Synthesis and properties of *N*-[1-hydroxyimino-2-methyl-1-(2-pyridyl)prop-2-yl]hydroxylamine and heterocyclic derivatives based on it

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N-[1-Hydroxyimino-2-methyl-1-(2-pyridyl)prop-2-yl]hydroxylamine, a new representative of the series of α-hydroxylamino oximes, was synthesized. Based on this compound, 3-imidazoline 3-oxide and 2-imidazoline 3-oxide derivatives were obtained, and some of their chemical properties were investigated.

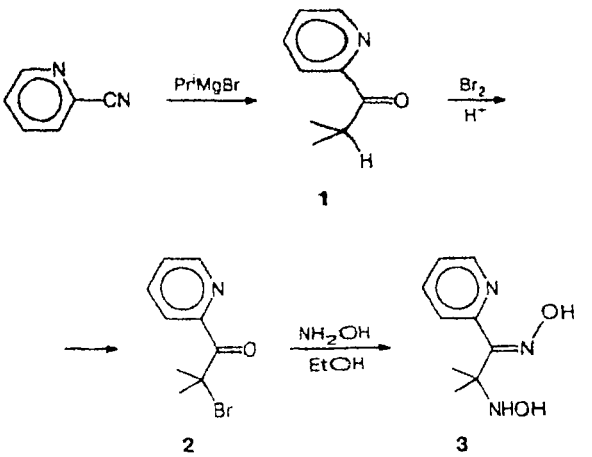
Key words: α-hydroxylamino oximes, *N*-[1-hydroxyimino-2-methyl-1-(2-pyridyl)prop-2-yl]hydroxylamine; 3-imidazoline 3-oxides; methylenenitrone, nitrones, nitroxyl radicals; pyridine.

α-Hydroxylamino oximes (HAO) have found application in the synthesis of nitroxyl radicals of the 3-imidazoline 3-oxide[1] and 2-imidazoline 3-oxide[2] series, which are used as spin labels, probes,[3] and paramagnetic ligands in the chemistry of coordination compounds.[4] In addition, HAO are initial compounds for the preparation of 1,2-diazetine 1,2-dioxide derivatives, which are nitrogen oxide donors.[5] Synthesis of HAO containing alkylaromatic and alkylheteroaromatic substituents at the C atom of the oxime group is based on the interaction of the corresponding α-haloketones with free hydroxylamine.[6] The first stage of this synthesis involves Friedel—Crafts acylation of aromatic compounds with isobutyryl chloride. However, this method for the preparation of hetaryl isopropyl ketones is inapplicable to compounds that are deactivated with respect to electrophilic substitution, in particular, to pyridine. In view of the interest of researchers in the chemistry of pyridines,[7—9] heterocyclic *N*-oxides,[10—12] and imidazoline nitroxyl radicals,[2] it seemed timely to synthesize a HAO containing a pyridine moiety and some of its heterocyclic derivatives. In our opinion, HAO with a 2-pyridyl group would be the most promising, since it may serve as the starting compound for the preparation of imidazoline derivatives, resembling topologically some well-known complexones such as 2,2'-bipyridine and 1,10-phenanthroline.

The high reactivity of nitriles towards Grignard reagents and the accessibility of 2-cyanopyridine (which is produced on an industrial scale) made it possible to choose the latter as the starting compound in the synthesis of 2-pyridyl isopropyl ketone (**1**) (*cf.* Refs. 13 and 14).

The interaction of a small excess of isopropylmagnesium bromide with 2-cyanopyridine followed by hydrolysis of the ketimine salt thus formed gave ketone **1** in an ~80% yield. Bromination of the latter compound and treatment of the resulting α-bromoketone **2** with an excess of free hydroxylamine led to the corresponding α-hydroxylamino oxime **3** (Scheme 1). The ^{1}H NMR spectrum of compound **3** (in DMSO), in addition to the signals for the aromatic protons and the *gem*-dimethyl group at δ 1.19, exhibits signals for the protons of the oxime (δ 10.71) and hydroxylamine (δ 7.10 and 5.69) groups.

Scheme 1



Heating HAO **3** with acetone in the presence of dilute HCl as a catalyst affords 3-imidazoline 3-oxide (**4**) in a high yield; oxidation of the latter compound with PbO_2 in chloroform yields nitroxyl radical **5** (Scheme 2).

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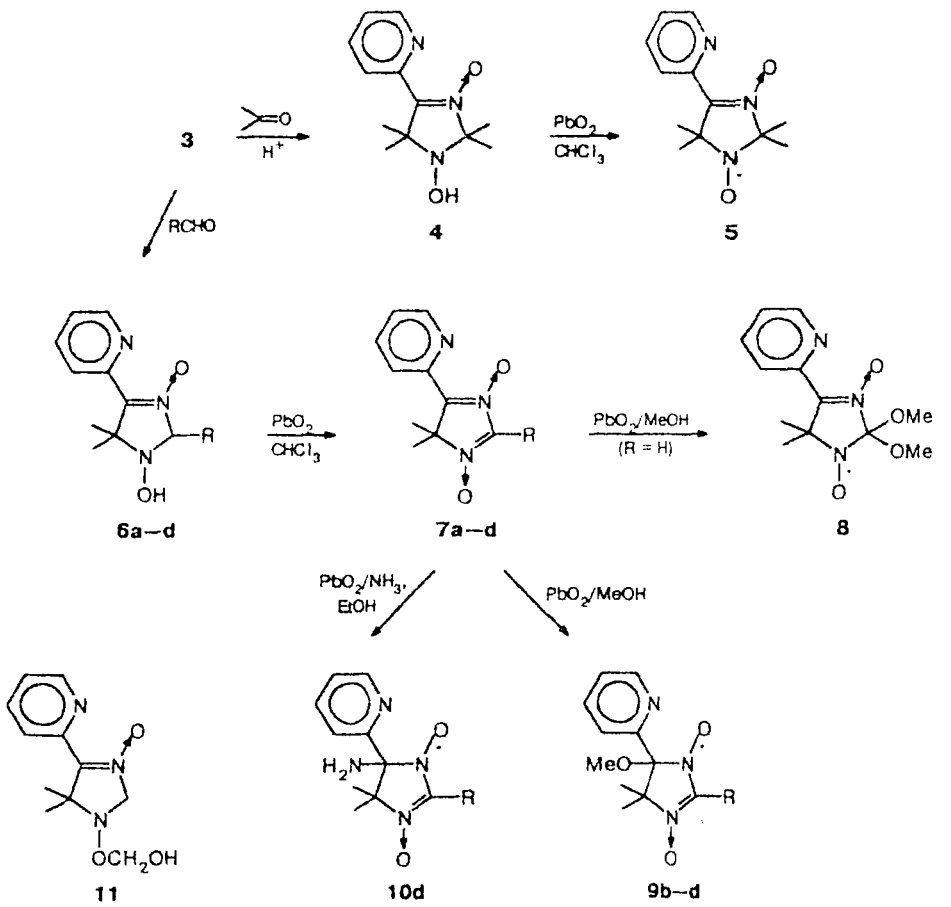
Scheme 2



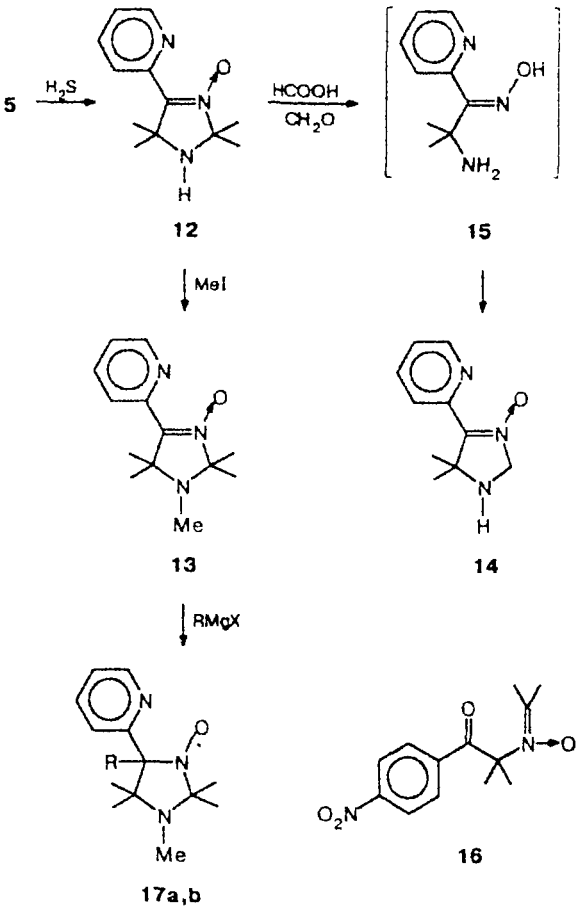
R = H (**a**), Ph (**b**), *p*-$C_{16}H_{33}OC_6H_4$ (**c**), 3-py (**d**)

The reactions of HAO **3** with formalin, benzaldehyde, *p*-(cetyloxy)benzaldehyde, and 3-pyridinecarbaldehyde in an ethanolic solution lead to the corresponding 3-imidazoline 3-oxides **6**, whose oxidation with PbO_2 in chloroform affords 4*H*-imidazole 1,3-dioxides **7**, and whose oxidation in methanol leads either to nitroxyl radical **8** containing methoxy groups in position 2 or to nitronylnitroxyl radicals (NNR) **9** (*cf.* Ref. 15). Oxidation of 4*H*-imidazole 1,3-dioxide **7d** with PbO_2 in ethanol, saturated with NH_3, occurs smoothly to give NNR **10d**, containing an amino group at the α-C atom of the nitroxyl group.[16] It is noteworthy that the condensation of HAO **3** with formalin yields initially semiacetal **11**, whose recrystallization from methanol gives *N*-hydroxy derivative **6a** (see Scheme 2).

The reduction of radical **5** with a solution of H_2S in methanol leads to 3-imidazoline 3-oxide (**12**) (Scheme 3). An attempt to alkylate secondary amine **12** with a mixture of formic acid and formaldehyde did not lead to the expected *N*-methyl derivative **13**; instead, it gave another compound, whose IR spectrum contained no band corresponding to vibrations of the C—H bond in the NMe group, and whose ^1H NMR spectrum exhibited a broadened triplet at δ 3.53 and a doublet at δ 4.72. Relying on these data, this product was identified as imidazoline **14**. The formation of compound **14** can be explained by hydrolysis of the imidazoline ring in an acidic medium followed by condensation of the amino-oxime **15** thus formed with excess formaldehyde occurring in the reaction mixture. This low hydrolytic stability of imidazoline **12** may be due to the presence of two electron-withdrawing centers in its molecule, *viz.*, the nitrone group and the N atom of the pyridine ring. This weakens the bond between the N atom of the nitrone group and the C atom in position 2 of the imidazoline ring and facilitates the ring opening. Apparently, these factors are favorable for the formation of nitrone **16** during the nitration of 1-hydroxy-2,2,5,5-tetramethyl-4-phenyl-3-imidazoline 3-oxide (see Experimental). Compound **13** was obtained by treatment of imidazoline **12** with methyl iodide in isopropyl alcohol.

The addition of RMgX to nitrones followed by oxidation of the resulting sterically hindered hydroxyl-

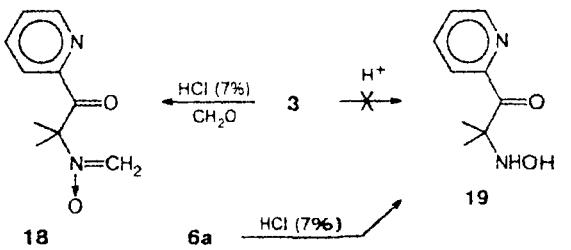
Scheme 3



amines is known to lead to nitroxyl radicals.[17] In the case of pyridylnitrone **13**, the addition of RMgX could afford nitroxyl radicals, in which the mutual arrangement of the nitroxyl group and the main donor site, *viz.*, the N atom of the pyridine ring, would be favorable for complex formation.[4] In fact, nitroxyl radicals **17** were obtained by treating imidazoline **13** with a small excess of RMgX (R = Ph, Me) (see Scheme 3).

α-Hydroxylamino ketones are initial compounds for the synthesis of 3-imidazoline derivatives and, in addition, they possess neurotropic activity.[18] These compounds are usually obtained by acid hydrolysis of the corresponding HAO.[1] However, heating compound **3** in dilute or in concentrated HCl, or in methanol saturated with HCl, led either to the recovery of the initial HAO or to resinification of the reaction mixture. Obviously, this is due to the basic N atom of the pyridine moiety being located close to the oxime group; this hampers protonation of the oxime N atom, which is the first step of the hydrolysis. The attempt to hydrolyze HAO **3** by a mixture of HCl with formalin unexpectedly gave a compound whose IR spectrum, along with the absorption band due to the C=O group, exhibited a band corresponding to the stretching vibrations of the C=N bond, while the ^{1}H NMR spectrum contained signals for methylene protons manifested at δ 6.55 and 6.90 as an AB system ($\delta \gg J$), in addition to the signals of the geminal methyl groups and the aromatic ring. Based on this data, this product was identified as methylenenitrone **18** (Scheme 4).

Scheme 4



α-Hydroxylamino ketone **19** was obtained by acid hydrolysis of imidazoline **6a** (see Scheme 4). Recently, another method for the synthesis of this compound has been proposed.[19]

Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker WP-200SY and Bruker AC-200 spectrometers. IR spectra were obtained on UR-20 and Specord-IR instruments (for pellets with KBr and for solutions in CCl_4). UV spectra were measured on a Specord UV-VIS spectrophotometer in ethanol. Elemental analyses of the compounds synthesized were carried out at the Laboratory of Microanalysis of the Institute of Organic Chemistry of the Siberian Branch of the Russian Academy of Sciences.

2-Methyl-1-(2-pyridyl)propan-1-one (1). A solution of 2-cyanopyridine (50 g, 0.48 mol) in 150 mL of ether was added dropwise with intense stirring to a solution of Pr^{i}MgBr (1.056 mol) in 300 mL of ether. The reaction mixture was stirred for 0.5 h, quenched with 100 mL of a saturated solution of NH_4Cl, and stirred for an additional 1 h. The ethereal layer was separated, the aqueous layer was extracted with chloroform, and the organic extracts were combined and dried with $MgSO_4$. The solvent was evaporated, and the residue was distilled *in vacuo*. Yield 60.5 g (80%), b.p. 107—110 °C (19 Torr) (Ref. 13: b.p. 87—88 °C (7 Torr)). Found (%): C, 72.71; H, 7.81; N, 9.17. $C_9H_{11}NO$. Calculated (%): C, 72.48; H, 7.38; N, 9.39. UV, λ_{max}/nm: 232 (ε 9143); 272 (ε 5143). IR (KBr), ν/cm^{-1}: 1700 (C=O). ^{1}H NMR ($CDCl_3$), δ: 1.11 (d, 6 H, 2 CH_3); 4.06 (m, 1 H, CH); 7.22—8.11 (m, 4 H, pyridyl) (*cf.* Ref. 20).

2-Bromo-2-methyl-1-(2-pyridyl)propan-1-one (2). Acetic acid (1.5 mL) and Br_2 (8.2 mL, 0.32 mol) were added to a solution of ketone **1** (41 g, 0.31 mol) in 250 mL of ether, and the reaction mixture was allowed to stand for 3 days, being stirred at some intervals. Then 100 mL of water and 150 mL of ether were added, and the ethereal layer was

separated and washed with a saturated solution of $Na_2S_2O_3$ (3×20 mL). The aqueous layers were combined and extracted with chloroform (3×20 mL), and the organic extracts were combined and dried with $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was percolated on SiO_2 (using a 3 : 1 hexane—$CHCl_3$ mixture as the eluent). Yield 62.4 g (95%). Found (%): C, 47.54; H, 4.11; N, 5.93; Br, 35.13. $C_9H_{10}NOBr$. Calculated (%): C, 47.37; H, 4.38; N, 6.14; Br, 35.08. UV, λ_{max}/nm: 238 (ε 6000); 270 (ε 4400). IR (CCl_4), ν/cm^{-1}: 1696 (C=O). ^{1}H NMR ($CDCl_3$), δ: 2.22 (s, 6 H, 2 CH_3); 7.22—8.05 (m, 4 H, pyridyl).

***N*-[1-Hydroxyimino-2-methyl-1-(2-pyridyl)prop-2-yl]hydroxylamine (3).** A solution of free NH_2OH (1.38 mol) in 650 mL of an H_2O—MeOH mixture (1 : 1) was added to a solution of ketone **2** (58 g, 0.276 mol) in 200 mL of MeOH, and the mixture was refluxed for 2 h. Then it was concentrated to dryness, the residue was dissolved in $CHCl_3$, the inorganic precipitate was filtered off, the filtrate was concentrated, and the residue was triturated in ether. Yield 40.38 g (75%), m.p. 119—121 °C (from Pr^{i}OH). Found (%): C, 55.57; H, 6.90; N, 20.89. $C_9H_{13}N_3O_2$. Calculated (%): C, 55.38; H, 6.66; N, 21.54. UV, λ_{max}/nm: 262 (ε 5950); 266 (ε 5500). ^{1}H NMR (DMSO-d_6), δ: 1.19 (s, 6 H, 2 CH_3); 5.69 (s, 1 H, NHOH); 7.1 (s, 1 H, NHOH); 7.30—8.59 (m, 4 H, pyridyl); 10.71 (s, 1 H, =NOH). ^{13}C NMR (DMSO-d_6), δ: 24.08 (2 CH_3); 61.75 ($\underline{C}(CH_3)_2$); 123.6, 125.5, 136.5, 148.9 (4 CH, pyridyl); 153.0 (C_{ipso}, pyridyl); 159.68 (C=NOH).

1-Hydroxy-2,2,5,5-tetramethyl-4-(2-pyridyl)-3-imidazoline 3-oxide (4). A 7% solution of HCl (0.3 mL) was added to a suspension of HAO **3** (2 g, 0.01 mol) in 40 mL of acetone, and the mixture was refluxed for 20 h. The colorless crystals that precipitated were filtered off, the mother liquor was evaporated, and the residue was triturated with ether. Yield 1.85 g (77%), m.p. 205—207 °C (from EtOH). Found (%): C, 61.20; H, 7.34; N, 17.25. $C_{12}H_{17}N_3O_2$. Calculated (%): C, 61.27; H, 7.23; N, 17.80. UV, λ_{max}/nm: 303 (ε 10600). IR (KBr), ν/cm^{-1}: 1575 (C=N→O); 3263 (OH). ^{1}H NMR (DMSO-d_6), δ: 1.45, 1.56 (both s, 12 H, 4 CH_3); 8.18 (s, 1 H, OH); 7.31—9.19 (m, 4 H, pyridyl). Oxidation of compound **4** with lead dioxide in $CHCl_3$ gave **2,2,5,5-tetramethyl-4-(2-pyridyl)-3-imidazolin-1-oxyl 3-oxide (5)**, m.p. 130—132 °C (from hexane). Found (%): C, 60.95; H, 6.98; N, 17.83. $C_{12}H_{16}N_3O_2$. Calculated (%): C, 61.50; H, 6.84; N, 17.90. UV, λ_{max}/nm: 226 (ε 9000); 302 (ε 14600). IR (KBr), ν/cm^{-1}: 1540 (C=N→O).

Condensation of HAO 3 with aldehydes (general procedure). An aldehyde (15 mmol) was added to a suspension of HAO **3** (2 g, 10 mmol) in 50 mL of EtOH, and the mixture was allowed to stand for 3—4 days. The course of the reaction was monitored by TLC (Silufol). In the case of 3-pyridinecarbaldehyde and benzaldehyde, the product precipitated from the reaction mixture as colorless crystals; in the case of *p*-(cetyloxy)benzaldehyde, it floated up as a waxy material. The solid products were filtered off and recrystallized from EtOH to give imidazolines **6b—d**.

1-Hydroxy-5,5-dimethyl-2-phenyl-4-(2-pyridyl)-3-imidazoline 3-oxide (6b). Yield 82%, m.p. 183—185 °C. Found (%): C, 67.19; H, 5.90; N, 14.65. $C_{16}H_{17}N_3O_2$. Calculated (%): C, 67.81; H, 6.06; N, 14.83. UV, λ_{max}/nm: 303 (ε 14000). IR (KBr), ν/cm^{-1}: 1562 (C=N→O); 3250 (OH). ^{1}H NMR (DMSO-d_6), δ: 1.63 (s, 6 H, 2 CH_3); 5.76 (s, 1 H, CH); 8.41 (s, 1 H, OH) 7.42—9.00 (m, 9 H, Ph, pyridyl).

2-(*p*-Hexadecyloxyphenyl)-1-hydroxy-5,5-dimethyl-4-(2-pyridyl)-3-imidazoline 3-oxide (6c). Yield 68%, m.p. 98—103 °C. Found (%): C, 73.83; H, 9.27; N, 8.12. $C_{32}H_{49}N_3O_3$. Calculated (%): C, 73.42; H, 9.37; N, 8.03. UV, λ_{max}/nm: 224 (ε 15500); 274 (ε 13800); 298 (ε 14200). IR (KBr), ν/cm^{-1}: 1550 (C=N→O). ^{1}H NMR ($CDCl_3$), δ: 0.86 (t, 3 H, CH_3); 1.24 (s, 26 H, $(CH_2)_{13}$); 1.70 (s, 6 H, $C(CH_3)_2$); 1.76 (m, 2 H, $OCH_2\underline{CH_2}$); 3.95 (t, 2 H, OCH_2); 5.16 (s, 1 H, OH); 5.65 (s, 1 H, CH); 6.92—9.10 (m, 8 H, C_6H_4, pyridyl).

1-Hydroxy-5,5-dimethyl-2-(3-pyridyl)-4-(2-pyridyl)-3-imidazoline 3-oxide (6d). Yield 79%, m.p. 185—187 °C. Found (%): C, 63.10; H, 5.63; N, 19.58. $C_{15}H_{16}N_4O_2$. Calculated (%): C, 63.38; H, 5.63; N, 19.7. UV, λ_{max}/nm: 303 (ε 15000). IR (KBr), ν/cm^{-1}: 1537 (C=N→O). ^{1}H NMR (DMSO-d_6), δ: 1.63 (s, 6 H, $C(CH_3)_2$); 5.91 (s, 1 H, CH); 7.40—8.96 (m, 8 H, pyridyl); 8.47 (s, 1 H, OH).

Condensation of HAO 3 with formalin. A 30% solution of formalin (0.52 mL, 5.4 mmol) was added to a suspension of HAO **3** (0.5 g, 2.5 mmol) in 20 mL of EtOH. The course of the reaction was monitored by TLC (Silufol, using a $CHCl_3$—1% MeOH mixture as the eluent). After 1 h, the reaction mixture was concentrated, and the residue was triturated in a 1 : 1 ether—hexane mixture. Recrystallization from a 3 : 1 hexane—EtOAc mixture gave **1-hydroxymethyloxy-5,5-dimethyl-4-(2-pyridyl)-3-imidazoline 3-oxide (11)**; yield 76%, m.p. 121—123 °C. Found (%): C, 55.25; H, 6.48; N, 17.61. $C_{11}H_{15}N_3O_3$. Calculated (%): C, 54.85; H, 6.33; N, 17.72. UV, λ_{max}/nm: 300 (ε 13600). IR (KBr), ν/cm^{-1}: 1565, 1582 (C=C, C=N). ^{1}H NMR ($CDCl_3$), δ: 1.65 (br.s, 6 H, $C(CH_3)_2$); 4.95 (br.s, 2 H, $OC\underline{H_2}OH$);* 5.04 (br.s, 2 H, CH_2); 5.17 (br.s, 1 H, $OCH_2\underline{OH}$); 7.16—9.10 (m, 4 H, pyridyl). ^{13}C NMR ($CDCl_3$), δ: 22.86 (br, $C(\underline{C}H_3)_2$); 75.76 ($\underline{C}(CH_3)_2$); 85.55 (CH_2); 92.39 (OCH_2OH); 142.30 (C=N→O); 124.03, 124.52, 136.20, 147.11, 148.82 (pyridyl). Recrystallization from MeOH gave **1-hydroxy-5,5-dimethyl-4-(2-pyridyl)-3-imidazoline 3-oxide (6a)**; yield 88%, m.p. 134—135 °C. Found (%): C, 57.77; H, 5.93; N, 20.31. $C_{10}H_{13}N_3O_2$. Calculated (%): C, 57.95; H, 6.34; N, 20.28. UV, λ_{max}/nm: 300 (ε 13600). IR (KBr), ν/cm^{-1}: 1553, 1582 (C=C, C=N); 3582 (OH). ^{1}H NMR ($CDCl_3$), δ: 1.64 (s, 6 H, $C(CH_3)_2$); 3.40, 3.48 (2 H, CH_2, AB-system, J_{gem} = 22 Hz); 7.04 (s, 1 H, OH); 7.16—9.05 (m, 4 H, pyridyl).

4*H*-Imidazole 1,3-dioxides 7 (general procedure). Lead dioxide (10 mmol) was added to a solution (or suspension) of imidazoline **6b—d** (3.5 mmol) in 80 mL of $CHCl_3$, and the mixture was stirred with a magnetic stirrer for 2—3 h. The course of the reaction was monitored by TLC (Silufol). When the initial imidazoline had disappeared, the oxidizing reagent was filtered off, and the chloroform solution was concentrated. Recrystallization of the solid residue gave the corresponding 4*H*-imidazole 1,3-dioxides **7b—d**. In the case of imidazoline **6a**, MnO_2 (0.8 g, 0.0092 mol) was added in one portion to a solution of the imidazoline (0.4 g, 0.0019 mol) in 80 mL of $CHCl_3$, and the mixture was stirred with a magnetic stirrer for 15 min. Then the oxidizing reagent was filtered off, the filtrate was concentrated, and the residue was triturated in a 5 : 1 hexane—ether mixture.

4,4-Dimethyl-5-(2-pyridyl)-4*H*-imidazole 1,3-dioxide (7a). Yield 0.33 g (83%), m.p. 173—175 °C (from a 1 : 8 hexane—EtOAc mixture). Found (%): C, 59.18; H, 5.30; N, 20.19. $C_{10}H_{11}N_3O_2$. Calculated (%): C, 58.54; H, 5.36;

* The choice between signals for the ring methylene protons and those for the $OC\underline{H_2}OH$ group was made by using the Overhauser effect.

N, 20.49. UV, λ_{max}/nm: 248 (ε 11400); 252 (ε 11200); 270 (ε 7800); 358 (ε 18800). IR (KBr), ν/cm^{-1}: 1563, 1581 (C=C, C=N).* ^{1}H NMR ($CDCl_3$), δ: 1.88 (s, 6 H, 2 CH_3); 7.82 (s, 1 H, HC=N→O); 7.2—9.2 (m, 4 H, pyridyl). ^{13}C NMR ($CDCl_3$), δ: 24.07 ($C(\underline{C}H_3)_2$); 81.69 ($\underline{C}(CH_3)_2$); 123.42, 124.54, 136.77, 145.47, 149.29 (pyridyl); 134.89 ($H\underline{C}$=N→O); 143.71 ($\underline{C}$=N→O).

4,4-Dimethyl-2-phenyl-5-(2-pyridyl)-4*H*-imidazole 1,3-dioxide (7b). Yield 88%, m.p. 143—144 °C (from a 10 : 1 hexane—EtOAc mixture). Found (%): C, 68.31; H, 5.54; N, 14.62. $C_{16}H_{15}N_3O_2$. Calculated (%): C, 68.30; H, 5.38; N, 14.94. UV, λ_{max}/nm: 290 (ε 19000); 365 (ε 10400). IR (KBr), ν/cm^{-1}: 1562, 1575 (C=C, C=N). ^{1}H NMR ($CDCl_3$), δ: 1.98 (s, 6 H, 2 CH_3); 7.31—9.38 (m, 9 H, Ph, pyridyl).

2-(*p*-Hexadecyloxyphenyl)-4,4-dimethyl-5-(2-pyridyl)-4*H*-imidazole 1,3-dioxide (7c). Yield 83%, m.p. 98—101 °C (from EtOAc). Found (%): C, 74.10; H, 9.79; N, 8.10. $C_{32}H_{47}N_3O_3$. Calculated (%): C, 73.70; H, 9.02; N, 8.06. UV, λ_{max}/nm: 310 (ε 30000); 370 (ε 10800). IR (KBr), ν/cm^{-1}: 1560, 1581 (C=C, C=N); 2850 (O—Alk). ^{1}H NMR ($CDCl_3$), δ: 0.85 (t, 3 H, CH_3); 1.24 (s, 26 H, $(CH_2)_{13}$); 1.79 (m, 2 H, $OCH_2C\underline{H}_2$); 1.96 (s, 6 H, $C(CH_3)_2$); 4.01 (t, 2 H, OCH_2); 7.00—9.36 (m, 8 H, Ph, pyridyl).

4,4-Dimethyl-2-(3-pyridyl)-5-(2-pyridyl)-4*H*-imidazole 1,3-dioxide (7d). Yield 90%, m.p. 170—172 °C (from a 1 : 2 hexane—EtOAc mixture). Found (%): C, 63.81; H, 4.94; N, 19.72. $C_{15}H_{14}N_4O_2$. Calculated (%): C, 63.82; H, 4.96; N, 19.86. UV, λ_{max}/nm: 298 (ε 20800); 366 (ε 10800). IR (KBr), ν/cm^{-1}: 1523, 1562, 1580 (C=C, C=N). ^{1}H NMR ($CDCl_3$), δ: 1.98 (s, 6 H, 2 CH_3); 7.33—9.84 (m, 8 H, pyridyl).

2,2-Dimethoxy-5,5-dimethyl-4-(2-pyridyl)-3-imidazolin-1-oxyl 3-oxide (8). Lead dioxide (11.47 g, 48 mmol) was added to a solution of imidazoline **6a** (1 g, 4.8 mmol) in 80 mL of MeOH, and the mixture was stirred with a magnetic stirrer for 8 h. Then the oxidizing reagent was filtered off, the filtrate was concentrated, and the residue was chromatographed on SiO_2 using $CHCl_3$ as the eluent. Yield 0.96 g (75%), m.p. 101—102 °C (from a 4 : 1 hexane—EtOAc mixture). Found (%): C, 53.86; H, 6.18; N, 15.70. $C_{12}H_{16}N_3O_4$. Calculated (%): C, 54.13; H, 6.01; N, 15.70. UV, λ_{max}/nm: 226 (ε 9200); 298 (ε 14800). IR (KBr), ν/cm^{-1}: 1550 ($\underline{C}$=$\underline{N}$→O); 2850 (OMe).

5-Amino-4,4-dimethyl-5-(2-pyridyl)-2-(3-pyridyl)-2-imidazolin-1-oxyl 3-oxide (9d). Lead dioxide (2.29 g, 9.6 mmol) was added to a solution of 4*H*-imidazole **7d** (0.68 g, 2.4 mmol) in 100 mL of a saturated ethanolic solution of NH_3, and the mixture was stirred with a magnetic stirrer for 3—4 h. After the initial compound disappeared (according to TLC), the oxidizing reagent was filtered off and washed with 20 mL of EtOH. The combined ethanolic solutions were concentrated, and the residue was chromatographed on SiO_2 using $CHCl_3$ as the eluent. The oily product resulting from chromatography was triturated with dry pentane. Yield 0.4 g (56%), m.p. 153—155 °C (from a 1 : 5 hexane—EtOAc mixture). Found (%): C, 59.95; H, 5.65; N, 23.51. $C_{15}H_{16}N_5O_2$. Calculated (%): C, 60.38; H, 5.42; N, 23.48. UV, λ_{max}/nm: 211 (ε 12800); 259 (ε 13200); 367 (ε 13200); 588 (ε 560). IR (KBr), ν/cm^{-1}: 3210, 3337 (N—H, NH_2).

* In the spectra of these 4*H*-imidazole 1,3-dioxide derivatives, bands due to vibrations of the phenyl and pyridyl groups fall into the region of C=N stretching vibrations (1510—1630 cm^{-1}); therefore, unambiguous assignment of the bands is difficult.

Nitronylnitroxyl radicals 10b—d (general procedure). Lead dioxide (14 mmol) was added to a solution or suspension of imidazoline **6b—d** (3.5 mmol) in 80 mL of MeOH, and the mixture was stirred with a magnetic stirrer for 3—4 h (in the case of imidazoline **6c**, the mixture was stirred for 2 days), the course of the reaction being monitored by TLC (Silufol). After the initial reactant disappeared, the oxidizing reagent was filtered off and washed with 20 mL of MeOH. The combined solutions were concentrated and chromatographed on silica gel using $CHCl_3$ as the eluent.

5-Methoxy-4,4-dimethyl-2-phenyl-5-(2-pyridyl)-2-imidazolin-1-oxyl 3-oxide (10b). Yield 67%, m.p. 133—135 °C (from a 5 : 1 hexane—EtOAc mixture). Found (%): C, 65.07; H, 5.64; N, 13.47. $C_{17}H_{18}N_3O_3$. Calculated (%): C, 65.36; H, 5.82; N, 13.45. UV, λ_{max}/nm: 265 (ε 15200); 363 (ε 12200); 610 (ε 940). IR (KBr), ν/cm^{-1}: 2837 (C—H, OMe).

2-(*p*-Hexadecyloxyphenyl)-5-methoxy-4,4-dimethyl-5-(2-pyridyl)-2-imidazolin-1-oxyl 3-oxide (10c). Yield 60%, m.p. 77—79 °C (from a 10 : 1 hexane—EtOAc mixture). Found (%): C, 71.33; H, 8.95; N, 7.24. $C_{33}H_{50}N_3O_4$. Calculated (%): C, 71.69; H, 9.13; N, 7.60. UV, λ_{max}/nm: 286 (ε 17200); 367 (ε 6000); 635 (ε 1000). IR (KBr), ν/cm^{-1}: 2850 (CH, $OC_{16}H_{33}$).

5-Methoxy-4,4-dimethyl-2-(3-pyridyl)-5-(2-pyridyl)-2-imidazolin-1-oxyl 3-oxide (10d). Yield 75%, m.p. 119—120 °C (from a 7 : 1 hexane—EtOAc mixture). Found (%): C, 61.24; H, 5.24; N, 17.60. $C_{16}H_{17}N_4O_3$. Calculated (%): C, 61.34; H, 5.43; N, 17.89. UV, λ_{max}/nm: 260 (ε 6400); 368 (ε 6000); 625 (ε 1700). IR (KBr), ν/cm^{-1}: 2837 (CH, OMe).

2,2,5,5-Tetramethyl-4-(2-pyridyl)-3-imidazoline 3-oxide (12). A saturated solution of H_2S (50 mL) in MeOH was added to a solution of imidazoline **5** (1 g, 4.3 mmol) in 10 mL of MeOH. After 6 h, the reaction mixture was concentrated, and the residue was percolated on a column with SiO_2 using $CHCl_3$ as the eluent. Yield 0.76 g (82%), m.p. 82—84 °C (from a 1 : 1 hexane—EtOAc mixture). Found (%): C, 65.88; H, 7.92; N, 19.13. $C_{12}H_{17}N_3O_2$. Calculated (%): C, 65.75; H, 7.76; N, 19.18. UV, λ_{max}/nm: 224 (ε 6800); 304 (ε 13800). IR (KBr), ν/cm^{-1}: 1540 (C=N→O); 3325 (N—H). ^{1}H NMR ($CDCl_3$), δ: 1.62, 1.68 (both s, 12 H, 4 CH_3); 2.02 (br.s, 1 H, NH); 7.19—9.30 (m, 4 H, pyridyl).

1,2,2,5,5-Pentamethyl-4-(2-pyridyl)-3-imidazoline 3-oxide (13). Methyl iodide (0.43 mL, 6.9 mmol) was added to a solution of imidazoline **12** (0.5 g, 2.3 mmol) in 15 mL of isopropyl alcohol, and the mixture was allowed to stand until the initial compound disappeared (according to TLC). Then the reaction mixture was concentrated to dryness, the residue was dissolved in 7 mL of a saturated solution of K_2CO_3, and the solution was extracted with chloroform. The extract was dried with $MgSO_4$, the solvent was evaporated, and the residue was percolated on SiO_2 using $CHCl_3$ as the eluent. Yield 0.36 g (68%), m.p. 80—82 °C (from hexane). Found (%): C, 67.01; H, 8.53; N, 17.86. $C_{13}H_{19}N_3O$. Calculated (%): C, 66.95; H, 8.15; N, 18.02. UV, λ_{max}/nm: 223 (ε 6200); 302 (ε 11200). IR (KBr), ν/cm^{-1}: 1545 (C=N→O); 2820 (CH, NMe). ^{1}H NMR ($CDCl_3$), δ: 1.55, 1.61 (both s, 12 H, 4 CH_3); 2.43 (s, 3 H, NCH_3); 7.18—9.33 (m, 4 H, pyridyl).

5,5-Dimethyl-4-(2-pyridyl)-3-imidazoline 3-oxide (14). Formic acid (0.2 mL, 5.3 mmol) was slowly added to a solution of imidazoline **12** (0.2 g, 0.9 mmol) in 0.5 mL of 30% formalin, and the reaction mixture was allowed to stand for 7 h. Then it was diluted with a twofold amount of water, neutralized with $NaHCO_3$, and extracted with chloroform. The extract was dried with $MgSO_4$, the solvent was evapo-

rated, and the residue was subjected to preparative TLC on SiO_2, using $CHCl_3$ as the eluent. Yield 59%, m.p. 135—137 °C (from a 3 : 2 hexane—EtOAc mixture). Found (%): C, 62.86; H, 7.20; N, 22.20. $C_{10}H_{13}N_3O$. Calculated (%): C, 62.83; H, 6.81; N, 21.98. UV, λ_{max}/nm: 222 (ε 9600); 302 (ε 23400). IR (KBr), ν/cm^{-1}: 1555 (C=N→O); 3265 (N—H). ^{1}H NMR ($CDCl_3$), δ: 1.56 (s, 6 H, 2 CH_3); 3.53 (t, 1 H, NH, J = 11 Hz); 4.72 (d, 2 H, CH_2, J = 11 Hz); 7.35—9.05 (m, 4 H, pyridyl).

α-(4-Nitrobenzoyl)-*N*-(2-propylidene)isopropylamine *N*-oxide (16).* Nitration of 1-hydroxy-2,2,5,5-tetramethyl-4-phenyl-3-imidazoline 3-oxide was carried out according to a procedure described previously (procedure *b*[21]). Yield 5.5%, m.p. 85—87 °C (from EtOH). Found (%): C, 59.12; H, 6.41; N, 10.61. $C_{13}H_{16}N_2O_4$. Calculated (%): C, 59.09; H, 6.06; N, 10.61. UV, λ_{max}/nm: 205 (ε 13180); 265 (ε 10470). IR (KBr), ν/cm^{-1}: 1695 (C=O); 1360, 1530 (NO_2). ^{1}H NMR (CCl_4), δ: 1.54 (s, 6 H, $C(CH_3)_2$); 1.68, 1.85 (both s, 6 H, $=C(CH_3)_2$); 8.19 (s, 4 H, C_6H_4). ^{13}C NMR (CCl_4), δ: 15.33, 20.99 (N=C($\underline{C}H_3)_2$); 24.18 (C($\underline{C}H_3)_2$); 85.67 ($\underline{C}(CH_3)_2$); 148.21 (N=$\underline{C}(CH_3)_2$); 155.96 (C—NO_2, C_6H_4); 122.78, 130.33 (CH, C_6H_4); 140.09 (C_{ipso}, C_6H_4); 201.37 (C=O).

Reaction of imidazoline 12 with RMgX (general procedure). A solution of imidazoline **12** (3.5 mmol) in 10 mL of anhydrous ether was added to a solution of a Grignard reagent (18 mmol) in 20 mL of ether, and the reaction mixture was refluxed for 4 h. A saturated solution of NH_4Cl (5 mL) was added to the mixture, the ethereal layer was separated, and the aqueous layer was extracted with ether (5×20 mL). The combined ethereal solutions were dried with $MgSO_4$ and filtered. MnO_2 (5 g) was added, and the mixture was stirred for 1 h. After that, the oxidizing reagent was filtered off, and the ethereal solution was concentrated. The residue was chromatographed on silica gel using $CHCl_3$ as the eluent.

1,2,2,4,5,5-Hexamethyl-4-(2-pyridyl)imidazolidin-1-oxyl (17a). Yield 70%, m.p. 103—105 °C (from hexane). Found (%): C, 68.12; H, 8.96; N, 16.9. $C_{14}H_{22}N_3O$. Calculated (%): C, 67.75; H, 8.87; N, 17.1. UV, λ_{max}/nm: 256 (ε 5000). IR (KBr), ν/cm^{-1}: 1600 (C=N, pyridyl); 2820 (C—H, NMe).

1,2,2,5,5-Pentamethyl-4-phenyl-4-(2-pyridyl)imidazolidin-1-oxyl (17b). Yield 68%, m.p. 72—74 °C (from hexane). Found (%): C, 73.12; H, 7.36; N, 13.49. $C_{19}H_{24}N_3O$. Calculated (%): C, 73.55; H, 7.74; N, 13.55. IR (KBr), ν/cm^{-1}: 2820 (C—H, NMe).

***N*-Methylene-α-(2-pyridylcarbonyl)isopropylamine *N*-oxide (18).** HAO **3** (1 g) was added to a mixture of formalin (10 mL) and concentrated HCl (10 mL), and the mixture was allowed to stand for 24 h, the course of the reaction being monitored by TLC (Silufol). Then the reaction mixture was concentrated to dryness, and the residue was dissolved in 5 mL of water, neutralized with K_2CO_3, and extracted with chloroform. The extract was dried with $MgSO_4$ and concentrated, and the residue was triturated with pentane. Yield 0.63 g (65%), m.p. 116—118 °C (from a 2 : 1 hexane—benzene mixture). Found (%): C, 62.49; H, 6.55; N, 14.42. $C_{10}H_{12}N_2O_2$. Calculated (%): C, 62.47; H, 6.30; N, 14.58. UV, λ_{max}/nm: 236 (ε 10400). IR (KBr), ν/cm^{-1}: 1695 (C=O); 3143 (H—C, HC=N→O); 1560 (C=N). ^{1}H NMR (DMSO-d_6), δ: 1.82 (s, 6 H, $C(CH_3)_2$); 6.55, 6.90 (both d, 2 H, CH_2=N→O, J = 6 Hz); 7.50—8.60 (m, 4 H, pyridyl). ^{13}C NMR (DMSO-d_6), δ: 25.06 (C($\underline{C}H_3)_2$); 78.64 ($\underline{C}(CH_3)_2$); 120.7 (H_2C=N→O); 122.7, 127.03, 137.44, 148.09, 152.63 (pyridyl); 194.32 (C=O).

***N*-[(2-Pyridylcarbonyl)isopropyl]hydroxylamine (19).** A solution of imidazoline **6a** (1 g, 4.8 mmol) in 20 mL of 10% HCl was allowed to stand for a week, and then neutralized with K_2CO_3 and extracted with chloroform. The extract was dried with $MgSO_4$, concentrated, and chromatographed on SiO_2 free of Fe^{3+} ions, using $CHCl_3$ as the eluent. The oily product resulting from chromatography was triturated in hexane with a small amount of dry ether. Yield 0.52 g (60%), m.p. 70—72 °C (from a 20 : 1 pentane—ether mixture). Found (%): C, 60.03; H, 6.89; N, 15.44. $C_9H_{12}N_2O_2$. Calculated (%): C, 59.97; H, 6.72; N, 15.55. UV, λ_{max}/nm: 231 (ε 5600); 269 (ε 3800). IR (KBr), ν/cm^{-1}: 1695 (C=O); 3265 (N—H). ^{1}H NMR (DMSO-d_6), δ: 1.47 (s, 6 H, 2 CH_3); 6.96 (br.s, 2 H, NHOH); 7.4—8.6 (m, 4 H, pyridyl). ^{13}C NMR (DMSO-d_6), δ: 22.50 (C($\underline{C}H_3)_2$); 68.08 ($\underline{C}(CH_3)_2$); 123.39, 126.73, 137.32, 147.68, 153.08 (pyridyl); 202.54 (C=O).

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References

1. L. B. Volodarsky and A. Ya. Tikhonov, *Synthesis*, 1986, 704.
2. L. B. Volodarsky, I. A. Grigor'ev, S. A. Dikanov, V. A. Reznikov, and G. I. Shchukin, in *Imidazolinovye nitroksil'nye radikaly* [*Imidazoline Nitroxyl Radicals*], Nauka, Novosibirsk, 1988, 24 (in Russian).
3. V. V. Lyakhovich and L. M. Weiner, in *Imidazoline Nitroxides*, Ed. L. B. Volodarsky, CRC Press, Florida, 1988, **2**, Ch. 1; V. V. Khramtsov and L. M. Weiner, in *Imidazoline Nitroxides*, Ed. L. B. Volodarsky, CRC Press, Florida, 1988, **2**, Ch. 2.
4. L. B. Volodarsky, V. A. Reznikov, and V. I. Ovcharenko, in *Synthetic Chemistry of Stable Nitroxides*, CRC Press, Florida, 1994, Ch. 4, 159.
5. D. I. Utepbergenov, V. V. Khramtsov, L. P. Vlassenko, A. L. Markel, D. G. Mazhukin, A. Ya. Tikhonov, and L. B. Volodarsky, *Biochem. Biophys. Res. Commun.*, 1995, **214**, 1023.
6. L. B. Volodarsky, V. A. Koptyug, and A. N. Lysak, *Zh. Org. Khim.*, 1966, **2**, 114 [*J. Org. Chem. USSR*, 1966, **2** (Engl. Transl.)].
7. E. F. V. Scriven, in *Comprehensive Heterocyclic Chemistry*, Eds. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, **2**.
8. F. S. Yates, in *Comprehensive Heterocyclic Chemistry*, Eds. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, **2**.
9. D. L. Comins and S. O'Connor, *Adv. Heterocycl. Chem.*, 1988, **44**, 199.
10. T. I. Godovikova, E. L. Ignat'eva, and L. I. Khmel'nitskii, *Khim. Geterotsikl. Soedin.*, 1989, 145 [*Chem. Heterocycl. Compd.*, 1989 (Engl. Transl.)].
11. H. Yamanaka, T. Sakamoto, and S. Niitsuma, *Heterocycles*, 1990, **31**, 923.
12. G. V. Nikitina and M. S. Pevzner, *Khim. Geterotsikl. Soedin.*, 1993, 147 [*Chem. Heterocycl. Compd.*, 1993 (Engl. Transl.)].
13. B. H. Walker, *J. Org. Chem.*, 1960, **25**, 1047.
14. Ch. K. F. Hermann, Y. P. Sachdeva, and J. F. Wolfe, *J. Heterocycl. Chem.*, 1987, **24**, 1061.

15. I. A. Grigor'ev, I. A. Kirilyuk, V. F. Starichenko, and L. B. Volodarsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 1624 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 1488 (Engl. Transl.)].
16. I. A. Grigor'ev, V. F. Starichenko, I. A. Kirilyuk, and L. B. Volodarsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 661 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 587 (Engl. Transl.)].
17. J. F. W. Keana, in *Spin Labeling in Pharmacology*, Academic Press, New York, 1984, 27.
18. USSR Pat. 657016; *Byul. Izobret.*, 1979, 14 (in Russian).
19. V. K. Khlestkin, V. A. Reznikov, D. G. Mazhukin, A. Ya. Tikhonov, and L. B. Volodarsky, *Mendeleev Commun.*, 1997, in press.
20. R. Deuchert, U. Hertenstein, S. Hünig, and E. F. Wehner, *Chem. Ber.*, 1979, **112**, 2045.
21. L. B. Volodarsky, I. A. Grigor'ev, L. N. Grigor'eva, I. A. Kirilyuk, and S. A. Amitina, *Zh. Org. Khim.*, 1985, **21**, 443 [*J. Org. Chem. USSR*, 1985, **21** (Engl. Transl.)].

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