PMR SPECTRA OF DERIVATIVES OF THE CIS AND TRANS ISOMERS OF 4-AMINO-3-HYDROXYTHIOPHANE

T. M. Filippova, S. D. Mikhno,
N. S. Kulachkina, I. M. Kustanovich,
and V. M. Berezovskii

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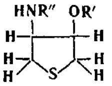
The PMR and proton magnetic double resonance (PMDR) spectra were obtained for five cis and trans isomer pairs of substituted 4-amino-3-hydroxythiophanes. A comparison of the PMR parameters of the cis and trans isomers made it possible to formulate the characteristic differences in their spectra. On the basis of the data obtained, the trans configuration is proposed for the ethoxycarbonylamino and hydroxy groups in 4-ethoxycarbonylamino-3-hydroxy-3-cyanothiophane, the configuration of which has not been previously determined.

A comparatively small number of papers devoted to the PMR study of the conformations and configurations of five-membered heterocycles have been published [1-4].

In this paper we have studied the possibility of establishing the cis and trans configurations of derivatives of 4-amino-3-hydroxythiophanes using PMR. Five cis and trans isomer pairs of substituted 4-amino-3-hydroxythiophanes (I-V), the structures of which have not previously been accurately established [5], were used for the study.



I $R' = H$, $R'' = COOC_2H_5$;
II $R' = COCH_3$, $R'' = COOC_2H_5$;
III $R' = COCH_3$, $R'' = COC_6H_5$;
IV $R' = COC_6H_5$, $R'' = COC_6H_5$;
V $R' = COCH_3$, $R'' = CONHCOCH_3$

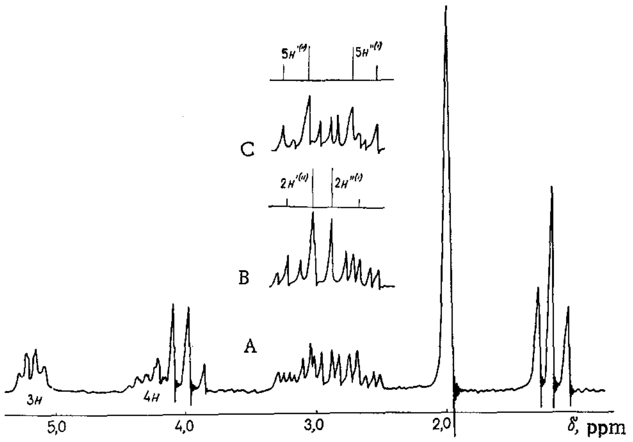


Fig. 1. PMR spectra (in deuterochloroform, c 0.5 M): A) trans isomer of II; B) the same during irradiation of the 3H nucleus; C) the same during irradiation of the 4H nucleus.

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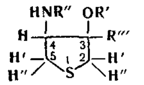
TABLE 1. Chemical Shifts of the Protons of the Cis and Trans Isomers of I-VI



Compound	R′	R″	R‴	Isomer	Conc., M	δ, ppm (deuterochloroform)										$\Delta\delta_{2H'-2H''}$	$\Delta\delta_{5H'-5H''}$
						2H′(″)	2H″(′)	3H	4H	5H′(″)	5H″(′)	a	b	c	d		
I	H	(a) (b) COOCH$_2$CH$_3$	H	cis	0,30	3,113	2,783	3,80—4,45	3,80—4,45	3,062	2,698	4,122	1,237	5,10—5,42	—	0,330	0,364
				trans		3,040	2,816	3,80—4,40	3,80—4,40	3,260	2,630	4,106	1,232	5,00—5,30	—	0,224	0,630
II	(d) COCH$_3$	(a) (b) COOCH$_2$CH$_3$	H	cis	0,25	3,166	2,864	5,286	4,21—4,64	3,092	2,764	4,130	1,242	5,07	2,102	0,302	0,328
				trans		3,146	2,860	5,275	4,20—4,53	3,225	2,697	4,113	1,242	5,05	2,060	0,286	0,528
III	(d) COCH$_3$	COC$_6$H$_5$	H	cis	0,70	3,182	2,898	5,401	4,777	3,187	2,851	—	—	6,707	2,088	0,284	0,336
				trans		3,146	2,882	5,408	4,738	3,303	2,781	—	—	6,865	2,023	0,264	0,522
IV	COC$_6$H$_5$	COC$_6$H$_5$	H	cis	0,50	3,288	3,028	5,663	4,862	3,288	2,968	—	—	—	—	0,260	0,260
				trans		*	*	5,644	4,927	*	*	—	—	—	—	—	—
V	(d) COCH$_3$	(a) (b) CONHCOCH$_3$	H	cis	0,50	3,195	2,909	5,395	4,566	3,096	2,860	10,247	2,115 (2,129)	8,948	2,129 (2,115)	0,286	0,236
				trans		3,176	2,854	5,355	4,530	3,215	2,795	10,218	2,062 (2,122)	8,828	2,122 (2,062)	0,322	0,420
VI	H	(a) (b) COCH$_2$CH$_3$	CN	trans	0,70	3,284	3,234	—	4,708	3,329	2,807	4,165	1,270	—	5,14—5,70	0,050	0,522

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*Poorly resolvable broad multiplet.

TABLE 2. Spin-Spin Constants in I-VI

Compound	Isomer	J spin-spin constants, Hz									Conc., M
		2H′—2H″	2H′(″)—3H	2H″(′)—3H	3H—4H	5H′(″)—4H	5H″(′)—4H	5H′—5H″	4H—c	b—a	
I	cis	12,0	4,0	2,7	—	6,7	9,0	10,1	—	7,7	0,30
	trans	12,0	4,5	3,3	—	4,8	3,3	11,5	—	6,7	
II	cis	11,9	4,7	3,4	3,4	6,2	8,7	10,5	—	7,0	0,25
	trans	12,3	5,2	3,3	3,3	5,2	3,3	12,0	—	7,0	
III	cis	12,2	4,8	3,0	3,9	6,7	9,3	10,1	8,0	—	0,70
	trans	11,9	5,3	4,3	4,3	5,7	4,7	11,4	7,1	—	
IV	cis	12,8	3,1	3,1	4,6	6,7	8,7	10,3	7,8	—	0,50
	trans	*	5,2	5,2	5,2	5,2	5,2	*	7,5	—	
V	cis	12,2	4,3	2,7	4,3	6,7	9,0	10,5	8,8	—	0,50
	trans	12,0	5,0	3,3	3,3	5,0	3,3	11,4	7,3	—	
VI	trans	12,0	—	—	—	5,9	4,5	11,4	8,4	—	0,70

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*Poorly resolvable broad multiplet.

On the basis of the chemical shifts, the integral intensity ratios, and the fine structure of the spectra the major groups of signals in the spectra of the cis and trans isomers of I-V can clearly be assigned to definite protons of the thiophane ring (Fig. 1A). The four protons attached to the carbon atoms in the 2- and 5-positions of the thiophane ring form a complex group of signals at 2.50-3.50 ppm. The C_3 proton for all of the compounds and the C_4 proton in the isomers of I are characterized by a multiplet with a chemical shift of 3.80-4.93 ppm. The signal of the C_4 proton for the cis and trans isomers of II-V lies at weaker field, at 5.25-6.10 ppm. In addition, the spectra contain signals characteristic for substituents attached to the amino group (R") and hydroxyl group (R'). For the isomers of III-V the signal of the proton attached to the nitrogen atom is a doublet ($J_{NH-4H} = 7.1$-8.8 Hz).

A more detailed interpretation of the PMR spectra of all of the investigated isomers of I-V was carried out by means of proton magnetic double resonance (PMDR, with a total double resonance $\gamma H_2/2\pi \gg J$). For example, irradiation of the C_3 proton ($\delta = 5.275$ ppm) in the trans isomer of II (Fig. 1B) simplifies the complex signal of the four geminal protons at C_2 and C_5 at 2.48-3.33 ppm and makes it possible to individually isolate the signals of the C_2 and C_5 geminal protons.

Visual analysis of the spectra immediately shows that all of the interacting protons have different chemical shifts. Thus, the spin-spin interaction constants and chemical shifts of the C_3 and C_4 protons can be determined to the first order of magnitude directly from the spectra. Two AB systems of the C_2 and C_5 protons [6] were isolated and calculated from the multiplet of the geminal protons ($\delta = 2.50$-3.50 ppm) (Tables 1 and 2). It is well known that for compounds with close PMR spectral parameters an analysis of the spin-spin constants to the first order of magnitude can give comparatively small errors in the determination of their values (up to 1 Hz) [7, 8]. A complete computer analysis of them is necessary to obtain more accurate values of the spectral parameters.

A comparison of the PMR parameters of the 3,4-substituted thiophanes (I-V) makes it possible to formulate the characteristic differences in the spectra of the isomers of these compounds with cis and trans orientation of the amino and hydroxy groups.

The chemical shift between the C_5 geminal protons in the spectra of the cis isomers ($\Delta\delta^{cis}_{5H'-5H''} = 0.236$-$0.364$ ppm) is substantially less than the chemical shift between the C_5 geminal protons in the trans isomers ($\Delta\delta^{trans}_{5H'-5H''} = 0.420$-$0.630$ ppm) (Table 1). For example, $\Delta\delta^{cis}_{5H'-5H''} = 0.336$ ppm for the isomers of III, while $\Delta\delta^{trans}_{5H'-5H''} = 0.522$ ppm.

A broad range of vicinal spin-spin interaction constants from $J_{5H'(H'')-4H} = 8.7$-9.3 Hz to $J_{3H-4H;2H'(H'')-3H} = 2.7$-$4.3$ Hz (Table 2) is characteristic for the cis isomers of the compounds under investigation here. The vicinal spin-spin interaction constants in the trans isomers are relatively close ($J = 3.3$-5.7 Hz, Table 2).

The results obtained here enabled us to assume the three-dimensional structure of 4-ethoxycarbonylamino-3-hydroxy-3-cyanothiophane [9], the configuration of which has not been determined previously. A study of the PMR spectrum of this compound yielded the parameters $\Delta\delta_{5H'-5H''} = 0.522$ ppm, $J_{5H'(H'')-4H} = 5.9$ Hz, and $J_{5H''(H')-4H} = 4.5$ Hz (Tables 1 and 2), and this made it possible to assign this compound to the trans series.

The differences in the spectra of the cis and trans isomers of 4-amino-3-hydroxythiophane derivatives are obviously conformational in nature. No high energy barriers exist for five-membered rings [10, 11], and their PMR spectra are therefore the result of averaging of the spectra of the individual conformers with allowance for the probability that the molecule exists in one or another conformation.

It is well known that the magnitudes of vicinal spin-spin interaction constants are associated with the dihedral angle between the planes of the carbon—carbon—hydrogen bonds [12]. This correlation is widely used in the investigation of the conformations of different compounds. The qualitative examination of the magnitudes of vicinal spin-spin constants of the cis isomers of the compounds under investigation here presupposes that one preferred conformation exists in solution for these compounds. If several cis isomer conformations had equal probability weight, the vicinal spin-spin interaction constants should have been averaged with respect to these conformations, and one would not observe such a wide diversity in the spin-spin constants (Table 2). It is not possible to draw any conclusions relative to the conformational state of the trans isomers of the compounds on the basis of a qualitative examination of the magnitudes of the vicinal spin-spin interaction constants since the constants for these isomers are close in magnitude (Table 2).

EXPERIMENTAL

The spectra were obtained with Varian DA-60, Perkin–Elmer R-12, and Hitachi–Perkin–Elmer R-20 spectrometers with deuterochloroform as the solvent. The chemical shifts (δ scale) were measured with an accuracy of ±0.005. The accuracy in the measurement of the spin-spin constants was ±0.1 Hz. Hexamethyldisiloxane ($\delta = 0.05$ ppm) was used as the internal standard.

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