AN INVESTIGATION IN THE ISOXAZOLE SERIES

XXI. The Isotopic Exchange of Hydrogen in the CH_3 Groups of 3,5-Dimethyl-4-X-isoxazoles with Diethyl[D]amine*

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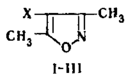
The hydrogen atoms in the CH_3 groups in position 5 of 3,5-dimethyl-4-nitroisoxazole (I) and 3,5-dimethyl-4-phenylazoisoxazole (II) undergo isotopic exchange with diethyl[D]amine. The position of entry of the deuterium has been established and the CH_3 groups of compounds I and II have been characterized by NMR spectroscopy. The possibility of a correlation of the reactivities of the methyl groups with their chemical shifts is discussed.

In this paper we give results obtained in a study of 4-substituted 3,5-dimethylisoxazoles, by the methods of hydrogen isotope exchange and NMR spectroscopy, characterizing the difference in the reactivities of the methyl groups on the $C_{(5)}$ atoms in these compounds. The comparison of these results appeared to us to be of interest because the method of isotopic hydrogen exchange enables the electronic effects of substituents in the isoxazole system in the reaction process to be characterized while the NMR method (from the chemical shifts of the protons of the CH_3 groups) permits an evaluation of the electronic effects of the substituents in the same compounds in the ground state.

Table 1

Content of Deuterium in the Samples

Compound	Reaction temperature, °C	Time, min	EDWC, γ/ml for 3 atoms of H	
			found	calculated
I	50	2880	8750	10790
I	30	14	7690	11010
I	15	30	7830	11180
II	30	330	4600	6350
III	30	8640	82	10000



I-III

I $X=NO_2$

II $X=C_6H_5N{=}N$

III $X=H$

The isotopic exchange of the hydrogen atoms of the CH_3 groups of 3,5-dimethyl-4-nitroisoxazole (I), 3,5-dimethyl-4-phenylazoisoxazole (II), and 3,5-dimethylisoxazole (III) with diethylamine enriched with deuterium in the N—H group was studied. It was found that the hydrogen of the CH_3 groups on the $C_{(5)}$ atoms in the isoxazoles studied behaves differently according to the nature of the substituent **X** in position 4 of the heterocycle. In the nitroisoxazole I, the isotopic exchange of the hydrogen takes place at such a rate that it is impossible to measure it by ordinary methods; for example, at 15° C isotopic equilibrium is set up in a few minutes. In the phenylazoisoxazole **II**, deuterioexchange takes place at a measureable rate and the rate constant of the reaction at 25° C is 1.6×10^{-4} sec^{-1}. The isoxazole **III** does not take part in an isotopic exchange reaction with diethyl[D]amine at all even under more severe conditions (30° C, 6 days).

It was possible to determine the position of entry of the deuterium in isotopic exchange from the change in the integral intensity of the signals of the protons of the methyl groups in positions 3 and 5 of the isoxazoles, since it is known that the signals from the CH_3 group on the $C_{(5)}$ atom is in the weaker-field region [2,3]. In the NMR spectra† of deuterated samples of compounds I and II a decrease in the signals of only the CH_3 groups on the $C_{(5)}$ atoms was observed, which showed the selective occurrence of deuterioexchange in the 3,5-dimethylisoxazoles investigated. The results obtained are in good agreement with our results on the activity of the 3,5-dimethylisoxazoles in the base-catalyzed condensation reaction, although condensation does not permit the fine differences in the reactivities of the CH_3 group detected by means of isotopic exchange with hydrogen to be shown up. Thus, the isoxazole II, unlike the nitroisoxazole I [4], does not react with benzaldehyde in the presence of piperidine and does not add to acridine, in spite of the use of far more severe reaction conditions.

An investigation of the NMR spectra of the isoxazoles I, II, and III has shown that electron-accepting substituents in position 4 of the ring have a more powerful influence on the chemical shifts of the CH_3 groups in position 5 and a smaller influence on the CH_3 groups in position 3, shifting the signals of these groups in the direction of weaker fields. The differences in the chemical shifts of the CH_3 groups in the spectra of compounds I and II as compared with the spectrum of the isoxazole III are, respectively, 0.36 and 0.33 ppm for position 5 and 0.25 and 0.22 ppm for position 3.

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*For part XX, see [1].

†The NMR spectra of these and other 3,5-dimethyl-4-X-isoxazoles were taken by E. I. Fedin and P. V. Petrovskii (INEOS AN SSSR [Institute of Heteroorganic Compounds AS USSR]) on a TsLA-5535 instrument (frequency 40 MHz, solvent CCl_4, internal standard hexamethyldisiloxane) for which the authors express their deep gratitude to them.

For comparison we may mention that the difference in the chemical shifts of an ortho proton for p-xylene and its o-nitro derivative is 0.25 ppm [5]. From the features of the NMR spectra presented it follows that the transfer of the influence of an NO_2 group to the $C_{(3)}$ atom in the isoxazole I is approximately the same as to the o-carbon atoms of a benzene ring. This analogy is apparently also valid for the transfer of the influence of a phenylazo group. Conversely, the influence of electron-accepting substituents in position 4 of the isoxazole nucleus on the $C_{(5)}$ atom in compounds I and II if far stronger than to the o-carbon atom in a benzene ring.

The substantial differences in the influence of one and the same substituents on hydrogen exchange and on the NMR spectra of the methyl groups that has been found may apparently be explained by differences in the electronic effects of the substituents in the isoxazole system present in the ground state (NMR spectra) and in the reaction process (hydrogen exchange).

EXPERIMENTAL*

The isoxazoles I, II, and III were obtained and purified by previously-published methods. The 3,5-dimethyl-4-nitroisoxazole (I) had mp 63°C (from methanol) [4], the 3,5-dimethyl-4-phenylazoisoxazole, zole (II), mp 46°C (from methanol) [6], and the 3,5-dimethylisoxazole, bp 79.5° C (119 mm); n_D^{20} 1.4416 [7]. The diethyl[D]amine containing 30 at. % of deuterium was obtained by the reaction of diethylamine with deuterium oxide and was purified by distillation through a column with an efficiency of 30 theoretical plates, its bp being 54.8–55.0° C.

Experiments on hydrogen exchange. A weighed sample of the isoxazole was dissolved in a fivefold molar amount of diethyl[D]amine. The solution was stirred in a thermostat and the diethylamine was distilled off in vacuum after predetermined intervals of time, and the residue was washed with 5% HCl solution and dissolved in benzene. The benzene solution was washed to neutrality with $NaHCO_3$ solution, the benzene was distilled off, and the residue of compound I or II was crystallized from aqueous methanol, while the isoxazole III was distilled in vacuum. Then substance I was sublimed in vacuum and substance II was dried in vacuum over phosphorus pentoxide. The purity of the isoxazoles isolated after an experiment was determined from their melting points, and, in individual cases, from their elementary analyses. The content of deuterium in the samples was determined from the excess density of the water of combustion (EDWC) by the drop method. In the calculation of the isotopic equilibrium, the distribution coefficient between the N—D and C—H bonds was arbitrarily taken as unity.

Table 2

Kinetics of the Isotopic Exchange of Hydrogen for 3,5-Dimethyl-4-phenylazoisoxazole at 25° C

Time, min	EDWC, γ/ml for 3 atoms of H		$K_{HE} \times 10^4$, sec^{-1}
	found	calculated	
22	915	5390	1.41
38	1838	5390	1.83
51	2140	5390	1.65
71	2480	5390	1.44

Table 1 gives the results of the individual experiments and Table 2 the results of the kinetics of the isotopic exchange of hydrogen in compound II at 25° C, $K_{mean} \sim 1.6 \times 10^{-4}$ sec^{-1}.

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