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SYNTHESIS AND REACTIVITIES OF IMIDAZOLIN-2-ONE 3-OXIDES

S. P. Épshtein, A. F. Rukasov,
V. P. Tashchi, and Yu. G. Putsykin

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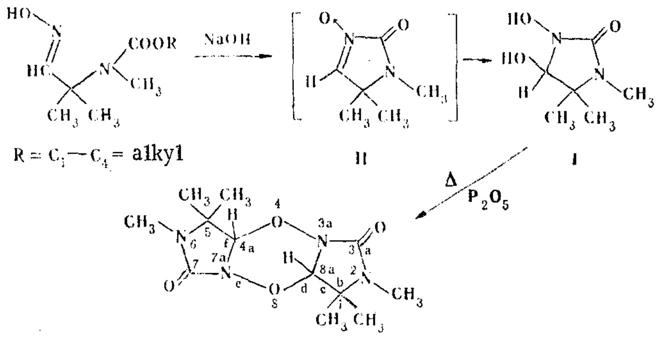
The cyclization of 3-[N-methyl-N-(ethoxycarbonyl)amino]-3-methyl-2-butanone oxime in an alkaline medium leads to 1-hydroxy-2,2'-dioxo-3,4,4,3',4'-hexamethylimidazolidine-spiro-5,6'-perhydroimidazo[2,3-c]-isoxazole, whereas the cyclization of 3-[N-(ethoxycarbonyl)amino]-3-methyl-2-butanone oxime leads to 2-oxo-4,5,5-trimethyl-Δ^3-imidazoline 3-oxide. The latter is converted to 1-hydroxyl-2,2'-dioxo-4,4,4',4'-tetramethylimidazolidine-spiro-5,6'-perhydroimidazo[2,3-c]isoxazole upon refluxing in water. 1,4,5,5-Tetramethyl-3-methoxy-4-hydroxyimidazolidin-2-one was synthesized by methylation of the compounds obtained by means of dimethyl sulfate. A scheme for the reactions is proposed.

We have previously shown [1] that 2-[N-methyl-N-(alkoxycarbonyl)amino]-2-methylpropanaldoximes undergo cyclization to 3,4-dihydroxy-1,5,5-trimethylimidazolidin-2-one (I), which is evidently the product of addition of water to the intermediately formed 1,5,5-trimethyl-2-oxo-Δ^3-imidazolin 3-oxide (II). However, an attempt to obtain N-oxide II by treatment of dihydroxy derivative I with phosphrus pentoxide led to the isolation of 1,1,2,5,5,6-hexamethyl-3,7-dioxo-4,8,2,3a,6,7a-dioxatetraazacyclopenta[f]hexahydroindan — the product of dimerization of two molecules of II [1].



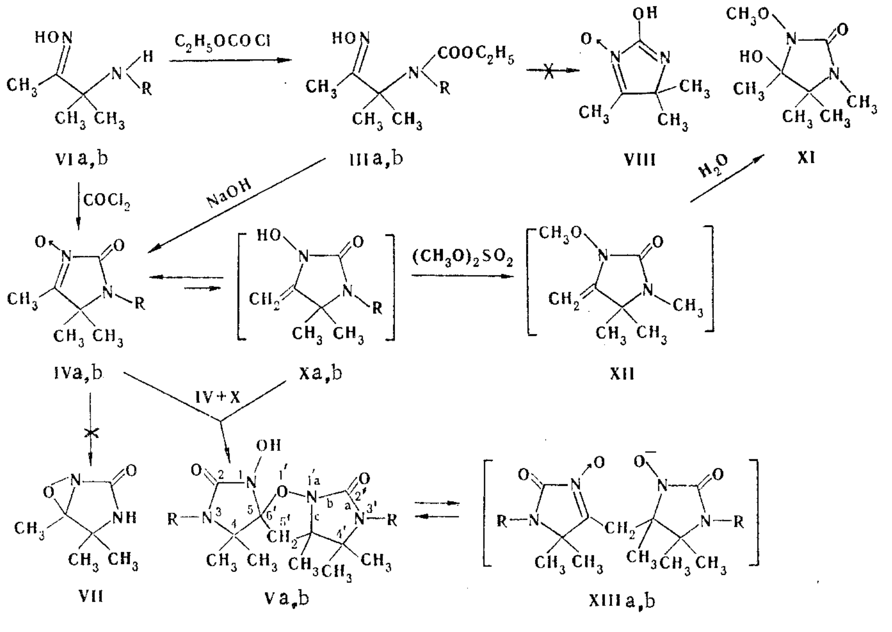
We examined the cyclization of 3-[N-methyl-N-(ethoxycarbonyl)amino]-3-methyl-2-butanone (IIIa) under alkaline conditions and found that it also does not lead to N-oxide IVa. However, according to the results of elementary analysis and the mass-spectrometric data, the product of this reaction (Va) has empirical formula $C_{14}H_{24}N_4O_4$. The presence in the mass spectrum of, in addition to a molecular-ion peak with m/z 312, an intense peak with m/z 156 (the mass of imidazolin-2-one N-oxide IVa) makes it possible to assume that dimerization of the intermediately formed IVa also occurs in this case.

All-Union Scientific-Research Institute of Chemical Agents for the Protection of Plants, Moscow 109088. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 667-670, May, 1983. Original article submitted August 2, 1982.

0009-3122/83/1905-0540$07.50

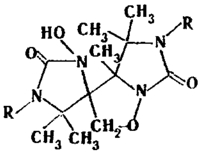
However, Va forms the bright-blue complex with an alcohol solution of ferric chloride that is characteristic for compounds that contain a hydroxamic acid fragment. The presence of two absorption bands of carbonyl groups at 1705 and 1735 cm^{-1} in the IR spectrum of this compound and the presence in the PMR spectrum (d$_6$-DMSO) of, in addition to five singlets of protons of methyl groups at 1.10, 1.15, 1.20, 1.27, and 1.48 ppm and two N—CH$_3$ singlets at 2.55 and 2.62 ppm, signals of protons of a CH$_2$ group at 1.98 and 2.52 ppm (AB system, J = 13.5 Hz) and a broad singlet of an N—OH proton at 9.33 ppm made it possible to assign the 1-hydroxy-2,2'-dioxo-3,4,4,3',4'4'-hexamethylimidazolidine-spiro-5,6'-perhydroimidazo[2,3-c]isoxazole structure to Va.

At the same time, alkaline treatment of 3-[N-(ethoxycarbonyl)amino]-3-methyl-2-butanone oxime (IIIb) makes it possible to obtain (in low yield) the unstable 2-oxo-Δ^3-imidazoline 3-oxide (IVb), which was previously synthesized by the action of phosgene on amino oxime VIb. Compound Vb, which, according to the melting point, results of elementary analysis, and the IR spectrum, corresponds to the product obtained in [2] under the same conditions from nitrone IVb and described as oxaziridine VII, as well as to the product obtained in [3] by alkaline cyclization of urethane IIIb but described as hydroxy nitrone VIII, is formed when N-oxide IVb is refluxed in water or is allowed to stand in air for a long time and is also formed when an alkaline solution of oxime IIIb is heated. Only three singlets of protons of the CH$_3$ group at 1.36 and 1.51 ppm (6H) and 1.8 ppm (3H) are noted in the PMR spectrum (d$_5$-pyridine, 60 MHz) presented in [2] for the oxaziridine. Moreover, we noted similar signals of protons of methyl groups at 1.33, 1.51, and 1.83 ppm with an integral intensity ratio of 2:1:2 and weakly expressed signals of protons of an AB system at ∿2.4 and 2.9 ppm in the PMR spectrum (d$_5$-pyridine, 80 MHz) that we recorded for Vb. At the same time, signals of protons of a CH$_2$ group at 2.43 and 2.89 ppm (AB system, J = 13.5 Hz) and five singlets of protons of methyl groups at 1.35, 1.36, 1.50, 1.83, and 1.86 ppm are observed in the PMR spectrum (d$_5$-pyridine, 250 MHz). In addition to signals of protons of methyl groups at 1.12, 1.20, 1.23 (12H), and 1.50 ppm (3H) and of a CH$_2$ group at 1.90 and 2.47 ppm (AB system, J = 13.5 Hz), broad signals of two NH protons at 6.91 and 7.57 ppm and of an OH group at 9.22 ppm are present when the PMR spectrum of Vb is recorded in d$_6$-DMSO. An alcohol solution of Vb gives a positive test with ferric chloride. On the basis of these data the 1-hydroxy-2,2'-dioxo-4,4,4',4'-tetramethylimidazolidine-spiro-5,6'-perhydroimidazo[2,3-c]isoxazole structure was assigned to product Vb. Gnichtel and co-workers [2] regard the positive reaction of the latter with an acetic acid solution of potassium iodide as evidence in favor of oxaziridine structure VII. However, this reaction cannot serve as evidence for the formation of oxaziridine VII, since Vb contains a hydroxyurea fragment, which, as we verified in the case of N-ethylhydroxyurea and 1,4-dihydroxy-3-aryl-5,5-dimethylimidazolidin-2-one [4], also oxidizes the iodine anion to molecular iodine.



III–VI, X, XIII a R=CH$_3$; b R=H

Alternative structure IX is unlikely, since, according to a calculation of the chemical shifts of the protons of the methylene group using the effective contributions of the shielding of the protons by the substituents in the α and β positions [5], δ CH_2 = 1.6 ppm for Va,b which is in good agreement with the experimental data, whereas this value is 3.8 ppm for IX.



IX R=CH_3 or H

Compounds Va,b are evidently products of 1,3-dipolar addition of 4-methyleneimidazolidin-2-ones (Xa,b) — tautomers of imidazoline 3-oxides IVa,b — to the latter. The following facts indicate that this tautomerism is possible. Signals of a $>C{=}CH_2$ group at 5 ppm appear in the PMR spectrum when N-oxide IVb is heated in d_6-DMSO, whereas the signal of the protons of the methyl group in the 4 position of the imidazole ring of IVb vanishes when it is heated in D_2O to 50°C. The qualitative reaction of N-oxide IVb with a solution of ferric chloride gives a slightly green coloration, which is evidently due to the presence of tautomer X.

It should be noted that although we were unable to isolate N-oxide IVa (or nitrone II), its existence in the reaction medium was observed by means of chromatography. The fact that a compound that, according to the PMR and IR spectra, was identical to imidazolidinone XI, which was also synthesized by methylation of N-oxide IVb with dimethyl sulfate, was obtained when excess dimethyl sulfate was added to an alkaline solution of urethane IIIa serves as a confirmation of its formation. Methlyation evidently proceeds through the intermediately formed 1,5,5-trimethyl-3-methoxy-4-methyleneimidazolidin-2-one (XII) via the scheme presented above.

We explain the observed (in the PMR spectrum of Vb) facile exchange of the hydrogen atoms of the methylene group in the 5' position for deuterium when Vb is dissolved in D_2O + NaOH by means of the equilibrium V $\rightleftharpoons$ XIII. This also constitutes evidence in favor of the proposed structure of V and negates structure IX.

EXPERIMENTAL

The IR spectra of KBr pellets and solutions of the compounds in CCl_4 were recorded with a Perkin-Elmer 457 spectrometer. The PMR spectra were recorded with Varian FT-80A, Brucker HX-90E, and Brucker-250WM spectrometers with tetramethylsilane as the internal standard. The mass spectra were recorded with an LKB-2091 mass spectrometer by direct introduction of samples into the ionization region at an ionizing-emission energy of 15 eV. The course of the reaction was monitored on Silufol UV-254 plates in a tetrahydrofuran—hexane—ethanol system (2:1:1); the chromatograms were developed by spraying with a mixture of 94% H_2O, 1% $KMnO_4$, and 5% H_2SO_4.

3-[N-Methyl-N-(ethoxycarbonyl)amino]-3-methyl-2-butanone Oxime (IIIa). A solution of 1.38 g (1 mmole) of potassium carbonate in 3 ml of water and a solution of 1.08 g (1 mmole) of ethyl chlorocarbonate in 20 ml of ether were added to a solution of 1.30 g (1 mmole) of VIa in 150 ml of ether, and the mixture was stirred for 30 min. The inorganic precipitate was removed by filtration, the filtrate was evaporated in vacuo, and 15-20 ml of ether—hexane (1:5) was added to the residue. The precipitate was removed by filtration to give 1.41 g (70%) of IIIa with mp 69-70°C. IR spectrum: 1690 (C=O), 940 (N—O), and 3590 cm^{-1} (OH). Found: C 53.4; H 8.7; N 13.4%. $C_9H_{18}N_2O_3$. Calculated: C 53.4; H 8.9; N 13.8%.

1-Hydroxy-2,2'-dioxo-3,4,4,3',4',4'-hexamethylimidazolidine-spiro-5,6'-perhydroimidazo-[2,3-c]isoxazole (Va). A solution of 2.02 g (1 mmole) of IIIa in 10-15 ml of 5 N NaOH was neutralized to pH 7 with 2 N HCl, after which the water was evaporated in vacuo, and the residue was extracted with ∿100 ml of alcohol until the color formed with ferric chloride vanished. The alcohol was evaporated in vacuo, 10-15 ml of tetrahydrofuran (THF) was added to the residue, and the precipitate was removed by filtration to give 0.93 g (30%) of Va with mp 211-212°C. Mass spectrum, m/z (%): M^+ 312 (5.28), 157 (100), 156 (59.6), 141 (18.7), 140 (13.5), 125 (13.5), 115 (20.2), 101 (25.9), 99 (24.5), 91 (9.61). Found: C 53.5; H 7.99; N 18.2%. $C_{14}H_{24}N_4O_4$. Calculated: C 53.5; H 7.96; N 18.2%.

1-Hydroxy-2,2'-dioxo-4,4,4'4'-tetramethylimidazolidine-spiro-5,6'-perhydroimidazo[2,3-c]-isoxazole (Vb). A solution of 1.42 g (1 mmole) of IVb in 10 ml of water was refluxed for 6 h, after which it was cooled, and the resulting precipitate was removed by filtration to give 0.8 g (56%) of Vb with mp 241-242°C. IR spectrum: 1710, 1400, 1375, 1348, 1160, 889, 816, 795, 775, 730 cm^{-1}. Mass spectrum, m/z (%): 142 (60), 127 (29), 126 (35.4), 125 (75.0), 111 (17.6), 99 (100), 94 (92.6), 84 (38.2), 73 (22), 69 (54.5). Found: C 50.7; H 7.17; N 19.7%. $C_{12}H_{20}N_4O_2$. Calculated: C 50.7; H 7.09; N 19.7%.

2-Oxo-4,5,5-trimethyl-Δ^3-imidazoline 3-Oxide (IVb). A solution of 1.88 g (1 mmole) of IIIb in 10-15 ml of 5 N NaOH was neutralized to pH 7 with 2 N HCl at 5-10°C, after which 50 ml of benzene was added, and the mixture was evaporated in vacuo. The residue was extracted with 100 ml of acetone, the solvent was evaporated, 10 ml of THF was added to the residue, and the mixture was cooled by —20°C. The resulting precipitate was removed by filtration to give 0.5 g (35.2%) of IVb with mp 241-242°C (transition 161-162°C) [3]. IR spectrum : 1800, 1610, 1385, 1300, 1250, 1185, 1135 cm^{-1}. PMR spectrum (d_6-DMSO): 1.36 [6H, s, $C(CH_3)_2$], 2.08 (3H, s, CH_3), and 9.69 ppm (1H, s, NH).

1,4,5,5-Tetramethyl-3-methoxy-4-hydroxyimidazolidin-2-one (XI). A) A 2.71-ml (3 mmole) sample of dimethyl sulfate was added gradually to an alkaline (1.2 g of NaOH in 20 ml of water) solution of 1.42 g (1 mmole) of IVb. At the end of the reaction (established by chromatographic monitoring) the reaction mixture was extracted with ether (three 50-ml portions), the ether layer was evaporated, and the residue was recrystallized from hexane to give 1.1 g (60%) of a product with mp 107-108°C. IR spectrum: 1710 (C=O), 1400, 1149, 1060, 2815 (OCH_3), 3580 (OH) cm^{-1}. PMR spectrum (d_6-DMSO): 1.01, 1.05 [6H, s, $C(CH_3)_2$]; 1.28 (3H, s, CH_3); 2.51 (3H, s, $N{-}CH_3$); 3.62 (3H, s, OCH_3); 5.72 ppm (1H, s, OH). Found: C 51.1; H 8.75; N 14.6%. $C_{18}H_{16}N_2O_3$. Calculated: C 51.0; H 8.55; N 14.8%.

B) A 2.71-ml (3 mmole) sample of dimethyl sulfate was added slowly at 10-15°C to a solution of 2.02 g (1 mmole) of IIIa in 10 ml of 5 N NaOH, and the mixture was neutralized to pH 7 with 2 N HCl and worked up as in method A to give 1.02 g (54%) of product. Testing for Va,b with an acetic acid solution of potassium iodide was conducted by the method in [6].

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