^{1}H AND ^{13}C NMR SPECTRA OF 2-SUBSTITUTED 5-NITROFURANS AND CONFORMATION OF CHEMOTHERAPEUTIC PREPARATIONS OF THE 5-NITROFURAN SERIES

Yu. Yu. Popelis, É. É. Liepin'sh,
and Ya. P. Stradyn'

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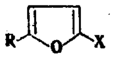
The ^{1}H and ^{13}NMR spectra of t-nitrofuran and 17 2-substituted 5-nitrofurans were investigated. The Δ^1H and Δ^{13}C substituent increments [$\Delta = \delta$(2-X-5-nitrofuran) – δ(5-nitrofuran)] in the spectra of these compounds were analyzed by comparison with the analogous 5-methylfuran and furan derivatives, and the change in the sensitivity of the chemical shifts of the ring protons and the carbon atoms to the effects of substituents X as a function of the electronic character of substituent R was also analyzed. The chemical shifts and the spin–spin coupling constants were used to determine the preferred orientation of the substituents relative to the furan ring. It was found that medicinal preparations of the 5-nitrofuran series (5-nitrofurfurylidenehydrazones) exist in the form of s-trans conformers in solutions in dimethyl sulfoxide and water, whereas furagin has primarily the structure of the E s-trans form.

The peculiarity of the structure of the furan ring has frequently been characterized by data on reactivities [1, 2] and quantum-chemical calculations [3]. It has been found that ^{1}H and ^{13}C NMR spectroscopy are extremely useful [4] for the study of problems of this sort (for example, to estimate the degree of transmission of the electronic effects of substituents through the furan ring). However, virtually no data are available regarding the characteristics of the NMR spectra for 5-nitrofuran derivatives I, the individual representatives of which, among other things, are of exceptional interest as active preparations that are widely used in medicine, veterinary science, and animal husbandry (furacillin, furadonine, furazolidone, furagin, solafur, etc.) [5].

We made a systematic study of the ^{1}H and ^{13}C NMR spectra to arrive at a reliable and complete interpretation of the NMR spectra of 5-nitrofuran derivatives (the I series) and to obtain structural-spectral correlations for these compounds. The parameters obtained are compared with the parameters of the II and III series to find the increments of the substituents and to estimate the role of the nitro group in the change in the principles of the transmission of electronic effects.



I–III

I R=NO_2; II R=CH_3; III R=H

The study made it possible to ascertain the configurations of the most important medicinal preparations of the 5-nitrofuran series, which constitute an important characteristic in the elucidation of the mechanism of their biological action.

Assignment of the Signals and Increments of the Substituents (X)

No difficulties in the assignment of the ^{1}H NMR signals (Table 1) for the H_3 and H_4 protons of the furan ring were encountered in any cases in which the substituent in the α position of the ring was a CH_α=, CH_3, or CF_3 group. Long-range spin–spin coupling (SSC) of the ring proton with the H_α protons or the three protons (^{19}F nuclei) of the $CH_3(CF_3)$ substituent in the form of splitting of H_3 and H_4, or at least in the form of broadening of the

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Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
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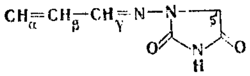
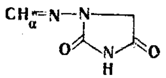
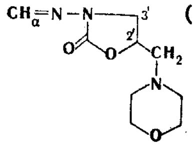
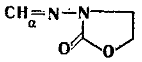
TABLE 1. Parameters of the ^{1}H Spectra of 2-Substituted 5-Nitrofurans

Compound No.	Substituent X[a]	δ, ppm			J, Hz	
		H_3	H_4	H_x	3–4	remaining H
1	NO_2	8,00 7,45[b]	8,00 7,45	— —	— —	— —
2	C≡N	7,89	7,98	—	4,0	—
3	$CH_\alpha O$	7,82	7,86	9,88 (H_α)	3,9	—
4	$COCH_3$	7,71	7,82	2,63 (CH_3)	4,0	—
5	CF_3	7,68	7,90	—	3,8	0,8 (H_3—F), 1,0 (H_4—F)
6	$COOCH_3$	7,61	7,81	3,96 (CH_3)	3,9	—
7	COOH	7,50	7,76	—	3,9	—
8	$CONH_2$	7,49	7,79	8,3, 7,9 (NH_2)	4,0	—
9	I	7,16	7,59	—	3,9	—
10	H	6,94	7,71	8,13 (H_5)	3,8	1,9 (H_2—H_3), 1,0 (H_2—H_4)
11	CH_3	6,60	7,62	2,49 (CH_3)	3,7	1,0 (H_3—CH_3), 0,6 (H_4—CH_3)
12	$CH_\alpha{=}CH_\beta{-}CH_\gamma O$	7,47	7,81	7,71 (H_α), 6,81 (H_β), 9,76 (H_γ)	3,9	0,2 (H_3—H_α), 0,3 (H_3—H_β), 7,4 (H_β—H_γ), 16,0 (H_α—H_β)
13	$CH_\alpha{=}CH_\beta{-}COOH$	7,30	7,77	7,50 (H_α), 6,56 (H_β)	3,9	0,2 (H_3—H_α), 16,0 (H_α—H_β)
14	$CH_\alpha{=}CH_\beta{-}CONH_2$	7,18	7,77	7,40 (H_α), 6,85 (H_β), 7,7, 7,4 (NH_2)	3,9	15,9 (H_α—H_β)
15	 **(furagin)**	7,03 6,89[c]	7,73 7,62	7,12 (H_β), 3,69 ($H_{5'}$), 6,74 (H_α), 7,34 (H_γ) 6,85 (H_α), 7,20 (H_β), 7,54 (H_γ), 2,96 ($H_{5'}$)	3,9 4,0	14,9 (H_α—H_β), 8,5 (H_β—H_γ) 15,0 (H_α—H_β), 8,5 (H_β—H_γ)
16	$CH_\alpha{=}NOH$ (*Z*)	7,47	7,79	7,80 (H_α)	3,9	0,4 (H_3—H_α), 0,8 (H_4—H_α)
17	$CH_\alpha{=}NOH$ (*E*)	7,11	7,78	8,24 (H_α)	3,9	0,2 (H_3—H_α)
18	$CH_\alpha{=}NNHCONH_2$ **(furacillin)**	7,26 7,00[c]	7,79 7,59	7,88 (H_α) 7,86 (H_α)	4,0 3,8	— —
19	 **(furadonine)**	7,16 7,13[c]	7,79 7,63	7,81 (H_α), 4,39 (CH_2), 11,6 (NH)	4,0 4,0	— —
20	 **(furazoline)**	7,17 7,14[c]	7,82 7,46	7,86 (H_α), 4,97 ($H_{2'}$), 4,07, 3,68 ($H_{3'}$), 2,70 (CH_2N), 2,51, 3,11 morpholine ring) 7,78 (H_α), 5,26 ($H_{2'}$), 4,23 ($H_{3'}$), 3,6—4,0 ($H_{3'}$) 3,78, 3,12 (morpholine ring)	3,9 3,9	— —
21	 **(furazolidone)**	7,20	7,82	7,86 (H_α), 4,58 (CH_2O), 3,95 (NCH_2)	3,9	—

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[a] The trivial names of the medicinal preparations used in the USSR are given in parentheses for compounds Nos. 15 and 18-21 (see also [5], pp. 2-5). [b] In $CDCl_3$. [c] In D_2O.

TABLE 2. Parameters of the ^{13}C NMR Spectra of 2-Substituted 5-Nitrofurans

Compound No.[a]	δ, ppm					J, Hz					
	C_2	C_3	C_4	C_5	C_X	C_3—H_3	C_4—H_4	C_X—H_X	C_3—H_4	C_4—H_3	Remaining C atoms
1	150,0	115,0	115,0	150,0	—	193,4	193,4	—	2,9	2,9	
2	126,7	126,5	113,2	153,4	110,7 ($C\equiv N$)	189,7	191,9	—	2,9	3,7	10,2 (C_2—H_3), 8,8 (C_2—H_4)
3	151,3[b]	120,4	112,4	153,6	178,6 (C_α)	183,8	189,0	186,8	1,5	2,9	32,2 (C_2—COH), 8,8 (C_2—H_3, C_2—H_4)
	151,5	123,0	113,7	153,7	180,5 (C_α)	185,6	189,7	189,7	2,2	3,7	33,7 (C_2—COH), 8,8 (C_2—H_3, C_2—H_4)
	151,8[c]	122,3	113,2	153,8	179,9 (C_α)						
4	151,6	120,0	114,8	152,9	187,1 (C=O), 27,2 (CH_3)	184,6	189,7	128,9	2,9	3,7	5,9 (CO—CH_3), 8,0 (C_2—H_3, C_2—H_4)
5	142,1	116,4	112,7	158,2	118,6 (CF_3)						268,1 (C—F), 44,2 (C_2—F), 2,8 (C_3—F)
6	144,9	120,5	113,7	153,4	157,9 (C=O), 53,7 (CH_3)	185,3	189,0	148,7	2,9	3,7	4,7 (COO—CH_3), 8,8 (C_2—H_3), 8,0 (C_2—H_4)
7	146,5	119,7	113,6	152,8	158,7 (C=O)	185,3	188,2	—	2,2	3,7	8,0 (C_2—H_3, C_2—H_4)
8	149,3	116,6	114,0	152,2	158,5 (C=O)	183,8	188,2	—	2,9	3,7	—
9	102,2	125,1	115,3	156,4	—	186,8	187,5	—	2,8	3,7	8,8 (C_2—H_3, C_2—H_4)
10	145,4[b]	111,3	113,8	153,5	—						
	147,2	113,5	114,8	152,7	—						
11	158,3	111,6	115,2	151,7	14,7 (CH_3)	179,4	189,7	129,6	3,7	3,0	3,7 (C_3—CH_3)
12	153,1	118,7	115,2	153,0	193,8 (C=O), 131,2 (C_α), 136,6 (C_β)						
13	153,3	117,3	115,1	152,6	166,9 (C=O), 129,6 (C_α), 123,9 (C_β)						
14	154,2	116,5	115,3	152,4	166,1 (C=O), 127,1 (C_α), 125,8 (C_β)						
15	153,9	116,0	114,0	152,0	169,3 ($C_{1'}$), 155,5 ($C_{2'}$), 143,9 (C_γ), 131,2 (C_α), 123,9 (C_β), 50,0 ($C_{5'}$)						
16	147,3	119,4	114,8	152,4	134,9 (C_α)						
17	151,4	115,0	114,2	152,4	138,9 (C_α)						
18	153,8	115,9	113,1	152,0	156,7 (C=O), 128,5 (C_α)						
19	153,9	115,3	115,2	152,6	169,1 ($C_{4'}$), 152,7 ($C_{2'}$), 132,0 (C_α), 50,1 ($C_{5'}$						
20	153,5	115,3	115,3	152,6	152,6 ($C_{2'}$), 132,7 (C_α), 67,2, 54,8 (morpholine ring), 46,9 (CH_2N), 61,7 ($C_{5'}$), 72,5 ($C_{4'}$)						
21	154,0	115,3	115,3	152,7	152,7 ($C_{2'}$), 132,1 (C_α), 62,8 ($C_{5'}$), 43,4 ($C_{4'}$)						

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[a] The numbers of the compounds and the designation of the atoms in the molecules correspond to the numbering and designation in Table 1. [b] In $CDCl_3$. [c] In d_7-DMF.

TABLE 3. Increments of the Substituents in 2-Substituted 5-Nitrofurans, 2-Substituted 5-Methylfurans, and α-Substituted Furans

Substituent X	ΔH_3, ppm			ΔH_4, ppm			ΔC_2, ppm		ΔC_3, ppm		ΔC_4, ppm		ΔC_5, ppm	
	I	II	III	I	II	III	I	III	I	III	I	III	I	III
NO_2	1,06	1,05	1,25	0,29	0,37	0,48	2,8	10,1	1,5	4,1	0,2	2,2	−2,7	3,3
COCl	—	1,23	1,15	—	0,42	0,32	—	—	—	—	—	—	—	—
$C\equiv N$	0,95	0,87	0,99	0,27	0,31	0,32	−20,5	−16,7	13,0	13,0	−1,6	2,2	0,7	5,8
CHO	0,88	1,04	1,09	0,15	0,38	0,37	4,3	10,1	9,5	11,9	−1,1	2,9	1,0	5,4
$COCH_3$	0,77	0,83	0,96	0,11	0,24	0,29	4,4	9,6	6,5	7,1	0,0	2,1	0,2	3,3
CF_3	0,74	—	—	0,19	—	—	5,1	—	2,9	—	−2,1	—	0,5	—
$COOCH_3$	0,67	0,84	0,87	0,10	0,19	0,25	−2,3	2,1	7,0	8,3	−1,1	2,5	0,7	4,2
COOH	0,56	1,00	0,87	0,05	0,22	0,23	−0,7	2,3	6,2	8,7	−1,2	2,5	0,1	4,3
I	0,22	—	0,19	−0,12	—	−0,04	−45,0	−55,1	11,6	10,4	0,5	3,0	3,7	5,1
H	0,00	0,00	0,00	0,00	0,00	0,00	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0.0
CH_3	−0,34	−0,49	−0,43	−0,09	−0,20	−0,14	11,1	9,1	−1,9	−4,1	0,4	0,7	−1,0	−1,9

H_3 signal, is observed in the spectra. If X = CHO, $COCH_3$, COOH, C≡N, $CONH_2$, I, and $COOCH_3$ the weak-field signal is always assigned to H_4 absorption, since according to the increments of these substituents in mono-X-substituted benzenes [6] and 2-X-substituted furans III [7], the nitro group induces the greatest deshielding of the proton in the ortho position, whereas X substituents in the meta position relative to H_4 deshield this proton additionally.

The assignment of the ^{13}C NMR signals (Table 2) was made from the spectra without proton decoupling. The signals of the C_2 and C_5 atoms, which do not display $^1J_{C-H}$ splitting, were isolated initially. There is, however, no difficulty in choosing between the C_2 and C_5 signals, since the nitro group markedly increases the spin-lattice relaxation time (T_1) of the C_5 atom, as a consequence of which its signal is considerably broader. The assignment of the C_3 and C_4 signals was based on a comparison of the long-range ^{13}C—^1H spin–spin coupling constants (SSCC) ($^3J_{C_4-H_3} > {}^3J_{C_3-H_4}$) for all of the X substituents except CH_3 [7]. The reverse order of these SSCC is characteristic for 2-methylfuran and 2-methyl-5-nitrofuran. We obtained an unambiguous assignment for the latter through the long-range spin–spin coupling of C_3 with the three protons of the methyl group.

In the analysis of the proton and carbon increments of the substituents we started from the prerequisite that the effects of substituents on the shielding of the protons or carbon atoms are additive to a greater [8-10] or lesser [11, 12] degree, while the increments of the nitro group are constant within the limits of the I series and are equal to the increment in the 2-nitrofuran molecule. The $\Delta\delta(^1H)$ and $\Delta\delta(^{13}C)$ increments of substituents X in three series of α,α'-disubstituted furans calculated with the aid of the chemical shifts of the protons and carbon atoms of I (Tables 1 and 2), II (from the data in [8]), and III (from the data in [7]) are presented in Table 3. The increments were calculated from the formulas

$$\Delta\delta_X{}^i = \delta^i(\text{I or II}) - \delta^i(\text{III})$$
$$(\text{for 2-X-5-R- furans}),$$

$$\Delta\delta_X{}^i = \delta^i(\text{III}) - \delta^i(\text{furan})$$
$$(\text{for 2-X- furans}),$$

where Δδ is the difference in the chemical shifts of the protons (ΔH) or carbon atoms (ΔC), and superscript i designates the position of the atom in the ring.

An analysis of the data in Table 3 shows that the additivity of the effect of substituents X in compounds of the I series is approximate and that the increments in the I, II, and III series differ from one another. At the same time, there is a satisfactory linear correlation:*

$$\begin{array}{lll}
\Delta H_3(\text{I}) = 0{,}020 + 0{,}820\Delta H_3(\text{III}) & r = 0{,}992 & s = 0{,}07 \\
\Delta H_3(\text{II}) = -0{,}026 + 0{,}978\Delta H_3(\text{III}) & r = 0{,}984 & s = 0{,}11 \\
\Delta H_4(\text{I}) = -0{,}038 + 0{,}625\Delta H_4(\text{III}) & r = 0{,}863 & s = 0{,}08 \\
\Delta H_4(\text{II}) = -0{,}018 + 1{,}006\Delta H_4(\text{III}) & r = 0{,}958 & s = 0{,}07 \\
\Delta C_2(\text{I}) = -1{,}983 + 0{,}815\Delta C_2(\text{III}) & r = 0{,}985 & s = 4{,}16 \\
\Delta C_3(\text{I}) = 0.910 + 0{,}868\Delta C_3(\text{III}) & r = 0{,}978 & s = 1{,}43
\end{array}$$

Linear correlations between the increments of the series are completely absent (the r values are 0.2-0.5) for the remaining increments, i.e., ΔC_4 and ΔC_5. Such a strange absence of a linear correlation and the sharp decrease in correlation coefficient r in the equation for ΔH_4(I) with respect to ΔH_4(II) suggests that the rotation of the nitro group about the C_5—N bond relative to the plane of the furan ring in compounds of the I type varies as a function of the nature of X. The complete absence of a linear correlation for compounds of the I series between ΔC_4 and ΔH_4 and the existence of such a correlation between ΔC_3 and ΔH_3 also constitute evidence in favor of this assumption.

One should immediately note the common (for all six correlation expressions) tendency for an increase in the slopes of the lines on passing from the I series to the II series. This means that the sensitivity of the chemical shifts of the ring protons to the effect of substituents X decreases in the order III $\approx$ II > I. This change in sensitivity is due to a

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*The X = COOH points are excluded from the correlation equations for I, since this group is virtually completely ionized in dimethyl sulfoxide. The II and III series were investigated in d_6-acetone and CCl_4, respectively.

sharp change in the electronic character of the substituent R in the 5 position: The electron-acceptor nitro group increases the susceptibility of the chemical shifts to the effect of substituent X appreciably.

LFE Correlation Equations

One- and two-parameter correlation changes in the chemical shifts of the protons and the carbon atoms with various reaction constants of the substituents, viz., σ^*, σ_I-σ_C, and F—R, were used for the quantitative estimate of the degree of transmission of the electronic effects of substituents X on the shielding of the various nuclei of the furan ring and to ascertain the effect of substituent R on this transmission. The most satisfactory linear dependences were obtained with the aid of the Swain—Lupton F and R constants of the C≡N, $COCH_3$, $COOCH_3$, H, and CH_3 substituents [13].

$$\begin{aligned}
\Delta H_3(I) &= 0{,}003+0{,}671F+2{,}102R & r&=0{,}999 & s&=0{,}01\\
\Delta H_4(I) &= -0{,}045+0{,}316F+0{,}050R & r&=0{,}959 & s&=0{,}05\\
\Delta C_3(I) &= -0{,}966+16{,}246F-2{,}926R & r&=0{,}991 & s&=1{,}11\\
\Delta C_4(I) &= 0{,}397-2{,}928F+3{,}173R & r&=0{,}882 & s&=0{,}57\\
\Delta C_5(I) &= -0.279+0{,}361F+3{,}414R & r&=0{,}896 & s&=0{,}44
\end{aligned}$$

Similar equations with the same set of substituents were also obtained for the II series (the chemical shifts from [8] were used for the construction of the correlations):

$$\begin{aligned}
\Delta H_3(II) &= 0{,}018+0{,}350F+3{,}377R & r&=0{,}989 & s&=0{,}13\\
\Delta H_4(II) &= -0{,}029+0{,}151F+1{,}043R & r&=0{,}994 & s&=0{,}03
\end{aligned}$$

We also recalculated the LFE equations published previously for III, since there was no "zero" point in the calculations in [7], i.e., the "changes" in the chemical shifts of furan itself were not taken into account (in addition, a more extensive set of X substituents was used):

$$\begin{aligned}
\Delta H_3(III) &= 0{,}047+0{,}470F+3{,}299R & r&=0{,}995 & s&=0{,}09\\
\Delta H_4(III) &= 0{,}005+0{,}170F+0{,}972R & r&=0{,}999 & s&=0{,}01\\
\Delta C_3(III) &= -1{,}152+13{,}863F+10{,}347R & r&=0{,}990 & s&=1{,}39\\
\Delta C_4(III) &= 0{,}539+2{,}636F-0{,}399R & r&=0{,}892 & s&=0.70\\
\Delta C_5(III) &= -0{,}436+6{,}062F+5{,}662R & r&=0.988 & s&=0{,}70
\end{aligned}$$

The results of an analysis of the transmission of the inductive and mesomeric effects of X substituents in the three series of furans are presented in Table 4. As explained [14], the transmission of the effect of substituents on the shielding of H_3 and H_4 in the I-III series is due primarily to transfer of the conjugation effect [$\rho_F/\rho_R < 1$ for all ΔH except ΔH_4 (I)]. In the case of 5-methylfuran derivatives (as compared with furan derivatives) the sensitivity of the chemical shifts to the inductive effects of the substituents is reduced somewhat; on the other hand, the conjugation effects in them are conducted better. However, the introduction of a strong acceptor such as the nitro group in the 5 position gives rise to withdrawal to it of the more mobile π electrons and thereby decreases the sensitivity of the resonance of H_3 and H_4 to conjugation effects.

We compared the sensitivity of the chemical shifts of the protons to the effects of substituents in nitrofuran derivatives I and in the corresponding substituted p-nitrobenzenes. For the latter we also calculated the LFE equations (the chemical shifts of the protons

TABLE 4. Sensitivity of the Chemical Shifts of the Ring Nuclei to the Transmission of the Inductive and Resonance Effects through the Furan Ring

Nucleus	ρ_F/ρ_R			$\frac{\rho_F\ (I)}{\rho_F\ (III)}$	$\frac{\rho_R\ (I)}{\rho_R\ (III)}$	$\frac{\rho_F\ (II)}{\rho_F\ (III)}$	$\frac{\rho_R\ (II)}{\rho_R\ (III)}$
	I	II	III				
H_3	0,32	0,10	0,14	1,43	0,64	0,74	1.02
H_4	6,32	0,14	0,17	1,86	0,05	0,45	1,74
C_3	−5,55	—	1,34	1,17	−0,28	—	—
C_4	−0,92	—	−6,61	−1,11	−7,95	—	—
C_5	0,11	—	1,07	0,06	0,60	—	—

published in [15] were used) with the set of substituents mentioned above:

$$\Delta H_{o\text{-}X} = 0.088 - 0.573F + 3.348R \qquad r = 0.973 \qquad s = 0.14$$

$$\Delta H_{o\text{-}NO_2} = -0{,}017 + 0{,}021F + 0{,}650R \qquad r = 0{,}991 \qquad s = 0{,}03$$

The changes in the sensitivity constants ρ_F and ρ_R on passing from the series of p-substituted nitrobenzenes to the series of 5-nitrofurans show that the chemical shifts of the protons in the latter are more sensitive to the inductive effects of the X substituents and less sensitive to their conjugation effects.

The effect of substituents on the resonance of the carbon nuclei of the furan ring differs qualitatively from the effect for protons: first, the ratio of the fractions of transfer of the inductive and mesomeric effects changes to favor an increase in the latter (the reverse tendency is observed for C_3); second, for C_3 the sensitivity to transfer of the inductive effect increases (maximally by a factor of 1.2), whereas the sensitivity to transfer of the conjugation effects decreases (maximally by a factor of four), as a result of which its resonance (like the resonance of the protons) in the I series is less sensitive to the electronic effect of the substituents. This is in agreement with the decrease in the coefficient of the linear term in the $\Delta C_3(I)$—$\Delta C_3(III)$ correlations.

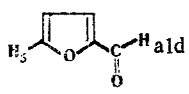
The ^{13}C—^1H SSCC (specifically, the $^1J_{C_3-H_3}$ constants) in the I series (as in the III series) correlate well with the F inductive constants:

$$^1J_{C_3-H_3} = -0.8 + 10.0F, \quad r = 0.980, \quad s = 0.8.$$

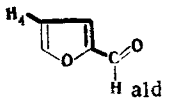
On the other hand, the $^1J_{C_4-H_4}$ constants do not display a satisfactory linear correlation with the X substituent constants.

Conformations of 2-Substituted 5-Nitrofurans

In several cases we measured the long-range interproton SSCC. Their values were used to determine the preferred conformations of the X substituents in the side chain. The ^5J SSCC in furfural is stereospecific: the aldehyde proton couples with H_5 in the s-trans (or O,O-cis) conformer, whereas coupling with H_4 is observed in the s-cis (or O,O-trans) conformer [16].



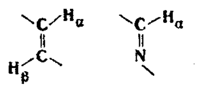
s-trans



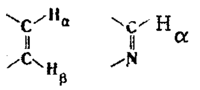
s-cis

Similar H_4—H_{ald} coupling is absent in the case of 5-nitro-2-furfural, and this compound consequently exists primarily in the s-trans form in solution in d_6-DMSO. This conclusion is in complete agreement with the measurements of the dipole moments [17] and with studies of the effects of the medium on the quantitative ratio of the two conformers in furfural [17, 18]; the fraction of the s-trans form increases as the polarity of the solvent increases.

Compounds with X substituents that contain a —CH_α=CH— or —CH_α=N— grouping can exist in two configurations

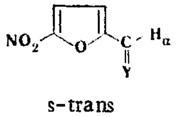


E

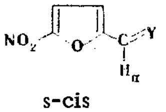


Z

and may also have a different conformation relative to the C_2—C_α single bond



s-trans



s-cis

Y = CH, N—N

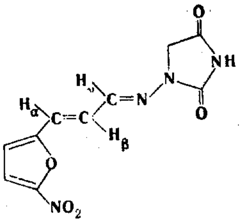
The investigated vinyl derivatives of 5-nitrofuran (Nos. 12-14) are E isomers, since the constants of spin—spin coupling between H_α and H_β range from 15.9 to 16.0 Hz (Table 1) and are typical for a trans orientation of the latter.

The configurations of both oximes (Nos. 16 and 17) were established by comparison of their C_2 and C_α chemical shifts. In the case of the Z isomer the resonance of these nuclei should be found at appreciably stronger field as compared with the resonance for E derivatives [19].

The E configuration of the hydrazones (Nos. 18-21) was established on the basis of the chemical shifts of the H_α, H_3, and C_3 nuclei for these compounds and the corresponding oximes. Compounds with a $-CH{=}Y$ group in the substituent do not display stereospecific $H-H_4$ spin–spin coupling (this constant is at least less than 0.2 Hz). This constitutes evidence for predominance of compounds Nos. 12-14 and 17-21 in the form of the s-trans conformers in solutions in d_6-DMSO.

A long-range $^5J_{H_\alpha-H_4}$ SSCC of 0.8 Hz is found in the ^1H NMR spectrum of the Z isomer of 5-nitrofurfural oxime (No. 16). The magnitude of this SSCC attests to predominance of the Z isomer in solutions in d_6-DMSO in contrast to the E isomer of the s-cis conformer.

Rotation about two single bonds, viz., C_2-C_α and $C_\beta-C_\gamma$, is possible in the furagin molecule and in its potassium salt (solafur) (No. 15) [20]. On the basis of the of the absence of an H_4-H_α SSCC we arrived at the conclusion that the conformational equilibrium in DMSO is shifted to favor the s-trans form. The magnitude of the vicinal constant of spin–spin coupling between H_β and H_γ (8.5 Hz, as compared with the ^3J values of 2 Hz for the s-cis and 8 Hz for the s-trans conformations in α,β-substituted aldehydes [21]) constitutes evidence for predominance of the same s-trans conformer relative to the $C_\beta-C_\gamma$ bond. According to the $^3J_{H_\alpha-H_\beta}$ value, furagin is the E isomer. Furagin also has an E configuration relative to the $C{=}N$ bond. The latter conclusion was drawn by comparison of the changes in the C_α, H_3, and H_α chemical shifts in pairs of compounds Nos. 3-17 with those for the "analogous" C_γ, H_α, and H_γ nuclei in pairs of compounds Nos. 12-15 (furagin).



We also investigated the ^1H NMR spectra of aqueous solutions of some derivatives of the medicinal preparations [furagin, furacillin, furadonine, and furazoline (Nos. 15 and 18-20)] that were water soluble. The signals of the H_4 and H_α protons did not display long-range spin–spin coupling, and this constitutes evidence for retention of the s-trans conformation on passing from DMSO to water. This result might have been expected from a comparison of the polarities of the two solvents (0.48 and 0.49, respectively). Thus, the problem of the conformations of all the widely used preparations of the 5-nitrofuran series has been solved.

EXPERIMENTAL

The ^1H NMR spectra of 7-10% solutions of the compounds in d_6-DMSO of saturated solutions in D_2O were obtained with a Perkin–Elmer R-12A spectrometer (60 MHz) at a sample temperature of 36.5°C. The ^{13}C NMR spectra of saturated solutions of the compounds in d_6-DMSO were obtained with a Bruker WH-90/DS spectrometer at a sample temperature of 35-40°C. The resonance at 22.63 MHz was excited with pulses of 5-μsec duration, which corresponded to 30° rotation of the magnetization vector. The decrease in the free-induction signal was recorded with an 8 kilobyte operative memory. After Fourier transformation, the spectra (at a scanning width of 6000 Hz) with noise decoupling of the protons and without it (at a scanning width of 1200 Hz) were recorded with a 4 kilobyte memory, and the accuracies in the measurement of the ^{13}C chemical shifts (± 0.1 ppm) and the $^{13}C-^1H$ SSCC (± 0.3 Hz) were thereby determined. Cyclohexane, the chemical shift of which relative to tetramethylsilane was δ 1.44 ppm for the protons and δ 27.44 ppm for the carbon nuclei, was used as the internal standard in both cases.

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LITERATURE CITED

1. G. Marino, Khim. Geterotsikl. Soedin., No. 5, 579 (1973).
2. A. I. Shatenshtein, A. G. Kamrad, I. O. Shapiro, and Yu. I. Ranneva, Khim. Geterotsikl. Soedin., No. 5, 643 (1966).
3. N. N. Zatsepina, I. F. Tupitsyn, Yu. L. Kaminskii, and N. S. Kolodina, Reakts. Sposobnost' Org. Soedin., 6, 766 (1966).
4. É. Ya. Lukevits (ed.) Advances in the Chemistry of Furans [in Russian], Zinatne, Riga (1978), p. 19.
5. V. Egerts, J. Stradins, and M. Shimanska, Analysis of 5-Nitrofuran Derivatives, Ann Arbor Science Publishers, Ann Arbor—London (1970), p. 143.
6. J. Beeby, S. Sternhell, T. Hoffmann-Ostenhof, E. Pretsch, and W. Simon, Anal. Chem., 45, 1571 (1973).
7. S. Gronowitz, I. Johnson, and A.-B. Hörnfeldt, Chem. Scripta, 7, 211 (1975).
8. J.-P. Morizur, Y. Pascal, and F. Vernier, Bull. Soc. Chim. Fr., No. 7, 2296 (1966).
9. R. Sornay, J.-M. Meunier, and P. Fournary, Bull. Soc. Chim. Fr., No. 3, 990 (1971).
10. J. Runsink, J. de Wit, and W. D. Weringa, Tetrahedron Lett., No. 1, 55 (1974).
11. M. T. W. Hearn, Austral, J. Chem., 29, 107 (1976).
12. A. Kiewiet, J. de Wit, and W. D. Weringa, Org. Magn. Reson., 6, 461 (1974).
13. A. Gordon and R. Ford, Chemist's Companion: A Handbook of Practical Data, Techniques, and References, Wiley (1973).
14. R. A. Gavar and Ya. P. Stradyn', Khim. Geterotsikl. Soedin., No. 1, 15 (1965).
15. P. W. Hickmott and O. Meth-Cohn, An Introduction to Spectroscopic Methods for the Identification of Organic Compounds, Vol. 1, Pergamon Press, New York (1970).
16. B. P. Roques and S. Combrisson, Can. J. Chem., 51, 573 (1973).
17. E. G. Derecha, Master's Dissertation Abstracts [in Russian], Rostov-on-Don (1973).
18. J. F. Bertrán and M. Rodriguez, Org. Magn. Reson., 6, 525 (1974).
19. G. C. Levy and G. L. Nelson, Manual of Carbon-13 Nuclear Magnetic Resonance for Organic Chemists, New York (1972).
20. S. A. Giller, V. É. Égert, M. V. Shimanskaya, and Ya. P. Stradyn', in: Furagin and Solafur [in Russian], Zinatne, Riga (1968), p. 7.
21. A. A. Bothner-By and R. K. Harris, J. Org. Chem., 30, 254 (1965).

PHOTOCHROMIC AND THERMOCHROMIC SPIROPYRANS. 11.* CALCULATION OF THE STABILITIES OF THE VALENCE TAUTOMERS OF SPIROPYRANS

B. Ya. Simkin and V. I. Minkin

UDC 541.145'623:547.814

A method was developed for the estimation of the relative stabilities of spirocyclic and merocyanine structures of spiropyrans on the basis of the Pariser—Parr—Pople method in σ,π parametrization with a corresponding estimate of the energy of formation of the spiro node. The results of the calculations are in satisfactory agreement with the experimental data and the results of calculation by the MINDO/3 method.

The photo- and thermocoloration reactions of spiropyrans [2] are due to $A \rightleftarrows B$ valence tautomerization, which is associated with electrocyclic cleavage of the C—O bond in A and is accompanied by the geometrical isomerization of B to the more stable merocyanine quinoneallid form C.

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*See [1] for communication 10.

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