SUBSTITUTED PHENYLCYCLOPROPANES IN THE SYNTHESIS OF 2-ISOXAZOLINES

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Diverse 2-isoxazolines with substituents in both the aromatic ring and the isoxazoline ring were obtained in the process of nitrosation of various substituted phenylcyclopropanes with sodium nitrite in a mixture of chloroform and trifluoroacetic acid.

It has been reported [1] that phenylcyclopropane, stereoisomeric 1,2-diphenylcyclopropanes, and isomeric methylphenylcyclopropanes are converted to 2-isoxazolines when they are treated with sodium nitrite in a mixture of chloroform and trifluoroacetic acid. In the case of methylphenylcyclopropanes it was shown that the position of the methyl group in the cyclopropane ring has a substantial effect on the results of the reaction. Thus only 5-methyl-5-phenylisoxazoline is formed in the case of 1-methyl-1-phenylcyclopropane, whereas two isomeric isoxazolines, viz., 3-methyl- and 4-methyl-5-phenylisoxazoline in a ratio of 4:4, are obtained from 1-methyl-2-phenylcyclopropane.

The present research was undertaken in order to ascertain the effect of the nature and position of the substituents in the aromatic and small rings on the behavior of arylcyclopropanes in the investigated reaction.

Since there is every reason to assume that the investigated reaction is electrophilic, one might have expected that electron-donor substituents in the benzene ring would facilitate the reaction, whereas electron-acceptor substituents would hinder it. In addition to this, it is evident that the position of the substituents would have an effect on the steric factors — substituents in the ortho position, by creating steric hindrance, should hinder the formation of isoxazolines.

The data presented in Table 1 confirm the assumptions expressed above.

It was found that successive conversion of the cyclopropyl groupings to isoxazoline fragments was possible in the case of 1,4-dicyclopropylbenzene:

TABLE 1. Conversion of o- and p-Substituted R-Phenylcyclopropanes to 5-Arylisoxazolines in a Mixture of Chloroform and Trifluoroacetic Acid (3:1, 30 min, −5°C)

R	Composition of the reaction mixture, %			R	Composition of the reaction mixture, %		
	isoxazoline	№	starting phenylcyclopropane		isoxazoline	№	starting phenylcyclopropane
H	75	I	14	*o*-Cl	78	VII	10
p-NO_2	44	II	45	*p*-Br	80	VIII	9
o-NO_2[a]	23	III	63	*o*-Br	69	IX	15
p-I	84	IV	7	*p*-CH_3[b]	92	X	—
o-I	75	V	14	*p*-OCH_3[b]	86	XI	—
p-Cl	86	VI	5	*p*-  [b]	89	XII	—

[a]The corresponding cinnamaldehydes were also detected in the reaction mixture. [b]Partial resinification of the reaction mixture was observed.

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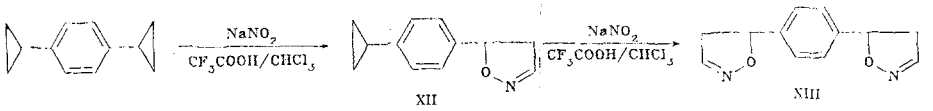
TABLE 2. Transformations of Phenylcyclopropanes with Substituents in the Small Ring upon Treatment with Sodium Nitrite in a Mixture of Chloroform and Trifluoroacetic Acid (3:1, 30 min, −5°C)

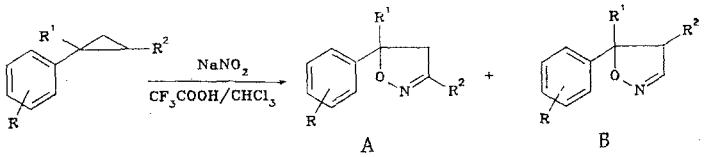
R	R¹	R²	Composition of the reaction mixture, %				
			isoxazoline				starting phenylcyclopropane
			A	No.	B	No.	
p-NO_2	H	CH_3	39	XVI	21	XVII	30
o-NO_2	H	CH_3	33	XVIII	18	XIX	41
o-I	H	CH_3	56	XX	21	XXI	14
H	H	Br	34	XXII	26	XXIII	36
H	CH_3	Cl	68	XXIV	18	XXV	5



XII XIII

To confirm the structures of the isoxazolines obtained we used NMR and mass spectrometry. The spectral characteristics of the synthesized compounds are presented in Table 3.

Substituents in the benzene ring do not have a substantial effect on nitrosation in the case of introduction of a methyl group in the benzyl position of phenylcyclopropanes, the presence of which significantly facilitates conversion of the later to isoxazolines. Thus 1-methyl-1-(p-nitrophenyl)cyclopropane and 1-methyl-1-(o-iodophenyl)cyclopropanes are converted to 5-methyl-5-(p-nitrophenyl)isoxazoline (XIV) and 5-methyl-5-(o-iodophenyl)isoxazoline (XV) in 82 and 91% yields (compare with the data for II and V, Table 1). The nitrosation of 1-methyl-2-phenylcyclopropanes with substituents in the benzene ring, as in the case of the unsubstituted hydrocarbon, leads to the corresponding 4-methyl- and 3-methyl-5-arylisoxazolines (B and A) with preponderance of the latter. The nature and position of the substituents in the benzene ring affect the degree of conversion of phenylcyclopropanes in the same way as in the cases described above.



A B

1-Bromo-2-phenylcyclopropane and 1-methyl-1-phenyl-2-chlorocyclopropane behave similarly. In the latter case the introduction of a methyl group in the 1 position leads to preferred opening of the small ring at the $C_{(1)}$-$C_{(2)}$ bond. The yields of isomeric isoxazolines are presented in Table 2. The structures of XIV-XXV were proved unambiguously by PMR and ^{13}C NMR spectroscopy and the mass spectra (Tables 3 and 4). The chemical shifts and multiplicities of the signals in the NMR spectra are in complete agreement with the proposed structures. The ^{13}C NMR spectra of all of the isoxazolines obtained contain the characteristic signal of a carbon atom doubly bonded to a nitrogen atom at 143-152.5 ppm. In a study of the mass spectra of 2-isoxazolines [1] we showed that the principal pathways in the fragmentation of 5-phenylisoxazolines involve cleavage of the isoxazoline ring and that the mass-spectral data unambiguously determine the positions of the substituents in the heteroring.

In the present research we investigated the effects of substituents in 5-arylisoxazolines on the character of their mass-spectral fragmentation. In most cases the dominating process in the fragmentation of II-XXV is cleavage of the isoxazoline ring at the C—O and $C_{(3)}$—$C_{(4)}$ bonds. In a comparison of the mass spectra of isoxazolines III, IV, XX, and XXI it was observed that a substituent in the ortho position destabilizes the molecular ion and is readily eliminated in the first step of the fragmentation; the [M − R] ion peaks have much higher relative intensities than the molecular-ion peaks. Cleavage of the interannular bond is approximately equally likely for the ortho and para isomers and leads to $[RC_6H_4]^+$ ions or $[RC_6H_5]^+$ ions if the process is accompanied by rearrangement of a hydrogen atom [1].

As noted above, two isomeric isoxazolines that differ with respect to R_f values and PMR and ^{13}C NMR spectra were formed in the nitrosation of 1,2-disubstituted cyclopropanes; the mass spectra of these compounds also differ substantially. The presence of an $[M-ONCH]^+$ ion

TABLE 3. Characteristics of 2-Isoxazolines

Compound	R_f[a]	mp, °C	PMR spectrum ppm					^{13}C NMR spectrum, ppm							M	yield, %
								aromatic C			isoxazoline ring C					
			H_{arom}	3-H	4-H	5-H	CH_3	C^{sb}	C^{sc}	other aromatic carbon atoms	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	CH_3		
II	0,31	84	7,40—8,23 (dd)	7,21(t)	2,77—3,90 (m)	5,50—5,80 (m)		143,5	148,2	123,9; 126,4	145,2	43,9	78,5		192	80
III	0,58	69	7,36—8,20 (m)	7,14 (t)	2,57—3,99 (m)	5,80—6,10 (m)		137,7	145,5	125,0—134,3	145,7	44,6	78,6		192	62
IV	0,36	62	7,30—7,94 (dd)	6,83 (t)	2,48—3,53 (m)	5,40—5,10 (m)		141,3	93,5	127,9; 137,8	144,5	43,8	79,0		273	90
V	0,62		7,30—7,94 (m)	7,07 (t)	2,50—3,90 (m)	5,43—5,73 (m)		139,33	95,7	126,8—129,5	143,9	43,8	82,6		273	87
VI	0,41		7,17 (s)	6,97 (t)	2,43—3,53 (m)	5,15—5,65 (m)		139,3	133,7	127,0—128,7	145,3	43,5	79,0		181 182	90
VII	0,65		7,10—7,40 (m)	7,03(t)	2,50—3,77(m)	5,53—5,87 (m)		142,37	138,9	126,6—131,8	145,7	43,4	74,6		181 182	86
VIII	0,09		6,89—7,33 (dd)	6,90 (t)	2,48—3,53 (m)	5,07—5,40(m)		140,90	122,0	127,3—131,7	145,3	43,6	75,3		225 227	88
IX	0,12		7,12—7,56 (m)	—[d]	2,53—3,90 (m)	5,30—5,90 (m)		142,2	121,1	125,2—129,8	145,3	43,4	78,5			82
X	0,52		6,83 (s)	6,81 (t)	2,38—3,46(m)	5,01—5,38(m)	2,13 (s)	138,4	137,4	125,9—129,4	145,2	43,6	79,7	21,2	161	92
XI	0,49		6,36—6,93 (dd)	6,70(t)	2,17—3,23 (m)	4,77—5,20 (m)	3,40 (s)								177	86
XII[e]	0,45	67	6,80 (s)	6,70 (t)	2,40—3,43 (m)	5,03—5,33(m)		143,4	138,5	125,8—125,9	143,9	43,6	79,5		187	89
XIII	0,04	100	7,07 (s)	6,94 (t)	2,41—3,50 (m)	5,11—5,30 (m)		138,6		123,8—126,5	143,4	41,3	75,3		216	76
XIV	0,39	60	7,47—8,20 (dd)	7,17(t)	3,20—3,23 (d)		1,70 (s)	146,9	152,4	123,6; 125,6	145,8	49,0	84,9	27,5	206	82
XV	0,62		6,63—7,90 (m)	6,87(t)	3,20—3,23 (d)		1,70 (s)	141,3	93,2	126,8—128,8	146,2	47,8	86,3	26,4		91
XVI	0,16		7,37—8,20 (dd)		2,60—3,77 (m)	5,43—5,80(m)	2,00 (s)								206	56
XVII	0,30		7,67—8,53 (dd)	7,37 (d)	3,16—3,70(m)	5,20—5,33 (dd)	1,43—1,63(d)	147,4	148,2	123,9; 126,4	145,3	43,8	77,0	29,6	206	36
XVIII	0,24	89	7,23—8,23 (m)		2,47—3,90 (m)	5,83—6,13 (m)	1,90 (s)								206	55
XIX	0,38		7,13—8,03 (m)	7,10 (d)	2,92—3,30(m)	5,57—5,70 (m)	1,36—1,57(d)									30
XX	0,67		7,00—8,06 (m)		2,41—3,89 (m)	5,53—5,80 (m)	1,97 (s)	144,1	95,5	126,6—138,9	152,5	46,6	83,9	12,8	287	65
XXI	0,80		6,80—7,86 (m)	6,80—7,20(m)	2,80—3,13 (m)	5,10—5,20 (d)	1,30—1,57(d)	139,1	89,3	126,6—139,1	149,8	51,9	76,9	17,5	187	24
XXII	0,70		7,33 (s)		2,77—3,79(m)	5,36—5,67 (m)		135,4		128,9—126,0	139,8	49,3	82,9		225 227	53
XXIII	0,79		7,40 (s)	7,24(t)	4,88—5,00 (m)	5,68—5,78 (d)		137,5		128,7—124,8	143,5	53,0	88,6		225 227	40
XXIV	0,76		7,25 (s)		3,13 (s)		1,60 (s)	143,9		124,4—128,6	145,8	51,8	89,6	28,1		71
XXV	0,82		7,25 (s)	7,20 (d)	5,00—5,03(d)		1,73 (s)	145,78		124,6—128,6	147,7	42,9	89,3	23,4		20

[a]Silufol UV-254 with ether—hexane (1:1). [b]Signal of the carbon atom bonded to the isoxazoline ring. [c]Signal of the carbon atom attached to substituent R. [d]Indistinguishable because of superimposition on the aromatic protons. [e]Chemical shifts of the three-membered ring; PMR, 0.47-0.97 (4H, CH_2) and 1.53-1.93 ppm (1H, CH); ^{13}C NMR, 15.4 (CH) and 9.3 ppm ($2CH_2$).

TABLE 4. Mass Spectra of 2-Isoxazolines

Compound	m/z values[a] (relative intensities of the ion peaks in percent relative to the maximum peak)
II	192 (5,68), 149 (67,21), 119 (41,48), 115 (57,49), 103 (54,75), 91 (62,84), 77 (100,00), 69 (72,68), 63 (36,94), 51 (95,85), 50 (77,27)
III	192 (5,0), 176 (57,1), 149 (88,7), 152 (45,8), 134 (83,3), 116 (36,0), 115 (47,0), 105 (54,3), 85 (60,0), 77 (100), 50 (30,1)
IV	273 (43,7), 230 (100,0), 204 (22,4), 115 (29,3), 103 (60,2), 77 (62,4), 76 (41,3), 69 (32,3), 63 (23,1), 51 (51,4), 50 (65,8)
V	273 (79,4), 230 (81,4), 146 (53,7), 116 (52,7), 115 (69,2), 103 (96,1), 77 (85,8), 76 (67,9), 63 (43,1), 51 (86,7), 50 (100,0)
VI	183 (4,96), 181 (13,64), 140 (33,8), 138 (100,0), 115 (17,5), 103 (30,7), 77 (22,8), 75 (21,8), 69 (23,9), 63 (14,2), 51 (21,7), 50 (23,9)
VIII	227 (12,1), 225 (13,3), 184 (96,9), 182 (100,0), 115 (43,3), 103 (75,3), 77 (89,1), 76 (34,0), 75 (36,4), 69 (47,9), 51 (66,2), 50 (80,3)
X	161 (20,0), 119 (25,1), 118 (100,0), 117 (57,9), 115 (15,6), 92 (18,2), 91 (40,5), 77 (12,7), 65 (20,1), 63 (13,0), 51 (45,0)
XI	177 (28,6), 162 (11,5), 135 (20,7), 134 (100,0), 119 (24,6), 91 (20,3), 77 (15,7), 65 (14,8), 63 (14,0), 51 (14,9), 50 (9,5)
XII	187 (26,9), 145 (20,0), 144 (100,0), 143 (19,7), 129 (57,1), 128 (31,1), 118 (18,9), 117 (51,8), 116 (22,4), 115 (55,1), 91 (33,8)
XIII	216 (10,5), 130 (100,0), 115 (28,8), 105 (17,9), 104 (34,1), 91 (19,6), 77 (44,2), 69 (20,9), 55 (19,3), 51 (40,3), 50 (21,1)
XIV	206 (1,1), 191 (18,6), 163 (13,9), 150 (62,1), 115 (33,4), 104 (15,9), 91 (17,3), 77 (14,5), 76 (15,5), 51 (16,2), 50 (17,7)
XV	159 (40,1), 104 (48,9), 92 (39,3), 91 (49,6), 79 (53,5), 77 (87,8), 76 (48,6), 65 (70,1), 51 (100,0), 54 (37,6), 50 (62,9)
XVI	206 (13,3), 149 (51,9), 130 (23,8), 119 (24,3), 103 (24,3), 91 (25,8), 76 (19,7), 55 (100,0), 54 (43,0), 51 (21,6), 50 (21,7)
XX	287 (100,0), 272 (25,0), 244 (65,0), 233 (40,0), 232 (95,0), 117 (70,0), 115 (65,0), 78 (45,0), 77 (30,0), 76 (42,5), 50 (30,0)
XXI	287 (100,0), 244 (67,9), 233 (42,9), 232 (92,9), 231 (32,1), 117 (60,7), 115 (46,4), 78 (53,6), 76 (46,4), 55 (57,1), 50 (33,9)
XXII	227 (10,6), 225 (11,4), 128 (47,5), 115 (61,7), 105 (75,5), 104 (63,0), 79 (42,8), 77 (100,0), 68 (80,2), 51 (94,3), 50 (5,0)
XXIII	227 (8,5), 225 (9,1), 146 (71,2), 119 (55,3), 115 (75,3), 105 (100,0), 91 (90,0), 89 (26,89), 77 (96,1), 63 (30,2), 51 (73,6), 50 (40,5)

[a]The M^+ peaks and the 10 most intense ion peaks are presented.

peak in the spectrum of XXI shows that the 3 position is unsubstituted. In contrast to the spectrum of XX, an intense peak of $[M - CH^3]^+$ ions is observed in the spectrum of this compound. The peak of a characteristic $[M - ONCH]^+$ ion is completely absent in the mass spectrum of XX, but a peak of $[M - ONCCH_3]^+$ ions also is not observed. The molecular ions eliminate a neutral fragment with 30 amu, i.e., an NO or OCH_2 molecule.

The presence of a nitro group in the benzene ring decreases the stability of the molecule with respect to electron impact to an even greater extent, and the molecular-ion peaks have low intensities. Peaks of [M − OH] ions, which are characteristic for the fragmentation of o-nitroalkylbenzenes [2], are observed in the high m/z region. In all cases the elimination of an NO group by the molecular and fragment ions of the nitro derivatives constitutes evidence that the nitro group exists in the nitrite form.

The facile detachment of the substituent in the 5 position and the subsequent cleavage of the heteroring at the C–O and $C_{(4)}$–$C_{(5)}$ bonds to give the corresponding benzoyl cations should also be noted.

All of the indicated fragmentation pathways are very valuable for the identification of the products of the nitrosation of arylcyclopropanes and, in particular, for the establishment of the positions of the substituents in the synthesized substances.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in CCl_4 or $CDCl_3$ were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane as the internal standard. The ^{13}C NMR spectra were recorded with a CFT-20 spectrometer. The mass spectra were obtained with a

Varian MAT-112 chromatographic mass spectrometer at an ionizing voltage of 80 eV. Monitoring of the purity of the starting substances and the individuality of the reaction mixtures were carried out by gas-liquid chromatography (GLC), thin-layer chromatography (TLC), and column chromatography on silica gel (40/100) by elution with hexane—ether in various ratios.

The starting phenylcyclopropanes were synthesized by previously described methods. The o- and p-nitrophenylcyclopropanes were obtained by fractional distillation of the products of nitration of the corresponding hydrocarbons by the method in [3]. The aromatic ring-halogenated arylcyclopropanes were synthesized from the corresponding nitro derivatives as described in [4, 5]. p-Tolylcyclopropane, p-methoxyphenylcyclopropane, and p-dicyclopropylbenzene were synthesized by the Mannich—Kishner method [6, 7]. 1-Bromo-2-phenylcyclopropane, with bp 118-126°C (18 mm) and n_D^{20} 1.5696, was obtained from gem-dibromophenylcyclopropane by the method in [8]. 1-Methyl-1-phenyl-2-chlorocyclopropane, with bp 101-104°C (10 mm) and n_D^{20} 1.5690, was obtained from 1-methyl-1-phenyl-2,2-dichlorocyclopropane by the method in [9].

The reaction of arylcyclopropanes with sodium nitrite and trifluoroacetic acid in chloroform was carried out at −5°K by the general method presented in [1]. The characteristics and yields of the isoxazolines obtained are presented in Tables 3 and 4.

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INVESTIGATION OF SUBSTITUTED 2- AND 3-THIOLENE 1,1-DIOXIDES BY PMR SPECTROSCOPY WITH THE AID OF A LANTHANIDE SHIFT REAGENT

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The reaction of lanthanide shift reagent $Eu(FOD)_3$ with 3-phenyl- and 3- and 4-chloro-2-thiolene 1,1-dioxides and with 3-phenyl-3-thiolene 1,1-dioxide was investigated by PMR spectroscopy. The geometrical structure of the adduct of the lanthanide shift reagent with 4-chloro-2-thiolene 1,1-dioxide was found.

Derivatives of 2- and 3-thiolene 1,1-dioxides display high biological activity [1], and a thorough study of their structures and conformational compositions is therefore urgent. Studies in which the conformations of the molecules of a number of thiolene 1,1-dioxides in solution were determined by PMR spectroscopy have been made [2]. Lanthanide shift reagents are effective agents for the analysis of the PMR spectra of these compounds [3].

In the present research we used europium(III) 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate [$Eu(FOD)_3$] as the lanthanide shift reagent to ascertain the three-dimensional structures of I-IV.

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