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SYNTHESIS OF ISOXAZOLINES FROM ARYLCYCLOPROPANES UNDER NITROSATION CONDITIONS

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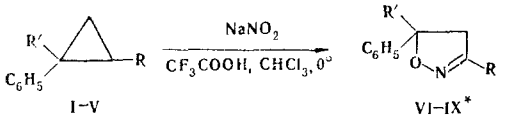
It is shown that the corresponding isoxazolines are formed in high yields when aryl-, diaryl-, and alkylarylcyclopropanes are treated with sodium nitrite in trifluoroacetic or trichloroacetic acid at 0°C. The reaction does not take place in acetic or chloroacetic acid. A possible mechanism for the formation of the isoxazolines is proposed. The latter were subjected to a mass-spectrometric study.

A study of the mutual effect of an aryl group and a small ring in arylcyclopropanes has given new information regarding the properties of the cyclopropane fragment, viz., its ability to enter into conjugation with unsaturated groupings [1, 2], the substantial dependence of the electron-donor properties on the nature of the aryl group [3, 4], its ability to undergo complexing [5], etc. From this point of view, a study of the reactivities of arylcyclopropanes under nitrosation conditions seemed of definite interest.

Previously, in a brief communication [6] we described the synthesis of R-5-phenyl- and 3,5-diphenylisoxazolines from arylcyclopropanes by treatment with sodium nitrite in trifluoroacetic acid. The formation of isoxazoles [7, 8], or isoxazolines [9] from arylcyclopropanes with certain structures was previously observed in the nitration of the latter under various conditions.

Isoxazolines are finding extensive application in organic synthesis [10, 11]. They can be used as starting compounds for the preparation of compounds that are inaccessible by other pathways. In this connection, the development of convenient methods for the preparation of isoxazolines is of undoubted interest.

In the present research we studied the behavior of aryl-, diaryl-, and arylalkylcyclopropanes (I-V) upon treatment with sodium nitrite in trifluoroacetic and trichloroacetic acids. As the subjects of our study we selected phenyl-, 1-methyl-2-phenyl-, cis-1,2-diphenyl-, trans-1,2-diphenyl-, and 1-methyl-1-phenylcyclopropanes (I-V). The reaction of these compounds with sodium nitrite in a mixture of trifluoroacetic acid and chloroform leads to the production of the corresponding isoxazolines in high yields:



I-V VI-IX*

I R=R'=H; II R=CH$_3$, R'=H; cis-III, trans-IV R=C$_6$H$_5$, R'=H; V R=H, R'=CH$_3$

*Compounds III and IV form the same compound, viz., VIII.

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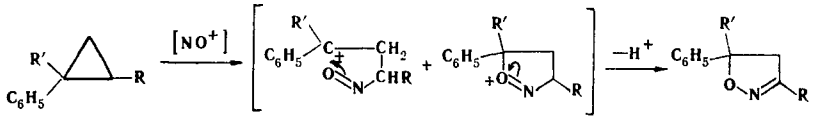
The reaction in all cases proceeds readily and rapidly, and the nature and position of the substituents do not have a substantial effect on the character of the transformations.

In order to ascertain the role of the acid in the transformation under consideration, the reaction was also carried out in acetic, chloroacetic, and trichloroacetic acids under the same conditions. The formation of isoxazolines in high yields was observed only when trichloroacetic acid was used; the reaction did not take place in acetic and chloracetic acids.

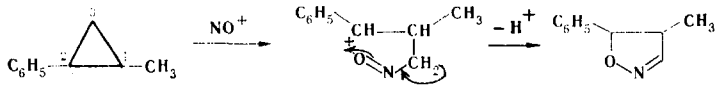
It is interesting to note that decreasing the reaction temperature to −10°C leads to a decrease in the yields of isoxazolines only in trichloroacetic acid, whereas the yields of reaction products do not change in trifluoroacetic acid.

The following general scheme for the formation of isoxazolines from arylcyclopropanes under the indicated conditions may be proposed:



The nature and strength of the acid in the reaction under consideration play a dual role: On the one hand, the rather strong trifluoroacetic (pK_a 0.23) and trichloroacetic (pK_a 1.66) acids promote, under the reaction conditions, the generation of a nitrosonium cation by protonating the nitrous acid, and, on the other hand, these acids may protonate the **trimethylene** ring in the arylcyclopropanes [12], thereby facilitating cleavage of the bonds and the formation of a cation of the benzyl type.

It is interesting to note that when 1-methyl-2-phenylcyclopropane (II) was subjected to the reaction, isomeric 3-methyl-5-phenyl- (VII, 48%) and 4-methyl-5-phenylisoxazolines (X, 37%) were isolated as the reaction products. The formation of isomer X can apparently be explained by the possibility of opening of the trimethylene ring at the $C_{(2)}$—$C_{(3)}$ bond:



II X

The literature contains information regarding the possibility of opening of the trimethylene ring at the $C_{(2)}$—$C_{(3)}$ bond in 1,2-disubstituted acrylcyclopropanes. Thus Shea and Skell [13] have shown that in the photochemical bromination of arylcyclopropanes with bromine at −78°C, in addition to the principal product of opening of the small ring at the $C_{(1)}$—$C_{(2)}$ bond, the isomeric dibromide, which is formed as a result of opening of the small ring at the $C_{(2)}$—$C_{(3)}$ bond, was detected in small amounts (4%). It is also known that trans-2-cyclohexyl-1-phenylcyclopropane [14] and trans-1,2-diphenylcyclopropane [15] upon treatment with mercuric acetate in acetic acid or alcohol also form products of opening of the trimethylene ring at the $C_{(2)}$—$C_{(3)}$ bond (in 47 and 40% yields, respectively).

The isoxazolines obtained were characterized by means of PMR and ^{13}C NMR spectroscopy, which made it possible to establish the presence and numbers of primary, secondary, tertiary, and quaternary carbon atoms.

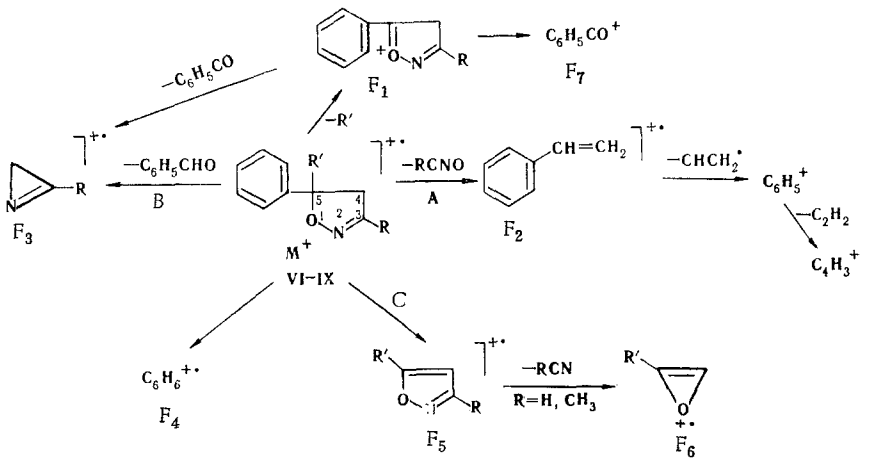
The mass spectra of the synthesized VI-X were also investigated, and it was established that the molecular-ion peaks (M^+) in all cases have odd-numbered m/z values (which constitutes evidence for the presence of an odd number of nitrogen atoms in the molecules and corresponds to the molecular masses of the substances). In the case of the methyl derivatives of isoxazolines the M^+ peaks have very low intensities; however, the introduction of a phenyl substituent increases the stability of the molecule with respect to electron impact markedly, and the relative intensity of the M^+ peak reaches 80% of the maximum value. The formation of $[M-H]^+$ ions might have been explained by splitting out of a hydrogen atom from the ortho position of the phenyl ring with simultaneous cyclization of the resulting radical center at the charged heteroring atom [16]; however, the elimination of H· from the 5 position of the oxazoline ring to give F_1 ions is more likely. This conclusion is confirmed by the fact that in the case of 5-methylisoxazoline IX the $[M-CH_3]^+$ ion peak is the maximum peak in the spectrum, while it is of low intensity or totally absent in the mass spectra of other methyl derivatives.

TABLE 1. Mass Spectra of VI-X*

Compound	m/z values (relative intesities of the ion peaks in percent of the maximum peak)
VI	147 (20,8), 146 (12,1), 115 (10,7), 105 (25,9), 104 (100), 103 (14,9), 91 (12,4), 78 (42,7), 77 (25,9), 69 (39,3), 51 (30,9), 50 (10,2), 42 (36,1), 41 (8,1)
VII	161 (10,8), 160 (5,2), 105 (15,1), 104 (100), 103 (15,6), 91 (20,4), 83 (16,9), 78 (32,9), 77 (18,1), 65 (6,3), 63 (6,0), 65 (44,1), 54 (14,1), 52 (5,9), 51 (30,3), 50 (1,0), 42 (35,8), 41 (8,7)
VIII	223 (79,8), 222 (22,9), 206 (10,2), 193 (13,9), 178 (12,5), 145 (5,7), 117 (17,1), 115 (24,0), 105 (14,7), 104 (100), 103 (19,1), 91 (19,7), 78 (30,0), 77 (50), 65 (12,7), 51 (36,5), 42 (6,1)
IX	161 (5,1), 147 (11,4), 146 (100), 145 (77,4), 118 (71), 117 (62,1), 116 (39,5), 114 (9,3), 105 (33,2), 104 (61,6), 103 (15,1), 77 (19,6), 63 (7,9), 51 (47,3), 50 (19), 43 (46,2), 42 (13,8), 41 (10,5), 40 (7,1)
X	161 (38,1), 160 (19,5), 146 (12,8), 145 (14,8), 131 (19,5), 118 (82,2), 117 (84,0), 116 (12,7), 115 (15,7), 78 (12,4), 77 (14,8), 56 (15,5), 55 (100), 54 (18,5), 52 (14,9), 51 (58,5), 50 (28,3), 43 (15,7)

*The molecular-ion peaks and the most intense peaks (>5%) of the fragment ions are presented.

The principal pathway of the fragmentation of the $[M^+]$ ions of VI-VIII are cleavage of the heteroring at the oppositely situated C–O and C–C bonds with the formation of styrene pseudomolecular ion F_2 (pathway A), which then successively eliminates a $\dot{C}H{=}CH_2$ radical and a molecule of acetylene (see the scheme).



Cleavage of the heteroring at the N–O and $C_{(4)}$–$C_{(5)}$ bonds (pathway B) leads to detachment of a molecule of formaldehyde and the formation of F_3 ions. A third fragmentation pathway (pathway C) consists in cleavage of the interannular bond, which is always accompanied by migration of a hydrogen atom from the heteroring (most likely from the 4 position) to the phenyl substituent; in this case the charge may be localized on both of the resulting fragments, and pseudomolecular benzene (F_4) and oxazole (F_5) ions are observed in the spectrum. In the case of VI and VII the F_5 ion loses a molecule of HCN or CH_3CN, respectively, to give the F_6 ion.

The fragmentation of the isoxazolines via pathway A makes it possible to determine the position of the substituent in the heteroring. Thus, when the methyl group is in the 4 or 5 position (X and IX) of the isoxazolines, the F_2 ion peaks are shifted 14 amu to the higher m/z value side, i.e., β- and, respectively, α-methylstyrene ions are formed and then subsequently eliminate a hydrogen atom to give F_2 ions (see Table 1). When we compared the spectra of the 4- and 5-methyl derivatives of isoxazolines (X and IX), we observed that for the former the maximum peak is the ion peak with m/z 55, which is formed in the fragmentation of the heteroring with the elimination of a molecule of aldehyde (pathway B). In the case of the 5-substituted isoxazoline (IX) this process is less characteristic (the F_3 ion has an intensity of 11%), and the maximum peak is the $[M{-}CH_3]^+$ ion peak (see Table 1), which has very low intensity in the mass spectrum of the X isomer. Thus the mass-spectrometric fragmentation of the investigated compounds is satisfactorily described by the general scheme, which completely confirms the structures of the substances and makes it possible to determine the position of the substituent in the heteroring.

EXPERIMENTAL

The PMR spectra of solutions of the compunds in CCl_4 and $CDCl_3$ were recorded with a Varian T-60 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The ^{13}C NMR spectra were recorded with a Varian XL-100 spectrometer under conditions of noise decoupling of the protons. The mass spectra were obtained with a Varian model MAT-44S chromatographic mass spectrometer at an ionizing voltage of 50 V and a cathode emission current of 0.4 mA.

General Method for the Preparation of Isoxazolines. A 0.01-mole sample of sodium nitrite was added in small portions in the course of 20 min to a solution of 0.01 mole of the arylcyclopropane in 10 ml of $CHCl_3$ and 0.3 mole of CF_3COOH or CCl_3COOH cooled to 0°C, after which the mixture was stirred at 0°C for 30 min. It was then poured into water, and the aqueous mixture was extracted with chloroform. The extract was washed with sodium carbonate solution and water and dried over $CaCl_2$. The solvent was removed, and the residue was chromatographed with a column with silica gel (40/100) as the stationary phase and hexane–ether (4:1) as the eluent. The isoxazolines listed below were obtained.

5-Phenylisoxazoline (VI).* This compound was obtained in 85% yield and had bp 125-126°C (10 mm) [17]. ^{13}C NMR spectrum (CCl_4, δ_{TMS}): $C_{(3)}$ 144.2, $C_{(4)}$ 43.4, $C_{(5)}$ 79.2, C_S 141.2, and C_{arom} 128.2-125.5 ppm.

3-Methyl-5-phenylisoxazoline (VII).* This compound was obtained in 48% yield and had bp 128-130°C (4 mm) [10]. ^{13}C NMR spectrum ($CDCl_3$, δ_{TMS}): $C_{(3)}$ 150.23, $C_{(4)}$ 41.78, $C_{(5)}$ 76.51, CH_3 8.13, C_S 136.5, and C_{arom} 123.74-120.88 ppm.

3,5-Diphenylisoxazoline (VIII).* This compound was obtained in 95% yield and had mp 72-73°C [18]. ^{13}C NMR spectrum ($CDCl_3$, δ_{TMS}): $C_{(3)}$ 155.91, $C_{(4)}$ 42.96, $C_{(5)}$ 82.41, C_S 140.79, and C_{arom} 129.93-125.71 ppm.

5-Methyl-5-phenylisoxazoline (IX). This compound was obtained in 90% yield and had bp 113-115°C (4 mm). PMR spectrum (CCl_4): 1.47 (s, 3H, CH_3), 2.87 (d, 2H, CH_2), 6.80 (m, 1H, CH), and 7.16 ppm (m, 5H, aromatic protons). ^{13}C NMR spectrum ($CDCl_3$, δ_{TMS}): $C_{(3)}$ 141.46, $C_{(4)}$ 44.71, $C_{(5)}$ 81.02, CH_3 23.41, C_S 140.9, and C_{arom} 123.95-120.2 ppm.

4-Methyl-5-phenylisoxazoline (X). This compound was obtained in 37% yield and had bp 119-122°C (4 mm). PMR spectrum (CCl_4): 1.12 (d, 3H, CH_3), 3.05 (m, 1H, CH–CH_3), 4.77 (d, 1H, CH–C_6H_5), 6.89 (d, 1H, CH=N), and 7.16 ppm (m, 5H, aromatic protons). ^{13}C NMR spectrum ($CDCl_3$, δ_{TMS}): $C_{(3)}$ 146.27, $C_{(4)}$ 47.51, $C_{(5)}$ 83.25, CH_3 12.23, C_S 135.83, and C_{arom} 124.3-121.28 ppm.

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*The PMR spectra of these isoxazolines coincided with those described in the literature [17, 18].

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REARRANGEMENT OF 2,2'-DIPROPIONYLAZOXYBENZENES TO 3-[1-ALKOXY-1-(2-PROPIONYLARYLAMINO)ETHYL]BENZO[c]ISOXAZOLES

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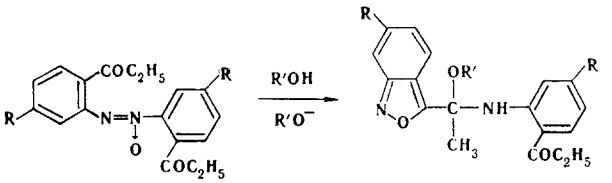
2,2'-Dipropionylazoxybenzenes undergo rearrangement to the corresponding 3-[1-alkoxy-1-(2-propionylarylamino)ethyl]benzo[c]isoxazoles in the case of base catalysis; this transformation is realized only in the case of ortho,ortho' orientation of the propionyl groups in the substrate molecule and with the participation of the solvent as a reagent. A mechanism for the rearrangement that assumed the participation of one of the propionyl groups in intramolecular reduction of the azoxy group to an azo group is proposed.

We have previously shown that 2,2'-dipropionylazoxybenzenes undergo rearrangement to 3-[1-alkoxy-1-(2-propionylarylamino)ethyl]benzo[c]isoxazoles under the influence of catalytic amounts of bases in alcohol [1]. It was noted that the solvent, viz., the alcohol, participates in the previously unknown transformation; the size of the alkyl group in the molecule of the latter may have a decisive effect on the course of the rearrangement. For example, in alcohols with normal and iso structures the corresponding benzo[c]isoxazoles are formed, whereas no reaction occurs in tert-butyl alcohol. Since this type of transformation of 2,2'-dipropionylazoxybenzenes was previously unknown, we made an attempt to establish its mechanism.

A study of the behavior of azoxy compounds I-V* under the conditions for the rearrangement that we found showed that neither the direction of the reaction nor the degree of transformation depends substantially on the type of substituent in the para position relative to both the propionyl fragment undergoing modification and the propionyl fragment that remains unchanged — the corresponding benzo[c]isoxazoles are formed in high yields (see Tables 1 and 2).



I-V VI-XIV

I R=H; II R=t-C$_4$H$_9$; III R=Br; IV R=NO$_2$; V R=

As we have already noted, only alcohols were used as the solvents in the study of the transformations of azoxybenzenes of the I-V type. We found that in aprotic solvents, viz., benzene, dioxane, tetrahydrofuran (THF), ether, and carbon tetrachloride, starting substrates I-V undergo virtually no transformations under the influence of catalytic amounts of bases,

*We have previously described the synthesis of the indicated azoxy compounds [2].

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