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Abstract

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A NEW REACTION OF THE ISOXAZOLE NUCLEUS

Isoxazole, one of the aromatic heterocycles, possesses distinctive properties, undergoing electrophilic substitution reactions and readily opening the ring under the action of nucleophilic reagents ([1]). At the same time, addition reactions at its double bonds have hitherto been unknown, for example hydrogenation, which is well known for other aromatic heterocycles; in the hydrogenation of isoxazole there occurs, as is known ([2]), hydrogenolysis of the nitrogen–oxygen bond. In the course of investigating the halogenation of isoxazoles we succeeded in discovering a new reaction, which is the first addition reaction at the double bonds of the isoxazole nucleus with retention of the isoxazole ring.

In the chlorination of isoxazoles with a mixture of hydrochloric acid and hydrogen peroxide in acetic acid (cf. ([3])), the result of the reaction depends on the amounts of reagents taken. When equimolecular amounts of isoxazole and the chlorinating mixture interact, the usual chlorination reaction occurs, as a result of which, for example, from 3,5-diphenylisoxazole (Ia) 3,5-diphenyl-4-chloroisoxazole (IIa) was obtained in 45% yield. However, if an excess of hydrochloric acid and hydrogen peroxide is present in the reaction mixture, the reaction proceeds further: 4-chloroisoxazole enters into a further reaction, which amounts to addition of the elements of hypochlorous acid to the double bond of the isoxazole nucleus. The reaction may occur either directly under the action of an excess of the chlorinating mixture on 3,5-disubstituted isoxazoles, or directly with 4-chloro-3,5-disubstituted isoxazoles; it proceeds at an appreciable rate already with a threefold excess of reagents, and with a 7–10-fold excess the yield of the addition products reaches 90%.

$$\text{(Ia–c)} \xrightarrow[\mathrm{H_2O_2}]{\mathrm{HCl}} \text{(IIa–c)} \xrightarrow[\mathrm{H_2O_2}]{\mathrm{HCl}} \text{(IIIa–c)} \longrightarrow \text{(IVa,b), (Va)}$$

$$\begin{aligned} &\text{(IVa,b)} \quad R = \mathrm{COCH_3} \\ &\text{(Va)} \quad R = \mathrm{CH_3} \end{aligned}$$

Everywhere: a) $R' = R'' = \mathrm{C_6H_5}$; b) $R' = \mathrm{CH_3},\ R'' = \mathrm{C_6H_5}$; c) $R' = R'' = \mathrm{CH_3}$.

$$\text{(Ig)} \longrightarrow \text{(IIIg)}$$

3,5-Diphenyl-, 3-methyl-5-phenyl-, 3,5-dimethyl-, and 3,5-diphenyl-4-methylisoxazoles (respectively Ia-g), as well as 3-methyl-4-chloro-5-phenylisoxazole (IIb), were subjected to this reaction; thus it is a general reaction of the isoxazole nucleus.

The structure of the substances IIIa-g obtained follows from the following data. Their elemental analysis corresponds to products of addition of the elements of hypochlorous acid to the corresponding isoxazole. On reduction of compounds IIIa and Va with zinc in acetic acid at 20° there was obtained

3,5-diphenyl-4-chloroisoxazole (IIa). This proves that the addition products retain the isoxazole ring. Nuclear quadrupole resonance (NQR) data indicate that the two chlorine atoms in them are located at different carbon atoms; the difference between the signals from the chlorine atoms is 0.7-1 MHz. Since oxidation with potassium permanganate of the compounds IIIa, b, g obtained gives only benzoic acid, without traces of chlorobenzoic acids, both halogen atoms enter the heterocyclic nucleus. The absence of oxidizing properties (test with KJ) confirms that in compounds IIIa-g the chlorine atom is not bonded to the nitrogen atom.

The presence of a hydroxyl group in the addition products IIIa-g is confirmed by spectroscopic data. In the NMR spectra of these compounds, peaks are observed which, in magnitude and position, correspond to the hydrogen atoms of OH groups; their chemical shift relative to tetramethylsilane is 5.7-6.6 ppm (the chemical shift of the hydrogen of the OH group in acetoxime is 9.2 ppm). In the IR spectra recorded for the solid substances, intense absorption bands are observed in the region 3150-3250 cm^{-1}, absent in solutions of these substances, which indicates intermolecular hydrogen bonds, evidently of the type $-OH \cdots O<$. The addition products IIIa-g do not give a cherry-red coloration with ferric chloride solutions, coloring only the chloroform solution of $FeCl_3$ in the presence of pyridine yellow. The hydroxyl groups in them are readily acetylated on heating with acetic anhydride, with formation of acetates IVa, b, having a characteristic absorption band in the IR spectra (1770 cm^{-1}, ester CO group). Treatment with methanol in the presence of hydrogen chloride does not lead to methylation of the addition products; however, the latter proceeds slowly when they are treated with diazomethane in ether; the methyl derivative Va thus obtained, as is seen from the IR spectrum, contains no free hydroxyl group.

Under the action of concentrated sulfuric acid, the addition products IIIa, b, g, but not IIIv, become colored: light green (in the case of IIIb), dark green (in the case of IIIa), and cherry-red (in the case of IIIg). These halochromic properties indicate the presence in the compounds studied, which contain benzene nuclei, of a system of conjugated bonds (^{4}). Since halochromy is exhibited by the substance obtained from 3-methyl-5-phenylisoxazole (Ib), but not from 3,5-dimethylisoxazole (Iv), then in IIIb, as well as in all the other addition products, there is apparently a double bond $C_4{=}C_5$, and addition occurs at the $C_3{=}N$ double bond of the isoxazole ring.

Thus, the entire body of the data presented makes it possible to propose, for the products of the interaction of isoxazoles with an excess of a mixture of hydrochloric acid and hydrogen peroxide, the structure of 2-hydroxy-3-chloroisoxazoline-4 derivatives (see scheme), although the less probable isomeric structure of 2-hydroxy-5-chloroisoxazoline-3, obtained by 2,5-addition to the isoxazole nucleus, cannot be completely excluded. These compounds are apparently the first stable compounds containing a trivalent nitrogen atom bonded to two oxygen residues. They are colorless crystalline substances, readily subliming in vacuum, stable in an acidic medium but labile toward alkalis. Thus, although the oxychloroisoxazolines themselves and their acetates are stable to the action of pyridine, they readily decompose under the action of alkalis and even carbonates of alkali metals, with formation of the corresponding nitriles $R'CN$, which were identified in the mixture by gas-liquid and thin-layer chromatography. Owing to the presence of the grouping $-\mathrm{N}<^{\mathrm{O}-}_{\mathrm{OH}}$, oxychloroisoxazolines are practically completely devoid of basic properties. Thus, for example, they do not even give picrates. Because of their instability toward alkalis it has not yet been possible to determine K_{diss} for them; however, judging from their

ability to be methylated by diazomethane, they must be compounds somewhat more acidic than alcohols, but inferior in acidity to phenols. In their IR spectra the characteristic absorption bands in the region up to 1800 cm^{-1} are absent —even in compounds containing benzene nuclei—and their UV spectra have no extrema.

The mechanism of the reaction found requires special study. According to preliminary data, it is homolytic in character. We are continuing the investigation of the reaction found and of related reactions in the isoxazole series.

Experimental part

3,5-Diphenyl-4-chloroisoxazole (IIa). To a solution of 2.21 g (0.01 mole) of 3,5-diphenylisoxazole (Ia) in 35 ml of acetic acid are added 1.2 ml (0.013 mole) of conc. HCl and 2.4 ml (0.02 mole) of 26% hydrogen peroxide; the mixture is heated for 3 hours at 85-90°, cooled, and the reaction product is filtered off; the mother liquor is diluted with water and 0.55 g of the starting isoxazole is isolated. The yield of chloroisoxazole IIa after crystallization from petroleum ether is 1.15 g (45% based on the amount taken into the reaction and 60% based on the reacted isoxazole), m.p. 84°; a mixed sample with an authentic specimen (^{5}) gives no depression of the melting point.

2-Oxo-3,4-dichloro-3,5-diphenylisoxazoline-4 (IIIa). A solution of 8.84 g (0.04 mole) of Ia, 25.2 ml (0.28 mole) of conc. HCl, and 33.6 ml (0.28 mole) of hydrogen peroxide in 250 ml of acetic acid is heated for 15 min on a boiling water bath, cooled, strongly diluted with water, and 10.9 g (88%) of IIIa is filtered off; after crystallization from a benzene—petroleum ether mixture and sublimation in vacuo (120°, 1 mm), m.p. 136-137° (in a sealed capillary). The molecular weight was determined cryoscopically in dibromomethane.

Found, %: C 58.61, 58.65; H 3.70, 3.71; Cl 22.99, 23.12. M 301
$C_{15}H_{11}Cl_2NO_2$. Calculated, %: C 58.45; H 3.60; Cl 23.01. M 308

2-Oxo-3,4-dichloro-3-methyl-5-phenylisoxazoline-4 (IIIb).

a) Similarly, from 1.59 g (0.01 mole) of 3-methyl-5-phenylisoxazole (Ib), 6.3 ml (0.07 mole) of hydrochloric acid, and 8.4 ml (0.07 mole) of hydrogen peroxide in 25 ml of acetic acid, 1.98 g (80%) of IIIb is obtained; after sublimation in vacuo (100°, 1 mm), m.p. 110.5–111.5° (in a sealed capillary).

b) Similarly, from 0.97 g (0.005 mole) of 3-methyl-4-chloro-5-phenylisoxazole (IIb), 4.5 ml (0.05 mole) of hydrochloric acid, and 6 ml (0.05 mole) of hydrogen peroxide in 18 ml of acetic acid, 0.97 g (79%) of IIIb with m.p. 110–111° is obtained. A mixed sample of both specimens gives no depression of the melting point.

Found, %: C 48.51, 48.42; H 3.73, 3.59; Cl 29.07; N 5.73, 5.51. M 246
$C_{10}H_9Cl_2NO_2$. Calculated, %: C 48.79; H 3.69; Cl 28.81; N 5.69. M 246

2-Oxo-3-chloro-3,5-diphenyl-4-methylisoxazoline-4 (IIIg).

Similarly, from 0.15 g (0.64 mmol) of 3,5-diphenyl-4-methylisoxazole (Ig), 0.6 ml (4.5 mmol) of hydrogen peroxide, and 0.45 ml (4.5 mmol) of hydrochloric acid in 10 ml of acetic acid, 0.12 g (65%) of IIIg is obtained. The melting temperature of the substance depends on the rate of heating; with a temperature rise of 1° per minute, m.p. 162–164° (from petroleum ether—benzene, with decomposition; in a sealed capillary).

Found, %: C 66.62, 66.42; H 4.57, 4.90; Cl 12.94, 13.02
$C_{16}H_{14}ClNO_2$. Calculated, %: C 66.77; H 4.90; Cl 12.32

2-Oxo-3,4-dichloro-3,5-dimethylisoxazoline-4 (IIIv). Upon action of the chlorinating mixture on 3,5-dimethylisoxazole (Iv) under the conditions described above, a spontaneous, strongly exothermic reaction occurs, with ejection of the reaction mixture. To a solution of 9.7 g (0.1 mole) of Iv in 50 ml of acetic acid, with vigorous stirring and heating on a water bath, 63 ml (0.7 mole) of hydrochloric acid and 84 ml (0.7 mole) of hydrogen peroxide are added simultaneously dropwise; the mixture is heated for another 45 min, evapor—

···evaporated in vacuum (because of the high volatility and solubility in water of IIIv, considerable losses of it occur), the residue is treated with cold acetone, and 5 g (27%) of IIIv is obtained; after sublimation in vacuum (50°, 1 mm), m.p. 74.5–75° (in a sealed capillary).

Found, %: C 32.83, 32.87; H 3.80, 3.75; Cl 38.53, 38.27; N 7.88, 8.13. M 185
$C_5H_7Cl_2NO_2$. Calculated, %: C 32.63; H 3.83; Cl 38.53; N 7.61. M 184

Acetate IIIa (IVa). To a solution of 1.8 g of IIIa in 10 ml of acetic anhydride, 1 drop of conc. H_2SO_4 is added; the mixture is heated for several minutes at

90-100°, cooled, diluted with water, and 2 g (98%) of IVa is filtered off, m.p. 130.5-132.5° (from a benzene-petroleum ether mixture).

Found, %: C 58.47, 58.59; H 3.74, 3.78; Cl 20.14, 20.42
$C_{17}H_{13}Cl_2NO_3$. Calculated, %: C 58.32; H 3.74; Cl 20.25

Acetate IIIb (IVb). Similarly, from 0.25 g of IIIb and 1 ml of acetic anhydride, 0.28 g (100%) of IVb is obtained, m.p. 110° (from a benzene-petroleum ether mixture).

Found, %: C 49.91, 49.92; H 3.92, 3.89; Cl 24.89, 24.83
$C_{12}H_{11}Cl_2NO_3$. Calculated, %: C 50.02; H 3.85; Cl 24.61

2-Methoxy-3,4-dichloro-3,5-diphenylisoxazoline-4 (Va). To an ethereal solution of 0.9 g (0.003 mole) of IIIa is added an ethereal solution of diazomethane prepared from 3.5 g (0.021 mole) of nitrosomethylurea; the mixture is kept for 110 h, evaporated, and the residue is crystallized from aqueous methanol to give 0.5 g (53%) of Va, m.p. 124-125°.

Found, %: C 59.72, 59.52; H 4.31, 4.16; Cl 21.59, 21.57
$C_{16}H_{13}Cl_2NO_2$. Calculated, %: C 59.62; H 4.06; Cl 22.01

Reduction of IIIa with zinc in acetic acid. To a solution of 1.54 g (5 mmoles) of IIIa in 40 ml of acetic acid, 0.35 g (5.3 mmoles) of zinc dust is added; the mixture is stirred for 3 h at 20°, during which all the zinc has time to react; it is diluted with water, and the precipitate is filtered off and crystallized from methanol. The yield of 3,5-diphenyl-4-chloroisoxazole (IIa) is 0.7 g (55%), m.p. 83-84°; a mixed-melting test with an authentic sample gives no depression of the melting point.

Reduction of Va with zinc in acetic acid. By analogous reduction of 0.54 g (1.7 mmoles) of Va with 0.13 g (2 mmoles) of zinc dust in 20 ml of acetic acid, 0.3 g (70%) of IIa is obtained, m.p. 83-84° (from petroleum ether); a mixed-melting test with an authentic sample gives no depression of the melting point.

Oxidation of IIIa, IIIb, and IIIg with potassium permanganate. A suspension of 1 mmole of IIIa, IIIb, or IIIg in an aqueous solution containing 1 g of potassium permanganate and 0.2 g of potassium hydroxide is boiled for several hours, acidified, and the benzoic acid is extracted with ether. The Beilstein test is negative; a mixed-melting test with an authentic sample gives no depression of the melting point.

The NMR spectra of the compounds obtained, which will be published separately, were recorded by G. K. Seminyi and V. I. Robas (Institute of Natural Compounds Chemistry, Academy of Sciences of the USSR), and the mass spectra by P. V. Petrovskii (Institute of Natural Compounds Chemistry) on a TsLA-40 instrument. The authors express their gratitude to the persons named.

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