RESEARCH IN THE ISOXAZOLE SERIES

XXVII.* "SUBSTITUTIVE" NITRATION OF 4-HALOISOXAZOLES

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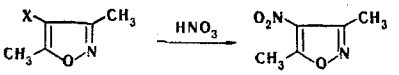
"Substitutive" nitration in the isoxazole series was studied for the first time in the case of 3,5-dimethyl-4-haloisoxazoles. The composition of the reaction mixtures was established by means of quantitative gas–liquid chromatography.

Reactions involving replacement of groupings other than a proton, for example, replacement of a halogen by a nitro group [2, 3], occupy a modest position among the widely spread electrophilic substitution reactions in heteroaromatic compounds. Data regarding the possibility of conversion of iodoimidazoles to nitroimidazoles were recently published [4].

We have found "substitutive" nitration in the isoxazole series. It was found that not only 3,5-dimethylisoxazole (I) but also its 4-halo derivatives [iodo (II), bromo (III), and chloro (IV)] undergo nitration in acetic anhydride in the presence of a catalytic amounts of sulfuric acid (method A). The formation of 2,5-dimethyl-4-nitroisoxazole (V) was proved primarily by means of gas–liquid chromatography (GLC) of the reaction mixture. The results are presented in Table 1.



I–IV V

I X=H; II X=I; III X=Br; IV X=Cl

As one should have expected, the reaction proceeds readily in the case of 4-unsubstituted isoxazole I, while its rate decreases in the order II > III > IV among the halo derivatives, i.e., it is determined by the energy of heterolytic cleavage of the carbon–halogen bond. The more difficulty with which this cleavage takes place, the greater the amount of side products formed.

"Substitutive" nitration also proceeds similarly in concentrated sulfuric acid (method B). This method was previously described for I, but we also studied this reaction for haloisoxazoles II-IV by GLC. The experimental results, which are presented in Table 1, attest to principles similar to those indicated above.

It follows from the data in Table 1 that "substitutive" nitration is promoted by carrying out the reaction in acetic anhydride without heating. Of the 4-haloisoxazoles, only iodo derivative II is smoothly converted to 4-nitroisoxazole V in sulfuric acid.

The resulting halogens are liberated either in free form or react further with the components of the reaction mixture. Under the selected conditions, various side reactions can occur. We are presently studying the most important side reaction – addition to the heterocyclic ring – in detail.

The mechanism of "substitutive" nitration in the isoxazole series has not been subjected to special study. The C_4 atom of the heteroring apparently undergoes attack by the nitronium cation. The alternative

*See [1] for communication XXVI.

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TABLE 1. Conditions for the Nitration of Isoxazoles I-IV and Composition of the Reaction Mixtures

Compound	Nitration conditions			Reaction mixture composition, %		
	method	HNO_3/ isoxazole, g-equiv.	time	4-nitroisoxazole V	starting compound	side products
I	A	1	6 h	39	61	—
I	A	1	24 h	60	40	—
I	A	1	130 h	78	22	—
II	A	3	48 h	58	35	7
III	A	5	72 h	60	8	32
III	A	5	1 week	70	—	30
IV	A	5	2 week	49	5	46
II	B	5	24 h	85*	—	—
III	B	5	2 month	26	54	20
III	B †	5	7,5h	12	33	55
IV	B	5	2 month	4	54	42
IV	B †	5	17 h	traces	93	7

*This is the yield of isolated, chromatographically pure nitro derivative V.

† At 50°C. The temperature in the remaining experiments was 20°.

mechanism with formation of a nitroso derivative and its subsequent oxidation to a nitro compound [6] is not realized in this case, since iodo derivative II does not react on heating in nitrous acid (sodium nitrate in acetic acid).

EXPERIMENTAL

Isoxazoles I-IV were obtained by described methods, and their physical constants were in agreement with the literature data. Gas-chromatographic analysis was carried out with a JGC-810 chromatograph with a flame-ionization detector (a 200 by 0.3 cm steel column filled with 10% SE-30 on Chromosorb W; column temperature 90°), and the carrier-gas (helium) flow rate was 60 ml/min. The relative retention times (the retention time of isoxazole I was 1) were as follows: II 4.94; III 2.40, IV 1.43, and V 4.11.

3,5-Dimethyl-4-nitroisoxazole (V). A solution of 4.46 g (0.02 mole) of iodo derivative II and 4.16 ml (0.1 mole) of nitric acid (sp. gr. 1.5) in 20 ml of concentrated H_2SO_4 was held at 20° for 24 h, after which it was poured over ice. The precipitate was removed by filtration, washed with sodium thiosulfate solution, and recrystallized from aqueous methanol (1 : 1). The yield of nitroisoxazole with mp 62-63° (mp 63.5° [15]) was 2.4g (85%).

LITERATURE CITED

1. S. D. Sokolov and I. M. Yudintseva, Khim. Geterotsikl. Soed., 1325 (1973).
2. H. Gilman and G. F. Wright, J. Am. Chem. Soc, 55, 3302 (1933).
3. C. Musante, Gazz. Chim. Ital., 78, 178 (1948).
4. S. S. Novikov, L. I. Khmel'nitskii, O. V. Lebedev, L. V. Enishina, and V. V. Sevost'yanova, Khim. Geterotsikl. Soed., 664 (1970).
5. G. T. Morgan and H. Burgess, J. Chem. Soc., 119, 697 (1921).
6. A. R. Butler and A. P. Sanderson, J. Chem. Soc., Perkin II, 989 (1972).