RESEARCH IN THE ISOXAZOLE SERIES

XXVIII.* NITRATION OF 3,5-DIPHENYLISOXAZOLE

S. D. Sokolov, T. N. Egorova,
and I. M. Yudintseva

UDC 547.786.2:542.958.1

The 4-nitro derivative is formed in the nitration of 3,5-diphenylisoxazole (I) in acetic anhydride. Mononitration of isoxazole I in concentrated H_2SO_4 gave 3-phenyl-5-(p-nitrophenyl)-isoxazole, while polynitration gave a mixture of dinitro derivatives, among which 3-(m-nitrophenyl)-5-(p-nitrophenyl)isoxazole was identified. The structures of the isolated products were established by means of the spectra, by reaction-chromatography methods, and gas–liquid chromatography, as well as by a comparison with genuine samples of the two mononitro and four dinitro derivatives of isoxazole I.

The nitration of 3- and 5-phenylisoxazoles has been studied in detail in recent years [2-4]. However, Musante [5] assigned the 3,5-di(p-nitrophenyl)isoxazole structure to the only isolated product of the nitration of 3,5-diphenylisoxazole (I). We decided to reinvestigate the behavior of 3,5-diphenylisoxazole under the conditions of the nitration reaction, inasmuch as this compound is a single conjugation system [6-7], and it is difficult to predict the site of entry of one or several nitro groups. In addition, the results might possibly be of assistance in finding the site of entry of nitro groups in a number of other similar systems (see [8-11]).

In contrast to diphenyl, which is readily nitrated in acetic acid [12],(I) remained unchanged in acetic acid at 20-120°C. Nitration in acetic anhydride at ~20° with an equimolar amount of nitric acid in the presence of catalytic amounts of concentrated H_2SO_4 [13] gives a mixture of mononitric derivatives, in which the principal product is 3,5-diphenyl-4-nitroisoxazole (II). The structure of II follows from a comparison of its spectra with the spectra of 3-phenyl-4-nitroisoxazole [2, 14]. The UV spectra of both substances contain an absorption maximum at 204 nm (log ε 4.3-4.4), and a second maximum lies in the longer-wave region for II, which has a large conjugation chain. Strong absorption bands at 756 and 830 cm^{-1}, which are characteristic for aryl-4-nitroisoxazoles [14], are found in the IR spectrum of nitro derivative II. Finally, the similar paths of disintegration of the molecular ions in the mass spectra† of both substances also provide evidence in favor of the proposed structure.

A fraction, which, from its melting point and chromatographic behavior, is phenyl(p-nitrophenyl)isoxazole containing starting I, was isolated from the same reaction.

A mixture containing nitro derivative II is formed by the action of a tenfold excess of nitric acid on isoxazole I.

The reactivity of the heterocyclic ring of isoxazole I during nitration in acetic anhydride is inferior to the reactivity of the benzene ring in chlorobenzene [13]. However, here, as in the case of chlorobenzene, the ion attacks the dipole of the (I) molecule; this leads to selective nitration of the heteroring. In this respect, (I) differs from conjugated systems of the p-polyphenylene type, which are nitrated predominantly in the 4 and 4' positions under the same conditions [11].

---

*See [1] for communication XXVII.

†The mass spectra will be discussed in detail separately. The authors thank K. K. Zhigulev for recording the mass spectra.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical Chemistry Institute, Moscow.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 597-601, May, 1974. Original article submitted March 2, 1973.

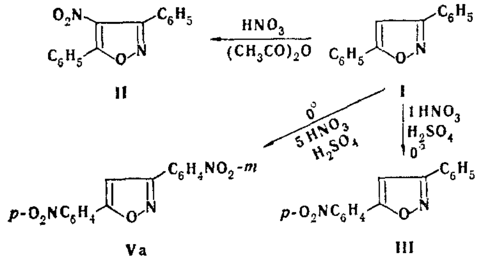
TABLE 1. 3,5-Di(nitrophenyl)isoxazoles (Va-d), Dinitrochalcones (VIa-d), and Dibromides (VIIa-d)

Compound	mp, °C	Yield %	Compound	mp, °C	Yield %	Compound	mp, °C	Found,%*		Calc. %
								C	H	
VIa	208 —209	68	VIIa	186 —188,5	96	Va	256—256,5	58,0	3,0	33
VIb	224,5—225	34	VIIb	146,5—147,5	96	Vb	261—261,5	57,9	2,9	12
VIc	211,5—212	94	VIIc	178,5—180,5	94	Vc	263—263,5	57,8	2,9	37
VId	195 —196	58	VIId	147 —150	94	Vd	287—289 (dec.)	57,6	2,8	29

*$C_{15}H_9N_3O_5$. Calculated %: C 57.9; H 2.9.

A mononitro derivative, which does not depress the melting point of a mixture with samples of both 3-phenyl-5-(p-nitrophenyl)isoxazole (III) and 3-(p-nitrophenyl)-5-phenylisoxazole (IV), was obtained by nitration of isoxazole I in concentrated H_2SO_4 at 0° (as previously described in [5]).

The similarly constructed isomeric arylphenylisoxazoles are isomorphic [15], and it has been proposed that they be characterized by conversion to N-methylisoxazolium chloroferrates, which are not isomorphic [16]. We obtained N-methylisoxazolium chloroferrates from the reaction products and reference compounds III and IV and established that the mononitro derivative has the III structure.



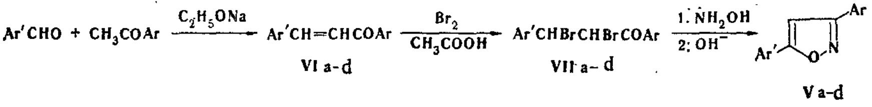
+ several isomers

The mixture of dinitro derivatives obtained by nitration of isoxazole I with excess nitric acid was separated into fractions A, B, and C by crystallization from benzene. Chromatographically pure substances were isolated from fractions A and B, and fraction C was found to be a mixture of isomers.*

We also synthesized the four isomeric 3,5-diarylisoxazoles (Va-d), which contain NO_2 groups in the meta or para positions of the benzene rings (Table 1).

All three steps of the scheme can be successfully realized only under specially selected conditions. When this was done, we were able to raise the yield of all of the dinitrochalcones (VIa-d) as compared with the yields presented in the literature [17]. The bromination of chalcones VI proceeds smoothly only in acetic acid. Finally, prior formation of oximes is necessary for successful cyclization.

A chromatographically pure substance with mp 254-255° was isolated by crystallization of the high-melting A fraction. Oxidation of the quaternary salt of this substance gave m- and p-nitrobenzoic acids, which were identified as the methyl esters by gas-liquid chromatography (GLC).



a Ar=m-$O_2NC_6H_4$, Ar'=p-$O_2NC_6H_4$; c Ar=Ar'=m-$O_2NC_6H_4$;
b Ar=p-$O_2NC_6H_4$, Ar'=m-$O_2NC_6H_4$; d Ar=Ar'=p-$O_2NC_6H_4$.

---

*Because of the very low solubility of the dinitro derivatives in organic solvents, we were unable to record their PMR spectra.

Hence, the substance in fraction A proved to be 3-(m-nitrophenyl)-5-(p-nitrophenyl)isoxazole (Va); this was proved by comparison of the mass spectra with the spectra of genuine samples of Va and Vb [by comparison of the intensities of the $C_7H_4O_2^+$ (m/e 120) and $C_7H_4O^+$ (m/e 104) characteristic ions formed during disintegration of the $O_2NC_6H_4CO^+$ fragments].* Consequently, the higher-melting 3,5-di(p-nitrophenyl)isoxazole (Vd) is not formed during polynitration as was previously reported [5].

Inasmuch as the substances in fractions B and C were resinified by methylation with dimethyl sulfate, they were analyzed by "reaction chromatography" [18]. Samples of the substances on plates containing silica gel were reduced with stannous chloride ($-NO_2 \rightarrow -NH_2$), and the products were oxidized with potassium permanganate, during which the aniline and isoxazole rings were completely destroyed. Under the conditions of this treatment, the unsubstituted phenyl groups in the arylisoxazoles were converted to benzoic acid, which was detected after chromatography. The method was tested on III and Va and gave positive results: benzoic acid was found only in the products of degradation of III. All of the substances of fraction B, according to the results of this analysis, contained only nitrophenyl groups. One of the compounds, with mp 228°, could be isolated in chromatographically pure form, and it contained at least one nitro group in the ortho position.

On the other hand, a dinitro derivative with an unsubstituted phenyl group enters into the composition of the low-melting C fraction. Inasmuch as dinitration of one benzene ring cannot occur under the mild conditions used [3], the 4-nitroisoxazole structure should be assigned to this substance. Despite repeated crystallization, it could not be obtained in analytically pure form.

Thus the nitration of 3,5-diphenylisoxazole is a complex process that depends on many factors. Both the direction of electrophilic attack of this compound and the reaction rate change as a function of the medium. Electronic effects in this system can apparently be realized by different paths.

EXPERIMENTAL†

The UV spectra were recorded with a Perkin–Elmer 402 spectrophotometer, and IR spectra were recorded with a Perkin-Elmer 457 spectrometer, and the mass spectra were recorded with a Varian FH-6 spectrometer.

Chromatographic Methods. Two variants of thin-layer chromatography (TLC) were used for the analysis of the reaction mixtures and establishment of the purity of the isolated substances: a) on a fixed layer of KSK silica gel in benzene–methanol (9 : 1) and detection of the substances with iodine; b) on Silufol UV-254 plates in cyclohexanone–chloroform–diethylamine (15 : 35 : 1) and development in UV light. The analysis by GLC was performed with a JGC-810 chromatograph on an XE-60 stationary phase at 140°.

Reaction chromatography was developed to establish the structure of the nitro derivatives obtained. A 1-mg sample of the mixture was applied to a plate (13 × 18 cm) with fixed KSK silica gel. A 10% solution of stannous chloride in concentrated HCl was applied at the same point, and the plate was heated at 180° for ~40 min. It was then cooled, a mixture of a 1% solution of potassium permanganate and a 2% solution of sodium carbonate (1 : 1) was added to this point, and the plate was again heated under the same conditions. It was then cooled and chromatographed in alcohol–water–2.5% ammonium hydroxide (25 : 3 : 4), and the benzoic acid (R_f 0.7) was detected in UV light after sprinkling with a solution of Bromcresol Purple.

Nitration of 3,5-Diphenylisoxazole (I) in Acetic Anhydride. A solution of 0.63 ml (0.015 mole) of nitric acid (sp. gr. 1.5) in 12 ml of acetic anhydride and two drops of concentrated H_2SO_4 were added at 0° to a solution of 3.32 g (0.015 mole) of isoxazole I in 220 ml of acetic anhydride, and the mixture was held at ~20° for 8 days. It was then poured over ice, and the aqueous mixture was allowed to stand for 2 days. The resulting precipitate was removed by filtration, washed on the filter with sodium bicarbonate solution (two 50-ml portions) and cold water (~500 ml), and dried to give 2.8 g of a mixture of substances with mp 127-130°, crystallization of which from alcohol and repeated crystallization of which from benzene–hexane gave 0.1 g of chromatographically pure 3,5-diphenyl-4-nitroisoxazole (II) with mp 170.5-171°. Found %: C 67.8; H 4.0. $C_{15}H_{10}N_2O_3$. Calculated %: C 67.7; H 3.8. UV spectrum (alcohol), λ_{max}, nm (log ε): 204 (4.44) and 238 (4.20).

Nitroisoxazole II, a basic substance, starting compound I, and a nitro derivative of the III or IV type were found in the other fractions and the mother liquors by TLC (variant b).

---

*The mass spectra will be examined in greater detail separately.

†Performed with the participation of N. F. Belova.

Nitration of 3,5-Diphenylisoxazole I in Concentrated H_2SO_4. 1. Mononitration. A 0.4-ml sample of nitric acid (sp. gr. 1.5) was added dropwise with stirring at 0° to a solution of 2.2 g of isoxazole I in 10 ml of concentrated H_2SO_4, and the mixture was held at 0° for 1 h. It was then poured over ice, and the precipitate was removed by filtration, washed with water, and dried. Fractional crystallization of the product from hexane–benzene (3 : 2), benzene, and alcohol gave 0.2 g of a chromatographically pure substance with mp 222-225°. This same substance was identified by TLC (variant *a*) as the basic substance in the mother liquors. N-Methylisoxazolium chloroferrate [16], with mp 110°, was obtained to establish its structure; no melting-point depression was observed for a mixture of it with 2-methyl-3-phenyl-5-(p-nitrophenyl)isoxazolium chloroferrate. The chloroferrate of the isomeric 2-methyl-3-(p-nitrophenyl)-5-phenylisoxazolium ion had mp 138-140°.

2. Polynitration. The reaction was carried out similarly by treating 5.5 g (0.025 mole) of isoxazole I in 50 ml of concentrated H_2SO_4 with a mixture of 5 ml (0.119 mole) of nitric acid (sp. gr. 1.5) and 5 ml of concentrated H_2SO_4 at 0° for 2 h. Workup of the mixture gave 8 g of a mixture of products with mp 200-210°. Two crystallizations from benzene gave 1.3 g of a substance with mp 245-251° (fraction A). Fractional crystallization from benzene and alcohol of the residue from the mother liquor from the second crystallization of fraction A gave 1.4 g of a substance with mp 220-230° (fraction B). The benzene mother liquor from the crystallization of fraction B was diluted with heptane and evaporated to give 1.8 g of a product with mp 140-156° (fraction C).

Two crystallizations of 0.8 g of the substance (from fraction A) from toluene–dichloroethane (1 : 1) gave 0.3 g of chromatographically pure 3-(m-nitrophenyl)-5-(p-nitrophenyl)isoxazole with mp 254-255°. Found %: C 57.6; H 2.9. $C_{15}H_9N_3O_5$. Calculated %: C 57.9; H 2.9. No melting-point depression was observed for a mixture with a genuine sample of Va, and a mixture with a sample of Vb melted at 257.5-258.5°. A 0.5 g sample of the substance from fraction A was methylated for 6 h by adding 3 ml of dimethyl sulfate to 30 ml of dichloroethane. The solvent was decanted, and 0.32 g of N-methylisoxazolium chloroferrate with mp 134-136° was obtained from the solid by the method in [16]; the quaternary salt was oxidized with aqueous potassium permanganate solution at 100°, concentrated HCl was added to the solution, and the mixture was treated with bisulfite until it was decolorized. The aqueous solution was then extracted with ether, and the acids in solution were methylated with diazomethane. The methyl esters of m- and p-nitrobenzoic acids were identified by GLC.

Recrystallization of fraction B from acetone gave 0.16 g of a chromatographically pure substance with mp 227-228°. Found %: C 57.9; H 3.1. $C_{15}H_9N_3O_5$. Calculated %: C 57.9; H 2.9. According to reaction chromatography, it contained nitro groups in the benzene rings, just as in the case of other substances from this fraction, which could not be purified. Complete resinification occurred under the methylation conditions.

Despite the use of solvents of different polarity – toluene, dichloroethane, methanol – fraction C could not be crystallized into individual compounds. The fraction as a whole is a mixture of isomeric dinitro derivatives; it was shown by reaction chromatography that at least some of them contain unsubstituted benzene rings. Found %: N 13.4. $C_{15}H_9N_3O_5$. Calculated %: N 13.5.

Phenyl(p-nitrophenyl)isoxazoles. These compounds were obtained from equimolar amounts of the appropriate arylacetylene and α-chloraldoxime in refluxing toluene by the method in [19]. The yield of 3-phenyl-5-(p-nitrophenyl)isoxazole III with mp 220.5-222° [20] was 30%, while the yield of 3-(p-nitrophenyl)-5-phenylisoxazole IV with mp 220-221° [21] was 20%.

3,5-Di(nitrophenyl)isoxazoles (Va-d). Equimolar amounts of the appropriate nitrobenzaldehyde and nitroacetophenone were dissolved by heating to 50-60° in the minimum amount of absolute alcohol, after which a few drops of 10% sodium ethoxide solution were added with stirring, and the mixture was acidified to pH ~ 5 after 5 min with 8% HCl. The resulting precipitated chalcone (VIa-d) was removed by filtration and recrystallized. A solution of 0.16 mole of bromine in 10 ml of glacial acetic acid was added dropwise with stirring at 60-70° to a solution of 0.134 mole of chalcone VIa-d in 240 ml of glacial acetic acid, after which the mixture was heated for another hour, cooled, and added dropwise to 1.4 liter of cold water. The precipitated bromides (VIIa-d) were removed by filtration, washed with water until the washings gave a neutral reaction to Congo Red, and dried at 30-35°. A solution of 6.6 mmole of hydroxylamine hydrochloride was added to a solution of 4.4 mmole of dibromides VIIa-d in alcohol, after which the mixture was refluxed for 2 h and cooled to 0°. A 4-ml sample of a 50% potassium hydroxide solution in alcohol was added dropwise, and the mixture was held at ~20° for 20 h. The precipitated diarylisoxazole (Va-d) was removed by filtration, washed with hot water until the washings gave a negative test for bromide ions, dried, and crystallized from dichloroethane–toluene or acetone. Data on Va-d, VIa-d, and VIIa-d are presented in Table 1.

LITERATURE CITED

1. S. D. Sokolov, T. N. Egorova, and N. S. Kuryatov, Khim. Geterotsikl. Soedin., 1329 (1973).
2. M. R. Langella and P. Vita Finzi, Chim. Ind. (Milano), 47, 996 (1965).
3. B. M. Lynch and L. Shiu, Canad. J. Chem., 43, 2117 (1965).
4. S. D. Sokolov and I. M. Yudintseva, Zh. Organ. Khim., 4, 2057 (1968).
5. C. Musante, Farm. Sci. Tec. (Pavia), 6, 32 (1951); Chem. Abstr., 45, 5879 (1951).
6. S. D. Sokolov, L. A. Kazitsyna, and L. K. Guseva, Zh. Organ. Khim., 2, 731 (1966).
7. T. A. Babushkina, G. K. Semin, S. D. Sokolov, and I. M. Yudintseva, Izv. Akad. Nauk SSSR, Ser. Khim., 2376 (1970).
8. G. E. Lewis, J. Org. Chem., 30, 2798 (1965).
9. G. P. Sharnin, I. E. Moisak, E. E. Gryazin, and I. F. Falyakhov, Zh. Organ. Khim., 3, 1836 (1967).
10. V. V. Zverev, G. P. Sharnin, and I. D. Morozova, Izv. Akad. Nauk SSSR, Ser. Khim., 404 (1968).
11. M. L. Scheinbaum, Chem. Commun., 1235 (1969).
12. F. Bell, J. Kenyon, and P. H. Robinson, J. Chem. Soc., 1239 (1926).
13. M. A. Paul, J. Amer. Chem. Soc., 80, 5332 (1958).
14. S. D. Sokolov, I. M. Yudintseva, P. V. Petrovskii, and V. G. Kalyuzhnaya, Zh. Organ. Khim., 7, 1979 (1971).
15. R. P. Barnes and L. B. Dodson, J. Amer. Chem. Soc., 67, 132 (1945).
16. A. H. Blatt, J. Amer. Chem. Soc., 71, 1861 (1949).
17. P. Klinke and H. Gibian, Chem. Ber., 94, 26 (1961).
18. J. Frank and K. Pospisilova, J. Chromatogr., 48, 207 (1970).
19. M. Arbasino and P. Grünanger, Ric. Sci., 34, (II-A), 561 (1964).
20. U. Türck and H. Behringer, Chem. Ber., 98, 3020 (1965).
21. G. Bianchetti, D. Pocar, and P. Dalla Croce, Gazz. Chim. Ital., 93, 1714 (1963).