STUDY OF THE STEREOCHEMISTRY OF N–H AND N-VINYL-4,5,7-TRIMETHYL-4,5,6,7-TETRAHYDROPYRROLO[3,2-c]PYRIDINES AND THEIR NITRO DERIVATIVES BY THE METHOD OF ^1H AND ^{13}C NMR

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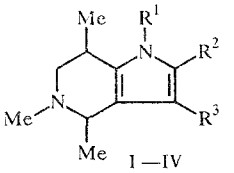
The configurations and conformational features of N–H and N-vinyl-4,5,7-trimethyl-4,5,6,7-tetrahydropyrrolo[3,2-c]pyridines and their nitro derivatives were established by the method of ^1H and ^{13}C NMR spectroscopy. It was shown that the conformational uniformity of the piperideine ring in the compounds studied is strongly dependent on the character of the substituents in the pyrrole ring. A method for the determination of the orientation of the substituent at the α-position to the nitrogen atom of the piperideine ring, according to the direct $^1J_{CH}$ SSCC, was proposed.

The chemistry and stereochemistry of tetrahydropyrrolopyridines have been virtually unstudied since there are no simple and convenient methods for their isolation. The utilization of oximes of piperidin-4-ones in the Trofimov reaction permitted a solution to the problem of the synthesis of tetrahydropyrrolo[3,2-c]pyridines substituted at the tetrahydropyridine ring [1, 2] and the commencement of the study of their chemical conversions [3, 4].

The present work presents a study of the stereochemistry of NH- and N-vinyl-4,5,6,7-tetrahydro-4,5,7-trimethylpyrrolo-[3,2-c]pyridines (I), (II) [3], as well as 2-nitro- and 3-nitro-substituted pyrrolopiperidines (III) and (IV) [4], using NMR spectroscopy.



I—IV

I $R^1 = R^2 = R^3 = H$; II $R^1 = CH=CH_2$, $R^2 = R^3 = H$; III $R^1 = CH=CH_2$, $R^2 = NO_2$, $R^3 = H$; IV $R^1 = CH=CH_2$, $R^2 = H$, $R^3 = NO_2$

The tetrahydropyrrolopyridines (I) and (II), as well as the initial oxime, may exist in the form of two configurational isomers with the trans and cis disposition of the methyl groups in the piperideine ring at the positions $C_{(4)}$ and $C_{(7)}$. The isomers with the cis configuration of the methyl groups are designated (Ic) and (IIc), and those with the trans disposition are designated (It) and (IIt). In the case of the compound (I), the mixture of the cis and trans isomers with the ratio of 1:3 for (Ic):(It) was investigated; the individual isomers (IIc) and (IIt) were isolated for (II). The configuration of the methyl groups 4-CH_3 and 7-CH_3 in the case of the tetrahydropyrrolopyridine (I) was established as follows.

The observed values of the SSCCs of the $H_{(6a)}$ and $H_{(6e)}$ protons (Table 1) for the predominant isomer in the mixture indicate that the piperideine fragment of the molecule occurs in the half-chair monoene (cyclohexene [5] and piperideine [6]) systems. The presence of the high (trans) vicinal SSCC for $H_{(6a)}$ and the low (cis) SSCC for $H_{(6e)}$ indicates the pseudoequa-

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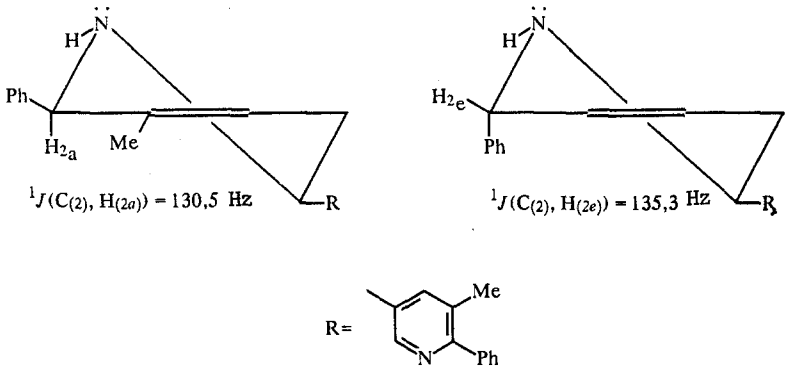
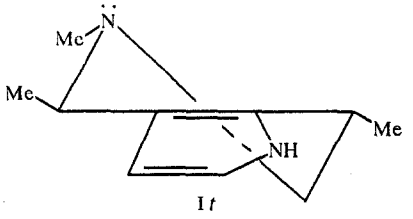
torial orientation of the methyl group at the position $C_{(7)}$ of the molecule of the predominating isomer (I). Moreover, the high trans-vicinal SSCC $^3J_{6a7a}$ = 10.13 Hz indicates the significant predominance of one conformer. However, it is necessary to establish the orientation of the 4-CH_3 group for the determination of the configuration. The absence of vicinal SSCCs for the $H_{(4)}$ proton in the molecule of (I) renders virtually impossible the solution to this question with the aid of traditional methods of ^1H NMR.

For this purpose, we acquired data on the values of the direct $^1J_{CH}$ SSCCs measured for the cis and trans isomers of 3-methyl-2-phenyl-5-(3-methyl-2-phenyl-3,4-dehydropiperidine-6)pyridine:

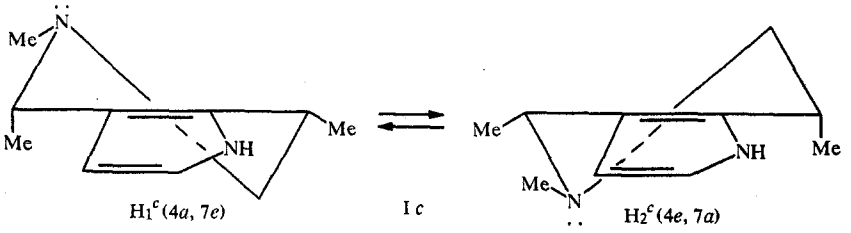


The given example indicates that the stereospecificity of the direct $^1J_{CH}$ SSCCs in regard to the unshared electron pair of the nitrogen atom is observed in the case of piperideines, as is the case for substituted γ-piperidones [7]: a high constant is observed for the C–H bond with the cis orientation to the unshared electron pair of the nitrogen atom ($^1J_{CH}^{cis}$ $^1J_{CH}^{trans}$). Taking this feature into account, the value of the direct $^1J(C_{(4)}, H_{(4)})$ SSCC (Table 2) for the predominating isomer (I) indicates the pseudo-equatorial orientation of the 4-CH_3 group and, correspondingly, the trans configuration of the methyl groups at the positions $C_{(4)}$ and $C_{(7)}$.



It

As follows from the values of the cis and trans SSCCs $^3J_{6,7}$ (cf. Table 2), the minor isomer (Ic) is characterized by the conformational equilibrium.



In the case of the pair of isomers (IIc) and (IIt), the introduction of the vinyl group leads to the reverse conformational situation by comparison with (Ic) and (It). The "fixing" of the conformation H(4e, 7a) for the isomer (IIc)

TABLE 1. ^{1}H NMR Data for the Compounds (I)-(IV)*

Isomer	Solvent	Chemical shifts (δ, ppm, 400 MHz, TMS)													SSCCs of protons (Hz)											
															geminal	vicinal									distant	
		2	3	4	4-CH_3	5-CH_3	6α	6ε	7	7-CH3	NH	X	A	B	6α,6ε	6,7-trans	6,7-cis	2,3	1,2	4,4-CH_3	7,7-CH_3	X,A*	X,B*	2,7	1,3
Ic	$CDCl_3$	6,66	5,94	2,89	1,22	2,44	2,65	2,73	3,45	1,31	8,21	—	—	—	-12,05	6,26	5,04	3,10	2,59	6,87	6,56	—	—	0,92	2,29
It	$CDCl_3$	6,58	5,96	3,22	1,37	2,43	2,24	2,97	3,10	1,13	8,21	—	—	—	-11,29	10,13	5,34	3,10	2,59	6,41	6,71	—	—	0,61	2,29
IIc	$CDCl_3$	6,71	6,02	3,09	1,38	2,45	2,71	2,74	2,86	1,35	—	6,82	4,63	5,06											
	C_6D_6	6,77	6,05	3,06	1,39	2,28	2,51	2,44	2,44	1,25	—	6,50	4,29	4,80	-11,41	3,91	1,83	3,17	—	6,35	6,71	8,91	15,72	—	—
IIt	$CDCl_3$	6,85	6,00	3,37	1,25	2,41	2,24	3,04	3,06	1,22	—	6,84	4,61	5,03											
	C_6D_6	6,77	6,04	3,54	1,19	2,29	2,08	2,81	2,68	1,09	—	6,53	4,28	4,79	-11,54	5,35	4,88	3,17	—	6,41	6,59	8,91	15,72	—	—
III	$CDCl_3$	—	7,05	3,10	1,38	2,44	2,73	2,76	2,99	1,31	—	7,05	5,42	5,35	-11,75	2,68	3,66	—	—	6,35	6,90	8,18	15,60	—	—
	C_6D_6	—	6,87	2,70	1,09	2,13	2,28	2,28	2,32	1,04	—	6,48	4,66	4,59											
IV	$CDCl_3$	7,04	—	—	1,33	2,43	2,24	3,09	3,23	1,20	—	7,20	5,39	5,31	11,96	8,54	5,80	—	—	6,47	6,65	8,06	15,56	—	—
	C_6D_6	7,31	—	3,90	1,46	2,20	2,30	2,37	2,20	0,88	—	5,99	4,18	4,45	-11,96	4,88	5,35	—	—	6,23	6,71	8,06	15,56	—	—

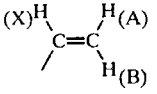
*Designation of the protons of the vinyl group 

TABLE 2. ^{13}C Chemical Shifts (δ, ppm) (100.6 MHz, TMS) and Direct ^{13}C–^{1}H SSCCs (in parentheses Hz)*

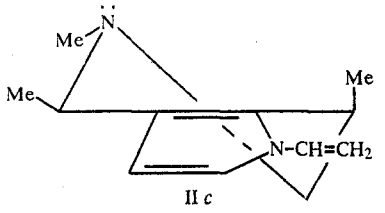
Isomer	Solvent	$C_{(2)}$	$C_{(3)}$	$C_{(3a)}$	$C_{(4)}$	$C_{(5')}$	$C_{(4')}$	$C_{(6)}$	$C_{(7)}$	$C_{(7')}$	$C_{(7a)}$	$C_{(\alpha)}$	$C_{(\beta)}$
Ic	$CDCl_3$	116,24 (183,5)	105,04 (168,3)	129,09 —	55,85 (132,5)	42,58 (133,3)	19,19 (125,9)	56,95 (133,8)	27,09 (128,0)	18,97 (126,3)	120,18 —	—	—
It	$CDCl_3$	116,38 (183,7)	104,68 (167,9)	129,34 —	57,38 (130,5)	42,55 (133,3)	19,63 (126,3)	62,32 (130,3; 136,2)	28,60 (129,5)	17,02 (126,1)	120,31		
IIc	C_6D_6	115,61 (184,5)	107,45 (168,3)	123,02 —	57,74 (129,0)	43,46 (132,3)	20,50 (126,1)	61,09 (130,5; 135,8)	28,16 (126,9)	20,68 (126,5)	130,59 —	130,43 (172,1)	95,57 (156,8; 163,1)
IIt	C_6D_6	116,13 (184,5)	107,53 (168,3)	124,13 —	55,51 (134,2)	42,23 (132,3)	16,48 (125,9)	57,65 (132,8)	28,35 (129,1)	19,77 (126,4)	130,35 —	131,41 (172,5)	96,06 (156,7; 162,8)
III	$CDCl_3$	137,58 —	111,07 (178,3)	139,40 —	56,42 (130,7)	43,22 (133,5)	19,43 (126,9)	59,74 (131,1; 137,7)	28,21 (130,4)	18,98 (128,0)	123,75 —	131,10 (187,3)	113,64 (159,3; 162,4)
IV	$CDCl_3$	110,96 (178,5)	137,90 —	139,44 —	56,00 (133,6)	42,03 (133,4)	17,94 (126,5)	60,21 (131,5; 136,0)	28,76 (131,6)	16,76 (127,0)	124,68 —	132,28 (188,6)	114,36 (159,1; 162,3)

*The designation of the carbon atoms of the vinyl group — $C_{(\alpha)}H=C_{(\beta)}H_2$.

TABLE 3. Data on the Conformational Composition of the Isomers (Ic), (IIt), (III), and (IV)

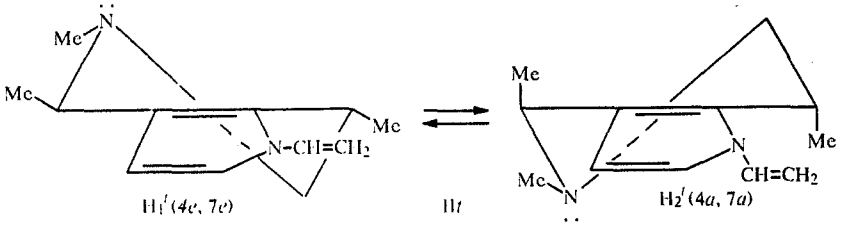
Isomer	Solvent	Occupancy of the conformers			
Ic	$CDCl_3$	$H^c(4a,7e)$	54%	$H^c(4e,7a)$	46%
IIt	C_6D_6	$H^t(4e,7e)$	43%	$H^t(4a,7a)$	57%
III	$CDCl_3$	$H^c(4a,7e)$	11%	$H^c(4e,7a)$	89%
IV	$CDCl_3$	$H^c(4a,7e)$	81%	$H^c(4e,7a)$	19%
	C_6D_6	$H^c(4a,7e)$	39%	$H^c(4e,7a)$	61%

proceeds on account of the steric interaction of the N-vinyl and 7-methyl groups. This follows from the vicinal $^3J_{6,7}{}^{trans}$ and $^3J_{6,7}{}^{cis}$ SSCCs (cf. Table 1), which indicate the practically complete predominance of the conformer H_2^c(4e, 7a).



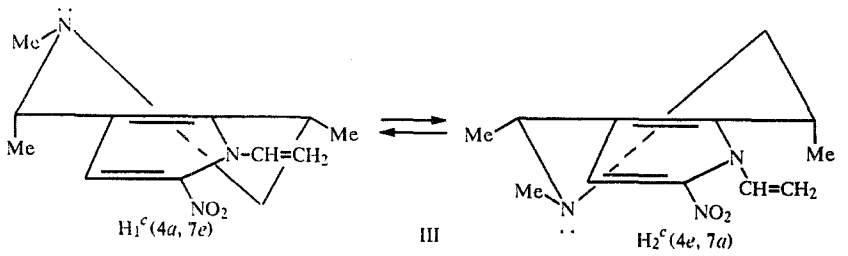
IIc

In the case of the trans isomer (It), the value of the same constants (cf. Table 2) indicate the presence of the conformational equilibrium.

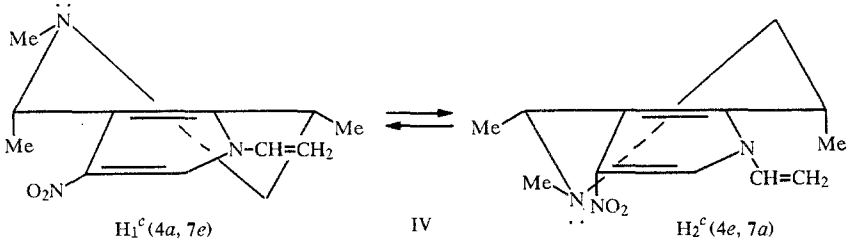


The occupancies of the conformers were evaluated by the method of averaged parameters taking the $^3J_{6e7e}$ = 1.8 Hz (IIc) and $^3J_{6a7a}$ = 10.1 Hz (It) as the limiting SSCCs (Table 3). The reason for the conformational heterogeneity of (IIt) by comparison with (It) is also explained by the steric interaction of the N-vinyl and 7-methyl groups. These examples indicate the high conformational lability of tetrahydropyrrolopyridine systems, which we also confirmed for the case of the nitro derivatives (III) and (IV). It should be expected that the introduction of the nitro group at the second position of the pyrrole ring in (III) may lead to the rotation of the vinyl group at the N–C bond and the increase in the occupancy of the rotamer with the approximate perpendicular disposition of the planes of the vinyl substituent and the pyrrole fragment. A decrease in the steric interaction of the vinyl and 7-methyl groups is possible with such a rotation.

In order to evaluate the dihedral angle φ between the planes of the vinyl substituent and the pyrrole ring, we utilized the empirical dependence of the difference Δ^1J = ^1J[C(β), H(A)] — ^1J[C(β), H(B)] on the φ, obtained specially for N-vinylpyrroles [8, 9]: $\Delta^1J = 2.02 + 5.48 \cos\varphi$. The values of Δ^1J_{CH} = 162.4 — 159.3 = 3.1 Hz both in $CDCl_3$ and in C_6D_6 for the Δ^1J_{CH} = 161.9 — 159.3 = 2.9 Hz indicate, according to the dependence presented above, the virtual perpendicular disposition of the vinyl group relative to the pyrrole ring: φ = 80°. Such a change in the dihedral angle φ in (III) by comparison with the initial tetrahydropyrrolopyridine (IIc) (Δ^1J_{CH} = 6.3 Hz, φ = 35°) influences the trans-SSCC $^3J_{6e7e}$ (cf. Table 1), the magnitude of which may be associated with a low content of the conformer H_1^c(4a, 7e) by comparison with the analogous SSCC in (IIc) (cf. Table 3):



Even more interesting conformational effects of distant action are observed in the case of the 3-nitro derivative (IV). According to the trans-vicinal SSCC $^3J_{6,7}$, the pyrrolopiperidine (IV) is characterized by the conformational equilibrium in which the conformer H_1^c(4a, 7e) is significantly predominant in the $CDCl_3$ solution, in contrast to the 2-nitro derivative (III) (cf. Table 3).



Such conformational behavior of the 3-nitro derivative (IV) is explained by the steric interaction of the 3-NO_2 and 4-CH_3 groups, as a result of which the preferred inversion of the piperideine ring occurs by comparison with the initial tetrahydropyrrolopyridine (IIc). The increase of the occupancy of the conformer H_1^c(4a, 7e), in its turn, leads to the forced rotation of the vinyl group at the N–C bond, as a result of which the dihedral angle φ, as in the case of the 2-nitro derivative (III), comprises ~80° notwithstanding the absence of a substituent at the second position of the pyrrole ring. Therefore, the virtual "distant steric influence" of the 3-NO_2 group on the conformation at the N–CH=CH_2 bond proceeds on account of the transmission of the steric interaction across the conformationally labile piperideine ring. It is interesting to note that a significant decrease in the content of the conformer H_1^c(4a, 7e) is observed in the solution of the isomer (IV) in C_6D_6 (cf. Table 3). Such a dependence of the occupancy of the conformers on the polarity of the solvent may be evidently explained by the different degree of the solvation of the nitro group in $CDCl_3$ and C_6D_6: the more effective solvation of the nitro group in the polar solvent ($CDCl_3$) leads to an increase in the steric interaction between the 3-NO_2 and 4-CH_3 groups.

It should be noted that a change in the occupancy of the conformers in the transition from the 2-nitro derivative (III) to the 3-nitro derivative (IV) is confirmed not only by the constant $J_{6,7}^{trans}$, but also by the change in the direct SSCC ^1J[C(4), H(4)] from 130.7 to 133.6 Hz (cf. Table 2). The increase in the $^1J_{CH}$ in the given case indicates an increase in the occupancy of the conformer with the pseudo-equatorial orientation of the $C_{(4)}-H_{(4)}-H_1^c$(4a, 7e) bond. Consequently, the stereospecificity of the direct $^1J_{CH}$ SSCC in relation to the unshared electron pair of the nitrogen atom may be further utilized as an independent spectral criterion in the conformational analysis of piperideine systems.

EXPERIMENTAL

The registration of the NMR spectra was performed on a Bruker WM-400 spectrometer with the working frequency of 400 MHz for the ^1H nuclei and 100.6 MHz for the ^{13}C nuclei. Narrow spectral regions were selected for the measurement of the NMR parameters with high accuracy (±0.02-0.1 Hz); the Lorentz–Gauss filter was employed for the narrowing of the lines. Analysis of the PMR spectra of strongly associated systems was performed by the iteration program PANIC,

coming into the mathematical provision of the ASPECT-2000 computer. The evaluation of the occupancies of the conformers was carried out by the method described in [10].

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