ISOMERISM OF 5-ARYLFURFURAL OXIMES (ACCORDING TO PMR SPECTROSCOPIC DATA)

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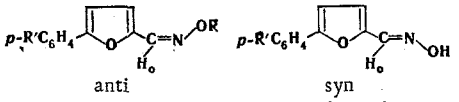
The stereochemistry of 5-arylfurfurals and their O-acetyl derivatives was studied by PMR spectroscopy. The configurations of each of the isomers were determined for the oximes of p-bromo- and p-chlorophenylfurfurals, which were isolated as two geometrical isomers, and also for their O-acetyl derivatives. The anti and syn configurations were established for the oximes of phenylfurfural and p-nitrophenylfurfural, respectively, which were obtained as single isomers. Conclusions regarding the preferred conformation of the side chain relative to the plane of the furan ring in all of the investigated isomers were drawn on the basis of an analysis of the of the long-range spin–spin coupling constants ($J_{H_0H_4}$).

The individual representatives of arylfurfural oximes that are described in the literature were isolated by the authors in the form of one isomer without establishment of the structure [1-3].

In an investigation of various conditions for the preparation of oximes, we observed that, depending on the concentration of the reaction mixture, either a high-melting isomer or a mixture of the high-melting and low-melting isomers (the amount of low-melting isomer in the mixture ranged from 50 to 80%) is formed. Under these conditions, phenylfurfural and p-nitrophenylfurfural oximes form only one isomer (Table 1). The synthesized oximes were converted to their O-acetyl derivatives, which were obtained either in the form of the individual isomers (VIb, VIIa, b, and VIIIb) or in the form of mixtures of the isomers (V, VI, and VIII).

In order to establish the configuration of the isomers of the 5-arylfurfural oximes and their O-acetyl derivatives and to study the conformation of the side chain relative to the furan ring, we examined their PMR spectra.

The establishment of the configuration was based on a comparison of the chemical shifts of the "aldehyde proton" (H_0) in both geometrical forms. It is known [4] that owing to the deshielding effect of the NOH group, the H_0 signal in the spectrum of the syn isomer is found at weaker field by 0.5-0.6 ppm than in the spectrum of the anti isomer. The signals of the H_0 proton of the low-melting isomers of II, III, VI, and VII are situated at weaker field than the signals of the corresponding high-melting isomers, and the difference in the chemical shifts is 0.51-0.56 ppm (Table 1). This makes it possible to relate the high-melting isomers (a) to the anti forms and the low-melting isomers (b) to the syn forms. We were able to obtain



anti — Ia–IIIa, Va–VIIIa

syn — IIb–VIIIb

R = R′ = H; II R = H, R′ = Cl; III R = H, R′ = Br; IV R = H, R′ = NO_2; V R = $COCH_3$, R′ = H; VI R = $COCH_3$, R′ = Cl; VII R = $COCH_3$, R′ = Br; VIII R = $COCH_3$, R′ = NO_2

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TABLE 1. Chemical Shifts (δ, ppm), Long-Range Spin–Spin Coupling Constants (J, Hz),* and Melting Points of I-IX

Compound	Isomer	δ_{H_0}	δ_{H_3}	δ_{H_4}	δ_{H_5}	δ_{COCH_3}	$^4J_{H_3H_0}$	$^5J_{H_4H_0}$	$^5J_{H_5H_0}$	Solvent	mp, °C
I	a	7,61	7,37	7,07	—	—	0,30	0,66	—	$DCON(CD_3)_2$	194—195
II	a	7,59	7,35	7,14	—	—	0,33[a]	0,72	—	$DCON(CD_3)_2$	159—161
	b	8,10	6,83	7,08	—	—	0,39	0,09	—	$DCON(CD_3)_2$	137—138
III	a	7,58	7,36	7,16	—	—	0,30	0,72	—	$DCON(CD_3)_2$	169—170
	b	8,09	6,83	7,09	—	—	0,30	0,09[a]	—	$DCON(CD_3)_2$	159,5—160
IV	b	8,14	6,93	7,38	—	—	0,39	0,15[a]	—	$DCON(CD_3)_2$	173—174
V	a†	7,78	7,32	6,79	—	2,26	0,30	0,66	—	$CDCl_3$	
	b†	8,19	6,95	6,71	—	2,17	0,36	0,31[b]	—	$CDCl_3$	
VI	a†	7,77	7,33	6,78	—	2,27	0,33	0,66	—	$CDCl_3$	
	b	8,19	6,96	6,71	—	2,19	0,36	0,27[b]	—	$CDCl_3$	142,5—145,0
		8,48	7,15	7,15	—	2,20	‡	‡	—	$DCON(CD_3)_2$	142,5—145,0
VII	a	7,74	7,32	6,79	—	2,27	0,33	0,64	—	$CDCl_3$	125—126
	b	8,18	6,95	6,72	—	2,19	0,36	0,27[b]	—	$CDCl_3$	149—150
		8,55	7,21		—	2,19	‡	‡	—	$DCON(CD_3)_2$	149—150
VIII	a**	7,84	7,41	7,01	—	2,29	0,30	0,66	—	$CDCl_3$	—
	b	8,25	6,96	7,04	—	2,20	0,30	0,27[b]	—	$CDCl_3$	161—163
		8,60	7,28	7,49	—	2,20	0,37	0,20[c]	—	$DCON(CD_3)_2$	161—163
IX	a†	7,74	7,29	6,57	7,58	2,27	0,33	0,66	0,06[d]	$CDCl_3$	
		7,99	7,42	6,73	7,89	2,27	0,30	0,67	0,09[e]	$DCON(CD_3)_2$	
	b†	8,20	6,90	6,53	7,57	2,19	0,36	0,27	0,37	$CDCl_3$	
		8,50	7,10	6,67	7,89	2,14	0,30	0,22	0,45	$DCON(CD_3)_2$	

*See the experimental section.

† The compounds could not be isolated in the form of individual geometrical isomers; fractions enriched in one of the isomers were investigated.

‡ The $^4J_{H_2H_3}$ and $^5J_{H_2H_4}$ constants could not be evaluated from the spectra, inasmuch as the H_3 and H_4 protons form an A_2 system.

**Compound VIIIa was obtained in a mixture with VIIIb after a solution of VIIIb in $CDCl_3$ had stood for a week at room temperature.

only one isomer each for I, IV, and VIII, but by comparing the H_0 chemical shifts of these isomers with the corresponding data for the other isomeric pairs we found it was possible to unambiguously assign the anti configuration to oxime Ia and the syn configuration to oximes IVb and VIIIb.

A double set of signals was present in the PMR spectrum of V, which indicated the presence of two geometrical isomers. It follows from an analysis of the H_0 chemical shifts in both forms that the anti form is predominant. A study of the PMR spectra of the isomers of VI showed that one of them (VIb) is the individual syn isomer, while the other (VIa) is a mixture of equal amounts of the syn and anti isomers.

These assignments are in good agreement with the known data on the melting points of the syn and anti isomers, in accordance with which the anti isomers are the higher-melting compounds.

We established that the anti form of the arylfurfural oximes can be isolated from the reaction without admixture of the syn isomer, while the syn isomer always contains the second isomer. The isomers of the oximes are capable of interconversion on storage [in the solid state and in solution in $DCON(CD_3)_2$], and the conversion of the syn form to the anti form occurs more rapidly than the reverse process. On the basis of the spectra, a mixture containing ~50% of each isomer corresponds to the equilibrium state. The isomers of the O-acetyl derivatives of the oximes also undergo interconversion on storage. Thus solutions of the individual isomers VIb, VIIa, b and of a nonequilibrium mixture of V in $CDCl_3$ have reached the equilibrium state with about identical amounts of the geometrical forms after a week. A mixture of the syn and anti forms (VIIIa, b) was formed as a result of isomerization when a solution of VIIIb in $CDCl_3$ was allowed to stand.

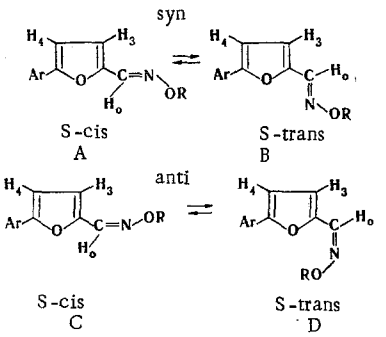
An investigation of the antitubercular activity (in vitro) of the oximes of 5-(p-bromophenyl)- and 5-(p-chlorophenyl)furfurals in the chemotherapy laboratory of the Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute showed that the activity of the anti isomers is higher than that of the corresponding syn isomers.

TABLE 2. δ_0 and Z_i Values [for solutions in $DCON(CD_3)_2$]

Parameter	Isomer	R′	Position 3	Position 4
δ_0, ppm (oxime)	syn	—	6,70	6,54
	anti		7,26	6,60
δ_0, ppm (acetate)	syn	—	7,10	6,67
	anti		7,42	6,73
Z_i, ppm		H	0,12	0,48
		Cl	0,12	0,50
		Br	0,14	0,56
		NO_2	0,26	0,86

In order to investigate the conformations of I-VIII, we used the long-range spin–spin coupling constants (SSCC) $^5J_{H_4H_0}$. The stereospecificity of these long-range SSCC in furfural oximes was recently used [5] to establish the relative percentages of the s-cis or s-trans conformations in solutions. An analysis of the experimental data on the magnitudes of the long-range SSCC showed that the anti isomer of furfural oxime exists almost entirely in the s-cis conformation in $CDCl_3$ solution ($^5J_{H_5H_0} = 0$ Hz, $^5J_{H_4H_0} = 0.7$ Hz), while the syn isomer under these conditions is present as a practically equal mixture of the s-cis and s-trans conformations ($^5J_{H_5H_0} = 0.35$ Hz, $^5J_{H_4H_0} = 0.25$ Hz).

The s-cis and s-trans conformations are also possible for each of the isomeric forms of the compounds that we



investigated. Inasmuch as the 5 position of the furan ring is substituted in these compounds, one can form a judgment regarding the conformational preferableness only from the $^5J_{H_4H_0}$ value. In this connection, it became necessary to unambigously assign the signals of the H_3 and H_4 protons; this was realized by means of a comparison of the calculated and experimentally obtained chemical shifts of the H_3 and H_4 protons.* The δ_{H_3} and δ_{H_4} values were calculated via an additive scheme with the use of the equation

$$\delta_H = \delta_0 + Z_i,$$

where δ_0 are the values of the chemical shifts of the H_3 or H_4 protons for furfural oxime or its O-acetyl derivative, and Z_i are the increments of the effect of the substituted aryl rings on the chemical shifts of the H_3 and H_4 protons of the furan ring, which we found from the spectra of the corresponding 5-phenylfurans (see Table 2).

The calculated and experimental δ_{H_3} and δ_{H_4} values are presented in Table 3. The large difference in the calculated chemical shifts of the H_3 and H_4 protons and the good agreement between each of the calculated shifts and one of the experimental values made it possible to make a reliable assignment of the signals of the H_3 and H_4 protons in the PMR spectra of the arylfurfural oximes. In the assignment of the H_3 and H_4 protons, it was assumed that the conformational states of the model and investigated compounds coincided. As shown below, this is not always the case, owing to which a certain disagreement between the calculated and experimental chemical shifts is observed. However, these deviations are nevertheless sufficiently small and do not interfere with the unambiguous assignment of the signals of the H_3 and H_4 protons.

A similar calculation was made for O-acetyl derivatives V-VIII. As in the case of the oximes, the observed difference in the chemical shifts of the H_3 and H_4 protons decreases as the electron-acceptor character of the substituent in the aryl ring increases, and for the syn isomer of VIII this difference changes sign (the H_4 signal is shifted to weaker field than H_3 signal). In $DCON(CD_3)_2$ solution, only the syn form of the O-acetyl derivatives could be investigated (the anti forms proved to be unstable in this solvent). The calculated δ_{H_3} and δ_{H_4} values for the syn forms proved to be in quite good agreement with the experimental values.

*The assignment of the signals of the H_3 and H_4 protons on the basis of multiplicity is impossible, inasmuch as $^4J_{H_3H_0}$ and $^5J_{H_4H_0}$ are comparable in absolute value.

TABLE 3. Calculated and Experimental Values of the Chemical Shifts of the H_3 and H_4 Protons (ppm)

Proton	Compound	δ calc.	δ exptl.	Δδ	Compound	δ calc.	δ exptl. $DCON(CD_3)_2$	$\Delta\delta_{DCON(CD_3)_2}$	δ_{exp} $(CDCl_3)$
H_3	Ia	7,38	7,37	0,01	Va	7,54	—	—	7,32
H_4		7,08	7,07	0,01		7,21	—	—	6,79
H_3	—	—	—	—	Vb	7,22	—	—	6,95
H_4						7,15	—	—	6,71
H_3	IIa	7,38	7,35	0,03	VIa	7,54	—	—	7,33
H_4		7,10	7,14	−0,04		7,23	—	—	6,78
H_3	IIb	6,82	6,83	−0,01	VIb	7,22	7,15	0,07	6,96
H_4		7,04	7,08	−0,04		7,17	7,15	0,02	6,71
H_3	IIIa	7,40	7,36	0,04	VIIa	7,56	—	—	7,32
H_4		7,16	7,16	0,00		7,29	—	—	6,79
H_3	IIIb	6,84	6,83	0,01	VIIb	7,24	7,21	0,03	6,95
H_4		7,10	7,09	0,01		7,23	7,21	0,02	6,72
H_3	—	—	—	—	VIIIa	7,68	—	—	7,41
H_4						7,59	—	—	7,01
H_3	IVb	6,96	6,93	0,03	VIIIb	7,36	7,28	0,08	6,96
H_4		7,40	7,38	0,02		7,53	7,49	0,04	7,04

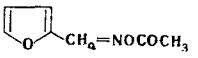
Recording of the spectra of V-VIII in $CDCl_3$ showed that in this solvent regularities are observed for H_3 and H_4, but the values themselves of the chemical shifts differ appreciably from the values calculated from the increments found for solutions in $DCON(CD_3)_2$ (see Table 3). At the same time, this did not prevent the reliable assignment of the H_3 and H_4 signals in the PMR spectra.

The values of the long-range SSCC $^5J_{H_4H_0}$ for all of the investigated compounds were determined from the signals of the H_4 protons. For anti isomers Ia-IIIa, $^5J_{H_4H_0}$ is 0.66-0.72 Hz, while $^5J_{H_4H_0}$ is close to zero for syn isomers IIb-IVb. Consequently, the anti isomers are present in solution primarily in the s-cis conformation C (as also in the case of the anti isomer of furfural oxime) [5], while the syn isomers are present primarily in s-trans conformation B (in contrast to the syn isomer of furfural oxime).

The position of the ν_{OH} band is practically the same in the IR spectra of IIIa and IIIb (3220 cm^{-1} in the crystals and 3585 cm^{-1} in solutions), and dilution does not affect the position of the band. Inasmuch as an intramolecular hydrogen bond cannot exist in the syn isomer by virtue of geometrical considerations, the data presented above negate the presence of this sort of bonding in the anti isomer; this is to a great degree in agreement with conformation C of the latter isomer.

The data obtained show that the introduction of an aryl substituent into the 5 position of the furan ring does not affect the conformational equilibrium of the anti isomers, while for the syn isomers it promotes great preferableness of the s-trans form.

In order to investigate the conformations of O-acetyl derivatives V-VIII, we used model compounds



IX a, b

IX (a is anti, and b is syn). From the values of the $^5J_{H_4H_0}$ and $^5J_{H_4H_0}$ long-range SSSC (see Table 1), it was established that s-cis conformation C ($^5J_{H_4H_0}$ ~ 0.66-0.67 Hz, $^5J_{H_5H_0}$ ~ 0.06-0.09 Hz) is preferable for the anti isomer, while the syn isomer is represented by a mixture of the s-cis and s-trans conformations (A and B) ($^5J_{H_4H_0}$ ~ 0.22-0.27 Hz, $^5J_{H_5H_0}$ ~ 0.37-0.45 Hz). From a comparison of the long-range SSCC, it follows that in $CDCl_3$ solutions the syn isomer is a mixture with practically identical amounts of conformations A and B, while this equilibrium is shifted to a certain degree in $DCON(CD_3)_2$ solution to favor conformation B. This situation is different from the case of the syn isomer of furfural oxime in which the effect of solvents on the conformational state of the investigated compound is absent [5].

For Va-VIIIa, $^5J_{H_4H_0}$ is 0.66-0.64 Hz which indicates predominance of s-cis conformation C in these compounds. For the syn isomers of V-VIII, $^5J_{H_4H_0}$ ~ 0.27-0.30 Hz ($CDCl_3$) and 0.20 Hz [VII, $DCON(CD_3)_2$]. These data show that the syn isomers, as in the case of model compound IXb, are present in $CDCl_3$ solution

in the form of a mixture with approximately identical amounts of the s-cis and s-trans conformations, while s-trans conformation B apparently becomes somewhat more preferable in $DCON(CD_3)_2$ solution.

Thus in solutions the anti isomers of the entire series of investigated and model compounds are present in the s-cis conformation. The syn isomers of furfural oxime and its O-acetate and of the O-acetyl derivatives of 5-aryl-furfural oximes are represented in solution by mixtures with approximately equal amounts of the s-cis and s-trans conformations, while the equilibrium is shifted to favor the s-trans conformation for the syn isomers of 5-aryl-furfural oximes.

EXPERIMENTAL

The PMR spectra were recorded with JNM-4H-100 and C-60-HL spectrometers with tetramethylsilane (TMS) as the internal standard. The IR spectra were recorded with a Perkin Elmer 457 spectrometer. The solvent was CCl_4.

The difference in the widths of the H_4 signal (at half its height) measured under monoresonance conditions and under conditions involving decoupling of the H_0 proton was taken for the $^5J_{H_4H_0}$ SSCC for IIb and VIIIb (c) (Table 1). The differences in the widths of the H_4 or H_3 signals at half their heights and the values that take into account the natural width of the line and the coupling of a given proton with the aromatic ring protons were taken for the $^5J_{H_4H_0}$ and $^5J_{H_3H_0}$ SSCC, denoted by *a*; the sum of the latter two values was determined from H_0 decoupling experiments for IIb and VIIIb (c). The $^5J_{H_4H_0}$ SSCC values, denoted by b, were determined from the H_0 signal with allowance for all of the interactions of the "aldehyde" proton. The natural width of the line, which was determined from the CH_2Cl_2 signal for a degassed sample [0.15 Hz in $CDCl_3$ and 0.20 Hz in $DCON(CD_3)_2$], was taken into account in the evaluation of $^5J_{H_5H_0}$ of IXa (d and e). The SSCC values denoted by *a* were determined with an accuracy of ± 0.06 Hz, while the remaining values were determined with an accuracy of ± 0.03 Hz (degassed samples were investigated).

5-(p-Bromophenyl)furfural Oxime, anti Isomer IIIa. See [1] for the synthetic method and the physical constants.

O-Acetyl Derivative VIIa. A mixture of 1.08 g of IIIa and 4.5 ml of acetic anhydride* was refluxed on a water bath for 30 min, after which it was poured into water. The precipitate was removed by filtration to give 0.83 g (70%) of a product with mp 125-126° (from alochol). Found: C 51.0; H 3.3; Br 25.5%. $C_{13}H_{10}BrNO_3$. Calculated: C 50.7; H 3.3; Br 25.8%.

5-(p-Bromophenyl)furfural Oxime, syn Isomer IIIb. A mixture of 7.5 g (29 mmole) of 5-(p-bromophenyl)furfural, 2.3 g (33 mmole) of hydroxylamine hydrochloride, and 2.7 g (33 mmole) of sodium acetate in 58 ml of 36% alcohol was refluxed for 4 h. The mixture was cooled, and the resulting precipitate was removed by filtration and recrystallized two or three times from 95% alcohol. The yield of IIIb in separate experiments ranged from 4.2 to 6.0 g (53-77%). The product had mp 159.5-160°. Found: C 50.1; H 3.0; Br 29.9%. $C_{11}H_8BrNO_2$. Calculated: C 49.7; H 3.0; Br 30.0%.

O-Acetyl Derivative VIIb. This compound was obtained in the same way as O-acetyl derivative VIIa. The yield of product with mp 149-150° (from alcohol) was 59%. Found: C 50.8; H 3.2; Br 25.5; N 4.4%. $C_{13}H_{10}BrNO_3$. Calculated: C 50.6; H 3.3; Br 25.8; N 4.5%.

5-(p-Chlorophenyl)furfural Oxime, anti Isomer IIa. See [1] for the synthetic method and the physical constants.

O-Acetyl Derivative VIa. This compound was obtained by the method used to prepare O-acetyl derivative VIIa. The yield of product with mp 108-120° (from alcohol) was 53%. Composition: 50% syn isomer and 50% anti isomer. Found: C 59.2; H 3.8%. $C_{13}H_{10}ClNO_3$. Calculated: C 59.2; H 3.8%.

5-(p-Chlorophenyl)furfural Oxime, syn Isomer IIb. This compound was prepared by the method used to obtain IIIb. The yield of product with mp 137-138° (from ethyl acetate) was 50-89%. Found: C 59.4; H 3.6; Cl 15.7; N 6.6%. $C_{11}H_8ClNO_2$. Calculated: C 59.6; H 3.6; Cl 16.0; N 6.3%.

O-Acetyl Derivative VIb. This compound was prepared by the method used to obtain O-acetyl derivative VIIa. The yield of product with mp 142.5-145° (from alcohol) was 65%. Found: C 59.2; H 3.7; Cl 13.0%. $C_{13}H_{10}ClNO_3$. Calculated: C 59.2; H 3.8; Cl 13.5%.

*The acetamides of 5-arylfuran-2-caboxylic acids are formed during the acetylation of the arylfurfural oximes with acetic anhydride. See our following communications for details of these sorts of transformations.

5-Phenylfurfural Oxime, anti Isomer Ia. See [3] for the synthetic method and the physical constants.

O-Acetyl Derivative Va. This compound was prepared by the method used to obtain O-acetyl derivative VIIa. The yield of product with mp 85-100° (from alcohol) was 70%. Composition: 30% of the syn isomer and 70% of the anti isomer. Found: C 68.1; H 4.7; N 6.1%. $C_{13}H_{11}NO_3$. Calculated: C 68.1; H 4.8; N 6.1%.

5-(p-Nitrophenyl)furfural Oxime, syn Isomer IVb. See [2] for the synthetic method and the physical constants.

O-Acetyl Derivative VIIIb. This compound was obtained by the method used to prepare VIIa. The product had mp 161-163° (from alcohol). Found: C 56.7; H 3.8; N 10.6%. $C_{13}H_{10}N_2O_5$. Calculated: C 56.9; H 3.7; N 10.2%.

O-Acetyl Derivative of Furfural Oxime (anti and syn isomers IXa, b). This compound was prepared by the method used to obtain O-acetyl derivative VIIa from the syn isomer of furfural oxime. Fractions with bp 107-109° (3 mm) and n_D^{20} 1.5339 (50% syn and 50% anti isomers) and bp 113-114° (3 mm) and n_D^{20} 1.5379 (90% syn and 10% anti isomers) were isolated. The results of analysis of both fractions were close and correspond to the empirical formula IX.

LITERATURE CITED

1. A. F. Oleinik, T. I. Vozyakova, G. A. Modnikova, and K. Yu. Novitskii, Khim. Geterotsikl. Soedin., 1448 (1972).
2. R. Frimm, S. Kovac, and S. A. Giller, Chem. Zvesti, 23, 916 (1969).
3. C. Davis and G. Zougheed, J. Heterocycl. Chem., 4, 153 (1967).
4. E. Lustig, J. Phys. Chem., 65, 491 (1961).
5. R. Wasylishen and T. Schaefer, Can. J. Chem., 50, 274 (1972).