NMR PARAMETERS, ISOMERISM, AND CONFORMATIONAL ANALYSIS OF 3-METHYL-2-PHENYL-5-(3-METHYL-2-PHENYL-3,4-DEHYDROPIPERID-6-YL)-PYRIDINE

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The configurational and conformational features of the trans and cis isomers of 3-methyl-2-phenyl-5-(3-methyl-2-phenyl-3,4-dehydropiperid-6-yl)pyridine, formed as by-products in the phenylation of β-picoline by phenyllithium, were established. The revealed stereospecificity of the $^5J_{HH}$ *and* $^1J_{CH}$ *SSCCs may be utilized as an independent criterion in the conformational analysis of piperideine systems.*

It was previously communicated that the by-product which is formed in considerable quantity in the phenylation of β-picoline by phenyllithium is 3-methyl-2-phenyl-5-(3-methyl-2-phenyl-3,4-dehydropiperid-6-yl)pyridine (I) — a structural analog [1]. On the basis of the ^1H and ^{13}C NMR data and taking into account information on the steric structure of substituted cyclohexenes [2], the cis configuration of the phenyl and pyridine substituents with the half-chair conformation of the piperideine ring was proposed for the isolated isomer [I]. Subsequently, the second possible geometrical isomer (II) was also isolated in the phenylation of β-picoline together with the pyridine (I). Thus, the presence of the second isomer places in doubt the correctness of the conclusion of the authors of [1] on the pseudo-equatorial orientation of the phenyl substituent at the $C_{(2')}$ of the piperideine ring, based only on the literature data for the stereochemistry of analogously substituted cyclohexenes.

With the object of the unambiguous establishment of the configuration of the isomers (I) and (II), we performed the joint analysis of the ^1H and ^{13}C NMR spectra (Tables 1 and 2) in the present work with attention given to the stereospecific $^5J_{HH}$ and $^1J_{CH}$ SSCCs. The preferred equatorial orientation of substituent at the $C_{(6')}$ atom in both isomers follows from the high vicinal trans-SSCCs $^3J_{5,6} = 9.64$ Hz (I) and $^3J_{5,6} = 10.56$ Hz (II). It can be seen from Table 1 that the greatest difference is observed in the case of the homoallyl $^5J_{HH}$ SSCCs, for which the π-contribution becomes determining since the value of the J decreases sharply with the increase in the number of bonds. Taking into account the values of the dihedral angles $\varphi\ [H_{(2'e)}, C_{(2')}, C_{(3')}, C_{(4')}]$, $\varphi[H_{2'a)}, C_{(2')}, C_{(3')}, C_{(4')}]$, $\varphi[H_{(5'a)}, C_{(5')}, C_{(4')}, C_{(3')}]$, and $\varphi[H_{(5'e)}, C_{(5')}, C_{(4')}, C_{(3')}]$, calculated by the method of possible cis and trans isomers (Table 3), as well as the angular dependence $^5J^{\pi}HH$ [3], it can be expected that $^5J_{2'a5'a} > {}^5J_{2'a5'e} = {}^5J_{2'e5'a} > {}^5J_{2'e5'e}$. The SSCCs are as follows: $^5J_{2'a5'a} = 3.78$ Hz, $^5J_{2'a5'e} = 2.54$ Hz, $J_{2'e5'a} = 2.44$ Hz, and $^5J_{2'e5'e} = 0.85$ Hz. Consequently, the homoallyl SSCCs indicate the cis-(2'e, 5'e)-configuration of the isomer (II) and the trans-(2'a, 5'e)-configuration of the isomer (I). The orientation of the phenyl substituent at $C_{(2')}$ is also confirmed by the direct $^1J[C_{(2')}, H_{(2')}]$ SSCCs in the isomers (I) and (II). The greater significance of this constant for the isomer (I) by comparison with (II) may be explained by the cis orientation of the $C_{(2')}-H_{(2')}$ bond in relation to the unshared pair of electrons of the nitrogen atom, i.e., $^1J(C, H^e) > {}^1J(C, H^a)$. Taking this feature into account, the observed $^1J[C_{(2')}, H_{(2')}]$ SSCCs in the isomers (I) and (II) (cf. Table 2) indicate the pseudo-axial orientation of the phenyl substituent in the isomer (I) and the pseudo-equatorial orientation in the isomer (II). Therefore, the stereospecificity of the $^5J_{HH}$ and $^1J_{CH}$ SSCCs allows the unambiguous establishment of the configuration of the isomers (I) and (II).

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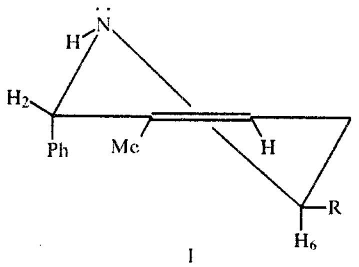
TABLE 1. ^{1}H NMR Data for the Isomers (I) and (II)

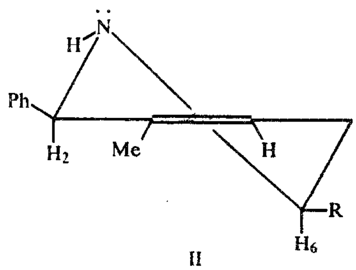
Isomer	Chemical shifts, δ, ppm (in C_6D_6, 400 MHz)										SSCCs, J_{HH}, Hz												
	2'	4'	5'a	5'e	6'a	3'-CH$_3$	4	6	3-CH$_3$	phenyl	2', 3'CH$_3$	2', 5'a	2', 5'e	3'CH$_3$, 4'	4', 5'a	4', 5'e	4', 2'	5'a, 5'e	5'a, 3'CH$_3$	5'e, 3'CH$_3$	5'a, 6'a	5'e, 6'a	4, 6
I	4,34	5,62	2,23	2,14	3,88	1,53	7,26	8,61	2,05	7,11...7,65	0,70	2,44	0,85	1,43	2,44	5,00	1,34	-16,91	2,32	1,43	9,64	4,52	2,19
II	4,23	5,50	2,36	2,02	3,73	1,40	7,45	8,66	2,08	7,14...7,69	1,22	3,78	2,54	1,31	1,89	6,06	1,91	-16,42	2,20	1,22	10,56	3,56	2,20

TABLE 2. ^{13}C Chemical Shifts (δ, ppm, TMS) and the Direct $^{13}C-^{1}H$ SSCCs (in parentheses, Hz) in the Isomers (I) and (II) (in C_6D_6, 100.6 MHz)

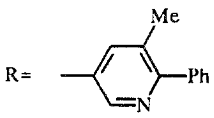
Isomer	2'-C	3'-C	3'-CH$_3$	4'-C	5'-C	6'-C	3-CH$_3$	2-C	6-C	3-C	4-C
I	62,13 (135,3)	133,50	21,51 (126,2)	122,76 (156,1)	34,65 (127,9)	48,81 (133,5)	20,09 (126,9)	157,71	146,43 (176,9)	130,11	136,82 (157,4)
II	65,29 (130,4)	138,69	20,68 (126,2)	121,69 (156,1)	35,45 (127,9)	55,89 (132,5)	20,11 (126,9)	158,06	146,65 (176,2)	130,39	136,53 (157,4)



I

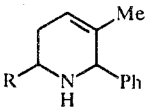


II



Numerous literature data testify in favor of the half-chair conformation in the case of cyclohexene and piperideine systems [4, 5]. The NMR parameters (cf. Tables 1 and 2) and calculations performed using the method of molecular mechanics [4] (the torsion angles in cyclohexene are also presented for comparison [6]) are in good agreement with the half-chair conformation for the piperideine ring:

cyclohexene



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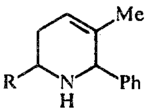
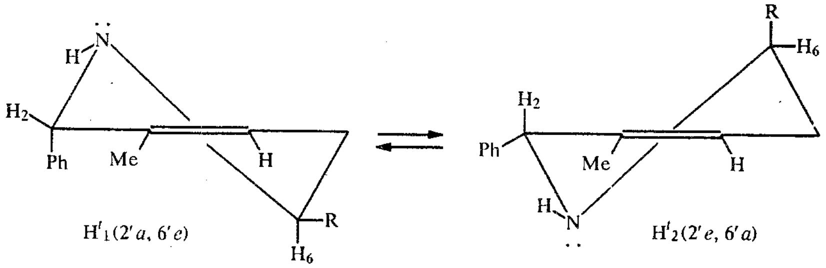


II

Utilizing the modified Karplus equations, proposed in [7, 8], the vicinal $^3J_5$ SSCCs were calculated according to determined MM2 methods for the dihedral angles φ between the corresponding protons (cf. Table 3). As was also expected, better agreement with the experimental values of $^3J_{HH}$ in the case of the conformationally uniform isomer (II) is achieved for the equation proposed in [7] taking into account the influence of the unshared electron pair of the nitrogen atom on the $^3J_{HH}$ values (cf. Table 3). The decrease in the experimental value of the trans-SSCC $^3J_{5,6}$ (cf. Table 1) in the case of the trans isomer (I) by comparison with the cis isomer (II) may be explained by the conformational heterogeneity of the first and the presence of a small portion of the second conformer:



In this connection, the conformer $H_2^t(2'e, 6'a)$ was also included in the calculation scheme using the method of molecular mechanics and according to the equation (4), proposed in the work [7] (cf. Table 3). Utilizing the $^3J_{aa}{}^0 = 10.4$ Hz and $^3J_{ee}{}^0 = 2.4$ Hz, calculated for the conformers $H_1^t(2'a, 6'e)$ and $H_2^t(2'e, 6'a)$, as limiting values of the SSCCs, the occupancies of the conformers in the case of the isomer (I) — $n(H_1^t) = 90\%$ and $n(H_2^t) = 10\%$ — were evaluated by the method of average parameters [9] using the experimentally determined trans-SSCC $^3J_{5,6}$ (cf. Table 1).

TABLE 3. Calculated Values of the Dihedral Angles (°) and Vicinal $^3J_{HH}$ SSCCs (Hz) for the Possible Conformations H^t_1(2′a, 6′e), H^t_2(2′e, 6′a), and H^c(2′e, 6′e) of the Isomers (I) and (II)

Parameter	H^t_1(2′a, 6′e)	H^t_2(2′e, 6′a)	H^c(2′e, 6′e)
$\varphi(H_{(2')},C_{(2')},C_{(3')},C_{(4')})$	130,5	104,4	107,0
$\varphi(H_{(5'a)},C_{(5')},C_{(4')},C_{(3')})$	106,0	105,2	102,4
$\varphi(H_{(5'e)},C_{(5')},C_{(4')},C_{(3')})$	137,0	138,6	139,5
$\varphi(H_{(5'a)},C_{(5')},C_{(6')},H_{(6')})$	168,0	41,5	172,0
$\varphi(H_{(5'e)},C_{(5')},C_{(6')},H_{(6')})$	49,1	76,4	52,7
$^3J_{5'e6'}$ [8]	4,4	1,3	3,8
[7]	*	2,4	*
$^3J_{5'a6'}$ [8]	11,6	6,2	11,8
[7]	10,4	*	10,5

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*Not calculated.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra of the compounds (I) and (II) in C_6D_6 were registered on a Bruker WM-400 spectrometer. The ^1H and ^{13}C CSs were measured relative to TMS with the accuracy of up to 0.01 ppm; the corresponding accuracy for the SSCCs was up to 0.05 Hz.

3-Methyl-2-phenyl-5-(3-methyl-2-phenyl-3,4-dehydropiperid-6-yl)pyridines (I), (II). To the solution of phenyllithium, obtained from 77 g (0.49 mole) of bromobenzene and 7 g (1.0 mole) of lithium in 250 ml of abs. ether, are added, dropwise, 45.5 g (0.49 mole) of β-picoline. The reaction mixture is stirred at room temperature for 3 h and boiled for 1 h. The reaction mass is then decomposed with 275 ml of water under conditions of cooling with ice water. The ether layer is separated, and the aqueous layer is extracted threefold with 75-ml portions of ether. The ether extracts are dried with magnesium sulfate. After the distillation of the ether, crystals of the isomer (I) are precipitated from the residue when it is left to stand for 7 days. The liquid phase is decanted from the crystals. The crystals of the isomer (I) are washed with acetone and filtered off; the mass obtained is 11.52 g, and the mp is 137-140°C after recrystallization from n-heptane. The decanted liquid subsequently provides a precipitate of 0.45 g more of crystals of the isomer (I) with the same melting temperature. After the separation of the isomer (I), 0.91 g of crystals with the mp 100-106°C is precipitated from the residue after the standing for approximately 2 weeks. Recrystallization from heptane afforded crystals which are those of the isomer (II) with the mp 104-107°C.

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