would give the *S* configuration at C-6 and C-12 of **3** and would retain the *P* twist of the biphenyl.

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Registry No.—(−)-**1**, 35053-29-3; **2a**, 35053-14-6; **2b**, 35048-36-3; **3b**, 57550-05-7.

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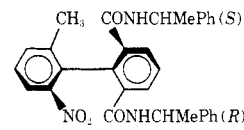

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Cyclization of Unsaturated Hydroxylamine Derivatives[1]

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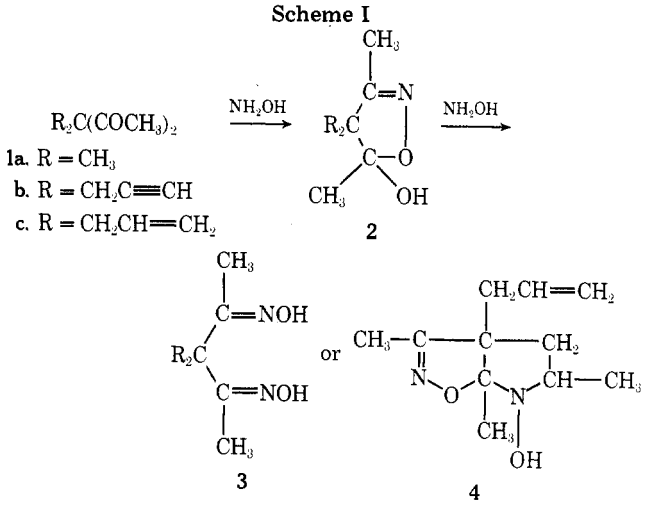
Reaction of the α-allyl β-diketones **5** with excess $HONH_2$ yielded the bicyclic pyrrolidine derivatives **7** in which a new N–C bond had been formed by cyclization of an intermediate *N*-(4-pentenyl)hydroxylamine **14**. Study of conversion of the *N*-alkenylhydroxylamine **20** to form the cyclic hydroxylamine **24a** and the electrochemical oxidation of hydroxylamines **20**, **24a**, and **31** suggested that these ring closures **14** → **15** occur by a radical chain process involving an intermediate nitroxide radical **37**.

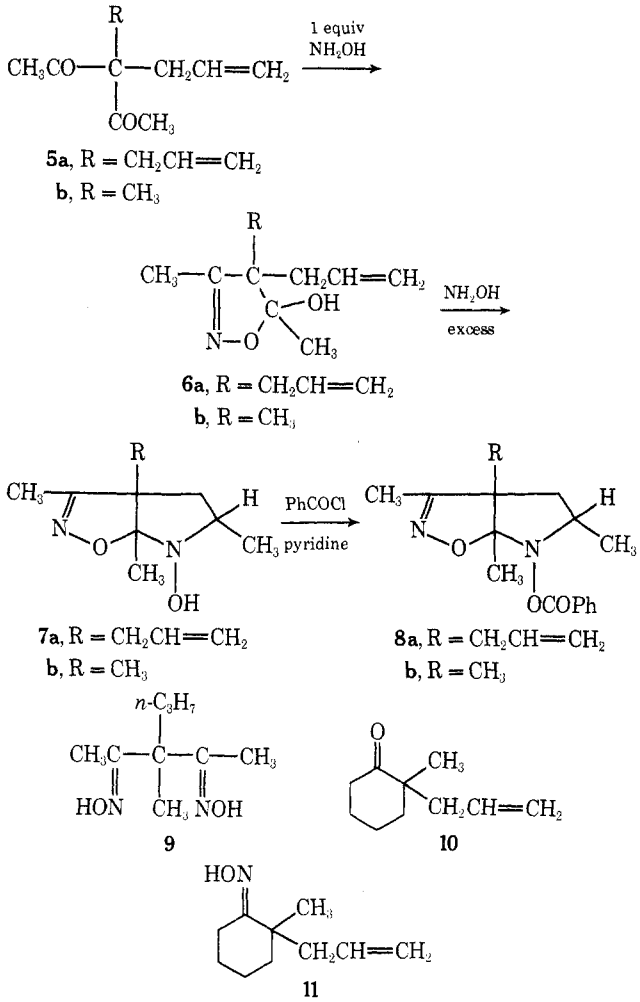
An earlier investigation[3] of the reaction of 3,3-disubstituted 2,4-pentanediones (**1**, Scheme I) with excess hydroxylamine had provided the curious observation that although the dimethyl derivative **1a** could be converted either to the isoxazoline **2** or the dioxime **3**, the dipropargyl derivative **1b** was remarkably resistant to conversion beyond the isoxazoline stage **2**. In seeking further information relating to these observations, reaction of the diallyl derivative **1c** with excess hydroxylamine was also examined. Again, formation of an isolable dioxime **3** was unfavorable; treatment of the isoxazoline **2** (R = allyl) with hydroxylamine under vigorous conditions led to the formation of an unexpected isomeric substance subsequently shown to have the structure **4**. In this paper we describe the evidence on which the assignment of structure **4** is based and also described are our observations pertaining to the mode of formation of this substance.

Two 1,3-diketone substrates, **5a** and **5b** (Scheme II),

Scheme I



Scheme II

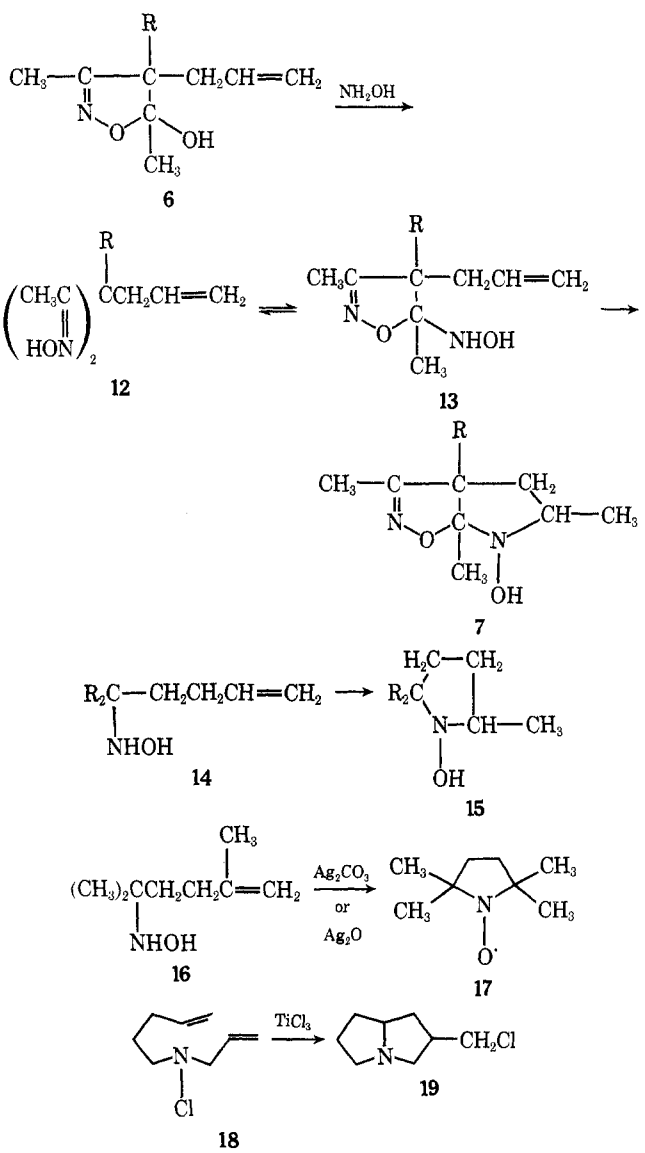


were selected for further study. Reaction of either of these products with 1 molar equiv of NH_2OH (from $HONH_3Cl$ + NaOAc) in aqueous dioxane or aqueous EtOH afforded the corresponding isoxazoline **6** that was isolated and fully characterized. Reaction of either the diketone **5** or the corresponding isoxazoline **6** with excess NH_2OH in refluxing aqueous EtOH or refluxing aqueous dioxane for a period of 6–24 h produced the bicyclic products **7**. In each case, the predominant product was one stereoisomer of structure **7**; from the reaction with the diallyl ketone **5a**, a second unidentified minor product, isomeric with **7a**, was isolated that appears to be a structural rather than a stereoisomer of **7a**. From reaction with the diketone **5b**, two stereoisomers of structure **7b** and a third minor component identified as the dioxime **9** were also isolated. This saturated dioxime **9** is not further altered by the conditions of the reaction and, consequently, is not an intermediate in the formation of the bicyclic hydroxylamine **7b**. When these same reaction conditions were applied to the α-allyl ketone **10**, only the expected oxime **11** was isolated indicating that the ring-closure reactions to form products **7** were not characteristic of prolonged reaction of simple α-allyl ketones with NH_2OH.[4]

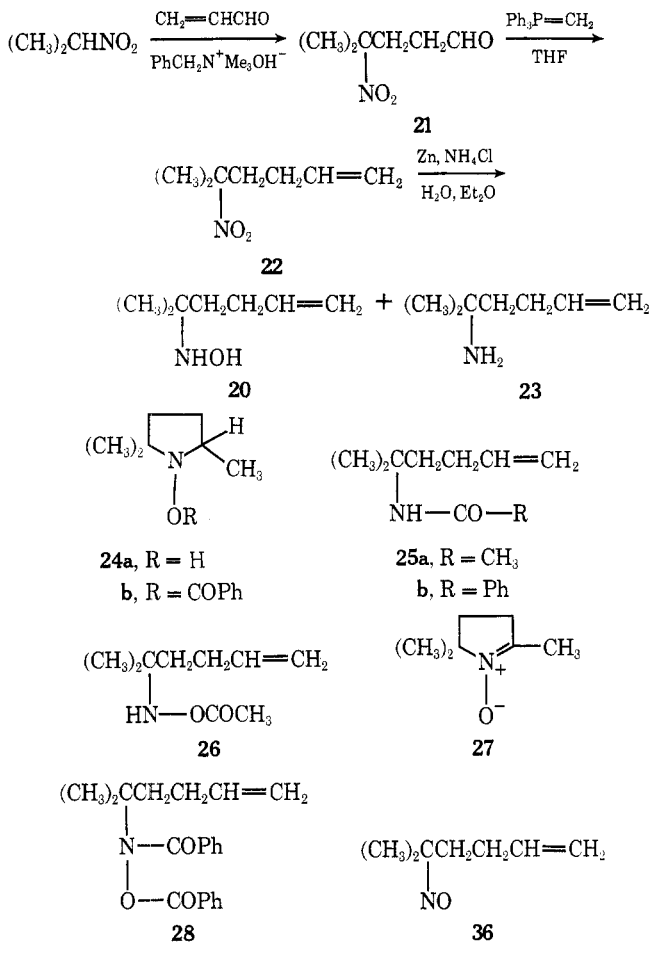
The spectroscopic properties (see Experimental Section) of the cyclic hydroxylamine derivatives **7** and the corresponding *O*-benzoates **8** taken with the structures of the starting materials **5** and the intermediates **6** served to define completely the structures **7**. It was therefore probable that the reaction pathway involved in these transformations was the transformation of the isoxazoline **6** (Scheme III) to the unsaturated hydroxylamine **13** (which is presumably in equilibrium with the dioxime **12**) followed by closure to cyclic product **7**. The unusual reaction in this sequence is the final cyclization **13** → **7** (or more generally, **14** → **15**) that results in the formation of a new C–N bond at an unactivated olefinic carbon under mild conditions. In considering the nature of this reaction, we were attracted by the apparently analogous oxidative cyclizations[5] of the unsaturated hydroxylamine **16** to the nitroxide **17**[5a] and the *N*-chloroamine **18** to the bicyclic amine **19**.[5b] To examine this cyclization further, the unsaturated hydroxylamine **20** was synthesized by the route indicated in Scheme IV.

The synthesis of hydroxylamine **20** was initially complicated by the fact that the nitro olefin **22** was not reduced by a mixture of aluminum amalgam and H_2O in Et_2O or THF, conditions which reduce the seemingly analogous 3-nitro-3-methylpropane to **31** in high yield.[6] Consequently, the more vigorous reducing system, Zn and aqueous NH_4Cl, was employed[7] resulting in partial overreduction of the nitro olefin **22** to form a mixture of the hydroxylamine **20** and the amine **23**. The synthesis was further complicated by the instability of **20**; when mixtures containing this hydroxylamine **20** were either heated or allowed to stand, conversion to the cyclic hydroxylamine **24a** occurred and exposure of mixtures containing **20** to air resulted in rapid oxidation either to the cyclized products **24a** or **27** or to a

Scheme III



Scheme IV

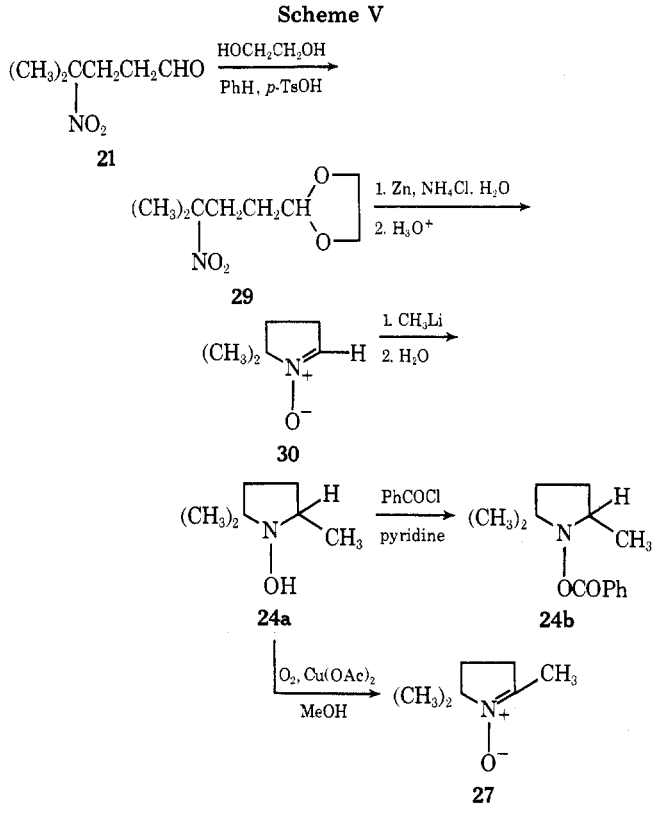


volatile blue material believed to be the nitroso compound **36**. These experimental difficulties were circumvented by acylating the mixture of the hydroxylamine **20** and the amine **23** to form mixtures of either the acetyl derivatives **25a** and **26** or the benzamide **25b** and the dibenzoyl derivative **28**. Each of these mixtures was separable by chromatography and the *N,O*-dibenzoyl derivative **28** was sufficiently stable to permit purification and complete characterization. Although the thermal instability of the liquid *O*-acetate **26** prevented us from obtaining it in analytically pure form, it was obtained in sufficient purity by chromatography to permit its use in a base-catalyzed methanolysis to generate solutions of the hydroxylamine **20** uncontaminated with the amine **23**. Solutions of this hydroxylamine **20**, obtained either from the nitro compound **22** or from the *O*-acetate **26**, underwent cyclization to the cyclic hydroxylamine **24a** (characterized as the benzoate **24b**) when either heated on a steam bath or allowed to stand overnight. Exposure of this cyclic hydroxylamine **24a** to O_2 (air), especially in the presence of a catalytic amount of a Cu(II) salt, resulted in oxidation to form the nitrone **27**.

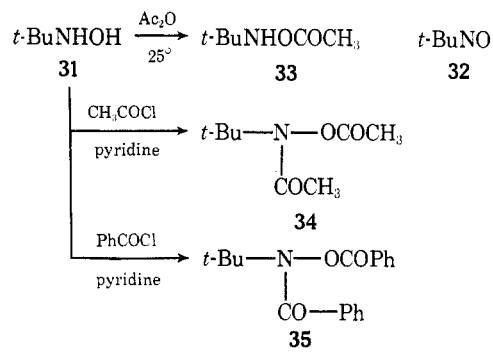
Authentic samples of the cyclic hydroxylamine **24a**, the benzoate **24b**, and the nitrone **27** were obtained from the nitrone **30** as indicated in Scheme V. Deliberate exposure of solution of the hydroxylamine **20** to O_2 resulted in the generation of a volatile, blue-colored material (presumable the nitroso compound **36**) and resulted in diminished yields of the cyclized products **24** and **27**. The best yield of benzoylated cyclized product **24b** (20% based on the *O*-acetate **26**)[8] was obtained when the most precautions were taken to minimize the concentration of O_2 present during the cyclization.

To examine the oxidation of *N*-alkyl hydroxylamines electrochemically, we studied the behavior of hydroxylamine derivatives **20**, **24a**, **26**, and also, as model compounds, hydroxylamine derivatives **31** and **33** (Scheme VI). It should be noted in passing that O-acylated *N*-alkyl hydroxylamines such as **26** and **33**, whose regioselective preparation has sometimes presented difficulty,[9] were readily prepared by reaction of the *N*-alkyl hydroxylamines **20** and **31** with Ac_2O *in the absence of pyridine*. By contrast, reaction of these hydroxylamines with either PhCOCl or CH_3COCl in the presence of pyridine yielded the N,O-diacylated derivatives **28**, **34**, and **35**. Neither the *O*-acetates **26** and **33** in MeOH solution nor the hydroxylamine **31** in DMF or in neutral (pH 7) aqueous solution exhibited a polarographic oxidation wave at a potential less positive than +0.2 V vs. SCE. As aqueous or methanolic solutions of **31** were made more basic, the oxidative wave shifted to progressively more negative potentials (corresponding to increasing ease of oxidation) with $E_{1/2}$ values of −0.20 V vs. SCE and −0.51 V vs. SCE being obtained for aqueous solutions of **31** at pH 10.0 and ca. 13, respectively.[10] This observation, taken with the estimated[9b] pK_a values 6 and 12–13 for the transformations $RN^+H_2OH - H^+ \rightarrow RNHOH - H^+ \rightarrow RNHO^-$, suggest that the hydroxylamine anion, $RNHO^-$, is probably the species responsible for the very

Scheme V



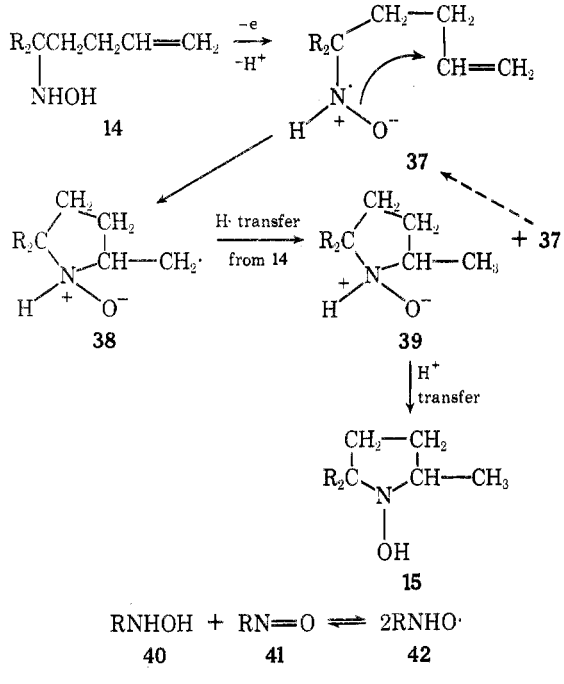
Scheme VI



ready air oxidation of RNHOH compounds in neutral and alkaline solution. In alkaline MeOH solution the hydroxylamines **31** ($E_{1/2}$ = −0.39 V vs. SCE), **20** ($E_{1/2}$ = −0.42 V vs. SCE, prepared from **26**), and **24a** ($E_{1/2}$ = −0.47 V vs. SCE) are all oxidized with about equal ease.

Consequently, our data suggest that the ring closure reaction being studied proceeds from the acyclic hydroxylamine **14** (or **20**) to the cyclic hydroxylamine **15** (or **24a**) and that subsequent formation of a nitrone such as **27** (or a nitroxide such as **17**[5a] where nitrone formation is not possible) is the result of oxidation of the intermediate cyclic hydroxylamine (e.g., **15**). Since the transformation **14** → **15** involves no net change in oxidation level and yet appears to be promoted by traces of oxidizing agents, we believe that the most reasonable interpretation involves a radical chain mechanism such as that illustrated in Scheme VII.[11c] In

Scheme VII



this scheme only a catalytic amount of the intermediate nitroxide **37** is required to propagate the reaction chain and the subsequently formed carbon radical **38** (whose formation is analogous to the cyclization of a 5-hexenyl radical and to cyclization of the N radical derived from **18**) should be readily reduced by the hydroxylamine **15** present. Although the generation of the nitroxide **37** is formulated as a direct oxidation, it is also possible that the nitroxide arises by initial oxidation of a small amount of the starting hydroxylamine **40** to a nitroso compound **41** followed by the known[11a,b] interaction of **40** and **41** to produce a nitroxide **42**. This latter equilibration involving a nitroso compound is consistent with our observations that a faint blue color (attributable to **36**) was always observed when we generated a solution of the hydroxylamine **20** in the absence of a reducing agent.

We hope to define the scope and limitations of this cyclization reaction in synthesis from experiments now in progress. One preliminary experiment (see Experimental Section) with a solution of the hydroxylamine **31** in cyclohexene suggested that intermolecular analogues of the reaction **14** → **15** are not favorable.

Experimental Section[12]

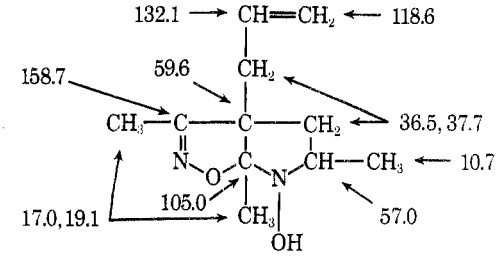
Reaction of the Diketone 5a with $HONH_2$. The diallyl diketone **5a**, obtained by the alkylation of 2,4-pentanedione,[13] exhibited the following NMR peaks (CCl_4): δ 4.8–5.9 (6 H, m, vinyl CH), 2.62 (4 H, d, J = 6 Hz, allylic CH_2), and 2.03 (6 H, s, CH_3CO). A solution of 60.0 g (0.33 mol) of the diketone **5a**, 23.2 g (0.33 mol) of $HONH_2$·HCl, and 27.9 g (0.33 mol) of NaOAc in 175 g of H_2O and 205 g of dioxane was refluxed for 6.5 h and then concentrated under reduced pressure. The residue was extracted with Et_2O and the Et_2O solution was dried and concentrated to leave 67.1 g of residual yellow liquid containing (GLC, silicone SE-30 on Haloport F) the diketone **5a** (retention time 3.4 min, ca. 2%), an unknown component (4.9 min, ca. 12%), and the isoxazoline **6a** (7.3 min, ca. 86%). A 34-g fraction of the crude product was distilled to separate 11.8 g of forerun [bp 84 °C (1.5 mm)–100 °C (0.5 mm)], and 17.2 g of the pure (GLC) isoxazoline **6a**: bp 100 °C (0.5 mm); ir (CCl_4) 3590, 3420 (broad, free and associated OH), and 1640 cm^{-1} (C=C); NMR (CCl_4) δ 4.8–6.2 (6 H, m, vinyl CH), 4.22 (1 H, s, OH), 1.9–2.9 (4 H, m, allylic CH_2), 1.83 (3 H, s, CH_3), and 1.47 (3 H, s, CH_3).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.37; H, 8.66; N, 7.15.

After a solution of 485 mg (2.69 mmol) of the diketone **5a**, 1.87 g (26.9 mmol) of $HONH_2$·HCl, and 220 mg (26.9 mmol) of NaOAc in 15 ml of H_2O and 15 ml of dioxane had been refluxed for 6 h, the reaction solution was partitioned between H_2O and CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O, dried, and concentrated to leave 539 mg of colorless liquid that was chromatographed on silica gel with Et_2O–hexane mixtures as eluents. After separation of 8 mg of an early fraction containing an uncharacterized solid (mp 192–198 °C), the subsequent fractions contained 441 mg (84%) of the liquid isoxazoline **6a** followed by 43 mg of the bicyclic hydroxylamine **7a**. The latter fraction was crystallized from hexane–Et_2O to separate 40 mg (7.1%) of one isomer of the bicyclic hydroxylamine **7a** as white prisms, mp 82–84 °C. When an analogous experiment was performed using 507 mg (2.59 mmol) of the isoxazoline with 1.80 g (25.9 mmol) of $HONH_2$·HCl and 2.13 g (25.9 mmol) of NaOAc, the bicyclic material **7a** isolated after chromatography and crystallization amounted to 40 mg (7.4%), mp 81.5–83.5 °C. Recrystallization raised the melting point of the bicyclic hydroxylamine **7a** to 88–89 °C: ir (CCl_4) 3580, 3420 (free and associated OH), and 1640 cm^{-1} (C=C); NMR (CCl_4) δ 4.9–6.0 (3 H, m, vinyl CH), 2.5–3.0 (1 H, m, NC<), 2.42 (2 H, d, J = 6.5 Hz, further partially resolved splitting apparent, allylic CH_2), 1.86 (3 H, s, CH_3), 1.53 (3 H, s, CH_3), 1.20 (3 H, d, J = 6 Hz, CH_3), and 1.1–2.0 (2 H, m, CH_2).

Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.88; H, 8.91; N, 13.24.

The natural abundance ^{13}C NMR spectrum of hydroxylamine **7a**, measured in $CDCl_3$ solution with added Me_4Si, is summarized in the following structure. The chemical shift assignments, indicated in parts per million, are consistent with the spectrum measured with off-resonance decoupling.



Reaction of the hydroxylamine **7a** with excess PhCOCl in pyridine yielded a benzoate **8a**: mp 87–88 °C (mixture with **7a**, mp 66–82 °C); ir (CCl_4) 1755 cm^{-1} (ester C=O) with no absorption in the 3-μ region attributable to NH or OH groups; uv maxima (95% EtOH) 225 nm (ε 12 500) and 271 (966); NMR (CCl_4) δ 8.0–8.3 (2 H, m, aryl CH), 7.3–7.7 (3 H, m, aryl CH), 5.0–6.2 (3 H, m, vinyl CH), 3.0–3.6 (1 H, m, NCH<), 2.48 (2 H, d, J = 6.5 Hz, allylic CH_2, further partially resolved splitting apparent), 1.85 (3 H, s, CH_3), 1.40 (3 H, s, CH_3), 1.3–2.1 (2 H, m, CH_2), and 1.13 (3 H, d, J = 6 Hz, CH_3).

Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.89, H, 6.99; N, 8.90.

Reaction of the Diketone 5b with $HONH_2$. The reaction of 3-methyl-2,4-pentanedione with allyl bromide and K_2CO_3 in acetone followed by fractional distillation afforded the diketone **5b** as a colorless liquid: bp 66–75 °C (5.7 mm), $n^{25}D$ 1.4504 [lit.[14] bp 85–89 °C (10 mm), $n^{25}D$ 1.4550]; ir (CCl_4) 1720, 1700 (C=O), and 1640 cm^{-1} (C=C); NMR (CCl_4) δ 4.8–5.9 (3 H, m, vinyl CH), 2.56 (2 H, d, J = 6.5 Hz, allylic CH_2), 2.3 (6, H, s, CH_3CO), and 1.27 (3 H, s,

CH_3). A solution of 17.79 g (115 mmol) of the diketone **5b**, 8.35 g (120 mmol) of $HONH_2$·HCl, and 9.84 g (120 mmol) of NaOAc in 100 ml of H_2O and 100 ml of dioxane was refluxed for 5 h and then concentrated under reduced pressure. The residue was partitioned between H_2O and CH_2Cl_2 and the organic layer was washed with H_2O, dried, and concentrated. Distillation of the residual liquid (17.32 g) separated 13.95 g (72%) of the crude isoxazoline **6b** as a colorless liquid, bp 87–89 °C (0.68 mm), that contained (TLC, silica gel coating) the stereoisomeric isoxazolines and a second more rapidly eluted component. Chromatography on silica gel with 40% Et_2O in hexane separated in the later fractions a mixture of the stereoisomeric isoxazolines **6b** as a colorless liquid: $n^{25}D$ 1.4831; ir (CCl_4) 3600, 3420 (broad, free and associated OH), and 1640 cm^{-1} (C=C); uv (95% EtOH) end absorption with ϵ 2860 at 210 nm; NMR (CCl_4) δ 4.8–6.3 (4 H, m, vinyl CH and OH, 1 H exchanged with D_2O), 2.0–3.0 (2 H, m, allylic CH_2), 1.87 (3 H, s, CH_3), 1.46 and 1.43 (two singlets, total 3 H, CH_3 of epimers), 1.12 (s, 39% of 3 H, CH_3 of one epimer), and 0.97 (s, 61% of 3 H, CH_3 of one epimer); mass spectrum *m/e* (rel intensity) 169 (11, M^+), 152 (42), 127 (33), 112 (60), 110 (59), 108 (69), 97 (76), 94 (37), 82 (56), 69 (58), 68 (94), 67 (100), 55 (30), 53 (49), 43 (69), 42 (45), 41 (39), and 39 (33).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.86; H, 8.97; N, 8.32.

To establish the stability of the isoxazoline **6b** to boiling H_2O, a solution of 111 mg of **6b** in 3 ml of H_2O was refluxed for 3 h and then cooled and extracted with $CHCl_3$. The extract was dried and concentrated to leave 109 mg of the unchanged isoxazoline **6b** that was identified by TLC analysis and comparison of ir spectra. A solution of 2.087 g (12.4 mmol) of the isoxazoline **6b**, 8.59 g (124 mmol) of $HONH_2$·HCl, and 10.12 g (124 mmol) of NaOAc in 45 ml of H_2O was refluxed for 2.5 h and then cooled, treated with $NaHCO_3$, and extracted with CH_2Cl_2. The organic extract was washed with H_2O, dried, and concentrated to leave 1.125 g of colorless liquid. Fractional crystallization from a PhH–hexane mixture separated 669 mg of isomer A of the hydroxylamine **7b** as white prisms, mp 85–92 °C, and 45 mg of isomer B of the hydroxylamine **7b** as white prisms, mp 147–156 °C. The mother liquor from these crystallizations was chromatographed on silica gel. The early fractions (eluent, 40% Et_2O in hexane) contained 28 mg of the crude solid dioxime **9**. Recrystallization (Et_2O–hexane) afforded the pure dioxime **9**, mp 167.5–169°, whose comparison with an authentic sample is described subsequently: ir ($CHCl_3$) 3580 and 3290 cm^{-1} (broad, free and associated OH); NMR (CD_3COCD_3) δ 9.67 and 2.91 (2 H, s, OH, exchanged with D_2O), 1.67 (6 H, s, CH_3), 1.20 (3 H, s, CH_3), and 0.8–1.9 (7 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 169 (18), 128 (100), 112 (34), 100 (21), 55 (32), 43 (37), 42 (47), and 41 (31).

Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 58.17; H, 9.82; N, 15.05.

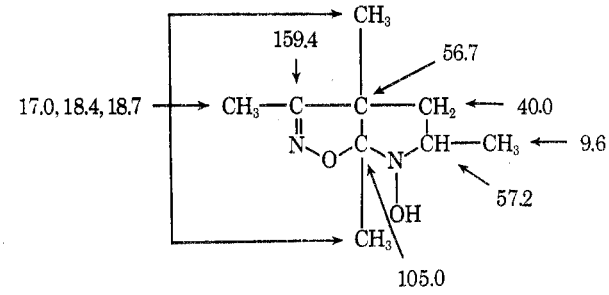
The next chromatographic fractions (eluent 70% Et_2O in hexane) contained 37 mg of isomer B of the hydroxylamine **7b**, mp 148–157 °C (total yield 82 mg or 3.6%). Recrystallization (Et_2O–hexane) separated the pure isomer B of the hydroxylamine **7b** as white prisms: mp 157–158.5 °C; ir ($CHCl_3$) 3570, 3350 (broad, free and associated OH), and 1620 cm^{-1} (C=N); uv (95% EtOH) end absorption with ϵ 2570 at 210 nm; NMR ($CDCl_3$) δ 6.25 (1 H, s, OH, exchanged with D_2O), 2.6–3.3 (1 H, m, NCH<), 1.88 (3 H, s, CH_3), 1.38 (3 H, s, CH_3), 1.21 (3 H, d, J = 6 Hz, CH_3), 1.18 (3 H, s, CH_3), and 1.2–1.8 (2 H, m, CH_2); mass spectrum *m/e* (rel intensity) 184 (44 M^+), 128 (16), 127 (100), 126 (13), 112 (33), and 43 (13).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.79; H, 8.82; N, 15.33.

The final fractions from the chromatography contained 143 mg of isomer A of the hydroxylamine **7b**, mp 91–92 °C (total yield 812 mg or 36%). Recrystallization (PhH–hexane) afforded the pure isomer A of the hydroxylamine **7b** as white prisms: mp 91.5–92.5 °C; ir ($CHCl_3$) 3580, 3430 (OH), and 1630 cm^{-1} (C=N); uv (95% EtOH) end absorption with ϵ 3330 at 210 nm; NMR ($CDCl_3$) δ 4.7 (broad, 1 H, OH, exchanged with D_2O), 2.4–3.0 (1 H, m, NCH<), 1.85 (3, H, s, CH_3), 1.46 (3 H, s, CH_3), 1.20 (3 H, CH_3), 1.20 (3 H, d, J = 6 Hz, CH_3), and 1.2–2.1 (2 H, m, CH_2); mass spectrum *m/e* (rel intensity) 184 (23, M^+), 127 (100), 112 (58), 110 (28), and 43 (14).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.82; H, 8.77; N, 15.10.

The natural abundance ^{13}C NMR spectrum of hydroxylamine **7b**, measured in $CDCl_3$ solution with added Me_4Si, is summarized in the following structure. The chemical shift assignments, indicated in parts per million, are consistent with the spectrum measured with off-resonance decoupling.



To a cold (0 °C) solution of 818 mg (4.45 mmol) of the hydroxylamine **7b**, isomer A, in 3 ml of anhydrous pyridine was added 1.0 ml of freshly distilled PhCOCl. The mixture, from which a white solid separated, was stirred for 30 min at 25 °C and then partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The organic layer was washed with H_2O, dried, and concentrated. The residual yellow liquid (1.724 g) was chromatographed on silica gel. The early fractions (473 mg, eluent 20% Et_2O in hexane) contained benzoic acid and the later fractions (1.262 g, eluent 50% Et_2O in hexane) contained the benzoate **8b** as a pale yellow liquid. Short-path distillation (150–152 °C at 0.03 mm) separated 981 mg (77%) of the benzoate **8b** as a viscous liquid: ir (CCl_4) 1755 cm^{-1} (ester C=O) with no absorption in the 3-μ region attributable to OH or NH groups; uv max (95% EtOH) 229 nm (ϵ 14 300), 278 (1050), and 280 (824); NMR (CCl_4) δ 7.8–8.3 (2, H, m, aryl CH), 7.2–7.7 (3 H, m, aryl CH), 2.9–3.6 (1 (1 H, m, NC<), 1.82 (3 H, s, CH_3), 1.34 (3 H, s, CH_3), 1.26 (3 H, s, CH_3), 1.12 (3 H, d, J = 6 Hz, CH_3), and 1.4–2.2 (2 H, m, CH_2); mass spectrum *m/e* (rel intensity) 288 (3, M^+), 125 (20), 122 (47), 111 (27), 105 (100), 96 (27), 77 (42), and 43 (20).

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.41; H, 7.00; N, 9.65.

Reaction of 3-Methyl-3-propyl-2,4-pentanedione with $HONH_2$. A solution of 3.557 g (23.1 mmol) of the diketone **5b** in 20 ml of EtOAc was hydrogenated at 1 atm and 25 °C over 745 mg of a 5% Pt on carbon catalyst. After 4 h when 670 ml (1.3 equiv) of H_2 had been absorbed, the reaction was stopped and the reaction mixture was filtered and concentrated. A cold (0 °C) solution of the residual liquid in 35 ml of acetone was treated with excess aqueous 8 N H_2CrO_4. After this mixture had been stirred at 0 °C for 10 min, isopropyl alcohol was added to destroy the excess oxidant, and the solution was concentrated and partitioned between CH_2Cl_2 and dilute aqueous HCl. The organic layer was washed with H_2O, dried, concentrated, and distilled to separate 3.084 g (83%) of 3-methyl-3-propyl-2,4-pentanedione as a colorless liquid: bp 68–73 °C (4.7 mm); $n^{25}D$ 1.4360–1.4369; ir (CCl_4) 1720 and 1695 cm^{-1} (C=O); uv max (95% EtOH) 291 nm (ϵ 137); NMR (CCl_4) δ 2.02 (6 H, s, CH_3CO), 1.26 (3 H, s, CH_3), and 0.8–2.0 (7 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 104 (97), 85 (100), 57 (21), 43 (68), and 41 (34).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.36; H, 10.38.

A solution of 830 mg (5.32 mmol) of 3-methyl-3-propyl-2,4-pentanedione, 1.11 g (15.9 mmol) of $HONH_2$·HCl, and 1.31 g (15.9 mmol) of NaOAc in 20 ml of H_2O was refluxed for 3 h and the resulting suspension was cooled and extracted with EtOAc. The organic solution was washed with H_2O, dried, and concentrated to leave 838 mg of semisolid residue. Recrystallization from EtOAc–hexane separated 313 mg (32%) of the dioxime **9** as white needles, mp 165.5–167 °C. The product was identified with the previously described material by a mixture melting point determination and by comparison of ir spectra.

Preparation of the Ketone 10 and Its Oxime 11. To a cold (5–10 °C) solution of the enolate, obtained by reaction of 332 mmol of MeLi (halide-free, Foote Mineral Co.) in 350 ml of DME with 24.17 g (157 mmol) of 1-acetoxy-2-methylcyclohexene,[15] was added, rapidly and with stirring, 40.2 g (332 mmol) of freshly distilled allyl bromide. The resulting solution was stirred for 3 min and then partitioned between hexane and aqueous $NaHCO_3$. The organic layer was dried, concentrated, and fractionally distilled to separate 11.7 g (48%) of the ketone **10** as a colorless liquid, bp 92–100 °C (20 mm), $n^{25}D$ 1.4693 [lit.[16] bp 85–87 °C (12 mm)]. This product **10** exhibited a single GLC peak (silicone gum, SE-30, on Chromosorb P) at 7.5 min and did not contain any significant amount of 2-methylcyclohexanone (GLC retention time 3.5 min): ir (CCl_4) 1710 (C=O) and 1642 cm^{-1} (C=C); uv max (95% EtOH) 288 nm (ϵ 45); NMR (CCl_4) δ 4.7–6.0 (3 H, m, vinyl CH), 2.0–2.5 (4 H, m, CH_2CO and allylic CH_2), 1.5–2.0 (6 H, m, aliphatic CH_2),

and 1.02 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity) 152 (M^+, 52), 137 (53), 109 (75), 95 (53), 93 (78), 83 (64), 81 (50), 68 (54), 67 (81), 55 (100), and 41 (68).

A solution of 1.271 g (8.37 mmol) of the ketone **10**, 1.81 g (26 mmol) of $HONH_2$·HCl, and 3.5 g (26 mmol) of NaOAc in 10 ml of H_2O and 10 ml of EtOH was refluxed for 6 h and then cooled and partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic solution was washed with aqueous NaCl, dried, and concentrated to leave 1.392 g of colorless liquid. Crystallization from H_2O–EtOH separated 1.069 g (77%) of the oxime **11** in fractions melting in the range 44–50 °C. Recrystallization afforded the pure oxime **11** as white plates: mp 48.5–50 °C; ir (CCl_4) 3240 (associated OH) and 1640 cm^{-1} (weak, C=C); uv (95% EtOH) end absorption with ϵ 2790 at 204 nm; NMR (CCl_4) δ 4.7–6.0 (3 H, m, vinyl CH), 1.5–3.1 (10 H, m, aliphatic CH), and 1.10 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity) 167 (M^+, 20), 152 (32), 126 (100), 81 (32), 67 (25), 55 (26), and 41 (47).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found, C, 71.89; H, 10.06; N, 8.60.

Preparation of the Aldehyde 21.[17] To a cold (−14 °C) mixture of 320 g (2.57 mol) of 2-nitropropane (freshly distilled) and 18 ml of methanolic 40% $PhCH_2N^+Me_3OH^-$ was added, dropwise with stirring and cooling (−10 to −14 °C) during 2 h, a solution of 27.0 g (0.477 mol) of acrolein in 110 g (1.26 mol) of 2-nitropropane (freshly distilled). The resulting dark green solution was acidified to pH 5 by the dropwise addition of aqueous 3 M HCl and the resulting pale yellow solution was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure (20 mm) to remove the excess 2-nitropropane. Short-path distillation of the residual yellow liquid separated 31.0 g of crude product as a yellow liquid, bp 85–90° (3 mm). The crude product was redistilled through a 17-cm Vigreux column, keeping the still pot temperature in the range 78–90 °C, to separate 29.9 g (41%) of the nitro aldehyde **21** as a colorless liquid: bp 61–64 °C (0.12 mm), $n^{25}D$ 1.4460 [lit.[18] bp 88.3–89.5 °C (3 mm), $n^{19}D$ 1.4469]; ir (CCl_4) 2721, 2825 (aldehyde CH), 1728 (C=O), 1538 and 1349 cm^{-1} (NO_2); NMR (CCl_4) δ 9.80 (1 H, s, aldehyde CH), 2.0–2.7 (4 H, m, CH_2), and 1.57 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 99 (10), 81 (100), 70 (21), 69 (38), 57 (21), 56 (31), 55 (76), 53 (21), 43 (72), 41 (79), and 39 (39). The product exhibited one major GLC peak (silicone SE-30 on Chromosorb P) at 4.8 min with a minor unidentified impurity at 3.7 min.

Preparation of the Nitro Olefin 22.[17] A solution of $Ph_3P{=}CH_2$, prepared from 64.0 g (0.18 mol) of $Ph_3P^+CH_3Br^-$ in 500 ml of THF and 0.17 mol of MeLi in 98 ml of Et_2O was treated with a solution of 20.0 g (0.138 mol) of the aldehyde **21** in 50 ml of THF. The resulting mixture, from which a white precipitate separated, was refluxed for 24 h and then cooled. After the reaction mixture had been washed with H_2O, the aqueous phase was extracted with Et_2O and the combined organic layers were dried and concentrated under reduced pressure. The residual brown liquid was triturated with pentane to separate the insoluble Ph_3PO and the resulting pentane solution was concentrated to leave 17.0 g of crude product as a yellow liquid. Distillation separated 11.5 g (58%) of the pure nitro olefin **22** as a colorless liquid: bp 45–47 °C (2 mm); $n^{25}D$ 1.4392; ir (CCl_4) 1640 (C=C), 1530, 1345 (NO_2), 992, and 918 cm^{-1} ($CH{=}CH_2$); NMR (CCl_4) δ 4.8–6.2 (3 H, m, $CH{=}CH_2$), 1.8–2.4 (4 H, m, CH_2), and 1.57 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 97 (32), 81 (51), 55 (65), 43 (41), 41 (55), 40 (42), and 39 (23). The product exhibits one major GLC peak (silicone SE-30 on Chromosorb P) at 4.9 min.

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.74; H, 9.16; N, 9.74.

Reduction of the Nitro Olefin 22. To a cold (10 °C) mixture of 5.60 g (39 mmol) of the nitro olefin **22**, 5 ml of H_2O, 10 ml of Et_2O, and 4.2 g (78 mmol) of NH_4Cl was added portionwise and with vigorous stirring during 20 min, 20.0 g (306 mg-atoms) of Zn dust. Throughout this reduction, the reaction mixture was kept under an N_2 atmosphere and was cooled with an ice–water bath. During the addition of Zn, the reaction mixture assumed a light blue color and the temperature rose to 15°. After the mixture had been stirred at 15 °C for 20 min, it was treated successively with 4 ml of H_2O, 2.00 g (37.4 mmol) of NH_4Cl, and 5 ml of Et_2O. Then an additional 5.0 g (76.4 mg-atoms) of Zn dust was added, portionwise with cooling and stirring during 10 min. After addition of this second portion of Zn dust, the pale blue color disappeared and the resulting colorless reaction mixture was stirred at 15–20 °C for 20 min. The reaction mixture was filtered and the residue was washed repeatedly with Et_2O. The combined ethereal filtrates were dried and added to 20 ml of Ac_2O. After the resulting solution had been allowed to stand for 20 min, it was stirred with 50 ml of saturated aqueous $NaHCO_3$ for 20 min and then the Et_2O layer was separated, washed successively with aqueous $NaHCO_3$ and aqueous NaCl, and then dried and concentrated. Fractional crystallization of the residual yellow liquid (4.25 g) from pentane at dry ice temperature separated 1.5 g (15%) of the acetamide **25a** as colorless needles: mp 53–55 °C; ir ($CHCl_3$) 3415 (NH), 1670 (amide C=O), 1640 (C=C), and 910 cm^{-1} ($CH{=}CH_2$); NMR ($CDCl_3$) δ 4.7–6.2 (4 H, m, NH and $CH{=}CH_2$), 1.6–2.3 (7 H, m, CH_2 and a CH_3CO singlet at 1.92), and 1.30 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 155 (M^+, 4), 100 (47), 98 (22), 81 (21), 60 (37), 58 (100), and 43 (20).

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.84; H, 11.05; N, 9.07.

The mother liquors from this crystallization were concentrated and the residual liquid (2.5 g) was chromatographed on 80 g of silica gel with Et_2O–pentane mixtures as the eluent. After separation of 58 mg of early fractions of unidentified liquid [1:99 to 3:97 (v/v) Et_2O–pentane eluent], subsequent fractions, eluted with a 1:9 (v/v) Et_2O–pentane mixture, contained 1.98 g (30%) of the *O*-acetyl hydroxylamine **26** as a colorless liquid: $n^{25}D$ 1.4410; ir (CCl_4) 3220 (NH), 1740 (ester C=O), 1640 (C=C), and 915 cm^{-1} ($CH{=}CH_2$); NMR ($CDCl_3$) δ 7.42 (1 H, broad NH), 4.8–6.2 (3 H, m, $CH{=}CH_2$), 1.8–2.4 (5 H, m, allylic CH_2 with a CH_3CO singlet at 2.04), 1.2–1.8 (2 H, m, CH_2), and 1.07 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 116 (22), 96 (23), 74 (49), 56 (96), 55 (100), and 43 (57). Our efforts to obtain an analytically pure sample of the *O*-actate **26** from these chromatographic fractions were thwarted by the partial thermal decomposition of this material during each attempt to distill it.

In another experiment 2.00 g (13.3 mmol) of the nitro olefin **22** was reduced with 1.50 g (28 mmol) of NH_4Cl, 10 ml of Et_2O, 4 ml of H_2O, and 11.0 g (167 mg-atoms) of Zn dust. An Et_2O solution of the product (141 ml) was divided into two aliquots (41 and 100 ml).

The 41-ml aliquot was concentrated under reduced pressure to leave 353 mg of yellow liquid that contained (NMR analysis) a mixture of the hydroxylamine **20** (ca. 75%) and the amine **23** (ca. 25%): NMR (CCl_4) δ 4.8–6.2 (ca. 5 H, m, $CH{=}CH_2$, NH, and OH), 1.3–2.4 (ca. 4 H, m, CH_2), and two singlets (total ca. 6 H) at 1.12 (CH_3 of amine **23**) and 1.05 (CH_3 of hydroxylamine **20**). After standing overnight under an N_2 atmosphere, the NMR absorption of the sample was very different with much less intense absorption attributable to the vinyl group and replacement of the singlet at δ 1.05 (CH_3 of **20**) with a series of peaks in the region δ 1.0–1.3 attributable to the CH_3 signals of the cyclic hydroxylamine **24a**. Because of the instability of the unsaturated hydroxylamine **20**, we were unable to separate the initially formed mixture of bases **20** and **23**. The sample (containing **23** and **24a**) was added to a cold (5 °C) solution of 2 ml of PhCOCl in 4 ml of pyridine. After the resulting solution had been allowed to stand at 25 °C for 1 h, it was partitioned between Et_2O and aqueous $NaHCO_3$. The ethereal layer was dried, concentrated, and chromatographed on silica gel with PhH as an eluent. After removal of the initial fractions containing $(PhCO)_2O$, subsequent fractions contained 459 mg of the crude benzoate **24b** which was dissolved in Et_2O, washed with aqueous $NaHCO_3$,[19] dried, and concentrated to leave 305 mg (34%) of the benzoate **24b** (ir and NMR analysis) as a yellow liquid. Further purification of this sample by preparative TLC [silica gel coating with a 5:1 (v/v) hexane–Et_2O eluent] and short-path distillation (at 0.3 mm with a Kragen tube) afforded a sample of the pure benzoate **24b** as a colorless liquid, $n^{25}D$ 1.5142, that was identified with a subsequently described authentic sample by comparison of ir, NMR, uv, and mass spectra.

The 100-ml aliquot of ethereal solution (containing **20** and **23**) from the previously described reduction was mixed with 15 ml of acetic anhydride and allowed to stand at 25 °C for 2 h, and subjected to the previously described isolation procedure to give 1.25 g of product as a pale yellow liquid containing [TLC, silica gel coating with a 1:1 (v/v) PhH–Et_2O eluent] a mixture of the acetate **26** (R_f 0.64) and the acetamide **25a** (R_f 0.30). A 520-mg aliquot of this mixture was chromatographed on silica gel to separate 220 mg (31%) of the acetate **26** as a yellow liquid, $n^{25}D$ 1.4420. The remaining aliquot containing a mixture of **25a** and **26** was stirred at 25° with 10 ml of aqueous 10% NaOH for 12 h. The resulting mixture was neutralized with aqueous HCl and extracted with Et_2O. After the ethereal extract had been dried and concentrated the residual liquid (360 mg) was crystallized twice from hexane at low tempera-

tures to separate 75 mg (9%) of the amide **25a** as white needles, mp 52–53 °C.

In another experiment, 1.50 g (10.5 mmol) of the nitro olefin **22** was reduced as described previously with a mixture of Zn, NH_4Cl, H_2O, and Et_2O and the crude product (TLC analysis, a mixture of unchanged **22**, amine **23**, and hydroxylamine **20**) was obtained as 140 ml of an Et_2O solution. An 80-ml aliquot was concentrated under reduced pressure and the residual liquid (0.32 g) was added to a solution of 3 ml of PhCOCl in 6 ml of pyridine. After this solution had been allowed to stand for 1 h at 25 ° C, it was partitioned between Et_2O and aqueous $NaHCO_3$. The ethereal phase was dried, concentrated, and chromatographed on silica gel with a 1:1 (v/v) hexane–PhH eluent. After separation of the early fractions containing $(PhCO)_2O$, subsequent fractions afforded 392 mg of a crude liquid product ($PhCO_2H$, **25b**, and **28**). An Et_2O solution of this material was washed with aqueous $NaHCO_3$, dried, concentrated, and fractionally crystallized from pentane at low temperatures to separate 78 mg (6%) of the benzamide **25b**, mp 88–90 °C. Recrystallization afforded the pure benzamide **25b** as colorless needles: mp 90–91°; ir (CCl_4) 3420 (NH), 1670 (amide C=O), 1640 (C=C), and 910 cm^{-1} ($CH=CH_2$); uv max (95% EtOH) 222 nm (ϵ 11 000); NMR (CCl_4) δ 7.0–7.8 (5 H, m, aryl CH), 5.7–6.2 (4 H, m, NH and $CH=CH_2$), 1.7–2.2 (4 H, m, CH_2), and 1.40 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 217 (M^+, 2), 162 (20), 122 (25), 105 (100), and 77 (36).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.35; H, 8.85; N, 6.51.

The mother liquor from crystallization of the amide **25b** was concentrated and the residual liquid (275 mg) was subjected to preparative TLC separation [silica gel coating with a 3:7 (v/v) Et_2O–pentane eluent]. The more rapidly moving component was separated as 119 mg of pale yellow liquid that crystallized from pentane at low temperatures to give 78 mg (4%) of the dibenzoyl derivative **28** as colorless needles: mp 62.5–63.5 °C; ir (CCl_4) 1768 (ester C=O), 1668 (broad, amide C=O), and 910 cm^{-1} ($CH=CH_2$); uv max (95% EtOH) 232 nm (ϵ 15 000); NMR (CCl_4) δ 7.0–7.9 (10 H, m, aryl CH), 4.8–6.0 (3 H, m, $CH=CH_2$), 1.7–2.7 (4 H, m, CH_2), and 1.48 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 242 (1), 200 (9), 162 (11), 122 (17), 105 (100), and 77 (28).

Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.66; H, 6.87; N, 4.17.

From an additional reduction of 2.0 g (14 mmol) of the nitro olefin **22** with Zn, NH_4Cl, H_2O, and Et_2O), the crude product contained (NMR analysis) a mixture of the hydroxylamine **20** (ca. 45%) and the amine **23** (ca. 55%). An aliquot (38% of the total) of this mixture was concentrated to leave 400 mg of crude product that was heated on a steam bath for 5 min after which NMR analysis indicated the crude product to be a mixture containing mainly the amine **23** and the cyclized hydroxylamine **24a**. This crude product was dissolved in 5 ml of MeOH containing 2 mg of $Cu(OAc)_2$ and air was passed through the solution for 5 min to oxidize the hydroxylamine **24a**. The resulting solution was concentrated and the residue was distilled in a short-path still to separate 55 mg (8% based on the starting nitro olefin **22**) of the nitrone **27** as a yellow liquid, $n^{25}D$ 1.4842. This product was identified with a subsequently described authentic sample of the nitrone **27** by comparison of ir, NMR, uv, and mass spectra.

Preparation of Authentic Samples of the Cyclic Hydroxylamine Derivatives 24 and the Nitrone 27. Following previously described procedures,[20] 8.00 g (55.2 mmol) of the nitro aldehyde **21** was converted to 8.00 g (77%) of the nitro acetal **29** as a colorless liquid: bp 98–99 °C (1 mm), $n^{25}D$ 1.4535 [lit.[20a] bp 105 °C (0.5 mm)]; ir (CCl_4) 1535 and 1345 cm^{-1} (NO_2); NMR (CCl_4) δ 4.78 (1 H, t, J = 4 Hz, acetal CH), 3.7–4.0 (4 H, m, CH_2O), 1.3–2.2 (10 H, m, CH_2 and a CH_3 singlet at 1.57). Subsequent reduction of 5.00 g (26.4 mmol) of the nitro acetal **29** with Zn dust and aqueous NH_4Cl[20b] followed by acidification and cyclization yielded 2.32 g (76%) of the nitrone **30** as a colorless liquid: bp 78 °C (1.4 mm), $n^{25}D$ 1.4940 [lit.[20b] bp 66–67 °C (0.6 mm)]; ir ($CHCl_3$) 1578 cm^{-1} ($CH=N^+-O^-$); uv max (95% EtOH) 234 nm (ϵ 8660) [lit.[20b] 234 nm (ϵ 7700)]; NMR ($CDCl_3$) δ 6.78 (1 H, t, J = 2.5 Hz, $CH=N^+-O^-$), 2.0–2.8 (4 H, m, CH_2), and 1.40 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 113 (M^+, 100), 81 (34), 67 (33), 57 (46), 56 (30), 55 (70), 43 (36), 41 (89), and 39 (61). To 5 ml of an Et_2O solution containing 8.5 mmol of MeLi was added a solution of 354 mg (3.13 mmol) of the nitrone **30** (dried by partial distillation of the solvent from a PhH solution) in 10 ml of Et_2O. The resulting solution was refluxed with stirring for 15 min and then hydrolyzed by addition of 0.5 ml of aqueous NH_4Cl. The Et_2O solution was separated, dried, and concentrated to leave 320 mg of the crude hydroxylamine **24a** as a yellow liquid: NMR (CCl_4) δ 2.7–3.3 (ca. 1 H, m, CHN), 0.9–2.1 [ca. 14 H, m, CH_2, OH, and CH_3 singlets at 1.17 and 1.00 as well as a CH_3 doublet (J = 6 Hz) at 1.17]. This crude product (320 mg) was dissolved in 6 ml of pyridine, cooled in ice, and treated with 2 ml of PhCOCl. After the resulting solution had been stirred for 15 min, it was partitioned between Et_2O and aqueous $NaHCO_3$. The Et_2O phase was dried and concentrated to leave 872 mg of residual brown liquid that was chromatographed on silica gel. After removal of early fractions, which were eluted with PhH and contained $(PhCO)_2O$ and $PhCO_2H$, subsequent fractions, eluted with PhH–Et_2O mixtures (20:1 v/v), were partitioned between Et_2O and aqueous $NaHCO_3$ and then dried and concentrated to leave 313 mg (43%) of the crude benzoate **24b** as a brown liquid. This material was further purified by preparative TLC (silica gel coating with a hexane–Et_2O eluent, 5:1 v/v) followed by short-path distillation under reduced pressure in a Kragen tube to separate the pure benzoate **24b** as a pale yellow liquid: $n^{25}D$ 1.5138; ir (CCl_4) 1750 cm^{-1} (ester C=O); uv max (95% EtOH) 228 nm (ϵ 12 000), 273 (1000), and 279 (820); NMR (CCl_4) δ 7.2–8.2 (5 H, m, aryl CH), 3.1–3.6 (1 H, m, CHN), 1.4–2.3 (4 H, m, CH_2), and three partially resolved CH_3 signals (9 H total) consisting of two singlets at 1.20 and 1.17 with a partially resolved doublet (J = ca. 6 Hz) at ca. 1.17; mass spectrum *m/e* (rel intensity) 122 (82), 111 (40), 105 (89), 96 (36), 83 (68), 77 (58), 70 (55), 55 (56), and 42 (100).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.93; H, 8.27; N, 5.97.

After a comparable reaction of 1.0 g (8.9 mmol) of the nitrone **30** with 14.1 mmol of MeLi in 13 ml of Et_2O, the crude hydroxylamine product **24a** (0.90 g) was dissolved in 5 ml of MeOH containing 1 mg of $Cu(OAc)_2$ and air was passed through the solution for 10 min. After the resulting mixture had been allowed to stand for 24 h, it was concentrated and the residual liquid was distilled under reduced pressure in a short-path still to separate 0.44 g (40%) of the nitrone **27** as a yellow liquid: $n^{25}D$ 1.4835; ir (CCl_4) 1600 cm^{-1} ($>C=N^+-O^-$); uv max (95% EtOH) 229 nm (ϵ 7300) [lit.[20c] 231 nm (ϵ 8400)]; NMR ($CDCl_3$) δ 2.4–2.9 (2 H, m, $CH_2C=N$), 1.8–2.2 (5 H, m, CH_2 and a broad CH_3 singlet at 2.02), and 1.40 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 127 (M^+, 77), 112 (36), 95 (24), 69 (23), 58 (37), 55 (46), 43 (85), 42 (39), 41 (100), and 39 (26).

Preparation of Acyl Derivatives of *t*-BuNHOH (31). Samples of *t*-BuNHOH (**31**) and the dimer of *t*-BuNO (**32**) were prepared by previously described procedures.[6] A solution of 1.00 g (11 mmol) of *t*-BuNHOH in 3.0 ml of Ac_2O was allowed to stand at 25° for 20 min and then the mixture was partitioned between Et_2O and aqueous $NaHCO_3$. After the Et_2O layer had been dried and concentrated, distillation of residual yellow oil (200 mg) under reduced pressure in a short-path still separated 157 mg (11%) of the acetate **33** as a colorless liquid: $n^{25}D$ 1.4100; ir (CCl_4) 3210 (NH) and 1735 cm^{-1} (ester C=O); NMR (CCl_4) δ 7.37 (1 H, broad, NH, exchanged with D_2O), 2.05 (3 H, s, CH_3CO), and 1.08 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 118 (1), 115 (4), 72 (15), 70 (16), 60 (25), 58 (100), 57 (73), 56 (42), 55 (31), 44 (38), 43 (62), 42 (45), 41 (60), and 39 (42).

Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 54.89; H, 10.01; N, 10.70.

A solution of 0.50 g (5.6 mmol) of *t*-BuNHOH in 6.0 ml of pyridine was treated with 3.0 ml of CH_3COCl and the resulting semisolid mixture was allowed to stand at 25 °C for 20 min. The reaction mixture was partitioned between Et_2O and aqueous $NaHCO_3$ and the Et_2O layer was dried and concentrated. The residual liquid (310 mg) was chromatographed on silica gel. After separation of early unidentified fractions (8 mg), the crude ester amide **34** was eluted with hexane–Et_2O (9:1 v/v) as 220 mg of pale yellow liquid. Distillation under reduced pressure in a short-path still separated 200 mg (21%) of the pure ester amide **34** as a colorless liquid: $n^{25}D$ 1.4350 [lit.[21] bp 102 °C (19 mm)]; ir (CCl_4) 1795 (ester C=O) and 1688 cm^{-1} (amide C=O); NMR (CCl_4) δ 2.15 (3 H, s, CH_3COO), 1.85 (3 H, s, CH_3CON), and 1.37 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 173 (M^+, 1), 131 (24), 57 (57), 56 (28), and 43 (100).

A cold (5 °C) solution of 300 mg (3.4 mmol) of *t*-BuNHOH in 6.0 ml of pyridine was treated with 3.0 ml of PhCOCl and the resulting mixture was allowed to stand at 25 °C for 1 h. After the reaction mixture had been partitioned between Et_2O and aqueous $NaHCO_3$, the Et_2O layer was dried and concentrated to leave 1.8 g of liquid. Chromatography on silica gel with a PhH–hexane eluent (1:1 v/v) separated $(PhCO)_2O$ in early fractions followed by 1.07 g of liquid containing the ester amide **35**. Crystallization from pentane afforded 200 mg (20%) of the pure ester amide **35** as colorless

needles: mp 97–99 °C (lit.[21] mp 98–99 °C); ir (CCl_4) 1768 (ester C=O) and 1678 cm^{-1} (amide C=O); uv max (95% EtOH) 233 nm (ϵ 17 000); NMR (CCl_4) δ 7.1–7.9 (10 H, m, aryl CH) and 1.58 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 105 (100), 77 (31), 51 (11), and 41 (5).

To examine the possibility of an intermolecular addition of *t*-BuNHOH to an olefin, a solution of 1.0 g (11.2 mmol) of *t*-BuNHOH and 1 mg of the dimer of *t*-BuNO in 10 g (122 mmol) of freshly purified cyclohexene was heated to 60° under an N_2 atmosphere with stirring for 16 h and then concentrated under reduced pressure. The NMR spectrum (CCl_4) of the residual solid (0.50 g) exhibited only NMR peaks attributable to *t*-BuNHOH with no indication that *N*-*tert*-butyl-*N*-cyclohexylhydroxylamine had been formed.

Methanolysis of the *O*-Acetates 26 and 33 and Cyclization of the Hydroxylamine 23. A solution of 30 mg (0.22 mmol) of the *O*-acetate **33** in 150 μl of MeOH exhibited NMR singlets at δ 2.08 ($COCH_3$) and 1.19 (*t*-Bu). Upon dropwise addition of methanolic 1 M NaOH, 10 μl (0.01 mmol) was required to catalyze the complete conversion of the *O*-acetate **33** to $MeOCOCH_3$ (NMR singlet at δ 2.02) and the hydroxylamine **31** (NMR singlet at δ 1.10) at 25 °C. Similarly, when a solution of 30 mg (0.18 mmol) of the *O*-acetate **26** in 200 μl of MeOH at 25° (NMR singlets at δ 2.09 and 1.01) was treated with 30 μl (0.03 mmol) of methanolic 1 M NaOH, the solution contained CH_3OCOCH_3 (NMR singlet at δ 2.02) and the hydroxylamine **26** (NMR singlet at δ 1.05). When this solution of the hydroxylamine **26** was refluxed for 5 min, the NMR spectra of the solution exhibited a multiplet in the region δ 1.0–1.2 characteristic of the cyclic hydroxylamine **24a**.

This conversion was repeated on a larger scale by treating a solution of 445 mg (2.6 mmol) of the *O*-acetate **26** in 5 ml of MeOH with 200 mg (5.0 mmol) of NaOH. The solution, which immediately turned pale blue in color, was stirred under N_2 for 2 min, neutralized with CO_2, and filtered to remove the $NaHCO_3$ precipitate. The residue was washed with Et_2O and the combined organic solutions were concentrated under reduced pressure to leave 220 mg of the crude liquid hydroxylamine **20**. This crude product was heated on a steam bath for 2 min and then cooled and treated with 1.0 ml of PhCOCl and 2.0 ml of pyridine. The resulting mixture was stirred for 10 min at 25° and then partitioned between Et_2O and aqueous 3 M HCl. After the ethereal layer had been washed with aqueous $NaHCO_3$, dried, and concentrated, the residual crude product (912 mg) was chromatographed on silica gel with Et_2O–pentane mixtures as eluents. After separation of the early fractions [mixtures of $(PhCO)_2O$ and $PhCO_2H$], the fractions (350 mg of yellow liquid) eluted with 1:1 (v/v) Et_2O–pentane mixtures were partitioned between Et_2O and aqueous $NaHCO_3$. The Et_2O layer was dried and concentrated and the residue (308 mg) was rechromatographed on silica gel to separate 180 mg (20% yield based on the acetate **26**) of the liquid benzoate **24b**, $n^{25}D$ 1.5130, that was identified with the previously described authentic sample by comparison of ir and NMR spectra.

Electrochemical Measurements. The polarographic and cyclic voltammetry measurements employed a custom-made polarographic module, utilizing solid-state amplifiers, that followed the typical three-electrode design. Descriptions of the cells, working electrodes (Pt sphere electrode for cyclic voltammetry and dropping Hg electrode for polarography), reference electrodes, reagent purification procedures, and procedures used to calculate $E_{1/2}$ values have been published previously.[22] The polarographic reduction of solutions of the nitroso compound **32** ($6.7–8.9 \times 10^{-3}$ M) in anhydrous DMF containing 0.5 M *n*-Bu_4NBF_4 gave $E_{1/2} = -1.48$ V vs. SCE ($n = 0.8$, $i_d = 39–44$ μA).[23] Reduction of the same solution by cyclic voltammetry (scan rate 500 mV/s) gave a cathodic peak at −1.86 V vs. SCE but no anodic peak was observed. When sufficient H_2O was added to make the solution 1.0 M in H_2O, the cathodic peak was shifted to −1.75 V vs. SCE and an anodic peak, attributable to an unidentified reaction product, was observed at −0.87 V vs. SCE. Attempts to examine the oxidation of *t*-BuNHOH by cyclic voltammetry in a 0.5 M solution of *n*-Bu_4NBF_4 in either anhydrous DMF or in DMF containing 1 M H_2O gave no oxidation peak within the range −1.3 to +0.5 V. Similarly, a solution of *t*-BuNHOH in an aqueous buffer (pH 7.0) exhibited no polarographic oxidation wave in the range −0.5 to +0.2 V vs. SCE. In more basic solution, the oxidation wave was shifted to more negative values.[24] In aqueous pH 10.0 buffer, the *t*-BuNHOH ($8.3–8.5 \times 10^{-3}$ M) solution exhibited an oxidation wave with $E_{1/2}$ −0.20 V vs. SCE ($n = 0.9$, $i_d = 48–52$ μA) and in a more alkaline aqueous solution (pH ~ 13, 1.5 M Na_2SO_3 and 0.14 M KOH),[25] *t*-BuNHOH ($6.7–7.6 \times 10^{-3}$ M) exhibited an $E_{1/2}$ value of −0.51 V vs. SCE ($n = 1.5$, $i_d = 46–47$ μA). A solution of the *O*-acetate **33** (0.009 M) in aqueous MeOH (15:85 v/v) containing 0.5 M *n*-Bu_4NBF_4 exhibited no polarographic oxidation wave in the range −0.5 to 0.0 V; when sufficient methanolic NaOH solution was added to saponify the *O*-acetate **33** and make the solution 0.05 M in NaOH, a polarographic oxidation wave attributable to **31** was observed with $E_{1/2} = -0.39$ V vs. SCE ($n = 1.0$, $i_d = 24$ μA). Comparable behavior was observed for the *O*-acetate **26** ($2.7–12 \times 10^{-3}$ M) whose solution in aqueous MeOH containing 0.5 M *n*-Bu_4NBF_4 exhibited no polarographic oxidation wave in the range −0.5 to 0.0 V. After addition of methanolic NaOH to saponify the acetate **26** and make the solution 0.05 M in NaOH, this solution of the hydroxylamine **20** exhibited a polarographic oxidation wave at $E_{1/2} = -0.42$ V vs. SCE ($n = 1.1$, $i_d = 5–27$ μA). The polarographic oxidation of this solution was reexamined at intervals after the solution had been stirred under N_2 and after the solution had been exposed to O_2 of the air. The i_d value decreased regularly as the solution was stirred but no new oxidation peak was observed. After exposure to O_2 of the air for 10 min, the oxidation wave attributable to hydroxylamines **20** and/or **24a** was no longer observed indicating that oxidation of **20** to the corresponding nitroso compound or **24a** to the nitrone **27** was complete. Polarographic oxidation of a solution of the cyclic hydroxylamine **24a** ($1.4–2.0 \times 10^{-2}$ M) in aqueous MeOH (15:85 v/v) containing 0.5 M *n*-Bu_4NBF_4 and 0.05 M NaOH gave $E_{1/2} = -0.47$ V vs. SCE ($n = 0.8$, $i_d = 19–24$ μA). Since the $E_{1/2}$ values for oxidation of the hydroxylamine **20** before (−0.42 V) and after cyclization (to form **24a**, $E_{1/2} = -0.47$ V) are very similar, our failure to observe two resolved oxidation waves during the change **20** → **24a** → **27** is understandable.

Registry No.—**5a**, 3508-79-0; **5b**, 53315-95-0; **6a**, 57620-40-3; **6b**, 57620-41-4; **7a**, 57620-42-5; **7b**, 57620-43-6; **8a**, 57620-44-7; **8b**, 57620-45-8; **9**, 57620-46-9; **10**, 16178-87-3; **11**, 57620-47-0; **20**, 57620-48-1; **21**, 57620-49-2; **22**, 57620-50-5; **23**, 819-45-4; **24a**, 57620-51-6; **24b**, 57620-52-7; **25a**, 57620-53-8; **25b**, 835-85-8; **26**, 57620-54-9; **27**, 4567-18-4; **28**, 57620-55-0; **29**, 57620-56-1; **30**, 3317-61-1; **31**, 16649-50-6; **33**, 51338-99-9; **34**, 53242-00-5; **35**, 51339-08-3; $HONH_2$·HCl, 5470-11-1; PhCOCl, 98-88-4; 3-methyl-2,4-pentanedione, 815-57-6; allyl bromide, 106-95-6; 3-methyl-3-propyl-2,4-pentanedione, 57620-57-2; methyllithium, 917-54-4; 1-acetoxy-2-methylcyclohexene, 1196-73-2; 2-nitropropane, 79-46-9; acrolein, 107-02-8; methylenetriphenylphosphorane, 3487-44-3; acetic anhydride, 108-24-7; acetyl chloride, 75-36-5.

References and Notes

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(2) (a) Georgia Institute of Technology; (b) Union Carbide Corp.

(3) D. T. Manning and H. A. Coleman, *J. Org. Chem.*, **34**, 3248 (1969).

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(7) This same reducing system was also employed to prepare the hydroxylamine **16**. See ref 5a.

(8) This relatively low isolated yield is attributable to the difficulties in isolating the hydrolytically and thermally unstable liquid benzoate **24b**. NMR analysis of the reaction mixture indicated that hydroxylamine **24a** is the major product formed from **20**.

(9) For examples, see (a) T. R. Juneja and H. Dannenberg, *Tetrahedron*, **31**, 695, 701 (1975); (b) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds", Vol. 2, W. A. Benjamin, New York, N.Y., 1966, pp 2–3 and 10–11.

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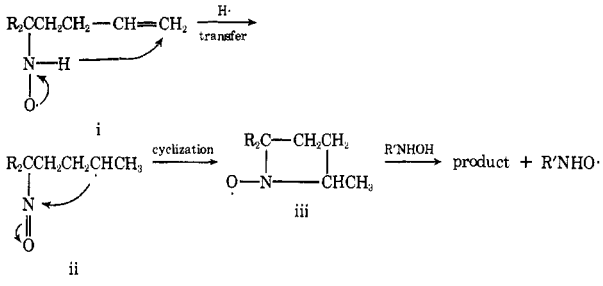
are unaware of precedent for the first step, i → ii, the transfer of an H· atom from a radical to a double bond. Consequently, we presently prefer the radical addition mechanism (**37** in Scheme VII) for which some precedent exists (ref 5b,c) but have no experimental basis for excluding the alternative radical chain process involving i → ii → iii.



(12) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 237 or Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The proton NMR spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 NMR spectrometer and the ^{13}C NMR spectra were obtained with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer Model RMU-7 or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

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(24) The shift of $E_{1/2}$ to more negative potentials with increasing pH has also been observed in the polarographic oxidation of PhNHOH. See ref 10.

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A New Synthesis of 2-Alkylpyrrolidines and 2-Alkylpiperidines[1]

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Each of the *N*-(4-pentenyl)hydroxylamine derivatives **7** and **17** underwent facile cyclization to the 2-methylpyrrolidine derivatives **10** and **18** when the starting materials were warmed briefly to 50–60 °C. Subsequently reduction and acetylation with Zn, HOAc, and Ac_2O afforded the corresponding amides **12** and **19**. Cyclization of the homologous *N*-(5-hexenyl)hydroxylamines **27** and **34** to the 2-methylpiperidine derivatives **28** and **35** (isolated after conversion to the amides **29** and **22**) required higher temperatures (130–140 °C) and longer reaction times (1–2 h). Attempts to cyclize the unsaturated hydroxylamines **38** and **39** were unsuccessful. The ease and direction of these various cyclizations, believed to be radical chain reactions, parallels the behavior of related alkenyl carbon radicals **5**.

In an accompanying paper[2] we have described a study of the cyclization of certain unsaturated hydroxylamines **1** (Scheme I) to the corresponding *N*-hydroxypyrrolidines **2**. We believe this cyclization to be a radical chain process involving the intermediate radicals **3** and **4** in which the step **3** → **4** is analogous to the cyclization **5** → **6** of certain carbon radicals **5**.[3–5] In the previous study[2] the synthetic attractiveness of the cyclization **1** → **2** was mitigated by the facts that synthesis of the starting hydroxylamines **1** by selective reduction of the corresponding nitro olefins was tedious and isolation of the thermally unstable, easily oxidized cyclic hydroxylamines **2** was difficult. In this paper we describe alternative procedures that overcome these problems.

An especially simple and efficient synthesis of unsaturated hydroxylamine derivatives, e.g., **7** (Scheme II), from the corresponding unsaturated carbonyl compounds **8** utilized the selective reduction of the oxime **9** with $NaB(CN)H_3$ in acidic MeOH.[6] Although the original procedure recommended[6a] performing the reaction at pH 4 (bromocresol blue indicator), we found the reduction of ketox-

Scheme I