A Study of the Favorskii Rearrangement with 3-Bromo-4-oxo-2,2,6,6-tetramethylpiperidin-1-oxyl

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Received January 4, 1995[⊗]

Favorskii rearrangement reactions of the title compound with sodium hydroxide, sodium ethoxide, ammonia, several aliphatic amines, and ethyl sodiomalonate resulting in pyrrolidine nitroxyl radicals are described.

Introduction

Organic nitroxyl (aminoxyl, "nitroxide") radicals have been known since the beginning of this century, and during the next half century, several nitroxyl radicals containing aliphatic, aromatic, and heterocyclic moieties have been prepared. Unfortunately, at that time, the misnomer nitroxide, implying an anionic species, was inadvertently introduced which, to date, still lingers on in the literature and often causes confusion. During that period, this esoteric class of compounds received, in general, little attention and no practical application. Perhaps the major reason for this neglect resides in the fact that the nitroxyl radicals discovered at that time were not amenable to facile derivations and that, during most of that period, no convenient, commercial instrumentation was available for "tracking" these species. This situation rapidly changed by the end of the 1950s and early 1960s when new classes of stable heteroalicyclic nitroxyl radicals with piperidine, pyrroline, and pyrrolidine ring systems were discovered and their chemistries intensely explored. These new, fairly stable nitroxyl radicals, suitably functionalized, could undergo a variety of reactions, often without affecting the nitroxyl group. These properties together with their revealing EPR spectroscopy made this class of compounds ideal "reporter" moieties for labeling of various, mainly organic, compounds, particularly those of biological interest. This technique of "spin labeling" and the related "spin trapping" extensively using the EPR spectroscopy became an indispensable tool in diagnostic and mechanistic investigations of biological systems, and as a consequence, a huge literature has been generated over the years.

The chronological developments of the nitroxyl chemistry until about the end of the 1960s were reviewed[1–4] on several occasions. Over the years, nitroxyl radicals and their diamagnetic analogs have also been extensively investigated in medicinal chemistry; these are only a few of the areas: antiarrhythmic agents,[5–7] contrast agents for NMR imaging (MRI),[8–11] and the design of anticancer drugs.[12] The overwhelming number of publications covering all of these areas during the past 30 years cannot be fairly reviewed in the present study, and only a small number of specific, and clearly, often arbitrarily chosen references pertaining to the present topic have been selected.

The most widely used nitroxyls have been derived from the piperidine, pyrroline, and pyrrolidine rings. While the piperidine derivatives can be easily obtained and functionalized[1–5] from readily available triacetonamine (**1**), the five-membered pyrroline and pyrrolidine homologs require additional multistep syntheses involving the Favorskii rearrangement of the 3,5-dibromo-4-oxo-2,2,6,6-tetramethylpiperidine (**2**) and other suitable reactions to give the target radicals (Scheme 1).[2–10,13–15] As a consequence of the use of the 3,5-dibromo derivative **2**, the Favorskii rearrangement inevitably results in the formation of the unsaturated pyrroline derivatives (**3**)[2,5,6,10] which requires additional reductive and oxidative steps for the formation of the unsaturated pyrroline radical **4** and saturated pyrrolidine compounds **5** and **6** (Scheme 1).

Although nitroxyl radicals are fairly resistant to a variety of reagents, they are rather sensitive to certain reducing conditions[8,16] *in vitro* and *in vivo*, whereby the six-membered piperidine nitroxyls are the least stable, while the corresponding functionalized five-membered pyrroline and pyrrolidine analogs are appreciably more resistant in that order. This difference in susceptibility to reduction can be of importance in experiments which have to be conducted over prolonged periods with an intact radical moiety, such as intracellular studies and MRI. Hence, it is of interest to have the shortest possible pathways, *i.e.* the most economical method, for the synthesis of pyrrolidine radicals. The Favorskii rearrangement has been known for about a century,[17–19] and there are also numerous references pertaining to the

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[⊗] Abstract published in *Advance ACS Abstracts,* May 15, 1995.

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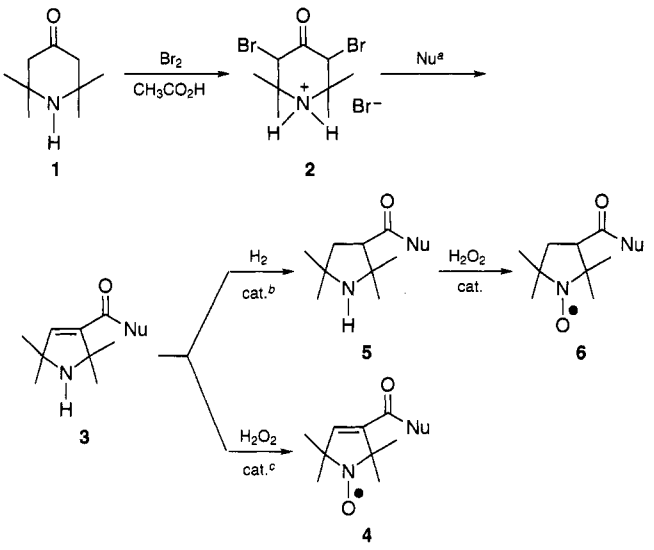
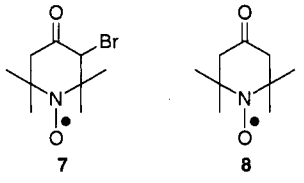
Scheme 1



[a] Nu = hydroxyl, methoxyl, ammonia, or amines. [b] Catalyst: either Raney nickel at elevated pressures or Pd/C. [c] Catalyst: usually Na_2WO_4.

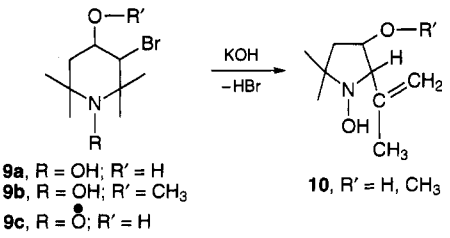
Favorskii rearrangement of 3,5-dibromo-4-oxo-2,2,6,6-tetramethylpiperidine (**2**) mediated by various nucleophiles (Scheme 1). However, surprisingly, there is little information available concerning the Favorskii rearrangement of 3-bromo-4-oxo-2,2,6,6-tetramethylpiperidin-1-oxyl radical (**7**) which should directly result in the formation of the saturated pyrrolidine ring system **6**. In 1977, an unsuccessful attempt to acylate benzylamine by **7** *via* the Favorskii rearrangement was described,[15] and although the reaction with sodium hydroxide was successful, resulting in a low yield of the 3-carboxyl-2,2,5,5-tetramethylpyrrolidin-1-oxyl (**6**, Nu = OH), the whole idea was abandoned, probably because of difficulties in obtaining pure **7** and its low reactivity as compared to **2**.

Another attempt was described[20] in 1980 using the reaction of triacetonamine (**1**) and the corresponding radical **8** with a mixture of iodine and potassium hydroxide which, presumably, formed *in situ* potassium hypoiodite. The resultant mixtures of 3-carboxylpyrroline

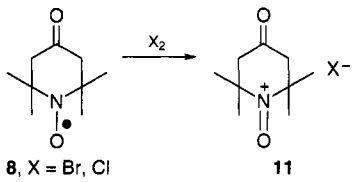


(**3** and **4**, Nu = OH) and -pyrrolidine (**5** and **6**, Nu = OH) derivatives, where the latter predominated, was, no doubt, formed *via* the mixture of 3-monoiodo and 3,5-diiodo intermediates. A similar result was obtained[20] with a mixture of iodine, potassium hydroxide, and ammonia, giving analogous mixtures of 3-aminocarbonyl derivatives **3** and **4**, Nu = NH_2, and **5** and **6**, Nu = NH_2. In these reactions, no interference of iodine with the amino and nitroxyl moieties was observed. The extension

Scheme 2



Scheme 3



of this reaction to hypobromite[21] with **1** and **8** gave a more complex mixture of mono-, di-, and tribromo derivatives which under Favorskii rearrangement were converted, not surprisingly, mainly to a mixture of brominated pyrroline derivatives which proved to be useful for other studies. An unusual rearrangement was described[22] in the reaction of 3-bromo derivatives of 1,4-dihydroxy-2,2,6,6-tetramethylpiperidine (**9a**), 1-hydroxy-4-methoxy-2,2,6,6-tetramethylpiperidine (**9b**), and 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl (**9c**) with potassium hydroxide which resulted in the five-membered 1,3-dihydroxy-2-(2′-propenyl)-5,5-dimethylpyrrolidine ring **10** (Scheme 2).

It was also observed[23] that the reactions of either 3-bromo- or 3-chloro-4-oxo-2,2,6,6-tetramethylpiperidine, 3-bromo(chloro)-1-hydroxy-4-oxo-2,2,6,6-tetramethylpiperidine, and 3-bromo(chloro)-4-oxo-2,2,6,6-tetramethylpiperidin-1-oxyl with various nucleophiles, including amines, failed. However, these substitution reactions without involvement of the Favorskii rearrangement could be accomplished[23] after conversion of the 4-oxo group to the oxime moiety. In contrast, it was well-established[19] that 2-halo derivatives of alicyclic ketones, such as cyclohexanone, readily undergo the nucleophilic reactions and the Favorskii rearrangement.

Furthermore, it was known[2,24] that the interaction of molecular bromine and chlorine with nitroxyl radicals results in an almost quantitative conversion of the nitroxyl group into a nitrosonium (oxoammonium) salt moiety; *e.g.* the reaction of **8** results in **11** (Scheme 3). Hence, in order to prepare the starting material **7** from radical **8**, it was necessary, prior to bromination, to derivatize the nitroxyl group by the reaction with either hydrogen chloride or concentrated aqueous hydrochloric acid to the 1-hydroxy derivative **12**.[6,25,26] Actually, the interaction of nitroxyl radicals with hydrogen chloride involves a disproportionation reaction[2,24] leading, in the case of **8**, to the formation of **12** and **11**, X = Cl. However,

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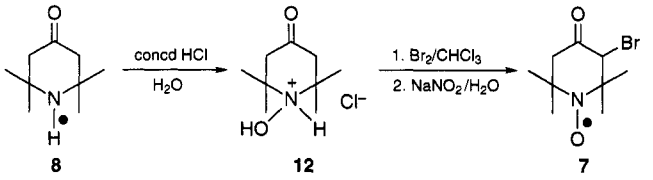
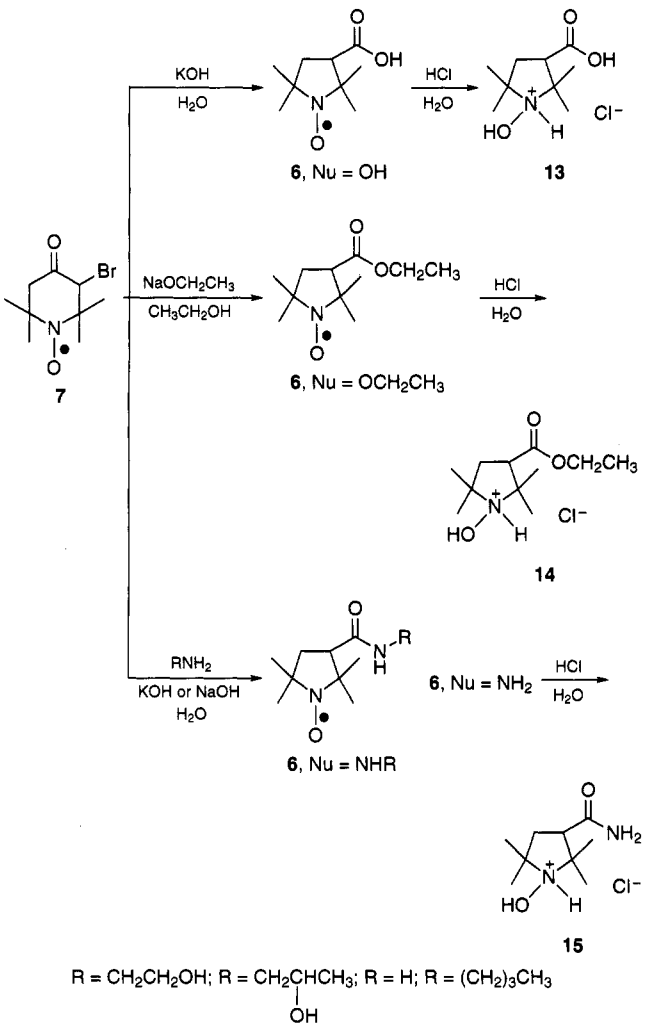
Scheme 4



8 12 7

Scheme 5



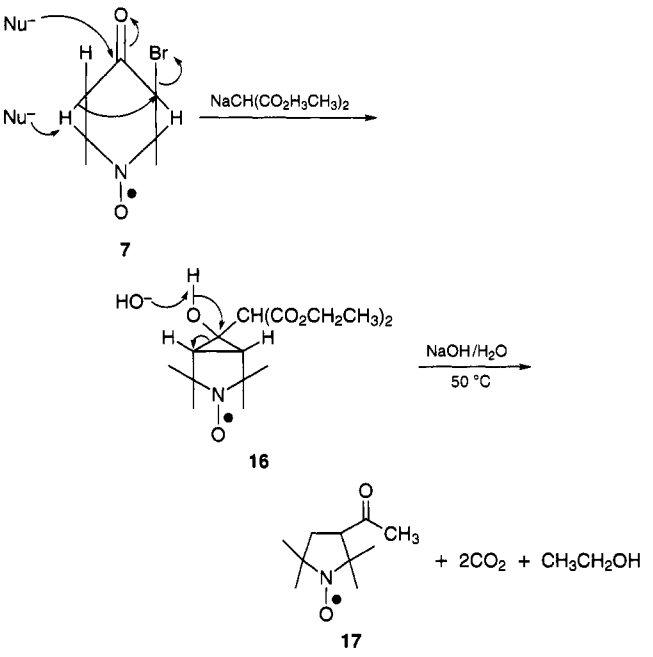
neither in the past investigations[6,25,26] nor in the present work have the nonessential byproducts of type **11** been isolated. Hence, these byproducts are omitted from Schemes 4 and 5, in line with other studies. After the bromination of **12**, the restoration of the nitroxyl function to give **7** can be accomplished *in situ* with a variety of oxidizing agents, most conveniently, however, with sodium nitrite (Scheme 4).[26] Similar results were also obtained with hydrochloride salts of triacetonamine.[25,26]

In the present study, an attempt was made to explore the Favorskii rearrangement of **7** in the presence of several nucleophiles, including amines, with the aim of obtaining directly and exclusively the saturated pyrrolidine radicals **6** (Scheme 5) without the necessity of using a reductive step which has been essential in the past syntheses starting with **2** (Scheme 1).

Results and Discussion

The synthesis of the key compound for the Favorskii rearrangement, *i.e.* the 3-bromo-4-oxo-2,2,6,6-tetramethylpiperidin-1-oxyl (**7**), can be readily accomplished by adaptations of known procedures,[25,26] as shown in Scheme 4. The starting material 4-oxo-2,2,6,6-tetramethylpiperdin-1-oxyl (**8**) can be conveniently obtained[2] by the oxidation of the readily available triacetonamine (**1**) with hydrogen peroxide in the presence of catalytic quantities of sodium tungstate. A number of modifications of this original oxidation reaction, including the use of other catalysts and oxidizing agents, have been reported.[27] The reaction of **8** with concentrated aqueous hydrochloric acid gave the isolable intermediate 1-hydroxy-4-oxo-2,2,6,6-tetramethylpiperidine hydrochloride (**12**) which then was brominated to the 3-bromo-1-hydroxy-4-oxo-2,2,6,6-tetramethylpiperidine derivative which, in turn, was converted *in situ* to the corresponding radical **7** by oxidation using sodium nitrite.[25,26]

Scheme 6[a]



[a] $Nu^- = {}^-CH(CO_2CH_2CH_3)_2$

Although, in a past study,[15] the Favorskii rearrangement of the radical **7** with sodium hydroxide formed a low yield of 3-carboxyl-2,2,5,5-tetramethylpyrrolidin-1-oxyl (**6**, Nu = OH) and an analogous reaction of 3-bromo-4-oxo-2,2,6,6-tetramethylpiperidine hydrobromide with sodium methoxide gave 3-(methoxycarbonyl)-2,2,5,5-tetramethylpyrrolidine (**5**, Nu = OCH_3) in a 65% yield,[25] the reactions of various amines and other nucleophiles with the nitroxyl radical **7** and it diamagnetic analog failed.[15,23]

In the present investigation, the reactions of aqueous potassium hydroxide and anhydrous sodium ethoxide produced the expected pyrrolidine derivatives **6**, Nu = OH, and **6**, Nu = OCH_2CH_3, in 53 and 73% yield, respectively, Similarly, the Favorskii rearrangement of the bromo radical **7** in the presence of ammonia and several aliphatic amines resulted in acylations of these nucleophiles with concomitant ring contraction of the piperidine ring system to give the pyrrolidine compound (**6**, Nu = NHR) in yields ranging from 61 to 79% (Scheme 6). In the case that further reactions are contemplated with the pyrrolidine products **6** which could affect the

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nitroxyl moiety, the reversible protection *via* the hydroxylamine hydrochloride derivative can be used as shown on the example of compounds **13**, **14**, and **15** (Scheme 5).

An interesting reaction was observed for **7** with the ethyl sodium malonate nuclephile resulting in a new, isolable Favorskii type intermediate (**16**) containing the cyclopropane and nitroxyl moieties (Scheme 6). This compound (**16**) can be readily degraded by aqueous sodium hydroxide at 50 °C to the 3-(methylcarbonyl)-2,2,5,5-tetramethylpyrrolidin-1-oxyl (**17**). These transformations are analogous to those which were previously observed[28,29] with alicyclic halo ketones, such as halocyclohexanones.

In conclusion, the described Favorskii reactions of 3-bromo-4-oxo-2,2,6,6-tetramethylpiperidin-1-oxyl radical (**7**) represent, in certain cases, a viable alternative method for the direct synthesis of saturated pyrrolidine derivatives, unlike the commonly used reactions of 3,5-dibromo-4-oxo-2,2,6,6-tetramethylpiperidine (**2**) with nucleophiles which almost unfailingly result in the unsaturated pyrroline analogs requiring further reductive and oxidative steps to give derivatives of pyrrolidine nitroxyl radicals.

Experimental Section

Materials. All chemicals were of the best quality available commercially. The silica gel 60 (finer than 230 mesh) for flash chromatography was obtained from Fluka Chemical Corp., Ronkonkoma, NY. Solvents were dried by standard procedures.[30]

Analytical Procedures. Melting points were determined on a Thomas-Hoover melting point apparatus model 406-K with a calibrated thermometer. Mass spectra were recorded on a Hewlett-Packard mass spectrometer, model 5985 GS, using either electron impact (EI) or chemical ionization (CI) with methane as reactant gas. ^{1}H NMR spectra were recorded on a Bruker 250 (250 MHz) spectrometer with TMS as internal standard. IR spectra of KBr pellets or film were recorded on a Mattson Instruments, Inc. model IR-10400 spectrometer. Microanalyses were obtained on a Perkin-Elmer elemental analyzer model 240C. Column chromatography was performed by the flash technique[31] using silica gel 60 (Fluka) finer than 230 mesh. All reactions, chromatographic procedures, and product purities were monitored by TLC. TLC analyses were performed on silica gel 60 F_{254} precoated sheets (EM Science), layer thickness 0.2 mM, with visualization using UV light and/or an iodine chamber. The EPR spectra of aminoxyls were obtained in nonpolar dilute solutions using a Varian E-115 EPR spectrometer.

Preparation of 3-Carboxyl-2,2,5,5-tetramethylpyrrolidin-1-oxyl (6, Nu = OH). Compound **7** (2.49 g, 10.0 mmol) was added, portionwise, to a stirred solution of potassium hydroxide (1.4 g, 25.0 mmol) in water (25 mL). The reaction mixture was stirred for 2 h at about 24 °C, acidified with 5 N aqueous HCl solution to pH 3, and quickly extracted with chloroform (3 × 20 mL). The organic layer was dried with anhydrous magnesium sulfate. After removal of the solvent in a rotating evaporator at 40 °C/20 Torr, the residue was recrystallized from a mixture of chloroform and hexane (3/1, v/v) to give 1.44 g (77%) of the yellow product **6**, Nu = OH, mp 192–193 °C dec (lit.[2,15,20] mp 193 °C dec). Purity control by TLC analysis (chloroform and methanol, 5/1, v/v) indicated one product. IR: ν (cm^{-1}) 3500 (br, OH), 1710 (s, C=O), 1365 (s, N$^{\cdot}$–O). EPR: 3 lines (a_N = 15.0 G). MS (CI): *m/e* (relative intensity) 187 (M^+ + 1, 31), 186 (M^+, 47). Anal. Calcd for $C_9H_{16}NO_3$ (186.23): C, 58.04; H, 8.66; N, 7.52. Found: C, 57.86; H, 8.74; N, 7.59.

Preparation of 3-(Ethoxycarbonyl)-2,2,5,5-tetramethylpyrrolidin-1-oxyl (6, Nu = OCH_2CH_3). Compound **7** (1.0 g, 4 mmol) was slowly added to a freshly prepared stirred solution of 1 M sodium ethoxide in ethanol (9 mL, 9 mmol). The reaction mixture was stirred for 4 h at about 24 °C/20 Torr. After removal of the solvent at 50 °C/20 Torr, water (10 mL) was added to the residue, the solution was extracted with chloroform, and the extract was dried with magnesium sulfate. Removal of the solvent in a rotating evaporator at 40 °C/20 Torr left an oil, which was purified by flash chromatography (chloroform) to give 454 mg (53%) of an orange liquid product **6**, Nu = OCH_2CH_3. Purity control by TLC analysis (chloroform) indicated one product. IR: ν (cm^{-1}) 1750 (s, C=O), 1370 (s, N$^{\cdot}$–O). EPR: 3 lines (a_N = 13.5 G). MS (CI): *m/e* (relative intensity) 215 (M^+ + 1, 70), 214 (M^+, 70), 200 (100).

Preparation of 3-(Aminocarbonyl)-2,2,5,5-tetramethylpyrrolidin-1-oxyl (6, Nu = NHR, R = H). Portionwise, **7** (0.25 g, 1.0 mmol) was added to a solution of potassium hydroxide (0.14 g, 2.5 mmol) in 29% aqueous ammonium hydroxide (8 mL). The reaction mixture was stirred for 1 h at about 24 °C, and then extracted with chloroform (3 × 10 mL). The chloroform layer was dried with anhydrous magnesium sulfate. After removal of the solvent in a rotating evaporator at 40 °C/20 Torr, the residue was triturated with hexane to give after vacuum sublimation 135 mg (73%) of a yellow product **6**, Nu = NHR, R = H, mp 172–174 °C dec (lit.[2] mp 174–174.5 °C; lit.[20,26] mp 169–170 °C). IR: ν (cm^{-1}) 3400 (br, OH), 1680 (s, C=O), 1360 (m, N$^{\cdot}$–O). EPR: 3 lines (a_N = 14.0 G). MS (EI): *m/e* (relative intensity) 185 (M^+, 54), 186 (M^+ + 1, 7). Anal. Calcd for $C_9H_{17}N_2O_2$ (185.30): C, 58.34; H, 9.25; N, 15.12. Found: C, 57.95; H, 9.16; N, 15.46.

Preparation of 3-[[*N*-(2-Hydroxyethyl)amino]carbonyl]-2,2,5,5-tetramethylpyrrolidin-1-oxyl (6, Nu = NHR, R = CH_2CH_2OH). Compound **7** (0.50 g, 2.0 mmol) was added to a stirred solution of ethanol amine (1.52 g, 25 mmol) and sodium hydroxide (0.20 g, 5 mmol) in dioxane (1.5 mL) and water (1.5 mL). The reaction mixture was stirred for 1 h at about 24 °C. Water (5 mL) was added to the reaction mixture, and the solution was extracted with chloroform (3 × 10 mL). The chloroform layer was dried with anhydrous magnesium sulfate. After removal of the solvent in a rotating evaporator at 40 °C/20 Torr, the residue was purified by flash chromatography using chloroform and methanol (9/1, v/v) as eluant to give 290 mg (63%) of a yellow product **6**, Nu = NHR, R = CH_2CH_2OH, mp 125–127 °C dec. IR ν (cm^{-1}) 3500 (br, OH), 1670 (s, C=O), 1370 (s, N$^{\cdot}$–O). EPR: 3 lines (a_N = 14.5 G). MS (CI): *m/e* (relative intensity) 230 (M^+ + 1, 75), 229 (M^+, 50). Anal. Calcd for $C_{11}H_{21}N_2O_3$ (229.30): C, 57.61; H, 9.23; N, 12.21. Found: C, 57.37; H, 9.17; N, 11.85.

Preparation of 3-[[*N*-(2-Hydroxypropyl)amino]carbonyl]-2,2,5,5-tetramethylpyrrolidin-1-oxyl (6, Nu = NHR, R = $CH_2CH(OH)CH_3$). Compound **7** (0.5 g, 2 mmol) was slowly added to a stirred solution of 2-hydroxy-1-propylamine (1.86 g, 25 mmol) and sodium hydroxide (0.2 g, 5 mmol) in dioxane (1.5 mL) and water (1.5 mL). The reaction mixture was stirred for 1 h at about 24 °C. Water (5 mL) was added to the reaction mixture, and the solution was extracted with chloroform and dried with anhydrous magnesium sulfate. After removal of the solvent in a rotating evaporator at 40 °C/20 Torr, the residue was purified by flash chromatography using chloroform and methanol (9/1, v/v) as eluant to give 295 mg (61%) of product **6**, Nu = NHR, R = $CH_2CH(OH)CH_3$, mp 140–142 °C dec. IR: ν (cm^{-1}) 3400 (br, OH), 1670 (s, C=O), 1365 (s, N$^{\cdot}$–O). EPR: 3 lines (a_N = 14.3 G). MS (CI): *m/e* (relative intensity) 244 (M^+ + 1, 100), 243 (M^+, 74). Anal. Calcd for $C_{12}H_{23}N_2O_3$ (243.13): C, 59.28; H, 9.46; N, 11.51. Found: C, 59.24; H, 9.41; N, 11.23.

Preparation of 3-[(*N*-Butylamino)carbonyl]-2,2,5,5-tetramethylpyrrolidin-1-oxyl (6, Nu = NHR, R = $(CH_2)_3CH_3$). Compound **7** was added, portionwise, to a stirred solution of

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n-butylamine (1.8 g, 25 mmol) and sodium hydroxide (0.2 g, 5 mmol) in dioxane (1.5 mL) and water (1.5 mL). The reaction mixture was stirred for 1 h at about 24 °C. Water (5 mL) was added to the reaction mixture, and the solution was extracted with chloroform (3 × 10 mL). The chloroform layer was dried with anhydrous magnesium sulfate. After removal of the solvent in a rotating evaporator at 40 °C/20 Torr, the residue was purified by flash chromatography with chloroform and methanol (95/5, v/v) as eluant to give 250 mg (52%) of a yellow product **6**, Nu = NHR, R = $(CH_2)_3CH_3$, mp 82–83 °C dec. IR: ν (cm^{-1}) 3400 (br, NH), 1670 (s, C=O), 1365 (s, N-O). EPR: 3 lines (a_N = 14.0 G). MS (EI): *m/e* (relative intensity) 241 (M^+, 59), 242 (M^+ + 1, 11). Anal. Calcd for $C_{13}H_{25}N_2O_2$ (241.35): C, 64.70; H, 10.44; N, 11.60. Found: C, 64.92; H, 10.52; N, 11.51.

Preparation of 3-Bromo-4-oxo-2,2,6,6-tetramethylpiperidin-1-oxyl (7). A solution of bromine (4.0 g, 22.2 mmol) in chloroform (5 mL) was added dropwise to a stirred solution of **12** (4.6 g, 22.2 mmol) in chloroform (45 mL). After a clear solution was observed, to this solution was added with vigorous stirring a solution of sodium nitrite (3.5 g, 50 mmol) in water (50 mL). The mixture was stirred for 30 min at about 24 °C. The chloroform layer was separated, washed with water, and dried with anhydrous magnesium sulfate. After removal of the solvent in a rotating evaporator at 40 °C/20 Torr, the residue was recrystallized from hexane to give 4.0 g (72%) of an orange product **7**, mp 75–77 °C dec (lit.[25,26] mp 75.5–77.5 °C). Purity control by TLC analysis (chloroform) indicated one product. IR: ν (cm^{-1}) 1735 (s, C=O), 1365 (s, N-O). EPR: 3 lines (a_N = 15.0 G). MS (EI): *m/e* (relative intensity) 250 (M^+ + 1, 52), 248 (M^+ − 1, 57). Anal. Calcd for $C_9H_{15}NO_2Br$ (249.13): C, 43.39; H, 6.07; N, 5.62. Found: C, 43.68; H, 6.22; N, 5.45.

Preparation of 1-Hydroxyl-4-oxo-2,2,6,6-tetramethylpiperidine Hydrochloride (12). Aqueous hydrochloric acid (37%, 7.0 mL, 83.7 mmol) was added dropwise at 5 °C to a stirred solution of 4-oxo-2,2,6,6-tetramethylpiperidin-1-oxyl (**8**, 11.0 g, 64.7 mmol) in ethanol (8 mL). The reaction mixture was stirred for 1 h at about 24 °C. The solvent was removed in a rotating evaporator at 50 °C/20 Torr, and the residue was recrystallized from 2-propanol to give 10.5 g (78%) of a white solid **12**, mp 163–165 °C dec, (lit.[25] mp 163–166 °C). IR: ν (cm^{-1}) 1725 (s, C=O). ^1H NMR (D_2O, TMS): δ (ppm) 2.75 (s, 4H, $2CH_2$), 1.42 (s, 12H, $4CH_3$). MS (EI): *m/e* (relative intensity) 171 (M^+ − 36, 20). Anal. Calcd for $C_9H_{18}NO_2Cl$ (207.70): C, 52.05; H, 8.74; N, 6.74. Found: C, 51.94; H, 8.75; N, 6.57.

Preparation of 1-Hydroxyl-3-carboxyl-2,2,5,5-tetramethylpyrrolidine Hydrochloride (13). Hydrochloric acid (37%, 3.6 mmol) was added to a solution of **6**, Nu = OH (558 mg, 3.0 mmol), in ethanol (2 mL) at 0 °C. The mixture was stirred for 2 h at about 24 °C. After removal of the solvent in a rotating evaporator at 50 °C/20 Torr, the residue was recrystallized with a mixture of 2-propanol and ethyl acetate to give 387 mg (58%) of a white salt **13**, mp 116–118 °C dec. IR: ν (cm^{-1}) 1730 (s, C=O). ^1H NMR (D_2O, TMS): δ (ppm) 3.33 (t, 1H, CH), 2.43 (d, 2H, CH_2), 1.40–1.80 (m, 12H, $4CH_3$). MS (CI): *m/e* (relative intensity) 187 (M^+ − 36, 41), 188 (89). Anal. Calcd for $C_9H_{18}NO_3Cl$ (223.70): C, 48.32; H, 8.10; N, 6.26. Found: C, 48.37; H, 8.16; N, 6.01.

Preparation of 1-Hydroxyl-3-(ethoxycarbonyl)-2,2,5,5-tetramethylpyrrolidine Hydrochloride (14). Hydrochloric acid (37%, 0.17 mmol) was added to a stirred solution of **6**, Nu = OCH_2CH_3 (30 mg, 0.17 mmol), in ethanol (1 mL) at 0 °C. The mixture was stirred for 1 h at about 24 °C. After removal of the solvent in a rotating evaporator at 50 °C/20 Torr, the residue was recrystallized with a mixture of ethyl acetate and diethyl ether to give 25 mg (71%) of a white salt **14**, mp 112–114 °C dec. IR: ν (cm^{-1}) 1750 (s, C=O). ^1H NMR (D_2O, TMS): δ (ppm) 3.93 (q, 2H, OCH_2), 3.10 (t, 1H, CH), 2.15 (d, 2H, CH_2), 1.0–1.5 (m, 15H, $5CH_3$). MS (EI): *m/e* (relative intensity) 215 (M^+ − 36, 12), 216 (2). Anal. Calcd for $C_{11}H_{22}O_3NCl$ (251.57): C, 52.51; H, 8.74; N, 5.56. Found: C, 52.62; H, 8.74, N, 5.31.

Preparation of 1-Hydroxyl-3-(aminocarbonyl)-2,2,5,5-tetramethylpyrrolidine Hydrochloride (15). Aqueous hydrochloric acid (37%, 1.2 mmol) was added to a stirred solution of **6**, Nu = NH_2 (186 mg, 1.0 mmol), in ethanol (2 mL) at 0 °C. The solution was stirred for 2 h at about 24 °C. After removal of the solvent in a rotating evaporator at 50 °C/20 Torr, the residue was recrystallized from a mixture of 2-propanol and ethyl acetate to give 175 mg (79%) of a white salt **15**, mp 229–230 °C dec. IR: ν (cm^{-1}) 3500 (br, OH), 1660 (s, C=O). ^1H NMR (D_2O, TMS): δ (ppm) 2.90 (t, 1H, CH), 2.17 (d, 2H, CH_2), 1.10–1.50 (m, 12H, $4CH_3$). MS (CI): *m/e* (relative intensity) 186 (M^+ - 36, 24), 187 (100), 188 (11). Anal. Calcd for $C_9H_{19}N_2O_2Cl$ (222.72): C, 48.53; H, 8.60; N, 12.58. Found: C, 48.46; H, 8.62; N, 12.30.

Preparation of 4-Hydroxy-4-[1,1-bis(ethoxycarbonyl)-methyl]bicyclo[3.1.0]-2,2,6,6-tetramethylpiperidin-1-oxyl (16). A mixture of sodium (23 mg, 1 mmol), benzene (2 mL), and ethyl malonate (1.6 g, 10 mmol) was boiled with reflux under nitrogen until the sodium was dissolved. After the mixture was cooled to 0–5 °C, **7** (249 mg, 1 mmol) was added. The reaction mixture was stirred at 0 °C for 3 h and at about 24 °C for an addition 7 h. After removal of the solvent in a rotating evaporator at 40 °C/20 Torr, the residue was purified by flash chromatography using a mixture of chloroform and methanol (95/5, v/v) as eluant to give 210 mg (64%) of a yellow product **16**, mp 82–85 °C dec. IR: ν (cm^{-1}) 3500 (br, OH), 1730 (s, C=O), 1365 (sh, N-O). EPR: 3 lines (a_N = 14.5 G). MS (CI): *m/e* (relative intensity) 329 (M^+ + 1, 54), 328 (M^+, 100). Anal. Calcd $C_{16}H_{28}NO_6$ (328.39): C, 58.52; H, 7.98; N, 4.26. Found: C, 58.24; H, 7.93; N, 4.08.

Conversion of Compound 16 to 3-(Methylcarbonyl)-2,2,5,5-tetramethylpyrrolidin-1-oxyl (17). A suspension of **16** (30 mg, 0.09 mmol) in 2 N aqueous sodium hydroxide (1.5 mL, 3 mmol) was stirred for 24 h at 50 °C. The reaction mixture was extracted with chloroform, and the combined extracts were dried with magnesium sulfate. Removal of the solvent in a rotating evaporator at 40 °C/20 Torr resulted in an oil which was purified by flash chromatography using chloroform as eluant to give 14 mg (78%) of an orange liquid **17**. Purity control by TLC analysis (chloroform) indicated one single spot. The verification of **17** was based on MS and IR. IR: ν (cm^{-1}) 1710 (s, C=O), 1365 (s, N-O). EPR: 3 lines (a_N = 14.0 G). MS (CI): *m/e* (relative intensity) 185 (M^+ + 1, 48), 184 (M^+, 56).

JO9500592