CONFORMATION OF THE PIPERIDINE RING IN ISOMERIC 1,2,5-TRIMETHYL-4-PHENYL(TRIORGANOSILYL)PIPERIDIN-4-OLS FROM THE PMR SPECTRA

A. A. Fomichev, N. I. Golovtsov, V. A. Rezakov, A. V. Varlamov, and M. S. Prostakov

UDC 543.422.25:547.823:541.63

A full analysis of the PMR spectra of isomeric promedol alcohols was undertaken for the first time. It was shown that the conformational equilibrium must be taken into account only in the case of the β isomer, where it is determined mainly by chair–chair interconversion. In the α isomers of 1,2,5-trimethyl-4-triorganosilylpiperidin-4-ols an equilibrium was found between the chair conformation and the two skew boat conformations, which are stabilized by an intramolecular hydrogen bond and by the large size of the triorganosilyl substituent.

The propionic esters of isomeric 1,2,5-trimethyl-4-phenylpiperidin-4-ols (promedol alcohols) are effective analgesics. However, they differ in the degree of pain-relieving effect which they give. Thus, for example, the ester of the α isomer is two to three times more active than the esters of the β and γ isomers [1]. Soon after the synthesis of these compounds researches were conducted into the stereochemical structure of the isomeric 1,2,5-trimethyl-4-phenylpiperidin-4-ols by chemical and spectral methods [2-10]. For the α and γ isomers of this alcohol there are in the literature exhaustive data obtained by various methods, including x-ray crystallographic analysis in the solid phase [9]. They agree well with or supplement each other and confirm the structure. However, contradictions in the analysis of the PMR [5] and ^{13}C NMR [8] spectra for the β isomer and the absence of other objective data left the question of the conformation of this isomer unresolved. For example, Vlasova and Sheinker [5] concluded on the basis of incomplete data from the PMR spectra that only one chair form participates in the conformational equilibrium of the β isomer, while Jones and co-workers [8] overstated the contribution from the skew form without sufficient grounds. We therefore tried to obtain the fullest possible data on the PMR spectra for the promedol alcohols, using spectra recorded at 360 MHz.

On the basis of the spectra with the appropriate choice of solvent we were able to determine all the PMR parameters of the α, β, and γ isomers of 1,2,5-trimethylphenylpiperid-4-ol (Table 1). In spite of the use of such strong polarizing fields, none of the spectra was capable of first-order interpretation, and during the analysis we used the INTRCAL program. The values of the vicinal spin–spin coupling constants of the γ isomer confirm its chair conformation with the equatorial orientation of the methyl groups at positions 2 and 5. Extremely characteristic here are the exceptionally large trans constants J_{56} = 12.0 and J_{23} = 11.5 Hz, characteristic of axial–axial interaction. It is also possible to note the minimal value of the cis constant (J_{23} = 3.0 Hz) compared with the α and β isomers and the ratio of the chemical shifts at the $C_{(3)}$ carbon atom not quite normal for the chair form: $\delta_{3a} > \delta_{3e}$. Together, the parameters from the PMR spectra of the γ isomer correspond to an absolutely predominant chair conformation with the equatorial orientation of the methyl groups at positions 2, 5 and the phenyl substituent (t-2-CH_3, c-5-CH_3, r-4-OH):

P. Lumumba People's Friendship University, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1496-1502, November, 1986. Original article submitted May 27, 1985.

 0009-3122/86/2211-1208$12.50

TABLE 1. The PMR Data (360 MHz) for the Isomeric Promedol Alcohols (Internal Standard TMS)

Isomers	Solvent	PMR spectrum, δ, ppm											SSCC, J, Hz							
		2e*	2a	3e	3a	5a	6e	6a	NCH_3	2-CH_3	5-CH_3	OH	3a3e	6a6e	cis 23	trans 23	cis 56	trans 56	2,2-CH_3	5,5-CH_3
α	DMSO-D_6	—	2,62	2,06	1,66	2,05	2,62	2,10	2,22	1,04	0,69	4,53**	−13,5	−11,5	3,5	10,5	4,0	10,5	7,0	7,0
β	$CDCl_3$	2,81	—	2,24	1,69	2,30	2,38	2,60	2,31	1,18	0,74	4,37**	−14,0	−11,5	4,0	6,0	5,0	8,5	6,7	6,7
γ	$CDCl_3$	—	2,38	1,70	1,83	2,31	2,69	2,33	2,34	1,09	0,63	1,68	−14,0	−11,5	3,0	11,5	4,0	12,0	6,5	6,0

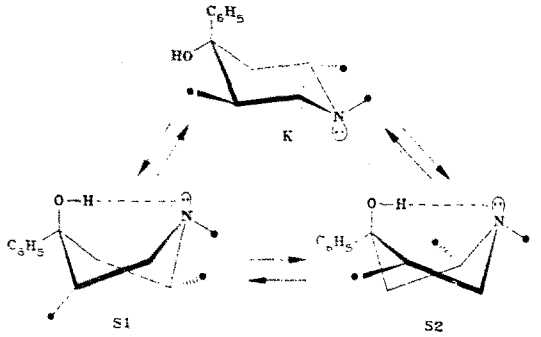
*For the β isomer the letters e and *a* refer to the more populated conformer.
**In DMSO-D_6.

TABLE 2. The Chemical Shifts and the Spin–Spin Coupling Constants for the Protons of 1,2,5-Trimethyl-4-organosilylpiperidin-4-ols (Internal Standard TMS)

Compound	Solvent	CS, δ, ppm											SSCC, J, Hz							
		2a	3a	3e	5a	6a	6e	N—CH_3	2-CH_3	5-CH_3	OH	$SiCH_3$	3a3e	6a6e	trans 23	cis 23	trans 56	cis 56	2,2-CH_3	5,5-CH_3
I-γ	C_6D_6	2,57	1,90	2,25	2,30	2,47	2,28	2,16	0,93	1,02	1,26	—	−13,7	−12,0	11,5	2,3	12,0	3,8	6,1	6,8
I-α	C_6D_6	2,25	1,77	2,45	2,25	1,70	2,55	1,84	1,01	0,99	2,81	—	−13,5	−12,0	6,5	5,5	8,5	5,5	6,5	7,0
I-α	$CDCl_3$	2,18	1,69	2,51	2,30	1,85	2,66	2,01	1,05	0,97	2,41	—	−13,7	−11,6	8,2	4,6	9,2	4,9	6,3	7,0
II-γ	CD_2Cl_2	2,30	1,54	1,64	2,02	2,20	2,30	2,18	0,96	0,70	1,15*	0,65	−13,5	−12,0	10,0	4,0	11,0	5,0	6,0	7,0
II-α	C_6D_6	2,18	1,34	2,14	1,93	1,89	2,47	2,01	0,89	0,87	1,40	0,75	−13,0	−11,0	10,5	3,5	11,0	6,0	7,0	6,0
III-γ	CD_2Cl_2	2,19	1,41	1,54	1,89	2,10	2,28	2,15	0,77	0,77	1,22	0,36**	−14,0	−11,0	11,0	3,5	11,5	4,0	6,0	7,0

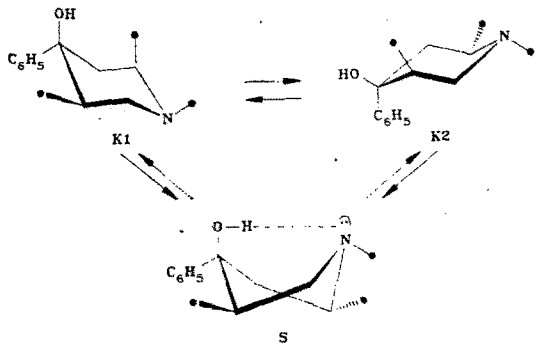
*In deuteromethylene chloride the OH signal is not detected on account of broadening, and the δ value in a dilute solution in deuterobenzene is given.
**The methyl groups are diastereotopic and anisochronous, Δν = 6.5 Hz (360 MHz).

The vicinal spin–spin coupling constants of the piperidine ring protons in the α isomer (Table 1) differ little from the analogous constants of the γ isomer. This is determined by the identical predominant orientation of the 2- and 5-methyl groups in the two isomers in the configuration of the α isomer: c-2-CH_3, t-5-CH_3, r-4-OH. In view of the IR spectroscopic data [5] the reduced values of the trans constants J_{23} and J_{56} (10.5 Hz) and the larger value of the cis constant J_{23} (3.5 Hz) in comparison with the γ isomer may be explained by a contribution from the two skew boat conformations S_1 and S_2, stabilized by an internal hydrogen bond. However, estimates of the populations in such a three-position equilibrium from the values of the trans constants J_{23} and J_{56} on the assumption that J_{aa} = 11.5 and J_{ee} = 2 Hz give values not exceeding 8-10% for each of the conformations S_1 and S_2, indicating that the K (chair) form predominates.



The possible three-position equilibrium in the conformations of the α isomer (● — methyl groups).

The protons in the PMR spectra of the β isomer differ substantially from the parameters of the other isomers, particularly the vicinal spin–spin coupling constants of the ring protons (Table 1). None of the possible conformers corresponds predominantly to the set of vicinal cis and trans constants J_{23} = 4.0, J_{23} = 6.0, J_{56} = 5.0, and J_{56} = 8.5 Hz in the β isomer. The increased values of the cis constants and the substantially reduced values of the trans constants can be explained only by conformational equilibrium between the various forms with populations which differ little. This fact was confirmed in addition by the low-temperature spectra of the β isomer in deuteromethylene chloride, where in contrast to the α and γ isomers, exchange broadening of the signals for the protons of the piperidine ring and the methyl substituents with disappearance of the spin–spin splittings, characteristic only of comparable populations of the exchanging conformations, was observed at temperatures below −10°C. The large vicinal spin–spin coupling constants for the gauche interaction (ee) and the obviously small constants for the trans-axial-axial (*aa*) interaction can be described well by the chair–chair equilibrium with alternate axial (equatorial) orientation of the 2- or 5-methyl groups. However, the data from IR spectroscopy, where the band for an intramolecular hydrogen bond in the β isomer was observed [5], make it necessary to include the skew boat form, which is the only form where such a bond can be realized, in the scheme of the conformational equilibrium. The contribution from the skew form is also demonstrated by the appreciably increased values of the cis constant J_{ae} in the β isomer compared with the γ isomer. Thus, a three-position conformational equilibrium appears.



The conformational equilibrium for the isomer.

TABLE 3. The Dependence of the Vicinal Spin–Spin Coupling Constants J_{HH}, Hz, for the (I–α) Isomer on the Solvent and Temperature

Isomer (I-α)	Solvent				T, °C		
	$(CD_3)_2CO$	$CDCl_3$	CD_2Cl_2	C_6D_6	5	15	20
cis 23	3,5	4,6	5,6	5,5	4,0	4,0	5,0
trans 23	9,5	8,2	7,5	6,5	8,5	8,5	7,5
cis 56	4,5	4,9	5,5	5,5	4,5	5,0	5,5
trans 56	10,0	9,2	9,0	8,5	10,0	9,5	9,0

TABLE 4. The Populations and the Differences in Free Energies of the Conformations in the (I–α) Isomer

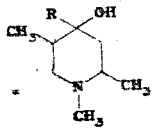
Solvent	n_K	n_{S1}	n_{S2}	ΔG_{K-S1}°, kJ/mole	ΔG_{K-S2}, kJ/mole
C_6D_6	0,2	0,6	0,2	+2,7	0
$(CD_3)_2CO$	0,6	0,2	0,2	−2,7	−2,7

The values for the populations of the conformers obtained from the values of the trans constants on the assumption that J_{5a6a} = 12 in K1, J_{2a3a} = 11.5 in K2, and $J_{5a6a} = J_{2a3a}$ = 10 in S with J_{ee} = 2 Hz led us to the following values for the two conformations K1 and K2: K1 (0.57), K2 (0.33), and S (0.10). Consequently, the values of the PMR parameters in the β isomer are largely determined by the two chair forms K1 and K2.

The conclusions reached in [5, 8] about the participation of only one chair form K1 in the conformational equilibrium of the β isomer, based on incomplete PMR data, must be recognized as erroneous, and the contribution from the skew form in [8] is overestimated.

Thus, investigation of the isomeric promedol alcohols in the present work by the PMR method in ultrastrong polarizing fields made it possible to determine for the first time all the parameters of the PMR spectra for the α, β, and γ isomers of the promedol alcohols. This in turn made it possible to refine the spectral–structural correlations and in the case of the β isomer to propose a model for the dynamic conformational equilibrium. The data which we obtained for the isomeric promedol alcohols were used as the basis for investigations of 4-triorganosilyl-substituted piperidols.

The PMR spectra of the isomers of 1,2,5-trimethyl-4-organosilylpiperidin-4-ols (I–III) were analyzed.



I-γ, I-α R=$Si(C_6H_5)_3$; II-γ, II-α R=$Si(C_6H_5)_2CH_3$; III-γ R=$Si(CH_3)_2C_6H_5$

The spectra were recorded in ultrastrong fields (200, 360, and 400 MHz) in various solvents [$(CDCl_3)$, C_6D_6, $(CD)_3CO$, $CDCl_2$] and at temperatures between −50 and 70°C, using double resonance for the assignment of the signals. As an example a fragment of the spectrum of the isomer (I-α) at 360 MHz is given in Fig. 1. The data from the PMR spectra of the isomers of the piperidols (I–III) are given in Table 2.

Analysis of the vicinal spin–spin coupling constants of the ring protons in the γ isomers of all the piperidols (Table 2) indicates a chair conformation for the piperidine ring in these conformers with the equatorial orientation of the 2- and 5-methyl groups. For example, the trans constants ($^3J_{23}$ = 11.5 and $^3J_{56}$ = 12.0 Hz) for the isomer (I-γ) (Table 2) correspond to axial–axial interaction 2a3a and 5a6a in the chair conformation. In the γ isomer of promedol alcohol (Table 1) these constants have the same values. Appreciable changes in the spin–spin coupling constants of the γ isomers were not observed either with change in

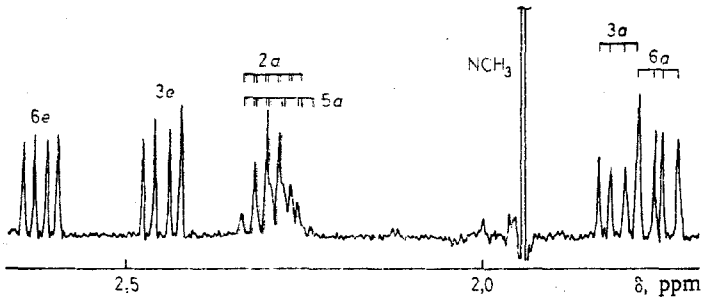
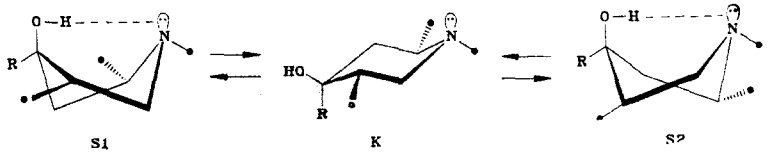


Fig. 1. Fragment of the PMR spectrum of the isomer (I-α) (deuterobenzene, 360 MHz, T = 313°K).

the solvent or with change in the temperature. All this makes it possible to consider that the γ isomers represent predominantly one chair form with the equatorial orientation of the methyl groups at position 2 and 5 and with the same configurations (t-2-CH_3, c-5-CH_3, r-4-OH) as in the γ isomer of promedol alcohol.

In the α isomer of (I) the observed trans-vicinal spin–spin coupling constants are smaller in value than in the γ isomer (6.5, 8.5, and 11.5, 12.0, respectively), and moreover their values depend on the solvent and on the temperature (Table 3). This can be explained by the existence of a conformational equilibrium in the isomer (I-α) between the chair conformation and the two skew boat conformations stabilized by an intramolecular hydrogen bond, where the methyl substituent either at $C_{(2)}$ (S1) or at $C_{(5)}$ (S2) has the axial orientation.



Conformational equilibrium in the α isomers of 1,2,5-triethyl-4-organosilylpiperidin-4-ols

In addition to the previously obtained IR-spectroscopic data [10], the existence of an intramolecular hydrogen bond in the α isomers of (I) and (II) was confirmed in the present work by examination of the chemical shifts of the protons in the hydroxy group (Table 2), for which in the α isomers in a protic solvent there is a downfield shift compared with the γ isomers, and this is particularly noticeable in the case of (I-α). Such a hydrogen bond can only be realized in the skew conformations. In the α isomer of the alcohol (II), however, we did not observe a decrease of $^3J_{trans}$ compared with its γ isomer (Table 2), and we could not therefore estimate the very small contributions from the S1 and S2 forms in this case.

The populations of the conformations in the isomer (I-α) were estimated from the values of the most strongly changing $^3J_{trans}$ constants. For this we assumed that $J_{trans}(aa)$ in the K conformation must be equal to the corresponding spin–spin coupling constants in the γ isomer. For such spin–spin coupling constants in the skew forms we used a value of 10 Hz, taking account of the smaller torsional angles than in the chair conformation. For J_{trans}-(ee) in the skew boat conformations we used the range of 1-2 Hz, according to published data [11-13]. Using the equation for the observed averaged parameters and the van't Hoff formula, we calculated the populations of the conformations of the isomer (I-α) in deuterobenzene and the corresponding differences in free energies (Table 4).

The small values of ΔG in the isomer (I-α) make its conformational equilibrium labile with variation in the solvent (Table 4) and even with slight change in temperature. Thus, for example, calculation of the populations from the values of the trans constants (Table 3) for a solution of the isomer (I-α) in deuterobenzene gives the following values: n_K = 0.4; n_{S_1} = 0.2; n_{S_2} = 0.4; (+20°) and n_K = 0.6; n_{S_1} = 0.3; n_{S_2} = 0.1 (+5°). The increase in the population of the chair conformation K in the transition to polar solvents, capable of giving intermolecular hydrogen bonds with the substrate molecules, and with decrease in temperature is explained by the concurrent cleavage in this case of the intramolecular

hydrogen bonds which stabilize the S1 and S2 conformations. The substantial preponderance of the chair form in the conformational equilibrium of the isomer (II-α) in contrast to (I-α) indicates that the volume of the triorganosilyl substituent at position 4, the axial position of which in the conformation K is energetically unfavorable, has deciding significance, and this promotes transition to the skew conformations S1 and S2.

Thus, in the case of the promedol alcohols, according to the PMR spectra, a conformational equilibrium was only detected in the case of the β isomers, while the absolute preponderance of a single chair form was established in α-promedol alcohol. In the α isomer of 1,2,5-trimethyl-4-triphenylsilylpiperindin-4-ol, on the other hand, according to the PMR data there is undoubtedly a substantial population of the skew conformations.

EXPERIMENTAL

The synthesis of the promedol alcohols was described in [2], and that of their triorganosilyl analogs was described in [10]. The PMR spectra of saturated solutions in $CDCl_3$, C_6D_6, CD_2Cl_2, $(CD_3)_2CO$, and DMSO-D_6 were obtained on XL-200, WH-360, and WM-400 spectrometers with superconducting solenoids. The ^1H chemical shifts were measured with reference to TMS with an accuracy of up to 0.01 ppm and the spin–spin coupling constants with an accuracy of up to 0.1 Hz. Homonuclear double resonance experiments were used to refine the assignments of the signals. To narrow the lines and measure the spin–spin coupling constants more accurately we used a Lorenz–Gauss filter before Fourier transformation. In the calculation of the theoretical PMR spectra and the iteration search for the PMR parameters we used the INTRCAL program, which is incorporated in the software of the BNC-28X computer on the WP-80 Fourier spectrometer. The samples were prepared in thoroughly dehydrated solvents, and for this purpose they were kept over calcium chloride, calcium hydride, and metallic sodium. After preparation the ampuls containing the samples were sealed. Greatly diluted solutions with sample concentrations of up to 0.1 wt.% were also investigated.

The authors convey their gratitude to K. F. Turchin and I. I. Cherbin for assistance in the recording of the PMR spectra.

LITERATURE CITED

1. I. N. Nazarov, N. S. Prostakov, and N. I. Shvetsov, Zh. Obshch. Khim., 26, 2798 (1956).
2. I. N. Nazarov, N. S. Prostakov, and N. N. Mikheeva, Zh. Obshch. Khim., 28, 2746 (1958).
3. N. I. Shvetsov and V. F. Kucherov, Dokl. Akad. Nauk SSSR, 126, 1017 (1959).
4. A. F. Casy, J. Med. Chem., No. 11, 188 (1968).
5. T. F. Vlasova and Yu. N. Sheinker, Zh. Strukt. Khim., 11, 640 (1970).
6. A. F. Casy and K. M. J. McErlane, J. Chem. Soc., Perkin Trans. 1, No. 3, 334 (1972).
7. K. M. J. McErlane and A. F. Casy, J. Chem. Soc., Perkin Trans. 1, No. 3, 339 (1972).
8. A. J. Jones, C. P. Beeman, A. F. Casy, and K. M. J. McErlane, Can. J. Chem., 51, 1790 (1973).
9. W. H. De Camp and F. R. Ahmed, J. Chem. Soc., Chem. Commun., No. 17, 1102 (1971).
10. N. S. Prostakov, A. V. Varlamov, V. P. Zvolinskii, G. I. Cherenkova, Butros Musa Butros, and Mariya Élena Sintra, Khim. Geterotsikl. Soedin., No. 4, 502 (1976).
11. M. F. Grenier-Loustalot, F. Metras, L. Cottier, and G. Descotes, Spectrosc. Lett., 15, 789 (1982).
12. M. F. Grenier-Loustalot, F. Metras, L. Cottier, and G. Descotes, Spectrosc. Lett., 15, 963 (1982).
13. M. M. A. Hassan and A. F. Casy, Tetrahedron, 26, 4517 (1970).