THE ^{13}C NMR SPECTRA, ISOMERISM, AND CONFORMATIONAL ANALYSIS OF SUBSTITUTED PIPERIDIN-4-ONES

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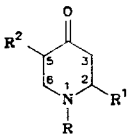
The ^{13}C NMR spectra of 15 stereoisomers of 1-mono-, 1,2-di-, and 1,2,5-trisubstituted piperidin-4-ones were investigated, and the stereochemical orientations of the substituents and the conformation relationships were established. For the series of piperidones a method for determination of the absolute confirmation of the $C_{(2)}$ center of the piperidone ring is proposed on the basis of the chemical shifts of the methyl groups in the 1-s-α-phenylethyl substituent at the nitrogen atom in the preferred rotamers with respect to the $C_{(1)}$—N bond.

The ^{13}C NMR spectra have proved extremely useful in stereochemical investigations [1-3]. Data on the chemical shifts of the ^{13}C carbon atoms make it possible to establish the structure of the stereoisomers and to determine the conformational composition at high temperatures under conditions of rapid conformational transitions [3]. This feature of the ^{13}C chemical shifts is due primarily to their additive characteristics [4, 5].

Earlier [6] we used the ^{13}C NMR spectra to determine the structure of some substituted decahydroquinolones. In the present work we give data from an investigation into the ^{13}C NMR spectra of some substituted piperidin-4-ones. Several dynamic processes can be realized in these compounds: 1) Ring inversion; 2) inversion at the nitrogen atom; 3) rotation about the N—R bond. It can be supposed [7, 8] that the barriers for these processes are small, and this leads to averaged structures at 20°C and to an equilibrium in the conformers and rotamers.

Previous investigations into the ^{13}C NMR spectra of piperidin-4-ones were comparatively limited with respect to the number of subjects [9, 10]. In the present work we studied the ^{13}C NMR spectra with proton decoupling for several series of compounds, i.e., piperidin-4-ones not substituted in the ring [A, compounds (I-V)], 2-methylpiperidin-4-ones [B, compounds (VI-VIII)], trans-2,5-dimethylpiperidin-4-ones [C, compounds (IX-XII)], and cis-2,5-dimethylpiperidin-4-ones [D, compounds (XIII-XV)].



I R=CH_3; II R=$CH_2C_6H_5$; III R=$CH(CH_3)CH_2CH_3$; IV R=$CH(CH_3)CH_2C_6H_5$; V R=$CH(CH_3)C_6H_5$; VI* R=$CH(CH_3)CH_2CH_3$; VII* R=$CH(CH_3)CH_2C_6H_5$; VIII* R=$CH(CH_3)C_6H_5$; IX R=$CH_2C_6H_5$; X R=$CH(CH_3)CH_2CH_3$; XI* R=$CH(CH_3)CH_2C_6H_5$; XII* R=$CH(CH_3)C_6H_5$; XIII R=CH_3; XIV R=$CH_2C_6H_5$; XV* R=$CH(CH_3)C_6H_5$; A R^1=R^2=H; B R^1=CH_3, R^2=H; trans-isomers C R^1=CH_3, R^2=CH_3; cis isomers D R^1=CH_3, R^2=CH_3

We note that certain compounds (containing asymmetric carbon atoms in the ring and in the substituent at the nitrogen atom) were represented by pairs of stereoisomers. (These pairs are marked in the list by an asterisk.) During examination of the possible types of isomers (and absolute configurations) in our case it was necessary to consider that according

*Chiral molecules.

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TABLE 1. The ^{13}C Chemical Shifts of 1-Substituted Piperidin-4-ones

Compound	δ, ppm		
	$C_{(2)}$, $C_{(6)}$	$C_{(3)}$, $C_{(5)}$	R
I[a]	55,40	40,89	45,14 (CH_3)
II[b]	52,56	40,92	61,55 (CH_2)
III[c]	48,22	42,23	60,65 (CH)
			27,07 (CH_2)
			14,01 (CH_3')
			11,60 (CH_3'')
IV	47,84	41,57	60,59 (CH)
			39,45 (CH_2)
			14,22 (CH_3)
V	49,60	41,10	62,91 (CH)
			18,91 (CH_3)

a) From [9]. b) See also [10]. c) In deuterobenzene solution.

to the conditions of synthesis (see the experimental section) the asymmetric carbon atom of the $C_{(1)}'$ substituent always has a fixed S configuration. Thus, compounds (III-V) represented optically active 1'S isomers; for compounds of series B the formation of two diastereomers with absolute configurations (1'S, 2S) and (1'S, 2R) is possible. For the compounds containing asymmetric $C_{(2)}$ and $C_{(5)}$ atoms (of series C and D) the formation of four stereoisomers is possible: (1'S, 2S, 5S); (1'S, 2S, 5R); (1'S, 2R, 5S); and (1'S, 2R, 5R). Two of these (1'S, 2S, 5R) and (1'S, 2R, 5S) are trans isomers, while the other two (1'S, 2S, 5S) and (1'S, 2R, 5R) are cis isomers. Subsequently, to abbreviate the designations for the isomers only the configuration of the $C_{(2)}$ atom will be indicated. For example, the VI-1'S, 2S and VI-1'S, 2R isomers will be described as the VI-S and VI-R isomers, while the XI-1'S, 2S, 5R and XI-1'S, 2R, 5S isomers will be described as the trans-XI-S and trans-XI-R (or simply as the XI-S and XI-R isomers).

The aim of the present investigation was to determine the structure of the stereoisomers by means of the data from ^{13}C NMR spectra and to undertake a conformational analysis of the conformationally mobile systems.

The chemical shifts of the ^{13}C carbon atoms of series A are given in Table 1. 1-Methylpiperidin-4-one (I) has been studied before [9]; in addition, our previously obtained data for 1-benzylpiperidin-4-one (II) were close to the published data [10]. The assignment of the signals for compounds (III-V) was made by the methods described in the experimental section. The ^{13}C chemical shifts for the $C_{(2)}$, $C_{(3)}$, $C_{(5)}$, and $C_{(6)}$ atoms of compounds of series A were then used as the initial data for calculations of the chemical shifts by the additive method for compounds of series B-D.

For all the investigated compounds we assumed that the equilibrium in the inversion at the nitrogen atom is fully shifted toward the equatorial orientation of the alkyl substituent R at the nitrogen atom. On the whole this is confirmed by the data for the alkyl substituents [11].

It is more reasonable to begin the examination of compounds (VI-XV) with the series of trans-2,5-dimethylpiperidin-4-ones (C), where it can be supposed that the equilibrium of the ring inversion is fully shifted toward the diequatorial conformation:

Thus, we will assume that the 2- and 5-methyl groups in compounds of series C have the equatorial orientation.

For further discussions it is necessary to analyze the effect of the methyl groups as substituents on the chemical shifts of the ring carbon atoms. For cyclohexanes these effects (in the form of the increments of the linear additive scheme) have been studied in

TABLE 2. Increments for the Effect of Methyl Groups on the ^{13}C Chemical Shifts in Cyclohexanes and Piperidin-4-ones (ppm)

Compound	Position of CH_3 group	Increments				Reference
		α	β	γ	δ	
Cyclohexane	CH_3 (*e*)	5,90	9,03	0,05	0,22	[12]
	CH_3 (*a*)	1,40	5,41	−6,37	−0,06	[12]
4-Piperidone	2-CH_3 (*e*)	3,58	8,03	0,55	0,20	[9]
	2-CH_3 (*a*)[a]	1,91	6,17	−6,39	−0,53	
	5-[illegible]	2,94	8,00	−0,32	0,80	[9]

a) The present work.

detail in a series of papers (e.g., see [5, 12]) both for the equatorial and for the axial orientation of the methyl groups. In the present work we used the values obtained by factorial analysis of data on the ^{13}C chemical shifts in methylcyclohexanes [12] as increments (Table 2).

In the general case the values of the increments for the methyl groups at positions 2(6) and 3(5) in the equatorial and axial conformations are required to describe the effect of the methyl groups on the ^{13}C chemical shifts in piperidin-4-ones. For the equatorial 2- and 5-CH_3 groups the increments (Table 2) were obtained on the basis of published data [9]. Thus, the value of the increment for the 3(5)-CH_3 group was obtained as the difference between the data for 1,3-dimethylpiperidin-4-one and 1-methylpiperidin-4-one (I). Here it was assumed that the 3-CH_3 group in 1,3-dimethylpiperidin-4-one has the equatorial orientation, which also agrees with numerous values for the conformational energies of the methyl groups [11]. To determine the increments of the methyl group at position 2 it would be possible to use the data for 1,2-dimethylpiperidin-4-one. In this compound, however, on the basis of certain data and also of our values (see the data for series B below) a certain proportion of the axially oriented 2-methyl group could be expected to appear on account of the interaction between the substituent at the nitrogen atom and the 2-CH_3 group. To calculate the increments of the 2-methyl group we therefore used comparison of trans-1,2,5-trimethylpiperidin-4-one and 1,3-dimethylpiperidin-4-one [9]. The corresponding increments for the methyl groups at positions 2 and 5 (in the equatorial orientation) are given in Table 2. We note that the α effect of the methyl groups in piperidones is significantly smaller than the α effect of methyl groups in cyclohexanes.

The ^{13}C chemical shifts of the $C_{(2)}$, $C_{(3)}$, $C_{(5)}$, and $C_{(6)}$ atoms of compounds (VI-VIII) were calculated by means of the initial values for the corresponding N-substituted compounds (Table 1) and the increments of the methyl groups (Table 2). The calculated data are given in Table 3 in comparison with the experimental values. It was found that the additive scheme describes the chemical shifts for the $C_{(3)}$ and $C_{(5)}$ atoms remote from the nitrogen quite satisfactorily; here the deviations as a whole do not exceed 1 ppm, which can be considered normal for the use of additive schemes [5].* Larger deviations Δδ were found for the chemishifts of the $C_{(2)}$ and $C_{(6)}$ atoms; as a rule the $C_{(2)}$ atom was additionally descreened (up to 2.0 ppm), while the $C_{(6)}$ atom was screened (−4.5 to −6.0 ppm) compared with the additive values (Table 3).

It can be supposed that the deviations from the additive scheme, observed for the $C_{(2)}$ and $C_{(6)}$ atoms, are due to changes in the populations of the rotational rotamers for the N–R fragment, since interactions between the 2-CH_3 group and the substituent at the nitrogen can arise in the transition from the compound unsubstituted in the ring to the 2-methyl-substituted compound. These deviations must, evidently, show up particularly clearly for bulky substituents.

Generally speaking, analysis of the populations of the rotamers requires detailed analysis of the potential surface of the molecule, e.g., in terms of a mechanical model [13]. For a qualitative assessment not pretending to accuracy, however, it is possible to use analysis of the nonbonding interactions by counting the number of gauche repulsions or

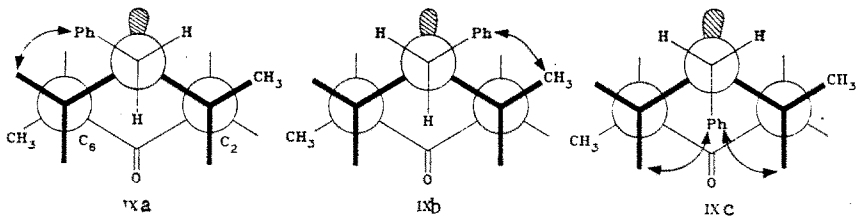
*The deviations Δδ are given in Tables 3-6 as the differences between the corresponding experimental and calculated chemical shifts.

TABLE 3. Experimental ^{13}C NMR Chemical Shifts of trans-2,5-Dimethylpiperidin-4-ones and the Values Calculated by the Additive Method (in parentheses)

Compound	δ, ppm						
	$C_{(2)}$	$C_{(3)}$	$C_{(5)}$	$C_{(6)}$	2-CH_3	5-CH_3	R
IX	57,99 (56,94) 1,05	48,88 (48,63) 0,25	43,93 (44,06) −0,13	56,02 (61,11) −5,09	19,48	11,23	58,88 (CH_2)
X-S	53,34 (52,60) 0,74	50,48 (49,94) 0,54	45,36 (45,37) −0,01	51,56 (56,77) −5,21	20,58	11,30	55,14 (CH) 28,38 (CH_2) 11,67[a] (CH_3') 11,55[a] (CH_3'')
XI-R	54,29 (52,22) 2,07	50,05 (49,28) 0,77	45,24 (44,71) 0,53	51,83 (56,39) −4,56	20,30	11,31	55,10 (CH) 34,58 (CH_2) 18,47 (CH_3)
XI-S	53,83 (52,22) 1,61	50,14 (49,28) 0,86	45,08 (44,71) 0,37	51,81 (56,39) −4,58	20,24	11,29	55,12 (CH) 42,33 (CH_2) 10,56 (CH_3)
XII-R	54,46 (53,98) 0,48	49,09 (48,81) 0,28	45,10 (44,24) 0,86	52,32 (58,15) −5,83	19,25	12,28	56,17 (CH) 19,60 (CH_3)
XII-S	54,02 (53,98) 0,04	49,23 (48,81) 0,42	44,66 (44,24) 0,42	51,57 (58,15) −6,58	19,12	11,50	54,67 (CH) 9,96 (CH_3)

a) The opposite assignment of the signals is possible.

syn-diaxial repulsions [14]. Thus, on the basis of molecular models for trans-2,5-dimethyl-1-benzylpiperidin-4-one (IX) it can be supposed that of the three possible rotamers (IXa, IXb, IXc) the rotamer (IXa), in which there is only one syn-repulsion between the phenyl group and a hydrogen atom (5e-H), is preferred. In the rotamer (IXc) there are two such interactions, i.e., with the 5a-H and 2a-H atoms, while in the rotamer (IXb) the most unfavorable syn-diaxial repulsion of the phenyl and methyl groups appears.



If it is assumed that the populations of the rotamers a and b in the unperturbed system, i.e., for the piperidin-4-ones not substituted in the ring, are equal it follows from this that the contribution from the γ-gauche interactions increases for the $C_{(6)}$ atom and decreases for the $C_{(2)}$ atom. This must lead to additional screening of the $C_{(6)}$ and descreening of the $C_{(2)}$ atom, which explains the above-mentioned nonadditivity for the chemical shifts of the $C_{(2)}$ and $C_{(6)}$ atoms.

Let us now dwell on the ^{13}C chemical shifts of the methyl groups at positions 2 and 5. The chemical shifts of the 2-CH_3 group (with the equatorial orientation in compounds of series C) lie in the range of 19-21 ppm, while those of the 5-CH_3 group (also with the equatorial orientation in compounds of series C) lie in the range of 11-12.5 ppm. The two regions do not overlap and can be used for the assignment of the signals for the methyl groups in compounds of series B and D. The above-mentioned difference in the chemical shifts of the methyl groups is due to the effect of the carbonyl group; it was found earlier in 2-methylcyclohexanones [15], in methyldecalones [16], and also in decahydroquinolones [6] (see also [17]).

For compounds (XI) and (XII) we observed the spectra of the pairs of stereoisomers experimentally (S and R with respect to the $C_{(2)}$ atom). However, we note that at the beginning of the investigation the assignment of the experimental data to any specific isomer was not known to us, i.e., the absolute configuration of each of the isomers was not known. Therefore, the chemical shifts of the ring atoms $C_{(2)}$, $C_{(3)}$, $C_{(5)}$, and $C_{(6)}$ were

TABLE 4. Experimental ^{13}C NMR Chemical Shifts of 2-Methylpiperidin-4-ones and the Values Calculated by the Additive Method (in Parentheses)

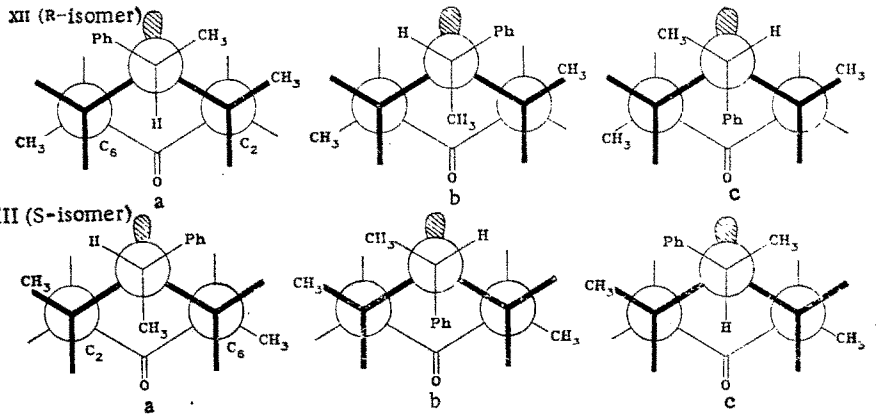
Compound	δ, ppm					R
	$C_{(2)}$	$C_{(3)}$	$C_{(5)}$	$C_{(6)}$	2-CH_3	
VI-S	53,58	50,01	41,92	42,86	19,85	53,64 (CH)
	(51,80)	(50,26)	(42,43)	(48,77)		28,03 (CH_2)
	1,78	−0,25	−0,51	−5,91		11,46[a] (CH_3')
						11,27[a] (CH_3'')
VI-R	54,27	50,12	42,19	42,68	18,63[a]	55,37 (CH)
	(51,80)	(50,26)	(42,43)	(48,77)		23,51 (CH_2)
	2,47	−0,14	−0,24	−6,09		11,43 (CH_3'')
						18,26[a] (CH_3')
VII-S	53,82	50,00	41,89	43,49	19,82	54,53 (CH)
	(51,42)	(49,60)	(41,77)	(48,39)		42,21 (CH_2)
	2,40	0,40	0,12	−4,90		11,56 (CH_3)
VII-R	54,14	50,00	42,01	43,00	19,37	55,49 (CH)
	(51,42)	(49,60)	(41,77)	(48,39)		36,45 (CH_2)
	2,72	0,40	0,24	−5,39		18,40 (CH_3)

a) The opposite assignment is possible.

calculated without allowance for this isomerism (Table 3). Analysis shows that the pairs of isomers are characterized by similar values of the chemical shifts for all the ring carbon atoms and also for the carbon atoms of the 2- and 5-methyl groups. Substantial differences between the isomers are only observed for the carbon atoms of the substituent at the nitrogen atom. Thus, the chemical shifts of the methyl groups in the phenylethyl radical of (XII) amount to 19.5 and 9.96 ppm. In addition, there is a difference between the shifts of the methine carbon atom of the substituent (56.17 and 54.67 ppm) and also the $C_{(1)}$ atoms of the phenyl radical (141.07 and 143.03 ppm).

We assumed that the discovered difference between the chemical shifts of the methyl groups is due to the fact that the **S** and **R** isomers differ in the type of preferred rotational isomer with respect to the N–R bond. It is then possible that the orientation of the methyl group in the substituent in one of the isomers is such that this group experiences an additional upfield shift according to the mechanism of the γ effect. Such additional shifts have been detected for an axially oriented methyl group in cyclohexanes [18].

For a more detailed examination of this difference we turn to analysis of the populations of the rotamers with respect to the N–R bond in the **S** and **R** isomers of compound (XII).



On the basis of analysis of the syn-diaxial interactions it can be supposed that the rotamer c is the most favorable for the R isomer and the rotamer *a* for the S isomer. Thus, the preferred orientations of the methyl groups of the substituent in the R and S stereoisomers differ. In the S stereoisomer the methyl group has the axial orientation (or is in the trans position) in relation to the unshared pair of the nitrogen atom. Groups oriented in such a way should undergo an upfield shift by the mechanism of the γ effect, involving interaction between the protons of the methyl group and the axially oriented C–H bonds.

TABLE 5. Experimental and Calculated (in Parentheses) ^{13}C NMR Chemical Shifts of 1-α-Phenylethyl-2-methylpiperidin-4-ones

Compound	δ, ppm					
	$C_{(2)}$	$C_{(3)}$	$C_{(5)}$	$C_{(6)}$	2-CH_3	R
VIII-R	52,08	47,98	40,82	42,83	14,45	58,51 (CH)
	(53,66)[a]	(49,13)[a]	(41,30)[a]	(44,32)[a]		21,54 (CH_3)
	(51,51)[b]	(47,27)[b]	(40,57)[b]	(43,21)[b]		
	(51,90)[c]	(47,60)[c]	(40,70)[c]	(43,41)[c]		
	0,18	0,38	0,12	−0,58		
VIII-S[d]	52,22	48,32	40,89	43,73	16,34	57,80 (CH)
	(53,22)[e]	(49,13)[e]	(41,30)[e]	(43,57)[e]		16,10 (CH_3)
	(51,51)[b]	(47,27)[b]	(40,57)[b]	(43,21)[b]		
	52,36 [f]	48,20 [f]	40,93[f]	43,39[f]		
	0,14	0,12	−0,04	0,34		

a) The chemical shifts were calculated for the R-2e-CH_3 conformer. The increments of 2e-CH_3 are given in Table 2. The corrections for the chemical shifts of the $C_{(2)}$ and $C_{(6)}$ atoms were taken from the spectrum of (XII-R) (Table 3).
b) The chemical shifts were calculated for the conformer with the axial orientation of the 2-CH_3 group. The increments of 2α-CH_3 are given in Table 2.
c) For the equilibrium mixture of the conformers (82% of the R-2α-CH_3 conformer).
d) In carbon tetrachloride solution.
e) The chemical shifts were calculated for the S-2e-CH_3 conformer. The corrections for the chemical shifts of the $C_{(2)}$ and $C_{(6)}$ atoms were taken from the spectrum of compound (XII-S) (Table 3).
f) For the equilibrium mixture of conformers (50% of the S-2α-CH_3 conformer).

Thus, the isomer of (XII) which exhibits an upfield shift of the methyl group is characterized by the preferred rotational isomer with the axially oriented methyl group of the substituent (or trans-oriented in relation to the unshared pair of the nitrogen). In view of the analysis of the populations of the rotamers given above it can be considered that the isomer of (XII) with the chemical shift of 9.96 ppm for the methyl group will be the **S** isomer. Accordingly, the isomer characterized by a chemical shift of 19.6 ppm for the methyl group is the R isomer.

An x-ray crystallographic investigation was undertaken for the isomer (XII-R) [19], and its configuration was rigorously established. In addition, it was found that in the crystal the N–C'$_{(1)}$ bond has the equatorial orientation and the phenyl group is oriented in the same way as we suggested for the solution. The agreement between the conclusions from the two methods with respect to the configuration of the isomer (XII-R) can be considered a serious argument in support of the stereochemical determinations by the NMR method (see below). At the same time the conformation of the preferred orientation of the phenyl group can be considered a happy coincidence.

Analogous spectral relationships are found in the other stereoisomeric pair (XI). Here a significant difference is also observed in the chemical shifts of the methyl groups in the substituent at the nitrogen atom (18.47 and 10.56 ppm, respectively). This makes it possible to assign them to the **R** and **S** isomers by analogy with the data for (XII). Thus, the isomer with a shift of 10.56 ppm for the methyl group must be assigned to the **S** isomer (Table 3). We note that in this case the chemical shifts of the signals for the CH_2 groups amount to 34.58 and 42.33 ppm for (XI-R) and (IX-S), respectively. This indicates the axial orientation of the benzyl group in the substituent for the isomer (XI-R).

Only one isomer was observed for compound (X), and its structure was not known at the initial stage. Using the above-mentioned relationships for the pairs of stereoisomers of (XI) and (XII), we can assume that the axial orientation of the methyl group in the preferred

TABLE 6. Experimental and Calculated (in Parentheses) ^{13}C NMR Chemical Shifts of cis-2,5-Dimethylpiperidin-4-ones[a]

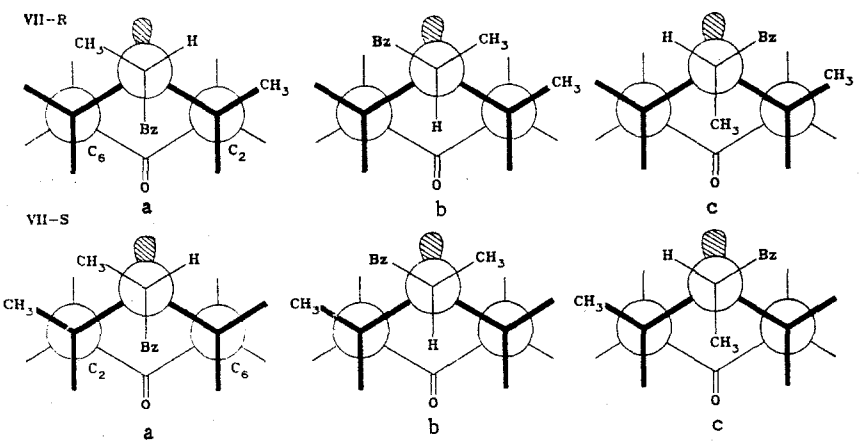
Compound	δ, ppm						
	$C_{(2)}$	$C_{(3)}$	$C_{(5)}$	$C_{(6)}$	2-CH_3	5-CH_3	R
XIII	57,97	46,57	43,68	57,97	14,49	13,21	42,19 (CH_3)
	(58,11)[b]	(46,74)[b]	(43,30)[b]	(57,01)[b]			
	−0,14	−0,17	0,38	0,96			
	(58,92)[c]	(42,55)[c]	(42,49)[c]	(61,36)[c]			
	−0,95	4,02	1,19	−3,39			
	(58,23)[d]	(46,11)[d]	(43,18)[d]	(57,66)[d]			
	−0,26	0,46	0,50	0,31			
XIV	55,27	46,77	43,33	54,17	13,41	11,67	57,90 (CH_2)
	(54,76)[e]	(46,01)[e]	(43,80)[e]	(54,19)[e]			
	−0,51	0,76	−0,47	−0,02			
	(56,08)	(42,58)	(42,52)	(58,52)			
	−0,81	4,19	0,81	−4,35			
XV	51,96	46,39	42,97	51,07	13,39	11,34	59,38 (CH)
	(52,31)[b]	(46,95)[b]	(43,51)[b]	(51,21)[b]			20,32 (CH_3)
	−0,35	−0,56	−0,54	−0,14			

a) All the investigated compounds were observed in a mixture with the corresponding trans isomers: Compound (XIII) at the rate of ~15% and compounds (XIV) and (XV) at the rate of ~50% in the mixture.
b) The calculation was made for form A with the increments for 2α-CH_3 obtained in the present work.
c) The calculation was made for form B.
d) For the equilibrium mixture of conformers (85% A, 15% B).
e) The calculation was made for form A with the increments for 2α-CH_3 in cyclohexane (Table 2).

rotamer is characteristic of (X) [as also in compound (XI-S)]. Thus, it can be concluded that compound (X) is the S isomer.

The results from analysis of the chemical shifts of the trans-2,5-dimethyl derivatives were used to analyze the ^{13}C NMR spectra of the two 2-methylpiperidin-4-ones [series B, compounds (VI) and (VII)] (Table 4). From the existing data for (VI) and (VII) it becomes clear that the 2-CH_3 group occupies the equatorial position (18-19 ppm). For the pairs of stereoisomers of (VI) and (VII) the chemical shifts of the ring carbon atoms are similar to each other, and the shifts of the $C_{(3)}$ and $C_{(5)}$ atoms as a whole are described well by the additive scheme. For the $C_{(2)}$ and $C_{(6)}$ there are deviations similar to those which were observed in the case of the trans-2,5-derivatives (i.e., positive shifts for $C_{(2)}$ and negative shifts for $C_{(6)}$).

Let us now turn to an analysis of the populations of the rotamers of the S and R isomers. In particular, for compound (VII) we have the following set of rotamers:



It can then be supposed that the rotamer *a* predominates for the R isomer and the rotamer c for the S isomer (on the basis of the minimum gauche repulsions). Since the above-mentioned isomers are characterized by significantly differing values for the chemical shifts of the methyl groups, using the approach proposed above we can assume that the isomer with a chemical shift of 18.4 ppm is the R isomer and that with the chemical shift of 11.56 ppm is the S isomer. As in the previously mentioned cases, the opposite arrangement of the chemical shifts for the methylene groups is observed [42.21 ppm for (VII-S) and 36.45 ppm for (VIII-R)]. For compound (VI) we also observed two isomers. Using the criteria set out above, we assigned the stereoisomer with the chemical shift of 11.46 ppm for the methyl group and 28.03 ppm for the CH_2 group to the stereosiomer S.

We note that the two pairs of isomers of 2-methylpiperidin-4-ones given in Table 2 are represented predominantly by one conformer; the third compound in this series, 2-methyl-1-α-phenylethylpiperidin-4-one (VIII), proved conformationally mobile (Table 5). However, before passing on to analysis of the data for this compound we will discuss the results from investigation of the cis-2,5-dimethyl derivatives [series D, compounds (XIII-XV)].

In the case of the cis isomers it is reasonable to suppose that two conformers due to ring inversion exist:

The value of the constant for the conformational equilibrium K = [A]/[B] could be obtained under the conditions of frozen equilibrium, but this requires experiments at low temperatures (probably below 120°K). For qualitative assessments it is also possible to use the method of averaged parameters [3]. Such a calculation requires the values of the increments for the axially oriented methyl group. Since the increments of the axial methyl group for substituted piperidones were not available in the literature, we used data for cyclohexane (Table 2) on the assumption that they were suitable for qualitative assessments.

We will begin the examination of the data for the cis-2,5-dimethyl derivatives with compound (XIV), where the chemical shift of the 5-CH_3 group (11.67 ppm) lies in the range characteristic of the equatorial orientation of this group (11-12 ppm). On this basis it can be concluded that compound (XIV) exists in conformation A. This conclusion is confirmed by the data from calculation by the additive method (Table 6), where the values for (II) and also the increments of the axial methyl group in cyclohexane were used as the initial values (Table 2). In form A the methyl group at position 2 is in the axial orientation; consequently, the chemical shift of the axially oriented 2-CH_3 group amounts to 13.4 ppm. Then, on the assumption that compound (XIV) exists in form A we can refine the increments for the axial 2-methyl group (Table 2). Subsequently, we used these values of the increments in the calculations.

In compound (XIII) the chemical shift of the 2-CH_3 group (14.49 ppm) occupies an intermediate position between the values characteristic of the axial and equatorial orientation of the methyl group [for 2*a*-CH_3 13.4 ppm according to data for (XIV) and for 2e-CH_3 20.84 ppm according to data for trans-2,5-trimethylpiperidin-4-one [9]]. The fraction of the conformer A can be determined by means of the equation:

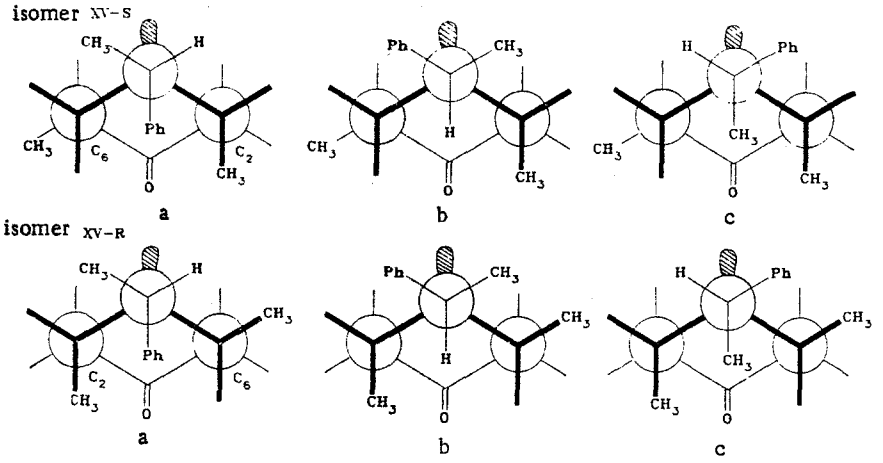
$$P_A = (\bar{\delta} - \delta_B)/(\delta_A - \delta_B)$$

Using the values given above for δ_A and δ_B (in the case of the 2-CH_3 group) and the experimental value of $\bar{\delta}$ (Table 6), we find that the content of form A with the axially directed 2-methyl group amounts to 0.85.

Unfortunately it is not possible to use the data for the chemical shift of the 5-CH_3 group to confirm this value, since the value of the shift for the 5-CH_3 group in the axial orientation is not known experimentally for piperidin-4-ones. However, it is possible to estimate the chemical shift of 5*a*-CH_3 qualitatively as 23.0 ppm by means of the value for the fraction of form A (0.85) in compound (XIII).

We note also that the calculation of the chemical shifts for the carbon atoms of the piperidone ring with allowance for the fraction of the conformers [for compound (XIII)] reveals somewhat better agreement with experiment than calculation for only conformer A or only conformer B (Table 6).

In the case of (XV) two stereoisomers are in principle possible. However, we only obtained one of these isomers, which was characterized by chemical shifts of 13.39 (2-CH_3) and 11.34 ppm (5-CH_3) for the methyl groups. This indicates that conformer A predominates. The two possible stereoisomers of (XV) can be represented by sets of three rotational isomers:



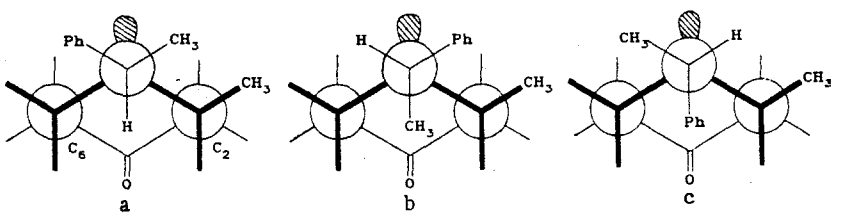
The conformation b with the minimum gauche repulsion is probably most favorable in both isomers. Thus, the axial orientation of the methyl group does not appear in both stereoisomers (trans in relation to the unshared pair of the nitrogen atom). This does not make it possible to use the test given above for the identification of the type of isomer. Thus, at this stage of the investigation it is impossible to make a choice between one or the other structure.

We will also consider the fact that for compounds (XIV) and (XV), which are characterized by the axial orientation of the methyl group at position 2, there are no significant deviations from the experimental values of the chemical shifts for the $C_{(2)}$, $C_{(3)}$, $C_{(5)}$, and $C_{(6)}$ atoms from the values calculated by the additive method (Table 6). This shows that with the axial orientation of the 2-CH_3 group there are evidently no changes in the populations of the rotamers (with respect to the N–R bond) compared with the unsubstituted compounds. Thus, it is possible (although unlikely) that both stereomers of (XV) are characterized by coinciding ^{13}C chemical shifts.

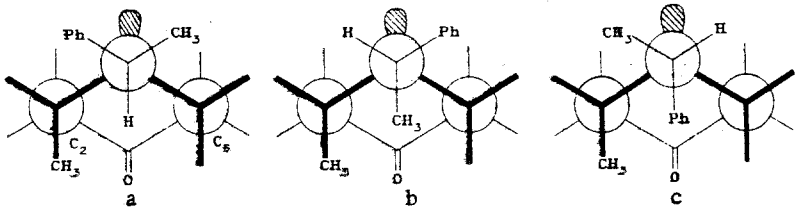
2-Methyl-1-α-phenylmethylpiperidin-4-one (VIII) is represented by two diastereomers (VIII-R) and (VIII-S) (in both cases with the phenylethyl group in the **S** configuration) (Table 6). The **R** and S stereoisomers can formally be represented as a set of ring conformers, nitrogen invertomers with the axial and equatorial orientation of the phenylethyl group, and rotamers with respect to the N–CH(CH_3)Ph bond. On the assumption that the configuration with the equatorial orientation of the phenylethyl group predominates in all cases each of the isomers can be represented in the form of two conformers with respect to the ring, and each of them will be realized in the form of three rotamers.

R stereoisomer

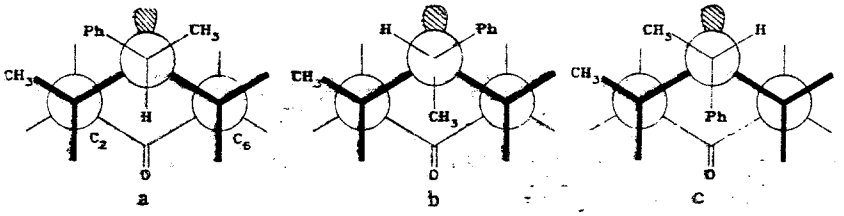
2e-CH_3 conformer



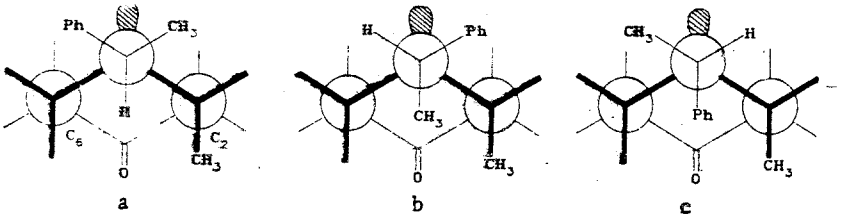
2α-CH_3 conformer



S stereoisomer
2e-CH_3 conformer

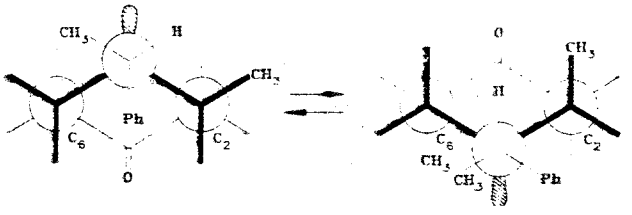


2α-CH_3 conformer

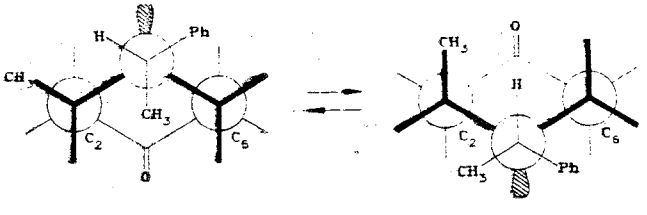


Analysis of molecular models shows that one rotamer is most favorable for the conformers with the equatorial orientation of the 2-CH_3 group; this is rotamer c for R-2e-CH_3 and rotamer b for S-2e-CH_3. Thus, a simplified scheme of the conformational equilibria can be presented in the following form:

R stereoisomer



S stereoisomer



First of all we will pay attention to the fact that the stereoisomers differ in the ^{13}C chemical shifts of the 2-CH_3 groups (14.5 and 16.3 ppm, respectively). Earlier it was indicated that the shifts of the model groups 2e-CH_3 and 2α-CH_3 amount to approximately 19.2 and 13.4 ppm, respectively). Thus, it can be concluded that both conformers with respect to the ring are present in both stereoisomers in appreciable quantities, while in the compound with a chemical shift of 14.5 ppm for the CH_3 group the equilibrium must be shifted toward the

axial conformation. Quantitative estimates by means of the formula for the averaged shifts give the following values for the fractions of the conformations: For (VIII') ($2a$-CH_3): ($2e$-CH_3) ≈ 80:20 (%); for (VIII") ($2a$-CH_3):($2e$-CH_3) ≈ 50:50 (%). We will now pay attention to the difference in the chemical shifts of the methyl group in the phenylethyl radical (21.54 and 16.1 ppm, respectively). The upfield shift of this group in one of the isomers must be attributed, according to our discussions, to the presence of rotamers with the trans orientation of the methyl group (in relation to the unshared pair of the nitrogen).

The analysis made of the rotamers above shows that such an axial orientation is only possible in the S isomer (for the $2e$-CH_3 orientation). Thus, this isomer with a signal for the CH_3 group at 16.1 ppm must be attributed to the S isomer (and, accordingly, the second isomer to the R isomer).

In order to confirm the assignment of the isomers and the conformational composition we calculated the ^{13}C chemical shifts of the $C_{(2)}$, $C_{(3)}$, $C_{(5)}$, and $C_{(6)}$ ring atoms (Table 5) by the additive method using the values given above for the contents of the conformers and the increments of the methyl group (Table 2). In the calculations we also took account of the additional effects due to the preference for one of the rotamers in the case of the equatorial orientation of the 2-methyl group, i.e., the additional screening of the $C_{(6)}$ and descreening of the $C_{(2)}$ atom. The values of these corrections $\Delta\delta$ were taken from the data for trans-2,5-dimethylpiperidin-4-ones [compounds (XII-R) and (XII-S)], given in Table 3.

Thus, the employed method, which involves determination of the preferred rotamer and allowance for the γ-gauche interaction for the ^{13}C chemical shifts, made it possible not only to determine the structure and the absolute configuration of the $C_{(2)}$ center in the stereoisomer but also in some cases to determine the constants of the conformational equilibrium. It can be supposed that this approach will prove useful in the treatment of other systems containing strong intramolecular steric repulsions.

EXPERIMENTAL

The cis-2,5-dimethylpiperidin-4-ones were studied in mixtures with the corresponding trans isomers. As a rule the NMR spectra were measured for solutions in chloroform. Cases where other solvents were used are mentioned in the notes to the respective tables. The ^{13}C NMR spectra were measured on Varian FT-80A and CFT-20 and JEOL FX-100 instruments with full proton decoupling.

The following methods were used for the assignment of the signals: a) Spectra with off-resonance proton decoupling; b) the use of selectively deuterated compounds [for (VII', VII", XIII)]; c) variation of the ratio of the isomers in the mixtures [for (XII-XV, IX'-XIV)]; d) selective proton decoupling [for compounds (XIII', IX, XII')]; e) APT pulse sequencing [20], which makes it possible to edit the spectra [for compounds (VII', VII", VI', VI", XI', XI")]; f) calculations with the use of various additive schemes. We also used published data [9, 10] for the analogous compounds. The use of the above-mentioned methods made it possible to obtain an unambiguous assignment of the signals in the spectra in nearly all cases. The chemical shifts of the carbonyl carbon atom ($C_{(4)}$) are not given in the tables. For the investigated compounds they lie in the region of 206-210 ppm.

1-sec-Butyl- and 1-α-Benzylethypiperidin-4-ones (III, IV). These compounds were obtained by the method described in [22].

1-α-Phenylethylpiperidin-4-one (V) [21]. A mixture of 5.1 g (0.02 mmole) of 1-methylpiperidin-4-one methiodide, 3.6 g (0.03 mmole) of α-phenylethylamine, and 2.3 ml (130 mmole) of water was stirred at 20°C until homogeneous. After 2 h the reaction mixture was saturated with potassium carbonate and extracted with ether (10•15). The extract was dried with magnesium sulfate. After removal of the ether the oily residue was deposited on a column of silica gel and eluted with ether, and chromatographically uniform fractions were combined. The yield was 1.48 g (35%). Mass spectrum, m/z: 203 (M^+), 188 ($M^+ - CH_3$), 105 (C_6H_5—CH—CH_3^+). IR spectrum (in film): 1730 cm^{-1} (C=O). Picrate, mp 157-158°C (from a mixture of benzene and ether). Found, %: C 52.8, H 4.7, N 12.9. $C_{13}H_{17}NO \cdot C_6H_3N_3O_7$. Calculated, %: C 52.8, H 4.7, N 13.0.

The diastereomers of 1-sec-butyl-2-methyl- and 1-α-benzylethyl-2-methylpiperidin-4-ones (VI, VII) were obtained by the method in [22], and those of 1-α-phenylethyl-2-methylpiperidin-4-one (VIII) were obtained by the method in [23].

Mixture of cis and trans Isomers of 1-Benzyl-2,5-dimethylpiperidin-4-one (IX) [24]. Similarly, from 7.1 g (25 mmole) of 1,2,5-trimethylpiperidin-4-one methiodide, 2.8 g (25 mmole) of benzylamine, and 1.1 ml (60 mmole) of water after chromatography on a column of silica gel we obtained 4.2 g (76%) of a mixture of the cis and trans isomers with R_f 0.7 and 0.9 (silufol, 4:1 benzene—acetone) in a ratio of 3:5 (according to ^{13}C NMR). Picrate of mixture of isomers, mp 154-155°C (from alcohol). Found, %: C 54.0, H 5.2. $C_{14}H_{19}NO \cdot C_6H_3N_3O_7$. Calculated, %: C 53.8, H 5.0.

Diastereomers of 1-sec-Butyl-2,5-dimethylpiperidin-4-one (X). From 5 g (18 mmole) of 1,2,5-trimethylpiperidin-4-one methiodide, 1.3 g (18 mmole) of sec-butylamine, and 1.1 g (60 mmole) of water after the usual treatment we obtained 1 g (39%) of a mixture of the cis and trans isomers with R_f 0.7 and 0.6 (Silufol, 3:2 benzene—acetone) with a preponderance of the trans isomer. Picrate of mixture of isomers, mp 163-164°C (from alcohol). Found, %: C 49.8, H 5.9. $C_{11}H_{21}NO \cdot C_6H_3N_3O_7$. Calculated, %: C 49.5, H 5.9.

Diastereomers of 1-α-Benzylethyl-2,5-dimethylpiperidin-4-one (XI). From 2.8 g (10 mmole) of 1,2,5-trimethylpiperidin-4-one methiodide, 1.35 g (10 mmole) of α-benzylethylamine with $[\alpha]_D^{20}$ (+) −36.6° (without a solvent) and 1.1 ml (60 mmole) of water we obtained 2.2 g of a reaction mixture, which we deposited on nine plates (18 × 24 cm) with a layer of thickness of 0.2 cm. After twofold elution in the 1:1 pentane—ether system we isolated three chromatographic bands, from which after elution we obtained 0.3 g of the trans isomer of (XI), 0.1 g of the cis isomer, and 0.1 g of a mixture of the isomers with an overall yield of 35%. The trans isomer of (XI): Mass spectrum m/z: 154 ($M^+ - C_3H_7$), 91 ($CH_2C_6H_6^+$). Picrate of mixture of isomers mp 152-153°C (from ethanol). Found, %: C 55.8, H 5.5, N 11.5. $C_{12}H_{23}NO \cdot C_6H_3N_3O_7$. Calculated, %: C 55.69, H 5.52, N 11.8. The diastereomers of 1-α-phenylethyl-2,5-dimethylpiperidin-4-one (XII, XV) were obtained by the method in [19].

LITERATURE CITED

1. E. L. Eliel and K. M. Pietrusiewicz, Top. ^{13}C NMR Spectrosc., 3, 172 (1979).
2. F. W. Wehrli and T. Wirthlin, Interpretation of Carbon-13 NMR Spectra, Heyden, London—New York (1976).
3. N. M. Sergeev and O. A. Subbotin, Usp. Khim., 47, 477 (1978).
4. H.-J. Schneider and V. Hoppen, J. Org. Chem., 43, 3866 (1978).
5. O. A. Subbotin, N. M. Sergeev, and N. G. Nikishova, Zh. Org. Khim., 20, 1024 (1984).
6. I. F. Leshcheva, N. M. Sergeev, G. V. Grishina, and V. M. Potapov, Khim. Geterotsikl. Soedin., No. 2, 230 (1983).
7. F. A. L. Anet and R. Anet, in: Dynamic NMR Spectroscopy (F. A. Cotton and L. M. Jackman, eds.), Academic Press, New York (1975).
8. P. J. Crowly, M. J. T. Robinson, and M. G. Ward, Tetrahedron, 33, 915 (1977).
9. A. J. Jones and M. M. A. Hassan, J. Org. Chem., 57, 2332 (1972).
10. J. A. Hirsh and E. Havinga, J. Org. Chem., 41, 455 (1976).
11. E. L. Eliel, D. Kandasamy, Ch.-Yu. Yen, and K. D. Hargrave, J. Am. Chem. Soc., 102, 3698 (1980).
12. D. Dalling and D. M. Grant, J. Am. Chem. Soc., 94, 5318 (1972).
13. M. Nogradi, Stereochemistry, Pergamon Press (1980).
14. H. Booth and J. R. Everett, J. Chem. Soc., Perkin Trans. 2, No. 2, 255 (1980).
15. S. H. Grover and J. B. Stothers, Can. J. Chem., 52, 870 (1974).
16. J. W. Blunt, J. M. Coxon, N. B. Lindley, and G. A. Lane, Aust. J. Chem., 29, 967 (1976).
17. N. M. Sergeev, NMR Spectroscopy [in Russian], Izd. MGU, Moscow (1981).
18. D. M. Grant and B. V. Cheney, J. Am. Chem. Soc., 89, 5315 (1967).
19. G. V. Grishina, V. M. Potapov, S. A. Abdulganeeva, T. A. Gudasheva, A. A. Karapetyan, A. A. Espenbetov, and Yu. T. Struchkov, Khim. Geterotsikl. Soedin., No. 12, 1656 (1985).
20. S. L. Patt and J. N. Schoolery, J. Magn. Reson., 46, 535 (1982).
21. Y. Kashman and S. Cherkez, Tetrahedron, 28, 1211 (1972).
22. G. V. Grishina, V. M. Potapov, S. A. Abdulganeeva, and E. Yu. Korchagina, Khim. Geterotsikl. Soedin., No. 12, 1648 (1985).
23. G. V. Grishina, V. M. Potapov, T. A. Gudasheva, and S. A. Abdulganeeva, Khim. Geterotsikl. Soedin., No. 10, 1378 (1985).
24. M. M. A. Hassan and A. F. Casy, Org. Magn. Reson., 2, 197 (1970).