extracted twice with ether, and the ether layer was separated and dried. The solvent was removed by distillation to give 1.5 g (79%) of colorless crystals with mp 182°C (from ethanol). IR spectrum: 1715, 1690, 1610, 1580, 1530, and 1275 cm^{-1}. Found: C 64.6; H 6.3%. $C_{12}H_{14}O_4$. Calculated: C 64.8; H 6.4%. Starting salt IVa was regenerated in quantitative yield when a solution of VIII in glacial acetic acid was acidified with 70% $HClO_4$.

LITERATURE CITED

1. I. V. Shcherbakova, G. N. Dorofeenko, and E. V. Kuznetsov, Khim. Geterotsikl. Soedin., No. 3, 313 (1981).
2. G. N. Dorofeenko, E. I. Sadekova, and V. M. Goncharova, Khim. Geterotsikl. Soedin., No. 10, 1308 (1970).
3. M. Vaida and F. Ruff, Acta Chim. Hung., 40, 225 (1964).
4. J. Joule and H. Smith, Heterocyclic Chemistry, Van Nostrand Reinhold (1972).
5. G. N. Dorofeenko and G. P. Safaryan, Khim. Geterotsikl. Soedin., No. 2, 278 (1970).
6. G. N. Dorofeenko, G. P. Safaryan, and E. V. Kuznetsov, Khim. Geterotsikl. Soedin., No. 8, 1013 (1970).
7. A. T. Balaban and C. D. Nenitzescu, Liebigs Ann., 74, 625 (1959).
8. O. Diels and K. Alder, Berichte, 66, 625 (1927).
9. I. V. Shcherbakova, N. A. Potemkina, G. N. Dorofeenko, and E. V. Kuznetsov, Khim. Geterotsikl. Soedin., No. 7, 996 (1977).
10. E. V. Kuznetsov, I. V. Shcherbakova, and G. N. Dorofeenko, Khim. Geterotsikl. Soedin., No. 6, 745 (1976).
11. V. I. Dulenko and N. N. Alekseev, Dokl. Akad. Nauk SSSR, 206, 351 (1972).

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^{13}C NMR SPECTRA AND THREE-DIMENSIONAL STRUCTURES OF ISOMERIC 3,4-SUBSTITUTED THIOPHANS

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The chemical shifts and the direct carbon–proton spin–spin coupling constants for a number of cis and trans isomers of 4-amino-substituted 3-hydroxy(acyloxy)-thiophans, the configurations of the substituents in which and the conformational states were previously established by an independent method, were studied. It was found that in the spectra of the cis isomers the signals of the vicinal ^{13}C atoms, which bear the substituents, are shifted to strong field as compared with the trans isomers ($\Delta\delta^{\text{trans-cis}}$ 1.7-4.3 ppm). Conformational γ effects of the substituents on the chemical shifts of the ring ^{13}C atoms were noted. It is shown that a relationship exists between the direct carbon–proton spin–spin coupling constants and the spatial orientations of the acyloxy and acylamino substituents for five-membered saturated rings.

The problem of the study of the three-dimensional structures of five-membered saturated rings has not been dealt with as thoroughly as the analogous problem in the case of six-membered saturated rings. It is known that, in contrast to six-membered rings, characteristic ranges of cis- and trans-vicinal proton–proton spin–spin coupling constants do not exist for five-membered rings. In a number of cases an examination of the vicinal proton–proton constants for all possible conformations of the five-membered ring within the framework of the angular dependence of these constants is useful in the study of the configuration of five-membered rings [1]. A method for the determination of the orientation of the substituents in five-membered saturated rings by means of temperature dependences

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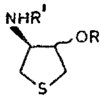
of the vicinal constants has been proposed [2]. However, these approaches are not applicable for the study of the orientation of the substituents attached to quaternary carbon atoms (there are no vicinal protons) or for the study of compounds with coincident or similar chemical shifts of the vicinal protons. The application of ^{13}C NMR spectroscopy has created new possibilities for the study of the stereochemistry of saturated five-membered rings. In particular, it has become traditional to use the γ-steric effects on the ^{13}C chemical shifts of the substituents to determine the relative orientation of the substituents [3-5]. The literature also contains examples of configuration determinations by means of the β-cis effects that give rise to changes in the chemical shifts of the ring ^{13}C atoms for a specific class of compounds, viz., furanosides [6-9]. The literature contains less data relative to the study of the conformations of saturated five-membered rings from the ^{13}C spectra [3, 4, 10].

The aim of the present research was to ascertain the possibilities of the determination of the three-dimensional structures of 3,4-disubstituted thiophans by means of ^{13}C NMR spectroscopy in the case of compounds with a known configuration and a known conformational state.

We studied the ^{13}C spectra of a number of isomers of 4-amino-substituted 3-hydroxy-(acyloxy)thiophans (Ia, b-VIIIa, b). The configuration of the investigated compounds and their conformational state were determined previously by ^{1}H NMR spectroscopy with the aid of the vicinal spin–spin coupling constants and their temperature dependences [2, 11-17]. In view of the closeness of the chemical shifts of the geminal 5-H protons, we were able to determine the orientation of the substituents in VIIIa, b only after their conversion to VIa, b. The chemical shifts and direct carbon–proton spin–spin coupling constants found are presented in Table 1.



Ia,b–VIIIa, b

a, b — cis and trans isomers
I R=H, $R'=COC_6H_5$; II $R=COCH_3$, $R'=COC_6H_5$; III $R=R'=COC_6H_5$; IV R=H, $R'=COOCH_3$;
V $R=COCH_3$, $R'=COOCH_3$; VI R=H, $R'=CONH_2$; VII $R=COCH_3$, $R'=CONH_2$; VIII R=H, $R'=H \cdot HCl$

We chose between the signals of the secondary, tertiary, and quaternary ^{13}C atoms on the basis of a comparison of the ^{13}C spectra obtained with complete suppression of the spin–spin coupling with the protons with the spectra without decoupling but with the Overhauser nuclear effect (gate decoupling). In the spectrum of each compound, of the two signals due to C_3 and C_4 (δ 71.4-78.8 and 56.0-61.3 ppm), we assigned the weakest-field signal to C_3, since the OH (OR) group shifts the α-C signal to weak field to a greater extent than the NHR group [18, pp. 141 and 166]. For the assignment of the signals to C_2 and C_5, we compared the chemical shifts of these nuclei within the series of investigated compounds; for this we used the fact that acylation of the hydroxy group attached to C_3 is accompanied by a characteristic high-field shift of the signal of the β-carbon atom (C_2) [18, p. 142]. Thus for each of the isomers on passing from I to II and III, from IV to V, and from VI to VII, the position of one of the high-field signals (C_5) remains almost unchanged (δ^{cis} 31.4-32.4 and δ^{trans} 32.7-33.5 ppm; $\Delta\delta_{acyl} \geqslant 0.2$ ppm, Table 1), whereas the other signal is shifted appreciably to strong field ($\Delta\delta^{cis}$ 2.9-3.1, $\Delta\delta^{trans}$ 1.9-2.9 ppm, Table 1), and this makes it possible to assign it to C_2 (see Table 1). In analogy with the remaining compounds, in the case of VIIIa, b we assigned the weaker-field signal of the examined two signals to C_2 (see Table 1).

In addition to the chemical shifts, the changes in them due to the change in the orientation of the substituents are presented in Table 1. It can be seen that in the spectra of the sterically more hindered cis isomers the C_3 and C_4 signals are shifted to stronger field as compared with the trans isomers: $\Delta\delta^{trans-cis}$ 3.2-4.3 ppm for C_3, and $\Delta\delta^{trans-cis}$ 1.7-2.5 ppm for C_4. Similar configurational shifts (the β-cis effect) were observed for C_2 ($\Delta\delta^{trans-cis}$ 4.0-5.0 ppm) and C_3 ($\Delta\delta^{trans-cis}$ 2.0-3.5 ppm) in furanosides [3-5]. Thus a simple comparison of the chemical shifts of the carbon atoms in disubstituted thiophans makes it possible to determine the mutual orientation of the vicinal substituents in the investigated compounds, including those for which a direct study of the configuration by ^{1}H NMR spectroscopy was impossible (VIIIa, b).

TABLE 1. ^{13}C Chemical Shifts and Direct Carbon–Proton Spin–Spin Couplings Constants ($^1J_{^{13}C,H}$) of 3,4-Substituted Thiophans

Compound	Solvent	Concn., mole/liter	Isomer	δ, ppm (^1J, Hz)				Δδ trans-cis, ppm				Δ^1j trans-cis, Hz	
				C_3 (C_3H)	C_4 (C_4H)	C_2 (C_2H)	C_5 (C_5H)	C_3	C_4	C_5	C_2	C_3H	C_4H
I	C_5D_5N	1,00	cis (a) trans (b)	72,4 (148) 76,3 (148)	57,5 (140) 60,0 (144)	36,5 (142) 35,8 (141)	31,6 (140) 32,8 (141)	3,9	2,5	1,2	−0,7	0	4
II	C_5D_5N	0,59	cis (a) trans (b)	75,0 (156) 77,8 (152)	55,6 (140) 57,5 (145)	33,4 (144) 32,9 (144)	31,5 (144) 32,7 (144)	2,8	1,9	1,2	−0,5	−4	5
III*	C_5D_5N	0,30	cis (a) trans (b)	75,6 (157) 78,6 (154)	56,2 (140) 57,7 (144)	33,6 (143) 33,0 (143)	31,4 (143) 32,8 (143)	3,0	1,5	1,4	−0,6	−3	4
IV	C_5D_5N	0,80	cis (a) trans (b)	72,9 (148) 77,0 (148)	59,4 (140) 61,3 (145)	36,4 (143) 36,0 (142)	31,8 (143) 33,4 (142)	4,1	1,9	1,6	−0,4	0	5
V	C_5D_5N	0,70	cis (a) trans (b)	75,5 (156) 78,8 (152)	57,3 (141) 59,1 (144)	33,4 (142) 33,8 (142)	31,9 (142) 33,4 (142)	3,3	1,8	1,5	−0,4	4	3
VI	C_5D_5N	0,15	cis (a) trans (b)	73,0 77,3	58,1 60,3	36,3 36,2	32,4 34,1	4,3	2,2	1,7	−0,1		
	CD_3COOD	0,48	cis (a) trans (b)	74,1 (153) 77,3 (151)	57,7 (141) 59,7 (144)	35,3 (144) 34,9 (144)	31,6 (144) 33,0 (144)	3,2	2,0	1,4	−0,4	−2	3
VII*	C_5D_5N	0,23	cis(a) trans (b)	76,2 (157) 79,5 (155)	56,2 (140) 57,9 (144)	33,3 (143) 34,3 (144)	32,4 (143) 33,5 (143)	3,3	1,7	1,1	1,0	−2	4
VIII	C_5D_5N	0,38	cis (a) trans (b)	71,9 75,3	57,0 59,4	36,0 34,7	31,0 30,7	3,4	2,4	−0,2	−1,2		
	$(CD_3)_2SO$	0,70	cis (a) trans (b)	71,4 (149) 74,8 (146)	56,0 (147) 58,4 (147)	35,3† 34,1 (143)	29,8 (144) 29,9 (144)	3,4	2,4	−0,1	−1,2	−3	0

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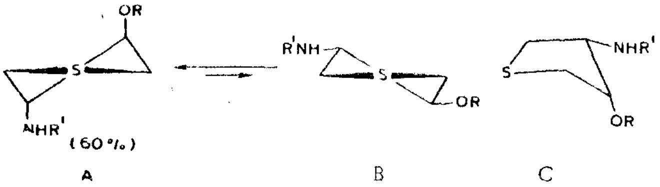
*The spectra were obtained with a Bruker WH-360 spectrometer (Federal Republic of Germany) with a ^{13}C nuclei operating frequency of 90 MHz.

†We were unable to determine the $^1J_{C_2H}$ value of overlapping of the C_2 signal by the signal of the solvent.

We have previously investigated the conformational state of 3,4-disubstituted thiophans by an independent method [11, 17]; we found that the A $\rightleftharpoons$ B conformational equilibrium with slight preference of the A conformation (3:2) is characteristic for trans-3,4-disubstituted thiophans. The cis isomers of 3,4-disubstituted thiophans have primarily the C conformation (90%).



In the present research we attempted to establish whether there is a relationship between the conformational state of the investigated molecules and the chemical shifts of the ring ^{13}C atoms, as well as the $^{1}J_{^{13}C,H}$ values.

The γ steric effect of an axial substituent on the chemical shifts of ring ^{13}C atom is widely used in the determination of the conformations of six-membered rings [19]. By analogy, for the investigated compounds, because of the preferableness of a pseudoaxial orientation of the substituent attached to C$_3$ in the cis isomers, one may expect a positive γ effect on the C$_5$ chemical shift in the case of a trans-cis configuration change. It is apparent from Table 1 that this sort of effect is observed for all of the compounds ($\Delta\delta^{trans-cis}$ 1.1-1.6 ppm) except the isomers of VIII ($\Delta\delta^{trans-cis}$ $\sim$0 ppm). Since the contribution of a pseudoaxial orientation of the substituent attached to C$_4$ in the trans isomers is somewhat greater than in the cis isomers, a negative γ effect on the C$_2$ chemical shift is possible in the case of a trans-cis change in the orientation of the substituents. In fact, a small negative effect ($\Delta\delta^{trans-cis}$ from -0.1 to -1.2 ppm) is observed for most of the investigated compounds; however, the effect is positive ($\sim$1.0 ppm) for VI. The observed conformational γ effects are much smaller than for six-membered rings (5-6 ppm); this is in agreement with the available literature data for cyclopentane derivatives [3, 4, 10] and is probably associated with smaller steric interactions in five-membered rings as compared with six-membered rings. Thus a small shift to strong field of the signal of the ring γ-carbon atom generally corresponds to a preferred axial orientation of the substituent for the investigated compounds; however, as in the case of other investigated five-membered rings, the γ-steric effects on the ring carbon atoms are small and variable.

In an analysis of the direct carbon-proton spin-spin coupling constants ($^{1}J_{^{13}C,H}$, Table 1) it was found that there is a correlation between these constants and the spatial orientation of the corresponding C-H bond if C is a carbon atom that bears an electronegative substituent that contains a carbonyl group. In the preferred A conformation of the trans isomers of I-VII (with an acylamino substituent attached to C$_4$) the C$_4$-H bond is pseudoequatorially oriented, whereas it is pseudoaxially oriented in the preferred C conformation of the cis isomers. It is apparent from Table 1 that the $^{1}J_{C_4,H}$ values for the trans isomers of these compounds are greater than for the cis isomers: $\Delta^{1}J^{trans-cis}_{C_4,H}$ is 3-5 Hz. The pattern is reversed for the orientation of the C$_3$-H bond in the preferred conformations of the cis and trans isomers: A pseudoaxial orientation of this bond is preferred for the trans isomers, while a pseudoequatorial orientation is preferred for the trans isomers, while a pseudoequatorial orientation is preferred for the cis isomers. Correspondingly, for compounds with a carboalkoxy substituent attached to C$_3$ (II, III, V, and VII) the $^{1}J_{C_3H}$ values for the trans isomers are 2-4 Hz smaller than for the cis isomers (the sign of $\Delta^{1}J^{trans-cis}_{C_3H}$ is the opposite of the sign of $\Delta^{1}J^{trans-cis}_{C_4,H}$; see Table 1). The effect is variable for compounds with a hydroxy substituent attached to C$_3$ (I, IV, VI, and VIII): $^{1}J^{trans-cis}_{C_3H}$ from 0 to -3 Hz.

Similar effects were previously noted for six-membered sugars [20, 21]. In the case of an axial orientation of the C-H bond, if C is a carbon atom attached to the oxygen atom of the pyranose ring, the corresponding $^{1}J_{CH}$ value proved to be smaller than in the case of an equatorial orientation [20, 21]. As in the case of conformational effects on the ^{13}C chemical shifts, the conformational effect on the $^{1}J_{CH}$ values for the investigated five-membered rings (2-5 Hz) is smaller than for six-membered rings (10 Hz). This may be associated with the fact that the conformational equilibrium is not completely shifted to favor the preferred conformation for the examined compounds. If it is assumed that the magnitude of the pure effect of a change in the C—H bond from pseudoequatorial to pseudoaxial coincides with that observed for six-membered rings (10 Hz), one may calculate the $\Delta^1J_{CH}^{trans-cis}$ value for IIa, b, the conformational state of which was previously determined quantitatively [11]. At the experimental temperature (∿50°C) the calculated $\Delta^1J_{CH}^{trans-cis}$ value is 4 Hz, i.e., it is close to the experimentally observed values (4 and 5 Hz). Thus the noted effect can be explained by starting from the change in the orientation of the C—H bond (and, correspondingly, from the orientation of the substituent) with respect to the five-membered ring. In addition, as we noted above, the magnitude of the observed effect clearly differs for different substituents (see Table 1), and the nature of this effect therefore cannot be regarded as definitively ascertained.

EXPERIMENTAL

The ^{13}C spectra were obtained with Bruker WP-80 and WH-360 spectrometers (Federal Republic of Germany) with carbon nuclei operating frequencies of 20.1 and 90.5 MHz, respectively. Tetramethylsilane was used as the internal standard in the measurement of the chemical shifts. The chemical shifts were measured with an accuracy of 0.1 ppm, and the spin—spin coupling constants were measured with an accuracy of 0.5 Hz. Deuteropyridine, deuteroacetic acid, and deuterodimethyl sulfoxide were used as the solvents. The use of such solvents as $(CD_3)_2SO$ and CD_3COOD in addition to deuteropyridine was due to the fact that not all of the investigated compounds were soluble in C_5D_5N in sufficiently high concentrations for the determination of the $^1J_{^{13}CH}$ values. The isomers of each of the compounds were investigated under identical conditions: in the same solvent at the same concentration at ∿50°C. The temperature was measured with a thermometer placed in the ampul for holding the samples in the NMR spectrometer.

LITERATURE CITED

1. R. J. Abraham and W. A. Tomas, J. Chem. Soc., 3739 (1964).
2. T. M. Filippova, B. D. Lavrukhin, and I. K. Shmyrev, Org. Magn. Reson., 6, 92 (1974).
3. M. Christl, H. J. Reich, and J. D. Roberts, J. Am. Chem. Soc., 93, 3463 (1971).
4. J. B. Stothers and C. T. Tan, Can. J. Chem., 52, 308 (1974).
5. F. Franke and R. R. Wells, J. Org. Chem., 44, 4055 (1979).
6. T. Usui, S. Tsushima, N. Jamaoka, K. Matsuda, K. Tuzimura, H. Sugiyama, S. Seto, K. Fujieda, and G. Miyajima, Agr. Biol. Chem., 38, 1409 (1974).
7. N. Yamaoka, Y. Usui, H. Sugiyama, and S. Seto, Chem. Pharm. Bull., 22, 2196 (1974).
8. A. S. Perlin, N. Cyr, H. J. Koch, and B. Korch, Ann. N. Y. Acad. Sci., 222, 935 (1973).
9. D. M. Vyas, H. C. Jarrel, and W. A. Szares, Can. J. Chem., 53, 2748 (1975).
10. N. K. Wilson and J. B. Stothers, in: Topics in Stereochemistry, (E. Eliel and N. L. Allinger, eds.), New York—London (1974), p. 26.
11. B. D. Lavrukhin, T. M. Filippova, and E. T. Fedin, Org. Magn. Reson., 6, 368 (1974).
12. T. M. Filippova, S. D. Mikhno, N. S. Kulachkina, I. M. Kustanovich, and V. M. Berezovskii, Khim. Geterotsikl. Soedin., No. 3, 316 (1971).
13. 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).
14. S. D. Mikhno, T. M. Filippova, I. G. Razumova, N. S. Kulachkina, I. K. Shmyrev, and V. M. Berezovskii, Khim. Geterotsikl. Soedin., No. 7, 913 (1974).
15. S. D. Mikhno, T. M. Filippova, N. S. Kulachkina, I. G. Razumova, V. A. Zamurenko, and V. M. Berezovskii, Khim. Geterotsikl. Soedin., No. 2, 183 (1975).
16. S. D. Mikhno, T. M. Filippova, N. S. Kulachkina, I. G. Razumova, and V. M. Berezovskii, Khim. Geterotsikl. Soedin., No. 3, 334 (1975).
17. T. M. Filippova, Master's Dissertation, Moscow (1972).
18. E. Breitmaier and W. Voelter, ^{13}C NMR Spectroscopy, Verlag Chemie, Weinheim (1974), p. 141.
19. D. M. Grant and B. V. Cheney, J. Am. Chem. Soc., 89, 5315 (1967).
20. K. Bock and C. Pedersen, J. Chem. Soc., Perkin Trans II, No. 3, 293 (1974).
21. K. Bock and C. Pedersen, Acta Chem. Scand., 29, 258 (1975).