RESEARCH IN THE ISOXAZOLE SERIES

XXIX.* STUDY OF HOMOLYTIC BROMINATION OF METHYLISOXAZOLES BY PMR SPECTROSCOPY

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The direction of homolytic bromination of 4-X-3,5-dimethylisoxazoles ($X = CH_3$, Cl, Br, p-$O_2NC_6H_4$) with N-bromosuccinimide (NBS) was studied by PMR spectroscopy. Two of the three CH_3 groups in 3,4,5-trimethylisoxazole react with NBS, and their activity decreases in the order 4-C > 5-C ≫ 3-C. Only the CH_3 groups in the 5 position react in the remaining compounds.

The bromination of a number of methylisoxazoles with N-bromosuccinimide (NBS) has been investigated [2, 3], and the behavior of completely ring-substituted compounds was determined by the position of the CH_3 groups and the character of the other substituents [3]. To prove the structure of the bromo derivatives obtained from 3,4,5-trimethylisoxazole (I) and 3,5-dimethyl-4-chloroisoxazole (II), they were oxidized to isoxazolecarboxylic acids [3]. This reaction did not proceed quantitatively, and one could therefore speak only of preferred bromination of the CH_3 groups in the 4 position of isoxazole I and in the 5 position of isoxazole II.

To obtain more nearly complete information regarding the activity of the CH_3 groups in homolytic bromination, we reinvestigated the reaction of I, II, and analogs of II that contain weak electron-acceptor substituents attached to the 4-C atom – 3,5-dimethyl-4-bromo- (III) and 3,5-dimethyl-4-(p-nitrophenyl)isoxazoles (IV) – with an equivalent amount of NBS.† After separation of the succinimide, the reaction mixtures were subjected to analysis by PMR spectroscopy, which was based on the different signals from all of the CH_3 groups [5] and, consequently, on the protons of the bromomethyl groups.

The most complex PMR spectrum was obtained for the products of bromination of I. Its interpretation (Table 1) showed that two isomeric bromomethylisoxazoles (Va and Vb) and a dibromo derivative (VI) are formed in yields of 58, 23, and 6%, respectively; the sum of all of the substances in solution was assumed to be 100%, and the solution also contained starting I. The signals of the protons of the methylene groups serve as the key to the interpretation of the spectrum. According to the literature data, the chemical shifts of these protons in the hydrocarbon side chain are found at ~2.5 ppm (on the δ scale) [6], and the presence of a halogen atom on the same carbon atom leads to a shift in the signals to weak field by ~2 ppm [7, 8]. The magnitude of the chemical shift of the protons of the side chain of 4-bromomethylisoxazole (4.2 ppm) [7] is almost equal to that observed in the spectrum of a mixture of isomers V for the most intense signal in this region. A comparison of the relative intensities of the signals of the methyl and methylene protons leads to the conclusion that the chemical shifts at 2.27, 2.39, and 4.25 ppm characterize the protons of 3,5-dimethyl-4-bromomethylisoxazole (Va).

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*See [1] for communication XXVIII.

†See [4] for the mechanism of bromination by means of NBS.

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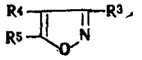
TABLE 1. Chemical Shifts of the Protons of the Side Chains of Methylisoxazoles I-IX (on the δ scale, ppm)*



Compound	R^3	δ_3	R^4	δ_4	R^5	δ_5
I	CH_3	2,12	CH_3	1,87	CH_3	2,27
II	CH_3	2,24	Cl	—	CH_3	2,38
III	CH_3	2,17	Br	—	CH_3	2,33
IV	CH_3	2,25	p-$O_2NC_6H_4$	—	CH_3	2,38
Va	CH_3	2,27	$BrCH_2$	4,25	CH_3	2,39
Vb	CH_3	2,18	CH_3	1,96	$BrCH_2$	4,39
VI	CH_3	2,27	$BrCH_2$	4,30	$BrCH_2$	4,47
VII	CH_3	2,25	Cl	—	$BrCH_2$	4,41
VIII	CH_3	2,22	Br	—	$BrCH_2$	4,35
IX	CH_3	2,25	p-$O_2NC_6H_4$	—	$BrCH_2$	4,33

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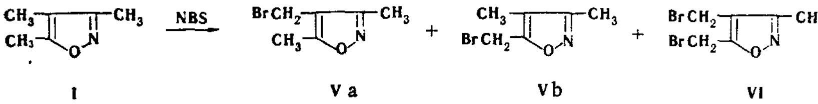
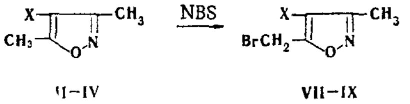
*The chemical shifts of the protons of the benzene rings in IV and IX are not presented in Table 1.

Similarly, the protons of 3,4-dimethyl-5-bromomethylisoxazole (Vb) have chemical shifts of 1.96, 2.18, and 4.39 ppm. Finally, the chemical shifts at 2.27, 4.30, and 4.47 ppm should be assigned to the protons of 3-methyl-4,5-di(bromomethyl)isoxazole (VI).



Judging from the PMR spectra, only the CH_3 groups in the 5 position react in the remaining three isoxazoles (II-IV), and 5-bromomethylisoxazoles (VII-IX) are formed. Here also, the reactions do not go to completion – all of the reaction mixtures contain starting materials.



II, VII X=Cl, III, VIII X=Br; IV, IX X=p-$O_2NC_6H_4$

Thus the methyl group in the 3 position does not undergo reaction with NBS in any of the four investigated compounds. A similar observation was previously made for other methylisoxazoles [3].

EXPERIMENTAL

The PMR spectra were recorded with a Perkin-Elmer R-12 spectrometer at 60 MHz with hexamethyldisiloxane (HMDS) as the internal standard at ~35°.

General Method. A 30-40-mg sample of benzoyl peroxide and (in portions) 5 mmole of NBS were added with stirring to a refluxing solution of 5 mmole of isoxazole I-IV in 10 ml of CCl_4, after which the mixture was refluxed for 4 h. It was then cooled to 0°, and the precipitated succinimide was removed by filtration and washed on the filter with 3 ml of carbon tetrachloride. The filtrate was vacuum evaporated to 5 ml to give 10% solutions, which were investigated by PMR spectroscopy.

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