Synthesis of new functionalized 5,5-dimethyl-1-pyrroline 1-oxides and their investigation as spin traps

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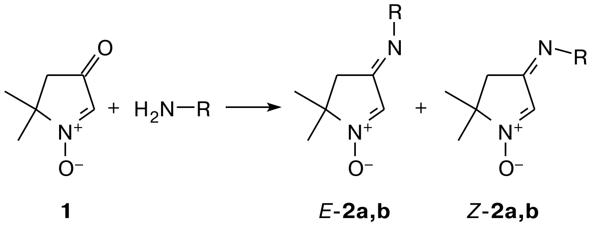
The reactions of 5,5-dimethyl-3-oxo-1-pyrroline 1-oxide (3-oxo-DMPO, **1**) with NH_2OH and N_2H_4 afforded oxime (**2a**) and hydrazone (**2b**), respectively. The reaction products were studied as spin traps for the short-lived radicals $HO^•$, $Ph^•$, $PhCO_2^•$, $NC(Me_2)C^•$, and $NC(Me_2)CO^•$. The nitroxides generated in the reactions of the above-mentioned short-lived radicals with nitrones **1** and **2a**,**b** were characterized by ESR spectroscopy. Of these nitrones, oxime **2a** is the most effective radical trap.

Key words: nitrones, spin traps, nitroxides, ESR spectroscopy, 5,5-dimethyl-1-pyrroline 1-oxide.

Spin traps, most of which are either heterocyclic or acyclic nitrones, are widely used for the detection of short-lived radicals in chemical and biological systems.[1,2] The spin trapping method is based on the addition of active radicals to nitrones to form nitroxides quite stable in solution and the detection of the latter by ESR spectroscopy. An advantage of cyclic nitrones, such as 5,5-dimethyl-1-pyrroline 1-oxide (DMPO) and its analogs, is that the ESR spectra of the nitroxides generated from these nitrones essentially depend on the nature of the added active radicals and, as a consequence, the ESR spectra are more informative.[3—5] Almost all known analogs of DMPO are oils, due to which they are difficult to purify and use. Recently,[6,7] we have developed the new method for the synthesis of 5,5-dimethyl-3-oxo-1-pyrroline 1-oxide (**1**), whose carbonyl group can be used for the preparation of derivatives. In the present study, we synthesized crystalline derivatives of nitrone **1**, *viz.*, oxime (**2a**) and hydrazone (**2b**) (Scheme 1), which can easily be purified. These compounds were studied as spin traps. Since these nitrones are antioxidants, they are of interest as biologically active compounds (see, for example, Ref. 8).

Scheme 1



R = OH (**a**), NH_2 (**b**)

Oxime **2a** was obtained in ~90% yield by the reaction of nitrone **1** with hydroxylamine. According to the HPLC data, oxime **2** exists as a mixture of *E* and *Z* isomers (67 : 33). Oxime *E*-**2a** with m.p. 149—150 °C was isolated by the triple crystallization from benzene. Oxime *Z*-**2a** was obtained by the preparative chromatography on silica gel and has m.p. 183—184 °C after the recrystallization from benzene. The structure of oxime *E*-**2a** was determined by X-ray diffraction and confirmed by IR, UV, and NMR spectroscopy and mass spectrometry. The structure of oxime *Z*-**2a** was determined by IR and UV spectroscopy and mass spectrometry and confirmed by the isomerization to oxime *E*-**2a**.

The structure of oxime *E*-**2a** is shown in Fig. 1. The bond lengths and bond angles in *E*-**2a** are given in Tables 1 and 2, respectively. The pyrroline ring of oxime *E*-**2a** is almost planar. The C(1) atom deviates from the C(2)C(3)N(1)C(4) plane toward the C(5) atom by only −0.051(2) Å. The oxygen atom O(1) of the nitrone group (−0.027(2) Å) is also almost in the plane of the ring, whereas the N(2) and O(2) atoms of the oxime group deviate from this plane by +0.171(2) and +0.194(2) Å, respectively. The N(1)—C(3) and N(1)—O(1) bond lengths are 1.309(4) and 1.285(3) Å, respectively, and are in the range typical[9] of cyclic nitrones. The C(2)—C(3) bond (1.429(4) Å) is shortened due to the conjugation of the oxime group with the nitrone moiety. The oxygen atom O(2) of the oxime group is in the *trans* position with respect to the C(3) atom of the pyrroline ring. Consequently, according to the *E*/*Z* nomenclature of oximes, the isomer with m.p.

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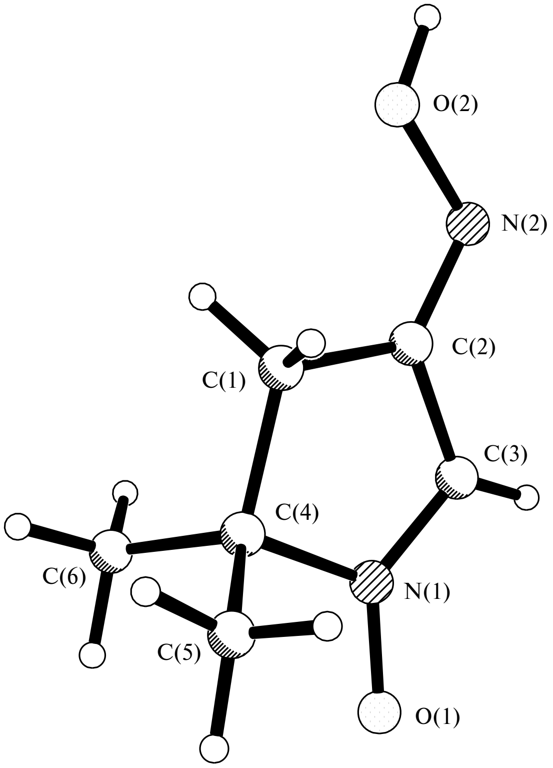


Fig. 1. Molecular structure of oxime *E*-**2a**.

149—150 °C is the *E* isomer. In the crystal structure, molecules *E*-**2a** are linked by the short O(2)—H...O(1) hydrogen bonds to form infinite chains. The O(2)—H(2) and H(2)—O(1) bond lengths are 0.82 and 1.84 Å, respectively.

Table 1. Bond lengths (*d*) in oxime *E*-**2a**

Bond	*d*/Å	Bond	*d*/Å
O(1)—N(1)	1.285(3)	C(2)—C(3)	1.429(4)
O(2)—N(2)	1.406(3)	C(2)—C(1)	1.491(4)
N(1)—C(3)	1.309(4)	C(4)—C(6)	1.507(5)
N(1)—C(4)	1.517(4)	C(4)—C(5)	1.520(5)
N(2)—C(2)	1.283(4)	C(4)—C(1)	1.538(4)

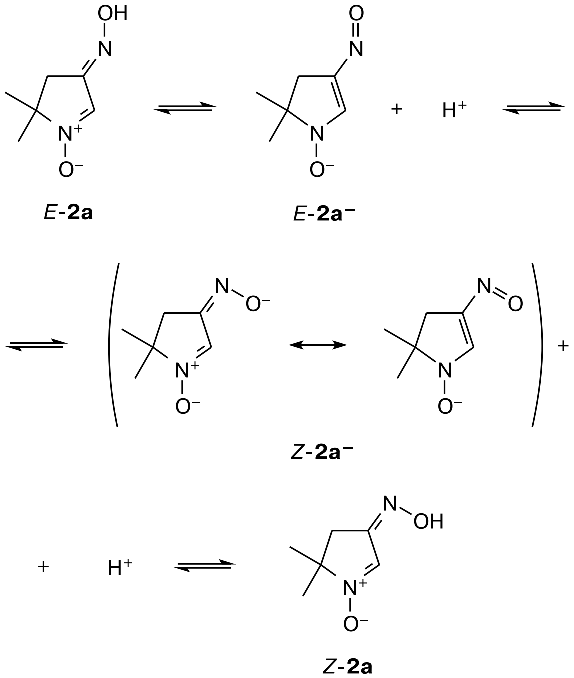
Table 2. Bond angles (ω) in oxime *E*-**2a**

Angle	ω/deg	Angle	ω/deg
O(1)—N(1)—C(3)	126.4(2)	N(1)—C(3)—C(2)	109.9(3)
O(1)—N(1)—C(4)	119.8(2)	C(6)—C(4)—N(1)	107.3(3)
C(3)—N(1)—C(4)	113.6(2)	C(6)—C(4)—C(5)	111.7(3)
C(2)—N(2)—O(2)	109.1(2)	N(1)—C(4)—C(5)	109.6(2)
N(2)—C(2)—C(3)	123.3(3)	C(6)—C(4)—C(1)	113.0(3)
N(2)—C(2)—C(1)	127.7(3)	N(1)—C(4)—C(1)	101.7(2)
C(3)—C(2)—C(1)	109.0(2)	C(5)—C(4)—C(1)	112.9(3)
C(2)—C(1)—C(4)	105.1(2)		

The UV spectrum of oxime *E*-**2a** substantially differs from the spectrum of *Z*-**2a**. The spectrum of the *E* isomer in water shows one intense band at λ_{max} = 272 nm (ε = 21000 L mol^{-1} cm^{-1}) assigned to the absorption of the nitrone group. The conjugation of the nitrone group with the oxime moiety results in the shift of the absorption maximum to longer wavelengths by 38 nm and an increase in its intensity by a factor of ~3 compared to the absorption band of DMPO.[10] In the spectrum of the *Z* isomer, the maximum of this absorption band is observed at 282 nm (ε = 13900 L mol^{-1} cm^{-1}).

In an alkaline medium, the UV spectra of oximes *E*- and *Z*-**2a** differ from the above-described spectra due to the ionization of the oxime group. At [OH$^-$] ≥ 0.9 mol L^{-1}, the equilibrium is completely shifted to anions *E*- and *Z*-**2a**$^-$ (Scheme 2).

Scheme 2



The UV spectrum of anion *E*-**2a**$^-$ shows two bands at λ_{max} = 303 (ε = 22600 L mol^{-1} cm^{-1}) and 250 nm (ε = 3300 L mol^{-1} cm^{-1}). The UV spectrum of anion *Z*-**2a**$^-$ also has two bands at λ_{max} = 326 (ε = 11600 L mol^{-1} cm^{-1}) and 251 nm (ε = 8300 L mol^{-1} cm^{-1}). The UV spectrum of anion *Z*-**2a**$^-$ is gradually transformed into the spectrum of anion *E*-**2a**$^-$ with a half-life of 3.7 days at 20 °C.

Hydrazone **2b** was formed in ~90% yield by the reaction of hydrazine with nitrone **1**. It is characterized by the distinct m.p. 144—145 °C and is one of the possible *E*/*Z* isomers. The structure of **2b** was confirmed by IR, UV, and NMR spectroscopy and mass spectrometry. The UV spectrum of hydrazone **2b** in water consists of one intense band at λ_{max} = 295 nm (ε = 17000 L mol^{-1} cm^{-1}). The IR spectrum of hydrazone **2b** shows absorption bands of the nitrone (1545 cm^{-1}) and methine (3060 cm^{-1}) groups, whose frequencies are similar to those of the corresponding bands of nitrones **1** and **2a**. In addition, the spectrum of hydrazone **2b** has stretching (3330 and 3355 cm^{-1}) and bending (1613 cm^{-1}) bands of the NH_2 group and a band at 1673 cm^{-1} (assigned to the $C=NNH_2$ double bond). The ^1H NMR spectrum of hydrazone **2b** has singlets at δ 1.34, 2.68, 7.27, and 6.45 of the methyl, methylene, methine, and amino groups, respectively.

We studied nitrones **1** and **2a,b** as traps for the $HO^{\bullet}$ radical and the radicals generated by the thermal decomposition of benzoyl peroxide (BzO_2Bz) and azoisobutyronitrile (AIBN). The relative efficiencies of nitrones **1** and **2a,b** and DMPO as spin traps were estimated based on their reactions with the $HO^{\bullet}$ radical. The intensities of the ESR signals of the resulting adducts indicate that oxime **2a** and DMPO are the most effective traps for the $HO^{\bullet}$ radical.

The $HO^{\bullet}$ radicals generated in the reaction of H_2O_2 with $FeSO_4$ add to oxime **2a** to form nitroxide **3**. The ESR spectrum of the latter consists of four lines with the splitting constants a_N = 1.54 and a_H = 1.40 mT (Fig. 2).

The spectrum of radical **3** is similar to the spectrum of the adduct of DMPO with the $HO^{\bullet}$ radical, where a_N = = a_H = 1.501 mT.[3] The intensity of the spectrum of radical **3** rapidly decreases due to the decay of **3** with a half-life of ~3 min. Presumably, radical **3** is transformed into disproportionation products, *viz.*, cyclic hydroxamic acid **4** and the starting oxime **2a** (Scheme 3). The formation of acid **4** is evidenced by the lilac color of the reaction solution characteristic[11] of complexes of hydroxamic acids with Fe^{3+} ions. The reaction of oxime **2a** with $HO^{\bullet}$ affords radical **3** along with the secondary nitroxide characterized by the triplet ESR spectrum and a_N = 1.67 mT (see Fig. 2).

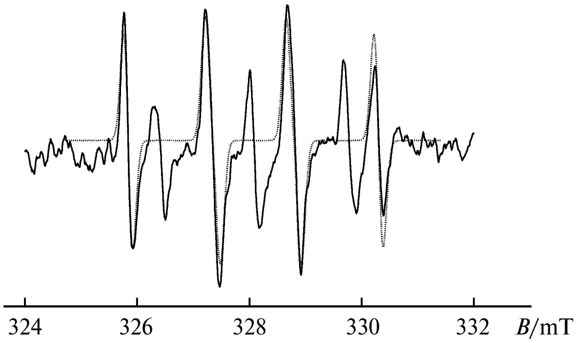
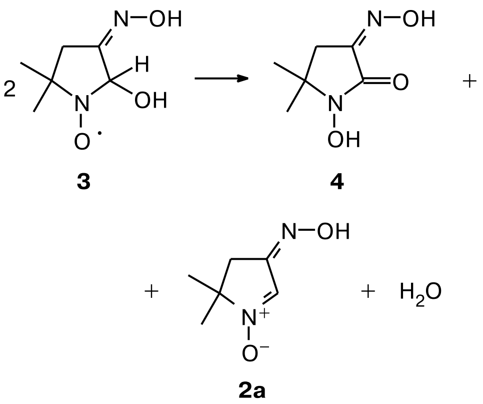


Fig. 2. ESR spectrum of the nitroxides, which were formed in the reaction of nitrone **2a** with the $HO^{\bullet}$ radicals generated by the reaction of $FeSO_4$ with H_2O_2 in a phosphate buffer (pH 6.8) at [**2a**] = 0.05 mol L^{-1}, [H_2O_2] = $1 \cdot 10^{-3}$ mol L^{-1}, [$FeSO_4$] = = $1 \cdot 10^{-3}$ mol L^{-1}, and 25 °C (solid line), and the simulation of the spectrum of nitroxide **6** with a_N = 1.54 mT and a_H = 1.40 mT (dashed line).

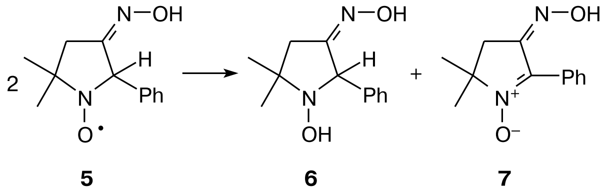
Scheme 3



Benzoyl peroxide is thermally decomposed to benzoyloxyl and phenyl radicals, which can add to oxime **2a** to form two nitroxides. The heating of a solution of BzO_2Bz and oxime **2a** in benzene at 70 °C over a short period of time affords one nitroxide as the major product, whose ESR spectrum consists of six lines with the splitting constants a_N = 1.43 and a_H = 1.80 mT. The spectrum with these constants is similar to the spectrum of the adduct of DMPO with the phenyl radical, where a_N = 1.378 and a_H = 1.921 mT, and differs from the spectrum of the adduct of DMPO with benzoyloxyl radical, where a_N = 1.224 and a_H = 0.963 mT.[12] Consequently, the sextet spectrum belongs to radical **5**.

At 20 °C, radical **5** decays with a half-life of ~6 min, apparently, as a result of the disproportionation to hydroxypyrrolidine **6** and nitrone **7** (Scheme 4).

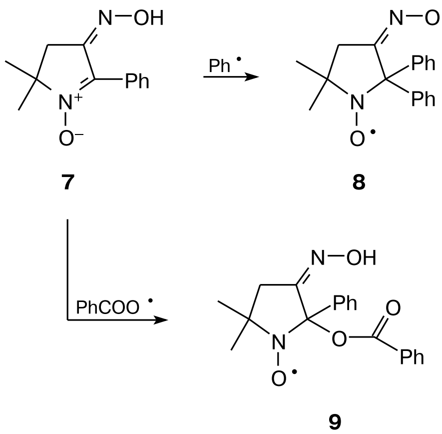
Scheme 4



The heating of a solution of BzO_2Bz and oxime **2a** over a long period of time (>5 min) affords radical **5** along with two other nitroxides, whose triplet spectra have the splitting constants a_N = 1.59 and 1.39 mT. Based on the a_N values, these can be radicals **8** and **9** generated as a result of the addition of the phenyl and benzoyloxyl radicals, respectively, to nitrone **7** (Scheme 5).

The thermal decomposition of AIBN under argon gives the cyanoisopropyl radicals $NC(Me)_2C^{\bullet}$, which react with oxime **2a** to form the corresponding nitroxide at a very low concentration. This makes it impossible to reliably characterize the latter by ESR spectroscopy. Oxime **2a** is a more effective trap for radicals generated by the thermal de-

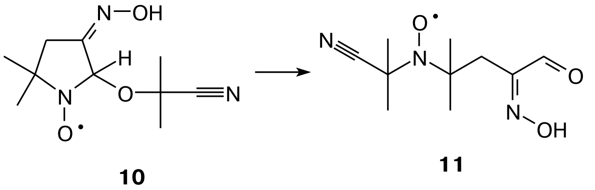
Scheme 5



composition of AIBN in air. In this case, the nitroxides characterized by sextet and triplet ESR spectra are formed. The sextet with the splitting constants a_N = 1.26 mT and a_H = 1.00 mT corresponds to radical **10**, which is the addition product of the $NC(Me)_2CO^•$ radical to oxime **2a**. The characteristics of this addition product are similar to those of the analogous adduct of DMPO (a_N = = 1.266 mT and a_H = 0.837 mT).[3,12]

Radical **10** is transformed into diamagnetic products according to the second-order law with a half-life of 3.7 min at 20 °C. Apparently, the triplet spectrum with a_N = 1.47 mT belongs to acyclic nitroxide **11** (Scheme 6), which is formed as a result of the rearrangement postulated previously[12] for the analogous adduct of DMPO.

Scheme 6



The product of the reaction of oxime **2a** with the peroxyl radical $NC(Me)_2CO_2^•$, like the analogous adduct of DMPO, was not detected. This product is unstable and, apparently, decomposes to hydroxamic acid **4** and the $NC(Me)_2CO^•$ radical, which is trapped by oxime **2a** to form nitroxide **10**.[3,12]

Therefore, we synthesized nitrones **1** and **2a,b** and found that oxime **2a** is a new promising spin trap. The ability of nitrone **2a** to trap active radicals and the ESR characteristics of the resulting adducts are similar to those of DMPO. In addition, oxime **2a** is a crystalline compound, which can easily be purified by the recrystallization. The functional carbonyl, oxime, and hydrazone groups of nitrones **1** and **2a,b** can be used for the synthesis of new traps (analogs of DMPO).

Experimental

5,5-Dimethyl-3-oxo-1-pyrroline 1-oxide (**1**) was synthesized from 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl according to a procedure described previously.[6] Hydroxylamine hydrochloride was recrystallized from methanol; DMPO and hydrazine hydrate (Aldrich) were used without additional purification.

The IR spectra were recorded on a Specord 75-IR spectrometer, the UV spectra were measured on a Specord UV—Vis spectrometer, and the ^1H NMR spectra were recorded on a DRX-500 spectrometer (500 MHz). The mass spectra were obtained on a Clarus-500 spectrometer with the ionization energy of 70 eV. The ESR spectra were measured at ~20 °C on a SE/X 2544 instrument at 2 mW microwave power and a modulation amplitude of 0.32 mT. The spectra of the nitroxides generated by the reactions of nitrones with active radicals were simulated with the use of the WINEPR-SimFonia program. The chromatographic analysis was carried out on a Milikhrom liquid chromatograph equipped with a 2×64 mm column packed with Separon C18 or Silasorb-600. The preparative separation was carried out on an HPP-5001 chromatograph equipped with a 10×250 mm column packed with Silasorb-600 (7 μm). The GLC analysis was performed on a Clarus-500 GLC-mass spectrometer equipped with a 30 m capillary column using diphenylpolysiloxane/dimethylpolysiloxane (1 : 19). The melting points were measured on a PHMK melting-point apparatus.

Single crystals of oxime *E*-**2a** were grown by the crystallization from benzene. The X-ray diffraction data were collected on a P-4 automated four-circle diffractometer (Bruker) (graphite monochromator, λ(Mo-Kα) = 0.71073 Å, 293 K, $\theta/2\theta$-scanning technique) from a single crystal with dimensions 0.4×0.3×0.15 mm. The unit cell parameters were determined and refined based on 35 reflections in the angle range θ = 10—15°. The experimental data were measured in the angle range θ = 2.46—24.99°. The total number of independent reflections was 1103; the number of reflections with $I > 2\sigma(I)$ was 757.

Principal crystallographic parameters are a = 5.970(1) Å, b = 7.872(1) Å, c = 8.012(3) Å, α = 77.020(10)°, β = 77.300(10)°, γ = 88.29(2)°, V = 357.86(15) Å^3, Z = 2, d_{calc} = 1.319 g cm^{-3}, space group P-1, triclinic centrosymmetric. The structure was solved by direct methods. The atomic positions and thermal parameters of nonhydrogen atoms were refined isotropically and then with anisotropic displacement parameters by the full-matrix least-squares method. The hydrogen atoms were located in difference Fourier maps and refined using the riding model. All calculations were carried out with the use of the SHELXTL program package.[13] The final R factors were as follows: R_1 = = 0.0551 based on 757 reflections with $I > 2\sigma(I)$ and R_1 = 0.0915 based on all 1103 reflections; GOOF = 1.001.

3-Hydroxyimino-5,5-dimethyl-1-pyrroline 1-oxide (2a). Sodium carbonate (509 mg, 4.8 mmol) was slowly added with stirring to a solution of pyrroline oxide **1** (763 mg, 6 mmol) and hydroxylamine hydrochloride (625 mg, 9 mmol) in water (6 mL). Then the reaction mixture was heated at 80 °C for ~1 h until nitrone **1** was completely consumed. After cooling, the reaction mixture was extracted with ethyl acetate (4×5 mL). The extract was dried with Na_2SO_4 and concentrated *in vacuo*. Oxime **2a** was obtained in a yield of 759 mg (89%) as a mixture of isomers *E*-**2a** (67%) and *Z*-**2a** (33%) (HPLC and TLC data). The triple recrystallization of the mixture of oximes **2a** from benzene afforded isomer *E*-**2a**, m.p. 149—150 °C. Found (%): C, 50.51;

H, 7.16; N, 19.90. $C_6H_{10}N_2O_2$. Calculated (%): C, 50.69; H, 7.09; N, 19.71. M = 142.16. MS (EI, 70 eV), m/z (I_{rel} (%)): 142 $[M]^+$ (65), 127 $[M - Me]^+$ (16), 126 $[M - O]^+$ (3), 111 $[M - HNO]^+$ (11), 94 (24), 84 (12), 80 (13), 59 (100). ^1H NMR (DMSO-d_6), δ: 1.34 (s, 6 H, 2 Me); 2.85 (s, 2 H, CH_2); 7.45 (s, 1 H, CH); 11.34 (s, 1 H, OH). IR ($CHCl_3$), ν/cm^{-1} (ε/L mol^{-1} cm^{-1}): 970 (190) [N—OH]; 1545 (560) [C=N—O]; 1635 (4) [C=NOH]; 3116 [=C—H]; 3206 [O—H bound]; 3566 [O—H free]. UV, λ_{max}/nm (ε/L mol^{-1} cm^{-1}) in MeCN: 277 (22600); in H_2O: 272 (21000); in 0.88 M NaOH: 303 (22600), 250 (3300).

Oxime Z-**2a** was isolated by preparative chromatography of a mixture of the isomers of oxime **2a** on a 10×250 mm Silasorb-600 column using the Et_2O—MeOH system (97 : 3) as the eluent. The retention volumes for Z-**2a** and E-**2a** were 33 and 42 mL, respectively. Oxime Z-**2a** was crystallized from benzene as colorless plates, m.p. 183—184 °C. MS (EI, 70 eV), m/z (I_{rel} (%)): 142 $[M]^+$ (73), 127 $[M - Me]^+$ (22), 126 $[M - O]^+$ (5), 111 $[M - HNO]^+$ (14), 94 (38), 84 (15), 80 (20), 59 (100). IR ($CHCl_3$), ν/cm^{-1} (ε/L mol^{-1} cm^{-1}): 953 (170) [N—OH]; 1540 (760) [C=N—O]; 1650 (5) [C=NOH]; 3131 [=C—H]; 3256 [O—H bound]; 3576 [O—H free]. UV, λ_{max}/nm (ε/L mol^{-1} cm^{-1}) in MeCN: 286 (14300), 260 sh (8900); in H_2O: 282 (13900), 260 sh (10300); in 0.88 M NaOH: 326 (11600), 251 (8300).

3-Hydrazono-5,5-dimethyl-1-pyrroline 1-oxide (2b). Nitrone **1** (127 mg, 1 mmol) and acetic acid (4 mg) were added to a solution of hydrazine hydrate (60 mg, 1.2 mmol) in a 2 : 1 ethanol—chloroform mixture (9 mL). The reaction solution was kept at 25—30 °C for 5 days. Then the mixture was refluxed for 4 h under argon. The solution was concentrated *in vacuo*, the residue was triturated with diethyl ether, and the solid product was filtered off, washed with diethyl ether, and dried. The yield of hydrazone **2b** was 127 mg (90%), colorless needles (from benzene), m.p. 144—145 °C. Found (%): C, 51.17; H, 7.67; N, 29.63. $C_6H_{11}N_3O$. Calculated (%): C, 51.05; H, 7.85; N, 29.77. M = 141.17. MS (EI, 70 eV), m/z (I_{rel} (%)): 141 $[M]^+$ (39), 126 $[M - Me]^+$ (2), 110 $[M - HNO]^+$ (2), 108 $[M - NH_2OH]^+$ (2), 85 (3), 83 (3), 82 (7), 81 (12), 80 (12), 68 (13), 58 (28), 56 (15), 55 (100). ^1H NMR (DMSO-d_6), δ: 1.34 (s, 6 H, 2 Me); 2.68 (s, 2 H, CH_2); 6.45 (s, 2 H, NH_2); 7.23 (s, 1 H, CH). IR (Nujol mulls), ν/cm^{-1}: 1545 (C=N—O); 1613 (NH_2); 1673 (C=N); 3060 (=C—H); 3330, 3355 (NH_2). UV, λ_{max}/nm (ε/L mol^{-1} cm^{-1}) in H_2O: 295 (17000); in ethanol: 305 (17500).

Reactions of nitrones 1 and 2 with Fenton's reagent. The reactions were carried out with the use of solutions with the following concentrations (mol L^{-1}): (a) $[FeSO_4 \cdot 7H_2O] = 2 \cdot 10^{-3}$ in water, (b) [nitrone] = 0.1 and $[H_2O_2] = 2 \cdot 10^{-3}$ in a phosphate buffer (pH 7). Aliquots of the solutions were mixed, the reaction solution was rapidly transferred to a quartz tube with an inner diameter of 1 mm, and the ESR spectra of the nitroxides that formed were immediately recorded.

Reactions of nitrones 1 and 2 with radicals generated by the thermal decomposition of benzoyl peroxide. The reactions were carried out in thin-walled glass tubes 4.0—4.5 mm in diameter. Solutions of nitrone and benzoyl peroxide (~0.02 mmol each) in benzene (0.4 mL) were placed in a tube and twice degassed at 10^{-2} Torr. The tube was sealed at 10^{-2} Torr, heated at 70 °C during a specified time, and rapidly cooled. The ESR spectra of the resulting nitroxides were immediately recorded.

Reactions of nitrones 1 and 2 with radicals generated by the thermal decomposition of azoisobutyronitrile (AIBN). The reactions were carried out in the absence of oxygen analogously to that described above. To trap the radicals, which were generated by the thermal decomposition of AIBN in air, the tube was heated at 60 or 70 °C for 1—2 min. Then the tube was rapidly cooled, and the ESR spectra of the nitroxides were recorded with purging of the solutions with argon.

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