Synthesis and recyclization reactions of 4-(*o*-R-phenyl)-3-imidazolines

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1-Hydroxy-4-phenyl-3-imidazoline reacts with butyllithium to give the product of *ortho*-metallation of the phenyl group. Reactions of this compound with electrophiles followed by oxidation afford 4-(*o*-R-phenyl) derivatives of nitroxyl radicals. When a hydroxyalkyl group is present in the *ortho*-position, an unusual pathway of the decay of stable nitroxyl radicals of the imidazoline series has been observed due to the existence of a spirobicyclic tautomer. The reaction of the *o*-metallated derivative with CS_2 leads to a profound transformation of the imidazoline ring and to the formation of isoindolethione. Fast recyclization into isoquinolines occurs in the case of the 4-(*o*-benzoyl)phenyl derivative of 3-imidazoline. The product of *o*-metallation reacts with methyl nitrate to yield the 4-(*o*-hydroxy)phenyl derivative (a potential paramagnetic chelate-forming reagent) and the *o*-nitro derivative, the starting material for further chemical transformations.

Key words: imidazoline, nitroxyl radical, *ortho*-metallation, recyclization.

Metallation reactions of 4-methyl substituted 3-imidazoline are efficiently used in the synthesis of functionally substituted nitroxyl radicals of the 3-imidazoline and imidazolidine series.[1] It is known that the reactions of imines unable to enolyze with organometallic compounds,[2] occur as addition at the C=N bond. We have found that the reactions of 1-hydroxy-2,2,5,5-tetramethyl-4-phenyl-3-imidazoline (**1**) with phenyl- and butyllithium give no products of the addition at the C=N bond incorporated into the heterocycle. After oxidation of the reaction mixture, the corresponding nitroxyl radical **2** can be isolated in quantitative yield.

Butyllithium also does not add to the C=N bond in the reaction of radical **2** under similar conditions, and after oxidation with MnO_2, 1-butoxy derivative **3** and the starting compound **2** are formed (in approximately equal amounts).[3] The reaction of compound **1** with excess butyllithium affords the *o*-metallated derivative **4** (Scheme 1). Treatment of this compound with benzaldehyde followed by oxidation yields product **5a**. The IR spectrum of compound **5a** exhibits an OH absorption band at 3450 cm^{-1} and an NH band at 3270 cm^{-1} as well as low-intensity bands at 1630 and 1600 cm^{-1}, which may be assigned to C=C and C=N vibrations. These data indicate that compound **5a** exists predominantly as the spirobicyclic tautomer **A** (see Scheme 1). The possibility of this tautomeric equilibrium indicates that the phenyl group is metallated in the *ortho*-position due to the coordination influence of the N atom in position 3 of the ring (*cf.* Ref. 4).

The ^1H NMR spectrum of compound **6a**, which is the diamagnetic analog of **5a**, exhibits a double set of signals: eight singlets for nonequivalent methyl groups in the region between 0.39 and 0.71 ppm, singlets for benzyl protons at 5.21 and 5.24 ppm, and a multiplet for the protons of phenyl groups in the region 6.4—6.8 ppm. These data suggest that in a DMSO—MeOH solution only spirobicyclic tautomer **A** exists as a mixture of two diastereomers in a ~1 : 10 ratio. This is also consistent with the ^{13}C NMR spectrum of compound **6a** in the same solvent. It should be noted that compound **5b** resulting from condensation of the metallated derivative **4** with benzophenone (see Scheme 1) probably has a similar structure.

We have found that compounds **5** are readily oxidized through the action of MnO_2 in organic solvents under mild conditions to give diamagnetic derivatives **7**, and that the rate of this reaction is comparable with that of the oxidation of hydroxylamino derivatives **6** to nitroxyl radicals **5**. The intense absorption band at 1710 cm^{-1} in the IR spectra of compounds **7** might be assigned to vibrations of the C=O bond, however, no signal for a carbonyl C atom occurs in the ^{13}C NMR spectrum of compound **7a**. The UV spectrum of **7a** exhibits a band at λ_{max} = 242 nm, which may be explained by the presence of an alkylnitrone group. According to the data from elemental analysis, the composition of the oxidation products **7** differs from that of the starting compounds **5** by one H atom. Acid hydrolysis of **7a** affords compound **8**. The fact that the lactone carbonyl group in a molecule of **8** is located near the phenyl

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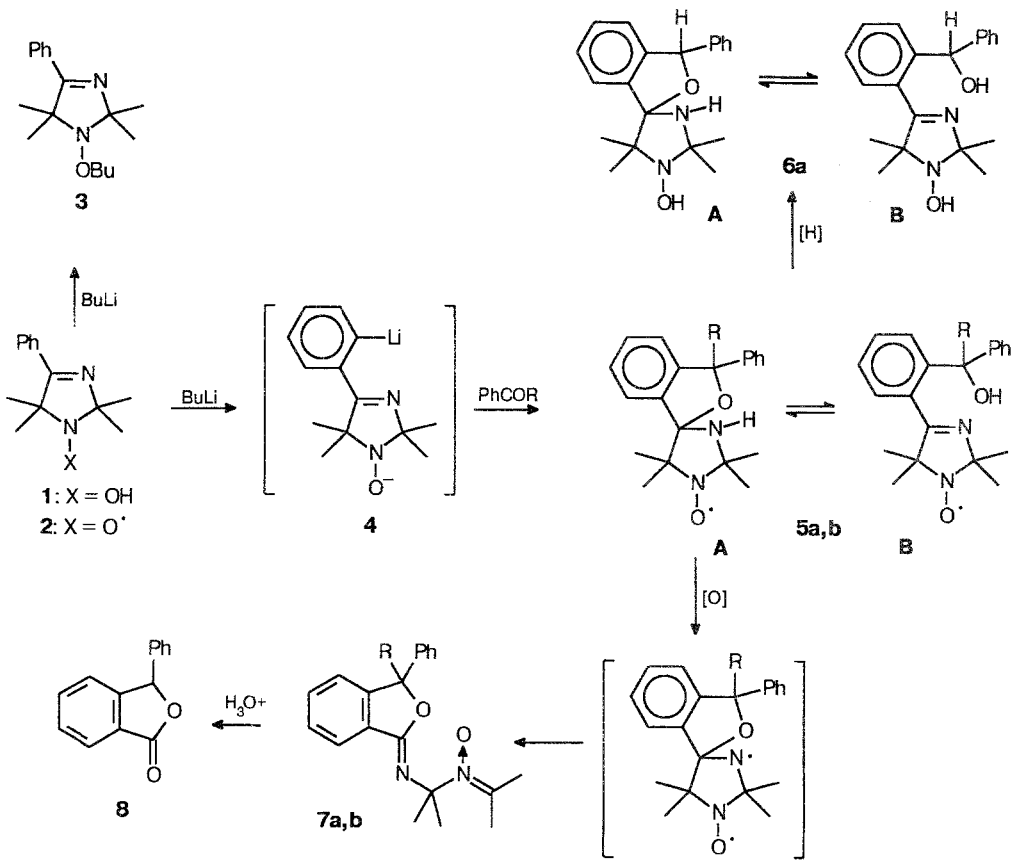
Scheme 1



group indicates that the oxidation involved the C(4) atom of imidazoline and, thus, the nitroxyl group is not oxidized to the oxammonium group, though oxidative destruction of nitroxyl radicals normally[5] begins with the oxidation of the nitroxyl group. Taking into account that this transformation of nitroxyl radicals of the 3-imidazoline series did not occur under similar conditions, one may believe that in this case the possibility of the oxidation of compounds **5** is due to the presence of spirobicyclic form **A** in the tautomeric mixture (see Scheme 1). In this connection, the scheme of the formation of compounds **7** may be represented as the oxidation of the N atom in position 3 of the ring in the spirobicyclic form to yield an aminyl radical, in which the homolytic cleavage of the C(4)—C(5) bond occurs. Further recombination of the resulting radical sites gives the reaction products. The structure suggested for compound **7a** is in agreement with the data from IR, UV, and ^1H and ^{13}C NMR spectra. In fact, the ^1H NMR spectrum displays signals for four nonequivalent methyl groups at 1.66, 1.68, 1.82, and 1.84 ppm, a singlet for the benzyl proton at 6.29 ppm and a multiplet for the aromatic protons in the region 7.0—7.9 ppm. The absorption band at 1710 cm^{-1} in the IR spectra of compounds **7** is obviously associated with the vibrations of the C=N bond of the imidate group.

Thus, oxidative destruction of the imidazoline ring that incorporates a nitroxyl group is a new atypical pathway for the decay of stable nitroxyl radicals.

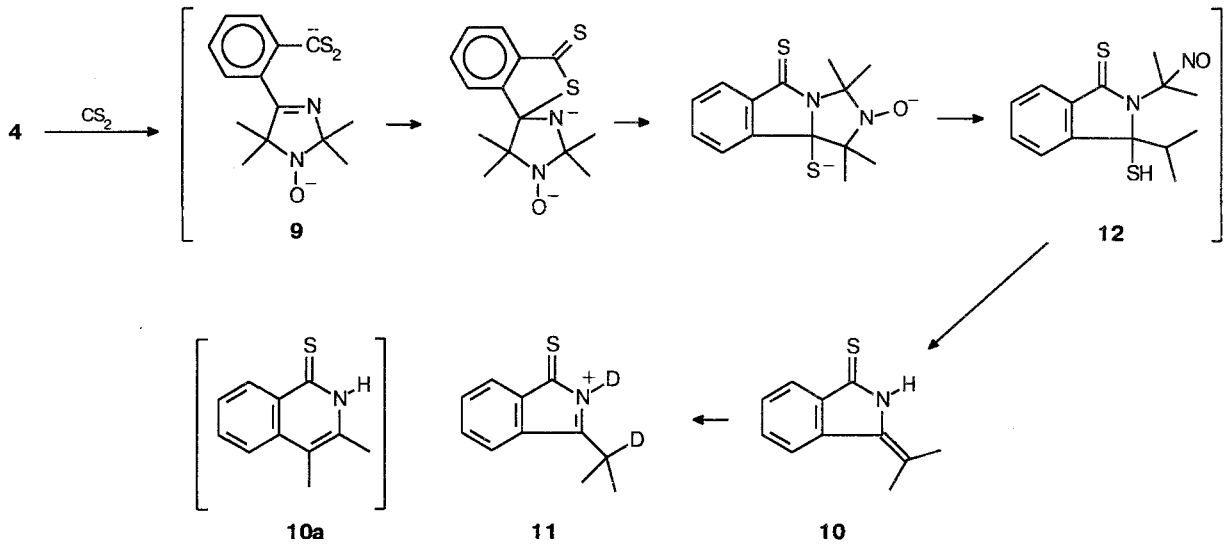
The reaction of the metallated derivative **4** with CS_2 (Scheme 2) affords compound **10** of the composition $C_{11}H_{11}NS$, according to elemental and mass spectral analyses,rather than the expected dithiocarboxylic acid **9**.

The ^1H NMR spectrum of the product exhibits singlets at 2.11 and 2.22 ppm due to the two nonequivalent methyl groups and signals for the protons of the *ortho*-disubstituted benzene ring. These data make it possible to propose two structures, **10** and **10a**, for the compound obtained. We have chosen structure **10** based on the ^1H NMR spectrum (in D_2SO_4) in which the methyl groups are equivalent due to conversion into cation **11**.

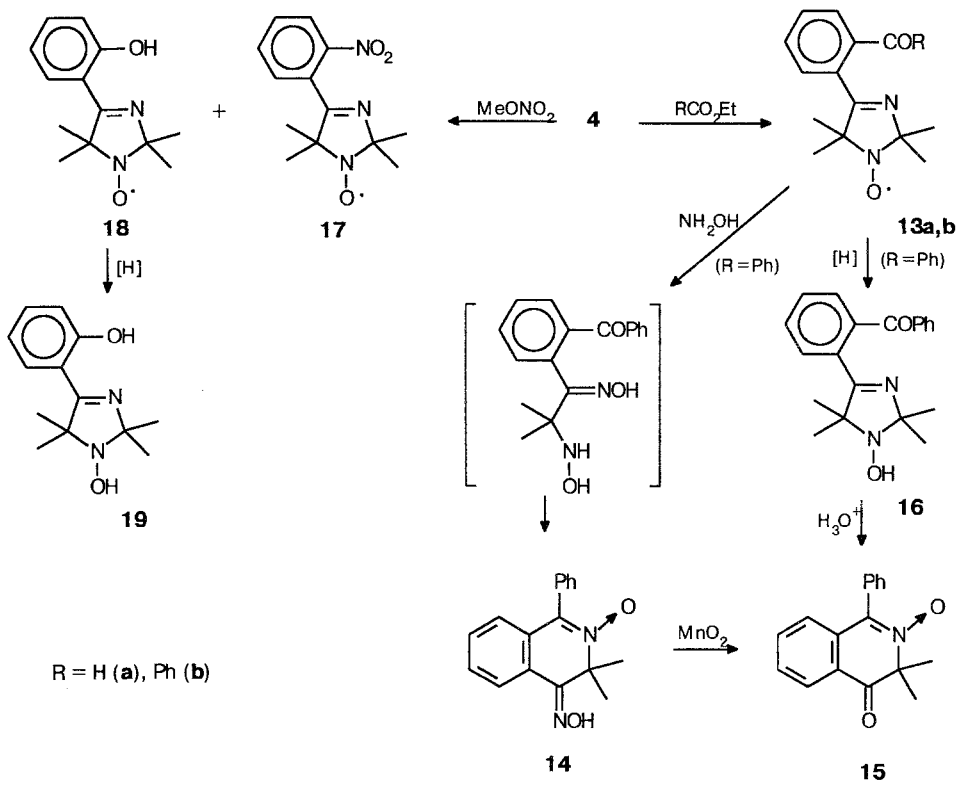
The route of the formation of compound **10** involves the addition of the dithiocarboxylate anion at the C=N bond (*cf.* Ref. 2) and the nucleophilic attack of N(3) at the thiocarbonyl group. Further opening of the imidazoline ring affords nitroso derivative **12**, whose hydrolytic cleavage yields compound **10**.

The interaction of the *ortho*-metallated derivative **4** with ethyl formate and ethyl benzoate (Scheme 3) gives *o*-acyl derivatives **13a,b**. The reaction of ketone **13b** with hydroxylamine and subsequent oxidation of the resulting diamagnetic compound **14** result in ketone **15**

Scheme 2



Scheme 3



rather than the expected paramagnetic oxime. The ^{1}H NMR spectrum of compound **14** only displays a singlet for two methyl groups at 2.01 ppm, a multiplet for the aromatic protons at 6.6—8.1 ppm, and a singlet for the proton of the oxime OH group at 11.67 ppm. The ^{13}C NMR spectrum of compound **14** shows, in the region of sp^2-hybridized carbon atoms, a signal for the nitrone-group C atom at 140.14 ppm and a signal for the oxime-group C atom at 150.41 ppm, in addition to the signals for the phenyl C atoms. Oxidation of oxime **14** with MnO_2 gives ketone **15**, which is also formed when the diamagnetic derivative **16** (see Scheme 3) prepared by the reduction of compound **13b** with zinc is kept in 10 % HCl (*cf.* Ref. 6). Based on these data the

Table 1. Characteristics of the compounds synthesized

Compound	Yield (%)	M.p.*/°C	IR (KBr), ν/cm^{-1}	UV, λ_{max}/nm (log ε)	Found / Calculated (%)			Molecular formula
					C	H	N	
3	45	Oil	1615 (C=N); 1580 (C=C)	240 (4.03)	74.3 74.5	9.2 9.5	10.0 10.2	$C_{17}H_{26}N_2O$
5a	40	128—130	1620 (C=N); 1605 (C=C); 3275 (NH); 3300—3500 (OH)	—	74.1 74.3	7.2 7.1	8.7 8.7	$C_{20}H_{23}N_2O_2$
5b	40	177—178	1605 (C=N, C=C); 3380 (NH); 3620 (OH)	—	78.5 78.2	6.4 6.8	7.0 7.0	$C_{26}H_{27}N_2O_2$
6a	90	170—172	1600 (C=N, C=C); 3350 (NH); 3580 (OH)	—	74.3 74.1	7.1 7.4	8.5 8.6	$C_{20}H_{24}N_2O_2$
7a	100	75—77	1710 (C=N)	242 (4.01), 280 (3.46)	74.2 74.5	7.0 6.8	8.6 8.7	$C_{20}H_{22}N_2O_2$
7b	100	106—107	1710 (C=N)	238 (3.95), 277 (4.09)	78.8 78.4	6.6 6.5	7.1 7.0	$C_{26}H_{26}N_2O_2$
10	30	267—269	3210 (NH)	222 (4.09), 285 (3.95), 370 (4.26)	70.0 69.8	5.8 5.8	7.4 7.4	$C_{11}H_{11}NS$**
13a	20	137—139	1620 (C=N); 1710 (C=O); 3060 (—CH=)	256 (4.42)	68.5 68.6	7.2 6.9	11.2 11.4	$C_{14}H_{17}N_2O_2$
13b	50	114—115	1560—1620 (C=C, C=N); 1675 (C=O)	250 (4.30)	74.5 74.8	6.5 6.5	8.6 8.7	$C_{20}H_{21}N_2O_2$
14	75	235—236	1540, 1590 (C=C, C=N)	273 (4.34), 345 (3.86)	72.8 72.9	5.5 5.7	10.2 10.0	$C_{17}H_{16}N_2O_2$
15	75	165—167	1520, 1590 (C=C, C=N); 1680 (C=O)	232 (4.04), 262 (4.07), 374 (3.19)	77.2 77.0	6.0 5.7	5.5 5.3	$C_{17}H_{15}NO_2$
17	30	132—133	1360, 1540 (NO_2); 1605, 1620 (C=C, C=N)	255 (4.20)	59.9 59.5	6.4 6.1	16.2 16.0	$C_{13}H_{16}N_3O_3$
18	15	84—85	2600—3100 (OH); 1560, 1595, 1615 (C=C, C=N)	253 (4.15), 322 (3.66)	67.2 67.0	7.3 7.3	12.0 12.0	$C_{13}H_{17}N_2O_2$

* Compounds **5a**, **13b**, **15**, and **17** were purified by recrystallization from a heptane—ethyl acetate mixture; **5b**, **7**, **13a**, and **18** were recrystallized from hexane; **6a** was recrystallized from aqueous ethanol; **10** was recrystallized from a CH_2Cl_2—ethyl acetate mixture, and **14** was recrystallized from ethyl acetate. ** Found/calculated: S, 16.7/16.9 %.

structures of isoquinoline derivatives were ascribed to compounds **14** and **15**.

The reaction of the metallated derivative **4** with methyl nitrate gives compounds **17** and **18** (see Scheme 3). The IR spectrum of product **17** exhibits absorption bands at 1355 and 1540 cm^{-1} due to the nitro group and bands at 1605 and 1620 cm^{-1} corresponding to the C=C and C=N bonds of the phenylimino group. The IR spectrum of compound **18** (in CCl_4) displays a broad band in the region 2600—3200 cm^{-1} associated with the vibrations of an OH group bound by a strong intramolecular hydrogen bond and bands at 1560, 1600, and 1620 cm^{-1} typical of C=C and C=N vibrations. The structure of **18** is supported by ^{1}H and ^{13}C NMR spectra of its diamagnetic analog (**19**) prepared by reducing compound **18** with hydroxylamine (see Scheme 3). The formation of phenol **18** must be due to the fact that methyl nitrate can act as an ambident electrophile: the attack of the O atom on anion **4** results in compound **18**. It should be noted that compound **18** is of interest as a paramagnetic ligand.

Experimental

IR spectra were recorded on Specord M-80 and UR-20 spectrometers in KBr pellets (at a concentration of 0.25 %) and in CCl_4 (5 %). UV spectra were obtained on a Specord UV-VIS spectrometer in ethanol. ^{1}H and ^{13}C NMR spectra were run on a Bruker AC-200 instrument in $CDCl_3$ or DMSO-d_6 (at a concentration of 5 %). Characteristics of the compounds synthesized are listed in Table 1.

1-Butoxy-2,2,5,5-tetramethyl-4-phenyl-3-imidazoline (3). A solution of 1 g (4.6 mmol) of imidazoline **2** in 5 mL of abs. ether was added dropwise under argon to a stirred solution of butyllithium prepared from 2 mL (19 mmol) of butyl bromide and 0.26 g (37 mmol) of lithium in 20 mL of abs. ether. The mixture was stirred for 30 min at 20 °C, 10 mL of water was added to it, the ethereal layer was separated, and the aqueous layer was extracted with ether. The ethereal solution was dried with $MgSO_4$ and filtered. 3 g of MnO_2 was added to the solution and the mixture was stirred for 20 min. The excess oxidant was filtered off, the solution was concentrated, and the mixture of compounds **2** and **3** was separated on a column with silica gel (elution with an 1 : 2 ether—hexane mixture) to give 0.45 g of the starting compound **2** and 0.55 g of butoxy

derivative **3**. ^{1}H NMR ($CDCl_3$), δ: 0.7—1.6 (m, 9 H, C_4H_9); 1.35 (s, 6 H, 5-Me_2); 1.41 (s, 6 H, 2-Me_2); 7.1—7.8 (m, 5 H, Ph).

4-[2-(α-Hydroxybenzyl)phenyl]-2,2,5,5-tetramethyl-3-imidazoline-1-oxyl (5a). At −60÷−70 °C under argon, 2.17 g (10 mmol) of imidazoline **1** was added portionwise to a stirred solution of butyllithium prepared from 4.3 mL (40 mmol) of butyl bromide and 0.56 g (80 mmol) of lithium in 30 mL of abs. ether. The mixture was stirred for 3 h, while the temperature was gradually increased to 0 °C and for an additional 2 h at 0±5 °C, and cooled to −40 °C. A solution of 2.5 mL (2.5 mmol) of benzaldehyde in 5 mL of abs. ether was added dropwise to the resulting solution of **4** with stirring and cooling at such a rate that the temperature of the mixture was maintained in the interval −35 to −40 °C (10—15 min). After warming the mixture to 20 °C, 20 mL of water was added to it. The organic layer was separated and the aqueous layer was extracted with chloroform (3×20 mL). The combined extract was dried with $MgSO_4$ and filtered. 5 g of MnO_2 was added to the solution and the mixture was stirred for 15 min at 20 °C. The excess oxidant was filtered off, the solution was concentrated, and the residue was diluted with 20 mL of hexane. Compound **5a**, which precipitated in the cold, was filtered off.

Compound **5b** was prepared from imidazoline **1** and benzophenone under similar conditions. When the duration of oxidation was increased to 3 h products **7a,b** formed rather than compounds **5**. ^{1}H NMR spectrum of compound **7a** ($CDCl_3$), δ: 1.65 (s, 3 H); 1.68 (s, 3 H, $N_2C(CH_3)_2$); 1.82 (s, 3 H); 1.84 (s, 3 H, $=C(CH_3)_2$); 6.29 (s, 1 H, —CHO—); 7.0—7.9 (m, 9 H, C_6H_4 and C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 15.58, 21.79 ($=C(\underline{C}H_3)_2$); 24.67, 25.16 ($N_2C(\underline{C}H_3)_2$); 84.88 (—CHO—); 91.53 (N—C—N); 121.34—131.03, 145.44 (C_6H_4, C_6H_5); 138.30 (C=N→O); 153.40 (O—C=N).

Hydrolysis of **7a** to phthalide **8** was carried out by keeping a solution of 0.2 g of compound **7a** in a mixture of 5 mL of methanol and 5 mL of 10 % HCl for 3 h at 20 °C. After neutralizing the mixture with a 10 % aqueous solution of NaOH the precipitate of compound **8** was filtered off; yield 100 %. Compound **8** was characterized by IR, UV, and ^{1}H NMR spectra, m.p. 116—117 °C (*cf.* Ref. 7).

The formyl and benzoyl derivatives **13a,b** were prepared by the reactions of compound **4** with ethyl formate and ethyl benzoate, respectively, under similar conditions. The reaction of **4** with CS_2 afforded isoindole **10**. Compound **10** precipitated after treatment of the reaction mixture with water. It was filtered off, washed with water and with ether, and dried. ^{1}H NMR (DMSO-d_6—CD_3OD (1 : 1)), δ: 2.11 (s, 3 H); 2.21 (s, 3 H); 7.44 (m, 1 H, *m*-H); 7.60 (m, 1 H, *m*-H); 7.88 (m, 2 H, *o*-H). ^{1}H NMR (D_2SO_4), δ: 2.45 (s, 6 H, $(CH_3)_2$); 7.8 (m, 4 H, C_6H_4).

4-(2-Nitrophenyl)-2,2,5,5-tetramethyl-3-imidazoline-1-oxyl (17) and 4-(2-hydroxyphenyl)-2,2,5,5-tetramethyl-3-imidazoline-1-oxyl (18) were prepared by treating compound **4** with methyl nitrate under similar conditions. Methyl nitrate was added to a solution of the metallated derivative **4** in one portion at −60 °C. Compounds **17** and **18** were separated by chromatography on a column with silica gel (ether—hexane (1 : 2) as the eluent). The first colored zone contained compound **18** and the second zone contained radical **2** (0.4 g). Then derivative **17** was isolated by elution with ether.

1-Hydroxy-4-[2-(α-hydroxybenzyl)phenyl]-2,2,5,5-tetramethyl-3-imidazoline (6a). A solution of 0.6 g of compound **5a** and 1 mL of hydrazine hydrate in 10 mL of ethanol was kept for 24 h at 20 °C, and the precipitate of compound **6** was filtered off. Concentration of the filtrate, dilution of the residue with water, and filtration afforded an additional amount of compound **6**. ^{1}H NMR (DMSO-d_6) δ: 0.39, 0.45, 0.52, 0.58, 0.64, 0.67 and 0.71 (all s, 12 H, 2,5-$(CH_3)_2$); 3.19 (br.s, 1 H, NH); 5.21 and 5.24 (both s, 1 H, $C\underline{H}C_6H_5$); 6.4—6.8 (m, 9 H, C_6H_4, C_6H_5).

Reduction of phenol **18** under similar conditions gave 1-hydroxy derivative **19**. ^{1}H NMR ($CDCl_3$), δ: 1.50 (s, 6 H, 5-$(CH_3)_2$); 1.62 (s, 6 H, 2-$(CH_3)_2$); 5.97 (br.s, 1 H, NOH); 6.64 (t, J = 7 Hz, 1 H, H(5)); 7.02 (d, J = 7 Hz, 1 H, H(3)); 7.32 (t, J = 7 Hz, 1 H, H(4)); 7.61 (d, J = 7 Hz, 1 H, H(6), C_6H_5); 13.80 (s, 1 H, OH). ^{13}C NMR ($CDCl_3$), δ: 24.69, 26.36 (2,5-$(CH_3)_2$); 71.61 (C(5)); 87.90 (C(2)); 114.00, 117.65, 117.96, 132.17, 161.78 (C_6H_5); 174.91 (C(4)).

4-Hydroxyimino-3,3-dimethyl-1-phenyl-3,4-dihydroisoquinoline 2-oxide (14). A solution of 0.45 g (8 mmol) of sodium methoxide in 5 mL of methanol was added to a solution of 0.98 g (14 mmol) of hydroxylamine hydrochloride in 10 mL of methanol. The precipitate of NaCl was filtered off, and 0.64 g (2 mmol) of compound **13b** was dissolved in the filtrate. The solution was kept for 12 h at 20 °C and concentrated. The residue was diluted with 10 mL of water, and the precipitate of oxime **14** was filtered off, washed with water, and dried. ^{1}H NMR (DMSO-d_6), δ: 2.01 (s, 6 H, 3-$(CH_3)_2$); 6.4—8.1 (m, 9 H, C_6H_5, C_6H_4); 11.67 (s, 1 H, OH). ^{13}C NMR (DMSO-d_6), δ: 22.15 (3-$(CH_3)_2$); 71.80 (C(3)); 122.75—132.02 (C_6H_5, C_6H_4); 140.14 (C(1)); 150.41 (C(4)).

4-Oxo-3,3-dimethyl-1-phenyl-3,4-dihydroisoquinoline 2-oxide (15). ***A.*** A solution of 1 g of compound **13b** in 20 mL of methanol was stirred with 5 g of zinc powder and 0.2 g of NH_4Cl for 20 min at 20 °C, the excess reducing agent was filtered off, and the solution was concentrated. The resulting 1-hydroxy derivative **16** was dissolved in a mixture of 10 mL of methanol and 10 mL of 10 % HCl and the solution was kept for 14 h at 20 °C. The precipitate of compound **15** was filtered off, washed with water, and dried; yield 75 %.

B. A solution of 0.2 g of oxime **14** in 10 mL of $CHCl_3$ was stirred with 2 g of MnO_2 for ~48 h at 20 °C. The excess oxidant was filtered off and the solution was concentrated. Compound **15** was purified by chromatography on a column with silica gel using $CHCl_3$ as the eluent. The yield of **15** was 90 %.

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