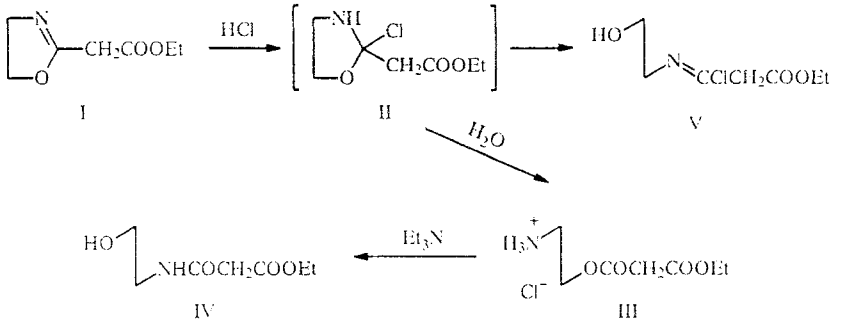
HYDROCHLORINATION OF Δ^2-1,3-OXAZOLINES AND 1,3-OXAZOLIDINES

D. A. Tikhomirov, O. S. Slyadenskaya, and A. V. Eremeev

The compounds 2-(ethoxycarbonylmethyl)-Δ^2-1,3-oxazoline and 1-methyl-2-(methoxycarbonylmethylene)-1,3-oxazolidine are hydrochlorinated at the C=N or C=C bond, respectively, with subsequent opening of the oxazolidine ring. Depending on the reaction conditions, this occurs regioselectively to form various products.

Functionalization of Δ^2-1,3-oxazolines and 1,3-oxazolidines at the 2-position [1] produces compounds of interest as potential biologically active compounds [2]. In particular, the hydrochlorides of these compounds are promising. An attempt is made in the present study to prepare these.

As it turned out, hydrochlorination of 2-(ethoxycarbonylmethyl)-Δ^2-1,3-oxazoline (I) with an equimolar amount of HCl occurs with opening of the oxazoline ring at the C—N bond to form the previously unknown hydrochloride of aminoethylethylmalonate (III).



The structure of III was confirmed by IR and PMR spectroscopies (Table 1) and by further chemical conversion using Et_3N to ethylmalonate hydroxyethylamide (IV).

If dry HCl is used, the reaction follows another pathway with opening of the heterocycle at the C—O bond and formation of the substituted α-chlorimine V.

Apparently, HCl adds in both the first and second reactions to the C=N bond of the oxazoline ring to form the intermediate 2-chloro-2-(ethoxycarbonylmethyl)-1,3-oxazolidine II. This hydrolyzes in the presence of H_2O to III. For dry HCl, the heterocycle opens to form the α-chlorimine V.

Treatment of 1-methyl-2-(methoxycarbonylmethylene)-1,3-oxazolidine (VI), a structural isomer of I, with dry HCl forms an equilibrium mixture of the isomers VII and VIII. This is consistent with the presence in the PMR spectrum of a mixture of doubled singlets for the NCH_3 and CH_2 protons and with doubled signals for the heterocyclic protons. The position of the equilibrium in the mixture depends on the solvent. It is primarily shifted toward VIII. For example, the ratio of VII to VIII in $CHCl_3$ is 1:2.5; in DMSO, 1:1.6. The resulting mixture is readily hydrolyzed to the hydrochloride of a mixed ester of malonic acid (IX). The same product is formed from VI on treatment with HCl. After removal of HCl from the amino group of IX by Et_3N, intramolecular amidation, like for the hydrochloride of III, occurs with formation of the amidoester of malonic acid X.

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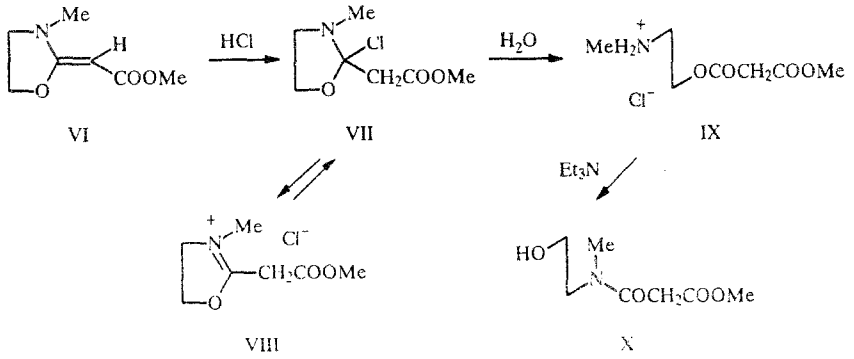
TABLE 1. PMR Spectra of Synthesized Compounds III-V and VII-X

Starting compound	Chemical shift, δ, ppm							
	CH_3, s	C_2H_5	CH_2, s	NCH_2	NCH_3, s	OCH_2	NH, br.s	OH, br.s
III	—	1,24 t; 4,18 q	3,56	3,38 t	—	4,51 t	8,27	—
IV	—	1.27 t; 4,18 q	3,31	3,44 t	—	3,71 t	7,47	3,02
V	—	1.27 t; 4,20 q	3,33	3,60 s	—	3,64 s	—	7,49
VII	3,73	—	3,53	3,64 s	2,98	3,64 s	—	—
VIII	3,73	—	3,47	3,69 s	3,11	3,69 s	—	—
IX	3,73	—	3,6	3,27 t	2,76	4,58 t	9,6	—
X	3,69; 3,73	—	3,47; 3,58	3,3...3,6 m	2,95; 3,06	3,7...3,9 m	—	3,38



VI VII IX

VIII X

The investigations established that hydrochlorination of Δ^2-1,3-oxazoline and 1,3-oxazolidine is accompanied by opening of the heterocycle. Depending on the reaction conditions, this occurs regiospecifically and produces compounds of various structure.

EXPERIMENTAL

IR spectra were recorded on a Perkin—Elmer 580-B instrument in nujol or as a liquid film. PMR spectra were taken on a Bruker WH-90 spectrometer in $CDCl_3$ or DMSO-D_6 with TMS internal standard. Mass spectra were obtained on an MS-905 (70 eV) spectrometer. The course of the reactions and the purity of the products were monitored using TLC on Silufol UV-254 plates.

***O*-(Ethoxycarbonylacetyl)-2-hydroxyethylammonium Chloride (III, $C_7H_{14}ClNO_4$).** An ethanol solution (5 ml) of I (0.4 g, 2.55 mmole) at −5 °C was treated with stirring with HCl (0.25 g, 2.55 mmole) in ethanol (5 ml). The reaction mixture was stirred at room temperature for 0.5 h. The ethanol was evaporated. The residue was dried and crystallized from ethylacetate. Yield 0.47 g (88%) of colorless crystals with mp 39-41 °C. IR spectrum: 1735, 1750 (C=O), 3420 cm^{-1} (NH).

***N*-(Ethoxycarbonylacetyl)-2-hydroxyethylamine (IV).** A $CHCl_3$ solution (3 ml) of III (0.2 g, 0.95 mmole) was treated with stirring with Et_3N (0.096 g, 0.95 mmole). The reaction mixture was kept for 24 h. The $CHCl_3$ was evaporated. The residue was chromatographed in CH_3CN on an alumina column. Yield 0.1 g (59%) of light-yellow oil. TLC: R_f 0.42 (CH_3CN). IR spectrum: 1660, 1735 (C=O), 3100 (NH), 3325 cm^{-1} (OH).

***N,N*-(1-Chloro-2-ethoxycarbonylethylidene)-2-hydroxyethylamine (V, $C_7H_{12}ClNO_3$).** Dry HCl was passed for 5 min through a dry $CHCl_3$ solution (10 ml) of I (0.3 g, 1.9 mmole) at 0 °C. The $CHCl_3$ was evaporated. The residue was dissolved in diethyl ether. The solution was passed over an alumina column. Evaporation of the ether yielded 0.23 g (62%) of colorless crystals with mp 34-35 °C. IR spectrum: 1640 (C=N), 1735 (C=O), 3240 cm^{-1} (OH). M = 193.

Reaction of VI with dry HCl. Dry HCl was passed for 5 min through a dry $CHCl_3$ solution (10 ml) of VI (0.25 g, 1.6 mmole). The $CHCl_3$ was evaporated. The residue was washed with diethyl ether. Evaporation of the ether yielded 0.2 g (64%) of colorless oil as an equilibrium mixture of VII and VIII. IR spectrum ($CHCl_3$): 1655 (C=N), 1745 cm^{-1} (C=O).

***N*-Methyl-*O*-(ethoxycarbonylacetyl)-2-hydroxyethylammonium Chloride (IX, $C_7H_{14}ClNO_4$).** A methanol solution (8 ml) of VI (0.4 g, 2.55 mmole) at −5 °C was treated with stirring with HCl (0.25 g, 2.55 mmole) in methanol (5 ml). The

reaction mixture was stirred at room temperature for 0.5 h. The methanol was evaporated. The residue was dried and crystallized from ethylacetate. Recrystallization from 2-propanol yielded 0.3 g (55%) of colorless crystals with mp 93-95 °C. IR spectrum: 1730, 1745 (C=O), 3420 cm^{-1} (NH).

***N*-Methyl-*N*-(methoxycarbonylacetyl)-2-hydroxyethylamine (X).** A $CHCl_3$ solution (3 ml) of IX (0.2 g, 0.95 mmole) was treated with stirring with Et_3N (0.096 g, 0.09 mmole). The reaction mixture was kept at room temperature for 48 h. The $CHCl_3$ was evaporated. The residue was washed with ethylacetate. The solvent was evaporated. The residue was chromatographed in CH_3CN on an alumina column. Yield 0.09 g (54%) of light-yellow oil. TLC: R_f 0.51 (CH_3CN). IR spectrum: 1650, 1745 (C=O), 3450 cm^{-1} (OH).

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4-AMINOFURAZAN-3-HYDROXIMIC HALIDES

V. G. Andrianov, V. G. Semenikhina, and A. V. Eremeev

The nitrile-N-oxide formed by dehydrohalogenation of 4-aminofurazan-3-hydroximic halides cyclizes to form 1,4,2,5-dioxadiazines, isoxazoles, isoxazolines, 1,2,4-oxadiazolines, tetrazoles, and 1,3,4-thiaoxazoles.

Nitrile-*N*-oxides, being very reactive compounds, are used to synthesize functionalized oximes and various heterocycles containing the C=N—O group (isoxazoles, 1,2,4- and 1,2,5-oxadiazoles, 1,2,4,5-oxatriazoles, 1,4,2-dioxazoles, 1,2,4-oxadiazines, 1,4,2,5-dioxadiazines, et al.) [1]. The possibility of preparing such a wide range of compounds from the nitrile oxides stimulates research in this area. Recently we prepared the first halides of a series of furazanhydroximic acids [2]. Hydroximic halides are direct precursors of nitrile oxides, into which they are converted by dehydrohalogenation. As a rule, dehydrohalogenation is effected by basic reagents (bases, amines) under very mild conditions, usually at temperatures near 0 °C. The high reactivity of acyl halides and nitrile oxides limits the number of functional groups that can be present in their molecules. Therefore, in particular, it was doubted that nitrile oxides containing a primary amine could exist [1].

Thus, the properties of 4-aminofurazan-3-hydroximic halides, which contain a primary amine on the furazan ring, are especially interesting. Obviously, the ability of two groups that are very reactive toward each other to exist simultaneously in the molecule is due to that fact that the reactivity of one of them is sharply decreased. It can be assumed that in this instance this is the amine group. The furazan ring is a strong electron acceptor and is known significantly to reduce the nucleophilicity of the amine in aminofurazans [3]. As a result, they difficultly react as ordinary amines. They do not form salts with dilute mineral acids. Obviously, they cannot cause oxime halides to lose hydrogen halide. However, the oximic halide in furazans I and II is still highly reactive. We have previously demonstrated that they readily react with amines to form *N*-substituted amidoximes [4].

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