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The bromination of phenylisoxazoles in 85% acetic acid is a second-order reaction. The ratios of the rate constants for the bromination of benzene and the investigated compounds are 1:100-10,000. The maximum reaction rate was observed when a twofold excess of the heterocycles was present, and this constitutes evidence for the intermediate formation of complexes of isoxazoles with bromine.

The halogenation of isoxazole and its derivatives always proceeds in the 4 position, and the benzene rings in phenylisoxazoles are not involved [2, 3]. We therefore selected bromination as a convenient reaction for kinetic investigation in order to ascertain the effects of substituents in the reacting molecules and to obtain information regarding complexes of isoxazoles with halogens.

The bromination of aromatic hydrocarbons in aqueous acetic acid is a second-order reaction — first-order in bromine and first-order in substrate — if it is carried out in the presence of excess bromide ion [4, 5]. Under these conditions a large amount of the bromine is tied up in the  $\text{Br}_3^-$  ion, so that one can disregard the bromide ions formed as a result of the reaction. In 50% acetic acid at 45°C the rate constant for the bromination of benzene is  $3.3 \cdot 10^{-6}$  liter·mole<sup>-1</sup>·sec<sup>-1</sup> as compared with  $4.14 \cdot 10^{-3}$  liter·mole<sup>-1</sup>·sec<sup>-1</sup> in the bromination of diphenyl [4].

We studied the kinetics of bromination of five phenylisoxazoles in 85% acetic acid at 50° in solutions with the same ionic strength. The results are presented in Tables 1 and 2.† The bromination products were identified by gas-liquid chromatography (GLC) and thin-layer chromatography (TLC), and genuine samples of 4-bromoisoxazoles [2] served as reference compounds during chromatography; 3-phenyl-4-bromo-5-methylisoxazole was obtained for the first time by this same method. For the four investigated compounds bromination is a second-order reaction overall (Table 1), i.e., in aqueous acetic acid the isoxazole derivatives and benzene react in the same manner.

The experimental rate constants are not the true rate constants, inasmuch as they depend on the bromide ion concentration [6]:

$$k_2 \text{ exp} = k_2 K / (K + [\text{Br}])$$

where K is the constant of equilibrium of  $\text{Br}_3^- \rightleftharpoons \text{Br}_2 + \text{Br}^-$  at a given temperature. However, inasmuch as the ionic strengths of all of the investigated solutions were identical, one can compare the reactivities of the phenylisoxazoles by using the experimental rate constants. Of the four substances (see Table 1), 5-phenylisoxazole has the lowest activity, whereas its 3-methyl homolog has the highest activity. This conclusion could not be drawn on the basis of the yields of 4-halo derivatives [2]. The +E effect of the phenyl group (transmission of conjugation along the  $\text{C}_4 = \text{C}_5$  bond) and the +I effect of the methyl group

\*See [1] for communication XXIX.

†The bromination of 3-phenylisoxazole proceeded so slowly that we were unable to measure the reaction rate.

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TABLE 1. Rate Constants for the Bromination of Phenylisoxazoles at 50° ( $k_2^{\text{exp}}$ , liter·mole<sup>-1</sup>·sec<sup>-1</sup>)

Compound	5-Phenylisoxazole	3,5-Diphenylisoxazole	3-Phenyl-5-methylisoxazole	3-Methyl-5-phenylisoxazole
$\frac{[\text{Ht}]}{[\text{Br}_2]}$	1,35, 2,01, 2,6	1,50, 1,97, 2,30	1,70, 1,80, 1,90, 2,20, 4,60	1,60, 1,80, 2,12, 2,60
$k_2 \cdot 10^4$	8,6, 8,8, 3,0	23, 27, 30	40, 46, 53, 38, 21,5	160, 300, 350, 260

are best realized in 3-methyl-5-phenylisoxazole, and the role of the +I effect is very great. The close rate constants for the 3-phenylisoxazoles can be explained by weak transmission of conjugation along the C<sub>3</sub>-C<sub>4</sub> bond.

Considering the increase in the reaction rate when acetic acid is diluted with water [5] and the statistical correction, it might be supposed that 5-phenylisoxazole is ~100 times more active than benzene, whereas the remaining three isoxazoles have reactivities that are comparable to or exceed the reactivity of diphenyl. It was also found by the method of competitive bromination that 3,5-dimethylisoxazole reacts ~600 times more rapidly than benzene.

Previously during the preparative bromination of isoxazole derivatives crystalline orange complexes, which, because of their very high instability, were not investigated in greater detail, were detected [2]. In the present research we have obtained new data that confirm the formation of such complexes. The rate constants presented in Table 1 depend on the ratio of the initial concentrations of the reagents and reach their maximum values when a twofold excess of the isoxazoles is present. This is convincing proof for the formation of intermediate complexes of the  $\text{N} \begin{array}{c} \parallel \\ \diagup \end{array} \text{Br} - \text{Br} \begin{array}{c} \parallel \\ \diagdown \end{array} \text{N}$  type, which also bring about autobromination. At the same time, one cannot completely exclude bromination by 1:1 complexes (particularly for 5-phenylisoxazole).

#### EXPERIMENTAL METHOD

**Reagents.** Pure-grade sodium bromide was crystallized from absolute methanol and dried at 110° prior to its use. Pure-grade potassium iodide was crystallized from water and dried at 110°. Analytically pure-grade bromine was used without additional purification. Commercial-grade glacial acetic acid was purified by the method in [7], and 85% acetic acid was prepared by mixing calculated volumes of the purified acid and thoroughly boiled distilled water. Chromatographically pure samples of the phenylisoxazoles were used.

**Kinetic Measurements.** Solutions of bromine (0.1 mole) and sodium bromide (1 mole) in 85% acetic acid were prepared and were then diluted to the desired concentration. Solutions of all of the other substances were similarly prepared. Solutions with the same ionic strength (0.1) were used for the kinetic measurements; the experiments were carried out at 50 ± 0.2° by the method in [6]. Usually five to six samples were selected after suitable time intervals, and the bromine concentration was determined iodometrically.

The experimental rate constants from individual experiments are presented in Table 2. The constants were calculated from the integral equation for a second-order reaction, and the accuracy in the determination was 5-7%.

The competitive bromination of 3,5-dimethylisoxazole and benzene (0.01 mole of each) was carried out in 2 ml of glacial acetic acid by means of 0.01 mole of bromine, which was added all at once. When this was done, there was a vigorous exothermic reaction with HBr evolution, and the temperature rose from 20 to 40°. The first sample was taken after 30 min at a solution temperature of 20°, the second sample was taken after 1 h, the third sample was taken after 2.5 h, and the fourth sample was taken after 5 h. Each sample (0.2 ml) was treated with 5 ml of water, and the aqueous mixture was neutralized with sodium carbonate and extracted with chloroform. The bromination products were determined by GLC under the following conditions: with a 1-m-long steel column containing 2% SE-30 on Chromosorb W at 65° and a carrier-gas (helium) flow rate of 60 ml/min. With allowance for the statistical correction, all of the samples contained ~600 times more 3,5-methyl-4-bromoisoxazole than bromobenzene. A parallel experiment gave the same results.

TABLE 2. Experimental Rate Constants for the Bromination of Phenylisoxazoles from Individual Experiments ( $k_2^{\text{exp}}$ , liter·mole<sup>-1</sup>·sec<sup>-1</sup>)

5-Phenylisoxazole, [Het] = 13.09 mmole, [Br <sub>2</sub> ] = 9.53 mmole		5,5-Diphenylisoxazole, [Het] = 9.98 mmole, [Br <sub>2</sub> ] = 5.08 mmole		3-Phenyl-5-methylisoxazole, [Het] = 11.75 mmole, [Br <sub>2</sub> ] = 5.49 mmole		3-Methyl-5-phenylisoxazole, [Het] = 11.75 mmole, [Br <sub>2</sub> ] = 5.49 mmole	
time, h	$k_2 \cdot 10^4$	time, h	$k_2 \cdot 10^3$	time, min	$k_2 \cdot 10^3$	time, min	$k_2 \cdot 10^2$
3,5	8,64	3	2,68	30	4,50	60	3,48
5	8,65	4	2,70	55	3,85	75	3,58
6,5	8,33	5	2,75	90	4,28	90	3,46
		7	2,65	120	4,13	105	3,50
		21,5	2,54	150	4,22	120	3,52
				180	4,02		

3-Phenyl-4-bromo-5-methylisoxazole. A solution of 3.18 g (0.02 mole) of 3-phenyl-5-methylisoxazole, 0.51 ml (0.01 mole) of bromine, and 0.84 ml (0.02 mole) of NH<sub>4</sub>O<sub>3</sub> (sp. gr. 1.5) in 30 ml of acetic anhydride was heated at 100° for 2 h, after which the solvent was evaporated, and the residue was vacuum fractionated with collection of the fraction with bp 130-135° (5 mm). The yield of product with bp 128-130° (5 mm) and  $n_D^{20}$  1.5816 was 3.08 g (65%).

#### LITERATURE CITED

1. S. D. Sokolov, T. N. Egorova, and P. V. Petrovskii, Khim. Geterotsikl. Soedin., 602 (1974).
2. N. K. Kochetkov, S. D. Sokolov, and N. M. Vagurtova, Zh. Obshch. Khim., 31, 2326 (1961).
3. S. D. Sokolov and I. M. Yudintseva, Khim. Geterotsikl. Soedin., 1325 (1973).
4. E. Berliner and J. C. Powers, J. Amer. Chem. Soc., 83, 905 (1961).
5. E. Berliner and F. Gaskin, J. Org. Chem., 32, 1660 (1967).
6. E. Berliner and M. C. Beckett, J. Amer. Chem. Soc., 79, 1425 (1957).
7. L. Altschuler and E. Berliner, J. Amer. Chem. Soc., 88, 5837 (1966).