REARRANGEMENT OF 1-OXA-2-AZOLES.

6.* REARRANGEMENT OF OXIMES OF 3-(PIPERIDINOCARBONYL) ISOXAZOLES

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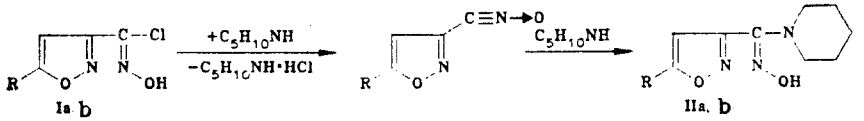
The Z isomers of oximes of 3-(piperidinocarbonyl)isoxazole are isomerized by acid to the thermodynamically more stable E isomers, which in the presence of base readily recyclize to the corresponding 3-amino-1,2,5-oxadiazoles.

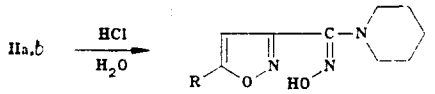
Earlier, we showed that Z—E isomerization of the N,N-disubstituted amidoxime of 1,2,4-oxadiazole-3-carboxylic acid is accompanied by a rearrangement with opening of the 1,2,4-oxadiazole ring and closure of the 1,2,5-oxadiazole ring [2]. The rearrangement takes place so easily that the intermediate E-oxime cannot be isolated. We have now studied the rearrangement of some analogous derivatives of the isoxazole series. The Z-isomers of the corresponding amidoximes were obtained by the reaction of the chloroximes Ia and Ib with piperidine. Excess piperidine was used as an acceptor for the hydrogen chloride:



Ia b IIa, b

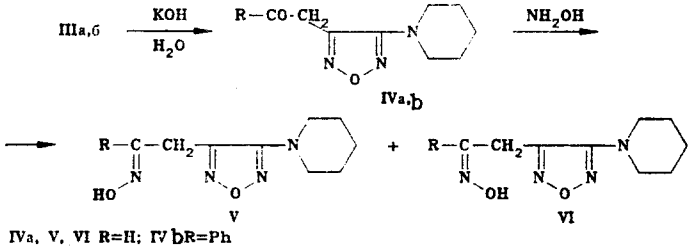
I–II a R=H; b R=Ph

Nitrile oxides are formed as intermediates in the reaction between amides and halogenoximes, and the addition of amines to these nitrile oxides proceeds stereospecifically with formation of the Z-isomers only [3]. The amidoximes IIa and IIb in dilute acid solutions were readily isomerized to the corresponding E-isomers IIIa and IIIb:



IIIa, b

The Z- and E-amidoximes are characterized by considerable difference in the chemical shifts of the OH proton [4] in the PMR spectra. The signal from the OH proton of the E-amidoximes IIIa, b showed an upfield shift of 0.6 ppm compared with that of the Z-isomers. As is known, signals due to protons in substituents attached to an oxime group show an upfield shift compared with protons where the substituent is in the anti position relative to the hydroxyl group [5]. In agreement with this, in the E-amidoximes IIIa, b the signals from the piperidine ring protons showed an upfield shift, and the signal from the isoxazole ring protons a downfield shift from those in the Z-amidoximes IIa, b (see Experimental).



IVa,b

V VI

IVa, V, VI R=H; IV bR=Ph

*For Communication 5, see [1].

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In contrast to the E-amidoximes 1,2,4-oxadiazole, the E-amidoximes of isoxazole were completely stable products, with no tendency to rearrange to the 1,2,5-oxadiazoles. However, the rearrangement occurs readily in the presence of alkali at room temperature (see above)

The rearrangement of the unsubstituted isoxazole derivative IIIa was carried out in the presence of hydroxylamine, and the product was isolated as the oxime, which PMR spectroscopic data showed was a 2:3 mixture of the syn- (V) and anti-isomers (VI). The structure of the isomers was determined from the PMR spectrum of the oxime V in which signals from the OH proton and the CH_2 group protons are upfield, and the aldoxime proton is downfield, compared with the corresponding proton signals in the oxime VI (data given in [5, 6]).

EXPERIMENTAL

PMR spectra were recorded on a Bruker WH-90 using DMSO-D_6 as solvent and TMS as internal standard. IR spectra were recorded on a Perkin—Elmer 580B instrument, samples were prepared as mulls with Nujol. The course of the reaction and the purity of the products were checked by TLC on Silufol UV-254 plates in 2:1 ether—hexane, and visualized in UV light. Elemental analysis data for C, H, and N were in good agreement with calculated values.

Z-Oxime-3-(piperidinocarbonyl)-5-isoxazole (IIa, $C_9H_{12}N_3O_2$). A solution of chloroxime Ia (0.2 g, 135 mmoles) in acetone (10 ml) was cooled to 5-10°C and added dropwise to a solution of piperidine (0.29 g, 3.40 mmoles) in acetone (3 ml). After 1 h the piperidine salt was filtered off, and the filtrate evaporated to dryness. Ethyl acetate was added to the residue, the solution washed with a small quantity of water, dried over Na_2SO_4, and evaporated to dryness. The product was washed with hexane to give 0.2 g (78%) of a crystalline material with mp 74-76°C. PMR spectrum: 1.55 (6H, broad s, 3'-5'-H); 3.23 (4H, broad s, 2',6'-H); 6.61 (1H, d, J = 2.0 Hz, 4-H); 8.89 (1H, d, J = 2.0 Hz, 5-H); 10.34 ppm (1H, s, OH). IR spectrum: 3200 (OH), 1645 (C=N), 957 cm^{-1} (N—OH [7]).

Z-Oxime-3-(piperidinocarbonyl)-5-phenylisoxazole (IIb, $C_{15}H_{17}N_3O_2$) was obtained by the preceding method from the chloroxime Ib in 71% yield, mp 99.0-99.8°C. PMR spectrum: 1.57 (6H, broad s, 3'-5'-H); 3.26 (4H, broad s, 2',6'-H); 7.03 (1H, s, 4-H); 7.53-7.89 (5H, m, C_6H_5); 10.33 ppm (1H, s, OH). IR spectrum: 3220 (OH), 1648 (C=N), 990 cm^{-1} (N—OH [7]).

E-Oxime-3-(piperidinocarbonyl)isoxazole (IIIa, $C_9H_{13}N_3O_2$). The Z-piperidonoxime IIa (0.14 g, 0.72 mmole) was dissolved in a mixture of concentrated HCl (0.2 ml) and water (0.5 ml). After 6 h, the reaction mixture was neutralized with saturated $NaHCO_3$ solution, and the precipitated material filtered off to give 0.11 g (82%), of the isoxazole IIIa. Mp 90.7-92.4°C. PMR spectrum: 1.53 (6H, broad s, 3'-5'-H); 2.98 (4H, broad s, 2',6'-H); 6.67 (1H, d, J = 2.0 Hz, 4-H); 8.98 (1H, d, J = 2.0 Hz, 5-H); 9.68 ppm (1H, s, OH). IR spectrum: 3270 (OH), 1630 (C=N), 945 cm^{-1} (N—OH [7]).

E-Oxime-3-(piperidinocarbonyl)-5-phenylisoxazole (IIIb, $C_{15}H_{17}N_3O_2$) was obtained in the same way as compound IIIa from Z-piperidinoxime IIb in 86% yield (0.13 g). Mp 110-11.5°C. PMR spectrum: 1.56 (6H, broad s, 3'-5'-H); 3.04 (4H, broad s, 2',6'-H); 7.15 (1H, s, 4-H); 7.54-7.9 (5H, m, C_6H_5); 9.77 ppm (1H, s, OH). IR spectrum: 3234 (OH), 1635 (C=N), 993 cm^{-1} (N—OH [7]).

3-Piperidino-4-phenacylfurazane (IVb, $C_{15}H_{17}N_3O_2$). A mixture of KOH (0.1 g, 1.78 mmoles), E-piperidinoxime IIIb (0.1 g, 0.37 mmole), and water (2.5 ml) was kept at room temperature for 1.5 h. The reaction mixture was neutralized with concentrated HCl, the precipitated material filtered off and washed with water to give 0.08 g (80%) of the furazane IVb with mp 61.5-63°C. PMR spectrum: 1.53 (6H, broad s, 3'-5'-H); 3.13 (4H, broad s, 2',6'-H); 4.81 (2H, s, 4-CH_2); 7.59-8.05 ppm (5H, m, C_6H_5). IR spectrum: 1685 (C=O), 1582 (C=N), 1000 cm^{-1} (furazane).

syn- and anti-Oximes of 3-piperidinofurazane-4-acetic aldehyde (V, VI, $C_9H_{14}N_4O_2$). A solution of E-piperidinoxime IIIa (0.06 g, 0.03 mmole), hydroxylamine hydrochloride (0.02 g, 0.35 mmole), and KOH (0.04 g, 0.7 mmole)in water (2 ml) was kept for 3 h at room temperature. The reaction mixture was neutralized with concentrated HCl, the product extracted with ethyl acetate, dried with Na_2SO_4, and evaporated to give 0.05 g (83%) of yellow oil, which from PMR data was shown to be a 2:3 mixture of syn- and anti-isomers V and VI. PMR spectrum: syn-isomer V: 1.61 (6H, broad s, 3'-5'-H), 3.20 (4H, broad s, 2',6'-H); 3.71 (2H, d, J = 5.0 Hz, 4-CH_2); 7.47 (1H, t, 4-CH); 10.88 ppm (1H, s, OH). PMR spectrum of anti-isomer VI: 1.61 (6H, broad s, 3'-5'-H); 3.20 (4H, broad s, 2',6'-H); 3.81 (2H, d, J = 5.0 Hz, 4-CH_2); 6.93 (1H, t, 4-CH); 11.37 ppm (1H, s, OH).

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