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^1H , ^{13}C , and ^{15}N CHEMICAL SHIFTS AND ^1H - ^{15}N
 AND ^{13}C - ^{15}N HETERONUCLEAR SPIN-SPIN COUPLING
 CONSTANTS IN THE NMR SPECTRA OF 5-SUBSTITUTED
 FURFURAL OXIMES

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The ^1H , ^{13}C , and ^{15}N NMR spectra of ^{15}N -enriched 5-substituted furfural oximes were investigated. It was shown that the chemical shifts of the ring atoms and the oxime group correlate satisfactorily with the F and R substituent constants, whereas their sensitivity to the effect of the substituents is lower than in monosubstituted furan derivatives. The constants of spin-spin coupling between the ring protons and the oxime group were determined. An analysis of the ^1H - ^1H spin-spin coupling constants (SSCC) on the basis of their stereospecificity indicates that the E isomers have primarily an s-trans conformation in polar dimethyl sulfoxide, whereas the Z isomers, on the other hand, have an s-cis conformation. The signs of the direct and geminal ^{13}C - ^{15}N SSCC were determined for 5-trimethylsilylfurfural oxime.

The present research was devoted to an investigation of the magnetic resonance parameters of the ^1H , ^{13}C , and ^{15}N nuclei of ^{15}N -enriched 5-substituted furfural oximes and their change as the substituents in the furan ring are replaced.



I R=CH₃; II R=H; III R=Si(CH₃)₃; IV R=Ge(CH₃)₃; V R=Br; VI R=NO₂

One set of signals is observed in the ^1H NMR spectra of I and II (see Table 1); this indicates the presence of only one isomer in solutions. On the other hand, a double set of signals is observed in the proton spectra of oximes III-VI, i.e., in solutions these compounds are represented by two isomers (E and Z) in almost equal amounts. For the assignment of their configurations we used the geminal SSCC $^2J_{^{15}\text{N}-\text{H}_\alpha}$, the values of which are stereospecific ($^2J = 14.0$ - 17.5 Hz for the Z isomers, and $^2J = 0.45$ - 2.60 Hz for the E isomers [1]). The oxime OH group has a deshielding effect [2], and the signals of the H_α protons in the spectra of the E isomers are therefore observed at a weaker field (by 0.4-0.5 ppm) than the signals in the spectra of the Z isomers. The assignment of the signals of the carbon atoms in the ^{13}C NMR spectra of the 5-R-furfural oximes (Table 2) was based on the established fact that the inequality $^2J > ^1J > ^3J$ is observed for the ^{13}C - ^{15}N SSCC [3]. Primarily the signals of the C(2), C(4), and C(3) carbons of the E isomers and the signals of the corresponding carbons of the other isomers were detected. The identification of the C(5) signals did not present any difficulties, since their intensities were considerably lower because of the increased spin-lattice relaxation time and the absence of intensification of the signal from the Overhauser nuclear effect. The C(4) chemical shifts (CS) of the two isomers

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TABLE 1. Parameters of the ¹H NMR Spectra of 5-R-Furfural Oximes

| Com- pound | R | Isomer | Chemical shifts, δ, ppm | | | | | SSCC, J, Hz | | | |
|---------------|-----------------------------------|--------|-------------------------|------|----------------|------|----------------|-------------|--------------------|-----|---------------------|
| | | | 3-H | 4-H | H _α | OH | H _R | 3-4 | α- ¹⁵ N | α-4 | HO- ¹⁵ N |
| I | CH ₃ | Z | 7,15 | 6,30 | 7,48 | 11,7 | 2,35 | 3,3 | 14,6 | 0,6 | 1,2 |
| II | H | Z | 7,26 | 6,68 | 7,58 | 11,9 | 7,81* | 3,4 | 14,5 | 0,7 | 1,4 |
| III | Si(CH ₃) ₃ | E | 6,88 | 6,72 | 8,08 | 11,3 | 0,30& | 3,3 | 2,2 | 0,2 | 1,5 |
| | | Z | 7,23 | 6,90 | 7,60 | 11,9 | 0,31 | 3,4 | 14,8 | 0,7 | 1,2 |
| IV | Ge(CH ₃) ₃ | E | 6,57 | 6,57 | 7,97 | 10,8 | 0,44& | — | 2,1 | 0,3 | 1,5 |
| | | Z | 7,28 | 6,63 | 7,47 | 11,3 | 0,50 | 3,4 | 14,6 | 0,6 | 1,0 |
| V | Br | E | 6,79 | 6,73 | 8,02 | 11,4 | — | 3,6 | 2,1 | 0,2 | 1,6 |
| | | Z | 7,23 | 6,79 | 7,58 | 12,0 | — | 3,5 | 14,3 | 0,4 | 1,3 |
| VI | NO ₂ | E | 7,11 | 7,80 | 8,23 | 12,2 | — | 3,9 | 2,2 | 0,2 | 1,5 |
| | | Z | 7,47 | 7,80 | 7,81 | 12,8 | — | 3,9 | 13,6 | 0,8 | 0,9 |

*For this compound SSCC ⁵J(α-s) = 0.1 Hz.

TABLE 2. Parameters of the ¹³C and ¹⁵N NMR Spectra of 5-R-Furfural Oximes

| R | Iso- mer | ¹³ C chemical shifts, δ, ppm | | | | | | ¹³ C- ¹⁵ N SSCC, J, Hz | | | | δ ¹⁵ N, ppm |
|-----------------------------------|-------------|---|------------------|------------------|------------------|------------------|------------------|--|-------------------|-------------------|-------------------|---------------------------|
| | | C ₍₂₎ | C ₍₃₎ | C ₍₄₎ | C ₍₅₎ | C _(α) | C _(R) | 2-N ¹⁵ | 3-N ¹⁵ | 5-N ¹⁵ | α-N ¹⁵ | |
| CH ₃ | Z | 145,4 | 118,8 | 109,7 | 153,6 | 136,5 | 14,2 | 2,6 | 1,6 | 1,2 | -1,2 | -19,4* |
| H | Z | 146,7 | 117,5 | 113,2 | 144,3 | 136,6 | — | 2,8 | 1,6 | 0,7 | -1,4 | -16,8 |
| Si(CH ₃) ₃ | E | 153,3 | 111,9 | 122,5 | 161,1 | 139,9 | -0,9& | -8,3 | 2,5 | 1,0 | -4,5 | -9,3 |
| | Z | 150,5 | 117,4 | 123,0 | 162,2 | 136,7 | -1,0 | 2,9 | 1,6 | 0,6 | -1,6 | -16,2 |
| Ge(CH ₃) ₃ | E | 152,6 | 112,1 | 120,8 | 162,5 | 139,8 | -1,1& | -6,3 | 2,2 | 0,0 | -4,4 | — |
| | Z | 150,2 | 117,4 | 121,3 | 163,4 | 136,6 | -1,2 | 3,0 | 1,5 | 0,0 | -0,7 | — |
| Br | E | 151,3 | 115,1 | 115,3 | 124,3 | 139,3 | — | -8,3 | 2,9 | 0,5 | -4,4 | -9,4 |
| | Z | 149,1 | 120,0 | 114,9 | 124,3 | 135,6 | — | 2,7 | 1,6 | 0,5 | 0,0 | -14,5 |
| NO ₂ | E | 151,8 | 114,8 | 115,2 | 151,7 | 139,3 | — | -8,9 | 2,4 | 0,0 | -4,8 | 7,6 |
| | Z | 147,8 | 119,8 | 115,5 | 152,8 | 135,3 | — | 2,4 | 1,4 | 0,0 | -1,0 | 3,1 |

*Positive δ¹⁵N values denote a shift to strong field of the ¹⁵NO₂ signal relative to the CH₃ signal, whereas negative values denote a shift to weak field.

differ little, and the difference in the quantitative ratio of the two isomers, which is readily measurable in the ¹H spectra, was therefore used for their assignment: the signal with lower intensity was assigned to the C₍₄₎ absorption of the E isomer in all cases.

The C₍₂₎ carbon in the Z isomer is shielded by 2.2-4.0 ppm relative to the signal in the spectrum of the E isomer. A similar shift (2.5 ppm) was found in the spectra of p-substituted acetophenones and was explained by the effect of the cis-oriented [relative to the C₍₂₎ atom] OH group [4].

Despite the limited number of compounds in the investigated series of furfural oximes, we compare the CS of the ring protons and the carbon atoms with those for the corresponding 2-substituted furans [5], and we also formulated two-parameter correlation equations for the analysis of the transmission of the effects of the substituents on the shielding of the ring atoms. Equations (1)-(12) show that the sensitivity of the CS of the ring H and C atoms to the effect of the substituents in the oximes is lower or almost the same as that in α-substituted furans.

$$\delta_{4-H}(Z\text{-oximes}) = 1.42 + 0.83\delta_{3-H}(2\text{-R-furans}) \quad (r=0.926; s=0.61); \quad (1)$$

$$\delta_{4-H}(E\text{-oximes}) = 1.25 + 0.85\delta_{3-H}(2\text{-R-furans}) \quad (r=0.871; s=0.67); \quad (2)$$

$$\delta_{3-H}(Z\text{-oximes}) = 4.67 + 0.41\delta_{1-H}(2\text{-R-furans}) \quad (r=0.942; s=0.19); \quad (3)$$

$$\delta_{3-H}(E\text{-oximes}) = 3.47 + 0.52\delta_{1-H}(2\text{-R-furans}) \quad (r=0.680; s=0.27); \quad (4)$$

$$\delta_{C_{(5)}}(Z\text{-oximes}) = 2.48 + 0.99\delta_{C_{(2)}}(2\text{-R-furans}) \quad (r=0.997; s=8.03); \quad (5)$$

$$\delta_{C_{(5)}}(E\text{-oximes}) = 6.24 + 0.96\delta_{C_{(2)}}(2\text{-R-furans}) \quad (r=0.996; s=2.28); \quad (6)$$

$$\delta_{C_{(4)}}(Z\text{-oximes}) = 7.96 + 0.95\delta_{C_{(3)}}(2\text{-R-furans}) \quad (r=0.985; s=0.31); \quad (7)$$

$$\delta_{C_{(4)}}(E\text{-oximes}) = -12.30 + 1.12\delta_{C_{(3)}}(2\text{-R-furans}) \\ (r=0.988; s=2.90); \quad (8)$$

$$\delta_{C_{(3)}}(Z\text{-oximes}) = -2.46 + 1.08\delta_{C_{(4)}}(2\text{-R-furans}) \\ (r=0.975; s=0.62); \quad (9)$$

$$\delta_{C_{(3)}}(E\text{-oximes}) = -25.74 + 1.25\delta_{C_{(4)}}(2\text{-R-furans}) \\ (r=0.981; s=1.09); \quad (10)$$

$$\delta_{C_{(2)}}(Z\text{-oximes}) = 32.68 + 0.80\delta_{C_{(5)}}(2\text{-R-furans}) \\ (r=0.897; s=0.54); \quad (11)$$

$$\delta_{C_{(2)}}(E\text{-oximes}) = -2.70 + 1.06\delta_{C_{(5)}}(2\text{-R-furans}) \\ (r=0.877; s=0.21); \quad (12)$$

A similar decrease in the sensitivity of the ^1H and ^{13}C CS to the effect of the substituents was observed in 5-substituted 2-nitrofurans [6]; this is probably due to the nonlinearity of the effect of substituents in the 2 position on the resonance effects of substituents in the 5 position, as was previously noted for disubstituted benzenes [7].

It has been previously shown that the linear free energy (LFE) principles are applicable for the quantitative evaluation of the behavior of the shielding of various nuclei of the furan ring as a function of the electronic properties of the substituents [6], since satisfactory linear dependences of the changes in the CS of the protons and carbons with the Swain-Lupton F and R substituent reaction constants were observed. In the present research we attempted to develop one- and two-parameter correlations of the CS of the various nuclei of 5-R-furfural Z-oximes with the σ^* , σ_p , σ_I , $\sigma_I - \sigma_C$, and F-R substituent constants. The most satisfactory approximation of the CS is achieved when the Swain-Lupton F and R constants were used:

$$\delta_{4\text{-H}} = 6.81 + 0.555F + 2.530R \quad (r=0.995; s=0.15); \quad (13)$$

$$\delta_{3\text{-H}} = 7.25 + 0.109F + 0.625R \quad (r=0.999; s=0.01); \quad (14)$$

$$\delta_{C_{(4)}} = 116.07 - 1.143F + 10.049R \quad (r=0.979; s=4.74); \quad (15)$$

$$\delta_{C_{(3)}} = 117.67 + 2.414F - 4.635R \quad (r=0.999; s=0.39); \quad (16)$$

$$\delta_{C_{(2)}} = 147.56 + 0.803F - 1.302R \quad (r=0.998; s=1.95). \quad (17)$$

The CS of the 3-H and 4-H ring protons are determined primarily by transmission of the conjugation effects ($\rho_F/\rho_R < 1.0$). Their sensitivity to the inductive effects of the substituents is lower and their sensitivity to the resonance effects is higher than in the case of nitrofurans derivatives [6]:

$$\delta_{4\text{-H}}\rho_F(\text{oxime})/\rho_F(\text{NO}_2\text{-furan}) = 0.34; \quad \rho_R(\text{oxime})/\rho_R(\text{NO}_2\text{-furan}) = 12.52;$$

$$\delta_{3\text{-H}}\rho_F(\text{oxime})/\rho_F(\text{NO}_2\text{-furan}) = 0.83; \quad \rho_R(\text{oxime})/\rho_R(\text{NO}_2\text{-furan}) = 1.20.$$

The CS of the ring carbon nuclei for the Z isomers are determined primarily by transmission of the conjugation effects ($\rho_F/\rho_R \leq 0.62$). However, a comparison of the changes in the sensitivities of the oximes and furans is hindered markedly because of the lack of a series with the same set of substituents.

The CS of the side-chain atoms also display sensitivity to the effects of the substituents. A satisfactory correlation of δ_{H_α} and δ_{C_α} with the F and R constants of substituents is observed:

$$\delta_{H_\alpha} = 7.595 + 0.114F + 0.596R \quad (r=0.999; s=0.02); \quad (18)$$

$$\delta_{C(\alpha)} = 136.60 - 1.25F + 0.67R \quad (r=0.999; s=0.05). \quad (19)$$

The ρ_F/ρ_R value of 0.19 in Eq. (18) is close to the ratio for the 3-H and 4-H ring protons in Eqs. (13) and (14). This is a confirmation of the fact that the furan ring and the oxime group form a unified π -electron system in these compounds.

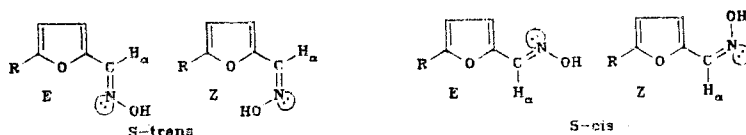
The ^{15}N spectra of oximes III, V, and VI are represented by two signals with different half widths, whereas the spectra of I and II are represented by one narrow line (Table 2). In experiments with population polarization transmission (INEPT and DEPT) it was demonstrated that the broader signal at weak field is related to the absorption of the ^{15}N nucleus in the Z isomer. The differences in the ^{15}N CS of the two isomers range from 4.5 to 6.9 ppm and have a tendency to increase as the electron-donor properties of the substituents become more pronounced.

The ^{15}N CS of 5-R-furfur-2-yl Z-oximes correlate best with the σ_p constants of R in accordance with Eq. (20):

$$\delta_{^{15}\text{N}} = 22.73\sigma_p - 16.42 \quad (r=0.981; s=1.05). \quad (20)$$

Since the furan ring is smaller, the effect of substituents on the shielding of nitrogen is transmitted through the furan ring better by a factor of ~ 1.5 than through the phenyl ring (in the system of p-substituted N-phenylbenzylideneimines $p\text{-R-C}_6\text{H}_4\text{-CH=}^{15}\text{N-C}_6\text{H}_5$, $\delta_{^{15}\text{N}} = 19.36 \sigma_p - 56.01$; $r = 0.993$; $s = 0.16$; the correlation was made on the basis of the data in [8]).

The magnitude of the vicinal constant of spin-spin coupling between the ring protons changes little when the substituents in the 5 position are replaced and when the geometry of the side chain changes. In the ^1H NMR spectra the 4-H signals display additional splitting from coupling with the H_α proton; this additional splitting is 0.2–0.3 Hz for the E isomers. At the same time, this constant is 0.6–0.8 Hz ($\text{R} = \text{Me}, \text{H}, \text{SiMe}_3, \text{GeMe}_3$) for the Z isomers. An analysis of these constants on the basis of the stereospecificity of the long-range ^5J SSCC in furfural and 2-furfural oxime [9] indicates that the E isomers in solutions in dimethyl sulfoxide (DMSO) have primarily an s-trans conformation, whereas the Z isomers, in contrast to the former, have an s-cis conformation:



In Z isomer V ($\text{R} = \text{Br}$) the SSCC decreases to 0.4 Hz, i.e., this isomer exists with almost equal probability in the s-cis and s-trans conformations.

The geminal ^{15}N - ^1H SSCC (see Table 1) of the Z isomers change little when the substituents are replaced (14.55 ± 0.25 Hz), and only the nitro group decreases this constant to 13.6 Hz. In the case of the E isomers the changes in these constants do not exceed the errors in the measurements. The second geminal constants for spin-spin coupling (SSCC) with the hydroxy proton are almost the same for the two isomers (1.2 ± 0.3 Hz for the Z isomer, and 1.5 ± 0.1 Hz for the E isomer). Nevertheless, this is completely sufficient for the determination of the primary conformation of the O-H bond relative to the unshared pair of electrons of the nitrogen atom. According to [3, 4, 10, 11] the O-H bond in the E isomers is trans-oriented, whereas in the Z isomers the orientation changes from trans ($\text{R} = \text{H}$) to cis (for the remaining R). We were unable to detect the ^{15}N - H_α SSCC in the spectra of the investigated compounds, since they are masked by coupling with H_α .

The ^{13}C - ^{15}N SSCC (Table 2) change little on passing from one substituent to another. It is extremely likely that perturbations of the π system play a secondary role here.

The high solubility of oxime III made it possible to record the ^{13}C NMR spectrum in CDCl_3 . The $^1\text{J}_{\text{C}_\alpha\text{-}^{15}\text{N}}$ constant of the E isomer in chloroform is 1.7 Hz smaller than in dimethyl sulfoxide, whereas $^2\text{J}_{\text{C}_2\text{-}^{15}\text{N}}$ increases from -8.3 Hz to -7.3 Hz. The observed effect of the medium provides a basis for the assumption that, just as in benzaldoxime [12], the direct $\text{C}(\alpha)$ - ^{15}N SSCC in the oximes are negative. On passing from CDCl_3 to dimethyl sulfoxide

one might expect destruction of the weak substance-solvent complexes and self-associates and the formation of stronger complexes with d_6 -DMSO. In this case, according to [13], an increase in the contribution (positive) of the orbitals of the unshared pair of electrons of nitrogen to the overall 1J SSCC occurs, and this makes it more positive. If the direct constant is also negative for the Z isomers, the larger $^1J_{C_\alpha-^{15}N}$ constants of the Z isomers of 5-R-furfural oximes as compared with the 1J constants of the E isomers are also explainable within the framework of the same model. The reverse trend of the changes in the geminal constant in E isomer III on passing from $CDCl_3$ to d_6 -DMSO also corresponds to an increase in the contribution from the orbitals of the unshared pair of the electrons of nitrogen. In contrast to $^1J_{C_\alpha-^{15}N}$, this contribution is negative, as a result of which, the $^2J_{C_2-^{15}N}$ SSCC becomes smaller (on the basis of this, the geminal constant of the E isomer can be considered to be < 0). This explanation is also in good agreement with the small (but positive) values of the geminal SSCC in the case of the Z isomers of 5-R-furfural oximes and with the decrease in their values on passing from $CDCl_3$ to d_6 -DMSO. A similar situation was previously observed for acetophenone oxime [4] and formaldoxime [14]: a negative (large in absolute value) geminal $^{13}C-^{15}N$ SSCC was found if the unshared pair of nitrogen and the coupling nucleus were cis-oriented. On the other hand, this constant became smaller in absolute value and positive in the case of a trans-orientation of the pair of unshared electrons and the coupling nucleus.

The changes in $^3J_{C_3-^{15}N}$ and the long-range $C_5-^{15}N$ SSCC in the E and Z isomers of the investigated oximes as a function of R are small and irregular. In order to understand them one should draw upon theoretical calculations, as Buchanan and Dawson [11] did for aromatic oximes.

EXPERIMENTAL

The 1H NMR spectra of 5-7% solutions of the compounds in $CDCl_3$ in d_6 -DMSO were obtained at room temperature (22°C) with a Bruker WH-90/DS spectrometer (90 MHz) by the standard method. The ^{13}C NMR spectra of 30-40% solutions of the compounds in d_6 -DMSO were obtained with the same spectrometer (22.63 MHz) at sample temperatures ranging from 35°C to 40°C. The resonance was excited with 5- μ sec pulses. The free-induction signal was recorded in an 8 K operative memory. After storage, the operative memory was increased to 16 K. This determined the accuracy in the measurement of the CS (± 0.1 ppm) and the SSCC (± 0.1 Hz). In both cases the internal standard was cyclohexane, the CS of which, relative to tetramethylsilane (TMS), were assumed to be $\delta = 1.44$ ppm (1H) and $\delta = 27.4$ ppm (^{13}C). The ^{15}N NMR spectra were also investigated with a Bruker WH-90/DS spectrometer (9.12 MHz) for samples prepared for the ^{13}C NMR investigations. The width of the excitation pulses was 10 μ sec, and their sequential frequency was 0.5 Hz. The volume of the operative memory was 8 K. At a spectral scanning width (with noise suppression) of 3 kHz the accuracy in the determination of the CS was ± 0.3 ppm. As the external standard we used ^{15}N -labeled nitromethane, the CS of which was assumed to be 0 ppm.

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SYNTHESIS AND REACTIONS OF SOME BENZOFURAN β -
 AND γ -KETOACIDS

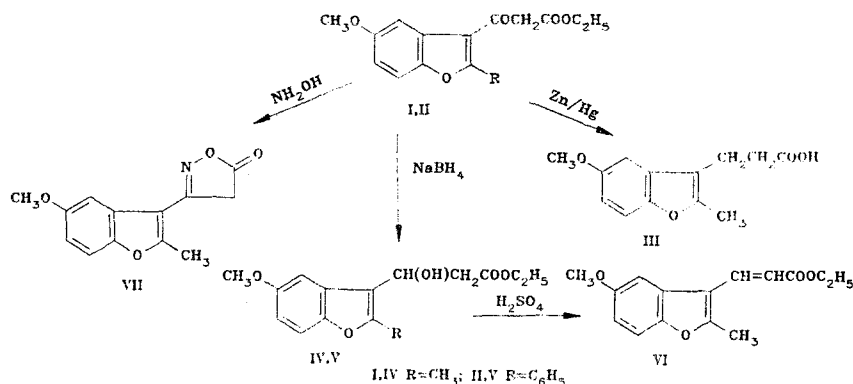
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Derivatives of 5-hydroxybenzofuroyl-3-acetic and propionic acids were synthesized, and some of the reactions were studied.

Esters of β -ketoacids are widely known as intermediates in the synthesis of a variety of aliphatic-aromatic, and, especially, heterocyclic compounds. However, their heterocyclic analogs — ethyl esters of benzofuroyl acids — have not been synthesized. Moreover, they are important compounds in the synthesis of benzofuran derivatives; for example, in the present work they are converted to benzofuroylpropionic, benzofuroylacrylic, and benzofuroylbutyric acid derivatives, compounds which have been used in a number of chemical and biological studies.

We obtained the ethyl esters of α -(2-methyl-5-methoxybenzofuroyl-3)-acetic acid (I) and α -(2-phenyl-5-methoxybenzofuroyl-3)-acetic acid (II) by the benzoyl-acetic ester synthesis [1] from the acid chlorides of 2-methyl- and 2-phenyl-5-methoxybenzofuran-3-carboxylic acids. The reduction of the ketoacid esters I and II was studied. The reduction of I with zinc amalgam gave β -(2-methyl-5-methoxybenzofuroyl-3)propionic acid (III), and the reduction of I and II with sodium borohydride gave the ethyl esters of β -(2-methyl- (IV) and β -(2-phenyl-5-methoxybenzofuroyl-3)- β -hydroxypropionic acids (V). The latter on dehydration in acetic acid in the presence of a catalytic amount of concentrated sulfuric acid gave the ethyl ester of β -(2-phenyl-5-methoxybenzofuroyl-3)acrylic acid (VI). Compound I with hydroxylamine gave 3-(2'-methyl-5'-methoxybenzofuroyl-3')isoxazolin- Δ^2 -5-one (VII).



The reaction of the sodium derivatives of the esters of the β -ketoacids I and II of bromoacetic ester gave the ethyl esters of β -carbethoxy- β -(2-methyl- (VIII) and β -carbethoxy- β -(2-phenyl-5-methoxybenzofuroyl-3)propionic acid (IX)) respectively. Heating compounds VIII and IX with hydrochloric acid in alcohol gave the ethyl esters of β -(2-methyl- (X) and β -(2-phenyl-5-methoxybenzofuroyl-3) propionic acid (XI)), and treatment of compound VIII with sulfuric acid in acetic acid gave β -(2-methyl-5-methoxybenzofuroyl-3)propionic acid (XII). From compound X was obtained the oxime XIII and the thiosemicarbazone XIV. Treatment of the ester X with zinc amalgam in hydrochloric acid gave γ -(2-methyl-5-methoxybenzofuroyl-3)

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