SYNTHESIS AND PROPERTIES OF AZOLES AND THEIR DERIVATIVES
27.* REACTION OF POTASSIUM SALTS OF 3,5-DIARYL-2-ISOXAZOLYL-4-NITRONIC ACIDS WITH MINERAL ACIDS

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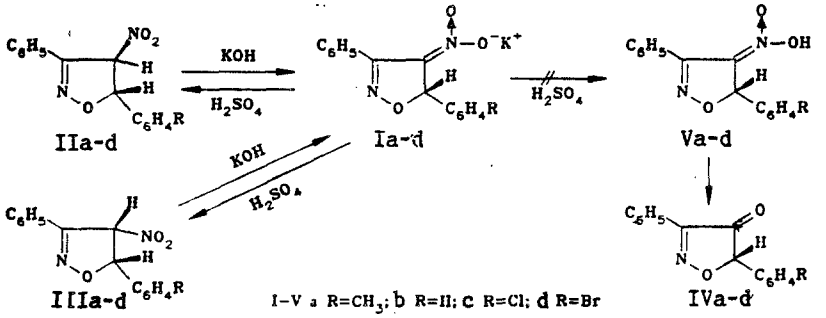
It has been shown that under the conditions of the Nef reaction potassium salts of 3,5-diaryl-2-isoxazolyl-4-nitronic acids form trans-3,5-diaryl-4-nitro-2-isoxazolines instead of the expected 3,5-diaryl-4-isoxazolones. The epimerization of the stereoisomeric 3,5-diaryl-4-nitro-2-isoxazolines in the presence of basic catalysts has been discussed.

Continuing our systematic studies in the chemistry of thenitroisoxazolines [2-4], we have studied the behavior of the potassium salts of 3,5-diaryl-2-isoxazolyl-4-nitronic acids Ia-d under the conditions of the Nef raction [5, 6].

It is known [5] that, under the action of dilute mineral acids, alkali salts of the aci-form of nitroalkanes form ketones. Since 3,5-diaryl-4-nitro-2-isoxazolines IIa-d, IIIa-d are formally secondary nitrocompounds, one might suppose that acid hydrolysis of the salts would lead to the 3,5-diaryl-4-isoxazolones IVa-d. Compounds of this class are of interest both from the point of view of their reactivity and also in the preparation of new physiologically active compounds [7, 8].

The potassium salts Ia-d were prepared by the method of [9] from trans-isoxazolines (IIa-d). The salts were reacted, without isolation, with H_2SO_4 (10-25N) or HCl (5-10N) at 0, 20, and 40°C. It was found, however, that under these conditions the isoxazolones IVa-d were not formed. Instead, a quantitative yield of the starting materials, the trans-isoxazolines II, was obtained.



Such unexpected behavior of the salts Ia-d under the conditions of the Nef reaction is evidently the results of resonance stabilization of the nitro-anion on account of conjugation of the C═NOO⁻ group with the C═N bond of the heterocyclic ring. This leads to a relative reduction in the electron density on the oxygen atoms of the nitro group and favors protonation at the $C_{(4)}$ atom of the ring. As a result, the starting material is formed and not the corresponding nitronic acid which would be a necessary intermediate in the formation of a carbonyl compound by the mechanism of the Nef reaction [10].

Quantum chemical calculations by the MNDO method showed, for the 2-isoxazolyl-4-nitronic acid anion, that the charges on the oxygen atoms of the nitro group and on the $C_{(4)}$ atom of the ring were practically indistinguishable (Fig. 1). In this case, according to PMO theory [11] the proton must be added at the point of highest electron density in [VZMO], i.e., at the $C_{(4)}$ atom, as we found in our experiments.

It should be noted that potassium salts prepared in a similar way from cis-2-isoxazolines IIIa-d are also completely converted under acid hydrolysis conditions to the trans-derivatives, i.e., there is an inversion of configuration of the $C_{(4)}$ atom of the initial isoxazoline. This shows that the reaction takes place via a nitronic acid anion Ia-d which is common to both epimers. Since there is no doubt that the dipole moments of the trans- and cis-isomers are different, their ratio in the reaction mixture must be sensitive to the dielectric constant ε of the medium: the more polar solvent

*See [1] for Communication 26.

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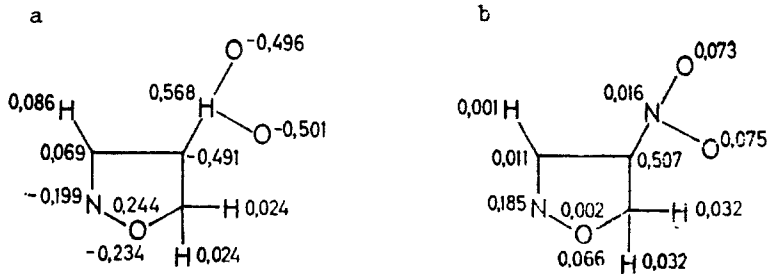

Fig. 1. Overall electron charges (a) and boundary electron densities (b) calculated by the MNDO method for the anion of 2-isoxazolyl-4-nitronic acid.

TABLE 1. Ratio of Stereoisomeric 2-Isoxazolines IIc and IIIc in Equilibrium Mixtures at 25°C (from PMR spectral data)

Initial compound	Solvent	ε	Base	Ratio of stereoisomers IIc/IIIc
IIc	CD_3OD	33,0	CD_3OK	>10:1
IIIc	CD_3OD	33,0	CD_3OK	>10:1
IIc	CD_3OD	33,0	$C_5H_{11}N$	>10:1
IIIc	CD_3OD	33,0	C_5H_5N	>10:1
IIc	CD_3OD	33,0	$(C_2H_5)_3N$	>10:1
IIc	C_6D_6	2,3	$(C_2H_5)_3N$	4:1
IIIc	C_6D_6	2,3	$(C_2H_5)_3N$	3,8:1
IIc	$CDCl_3$	4,5	$(C_2H_5)_3N$	4:1
IIIc	$CDCl_3$	4,5	$(C_2H_5)_3N$	4,1:1

must favor the more polar isomer [12]. In fact, in solution in deuteromethanol in the presence of catalytic quantities of potassium deuteromethoxide, morpholine, deuteropyridine, or triethylamine the equilibrium trans-3-phenyl-5-(p-chlorophenyl)-4-nitro-2-isoxazoline (IIc) ⇄ cis-3-phenyl-5-(p-chlorophenyl)-4-nitro-2-isoxazoline (IIIc) is shifted, according to the PMR spectra,* in the direction of the trans-isomer by more than 90%. In the less polar deuterobenzene or deuterochloroform the trans-isomer content is lower although still greater than that of the cis-isomer (Table 1).

This denotes that attack by a proton on the prochiral center of the anion of I takes place preferably from the more shielded enantiotopic side. This, at first sight unintelligible, fact can apparently be explained from kinetic considerations: the trans-isomer has fewer torsional stresses, originating in the aryl substituent at position 5 and the nitro group in position 4, than the cis-isomer. Consequently, the corresponding transition state must be energetically more favorable.

It is interesting to note that trans-3,4-diaryl-5-nitro-2-isoxazolines which are regioisomers of compound II react quite differently with nucleophilic reagents: independently of the polarity of the solvent, rupture of the heterocyclic ring occurs [2].

EXPERIMENTAL

PMR spectra were run on a Tesla BS 487C instrument with TMS internal standard. Control of the purity of the reagents was effected by TLC on Kieselgel HF 254 plates from Merck. The eluent was 1:1 cyclohexane and visualization was by iodine vapor.

Potassium salts Ia-d were prepared by the action of equimolar quantities of potassium hydroxide on trans- and cis-2-isoxazolines IIa-d and IIIa-d at 20°C by the method of [9]. The synthesis and physical characteristics of compounds IIa-d and IIIa-d are given in [13, 14].

Hydrolysis of Potassium Salts of 3,5-Diarylisoxazolyl-4-nitronic Acid Ia-d. To 30 ml of 10-25 N H_2SO_4 or 5-10 N HCl was added, dropwise with vigorous stirring, a solution of 5 mmole of the appropriate potassium salt in 10-20 ml water. The precipitate which formed was filtered off, washed several times on the filter with cold water, dried in air, and analyzed. The melting points R_f, and PMR spectra of the compounds prepared were in complete agreement with those given in [13] for compounds IIa-d.

*A doublet of doublets at 5.11 ppm with coupling constant 9.3 Hz is assigned to the protons of the azoline ring of the cis-isomer, and at 5.72 ppm (3.7 Hz) to the protons of the trans-isomer.

Epimerization of cis- and trans-3-Phenyl-5-(p-chlorophenyl)-4-nitro-2-isoxazolines (IIIc, IIc). A solution of 0.05 g of the appropriate stereoisomer in 0.5 ml deuterated solvent was placed in an NMR tube and a drop of ~1% solution of base added. The solution was kept for 20-30 min and then the PMR spectrum was run. The ratio of the stereoisomers in the reaction mixture was established by comparison of the integrals of the proton signals from the heterocycle ring of both isomers (Table 1).

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SYNTHESIS OF 2-FUNCTIONALLY SUBSTITUTED OXAZOLINES AND OXAZOLIDINES FROM METHYL BROMOPROPIOLATE AND β-AMINO ALCOHOLS

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The reaction of methyl bromopropiolate with β-amino alcohols containing a primary amino group generally results in the formation of 2-(methoxycarbonylmethyl)-Δ^2-1,3-oxazolines, while in the reaction with N-methyl- and N,N-dimethyl-substituted β-aminoalcohols, 2-(methoxycarbonylmethylene)-1,3-oxazolidines, or their salts are formed.

The reactions of carbonyl-containing acetylenic compounds and difunctional nucleophiles have already been investigated quite comprehensively and are widely used in the synthesis of various heterocyclic compounds [1-3]. However, data on the reaction of difunctional nucleophiles with carbonyl-containing haloacetylenes are sparse [4-6] and are limited mainly to ketones of the haloacetylene series. A thorough investigation of such reactions could serve as a basis for synthesis of new functionally substituted nitrogen- and oxygen-containing heterocyclic compounds.

In the present work we studied the reaction of methyl bromopropiolate (I) with β-amino alcohols. The synthesis was carried out in tetrahydrofuran with two equivalents of the β-amino alcohol. The additional equivalent of the amino alcohol is required for binding hydrogen bromide.

Using PMR spectroscopy (Table 1), it was found that oxazolines IIIa, c, d are formed in the reaction of β-amino alcohols IIa, c, d with methyl bromopropiolate, while in the case of amino alcohol IIb, an imine—enamine tautomerism IIIb ⇄ IVb takes place, whose equilibrium is shifted in the direction of oxazoline IIIb. Oxazolidine IVb exists in the form of an E-isomer, the higher thermodynamic stability of which is due to the formation of an intramolecular hydrogen bond.

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