DETERMINATION OF THE ORIENTATION OF THE PHENYL SUBSTITUENT IN ISOMERIC 1-ETHYL-2,5-DIMETHYL-4-PHENYL-4-PIPERIDINOLS BY TWO-DIMENSIONAL NUCLEAR OVERHAUSER EFFECT (NOESY) SPECTROSCOPY. CONFORMATION OF THE β ISOMER OF 1,2,5-TRIMETHYL-4-PHENYL-4-PIPERIDINOL

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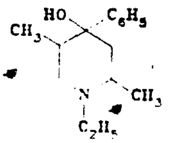
In the case of three isomers (α, β, and γ) of 1-ethyl-2,5-dimethyl-4-phenyl-4-piperidinol it is shown that NOESY spectroscopy can be successfully used in the determination of the orientation of the phenyl substituent. It was observed that the chemical shifts of the protons and the carbon atoms in the ortho position and of the quaternary C atom of the phenyl substituent and the ${}^1J_{C_{(5)}H_{(5a)}}$ *direct spin-spin coupling constant (SSCC) satisfactorily reflect the change in the orientation of the phenyl substituent on passing from the α isomer to the β and γ isomers. A chair (2a, 5e)* $\rightleftharpoons$ *twist-boat (2e, 5e) conformational equilibrium in which the twist-boat conformation is stabilized by an intramolecular hydrogen bond is proposed for the β isomer of 1,2,5-trimethyl-4-phenyl-4-piperidinol on the basis of the NMR data.*

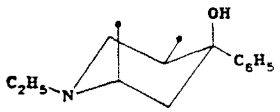
Data from an x-ray diffraction analysis have been previously used [1] to determine the configurations of the substituents attached to the $C_{(4)}$ atom of the piperidine ring in promedol alcohols (1,2,5-trimethyl-4-phenyl-4-piperidinols). It was later shown that the width of the unresolved multiplet of the signal of the quaternary carbon atom of the phenyl ring in the ^{13}C NMR spectra without decoupling of the protons can also be used for the same purpose [2].

In the present research in the case of three isomers of 1-ethyl-2,5-dimethyl-4-phenyl-4-piperidinol (IA, mp 93-94°C; IB, mp 99-100°C; IC, mp 105-106°C) with unknown configurations we investigated the question of the applicability of nuclear Overhauser effect spectroscopy (NOESY) for the determination of the configuration of the substituents attached to the $C_{(4)}$ atom in 4,4-disubstituted piperidines.

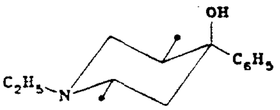


The vicinal $^3J_{HH}$ spin-spin coupling constants (SSCC) (Table 1) of the protons of the piperidine ring for IA and IC constitute evidence for a primary equatorial orientation of the 2- and 5-methyl groups in them, while the vicinal $^3J_{HH}$ SSCC for IB constitute evidence for an axial orientation of the 2-CH_3 group and an equatorial orientation of the 5-CH_3 group. According to the two-dimensional NOESY spectra (Fig. 1) cross peaks from the $H_{(o)}$–$H_{(2a)}$ and $H_{(o)}$–$H_{(6a)}$ proton pairs, which indicate an axial orientation of the phenyl group in IA, are observed only in the case of isomer IA.

Cross peaks from the $H_{(o)}$–$H_{(3a)}$ and $H_{(o)}$–$H_{(5a)}$ proton pairs (Fig. 1), which constitute evidence in favor of an equatorial orientation of the phenyl group in them, are present in the NOESY spectra of isomers IB and IC:



I B (β isomer)



IC (γ isomer)

IA (α isomer, according to [3])

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TABLE 1. PMR Spectra of the Isomeric IA-IC

Isomer	Chemical shifts, δ, ppm*													^1H-^1H SSCC, Hz							
	$H_{(2)}$	$H_{(3a)}$	$H_{(3e)}$	$H_{(5a)}$	$H_{(6a)}$	$H_{(6e)}$	2-CH_3	5-CH_3	N—CH_2	CH_3	C_6H_5			3a3e	6a6e	23 cis	23 trans	56 cis	56 trans	2,2′	5,5′
											o-	m-	p-								
IA	2,92	1,82	2,28	2,17	2,26	2,79	1,14	0,84	2,47; 2,84	1,07	7,63	7,31	7,21	−13,7	−11,8	3,7	10,4	3,7	10,6	6,2	6,8
IB	3,19	2,31	1,69	2,20	2,66	2,44	1,24	0,62	2,57	1,13	7,47	7,29	7,17	−14,4	−11,8	5,9	2,0	4,2	11,2	7,0	6,8
IC	2,81	1,86	1,68	2,20	2,49	2,67	1,07	0,62	2,52; 2,89	1,07	7,49	7,30	7,17	−14,0	−11,5	2,8	11,5	4,3	11,5	6,1	6,8

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*The internal standard was tetramethylsilane (TMS).

TABLE 2. ^{13}C NMR Spectra of Piperidinols IA-IC

Isomer	Chemical shifts, δ, ppm* (SSSCC, ^1JCH Hz) in CD_3OD												
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(1')}$	$C_{(1'')}$	$C_{(2')}$	$C_{(5')}$	$C_{(4')}$	$C_{(o)}$	C (m)	C(p)
IA	55,15 (132,2)	48,76	74,97	42,87 (128,6)	55,36	47,97	11,25 (125,6)	19,60 (126,3)	14,76 (125,9)	146.08	128.48	128,44	127,66
IB	52,11 (135,2)	45,44	75,68	40,24 (126,4)	50,54	48,93	12,40 (125.3)	12,47 (125,9)	12,65 (125,9)	149.40	126,14	128,62	127,17
IC	52,20 (133,8)	49,93	75,00	40,31 (126,4)	55,24	47,81	9,88 (125,8)	19,96 (125,6)	12,75 (126,2)	148,75	125,95	128,92	127,26

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*The internal standard was tetramethylsilane (TMS).

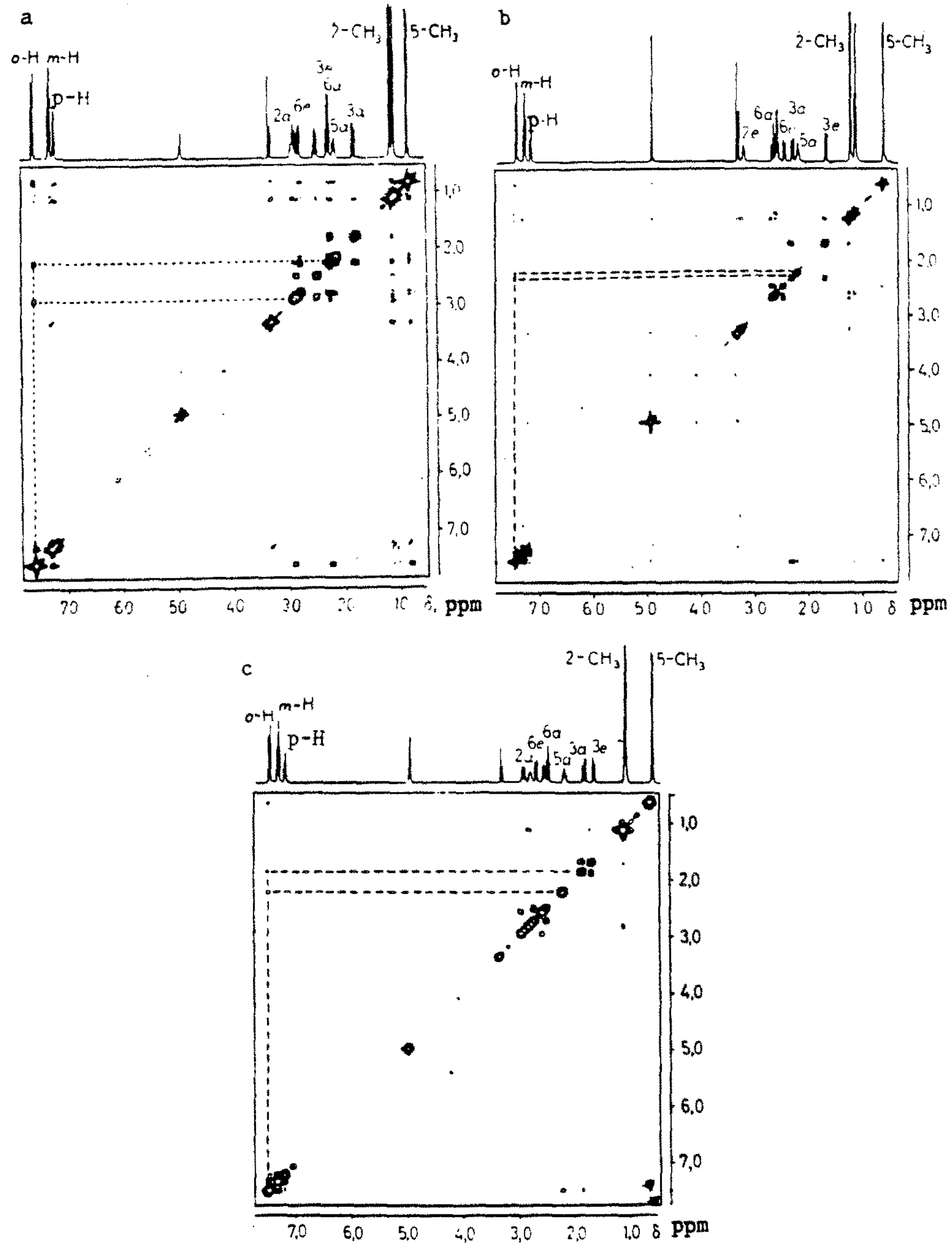
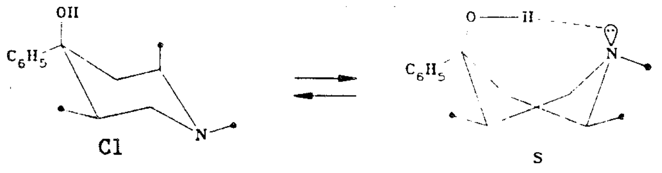


Fig. 1. NOESY spectra (τ_m = 1 sec) of isomers IA-IC. The cross peaks, which attest to drawing together of the protons in space, are shown by the dashed lines: a) H_o with $H_{(2a)}$ and $H_{(6a)}$ (IA); b) H_o with $H_{(3a)}$ and $H_{(5a)}$ (IB); c) H_o with $H_{(3a)}$ and $H_{(5a)}$ (IC).

It is apparent from Tables 1 and 2 that the $\delta_{(H_{(o)})}$, $\delta_{(C_{(4')})}$, and $\delta_{(C_{(o)})}$ chemical shifts (CS) reflect quite well the change in the orientation of the phenyl substituent on passing from isomer IA to IB and IC, while the greater value of the $^1J_{(C_{(5)},H_{(5a)})}$ direct SSCC in IA as compared with the SSCC of IB and IC is due to the adjacency (the cis orientation) of $C_{(5)}$–$H_{(5a)}$ and the unshared electron pairs of the oxygen atom of the hydroxy group. As regards the orientation of the 2-methyl group, it should be noted that its axial orientation in IB, together with the CS of the $C_{(2')}$ atom and the $^1J_{(C_{(2)},H_{(2)})}$ SSCC (Table 2), is also satisfactorily described by the $^3J_{(H_{(2)},H_{(2')})}$ SSCC (Table 1).

It is quite apparent from Table 1 that an axial orientation of the methyl substituent attached to the $C_{(2)}$ atom in the β isomer leads to more pronounced deshielding of the $H_{(3a)}$ proton than in the α and γ isomers with an equatorial orientation of this group. Similar changes in the CS of the $H_{(3a)}$ proton are also observed in the cis and trans isomers of N-substituted 2,5-

dimethyl-4-piperidinones [4] and are in agreement with the known effects of the magnetic anisotropy of a C–C single bond (the $C_{(2)}$–CH_3 bond in this case) [5]. The data presented above constitute evidence for the erroneous assignment of the $H_{(3a)}$ and $H_{(3e)}$ protons in [6] for the β isomer of 1,2,5-trimethyl-4-phenyl-4-piperidinol (promedol alcohol). On the basis of the correct assignment of the $H_{(3a)}$ (2.24 ppm) and $H_{(3e)}$ (1.69 ppm) protons and, correspondingly, the J_{23}^{cis} (6.0 Hz) and J_{23}^{trans} (4.0 Hz) SSCC it can be established that the J_{23}^{trans} and J_{56}^{trans} SSCC (8.5 Hz) constitute evidence in favor of a two-position conformational equilibrium since according to the data on the populations of the conformers from the boundary $J_{5a,6a}$, $J_{2a,3a}$, and J_{ee} SSCC presented in [6] within the framework of a three-position conformational equilibrium C1(2*a*, 5e)$\rightleftharpoons$C2(2e, 5*a*) $\rightleftharpoons$S(2e, 5e), we obtain C1 (0.75), C2 (0), and S (0.25).



C1

S

Consequently, the PMR parameters in the spectrum of the β isomer of 1,2,5-trimethyl-4-phenyl-4-piperidinol are determined primarily by the chair (2*a*, 5e) and twist-boat (2e, 5e) conformations.

EXPERIMENTAL

The NMR spectra were recorded with Bruker WM-400 spectrometers (400 MHz for the ^1H nuclei and 100.6 MHz for the ^{13}C nuclei). In obtaining the ^{13}C NMR spectra without decoupling of the protons we used 30% solutions of the 4-piperidinols in CD_3OD; 5% solutions were investigated in all of the remaining cases. The ^1H and ^{13}C CS were measured relative to tetramethylsilane (TMS) with an accuracy of up to 0.01 ppm, while the SSCC were measured with an accuracy of up to 0.1 Hz. To obtain the two-dimensional (2D) NOESY spectra we used the standard pulse sequence [7]; the mixing time $\tau_m = 1$ sec. The τ_m time was varied randomly during the experiments within the limits of 5% to suppress the coherent transfer of magnetization. The data matrix containing 256 × 1024 points, was supplemented up to dimensions of 512 × 1024, which corresponds to a resolution of 5.7 Hz per point. Prior to measurement of the NOESY spectra the solutions were purged with argon.

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