SPATIAL STRUCTURE OF SOME DERIVATIVES OF PIPERIDIN-4-OL

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A piperidine ring with a hydroxy group in position 4 is an important constituent of the molecules of the alkaloid cocaine and compounds related to it (ecgonine, tropine, etc.).

In view of this, the appearance of biological activity might be expected in derivatives of piperidin-4-ol. This idea has served as the basis for investigations concerning the synthesis of a large number of compounds of this series [1-6].

The most widely used method for obtaining piperidinols is the reduction of the carbonyl group of the corresponding piperidinone to a hydroxy group; the spatial orientation of the hydroxy groups so produced may vary according to the nature of the reducing agent used.

Literature information on the spatial structure of some of these compounds, based as a rule on the results of chemical studies [1-6], is only of a provisional nature and requires further confirmation.

This paper gives the results of a study of the stereochemistry of a number of piperidin-4-ol derivatives (I-VI) by means of proton magnetic resonance spectroscopy (PMR).

The spectra of such derivatives are extremely suitable for analysis because of the considerable difference in the chemical shifts (CS) of the protons present in the various positions of the piperidine ring. The signals of the H-4 protons attached to the carbon bearing the hydroxyl group are in the weakest field (δ 3-4 ppm), as a rule. The signals of the H-2 and H-6 protons, occupying the position α with respect to the nitrogen, are in a stronger field (δ 2-3 ppm) and, finally, the signals of the H-3 and H-5 protons are in the strongest field (δ 1-2 ppm).

The spin–spin coupling constants (SSCC) of the protons show that the compounds studied are conformationally similar and undergo no conversions, since the values of the vicinal SSCC range from 10-14 and 2-4 Hz [7]. The values of the CS and SSCC of all the compounds studied are given in Tables 1 and 2.

Results of an analysis of the PMR spectra of the simplest of them, 1-methylpiperidin-4-ol (I), correlate with an equatorial orientation of its hydroxy group.* This is shown by the width of the H-4 signal resulting from a combination of its SSCC with the four neighboring protons. The magnitude of the sum (27 Hz) corresponds to the splitting of the H-4 signal by two large (of the order of 10 Hz) and two small (about 3.5 Hz) constants, which is possible only if this proton has an axial position, i.e., the OH group has the equatorial orientation; this is in agreement with previous results [9]. It was impossible to determine the individual SSCC's of the H-4 proton because of the propinquity of the CS's of the axial and equatorial H-3 and H-5 protons.

Figure 1 shows the spectra of the three geometrical isomers of 2,6-dimethoxycarbonyl-1-methylpiperidin-4-ol (IIα) with mp 92-94°C [10], IIβ with mp 85-88°C, and IIγ with bp 137-138°C (0.4 mm), each

*We assume the orientation of the methyl substituent on the nitrogen atom to be equatorial, according to the results of previous work [7, 8].

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TABLE 1. Chemical Shifts, δ, ppm, of Piperidin-4-ol Derivatives

Substance	H-2		H-6		H-3		H-5		H-4	R-1	R-2	R-3	R-5	R-6
	a	e	a	e	a	e	a	e						
I	2,05	2,71	2,05	2,71	1,36		—	1,94	3,59	2,22	—	—	—	—
II_α	2,93	—	2,93	—	1,75	2,17	1,75	2,17	3,78	2,22	3,78	--	—	3,78
II_β	3,39	—	3,39	—	1,88	1,99	1,88	1,99	4,28	2,26	3,74	—	—	3,74
II_γ	~3,80	—	—	~3,80	—	1,61	—	2,26	3,87	2,39	3,73	—	—	3,70
III_α	2,01	2,86	2,51	3,04	1,66	—	2,03	1,89	3,74	2,26	—	3,70	—	—
III_β	2,36		2,52		2,70	—	1,70	—1,88	4,16	2,30	—	3,70	—	—
IV_β	2,02	3,10	1,71	1,51	—	2,60	—	2,91	2,53	1,99	—	—	—	—
V_α	2,44	—	—	—	2,89	—	2,11	1,77	3,81	2,23	1,20	3,70	—	1,27
V_β	2,82	—	—	—	2,54	—	1,54	1,75	4,11	2,27	1,11	3,71	—	1,11
VI_β	3,31	—	2,90	2,70	2,34	—	—	—	4,00	—	1,18	—	0,95	—

TABLE 2. Spin–Spin Coupling Constants, J (Hz) of Piperidin-4-ol Derivatives

Substance	J_2^{gem}	J_{23}^{aa}	J_{23}^{ae}	J_3^{gem}	J_{34}^{aa}	J_{34}^{ae}	J_{45}^{aa}	J_{45}^{ae}	J_5^{gem}	J_{56}^{aa}	J_{56}^{ae}	J_6^{gem}
I	—	Σ=21		—		Σ=27		—	—	Σ=21		—
II_α	—	11,2	3,0	13,0	11,5	—	11,5	—	13,0	11,2	3,0	—
II_β	—	Σ=16		—		Σ=13		—	—	Σ=16		—
II_γ	—		—	—		Σ=15		—	—	—	—	—
III_α	11,0	11,2	4,1	—	12,7	—	10,8	—	—	10,2	3,9	11,6
III_β	—	—	—	—	—	~4,0	—	~4,0	—	—	—	—
IV_β	12,4	—	3,6	—	—	3,6	11,6	3,4	—	11,2	3,0	11,2
V_α	—	—	3,0	—	—	4,0	~11,0	3,1	~11,0	~11,0	3,1	—
V_β	—	11,1	—	—	—	2,5	—	3,5	13,9	13,5	3,5	—
VI_γ	—	11,0	—	—	—	2,5	—	3,0	—	11,0	—	12,0

of which was obtained by methylating the isomeric nor compounds described previously [11]. On considering the spectra of IIα, β, γ, we see that they have structures similar to the corresponding isomers with no substituent on the nitrogen atom.

An analysis of the experimental results indicates symmetrical structures for the isomers IIα and IIβ with the diequatorial position of the methoxycarbonyl groups and different orientations of the hydroxy group. The symmetry of these molecules is confirmed by comparing the CS's of the signals of the protons of the $COOCH_3$ groups (singlets in the 3.8 ppm region).

The equatorial orientation of these substituents derives from the SSCC's of the H-2 and H-3 (H-5 and H-6) protons. In the spectrum of the isomer IIα, a quartet appears in the 2.93 ppm region (J_{23a} = 11.2, J_{23e} = 3 Hz) which belongs, according to the SC, to the α-protons of the nitrogen atom; the existence of a large constant simultaneously answers the question of the equatorial nature of the substituents at C_2 and C_6 of the piperidine ring.

The equatorial position of the OH group of this compound is shown by the quartet signal of the axial H-3 (H-5) proton, with $J_{3a3e}^{gem} \approx J_{3a2a}^{vic} \approx J_{3a4a}^{vic}$ = 12 Hz. The H-4 signal in IIα coincided in the spectrum with the signal of the protons of the methoxycarbonyl group.

In the spectrum of the isomer IIβ, the CS's of the signals of the axial and equatorial H-3 and H-5 protons are very close. Consequently, first-order analysis of the spectrum of the system of interacting protons of the molecule cannot be carried out. The H-3 and H-2 protons, like the H-5 and H-6 protons, form a system approximating the AA'X type, from the X part of which (multiplet of the α protons) only the sum of the SSCC's $J_{23a} + J_{23e}$ (and, analogously, $J_{65a} + J_{65e}$), equal to 16 Hz, can be calculated. This agrees well with the axial orientation of the H-2 and H-6 protons (J_{2a3a} = 12 and J_{2a3e} = 4 Hz).

The H-4 signal is represented in the spectrum by a comparatively narrow multiplet with a width of 13 Hz; since the width of the signal corresponds to the sum of the SSCC's, the hydroxy group in IIβ is axial.

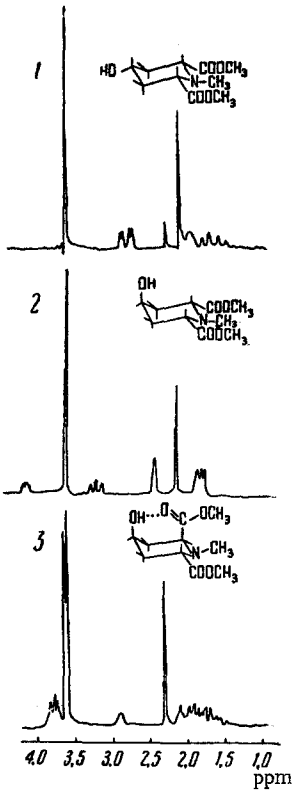


Fig. 1

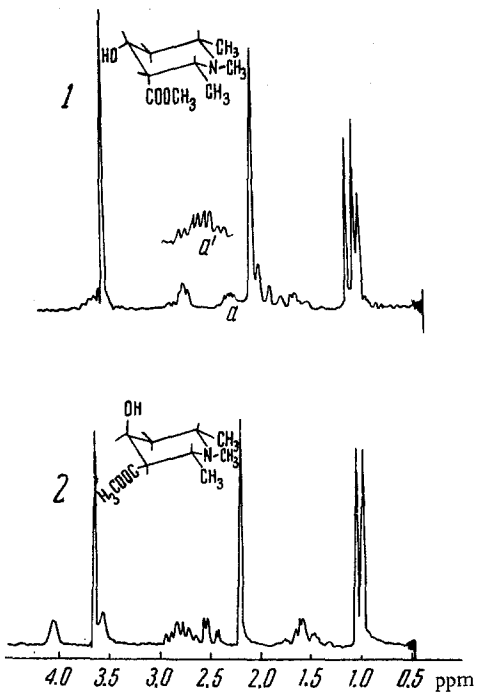


Fig. 2

Fig. 1. PMR spectra of 1) α-isomer of 2,6-dimethoxycarbonyl-1-methylpiperidin-4-ol; 2) the β-isomer; 3) the γ-isomer.

Fig. 2. PMR spectra of 1) α-isomer of 3-methoxycarbonyl-1,2,6-trimethylpiperidin-4-ol; 2) the β-isomer.

In the spectrum of the isomer IIγ, the signals of the methoxycarbonyl groups do not coincide (singlets at 3.73 and 3.70 ppm), which shows that these groups have different spatial orientations. Here the pattern of the spectrum is also complicated by the close CS's of the axial and equatorial H-3 and H-5 protons.

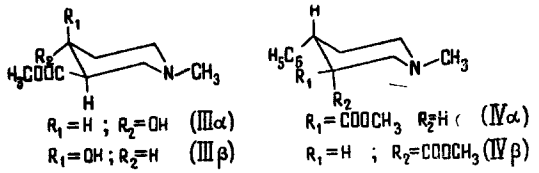
In the spectrum the H-4 signal is overlapped by the signals of the H-2 and H-6 protons. The combined width of the signals does not exceed 15 Hz, which shows the axial position of the hydroxy group in the isomer IIγ. The presence of two axial substituents in the molecule of IIγ (the OH group and one of the $COOCH_3$ groups) may appear unlikely according to the principles of conformational analysis, but on examining a model of this molecule it can be seen that such a structure is capable of being fixed as the result of an intramolecular hydrogen bond between the hydroxyl and the carbonyl of the methoxycarbonyl group. IR spectra of solutions of IIγ in CCl_4 have shown the existence of this bond by the presence of two hydroxy-group absorption bands at 3630 and 3480 cm^{-1} whose intensities do not change on successive dilution (0.1, 0.01, and 0.003%). The second frequency must obviously be due to the vibrations of the bound hydroxyl. The latter band is not observed in the IR spectra of the isomers IIα and IIβ.

The signals of the protons of the OH groups in the three isomers are located, respectively, at 2.33 ppm (α), 2.57 ppm (β), and 2.97 ppm (γ). The position and width of the last signal is in agreement with the existence of an intramolecular hydrogen bond in the γ isomer. Thus, the geometrical isomer IIα consists of a molecule with the equatorial orientation of all the substituents; in the isomer IIβ the hydroxy group is axial and the two methoxycarbonyl groups are both equatorial; while in the isomer IIγ one of the $COOCH_3$ groups is equatorial and the hydroxyl and the second $COOCH_3$ are axial.

The other piperidin-4-ol derivatives studied, like IIγ, do not have a symmetrical structure. One of them, obtained with a view to the synthesis of the alkaloid arecoline, 3-methoxycarbonyl-1-methylpiperidin-4-ol, was represented by two isomers, IIIα with mp 95-96°C and IIIβ with mp 84-85°C [3]. The lower-melting of them, IIIβ, was ascribed the configuration with the cis arrangement for the substituents at C_3 and C_4, and the high-melting one, IIIα, the trans configuration, which is in agreement with the behavior of these isomers on dehydration with thionyl chloride [3].

The PMR spectra of the geometrical isomers IIIα and IIIβ confirm their suggested structures.

The diequatorial orientation of the methoxycarbonyl and hydroxy groups in IIIα derives from the SSCC's of the octet signal ($J_{32a} \approx J_{34a} \approx 12$ Hz, $J_{32e} = 4.1$ Hz) at δ 1.66 ppm due, according to the CS and the results of double resonance, to the H-3 proton. The width of the H-4 signal, approximately 25 Hz, also shows the equatorial orientation of the OH group.



The spectrum of the isomer IIIβ is very complicated because of the propinquity of the CS's of the ring protons (except for H-4).

The width of the H-4 multiplet signal (12 Hz) shows its equatorial orientation. Consequently, the hydroxyl in compound IIIβ is axial. The methoxycarbonyl group in this isomer must be equatorial, since a diaxial arrangement of the substituents at C_3 and C_4 is energetically unfavorable, and in this case the ring would be inverted into the conformation with the diequatorial orientation of these substituents. Since IIIα and IIIβ differ in their properties, the latter must contain the $COOCH_3$ group in the equatorial position; it is the cis isomer.

Similar in structure to these compounds III are the isomers of 3-methoxycarbonyl-1-methyl-4-phenylpiperidine IVα and IVβ, the more stable of which was ascribed the trans configuration and the less stable the cis configuration [4].

An analysis of the PMR spectrum of the isomer IVβ is best begun with a consideration of the signal at δ 3.1 ppm, assigned to the equatorial H-2 proton and consisting of an octet in which $J_{2a2e} = 12.4$, $J_{2e3e} = 3.5$, and $J_{2a6e} = 1.5$ Hz. The latter SSCC is due to long-range coupling of the diequatorial α protons [12]. The signal of the H-2 axial proton, identified by double resonance, has, together with the geminal SSCC, the constant $J_{2a3e} = 3.6$ Hz, which shows the axial orientation of the $COOCH_3$ group in the isomer IVβ. This is confirmed by the nature of the splitting of the H-4 signal, containing one large SSCC, $J_{45a} = 11.6$ Hz, which determines the axial position of the methoxycarbonyl group at C_3, and the equatorial position of the phenyl group in position 4 and, therefore, the cis configuration of this isomer.

The spectrum of the trans isomer of this compound (IVα) could not be analyzed because of the overlapping of the signals for the protons. If we think that the diaxial orientation of the substituents at C_3 and C_4 does not exist because of energetic unsuitability, the diequatorial arrangement of these substituents is perhaps more likely for the isomer IVα.

The spatial structure of the geometrical isomers of 3-methoxycarbonyl-1,2,6-trimethylpiperidin-4-ol (Vα and Vβ), whose benzoates are the "open" analogs of cocaine and possess an anesthetic action, has not hitherto been established. However, it has been suggested that the initial piperidinone most probably has the cis-diequatorial arrangement for the methyl groups at C_2 and C_6 and an equatorial methoxycarbonyl group [5]. Then the reduction products would differ by the orientation of the hydroxy group with an equatorial arrangement for the substituents in positions 2, 3, and 6.

According to the PMR spectrum (Fig. 2), in the isomer Vα, the hydroxy group occupies the equatorial position. This is shown by the width of the H-4 signal, partially overlapping the signal of the protons of the $COOCH_3$ group. This width (not less than 20 Hz) shows that the signal contains at least one large SSCC (of the order of 10-12 Hz) which, in its turn, determines the axial orientation of the H-4 proton.

The equatorial arrangement of the hydroxyl in Vα is also confirmed by the SSCC's of the H-5 axial proton ($J_{5a5e} \approx J_{5a4a} \approx J_{5a6a} \approx 11$ Hz). The existence of a large SSCC J_{5a6a} shows the equatorial orientation of the methyl group at C_6.

The H-3 signal, whose position in the spectrum was shown by simplifying its multiplet by means of double resonance (irradiation with the H-2 signal) is present at 2.89 ppm and contains no large SSCC, which shows the equatorial orientation of the H-3 proton, i.e., the axial orientation of the methoxycarbonyl group.

The nature of the splitting of the signal of the H-2 protons, expressed by a doublet of overlapping quartets (J_{3eCH_3} = 7.0, J_{23e} = 3.0 Hz) agrees with the equatorial position of H-3. It is impossible from the spectrum to determine the orientation of the H-2 proton and, consequently, of the methyl group at C_2. It can only be assumed that the orientation of CH_3-2 is similar to that in the isomer Vβ, i.e., as shown below, it is equatorial.

The spectrum of the isomer Vβ shows the axial position of the OH group, since the signal of the H-4 proton is a multiplet with a width of 12 Hz.

The signal of the H-3 proton, split into a quartet with large (J_{3a2a} = 11.1 Hz) and small (J_{3a4e} = 2.5 Hz) constants shows the axial orientation of H-3, and of the H-2 proton adjacent to it.

The existence of two SSCC's of the order of 13 Hz (one of which is the coupling constant of the geminal protons, J_{5a5e}) and one small SSCC, J_{5a4e} = 3.5 Hz, in the axial H-5 proton shows the axial position of one of the neighboring protons, i.e., H-6. Consequently, both the CH_3-2 and the CH_3-6 methyl groups in the isomer Vβ are equatorial.

The monotypical orientation of these groups in the spectrum of the isomer Vβ is also shown by the agreement of the CS's of the signals of their protons (obviously the influence of an equatorial $COOCH_3$ group at C_3 on the CH_3-2 proton is too small to cause the nonequivalence of the methyl groups at C_2 and C_6).

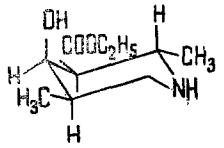
Thus, according to the PMR spectra, Vα and Vβ differ not only in the orientation of the hydroxy group but also in the arrangement of the methoxycarbonyl group at C_3.

The results obtained show a change in the position of the substituents at the C_3 atom occurring during the reduction of the initial ketone which, in its turn, refutes the previous hypotheses on the structure of these compounds [5].

By the catalytic reduction and subsequent deacetylation of 1-acetyl-3-ethoxycarbonyl-2,5-dimethyl-piperidin-4-one, Nazarov et al. obtained a mixture of three isomers of 3-ethoxycarbonyl-2,5-dimethyl-piperidin-4-ol (VIα, VIβ, and VIγ) of undetermined configuration.

An analysis of the spectrum of VIβ (the only one available to us) showed a comparatively narrow signal due to the H-4 proton in the weak field. Its width, not exceeding 6 Hz, shows the axial orientation of the hydroxy group. A quartet of signals at δ 2.34 ppm, ascribed, according to the nature of the splitting, to the H-3 proton with J_{2a3a} = 11.0 and J_{3a4e} = 2.5 Hz, shows the diaxial arrangement of the H-3 and H-2 protons. This is also confirmed by the nature of the multiplicity of the signal of the H-2 axial proton, consisting of a doublet of overlapping quartets (split because of the protons of the methyl group and the H-3 proton).

The triplet signal at δ 2.90 ppm with two large SSCC's, $J_{6a6e} \approx J_{6a5a} \approx 12$ Hz, which we ascribe to the H-6 axial proton, leads to the conclusion that the methyl group at C_5 is equatorial. Consequently, the isomer VIβ contains three equatorial substituents at C_2, C_3, and C_5 and an axial hydroxy group.



Thus, the PMR spectra that we have obtained in our study of the spatial structure of a number of piperidin-4-ol derivatives agree in the main with the structures proposed for them, except for 3-methoxycarbonyl-1,2,6-trimethylpiperidin-4-ol, whose isomers, it has been shown, differ by the orientation of their hydroxy and methoxycarbonyl groups.

EXPERIMENTAL

The PMR spectra of the compounds studied were taken on a JNM-4H-100 instrument with a working frequency of 100 MHz.

Chloroform was used as the solvent for all the piperidin-4-ols except for IVβ, whose spectrum was taken in benzene. The CS values are given in the δ scale in parts per million, with tetramethylsilane as the internal standard.

CONCLUSIONS

The spatial structures of a number of piperidine-4-olderivatives having substituents in the ring such as methyl, methoxy- and ethoxycarbonyl, and phenyl groups, have been determined by means of their PMR spectra.

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