of K1 and K2 as n_{K1} = 56% and n_{K2} = 44%.

The PMR spectrum of azomethine I in the region 0.9-1.6 ppm showed the methyl group doublets of isomers IA, IB, and IC but also a singlet at 1.56 δ assigned to a fourth isomer ID (ratio IA:IB:IC:ID = 19.3:8.9:5.6:1). With the integrated intensities in mind for ID there were also observed two broadened doublets (each 1 proton) at 2.94 and 3.20 ppm with SSC 16.1 Hz. These signals can be assigned to the protons 5-CH_3, 6a and 6e (with ^2J = −16.1 Hz) of the Δ^4 piperidine fragment in ID.



ID

TABLE 3. ^{13}C Chemical Shifts (δ, ppm) (100.6 MHz, TMS) and Direct ^{13}C-^{1}H Spin-Spin Interactions (values in brackets in Hz) in Isomers IA, IB, IC

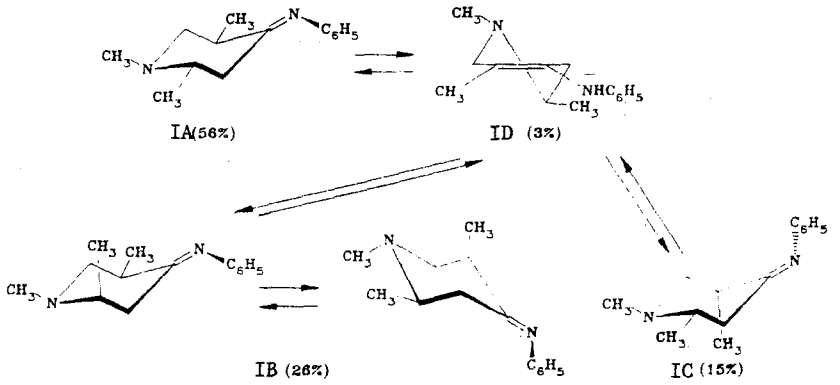
Isomer	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(1')}$	$C_{(2')}$	$C_{(5')}$	$C_{(q)}$	$C_{(o)}$	$C_{(m)}$	$C_{(p)}$
IA	59,42 (129,0)	38,10 (124,5) (132,0)	172,48 —	40,05 (127,6)	64,16 (127,6) (138,5)	41,28 (132,6)	19,88 (125,8)	12,94 (126,5)	150,45 —	118,98 (*)	128,21 (*)	122,15 (*)
IB	57,28 (135,2)	35,43 (126,7) (130,4)	173,17 —	40,24 (128,4)	58,94 (129,0) (139,5)	41,73 (132,4)	15,24 (125,5)	15,50 (126,7)	150,23 —	118,92 (*)	128,33 (*)	122,23 (*)
IC	60,07 (128,9)	42,45 (124,5) (132,6)	175,06 —	34,32 (131,4)	62,46 (127,6) (138,4)	41,79 (132,8)	20,30 (125,4)	17,68 (127,4)	149,93 —	118,71 (*)	128,37 (*)	122,31 (*)

*Not measured.

TABLE 4. Direct ^{13}C-^{13}C SSC (Hz) in Isomers IA, IB, and IC

Isomer	2,2′	2,3	3,4	4,5	5,5′	5,6
IA	39,1	34,5	36,7	45,3	37,5	34,4
IB	37,0	34,2	36,1	45,4	35,9	34,0
IC	38,8	34,9	45,5	36,1	33,9	34,4

From this ^{1}H and ^{13}C NMR data the following scheme for imine-enamine tautomerism of the Schiff base I can be invoked (the percentage of each isomer is shown in brackets):



EXPERIMENTAL

N-(1,2,5-Trimethyl-4-piperidylidene)aniline was obtained by the method in [7]. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM-400 spectrometer. Direct ^{13}C-^{13}C SSC were measured using the INADEQUATE pulse sequence [4] with natural isotopic abundance. The ^{1}H and ^{13}C COSY 2D spectra were obtained using a standard pulse sequence [5].

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