INVESTIGATION OF THE DIRECTION OF ENOLIZATION OF SOME FURYL-SUBSTITUTED β-DIKETONES

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It was found that ω-benzoyl-2-acetyl-, ω-benzoyl-2-acetyl-5-bromo-, ω-(2-thenoyl-2-acetyl-, and ω-(5-bromo-2-thenoyl)-2-acetyl-bromofurans are enolized at the carbonyl group in the α position relative to the furyl grouping.

Yur'ev and co-workers have shown that heterocyclic substituents are arranged in the following order with respect to their capacity for enolization of the methylene-1,3-dicarbonyl system of β-diketones: phenyl <2-selenienyl<2-thienyl (for example, see [1, 3] and the literature cited therein).

In order to ascertain the effect of the 2-furyl group on the enolization of the $-COCH_2CO-$ system, we successfully used the reaction of furyl-substituted β-diketones with hydroxylamine, which gives isoxazole derivatives, the structure of which was proved by alternative synthesis.

ω-Benzoyl-2-acetylfuran (VIIa) and ω-benzoyl-2-acetyl-5-bromofuran (VIII) react with an equivalent amount of hydroxylamine hydrochloride to give only 3-phenyl-5-(2-furyl)isoxazole (Va) and 3-phenyl-5-(5-bromo-2-furyl)isoxazole (VI), respectively. This unambiguously indicates that diketones VIIa and VIII are enolized primarily at the carbonyl group in the α position relative to the heterocyclic substituent.

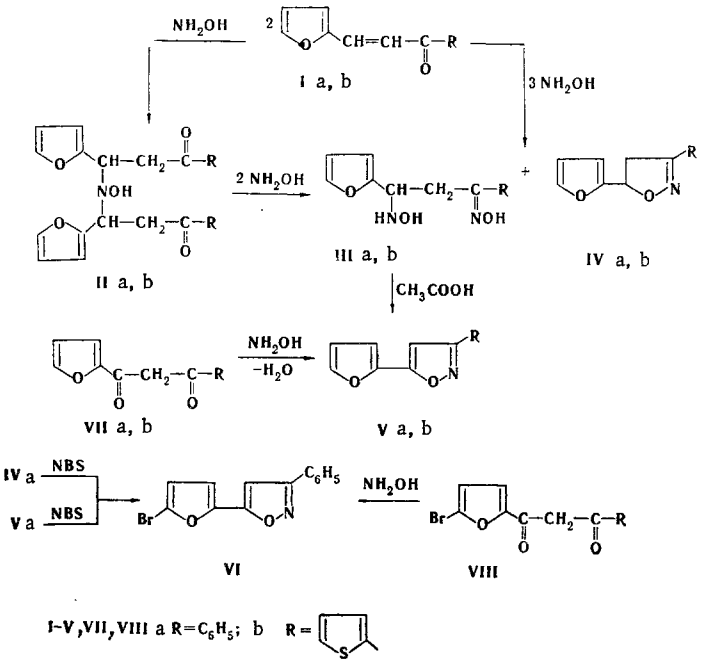

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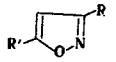
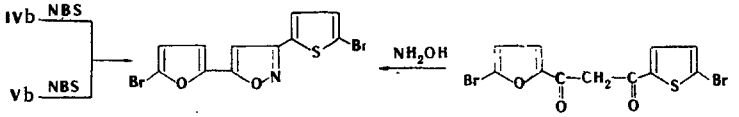
TABLE 1. UV Spectra of Isoxazole Derivatives



Compound	R	R′	λ_{max}, nm	lg ε	Literature data (6)	
					λ_{max}, nm	lg ε
Va	Phenyl	2-Furyl	245 281	4,25 4.34	244 284	4,23 4,31
VI	Phenyl	5-Bromo-2-furyl	245 288	4,12 4.26	244 292	4,20 4,39
Vb	2-Thienyl	2-Furyl	250 290	4,12 4,25	—	—
IX	5-Bromo-2-thienyl	5-bromo-2-furyl	265 300	4,21 4.45	—	—

Isoxazole Va was also obtained from 2-furfurylideneacetophenone (Ia). Reaction of isoxazole Va with N-bromosuccinimide (NBS) gave 3-phenyl-5-(5-bromo-2-furyl)isoxazole (VI), which was identical to the compound obtained from ω-benzoyl-2-acetyl-5-bromofuran (VIII). (Bromofuryl)isoxazole VI is also formed as a result of dehydrogenation and bromination of 3-phenyl-5-(2-furyl)-Δ^2-isoxazoline (IVa).

A comparison of the enolizing capacity of unsubstituted and substituted furan rings with the analogous properties of the thienyl grouping was accomplished on the basis of ω-(2-thenoyl)-2-acetylfuran (VIIb) and ω-(5-bromo-2-thenoyl)-2-acetyl-5-bromofuran (X), which we have previously described [4, 5]. It was found that under the influence of hydroxylamine, VIIb forms exclusively 3-(2-thienyl)-5-(2-furyl)isoxazole (Vb), whereas X gives 3-(5-bromo-2-thienyl)-5-(5-bromo-2-furyl)isoxazole (IX). Compounds Vb and IX were obtained by alternative synthesis from 2-furfurylidene-2-acetylthiophene (Ib). On reaction with insufficient hydroxlamine, ketone Ib formed N,N-bis[1-(2-furyl)-2-(2-thenoyl)ethyl]hydroxylamine (IIb), whereas on reaction with excess hydroxylamine it gave a mixture of 2-[β-(2-furyl)-β-hydroxylaminopropionyl]thiophene oxime (IIIb) and 3-(2-thienyl)-5-(2-furyl)-Δ^2-isoxazoline (IVb). A mixture of IIIb and IVb was also obtained as a result of heating hydroxylamine hydrochloride with hydroxylamino ketone IIb. Substituted isoxazole Vb, which was identical to the product of cyclization of diketone VIIb, was obtained by heating the hydroxylamino oxime with acetic acid. On reaction with NBS isoxazole Vb readily forms 3-(5-bromo-2-thienyl)-5-(5-bromo-2-furyl)isoxazole (IX), which is identical to the preparation obtained from ω-(5-bromo-2-thenoyl)-2-acetyl-5-bromofuran (X).



IX X

The structures of IVa,b and the Δ^2-isoxazoline derivatives were confirmed by their UV (absorption maximum at 260-280 nm) and IR (the absence of an NH band above 3000 cm^{-1}) spectra. In addition to the multiplet of aromatic protons (τ 2.5-4.2), a two-proton doublet (τ 6.45, J = 9.8 Hz) of a CH_2 group and a one-proton triplet (τ 4.46, J = 9.8 Hz), corresponding to the α-proton of the Δ^2-isoxazoline ring, are also observed in their PMR spectra.

The UV spectra, in which two characteristic absorption maxima at 245-265 and 280-300 nm are observed (Table 1), proved to be particularly useful for the identification of 3,5-disubstituted isoxazoles Va,b, VI, and IX, whereas the known [6] isomers of isoxazoles Va and VI [3-(2-furyl)- and (5-bromo-2-furyl)-5-phenylisoxazoles] have only one absorption maximum at 270-294 nm.

Thus β-diketones VIIa,b, VIII, and X are enolized at the carbonyl group adjacent to the furyl grouping, and the capacity of substituents for enolization of the $-COCH_2CO-$ β-dicarbonyl system increases in the order phenyl<2-selenienyl<2-thienyl<2-furyl.

EXPERIMENTAL

ω-Benzoyl-2-acetylfuran (VIIa), ω-benzoyl-2-acetyl-5-bromofuran (VIII), ω-(2-thenoyl)-2-acetylfuran (Vb), and ω-(5-bromo-2-thenoyl)-2-acetyl-5-bromofuran (X) were obtained by the methods in [4, 5].

N,N-Bis[1,2-furyl)-2-benzoylethyl]hydroxylamine (IIa). A solution of 1.8 g (0.026 mole) of hydroxylamine hydrochloride in 3 ml of water was added to a solution of 2.1 g (0.037 mole) of potassium hydroxide in 100 ml of methanol, and the precipited KCl was removed by filtration and washed with 10 ml of methanol. A 9.9-g (0.05 mole) sample of freshly distilled 2-furfurylideneacetophenone (Ia) was added to the filtrate, and the mixture was held at room temperature for 20 h. The crystalline precipitate was removed by filtration and washed with cold methanol to give 9.6 g (90 %) of colorless needles with mp 116° (from methanol). Found: N 3.3 %. $C_{26}N_{23}NO_5$. Calculated: N 3.3%.

β-(2-Furyl)-β-hydroxylaminopropiophenone Oxime (IIIa) and 3-Phenyl-5-(2-furyl)-Δ^2-isoxazoline (IVa). A) A solution of 13.8 g (0.2 mole) of hydroxylamine hydrochloride in 30 ml of water and a solution of 16.8 g (0.3 mole) of potassium hydroxide in 40 ml of water were added to a solution fo 9.9 g (0.05 mole) of 2-furfurylideneacetophenone (Ia) in 200 ml of methanol, and the mixture was heated on a water bath for 3 h. The methanol was removed by vacuum distillation, and the residue was treated with 200 ml of water. The resulting oil was extracted with ether, and the combined extracts were washed with water and dried over magnesium sulfate. The solvent was removed by distillation, and residual isoxazoline IV was crystallized from dilute methanol to give 1.9 g (18 %) of colorless needles with mp 80-81 deg (mp 81-82 deg [7]) and λ_{max} 263 nm (log ε 3.86).

The aqueous layer remaining after extraction with ether was neutralized with dilute hydrochloric acid, and the resulting precipitate was removed by filtration and washed with water to give 5 g (40%) of oxime IIIa as colorless needles with mp 162° (from benzene). Found: N 11.4 %. $C_{13}H_{14}N_2O_3$. Calculated: N 11.4%.

B) A solution of 5.6 g (0.08 mole) of hydroxylamine hydrochloride in 15 ml of water and a solution of 6.7 g (0.12 mole) of potassium hydroxide in 15 ml of water were added to a suspension of 15.9 g (0.037 mole) of hydroxylamino ketone IIa in 350 ml of methanol, and the mixture was heated on a water bath for 1 h. The methanol was removed by vacuum distillation, and the residue was poured into 200 ml of cold water. The resulting oil was extracted with ether, and the extracts were washed with water and dried with anhydrous magnesium sulfate. The ether was removed by distillation, and the residue was crystallized from dilute methanol to give 3.5 g (22 %) of isoxazoline IVa. The product was identical to the preparation obtained by method A. Oxime IIIa [4.65 g (24 %)] was then isolated as described above.

3-Phenyl-5-(2-furyl)isoxazole (Va). A) A 4.9-g (0.02 mole) sample of oxime IIIa was heated in 100 ml of glacial acetic acid on an oil bath for 3.5 h, after which the mixture was cooled and poured into 150 ml of cold water. The aqueous mixture was then shaken repeatedly with 2 N sodium hydroxide solution. The undissolved solid was removed by filtration and washed repeatedly with water to give 3.6 g (80 %) of colorless needles of Va with mp 82° (from petroleum ether) (mp 78-79 [8] and 95-96° [9]). Found: N 6.6 %. $C_{13}H_9NO_2$. Calculated: N 6.6%.

B) A mixture of 2 g (0.009 mole) of ω-benzoyl-2-acetylfuran (VIIa), 1 g (0.014 mole) of hydroxylamine hydrochloride, 10 ml of pyridine, and 50 ml of ethanol was heated on a water bath for 4 h after which it was allowed to stand at room temperature for 24 h. It was then poured into 200 ml of water, and the resulting precipitate was removed by filtration and washed repeatedly with water to give 1.6 g (84 %) of colorless needles with mp 82° (from petroleum ether). No melting-point depression was observed for a mixture of products obtained by methods A and B.

3-Phenyl-5-(5-bromo-2-furyl)isoxazole (VI). A) A 10.2-g (0.056 mole) sample of NBS and a few crystals of azobisisobutyronitrile (AIBN) were added to a solution of 5.97 g (0.028 mole) of isoxazoline IVa in 80 ml of carbon tetrachloride, and the mixture was heated on a water bath for 15 min. The succinimide was separated, the solution was concentrated, and precipitated isoxazole VI was removed by filtration to give 3.3 g (44 %) of colorless needles with mp 108° (from methanol) (mp 108° [6] and 129-131° [8]). Found: Br 27.3; N 4.8 %. $C_{13}H_{10}BrNO_2$. Calculated: Br 27.4; N 4.8%.

B) A 10.2-g (0.056 mole) sample of NBS and a few crystals of AIBN were added to a solution of 5.91 g (0.028 mole) of isoxazole Va in 80 ml of carbon tetrachloride, and the mixture was stirred at room temperature for 30 h. Workup of the reaction mixture as described above gave 3.4 g (42 %) of bromide VI with mp 108° (from methanol).

C) A mixture of 2.6 g (0.009 mole) of diketone VIII, 1 g (0.014 mole) of hydroxylamine hydrochloride, 10 ml of pyridine, and 50 ml of ethanol was heated on a water bath for 4 h, after which it was poured into 200 ml of cold water. The resulting precipitate was removed by filtration and washed with water to give 2.2 g (86 %) of (bromofuryl)isoxazole VI with mp 108°. No melting-point depression was observed for a mixture of all three preparations obtained by methods A-C.

N,N-Bis[1-(2-furyl)-2-(2-thenoyl)ethyl]hydroxylamine X(IIb). The method used to prepare hydroxylamine II was used to prepare colorless needles with mp 112° in 90% yield. Found: N 3.2%. $C_{22}H_{19}NO_5S_2$. Calculated: N 3.2%.

2-[β-(2-Furyl)-β-hydroxylaminopropionyl]thiophene Oxime (IIIb) and 3-(2-Thienyl)-5-(2-furyl)-Δ^2-isoxazoline (IVb). A) The method used to prepare IIIa and IVa (method A) was used to obtain a mixture of these compounds from 2-(1-furfurylideneacetyl)thiophene. Oxime IIIb with mp 157° was obtained in 57% yield. Found: N 11.1%. $C_{11}H_{12}N_2O_3S$. Found: N 11.1%. Isoxazoline IVb with mp 61-62° and λ_{max} 280 nm (log ε 4.05) was obtained in 20% yield. Found: N 6.4%. $C_{11}H_9NO_2S$. Found: N 6.4%.

B) The method used to prepare IIIa and IVa (method B) was used to obtain a mixture of these compounds. The yield of oxime IIIb was 20%, and the yield of isoxazoline IVb was 20%.

3-(2-Thienyl)-5-(2-furyl)isoxazole (Vb). A) The method used to obtain isoxazole Va (method A) was used to prepare this compound in 66% yield as colorless needles with mp 92° (from petroleum ether). Found: N 6.4%. $C_{11}H_7NO_2S$. Calculated: N 6.4%.

B) This compound was also obtained in 84% yield by the method used to prepare isoxazole Va (method B). No melting-point depression was observed for a mixture of the compounds obtained by methods A and B.

3-(5-Bromp-2-thienyl)-5-(5-bromo-2-furyl)isoxazole (X). A) As in the preparation of isoxazole VI, workup of the reaction mixture obtained from 6.13 g (0.028 mole) of isoxazoline IVb and 15.3 g (0.084 mole) of NBS in 100 ml of carbon tetrachloride in the presence of AIBN gave 3.7 g (35%) of colorless needles with mp 157° (from methanol). Found: Br 42.6; N 3.8%. $C_{11}H_5Br_2NO_2S$. Calculated: Br 42.6; N 3.7.

B) As in the preparation of isoxazole Va, 6.08 g (0.028 mole) of isoxazole Vb was brominated with ~15.3 g (0.084 mole) of NBS in 100 ml of CCl_4 in the presence of AIBN. The yield was 3.15 g (30%).

C) The method used to obtain isoxazole VI (method C) gave this compound in 80% yield.

No melting-point depression was observed for a mixture of all three preparations obtained by methods A-C.

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