

UTILIZATION OF  $N^{15}H^1$  HETERONUCLEAR  
SPIN - SPIN COUPLING CONSTANTS  
FOR THE INVESTIGATION OF THE THREE-  
DIMENSIONAL STRUCTURES OF OXIMES  
OF FURFURAL AND p-BROMOPHENYLFURFURAL  
AND THEIR O-ACETYL DERIVATIVES

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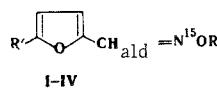
UDC 543.422.25 : 547.724.1'727 : 541.63

On the basis of the large difference in the  $^2J_{N^{15}H_{\text{ald}}}$  values for the E and Z isomers, the configurations of the isomeric oximes of furfural and p-bromophenylfurfural and their O-acetyl derivatives were determined. The stereospecificity of the long-range spin-spin coupling constants of the nitrogen atom and the  $H_4$  proton of the furan ring ( $^6J_{N^{15}H_4}$ ) was investigated, and the possibility of the utilization of these constants for the stereochemical analysis of oximes of the furan series was shown.

We have previously investigated the configurations and conformations of oximes of 5-arylfurfurals and their O-acetyl derivatives by PMR spectroscopy [1]. The configurations of these compounds were established on the basis of a comparison of the chemical shifts of the aldehyde proton for the various isomeric forms, and their conformational states were determined by means of the long-range  $^5J_{\text{Hald}H_4}$  spin-spin coupling constants (SSCC).

The magnitudes of the geminal heteronuclear  $^2J_{N^{15}H}$  heteronuclear spin-spin coupling constants began to be used relatively recently for configurational investigations [2-5]. It was found that the orientation of the unshared pair of the electrons of the nitrogen atom relative to this proton has an appreciable effect on the spin-spin coupling between the  $N^{15}$  atom and the coupling proton [2-3]. It was found for  $N^{15}$ -formaldoxime and several other aldoximes of this series that  $^2J_{N^{15}H} \sim 14-16$  Hz for an E orientation\* of the unshared pair of electrons of the N atom and the H atom, whereas  $^2J_{N^{15}H} \sim 2.5-4$  Hz for a Z orientation of H and the unshared pair of electrons. Thus the  $^2J_{N^{15}H}$  values are stereospecific [2-3].

We applied the relationships presented above to a configurational analysis of 5-arylfurural oximes I-IV.



I R = R' = H; II R = COCH<sub>3</sub>, R' = H; III R = H, R' = p-BrC<sub>6</sub>H<sub>4</sub>; IV R = COCH<sub>3</sub>, R' = p-BrC<sub>6</sub>H<sub>4</sub>

The  $^2J_{N^{15}H_{\text{ald}}}$  values of I-IV are presented in Table 1. In fact, a large difference in the  $^2J_{N^{15}H_{\text{ald}}}$  values is observed for the E and Z isomers ( $Z = ^2J_{N^{15}H_{\text{ald}}} \sim 14.0-17.5$  Hz, and  $E = ^2J_{N^{15}H_{\text{ald}}} \sim 0.45-2.6$  Hz), and this difference increases for the O-acetyl derivatives: for the Z isomer of IV,  $^2J_{N^{15}H_{\text{ald}}}$  becomes 17.5

\* The E and Z isomers correspond to the syn and anti isomers with respect to the previously used classification.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 890-893, July, 1975. Original article submitted July 15, 1974.

TABLE I. Chemical Shifts (ppm) and SSCC (Hz)\* for I-IV

Compound	Isomer	$\delta_{\text{H,ald}}$	$\delta_{\text{H}_3}$	$\delta_{\text{H}_4}$	$\delta_{\text{H}_5}$	$\delta_{\text{H}^{\text{Pd}}_{I_1}}$	$\delta_{\text{H}^{\text{Pd}}_{I_2}}$	$\delta_{\text{H}^{\text{Pd}}_{I_3}}$	$\delta_{\text{H}^{\text{Pd}}_{I_4}}$	$\delta_{\text{H}^{\text{Pd}}_{I_5}}$	$\delta_{\text{H}_{\text{EtN}_2^{\text{d}}}}$	$\delta_{\text{H}_{\text{EtN}_2^{\text{f}}}}$	$\delta_{\text{H}_{\text{EtN}_2^{\text{f}}}}$	Confor-mation	Solvent
I	Z	7.53	7.35	6.52	7.46	0.74	1.79	0.35	0.69	~0	14.0a	0.41b	<0.10a	†	CDCl <sub>3</sub> DCON(CD <sub>3</sub> ) <sub>2</sub>
	E	7.47	7.25	6.59	7.70	0.78	1.84	0.35	0.72	~0	14.5a	0.52a	0.11a	†	CDCl <sub>3</sub> DCON(CD <sub>3</sub> ) <sub>2</sub>
II	Z	7.59	7.36	7.14	—	—	—	0.33	0.69	—	14.5a	0.48b	<0.03c	—	CDCl <sub>3</sub> CDCl <sub>3</sub> <sup>15</sup>
	E	8.11	6.84	7.10	—	—	—	0.39	0.10	—	17.5a	0.43b	0.33 <sup>g</sup>	—	CDCl <sub>3</sub> CDCl <sub>3</sub> <sup>15</sup>
III	Z	7.76	7.32	6.60	7.58	0.73	1.83	0.32	0.67	~0	—	0.50b	0.15a	0.21a	DCON(CD <sub>3</sub> ) <sub>2</sub>
	E	8.22	6.93	6.54	7.58	0.78	1.83	0.36	0.30	—	0.36	0.63 <sup>f</sup>	0.42b	0.45b	CDCl <sub>3</sub> CDCl <sub>3</sub> <sup>15</sup>
IV	Z	7.79	7.35	6.81	—	—	—	0.33	0.63	—	17.5a	0.52b	0.10c	—	DCON(CD <sub>3</sub> ) <sub>2</sub>
	E	8.21	6.98	6.75	—	—	—	0.39	0.30	—	0.69 <sup>b</sup>	0.42b	0.27c	—	CDCl <sub>3</sub> CDCl <sub>3</sub> <sup>15</sup>
		8.55	—	7.22 <sup>†</sup>	—	—	—	—	—	—	—	0.45a	—	‡	DCON(CD <sub>3</sub> ) <sub>2</sub>

\* See the experimental section.

† Mixtures of the E and Z isomers were investigated for the E isomers of I and II in CDCl<sub>3</sub> solution; the H<sub>5</sub> signals of both isomerswere overlapped, hindering the determination of  $^5\text{JN}^{15}\text{H}$ .‡ The H<sub>3</sub> and H<sub>4</sub> protons form an AB system (when  $\Delta\delta_{\text{AB}} \rightarrow 0$ ); we were unable to determine the  $^4\text{JHaldH}_3$ ,  $^5\text{JHaldH}_4$ ,  $^4\text{JN}^{15}\text{H}_3$ , and  $^5\text{JN}^{15}\text{H}_4$  values.

Hz, whereas the constant for the corresponding E isomer decreases to 0.69 Hz. The difference in the  $^2J_{N^{15}H_{\text{ald}}}$  values for the Z and E isomers is so high that it is possible to determine the configuration of a single isomeric compound (when the pair isomer is absent) only from the absolute magnitude of  $^2J_{N^{15}H_{\text{ald}}}$ .\* This method of configurational investigation is a more universal method than the previously used methods, for which pairs of isomeric compounds (of unknown configuration) or model compounds whose configuration is already known, are used.

In addition to the geminal  $^2J_{N^{15}H_{\text{ald}}}$  heteroconstants, we also detected the long-range SSCC of the  $N^{15}$  nucleus with the  $H_3$  and  $H_4$  protons of the furan ring (through four and five bonds, respectively) for these compounds. It follows from an analysis of the  $^4J_{N^{15}H_3}$  values (Table 1) that this constant is not stereospecific ( $^4J_{N^{15}H_3} \sim 0.41\text{--}0.52$  Hz), whereas the  $^5J_{N^{15}H_4}$  constant depends markedly on the conformational state of the investigated compounds. Thus for the Z isomers of I-IV, the conformation of which in solution (as previously established in [1]) is s-cis, the  $^5J_{N^{15}H}$  values are 0.03-0.15 Hz.

These constants are appreciably larger for the E isomers, and  $^5J_{N^{15}H_4}$  is 0.27-0.45 Hz for I, II, and IV, the conformational state of which in solution is determined to be practically equal to the percentage of s-cis and s-trans forms [1]. This constant is 0.33 Hz for the E isomer of oxime III (the conformation of which is s-trans [1]). Using this value (0.33 Hz), we estimated the  $^5J_{N^{15}H_4}$  value for the individual s-cis conformation in the E isomer. It was found to be 0.3-0.4 Hz. It hence follows that for the E isomers of the entire series of investigated compounds the long-range SSCC through five bonds ( $^5J_{N^{15}H_4}$ ) differ appreciably from the analogous constants for the Z isomers, i.e.,  $^5J_{N^{15}H_4}$  is stereospecific. The possible reason for this may be both the favorable (for long-range coupling) orientation of the bonds between the  $N^{15}$  and  $H_4$  nuclei (in the s-trans conformation) and the drawn-together three-dimensional orientation of the unshared pair of electrons of the  $N^{15}$  nitrogen atom and  $H_4$  (in the s-cis conformation).

Thus the utilization of the geminal  $^2J_{N^{15}H_{\text{ald}}}$  constants and the long-range  $^5J_{N^{15}H_4}$  hetero-SSCC is an extremely effective method for the stereochemical investigation of oximes of the furan series.

## EXPERIMENTAL

The PMR spectra of the compounds were recorded with a C-60HL spectrometer with tetramethylsilane as the internal standard. Degassed samples were investigated, and the accuracy in the determination of the SSCC was  $\pm 0.03$  Hz.

The spin-spin coupling heteroconstants (denoted by  $a$  in Table 1) were determined directly from the spectra from the splitting of the signals of the investigated protons, whereas the SSCC (denoted by  $b$  in Table 1) were estimated from the distance between the extreme components of the multiplet of the appropriate proton with allowance for coupling of this proton with  $H_{\text{ald}}$  and the protons of the furan ring. The difference in the widths of the signals of the investigated protons at half the height with allowance for the natural width of the line and the coupling of a given proton with the aldehyde proton and the protons of the aromatic ring (the sum of the last two values was determined in [1]) was taken for the SSCC values, denoted by  $c$  in Table 1. The proton SSCC were determined as described in [1], during which some of the constants were determined more precisely.

The  $N^{15}$ -hydroxylamine hydrochloride used for the syntheses was of a quality in keeping with the requirements of Tu 6-02-628-71 and was 95.5 atomic % enriched in the isotope.

Furfural  $N^{15}$ -Oxime (I-Z isomer). A mixture of 1.12 g (12 mmole) of furfural, 1 g (14 mmole) of  $N^{15}$ -hydroxylamine hydrochloride, and 1.95 g (19 mmole) of sodium acetate in 10 ml of 50% methanol was stirred at 20° for 3 h, after which it was cooled, and the resulting precipitate was removed by filtration. The filtrate was vacuum-evaporated, and the residual oil began to crystallize when 7 ml of water was added. The precipitate was removed by filtration to give 1.1 g (79%) of a product with mp 90-92° (from alcohol). Found: C 53.4; H 4.4%.  $C_5H_5N^{15}O_2$ . Calculated: C 53.6; H 4.4%.

O-Acetyl Derivatives of the I-Z Isomer (II-Z isomer). A mixture of 0.41 g of I and 2 ml of acetic anhydride was heated at 30° for 30 min, after which it was cooled, and 15 ml of 2 N  $Na_2CO_3$  was added in portions with stirring. The mixture was then extracted with ether, and the extract was dried with  $MgSO_4$  and evaporated. The residue was vacuum-distilled to give 0.4 g (72%) of a product with bp 50-52° (1 mm). Found: C 54.2; H 4.6%.  $C_7H_7N^{15}O_3$ . Calculated: C 54.1; H 4.6%.

\*This method has been successfully applied for the investigation of the configuration of 1-substituted benzimidazole-2-aldoximes [4].

Furfural N<sup>15</sup>-Oxime (I-E isomer). A mixture of 1.12 g (12 mmole) of furfural, 1 g (14 mmole) of N<sup>15</sup>-hydroxylamine hydrochloride, and 1.17 g (28 mmole) of NaOH in 4 ml of water was stirred at 20° for 1 h, after which 10 ml of saturated NH<sub>4</sub>Cl solution was added, and the mixture was cooled and extracted with ether. The extract was dried with magnesium sulfate and vacuum-evaporated, and the residual oil began to crystallize on cooling. Workup gave 0.5 g (40%) of a product with mp 49-52° (from alcohol). Found: C 53.3; H 4.3%. C<sub>5</sub>H<sub>5</sub>N<sup>15</sup>O<sub>2</sub>. Calculated: C 53.6; H 4.4%.

O-Acetyl Derivative of the I-E Isomer (II-E Isomer). This compound, with bp 52-55° (1 mm), was obtained in 65% yield by the method used to prepare the II-Z isomer. Found: C 54.2; H 4.9%. C<sub>7</sub>H<sub>7</sub>N<sup>15</sup>O<sub>3</sub>. Calculated: C 54.1; H 4.6%.

5-(p-Bromophenyl)furfural N<sup>15</sup>-Oxime (III-Z isomer). A mixture of 3.26 g (13 mmole) of 5-(p-bromophenyl)furfural, 1 g (14 mmole) of N<sup>15</sup>-hydroxylamine hydrochloride, and 1.95 g (19 mmole) of sodium acetate in 34 ml of 50% alcohol was refluxed for 2 h, after which the mixture was cooled, and the resulting precipitate was removed by filtration and washed with water to give 2.61 g (75%) of a product with mp 174-176° (from alcohol). Found: C 49.6; H 3.1; Br 30.1%. C<sub>11</sub>H<sub>8</sub>BrN<sup>15</sup>O<sub>2</sub>. Calculated: C 49.5; H 3.0; Br 29.9%.

O-Acetyl Derivative of the III-Z Isomer (IV-Z isomer). A mixture of 1.36 g of III and 4.7 ml of acetic anhydride was heated on a boiling-water bath for 1 h, after which it was poured into water, and the resulting precipitate was removed by filtration and washed with water to give 1.2 g (71%) of a product with mp 124-126°. Found: C 50.3; H 3.2; Br 25.9%. C<sub>13</sub>H<sub>10</sub>BrN<sup>15</sup>O<sub>3</sub>. Calculated: C 50.5; H 3.3; Br 25.9%.

5-(p-Bromophenyl)furfural N<sup>15</sup>-Oxime (III-E isomer). A mixture of 3.26 g (13 mmole) of 5-(p-bromophenyl)furfural, 1 g (14 mmole) of N<sup>15</sup>-hydroxylamine hydrochloride, and 1.95 g (19 mmole) of sodium acetate in 26 ml of 36% alcohol was refluxed for 3 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with water to give 2 g (60%) of a product with mp 158-160° (from alcohol). Found: C 49.6; H 3.1; Br 30.2%. C<sub>11</sub>H<sub>8</sub>BrN<sup>15</sup>O<sub>2</sub>. Calculated: C 49.5; H 3.0, Br 29.9%.

O-Acetyl Derivative of the III-E Isomer (IV-E isomer). This compound, with mp 148-150° (from alcohol), was obtained in 51% yield by the method used to prepare the IV-Z Isomer. Found: C 50.6; H 3.1; Br 25.6%. C<sub>13</sub>H<sub>10</sub>BrN<sup>15</sup>O<sub>3</sub>. Calculated: C 50.5; H 3.3; Br 25.9%.

#### LITERATURE CITED

1. N. P. Kostyuchenko, A. F. Oleinik, T. I. Vozyakova, K. Yu. Novitskii, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., 312 (1974).
2. D. Crepaux and J. M. Lehn, Mol. Phys., 14, 547 (1968).
3. J. P. Kintzinger and J. M. Lehn, Chem. Commun., 660 (1967).
4. I. N. Somin and V. A. Gindin, Khim. Geterotsikl. Soedin., 572 (1972).
5. W. B. Jennings, D. R. Boyd, C. G. Watson, E. D. Becker, R. B. Bradey, and D. M. Jerina, J. Amer. Chem. Soc., 94, 8501 (1972).