3 g (54%) of XIII with mp 164-166°C. Mass spectrum: $M^{+\cdot}$ 296.

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REACTION OF 2-ALKOXYCARBONYLMETHYL DERIVATIVES OF Δ^2-OXAZOLINE AND Δ^2-IMIDAZOLINE AND THEIR TAUTOMERS WITH 4-NITROBENZONITRILE N-OXIDE

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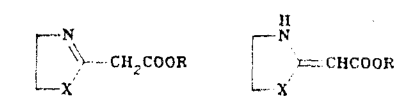
It was established that 2-alkoxycarbonylmethylene derivatives of oxazolidine and imidazolidine react readily with 4-nitrobenzonitrile N-oxide; the reaction takes place at the methylidyne carbon atom to give intermediate oximes, which can then undergo cyclization to isoxazoles. Their tautomers — benzimidazole and Δ^2-oxazoline derivatives — react with considerably greater difficulty; in the first case the reaction takes place at a different center, viz., the ring nitrogen atom.

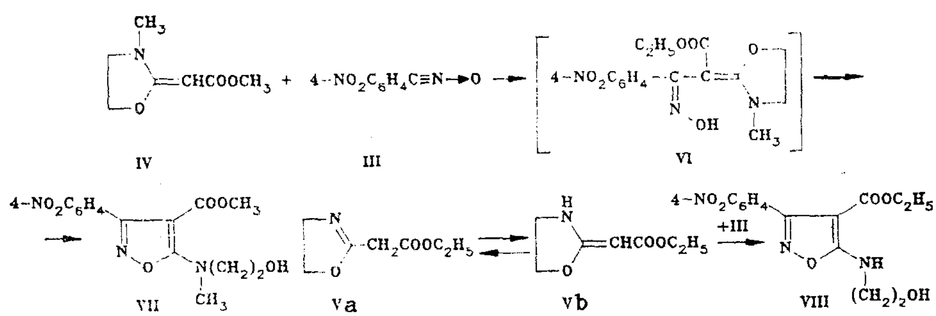
It is known that oxazolines and imidazolines in which a methylene fragment bonded to an electron-acceptor substituent (an ester group) is present in the 2 position can exist in two tautomeric forms [1-3]:



I II

X=O, NH

To study the effect of the tautomerism of derivatives I and II on their reactivities we investigated the reaction of these compounds with 4-nitrobenzonitrile N-oxide (III). The N-oxide was generated in situ by dehydrochlorination of 4-nitrobenzhydroxamic acid chloride with triethylamine. The starting I and II molecules contain several potential reaction centers, viz., an unsaturated bond (C=C or C=N), the ring nitrogen atom, and the methylene or methylidyne fragment. Since the reaction centers in tautomers I and II differ substantially, one might have expected that their reactions with nitrile oxide III would lead to different products. Nevertheless, we found that IV and V give derivatives of the same type in this reaction:



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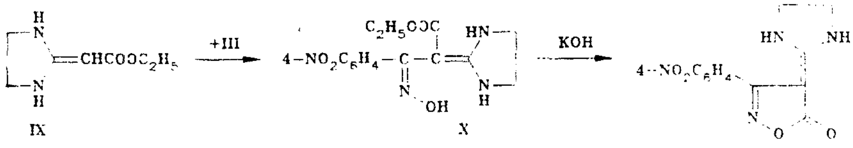
Oxazolidine IV, in which the structure is fixed and tautomerism is impossible, reacts very rapidly with nitrile oxide III, and the reaction is virtually complete immediately after mixing of the reagents at room temperature. In contrast to this, oxazoline V, for which tautomer Va predominates [2], reacts considerably more slowly. For the completion of the reaction 6-8 h are necessary. This difference in the reactivities can be explained by the fact that isoxazoline V reacts only in the tautomeric Vb form, the amount of which in the equilibrium mixture is small.

A similar pattern is observed in the imidazoline series. Derivative IX, which has a tautomeric form that is similar to oxazolidine IV, also reacts readily with nitrile oxide III:

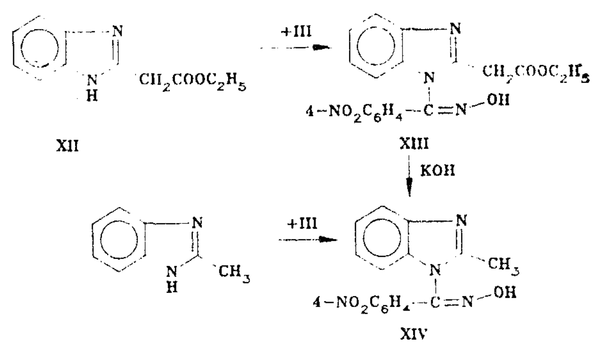


However, in the case the reaction stops at the first step, and an acyclic addition product — oxime X — is formed. A product with a similar structure (VI) is evidently also an intermediate in the reactions of oxazolidines.

The reaction of alkenes with nitrile oxides usually leads to cycloaddition products — isoxazolines [4]. The formation of acyclic products — unsaturated oximes — is observed extremely rarely, and only isolated examples of such reactions are known [5].

Under the influence of catalytic amounts of alkali oxime X readily undergoes cyclization to isoxazolone XI; in contrast to oxazolidine derivatives, the heteroring is retained, and the ester group enters into the reaction.

According to PMR data, benzimidazole XII exists in only one tautomeric form similar to that which oxazoline Va has. This also evidently explains the fact that addition products similar to those obtained in the preceding cases are not formed in the reaction of XII with the nitrile oxide. The reaction proceeds very slowly and at a different reaction center, viz., the ring nitrogen atom:



Under the influence of alkali the ester group in benzimidazole XIII undergoes hydrolysis and decarboxylation to give 2-methyl derivative XIV, the structure of which was proved by alternative synthesis from 2-methylbenzimidazole and nitrile oxide III.

Thus, from the results obtained one may conclude that 2-methylene derivatives of imidazolidine and oxazolidine react readily with the nitrile oxide at the methylidyne fragment to give, in the first step, an acyclic addition product — an unsaturated oxime — which then can undergo cyclization to isoxazoles with the participation of the heteroring or the ester group. The Δ^2-oxazoline reacts with the nitrile oxide with considerably greater difficulty but gives a similar product. The reaction evidently proceeds through a step involving tautomeric conversion of the Δ^2-oxazoline to a 2-methyleneoxazolidine derivative. The benzimidazole derivative, for which this sort of tautomeric conversion is not observed, reacts differently — addition takes place at the ring nitrogen atom.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in d_6-DMSO were recorded with a Bruker WH-90 spectrometer with tetramethylsilane (TMS) as the internal standard. The IR spectra of suspensions of the compounds in Nujol were recorded with a Perkin—Elmer 580B spectrometer. The course of the reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates with elution with ether and development in UV light.

The results of elementary analysis for C, H, and N were in agreement with the calculated values.

3-(4-Nitrophenyl)-4-ethoxycarbonyl-5-(2-hydroxyethylamino)isoxazole (VIII, $C_{14}H_{15}N_3O_6$). A solution of 0.40 g (2 mmole) of 4-nitrobenzhydroxamic acid chloride in 10 ml of acetonitrile was added dropwise at room temperature to a solution of 0.31 g (2 mmole) of 2-ethoxycarbonylmethyl-Δ^2-oxazoline and 0.22 g (2.2 mmole) of triethylamine in 15 ml of acetonitrile. After 6-8 h, the triethylamine hydrochloride was removed by filtration, the filtrate was evaporated, and the residue was dissolved in ether and chromatographed on silica gel (elution with ether) to give 0.35 g (55%) of a product with mp 96-98°C [from water—alcohol (1:1)]. PMR spectrum: 1.07 (3H, t, CH_3), 3.47 (4H, m, C_2H_6), 4.04 (2H, q, CH_2O), 4.87 (1H, t, OH), 7.73 (1H, t, NH), 7.78 (2H, d, o-C_6H_2), 8.22 ppm (2H, d, m-C_6H_2). IR spectrum: 3319 (NH), 3220 (OH), 1682 cm^{-1} (C=O).

3-(4-Nitrophenyl)-4-methoxycarbonyl-5-(2-hydroxyethylmethylamino)isoxazole (VII, $C_{14}H_{15}N_3O_6$). This compound was similarly obtained. After the reagents were mixed, the mixture was allowed to stand for 10 min, after which the triethylamine hydrochloride was removed by filtration, and the filtrate was evaporated. Water was added to the residue, and the product was removed by filtration to give 0.46 g (72%) of isoxazole VII with mp 100-102°C (from isopropyl alcohol). PMR spectrum: 3.16 (3H, s, CH_3N), 3.44 (3H, s, CH_3O), 3.62 (4H, s, C_2H_4), 4.78 (1H, broad s, OH), 7.62 (2H, d, o-C_6H_2), 8.22 ppm (2H, d, m-C_6H_2). IR spectrum: 3420 (OH), 1713 cm^{-1} (C=O).

2-[(4-Nitrobenzoyl)(ethoxycarbonyl)methylene]imidazolidine Oxime (X, $C_{14}H_{16}N_4O_5$). This compound was obtained in the same way as derivative VII. The yield was 0.45 g (71%). When oxime X was heated slowly at 170-175°C, the color of the product changed from yellow to brown, and on further heating the product did not melt up to 300°C. Melting accompanied by decomposition and the formation of a sintered solid mass occurred in the case of rapid heating at 175°C. PMR spectrum: 0.77 (3H, t, CH_3), 3.43 (4H, m, C_2H_4), 3.72 (2H, q, CH_2O), 6.07 (1H, broad s, NH), 7.66 (2H, d, o-C_6H_2), 7.96 (1H, broad s, NH), 8.12 (2H, d, m-C_6H_2), 11.39 ppm (1H, s, OH). IR spectrum: 3458 (NH), 3322 (NH), 3280 (OH), 1655 cm^{-1} (C=O).

2-(4-Nitrophenyl)-3-(2-imidazolidinylidene)-5-isoxazolone (XI, $C_{12}H_{10}N_4O_4$). A 0.32-g (1 mmole) sample of oxime X was dissolved in a solution of 20 mg of potassium hydroxide in 10 ml of ethanol. After 10 min, the alcohol was removed by distillation, water was added to the residue, and the precipitate was removed by filtration to give 0.22 g (32%) of a product with mp > 300°C (from water). PMR spectrum: 3.49 (4H, s, C_2H_4), 7.64 (2H, d, o-C_6H_2), 7.76 (2H, broad s, NH), 8.20 ppm (2H, d, m-C_6H_2). IR spectrum: 3440 and 3325 (NH), 1695 cm^{-1} (C=O).

1-(4-Nitrobenzoyl)-2-ethoxycarbonylmethylbenzimidazole Oxime (XIII, $C_{18}H_{16}N_4O_5$). This compound was obtained under conditions similar to those described above. The reaction mixture was allowed to stand for 24 h, after which the product was isolated by chromatography on silica gel (elution with ether) to give 0.40 g (54%) of oxime XIII with mp 205-207°C (from ethanol). PMR spectrum: 0.99 (3H, t, CH_3), 3.71 (1H, d, CH), 3.86 (2H, q, CH_2O), 3.96 (1H, d, CH), 6.77-7.74 (4H, m, C_6H_4), 7.61 (2H, d, o-C_6H_2), 8.23 (2H, d, m-C_6H_2), 12.94 ppm (1H, s, OH). IR spectrum: 2700 (OH), 1740 cm^{-1} (C=O).

1-(4-Nitrobenzoyl)-2-methylenebenzimidazole Oxime (XIV, $C_{15}H_{12}N_4O_3$). A. A 0.11-g (2 mmole) sample of potassium hydroxide and 0.37 g (1 mmole) of oxime XIII were dissolved in 10 ml of alcohol. After 1 h, the mixture was neutralized with hydrochloric acid and evaporated to dryness. Water was added to the residue, and the precipitate was removed by filtration to give 0.19 g (64%) of oxime XIV with mp 252-254°C [from water—acetone (1:1)]. PMR spectrum: 2.29 (3H, s, CH_3), 6.78-7.29 (4H, m, C_6H_4), 7.56 (2H, d, o-C_6H_2), 8.20 (2H, d, m-C_6H_2), 12.84 ppm (1H, s, OH).

B. A 0.13-g (1 mmole) sample of 2-methylbenzimidazole and 0.16 g (1 mmole) of 4-nitrobenzonitrile N-oxide were dissolved in 10 ml of acetonitrile. After 24 h, the solvent was removed by distillation, and the product was recrystallized. The characteristics of the product obtained were in agreement with the characteristics of the oxime obtained by decarboxylation of derivative XIII.

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