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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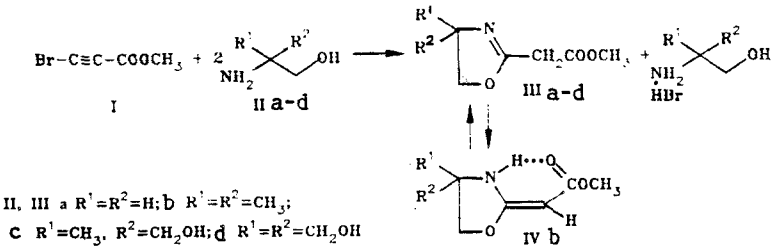
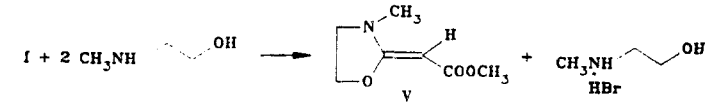
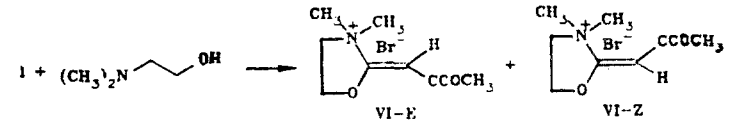


Oxazolines IIIa-d are low-melting or oily compounds, which are hygroscopic and readily soluble in polar solvents. Their structure is confirmed by mass spectroscopy data.

Oxazolidine V is obtained by the reaction of compound I with N-methyl-substituted β-amino alcohol, in particular 2-(methylamino)ethanol. In this case, in the absence of an intramolecular hydrogen bond, the Z-isomer is thermodynamically more convenient because of a greater effectiveness of conjugation in the transposition of the nitrogen atom and the carboxylic group.



We also studied the reactions of methyl romopropiolate with N,N-disubstituted β-amino alcohols. Thus, in the reaction of equimolar amounts of compound I with 2-(dimethylamino)ethanol, a crystalline product is formed in good yield, which in its elemental composition corresponds to a 1:1 adduct. In the IR spectrum of the compound obtained, there is no absorption band of the triple bond and of the hydroxyl group, but an intense absorption band is observed in the 1680-1670 cm^{-1} region, which can be assigned to the stretching vibrations of the C=C bond, as well as an absorption band of the ester group at 1728 cm^{-1}. Analysis of the PMR spectrum (Table 1) indicates that the crystalline product is a mixture of Z- and E-isomers of oxazolidinium bromide VI in a ratio of 1:2.5.

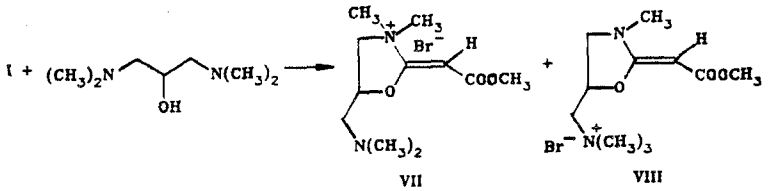


After the recrystallization from ethanol, only the isomer E-VI remains. Moreover, a small amount of oxazolidine V was isolated from the filtrate. Its formation can be attributed to the thermal dequaternization of oxazolidinium bromide VI. N,N-Dialkyl oxazolidinium chlorides with an endocyclic double bond were previously obtained from tertiary 2-hydroxyethylamines and chloroethynyl sulfides [7]. It was found that the reaction proceeds through an intermediate stage of alkylation of the amino alcohol by chloroethynyl sulfide, followed by cyclization into oxazolidinium chloride.

TABLE 1. PMR Spectra of Synthesized Compounds III-VI

Compound	Chemical shift, δ, ppm								
	OCH_2	NCH_2	R^1	R^2	OCH_3, s	CH_2S	NH, br.s	=CH–, s	NCH_3, s
IIIa	4,27 m	3,89 m	—	—	3,70	3,36	—	—	—
IIIb	3,98 s	—	1,36 s	1,29 s	3,73	3,33	—	—	—
IIIc	4.42 and 4.16 (AB type) $J=8$)	—	3,64 (d, CH_2); 2,3 (br. s, OH)	1,24 s	3,71	3,36	—	—	—
IIId	4,1 d	—	3,51 (s, CH_2); 4,6 (br.s OH)	3,42 (s, CH_2); 4,6 (br.s OH)	3,6	3,35	—	—	—
IVb	4,04 s	—	1,42 s	1,24 s	3,62	—	7,67	4,31	—
V	4,49 (t, $J=8$)	3,49 (t, $J=8$)	—		3,62	—	—	4,0	2,84
E-VI	4,82 t	4,16 t	—		3,66	—	—	5,84	3,56
Z-VI	4,76 m	4,22 t	—		3,70	—	—	5,76	3,76

In the reaction of compound I with 1,3-bisdimethylaminopropanol we obtained a substituted oxazolidinium bromide VII and a trimethylammonium salt of oxazoline VIII in a ratio of 1:1.



VII VIII

The route of formation of VIII is probably the dealkylation of oxazolidinium bromide VII, followed by the methylation of the dimethylamino group in the side chain.

On the basis of the data obtained, the formation of heterocyclic compounds in the reactions of methyl bromopropiolate with β-amino alcohols could be regarded as the result of the nucleophilic substitution of the bromine atom at the activated triple bond, followed by the cyclization of the intermediately formed ynamino alcohols into oxazolines and oxazolidines.

Thus, the reaction of methyl bromopropiolate with β-amino alcohols can serve as a convenient method for the synthesis of functionally substituted oxazolines and oxazolidines.

EXPERIMENTAL

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

2-(Methoxycarbonylmethyl)-Δ^2-1,3-oxazoline (IIIa). A solution of 500 mg (3.2 mmoles) of compound I in 10 ml of THF was added dropwise, with stirring, at 0°C to 380 mg (6.2 mmoles) of amino alcohol IIa in 10 ml of THF. The reaction mixture was stirred at room temperature for 24 h. The precipitate of amino alcohol hydrobromide was filtered off, the filtrate was evaporated, and the residue was chromatographed on a column with aluminum oxide in ether. Yield 290 mg (66%) of a crystalline product, mp 34-36°C. IR spectrum 1670 (C═N), 1745 cm^{-1} (C═O).

Compounds IIIb and IVb were obtained in a similar way as oxazoline IIIa in the form of a mixture of two tautomers. IR spectrum: 1700, 1750 (C═O), 1670 (C═N, C═C), 1605, 3340 cm^{-1} (NH). M 171. Yield 60%.

4-Hydroxymethyl-4-methyl-2-(methoxycarbonylmethyl)-Δ^2-1,3-oxazoline (IIIc) was obtained in a similar way as oxazoline IIIa in the form of an oily liquid. IR spectrum: 1745 (C═O), 1670 (C═N), 1600, 3350 cm^{-1} (OH). Yield 60%.

4,4-Dihydroxymethyl-2-(methoxycarbonylmethyl)-Δ^2-1,3-oxazoline (IIId). A solution of 500 mg (3.1 mmoles) of compound I in 10 ml of methanol was added at 20°C, with stirring, to 750 mg (6.2 mmoles) of amino alcohol IId in 20 ml of methanol. The reaction mixture was allowed to stand for 72 h. Methanol was evaporated, and the amino alcohol hydrobromide was washed out with 20 ml of THF, THF was evaporated, and the residue was chromatographed on a column with aluminum oxide in ethanol. Yield 210 mg (33%) of a viscous oily liquid. IR spectrum: 1750 (C═O), 1665 (C═N), 3300-3400 cm^{-1} (OH). M 203 (mass spectrally).

3-Methyl-2-(methoxycarbonylmethylene)-1,3-oxazoline (V). A solution of 330 mg (4.4 mmoles) of 2-(N-methylamino)ethanol in 15 ml of acetonitrile was added dropwise at —5°C, with stirring, to 360 mg (2.2 mmoles) of compound I in 30 ml of acetonitrile, and the mixture was stirred at room temperature for 1 h. Acetonitrile was evaporated, the amino alcohol hydrobromide was washed out with ethyl acetate, the solvent was evaporated, and the residue was crystallized from 2-propanol with the addition of ether. Yield 210 mg (62%) of a crystalline product, mp 89-90°C. IR spectrum: 1680 (C═C), 1695 cm^{-1} (C═O).

3,3-Dimethyl-2-(methoxycarbonylmethylene)-1,3-oxazolidinium Bromide (VI). A solution of 1.6 g (18 mmoles) of 2-(N,N-dimethylamino)ethanol in 20 ml of dry ether was added dropwise at 0-5°C, with stirring, to 3 g (18 mmoles) of compound I in 50 ml of dry ether, and the mixture was stirred at 20°C for 1 h. The precipitate that separated out was filtered off. Yield 3.6 g (80%) of a crystalline product in the form of a mixture of E- and Z-isomers. After recrystallization from ethanol, 1.85 g of compound E-VI was obtained, mp 114-115°C. IR spectrum: 1675 (C═C), 1728 cm^{-1} (C═O).

From the ethanolic solution 0.45 g of a colorless crystalline product was obtained, which in its physicochemical properties was identical to oxazolidine V.

Reaction of I with 1,3-Bisdimethylamino-2-propanol. A solution of 0.56 g (3.4 mmoles) of compound I in 10 ml of ether was added at 0°C, with stirring, to 0.5 g (3.4 mmoles) of 1,3-bisdimethylamino-2-propanol in 30 ml of a dry ether and the mixture was stirred at 20°C for 1 h. The precipitate that separated out was filtered off and dried. Yield

0.6 g (57%) of a crystalline product in the form of a mixture of compounds VII and VIII. PMR spectrum of VII (DMSO-D_6), δ, ppm: 2.24 (3H, s, NCH_3), 2.69 (2H, d, NCH_2), 3.53 (6H, N^+CH_3), 3.62 (3H, s, OCH_3), 4.3 and 5.3 (3H, m, H of the ring), 5.84 ppm (1H, s, =CH–). VIII: 2.75 (3H, s, NCH_3), 3.22 (6H, s, N^+CH_3), 3.4 (2H, m, N^+CH_2), 3.62 (3H, s, OCH_3), 3.76 and 5.30 (3H, m, H of the ring), 3.93 ppm (1H, s, =CH–).

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SYNTHESIS OF 5-(5-AMINO-3,6-DICHLORO-1,4-BENZOQUINON-2-YL)-2-DIMETHYLAMINOTHIAZOLES AND THEIR PROPERTIES

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In the reaction of 2-dimethylamino-5-(3,5,6-trichloro-1,4-benzoquinon-2-yl)thiazole with primary and secondary amines, the chlorine atom at the 5-position of the benzoquinone ring is substituted, according to the ^{13}C NMR spectroscopy data, by an amino group. The chemical, spectroscopic, and electrochemical properties of 5-(5-amino-3,6-dichloro-1,4-benzoquinon-2-yl)-2-dimethylaminothiazoles were revealed.

We have previously developed [1-3] a method for the synthesis of 2-amino-5-(3,5,6-trichloro-1,4-benzoquinon-2-yl)thiazoles simultaneously containing electron-donor and electron-acceptor fragments in the molecule. It is known [4] that haloquinones readily undergo nucleophilic substitution reactions with amines and other nucleophilic agents. The aim of the present work was to study the nucleophilic substitution reaction of 2-dimethylamino-5-(3,5,6-trichloro-1,4-benzoquinon-2-yl)thiazole (I) with primary and secondary amines.

In the reactions of thiazole I with primary and secondary amines, a series of N-substituted 5-(5-amino-3,6-dichloro-1,4-benzoquinon-2-yl)-2-dimethylaminothiazoles (IIa-f, Table 1) were obtained. These compounds are deeply colored crystalline substances (IIa, b, d-f — violet; IIc — green). Compared with the starting thiazole, which dissolves readily only in bipolar aprotic solvents, the amino derivatives IIa-f also dissolve in slightly polar solvents.

The reduction of quinones IId, e leads to the formation of 2-dimethylamino-5-(4-piperidino- and -(4-morpholino-2,5-dhydroxy-3,6-dichlorophenyl)thiazoles (IIId, e). Hydroquinones IIId, e are colorless and dissolve readily in organic solvents. They are characterized by comparatively low oxidation potentials, which is confirmed by their prompt oxidation by atmospheric oxygen to colored quinones IId, e (see scheme on page 334).

The examination of quinones I and IId-f by cyclic voltamperometry (Table 2) showed that, compared with the starting quinone I, aminoquinones IId-f are reduced at more negative potentials. At the first stage of the reduction ($Q + e \rightarrow Q^-$), E_1 decreases by approximately 0.3 V. The values of E_2 for aminoquinones IId-f could not be measured by using tetrabutylammonium perchlorate as the polarographic background. They were measured on the background of tetraethylammonium perchlorate and $NaClO_4$ (Fig. 1). According to the data in {5], this can be explained by the fact that E_2 is more strongly influenced by the radius of the M^+ cation than E_1. Increase in its radius leads to a shift

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