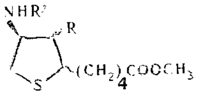
^{13}C NMR SPECTRA OF ISOMERIC 2,3,4-TRISUBSTITUTED TETRAHYDROTHIOPHENES

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

UDC 547.732:543.422.25:541.621.2

The chemical shifts and direct carbon–proton spin–spin coupling constants in the ^{13}C NMR spectra of a number of isomeric 2,3,4-trisubstituted tetrahydrothiophenes were found. It is shown that the ^{13}C spectra, in contrast to the ^{1}H NMR spectra, can be used not only for the determination of the structures of individual isomers but also for the analysis of the isomeric composition of a mixture of compounds.

We have previously begun a study of the effect of the three-dimensional structures on the parameters of the ^{13}C NMR spectra of substituted tetrahydrothiophenes in the case of isomeric 3,4-disubstituted compounds [1]. In a continuation of these investigations we studied the ^{13}C NMR spectra of isomeric 2,3,4-trisubstituted tetrahydrothiophenes I-V:



I-VI a-d

I R=OH, R'=COC$_6$H$_5$; II R=OH. R'=CONH$_2$; III R=OH, R'=H · HCl; IV R=NHCONH$_2$, R'=CONH$_2$; V R=NH$_2$ · HBr, R'=H · HBr;
a-d — **isomers** : **a** — 4-*r*, 3-*t*, 2-*t*; **b** 4-*r*, 3-*t*, 2-*c*; **c** — 4-*r*, 3-*c*, 2-*c*; **d** — 4-*r*, 3-*c*, 2-*t*

Compound Va was investigated in a mixture with isomer Vb.

The configurations of Ia-d, IIa-d, IIIc,d, and IVa,b were previously established [2-7] by means of the characteristic peculiarities of the ^{1}H NMR spectra of the isomers of trisubstituted tetrahydrothiophenes [2, 8] and by means of the temperature dependences of the vicinal proton–proton spin–spin coupling constants [9]. The configurations of tetrahydrothiophenes IIIa,b [4] and Va-c [6, 7] were determined indirectly from the ^{1}H NMR spectra of the derivatives of these compounds.

It should be noted that it is not possible to determine the configurations of Va and Vc by ^{1}H NMR spectroscopy. The chemical shifts of the 3- and 4-H protons, as well as the 5'- and 5"-H protons, in the spectra of these compounds are close (Table 1), and the developed method for the determination of the form of the isomer from the temperature dependences is therefore unsuitable, and, from the point of view of the established characteristic peculiarities, their spectra are anomalous. One might have expected that the ^{13}C NMR method would prove to be more promising for the study of the isomerism of these and other compounds similar to them with identical substituents attached to $C_{(3)}$ and $C_{(4)}$. In addition, the ^{13}C NMR method may be useful for the determination of the composition of a mixture of isomers with close chemical shifts of the 3- and 4-H protons, as, for example, in the case of mixtures of IIIa-d and Va-c (see Table 1 and the literature cited in [5]).

In the assignment of the signals in the ^{13}C spectra of I-III (Table 2) the choice between the signals of secondary and tertiary ^{13}C atoms was made on the basis of a comparison of the spectra obtained with complete suppression of the spin–spin coupling with the protons with the spectra without decoupling but also with the Overhauser nuclear effect. For the compounds investigated in low concentrations (IVa,b, and Va-c) the data obtained for disubstituted tetrahydrothiophenes [1] and for the isomers of I-III were used for this purpose.

All-Union Scientific-Research Vitamin Institute, Moscow 117246. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 908-911, July, 1983. Original article submitted August 17, 1982; revision submitted January 10, 1983.

0009-3122/83/1907-0727$07.50

TABLE 1. ^1H Chemical Shifts in the Spectra of Solutions of IIIa,b and Va-c in Deuteropyridine[a]

Compound	δ, ppm					
	2-H	3-H	4-H	5′-H	5″-H	$\Delta\delta_{5'5''}$
IIIa[b]	3,760	5,274	4,441	3,624 (3,575)	3,575 (3,624)	0,049
IIIb[c]	3,421	4,648	4,148	3,394	3,692	0,298
Va	4,14	4,80—5,15		3,55—3,75		
Vb	3,78	4,32	4,45—5,20	3,62	3,62	0
Vc	4,30	4,80—5,45		3,72	3,72	0

---

[a] The chemical shifts were determined as the centers of the multiplets, and the spin—spin coupling constants (J) were determined as the distances between the corresponding lines in the multiplets. [b] J_{23} = 5.7, J_{34} = 5.9, ΣJ_{45} = 12.0, and $J_{5'5''}$ = 11.6 Hz. [c] J_{23} = J_{34} = 9.2 Hz, $J_{45'}$ = 7.3 Hz, $J_{45''}$ = 10.3 Hz, and $J_{5'5''}$ = 10.3 Hz.

TABLE 2. Parameters of the ^{13}C NMR Spectra of Solutions of Isomers of I-V in Deuteropyridine[a]

Compound	δ, ppm ($^1J_{CH}$, Hz)								$\Delta\delta C_{(3)}$	$\Delta\delta C_{(4)}$	$\Delta\delta C_{(4')}$	$\Delta ^1JC_{(3)}H$	$\Delta ^1JC_{(4)}H$
					substituent attached to $C_{(2)}$								
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(4')}$	$C_{(3')}$ ($C_{(2')}$)	$C_{2'}$ ($C_{3'}$)	$C_{(1')}$					
Ia	50,3 (140)	77,1 (146)	60,1 (146)	33,0 (144)	30,7	25,1	28,5	33,8	−4,5	0	−5,7	2	3
Ib	50,5 (140)	81,6 (144)	59,8 (143)	30,2 (144)	35,2	25,1	28,1	34,0	0	−0,3	−1,2	0	0
Ic	50,5 (140)	73,5 (147)	57,9[b]	31,6 (143)	31,0	25,0	28,1	33,8	−8,1	−2,2	−5,4	3	
Id	53,4 (142)	77,5 (147)	56,0 (143)	31,9 (143)	36,4	24,7	27,7	33,5	−4,1	−4,1	0	3	0
IIa	50,1	77,6	60,1	33,9	30,6	25,0	28,6	33,9	−4,4	0	−5,6		
IIb	50,1	82,0	59,4	31,0	34,9	24,9	27,9	33,9	0	−0,7	−1,3		
IIc	50,5	74,3	58,6	32,6	31,4	25,0	28,2	33,9	−7,7	−1,5	−4,8		
IId	52,7	78,4	56,6	32,7	36,2	24,8	27,9	33,8	−3,6	−3,5	0		
IIa[c]	50,1 (140)	78,5 (146)	60,1 (145)	33,5 (143)	30,7	25,5	29,0	34,4	−3,5	0	−4,1	3	6
IIb[c]	49,4 (140)	82,0 (143)	60,8 (140)	30,3 (144)	34,8[d]	25,2	28,0	34,4[d]	0	0,7	0	0	1
IIc[c]	49,9 (140)	74,8 (146)	57,9 (139)	31,5 (142)	30,7	25,2	28,2	34,1	−7,2	−2,2	−4,1	3	0
IIIa	49,0 (141)	76,0 (146)	59,2 (149)	30,2 (144)	30,9	24,9	27,9	33,8	−4,4	0	−4,6	2	3
IIIb	48,6 (141)	80,4 (144)	58,8 (146)	28,2[d] (144)	34,7	25,3	27,9[d]	34,5	0	−0,4	−0,8	0	0
IIIc	51,0[b]	73,2 (148)	57,8[b]	30,7 (144)	31,0	25,2	28,4	34,0	−7,2	−1,4	−4,5	4	
IIId	52,6 (141)	77,1 (147)	56,2 (146)	30,9 (144)	35,5	24,7	27,8	33,7	−3,3	−3,0	0	3	0
IVa	47,5	61,1	58,3	33,1	31,4	25,1	28,3	33,9	−1,5	0	−3,9		
IVb	47,7	62,6	59,0	32,1	35,3	25,0	27,9	33,9	0	0,7	0		
Va	48,4	60,3	58,0	32,6	30,5	24,7	28,1	33,5	−2,0	0	−1,5		
Vb	48,7	62,3	58,3	30,6	32,0	25,4	28,7	34,5	0	0,3	0		
Vc	49,7	56,9	56,1	30,7	30,4	24,8	28,0	33,5	−5,4	−1,9	−1,6		

---

[a] Solution concentrations (mole/liter): 0.7 (Ia-d), 0.33 (IIa-d), 0.7 (IIIa-d), 0.06 (IVa,b), and 0.09 (Va-c). [b] The $J_{^{13}CH}$ value cannot be determined with sufficient accuracy because of overlapping of the lines in the spectrum. [c] The solvent was CD_3COOD. [d] The assignment was ambiguous.

In the spectra of compounds with different substituents attached to $C_{(3)}$ and $C_{(4)}$ (Ia-d, IIa-d, and IIIa-d), of the two weak-field signals of the tetrahydrothiophene ring, the most weak-field signal [δ 73.2-82.0 ppm (Table 2)] was assigned to $C_{(3)}$, since the OH (OR) group shifts the C_α signal to weak field to a greater extent than the NHR group [10, pp. 141, 166]. The most weak-field signal in the ^{13}C spectra of compounds with identical substituents attached to $C_{(3)}$ and $C_{(4)}$ (IVa,b and Va-c) was also assigned to $C_{(3)}$, since the weak-field β effect of an alkyl substituent in the 2 position is greater than the γ effect.

The selection of the $C_{(5)}$ signal from the five ^{13}C signals of the methylene groups was made from the $^1J_{CH}$ values on the basis of the fact that the $^1J_{CH}$ value increases as the electronegativity of the substituent increases [11]: $^1J_{C_{(5)}H}$ > (140–144 Hz) > $J_{C(1',2',3',4')H}$ (125–130 Hz). It is apparent from Table 2 that the chemical shift of one of the four methylene groups of the side chain changes significantly, depending on the orientation of the substituents attached to $C_{(2)}$ and $C_{(3)}$ (30.4–36.4 ppm), while the chemical shifts of the three other methylene groups remain virtually constant for all of the investigated compounds (24.7–25.5, 27.7–29.0, and 33.5–34.5 ppm, Table 2). A change in the mutual orientation of the substituents attached to $C_{(2)}$ and $C_{(3)}$ should be reflected in the position of the $C_{(4)}$ signal in the spectrum because of the contribution to the chemical shift of this signal for 2,3-cis isomers of the steric γ effect, which is widely used in the determination of configurations [12–14]. The signal with the changed chemical shift was therefore assigned to $C_{(4')}$, while the remaining signals were assigned to $C_{(1')}$, $C_{(2')}$, and $C_{(3')}$. This assignment was confirmed by analysis of the ^{13}C spectra of deuterium-labeled (in the 2, 4, and 4' positions) Ia and Ib [15].

It can be seen from Table 2 that the ^{13}C spectra of the isomers of all of the investigated 2,3,4-trisubstituted tetrahydrothiophenes differ appreciably, including the spectra for Va–c, which have similar ^1H NMR spectra (Table 1). Differences are observed not only in the chemical shifts but also in the direct carbon–proton spin–spin coupling constants (Δ^1J_{CH} = 2–6 Hz, Table 2). As one might have expected [16], a stable steric γ effect is observed for $C_{(4')}$: the $C_{(4')}$ signals of the isomers with a cis orientation of the substituents attached to $C_{(2)}$ and $C_{(3)}$ (isomers a and c) are shifted to strong field as compared with the trans-2,3 isomers (b, d). For the 3-OH group (isomers of I–III) the magnitude of the effect (from −4.1 to −5.7 ppm) is close to that previously observed for isomeric 2-methylcyclopentanols (−4.6 ppm [12]). The effect is somewhat smaller (−3.9 ppm) for the $NHCONH_2$ group (IVa,b), whereas it is substantially smaller (from −1.5 to 1.6 ppm) for the $NH_2 \cdot HCl$ group (Va–c). Nevertheless, the difference in the $\delta_{C(4')}$ [$\Delta\delta_{C(4')}$] values may serve as a reliable criterion for the determination of the orientation of the substituents attached to the $C_{(2)}$ and $C_{(3)}$ atoms in 2,3,4-trisubstituted tetrahydrothiophenes.

We have previously noted that in the spectra of cis-3,4-disubstituted tetrahydrothiophenes the signals of the vicinal ^{13}C atoms that bear substituents are shifted to strong field as compared with the trans isomers [1]. It is apparent from Table 2 that this effect is retained for the $C_{(3)}$ atoms of the investigated 2,3,4-trisubstituted tetrahydrothiopenes. The weakest-field signal is the $C_{(3)}$ signal in the spectra of the isomers with a di-trans orientation of the substituents attached to $C_{(2)}$ and $C_{(4)}$ with respect to the substituent attached to $C_{(3)}$ [two trans orientations, isomer b, $\Delta\delta_{C(3)}$ 0 ppm]. In the spectra of isomers with one cis and one trans orientation (isomers a and d) the $C_{(3)}$ signal is shifted to strong field [$\Delta\delta_{C(3)}$ from −1.5 to −4.5 ppm]. For the isomers with a di-cis orientation (isomers c) the magnitude of the shift of the $C_{(3)}$ signal to strong field [$\Delta\delta_{C(3)}$ from −5.4 to −8.1 ppm] is approximately twice that for the isomers with one cis and one trans orientation (isomers a and d). The values of the effects observed for $C_{(3)}$ in the spectra of 2,3,4-trisubstituted and 3,4-disubstituted tetrahydrothiophenes are close (Table 2, [1]). The $C_{(4)}$ signal is also shifted to strong field in the spectra of compounds with a cis-3,4 configuration (d and c as compared with a and b). For compounds with a trans orientation of the side chain with respect to the substituent attached to $C_{(4)}$ (4-r, 2-t) the magnitudes of the observed effects are greater [$\Delta\delta^{d-a}_{C(4)}$ from −3.0 to −4.1 ppm] than for compounds with a cis configuration [$\Delta\delta^{c-b}_{C(4)}$ from −0.8 to −2.9 ppm]. The $C_{(2)}$ chemical shifts for isomers a–c virtually coincide (Table 2), whereas for the d isomers (4-r, 3-c, 2-t) the $C_{(2)}$ signal is shifted appreciably to weak field [$\Delta\delta_{C(2)}$ 2.2–3.1 ppm, Table 2].

Thus regularities associated with the configurations of these compounds are observed in the ^{13}C NMR spectra of 2,3,4-trisubstituted tetrahydrothiophenes. The peculiarities found in this research can also be used for the analysis of a mixture of isomers, since the differences in the chemical shifts of the isomers are significant. In the present research we used the ^{13}C NMR spectra to analyze the isomeric composition of Va,b. The compound with the stronger-field $C_{(4')}$ and $C_{(3)}$ signals (30.5 and 60.3 ppm, Table 2) was assigned to the 4-r, 3-t, 2-t series [Va, cis orientation of the substituents attached to $C_{(2)}$ and $C_{(3)}$]. The ^1H NMR method is not applicable for the solution of such problems.

EXPERIMENTAL

The ^1H NMR spectra of compounds IIIa,b were taken on a Bruker Wm-250 spectrometer (working frequency on the protons 250.13 MHz). The ^1H NMR of compounds Va-c and all the ^{13}C NMR spectra were taken on a Bruker WP-80 spectrometer (working frequency on the protons 80 MHz; on the ^{13}C nuclei, 20.1 MHz). Pulse duration 1.5 µsec for ^1H and 4.5 µsec for ^{13}C (30°C). We used computer memories 4K/1000 Hz for ^1H and 16K/5000 Hz for ^{13}C. The data were taken over 2.048 sec for ^1H and over 1.638 sec for ^{13}C. The interval between pulses for ^1H was 2 sec. TMS was used as internal standard. Solvents were C_5D_5N and CD_3COOD. The isomers of each compound were investigated under one set of conditions — in the same solvent, at the same concentration, and at the same temperature (∿50°C for ^{13}C and 28°C for ^1H). The temperature was measured with a thermometer placed in the ampul with the sample in the pickup of the NMR spectrometer.

LITERATURE CITED

1. T. M. Filippova, S. D. Mikhno, N. S. Kulachkina, I. C. Suchkova, and V. M. Berezovskii, Khim. Geterotsikl. Soedin., No. 12, 1612 (1981).
2. S. D. Mikhno, T. M. Filippova, N. S. Kulachkina, T. N. Polyanskaya, I. M. Kustanovich, and V. M. Berezovskii, Khim. Geterotsikl. Soedin., No. 7, 897 (1972).
3. T. M. Filippova, Master's Dissertation, Moscow (1972).
4. S. D. Mikhno, T. M. Filippova, N. S. Kulachkina, I. G. Suchkova, and V. M. Berezovskii, Khim. Geterotsikl. Soedin., No. 5, 616 (1980).
5. S. D. Mikhno, T. M. Filippova, N. S. Kulachkina, I. G. Suchkova, and V. M. Berezovskii, Khim. Geterotsikl. Soedin., No. 4, 459 (1976).
6. S. D. Mikhno, T. M. Filippova, N. S. Kulachkina, I. G. Suchkova, and V. M. Berezovskii, Zh. Org. Khim., 14, 1706 (1978).
7. S. D. Mikhno, N. S. Kulachkina, T. M. Filippova, I. G. Suchkova, and V. M. Berezovskii, Khim. Prir. Soedin., No. 2, 220 (1981).
8. S. D. Mikhno, T. M. Filippova, N. S. Kulachkina, T. N. Polyanskaya, V. V. Mishchenko, I. N. Shmyrev, I. M. Kustanovich, and V. M. Berezovskii, Khim. Geterotsikl. Soedin., No. 6, 760 (1972).
9. T. M. Filippova, B. D. Lavrukhin, and I. K. Shmyrev, Org. Magn. Reson., 6, 92 (1974).
10. E. Breitmaier and W. Voelter, ^{13}C NMR Spectroscopy, Verlag Chemie, Weinheim (1974).
11. G. C. Levy and G. L. Nelson, Carbon-13 Nuclear Magnetic Resonance for Organic Chemists, New York (1972).
12. M. Christl, H. J. Reich, and J. D. Roberts, J. Am. Chem. Soc., 93, 3463 (1971).
13. J. B. Stothers and C. T. Tan, Can. J. Chem., 52, 308 (1974).
14. F. Franke and R. R. Wells, J. Org. Chem., 44, 4055 (1979).
15. S. D. Mikhno, T. M. Filippova, I. G. Suchkova, and V. M. Berezovskii, Khim. Geterotsikl. Soedin., No. 10 (1983, in press).
16. D. K. Dalling and D. M. Grant, J. Am. Chem. Soc., 94, 5318 (1972).