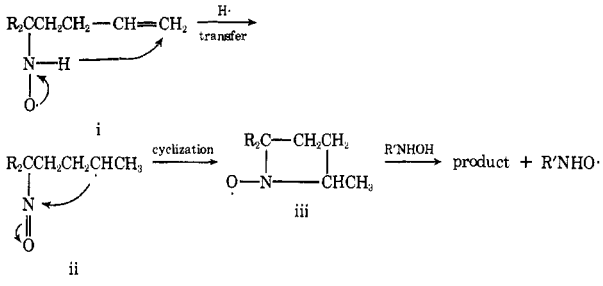
are unaware of precedent for the first step, i → ii, the transfer of an H· atom from a radical to a double bond. Consequently, we presently prefer the radical addition mechanism (**37** in Scheme VII) for which some precedent exists (ref 5b,c) but have no experimental basis for excluding the alternative 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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(23) (a) An $E_{1/2}$ value of −1.36 V vs. SCE has been reported for *t*-BuNO in acetonitrile solution: H. Sayo, Y. Tsukitani, and M. Masui, *Tetrahedron*, **24**, 1717 (1968). (b) The reduction of PhNO in aqueous solutions of varying pH has been studied polarographically (ref 10) and the reduction of PhNO in aprotic solvents has been studied by cyclic voltammetry [M. R. Asirvatham and M. D. Hawley, *Electroanal. Chem., Interfacial Electrochem.*, **57**, 179 (1974)].

(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.

(25) These conditions for the polarographic determination of *N*-alkylhydroxylamines were described by P. E. Iverson and H. Lund, *Anal. Chem.*, **41**, 1322 (1969). These authors report an $E_{1/2}$ value of −0.47 V vs. SCE for *t*-BuNHOH.

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

Herbert O. House* and Len F. Lee

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

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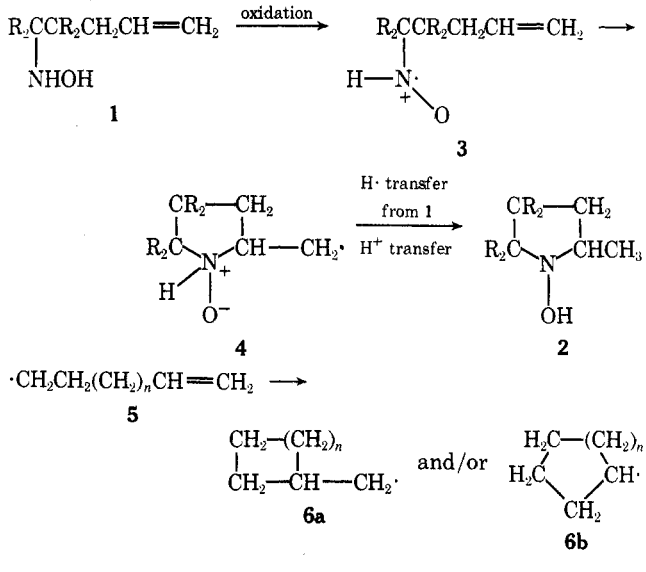
Each of the *N*-(4-pentenyl)hydroxylamine derivatives **7** and **17** underwent facile cyclization to the 2-methylpyrrolidine derivatives **10** and **18** when the starting materials were warmed briefly to 50–60 °C. Subsequently reduction and acetylation with Zn, HOAc, and Ac_2O afforded the corresponding 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**.

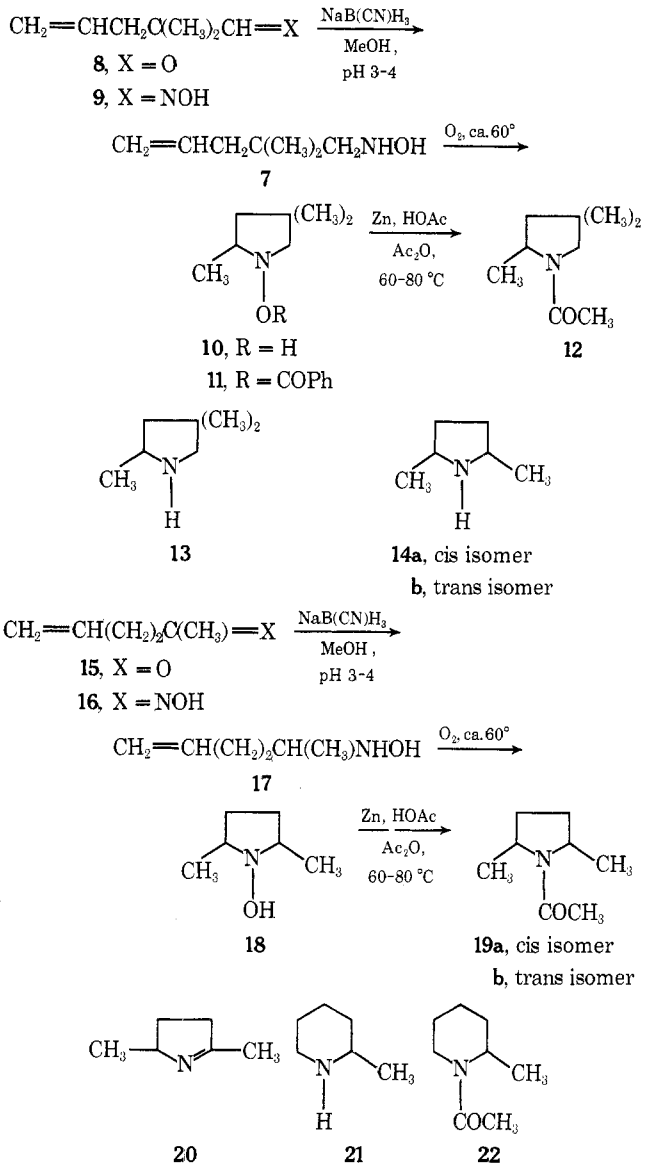
In an accompanying paper[2] we have described a study of the cyclization of certain unsaturated hydroxylamines **1** (Scheme I) to the corresponding *N*-hydroxypyrrolidines **2**. We believe this cyclization to be a radical chain process involving the intermediate radicals **3** and **4** in which the 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



Scheme II

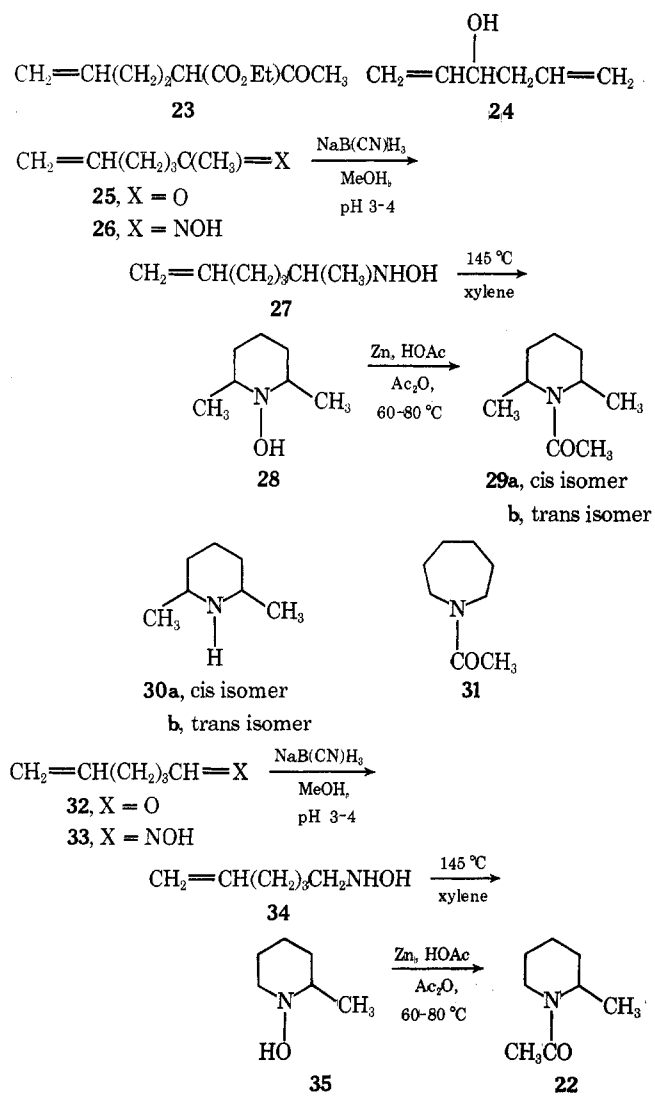


imes at this pH to be rather slow and recommend use of a reaction mixture at pH 3–4 (methyl orange indicator). For our purposes the reduction of the unsaturated oximes to hydroxylamines with BH_3 in THF[7] was not a suitable alternative because of a competing reaction of the olefin with BH_3. Although the reductions of oximes **9** and **16** with $NaB(CN)H_3$ produced solutions of the unsaturated hydroxylamines **7** and **17**, even brief warming of these intermediates during product isolation, like previously studied *N*-(4-pentenyl)hydroxylamine derivatives,[2] resulted in cyclization to form the pyrrolidine derivatives **10** and **18**.

Although NMR analysis indicated that pyrrolidine **10** was the major, if not exclusive, product obtained on cyclization of **7**, the isolation of pure samples of either the water-soluble, easily oxidized hydroxylamine **10** or its thermally unstable benzoyl derivative **11** was not satisfactory procedures. Consequently, we subjected the crude cyclized products **10** and **18** to reduction with Zn in a mixture of HOAc and Ac_2O in order to produce the more easily isolated acetamide derivatives **12** and **19**. Although both the intermediate hydroxylamine **18** (NMR analysis) and the final amide **19** were mixtures of stereoisomers, we presume that the composition of the final isolated product (ca. 35% **19a** and 65% **19b**) does not necessarily reflect the stereoisomeric composition of the intermediate hydroxylamine **18** because the imine **20** is a probable intermediate in the reduction process. By use of an authentic sample of the isomeric piperidine derivative **22**, we demonstrated that the amounts of this six-membered cyclic product present were below the limits we could detect by GLC analysis. Consequently, cyclization of the nitroxide radical from **17**, like the analogous carbon radical **5** (n = 2),[3] proceeds to form predominantly, if not exclusively, a five-membered ring (analogous to **6a**, n = 2) rather than a six-membered ring (analogous to **6b**, n = 2). The overall yields of the amides **12** and **19**, based on the starting oximes, were 51 and 65%, respectively.

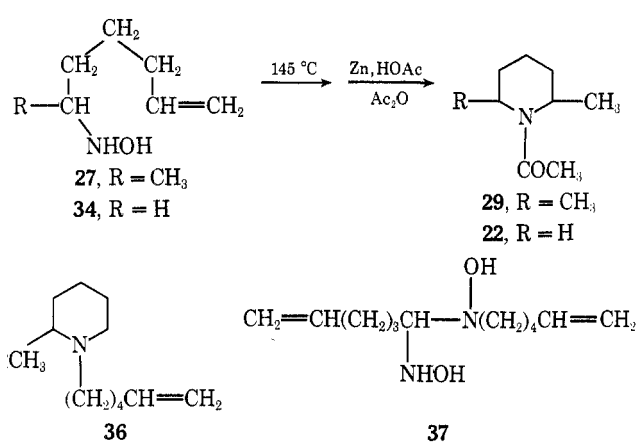
To explore the use of this free-radical cyclization reaction for the preparation of six-membered rings, the two oximes **26** and **33** (Scheme III) were reduced with $NaB(CN)H_3$ to form the unsaturated hydroxylamines **27** and **34**. The cyclization of these materials **27** and **34** was clearly less facile than cyclization of the lower homologues **7** and **17** since the hydroxylamines **27** and **34** could be isolated after solutions containing them had been heated on a steam bath to remove solvents. Cyclization of these intermediates **27** and **34** was accomplished by adding them in xylene solution to refluxing xylene (ca. 145 °C) under high-dilution conditions. Although cyclization was observed when the hydroxylamines **27** and **34** were heated to 160 °C without solvent, various by-products were formed under these conditions. Application of the Zn–HOAc–Ac_2O re-

Scheme III



duction procedure to the two crude cyclic products **28** and **35** yielded the amides **29** (mainly the trans isomer **29b**) and **22.** By use of an authentic sample of the amide **31,** we were able to demonstrate that the cyclization of hydroxylamine **34** and subsequent reduction yielded the six-membered ring product **22** with none of the seven-membered ring product **31** being detected by our GLC analysis. Both the slower rates of cyclization of nitroxides from **27** and **34** compared to the nitroxides from **7** and **17** and the cyclizations to form six- rather than seven-membered products are again in accord with studies of analogous carbon-centered radicals **5** (n = 3).[3,8] These observations are also in agreement with the observation that N-centered radicals (from N-chloro amides) were successfully cyclized to form five-membered rings but not the isomeric six-membered rings.[5d] The overall yields of amides **22** and **29,** based on the starting oximes, were ca. 28 and 40%, respectively.

Although the cyclization of the hydroxylamine **27** under high-dilution conditions followed by reduction and acetylation yielded the amide **29b** accompanied by only minor amounts of by-products, the analogous reactions with the hydroxylamine **34** formed both the amide **22** and several by-products even when the cyclization was performed under high-dilution conditions. The principal by-products obtained from hydroxylamine **34** were mixtures of higher molecular weight materials and a volatile by-product shown to be amine **36.** While the origin of this by-product **36** is uncertain, it may result from a bimolecular reaction of the hydroxylamine **34** with the oxime **33** (from oxidation of **34**) to form a bimolecular product such as **37** that undergoes cyclization and reduction. In any event, it is apparent that the cyclization is facilitated by the methyl substituent present in **27** but not **34.** The ability of alkyl substituents to facilitate ring closures (the Thorpe–Ingold effect) has been noted previously in cyclization of derivatives of the carbon radical **5** (n = 2).[9]



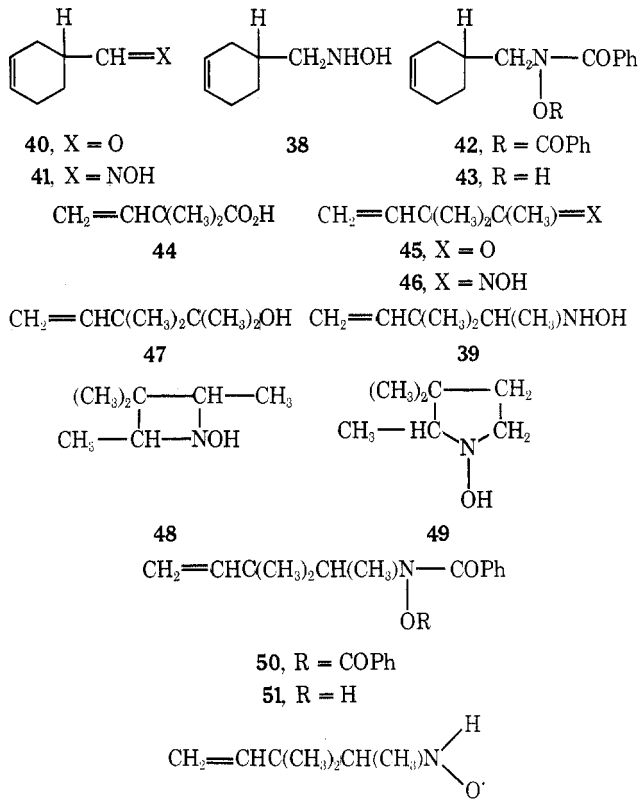
27, R = CH_3
34, R = H

29, R = CH_3
22, R = H

36 **37**

To further explore the scope of this cyclization, we examined the hydroxylamines **38** and **39** (Scheme IV). After the hydroxylamine **38** (characterized as the hydroxamic acid **43**) had been heated to 170 °C for 1 h, we could discern no evidence of cyclization (NMR analysis) suggesting that the extra strain involved in forming either of the two possible bicyclic hydroxylamines was sufficient to prevent cyclization. The hydroxylamine **39,** obtained by the usual reduction of the oxime **46,** was characterized as the crystalline hydroxamic acid **51.** Heating the hydroxylamine **39** under a variety of conditions failed (NMR analysis) to form either of the cyclized products **48** or **49.** Instead, the hydroxylamine **39** was partially converted to the oxime **46** by oxidation to the nitroxide **52** which failed to cyclize and underwent disproportionation to form the oxime. This observation is again compatible with the behavior of the corresponding carbon radical **5** (n = 1) where cyclization (to form **6b,** n = 1) usually is not observed.[3] In the previously mentioned study[5d] of the photochemically induced cyclization of N-chloro amides, the N-centered radical analogous to that derived from hydroxylamine **38** did cyclize but the radical analogous to the nitroxide from hydroxylamine **39** failed to undergo cyclization.

Scheme IV



40, X = O
41, X = NOH

38

42, R = COPh
43, R = H

44

45, X = O
46, X = NOH

47 **39**

48 **49**

50, R = COPh
51, R = H

52

Experimental Section[10]

Preparation and Cyclization of the Hydroxylamine 17. Reaction of 49 g (0.50 mol) of the ketone **15** (Aldrich Chemical Co.), with a refluxing solution of 104 g (1.50 mol) of $HONH_3Cl$, 123 g (1.50 mol) of NaOAc, and 20 ml of EtOH in 500 ml of H_2O for 40 h yielded 44.4 g (88%) of the oxime **16** as a colorless liquid: bp 64–66 °C (2.5 mm), $n^{25}D$ 1.4632 [lit. bp 187,[11a] 190 °C[11b]]; ir (CCl_4) 3580, 3250 (OH), 1640 (C=N), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 9.67 (1 H, broad s, OH), 4.8–6.2 (3 H, m, vinyl CH), 2.1–2.7 (4 H, m, CH_2), and 1.83 (3 H, s, CH_3); mass spectrum m/e (rel intensity) 113 (M^+, 11), 112 (9), 98 (35), 96 (35), 81 (35), 73 (40), 55 (89), 54 (70), 53 (32), 43 (20), 42 (100), 41 (85), and 39 (63). The product exhibits two GLC peaks (Carbowax 20M on Chromosorb P) with retention times of 14.0 (ca. 8%) and 21.2 min (ca. 92%) that presumably correspond to the two geometrical isomers of oxime **16.**

To a solution of 5.65 g (50 mmol) of the oxime **16,** 3.4 g (54 mmol) of $NaB(CN)H_3$, and 1 mg of methyl orange in 50 ml of MeOH was added, dropwise and with stirring, a mixture (1:1 v/v) of MeOH and aqueous 12 M HCl. The rate of addition was controlled so that the color of the reaction mixture remained reddish-orange (pH 3–4)[6] for a period of 1 h. Then the solution was concentrated under reduced pressure, made basic by the addition of aqueous 6 M KOH, and extracted with Et_2O. The ethereal extract was dried (K_2CO_3) and concentrated in a water bath (50–70 °C) to leave 5.54 g of crude liquid hydroxylamine **18.** From two comparable reactions where the reduction was effected either at pH 3–4 (methyl orange indicator) for 1 h or at pH 4–5 (bromocresol blue indicator)[6a] for 5 h, the crude liquid product (83–95% yield) was found to contain (NMR analysis) mainly the stereoisomers of the cyclic hydroxylamine **18:** NMR (CCl_4) δ 7.63 (ca. 1 H, broad s, OH), 1.2–3.5 (ca. 6 H, m, aliphatic CH), and two doublets (J = 6.5 Hz) at 1.18 (minor) and 1.13 (major) (ca. 6 H, CH_3 groups of stereoisomers of **18**). When the crude product was not heated during concentration of the solvents, the NMR spectrum of the crude

product also exhibited a multiplet in the region δ 4.8–6.2 (vinyl CH) suggesting that the cyclization **17** → **18** was incomplete.

The crude hydroxylamine **18** (5.54 g) from the above experiment was dissolved in a mixture of 20.4 g (0.20 mol) of Ac_2O and 18 g (0.30 mol) of HOAc and then 14.0 g (0.15 g-atom) of Zn dust was added, portionwise with vigorous stirring during 30 min. The reaction mixture, whose temperature rose to 100 °C during the addition of the Zn, was cooled to 70 °C and then stirred at 60–70 °C for an additional 3 h. The resulting mixture was filtered and the residue was washed thoroughly with Et_2O. The combined filtrate and washings were concentrated under reduced pressure and then made basic (aqueous NaOH) and continuously extracted with Et_2O. After the ethereal extract had been dried and concentrated, distillation of the residual liquid (6.3 g) separated 4.58 g (65%) of a mixture of the stereoisomers of amide **19** as a colorless liquid: bp 61–66 °C (1 mm); $n^{25}D$ 1.4662; ir (CCl_4) 1645 cm^{-1} (amide C=O); NMR (CCl_4) δ 3.7–4.3 (2 H, m, CHN), 1.3–2.4 (7 H, m, CH_2 including a CH_3CO singlet at 1.92), and three overlapping doublets (J = 6.5 Hz) at 1.22, 1.17, and 1.10 (6 H, CH_3 of stereoisomeric amides); mass spectrum m/e (rel intensity) 141 (M^+, 66), 126 (35), 99 (38), 98 (18), 85 (23), 84 (100), 67 (19), 57 (25), 43 (69), 42 (35), and 41 (28). The product exhibited two GLC peaks (Carbowax 20M on Chromosorb P) with retention times of 32.9 (ca. 35%) and 34.8 min (ca. 65%) attributable to the cis (**19a**) and trans (**19b**) isomers of amide **19**. However, no peak was observed at 46.4 min, the retention time of the structurally isomeric amide **22**.

To obtain an authentic sample of the amide **19**, a cold (5 °C) solution of 500 mg (5.05 mmol) of the amine **14** (a mixture of stereoisomers obtained from Aldrich Chemical Co.) and 2.0 g of Et_3N in 10 ml of PhH was treated with 2.0 g of CH_3COCl. After the resulting mixture had been allowed to stand for 30 min, it was partitioned between aqueous 6 M KOH and Et_2O, and the ethereal layer was dried and concentrated. Distillation of the residual liquid in a short-path still separated 249 mg (35%) of the crude amide **19**. A pure sample of the mixture of amide **19** stereoisomers was collected (GLC) as a colorless liquid, $n^{25}D$ 1.4647, that contained (GLC, 8-m column of TCEP on Chromosorb P) the cis amide **19a** (ca. 64%, 138.0 min) and the trans amide **19b** (ca. 36%, 147.2 min).

To complete the characterization of the amides **19**, the mixture of amines **14**[12] (Aldrich Chemical Co.) was separated by collection from GLC (8-m column packed with Carbowax 20M on base-washed Chromosorb P). The retention times follow: cis amine **14a**, 53.0 min; trans amine **14b**, 59.8 min. The collected cis amine **14a** formed a picrate as yellow needles from PhH, mp 118–119 °C (lit.[12] mp 116–118 °C), and the collected trans amine **14b** formed a picrate as yellow needles from PhH, mp 130–131 °C (lit.[12] mp 126–127, 130–131 °C). Reaction of 0.13 g of the cis amine **14a** with excess Ac_2O in pyridine for 2 h followed by separation of the neutral material gave 196 mg of crude product. A collected (GLC, Carbowax 20M on Chromosorb P) sample of the pure cis amide **19a** (yield 90 mg or 42%) was obtained as a colorless liquid: $n^{25}D$ 1.4649; ir (CCl_4) 1640 cm^{-1} (amide C=O); NMR (CCl_4) δ 3.7–4.3 (2 H, m, CHN), 1.5–2.4 (7 H, m, aliphatic CH including a CH_3CO singlet at 1.97), and 1.25 (6 H, d, J = 6.5 Hz, CH_3); mass spectrum m/e (rel intensity) 141 (M^+, 21), 126 (9), 99 (11), 84 (100), and 43 (21).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.04; H, 10.72; N, 9.85.

After reaction of 0.16 g of the trans amine **14b** with excess Ac_2O in pyridine, the crude neutral product was separated and 135 mg (51%) of the trans amide **19b** was collected (GLC) as a colorless liquid: $n^{25}D$ 1.4700; ir (CCl_4) 1640 cm^{-1} (amide C=O); NMR (CCl_4) δ 3.7–4.4 (2 H, m, CHN), 1.4–2.4 (7 H, m, aliphatic CH including a CH_3CO singlet at 1.97), 1.21 (3 H, d, J = 6.5 Hz, CH_3), and 1.15 (3 H, d, J = 6.5 Hz, CH_3); mass spectrum m/e (rel intensity) 141 (M^+, 55), 126 (34), 99 (20), 98 (18), 85 (20), 84 (100), 43 (64), 42 (33), and 41 (23).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.02; H, 10.74; N, 9.85.

When mixtures of the two stereoisomeric amides **19** were subjected to GLC analysis (8-m column packed with TCEP on Chromosorb P), the retention times were as follows: cis amide **19a**, 155 min, and trans amide **19b**, 165 min. Comparison of the GLC retention times and ir, NMR, and mass spectra of the mixture of amides **19** obtained from the hydroxylamine **18** with the corresponding data for the pure amides **19a** and **19b** allowed us to confirm the identities of the amide products.

To obtain an authentic sample of the amide **22**, 10.1 g (102 mmol) of 2-methylpiperidine (**21**, Aldrich Chemical Co.) was treated with 11.0 g (108 mmol) of Ac_2O and the resulting mixture was stirred for 1 h. Then 20 ml of aqueous 6 M KOH was added, stirring was continued for 30 min, and the mixture was extracted with Et_2O. After the ethereal extract had been washed with aqueous 3 M HCl, dried, and concentrated, distillation separated 9.09 g (64%) of the amide **22**, bp 75–79 °C (2 mm). This sample was washed with aqueous 5% NaOH, dried, and redistilled to afford 5.9 g of the pure amide **22** as a colorless liquid: bp 88–89 °C (2.5 mm), $n^{25}D$ 1.4785 [lit. bp 55–56 °C (0.15 mm),[13a] 86.5–87.5 °C (3.5 mm)[13b]]; ir (CCl_4) 1640 cm^{-1} (amide C=O); NMR (CCl_4) δ 2.2–4.5 (3 H, m, CH_2N and CHN), 1.93 (3 H, s, $COCH_3$), 1.3–1.9 (6 H, m, CH_2), and 1.15 (3 H, d, J = 7 Hz, CH_3); mass spectrum m/e (rel intensity) 141 (M^+, 20), 126 (18), 84 (100), 70 (11), 57 (10), 56 (22), 55 (10), 43 (49), 42 (20), and 41 (14).

Preparation of the Oxime 26. To a solution of the Na enolate, prepared from 47 g (0.36 mol) of ethyl acetoacetate, 8.7 g (0.38 g-atom) of Na, and 125 ml of EtOH, was added, dropwise and with stirring during 2 h, 50 g (0.37 mol) of 4-bromo-1-butene. The resulting mixture was refluxed with stirring for 1 h and then cooled, filtered, and concentrated. Fractional distillation of the residual liquid separated 33.5 g (51%) of the alkylated β-keto ester **23** as a colorless liquid: bp 111–116 °C (15 mm), $n^{25}D$ 1.4402 [lit.[14] bp 103–110 °C (22 mm)]; ir (CCl_4) 1740 (ester C=O), 1720 (C=O), 1640 (C=C), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.7–6.1 (3 H, m, CH=CH_2), 4.15 (2 H, q, J = 7 Hz, ethoxyl CH_2), 3.33 (1 H, t, J = 6.5 Hz, COCHCO), 1.7–2.3 (7 H, m, CH_2 including a CH_3CO singlet at 2.12), and 1.25 (3 H, t, J = 7 Hz, ethoxyl CH_3); mass spectrum m/e (rel intensity) 184 (M^+, 2), 130 (26), 73 (21), 55 (40), and 43 (100). A mixture of 33 g (179 mmol) of the β-keto ester **23** and 400 ml of aqueous 5% NaOH was refluxed with stirring for 10 h and then cooled and extracted with Et_2O. The ethereal solution was dried and fractionally distilled to separate 15.7 g (79%) of the ketone **25** as a colorless liquid: bp 72–73 °C (50 mm), $n^{25}D$ 1.4240 [lit.[14] bp 71–73 °C (50 mm), $n^{25}D$ 1.4223]; ir (CCl_4) 1720 (C=O), 1640 (C=C), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.7–6.1 (3 H, m, CH=CH_2), 2.37 (2 H, t, J = 6.5 Hz, CH_2CO), and 1.3–2.2 (7 H, m, CH_2 including a CH_3CO singlet at 2.00); mass spectrum m/e (rel intensity) 112 (M^+, 17), 94 (10), 58 (72), 55 (12), 43 (100), 42 (22), and 39 (10). The product exhibited a single peak on GLC analysis (silicone SE-30 on Chromosorb P). Our attempts to prepare this ketone **25** by the vapor phase pyrolysis (Cope rearrangement) of 3-methyl-1,5-hexadien-3-ol (from CH_2=$CHCOCH_3$ and CH_2=$CHCH_2MgBr$) in a tube heated to 400–450 °C resulted in the formation of a mixture (NMR and GLC analysis, $AgNO_3$ in Carbowax 20M on Chromosorb P) of the desired ketone **25** (ca. 64%, retention time 49.6 min) and three other components: 31.2 min, ca. 11%; 40.0 min (ca. 19%); and 54.2 min (ca. 1%). The second most abundant component in the mixture (a methyl ketone, ir and NMR analysis) is believed to be methyl 2-methylcyclobutyl ketone formed by thermal rearrangement of the ketone **25**.[15]

To a cold (5 °C) mixture of 15.0 g (134 mmol) of the ketone **25**, 14 g (0.20 mol) of $HONH_3Cl$, and 60 ml of H_2O was added, dropwise and with stirring during 20 min, a solution of 9.9 g (94 mmol) of Na_2CO_3 in 80 ml of H_2O.[16] After the reaction mixture had been stirred in an ice bath for 1 h, and at 25 °C for 1 h, it was extracted with Et_2O and the ethereal extract was dried and concentrated. Distillation of the residual liquid separated 16.2 g (96%) of the oxime **26** as a colorless liquid: bp 73–75 °C (2 mm), $n^{25}D$ 1.4652; ir (CCl_4) 3580, 3230 (OH), 1640 (C=N), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 9.5 (1 H, broad s, OH), 4.7–6.2 (3 H, m, CH=CH_2), and 0.9–2.6 (9 H, m, CH_2 including a CH_3C=N singlet at 1.82); mass spectrum m/e (rel intensity) 127 (M^+, 15), 112 (24), 86 (10), 73 (100), 69 (10), 68 (12), 67 (11), 55 (44), 42 (36), 41 (47), and 39 (32).

Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.20; H, 10.33; N, 10.94.

Preparation and Cyclization of the Hydroxylamine 27. A solution of 674 mg (5.3 mol) of the oxime **26**, 346 mg (5.5 mmol) of $NaB(CN)H_3$, and cresol blue indicator in 20 ml of MeOH was treated with a 6 M HCl solution in H_2O–MeOH during 5 h to maintain a yellow (pH 4) reaction solution and then subjected to the previously described isolation procedure to yield 596 mg (86%) of the crude solid hydroxylamine **27**, mp 38–42 °C. The crude hydroxylamine **27** was sublimed under reduced pressure to give the pure hydroxylamine **27** as colorless needles: mp 42–44 °C; ir (CCl_4) 3590, 3230 (OH, NH), 1640 (C=C), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 6.29 (2 H, s, OH, NH), 4.8–6.2 (3 H, m, CH=CH_2), 2.7–3.2 (1 H, m, CHN), 1.2–2.3 (6 H, m, CH_2), and 1.07 (3 H, d, J = 6 Hz, CH_3); mass spectrum m/e (rel intensity) 129 (M^+, 14), 114 (100), 98 (11), 81 (13), 70 (14), 69 (12), 60 (33), 56 (15), 55 (41), 44 (24), 43 (26), 42 (73), 41 (53), and 39 (31).

Anal. Calcd for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.19; H, 11.72; N, 10.78.

In a subsequent experiment 3.81 g (30 mmol) of the oxime **26** in 50 ml of MeOH was reduced with 2.20 g (35 mmol) of $NaB(CN)H_3$ at pH 3–4 (methyl orange indicator) for 1 h to give 3.9 g of the crude hydroxylamine **27**. A solution of this hydroxylamine in 25 ml of xylene was added, dropwise during 40 min through a high-dilution head,[17] to 25 ml of refluxing xylene. After the addition was complete, the solution was concentrated and the crude cyclic hydroxylamine **28** (NMR analysis) was reduced with 5.9 g (90 mg-atoms) of Zn, 12.2 g (120 mmol) of Ac_2O, and 10.8 g (180 mmol) of HOAc following previously described reaction and isolation procedures. Distillation of the crude liquid product (2.6 g) separated 1.84 g (40%) of the trans amide **29b** as a colorless liquid, bp 85–90 °C (1.5 mm), $n^{25}D$ 1.4788. Comparison of the GLC retention times and ir and NMR spectra of this product with the subsequently described samples of amide **29** established that this material was the trans amide **29b**. In another experiment where 2.35 g (18.5 mmol) of the oxime **26** was reduced with $NaB(CN)H_3$ and the crude hydroxylamine **27** was heated to 160 °C for 1 h with no solvent, subsequent reduction with Zn, Ac_2O, and AcOH yielded 42% of a crude product containing (GLC, Carbowax 20M on Chromosorb P) the amide **29** (ca. 85%, retention time 52.0 min) accompanied by several minor unidentified impurities: 9.0 min, ca. 3%; 11.6 min, ca. 2%; 14.0 min, ca. 1%; 46.4 min, ca. 4%; and 61.2 min, ca. 5%.

To obtain an authentic sample of this cis amide **29a**, a mixture of 11.3 g (0.10 mol) of the cis amine **30a**[18] (Aldrich Chemical Co.) and 12 g of Ac_2O was stirred for 1 h and then treated with 20 ml of aqueous 6 M KOH and extracted with Et_2O. The ethereal extract was washed with aqueous 3 M HCl, dried, concentrated, and distilled to separate 4.07 g (26%) of the cis amide **29a** as a colorless liquid: bp 83–86 °C (3.5 mm), $n^{25}D$ 1.4772 [lit.[13a] bp 62–63 °C (0.15 mm), $n^{25}D$ 1.4785]; ir (CCl_4) 1645 cm^{-1} (amide C=O); NMR (CCl_4) δ 4.1–4.7 (2 H, m, CHN), 1.97 (3 H, s, CH_3CO), 1.4–1.9 (6 H, m, CH_2), and 1.22 (6 H, d, J = 6.5 Hz, CH_3); mass spectrum *m/e* (rel intensity) 155 (M^+, 24), 140 (18), 112 (14), 98 (100), 70 (21), 43 (32), and 42 (17).

Following a previously described procedure,[18] a solution of 50 g (0.47 mol) of 2,6-dimethylpyridine in 800 ml of anhydrous EtOH was reduced by the portionwise addition of 86 g (3.74 g-atoms) of Na. The crude basic product was separated and distilled to give 29 g (55%) of colorless liquid, bp 131–139 °C (lit.[18] bp 125–132 °C) that contained (GLC, 8-m column packed with Carbowax 20M on base-washed Chromosorb P) the cis amine **30a** (ca. 47%, retention time 15.2 min), the trans amine **30b** (ca. 21%, 19.2 min), a material believed to be a tetrahydropyridine (ca. 20%, 26.0 min), and the starting 2,6-dimethylpyridine (ca. 12%, 34.8 min). Samples of the pure trans amine **30b** were collected (GLC) from the mixture as a colorless liquid with NMR absorption corresponding to the published spectrum.[18] Reaction of 150 mg of this trans amine **30b** with excess PhCOCl in pyridine followed by separation of the crude neutral material and crystallization from cold hexane afforded 106 mg (37%) of the *N*-benzoyl derivative of amine **30b** as colorless needles, mp 53–55 °C. Recrystallization sharpened the melting point of this benzamide to 54–55 °C (lit.[19] mp 54–55 °C); ir (CCl_4) 1650 cm^{-1} (amide C=O); NMR (CCl_4) δ 7.1–7.5 (5 H, m, aryl CH), 3.6–4.1 (2 H, m, CHN), and 1.0–2.0 (12 H, m, aliphatic CH including a CH_3 doublet, J = 7 Hz, at 1.23); mass spectrum *m/e* (rel intensity) 217 (M^+, 15), 205 (16), 105 (100), and 77 (30). A 70-mg sample of the collected trans amine **30b** was treated with picric acid in PhH to yield 200 mg (99%) of the picrate of the trans amine **30b** as yellow needles, mp 144–146 °C.[20]

A collected (GLC) sample of the trans amine **30b** was treated with excess Ac_2O in pyridine and the crude neutral product was separated in the usual way. A pure sample of the trans amide **29b** was collected (GLC, Carbowax 20M on Chromosorb P) as a colorless liquid: $n^{25}D$ 1.4800; ir (CCl_4) 1640 cm^{-1} (amide C=O); NMR (CCl_4) δ 3.8–4.3 (2 H, m, CHN) and 1.0–2.2 (15 H, m, aliphatic CH including a CH_3CO singlet at 1.93 and a CH_3 doublet, $J \approx 7$ Hz, at 1.20); mass spectrum *m/e* (rel intensity) 155 (M^+, 15), 140 (18), 98 (100), 70 (25), 55 (25), 44 (30), 43 (75), 42 (38), and 41 (35).

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.58; H, 11.07; N, 9.01.

The two stereoisomeric amides were partially resolved on an 8-m GLC column packed with TCEP on Chromosorb P. The retention times follow: trans amide **29b**, 300 min; and cis amide **29a**, 313 min.

Preparation of the Oxime 33. The previously described[21] reaction of CH_2=$CHCH_2MgBr$ with acrolein yielded 43% of the alcohol **24** as a colorless liquid: bp 50–52 °C (25 mm), $n^{25}D$ 1.4458 [lit.[21] bp 42–48 °C (17 mm)]; ir (CCl_4) 3590, 3400 (OH), 1645 (C=C), and 930 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.8–6.2 (6 H, m, CH=CH_2), 3.8–4.3 (1 H, m, CHO), 3.17 (1 H, broad, OH, exchanged with D_2O), and 2.1–2.5 (2 H, m, allylic CH_2); mass spectrum *m/e* (rel intensity) 57 (100), 55 (6), 43 (5), 42 (6), 41 (10), and 39 (14). The alcohol **24** (57 g or 0.58 mol) was rearranged by passing it through a tube packed with glass beads and heated to 410 °C as previously recommended.[22] Distillation of the pyrolysate separated 23.8 g (42%) of the aldehyde **32** as a colorless liquid: bp 128–129 °C, $n^{25}D$ 1.4236 (lit. bp 120–121,[22] 118–118.5,[23] 118–121 °C,[14] $n^{20}D$ 1.395,[22] 1.4109,[23] 1.4113[14]). The product exhibited one major GLC peak (Carbowax 20M on Chromosorb P) at 10.0 min with minor peaks at 5.8 (ca. 1%, unidentified impurity) and 20.4 min (ca. 2%, alcohol **24**) and had the following spectral properties: ir (CCl_4) 2690, 2790 (aldehyde CH), 1725 (C=O), 1640 (C=C), and 910 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 9.75 (1 H, t, J = 1.3 Hz, CHO), 4.7–6.2 (3 H, m, CH=CH_2), and 1.4–2.6 (6 H, m, CH_2); mass spectrum *m/e* (rel intensity) 98 (M^+, 2), 81 (40), 57 (20), 55 (41), 54 (100), 44 (20), 42 (31), 41 (75), and 39 (58).

A solution of 15.3 g (144 mmol) of Na_2CO_3, 20.1 g (205 mmol) of the aldehyde **32**, and 21.3 g (307 mmol) of $HONH_3Cl$ in 300 ml of H_2O was stirred in an ice bath for 1 h and at 25 °C for 14 h. After the usual isolation procedure, distillation separated the oxime **33** as 20.2 g (87.4%) of colorless liquid: bp 63–64 °C (2 mm), $n^{25}D$ 1.4612; ir (CCl_4) 3590, 3260 (OH), 1640 (C=N, C=C), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 9.50 (1 H, broad, OH, exchanged with D_2O), two triplets (J = 6 Hz) at 7.32 and 6.63 (total 1 H, CH=N of syn and anti isomers), 4.7–6.2 (3 H, m, CH=CH_2), and 1.3–2.6 (6 H, m, CH_2); mass spectrum *m/e* (rel intensity) 113 (M^+, 5), 98 (16), 59 (100), 55 (40), 41 (64), and 39 (41).

Anal. Calcd for $C_6H_{11}NO$: C, 63.68; H, 9.80; N, 12.39. Found: C, 63.61; H, 9.82; N, 12.28.

Preparation and Cyclization of the Hydroxylamine 34. Reduction of 5.65 g (50 mmol) of the oxime **33**, with 3.36 g (55 mmol) of $NaB(CN)H_3$ in 50 ml of MeOH containing methyl orange at 25 °C for 1 h with periodic addition of 6 M HCl in H_2O–MeOH yielded 5.31 g (93%) of the crude hydroxylamine **34** (NMR analysis) as a liquid that solidified on cooling. A solution of this hydroxylamine **34** in 35 ml of xylene was added dropwise during 30 min to 35 ml of refluxing xylene and the resulting solution was refluxed for an additional 1 h and then concentrated under reduced pressure. A solution of the residual crude hydroxylamine **35** (NMR analysis) was reduced with 9.8 g (0.15 g-atom) of Zn, 20 g (0.20 mol) of Ac_2O, and 18 g (0.30 mol) of HOAc at 70–80 °C for 9 h. After the usual isolation procedure, distillation separated 2.427 g of fractions, bp 73–81 °C (2.5 mm), $n^{25}D$ 1.4705–1.4770, containing (GLC, Carbowax 20M on Chromosorb P) 70–98% of the amide **22** (retention time 36.4 min, total yield ca. 27%), accompanied by 2–30% of several impurities (6.4, 7.6, and 10.8 min). The major by-product was the subsequently identified amine **36** (retention time 10.8 min). However, the GLC curve did not exhibit a peak at 52.5 min, the corresponding retention time for the isomeric amide **31**. A distillation fraction, bp 79–81 °C (2.5 min), $n^{25}D$ 1.4770, containing (GLC) >98% of the amide **22** was identified with the previously described sample by comparison of ir, NMR, and mass spectra and GLC retention times.

In another experiment 2.07 g (18.3 mmol) of the oxime **33** was reduced and the crude hydroxylamine product **34** (2.13 g) was heated to 140 °C for 20 min without solvent. After reduction with Zn and acetylation, distillation of the crude product gave 468 mg of a lower boiling fraction [bp 72–85 °C (2.5 mm), $n^{25}D$ 1.4635] containing (NMR analysis) mainly the amine **36** and 463 mg of a fraction [bp 85–160 °C (2.5 mm), $n^{25}D$ 1.4730] that contained (NMR analysis) mainly the amide **22**. To explore the effect of high dilution, a solution of 6.7 g of the crude hydroxylamine **34** (from reduction of 6.35 g or 50 mmol of the oxime) in 25 ml of xylene was added, dropwise through a high-dilution head[17] during 2 h, to 150 ml of refluxing xylene. After the resulting mixture had been refluxed for 4 h it was concentrated by fractional distillation and the residual crude liquid (3.9 g) was reduced in the usual way with 13.1 g (0.2 g-atom) of Zn dust, 25.5 g of Ac_2O, and 24.8 g of HOAc. Distillation of the resulting crude product separated 2.60 g of colorless liquid, bp 73–94 °C (1 mm), $n^{25}D$ 1.4725, that contained (GLC and NMR analysis) the amide **22** (ca. 75% of the mixture, retention time 14.8 min, yield ca. 28%), the amine **36** (ca. 21% of the mixture, 4.4 min), and a minor unidentified impurity (ca. 4%, 26.8 min).

To obtain an authentic sample of the amide **31**, a solution of 9.9 g (0.10 mol) of hexamethylenimine (Aldrich Chemical Co.) in 15 g (0.15 mol) of Ac_2O was stirred at 25°C for 16 h, and then subjected to the usual isolation procedure. Distillation separated 1.70 g (11%)

of the amide **31** as a colorless liquid: bp 88–93 °C (2 mm), n^{25}D 1.4822 [lit.[24] bp 113–115 °C (8 mm), n^{25}D 1.4890]; ir (CCl_4) 1640 cm^{-1} (amide C=O); NMR (CCl_4) δ 3.2–3.6 (4 H, m, CH_2N), 1.95 (3 H, s, CH_3CO), and 1.3–1.9 (8 H, m, CH_2); mass spectrum *m/e* (rel intensity) 141 (M^+, 31), 98 (23), 84 (32), 70 (38), 57 (28), 56 (44), 44 (30), 43 (100), 42 (30), and 41 (27).

A collected (GLC) sample of the by-product, amine **36**, was obtained as a colorless liquid: n^{25}D 1.4632; ir (CCl_4) 1640 (C=C) and 915 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.7–6.1 (3 H, m, CH=CH_2), 1.2–3.0 (17 H, m, aliphatic CH), and 1.00 (3 H, d, J = 6 Hz, CH_3); mass spectrum *m/e* (rel intensity) 181 (M^+, 6), 166 ($M^+ - CH_3$, 32), 112 ($M^+ - C_5H_9$, 100), 84 (13), 56 (13), 55 (25), 44 (21), 42 (18), and 41 (41).

Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.40; H, 12.80; N, 7.79.

Employing a general reductive amination procedure described previously,[6a] a mixture of 1.35 g (13.6 mmol) of the amine **21**, 0.22 g (2.2 mmol) of the aldehyde **32**, 145 mg (2.2 mmol) of $NaB(CN)H_3$, and 1.8 ml of an aqueous MeOH solution containing 4.4 mmol of HCl was stirred at 25 °C for 5 days. After the resulting mixture had been concentrated and partitioned between Et_2O and aqueous NaOH, the ethereal layer was dried and concentrated to leave 190 mg of crude liquid product containing (GLC, KOH and Carbowax 20M on Chromosorb P) the amine **36**. The amine **36** was collected as 71 mg (18%) of colorless liquid, n^{25}D 1.4638, that was identified with the previously described sample by comparison of ir and NMR spectra and GLC retention times.

Preparation of the Oxime 9. Reaction of 22.4 (0.20 mol) of the aldehyde **8**[25] with 20.8 g (0.30 mol) of $HONH_3Cl$ and 14.9 g (0.14 mol) of Na_2CO_3 in 150 ml of H_2O at 0–5 °C for 1 h and at 25 °C for 2 h yielded 21 g (83%) of the oxime **9** as a colorless liquid: bp 64–65 °C (2 mm), n^{25}D 1.4589 [lit.[26] bp 85 °C (17 mm), n^{25}D 1.4565]; ir (CCl_4) 3580, 3300 (OH), and 1640 cm^{-1} (C=N); NMR (CCl_4) δ 8.57 (1 H, s, OH, exchanged with D_2O), 7.27 (1 H, s, CH=N), 4.8–6.1 (3 H, m, vinyl CH), 2.18 (2 H, d, J = 7 Hz, allylic CH_2), and 1.10 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 127 (M^+, 2), 112 (3), 86 (40), 55 (25), 42 (20), 41 (100), and 39 (45).

Preparation and Cyclization of the Hydroxylamine 7. Reduction of 592 mg (4.65 mmol) of the oxime **9** with 300 mg (4.76 mmol) of $NaB(CN)H_3$ in 5 ml of MeOH (containing methyl orange) for 1 h with the periodic addition of 6 M HCl in H_2O–MeOH yielded the crude hydroxylamine **7**. From a comparable reaction, performed in CH_3OD solution, the NMR of the reaction mixture (in CH_3OD) at this stage exhibited the following peaks attributable to the solvent and the hydroxylamine **7**: δ 4.8–6.3 (m, vinyl CH, OH, and/or NH), 3.85 (s, CH_3O of solvent), 3.17 (s, CH_2N), 2.12 (d, J = 7 Hz, allylic CH_2), and 1.08 (s, CH_3). The reaction mixture was concentrated in a water bath (50–70 °C) under reduced pressure and the residual mixture was made basic with aqueous NaOH, saturated with NaCl, and extracted with Et_2O. After the Et_2O extract had been dried and concentrated, a solution of the residual yellow liquid (the crude hydroxylamine **10**, NMR analysis) in 4.0 ml of pyridine was treated with 2.0 ml of PhCOCl and allowed to stand for 30 min. Then the reaction mixture was partitioned between Et_2O and aqueous 3 M HCl and the Et_2O phase was washed with aqueous $NaHCO_3$, dried, and concentrated. The residual crude product (2.75 g) was chromatographed on silica gel to separate a mixture of $(PhCO)_2O$ and $PhCO_2H$ in early fractions eluted with PhH. The subsequent fractions, eluted with PhH, were washed with aqueous $NaHCO_3$, dried, and concentrated to leave 878 mg of the crude benzoate **11** as a yellow liquid, n^{25}D 1.5096. This material was partially purified by preparative TLC (silica gel coating with a PhH–Et_2O eluent, 1:10 v/v) to separate 691 mg of the benzoate **11** as a yellow liquid, n^{25}D 1.5079. Distillation under reduced pressure in a short-path still afforded 645 mg (60%) of the benzoate **11** as a yellow liquid: n^{25}D 1.5080; ir (CCl_4), 1742 cm^{-1} (C=O); uv max (95% EtOH) 225 nm (ε 14 200), 273 (860), and 280 (710); NMR (CCl_4) δ 7.1–8.1 (5 H, m, aryl CH), 2.0–3.7 (2 H, m, CHN and part of AB system for CH_2N), 2.67 (1 H, d, J = 9.5 Hz, part of AB system for CH_2N), 1.0–2.5 (11 H, m, CH_2 with CH_3 singlets at 1.15 and 1.22 and a CH_3 doublet, J = 7 Hz, at 1.20); mass spectrum *m/e* (rel intensity) 122 (26), 105 (40), 96 (21), 77 (38), 69 (24), 55 (100), 51 (27), and 41 (32). Our efforts to obtain an analytically pure sample of this benzoate **11** were thwarted by the partial decomposition that occurred during each attempt to distill the material.

Reduction of 6.35 g (50 mmol) of the oxime **9** with 3.46 g (55 mmol) of $NaB(CN)H_3$ in 50 ml of MeOH with added methyl orange and 6 M HCl in MeOH–H_2O, followed by concentration of the crude basic product on a steam bath under reduced pressure, left 6.2 g (96%) of the crude liquid hydroxylamine **10**. Reduction of this crude product with 13.1 g (0.20 g-atom) of Zn, 25.5 g (0.25 mol) of Ac_2O, and 24 g (0.40 mol) of HOAc at 80–90 °C for 2 h yielded a crude neutral product. Fractional distillation separated 386 mg of a fraction, bp 70–71 °C (1 mm), n^{25}D 1.4570, containing (GLC, Carbowax 20M on Chromosorb P) ca. 95% of the amide **12** and 3.55 g (total yield 3.93 g or 51%) of the pure amide **12** as a colorless liquid: bp 72–75 °C (1 mm); n^{25}D 1.4580; ir (CCl_4) 1640 cm^{-1} (amide C=O); NMR (CCl_4) δ 2.8–4.3 (3 H, m, CH_2N and CHN) and 0.8–2.2 [14 H, m, aliphatic CH including a CH_3CO singlet at 1.90, a CH_3 doublet (J = 6 Hz) at 1.25, and two CH_3 singlets at 1.12 and 1.01]; mass spectrum *m/e* (rel intensity) 155 (M^+, 20), 140 (20), 99 (22), 98 (100), 57 (70), 56 (26), 55 (18), 43 (52), 42 (18), and 41 (25).

Anal. Calcd for $C_9H_{17}NO$: C, 67.63; H. 11.04; N, 9.02. Found: C, 69.67; H, 11.07; N, 9.07.

Preparation of the Hydroxylamine 38. Following a previously described[16] procedure with 20.32 g (0.20 mol) of the aldehyde **40**, 20.85 g (0.30 mol) of $HONH_3Cl$, 14.8 g (0.14 mol) of Na_2CO_3, and 50 ml of H_2O, the oxime **41** was obtained as 20.55 g (82%) of colorless liquid: bp 80–82 °C (1.5 mm), n^{25}D 1.5065 [lit.[16] bp 106–107 °C (10 mm), n^{20}D 1.5040]; ir (CCl_4) 3570, 3300 (OH), and 1645 cm^{-1} (C=N and C=C); NMR (CCl_4) δ 9.25 (1 H, broad, OH), two doublets at 7.32 (J = 6 Hz) and 6.58 (J = 7 Hz) (total 1 H, CH=N of syn and anti isomers), 5.4–5.8 (2 H, m, vinyl CH), and 1.3–3.5 (7 H, m aliphatic CH); mass spectrum *m/e* (rel intensity) 125 (M^+, 16), 108 (20), 93 (64), 91 (40), 81 (31), 80 (100), 79 (69), 77 (32), 67 (35), 54 (76), 53 (32), 41 (53), and 39 (62). Reduction of 1.25 g (10 mmol) of the oxime **41** with 755 mg (12 mmol) of $NaB(CN)H_3$ in 10 ml of MeOH with added methyl orange and 6 M HCl in H_2O–MeOH for 1 h gave 1.28 g of the crude hydroxylamine **38** as a pale yellow liquid: NMR (CCl_4) δ 6.22 (2 H, broad, NH and OH), 5.4–5.7 (2 H, m, vinyl CH), 1.3–3.0 (9 H, m, aliphatic CH). After a sample of this hydroxylamine **38** had been heated to 170 °C for 1 h, NMR analysis of the crude product indicated that the vinyl CH absorption was undiminished and, consequently, cyclization had not occurred. A solution of 1.09 g of the crude hydroxylamine **38** and 4 ml of PhCOCl in 6 ml of pyridine was stirred for 30 min and then partitioned between Et_2O and aqueous $NaHCO_3$. The ethereal layer was dried and concentrated and the residue (4.2 g) was chromatographed on silica gel with PhH–hexane mixtures as eluents. After separation of early fractions containing $(PhCO)_2O$, subsequent fractions contained 2.61 g of the crude dibenzoyl compound **42** as a yellow liquid, ir (CCl_4), 1765 (ester C=O) and 1680 cm^{-1} (amide C=O). A solution of 1.75 g of this dibenzoyl compound **42** and 4 g of KOH in 10 ml of MeOH was stirred at 25 °C for 24 h and then acidified, concentrated, and extracted with Et_2O. After the ethereal extract had been dried and concentrated, the residual yellow solid (868 mg, mp 105–109 °C) was recrystallized from a $CHCl_3$–hexane mixture to separate 663 mg (43%) of the hydroxamic acid **43** as colorless needles: mp 112–113 °C; ir (CCl_4) 3220 (OH) and 1610 cm^{-1} (amide C=O); NMR (CCl_4) δ 7.3–7.7 (5 H, m, aryl CH), 5.5–5.7 (2 H, m, vinyl CH), 3.58 (2 H, d, J = 6.5 Hz, CH_2N), and 1.0–2.5 (8 H, m, OH and aliphatic CH); uv max (95% EtOH) 235 nm (broad, ε 4600); mass spectrum *m/e* (rel intensity) 231 (M^+, 1), 213 (5), 150 (6), 105 (100), 94 (7), 77 (41), 41 (9), and 39 (7).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.65; H, 7.42; N, 6.02.

Preparation of the Oxime 46. Following a previously described procedure,[27] a THF solution of $(CH_3)_2C$=$CHCH_2MgCl$ was carbonated with crushed dry ice to yield 74% of the acid **44** as colorless liquid: bp 101–102 °C (26 mm), n^{25}D 1.4280 [lit. bp 100–102 °C (28 mm),[27] n^{25}D 1.4272,[28] 1.4295[27]]; ir (CCl_4) 3000 (broad, carboxyl OH), 1695 (C=O), 1637 (C=C), and 925 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 12.15 (1 H, s, OH), 4.8–6.3 (3 H, m, CH=CH_2), and 1.28 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 114 (M^+, 3), 99 (14), 69 (72), 41 (100), and 39 (20). Although the same acid **44** was obtained by the previously described[28] carbonation of $(CH_3)_2C$=$CHCH_2MgBr$, the overall yield (36%) was lower. To a cold (−40 to −60 °C) solution of 22.8 g (200 mmol) of the acid **44** in 100 ml of Et_2O was added, dropwise and with stirring and cooling, 500 ml of an Et_2O solution containing 0.46 mol of MeLi.[29] After approximately 1 equiv of the MeLi solution had been added and the vigorous evolution of CH_4 subsided, the mixture was warmed and maintained at −10 °C while the second equivalent of MeLi was added. Use of this procedure diminished the amount of alcohol **47** by-product that was formed. After the resulting suspension had been stirred at 25 °C for 2 h, it was added, slowly with vigorous stirring, to dilute aqueous HCl and then extracted with Et_2O. The ethereal extract was washed with aqueous NaOH, dried, and fractionally distilled to separate 16.6 g (74%) of the pure (GLC) ketone

45, bp 52–55 °C (55 mm), n^{25}D 1.4221 (lit.[30] bp 129.5 °C), and 1.3 g (6%) of a fraction, bp 56–58 °C (55 mm), n^{25}D 1.4230, that contained (GLC, Carbowax 20M on Chromosorb P) the desired ketone **45** (ca. 95%, retention time 4.4 min) accompanied by the alcohol **47** (ca. 5%, 6.8 min). The spectral properties of the ketone **45** were: ir (CCl_4) 1710 (C=O), 1635 (C=C), and 935 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.8–6.2 (3 H, m, CH=CH_2), 2.01 (3 H, s, $COCH_3$), and 1.20 (6 H, s, CH_3). Reaction of 15.0 g (134 mmol) of the ketone **45** with 14.0 g (200 mmol) of $HONH_3Cl$ and 10.0 g (94 mmol) of Na_2CO_3 in 150 ml of H_2O for 1 h at 0 °C and for 1 h at 25 °C yielded 7.44 g (43%) of the oxime **46** as a colorless liquid: bp 57–58 °C (1 mm), n^{25}D 1.4670; ir (CCl_4) 3580, 3250 (OH), 1635 (C=N), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 9.45 (1 H, broad, OH), 4.8–6.2 (3 H, m, CH=CH_2), 1.75 (3 H, s, CH_3C=N), and 1.20 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 112 (24), 69 (34), 68 (14), 67 (18), 42 (25), 41 (100), 40 (33), and 39 (29).

Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.15; H, 10.30; N, 11.00.

Preparation of the Hydroxylamine 39. Reduction of 508 mg (4.0 mmol) of the oxime **46** with 284 mg (45 mmol) of $NaB(CN)H_3$ in 20 ml of MeOH at pH 3–4, following previously described reaction and isolation procedures, yielded the crude liquid hydroxylamine **39**: NMR (CCl_4) δ 4.7–6.1 (5 H, m, CH=CH_2, OH, and NH), 2.75 (1 H, q, J = 6.5 Hz, CHN), 1.08 (3 H, partially resolved d, J = 6.5 Hz, CH_3) and two partially resolved CH_3 singlets (total 6 H) at 1.00 and 0.97. This crude hydroxylamine **39** was mixed with 1.0 g (12.7 mmol) of pyridine and 2.0 g (14.2 mmol) of PhCOCl and allowed to stand for 10 min. After the resulting mixture had been stirred with 10 ml of aqueous 6 M KOH for 3 min, it was extracted with Et_2O and the ethereal extract was dried and concentrated to leave a residual liquid containing (ir analysis) a mixture of $(PhCO)_2O$ and the dibenzoyl derivative **50**. A solution of this crude product and 4.0 g of NaOH in 20 ml of MeOH was heated on a steam bath for 5 min and then diluted with H_2O, concentrated to remove the MeOH, acidified, and extracted with Et_2O. After the ethereal extract had been washed with aqueous $NaHCO_3$, dried, and concentrated, the residue was crystallized from cold hexane to separate 615 mg (66% from the oxime **46**) of the hydroxamic acid **51** as pale yellow needles, mp 72–75 °C. Recrystallization afforded 470 mg (51%) of the pure hydroxamic acid **51** as colorless needles: mp 76–77 °; ir (CCl_4) 1640 (shoulder, C=C), 1615 (hydroxamic acid C=O), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 8.33 (1 H, broad, OH, exchanged with D_2O), 7.2–7.6 (5 H, m, aryl CH), 4.7–6.2 (3 H, m, CH=CH_2), 3.88 (1 H, q, J = 7 Hz, CHN), 1.25 (3 H, d, J = 7 Hz, CH_3), 1.08 (3 H, s, CH_3), and 1.03 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity), 164 (4), 148 (12), 105 (100), 77 (36), 51 (13), 42 (14), and 41 (23); uv (95% EtOH) end absorption (ϵ 7910 at 210 nm) with shoulders at 219 nm (ϵ 6940) and 240 (5520).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.04; H, 8.22; N, 5.95.

A solution of the crude hydroxylamine **39** (uncontaminated with the oxime **46**, NMR analysis), from 2.54 g (20 mmol) of the oxime **46** and 1.57 g (25 mmol) of $NaB(CN)H_3$, in 25 ml of $PhCH_3$ was added through a high-dilution head[17] to 50 ml of refluxing $PhCH_3$ during 40 min. After the resulting solution had been refluxed for an additional 1 h, it was concentrated to leave a residual liquid with NMR absorption corresponding to the starting material **39**. After a solution of the crude hydroxylamine **39** in xylene had been refluxed for 4 h and concentrated, the residual liquid contained (NMR analysis) a mixture of the starting hydroxylamine **39** and the oxime **46** formed by oxidation of the hydroxylamine **39** during the heating process.

Registry No.—**7**, 57606-67-4; **8**, 5497-67-6; **9**, 10533-71-8; **10**, 54408-36-5; **11**, 57606-68-5; **12**, 57606-69-6; **14a**, 39713-71-8; **14b**, 39713-72-9; **15**, 109-49-9; *syn*-**16**, 57606-70-9; *anti*-**16**, 57606-71-0; **17**, 57606-72-1; *cis*-**18**, 57606-73-2; *trans*-**18**, 57606-74-3; **19a**, 57606-75-4; **19b**, 57606-76-5; **21**, 109-05-7; **22**, 4593-15-1; **23**, 42185-42-2; **24**, 924-41-4; **25**, 21889-88-3; **26**, 57606-77-6; **27**, 57606-78-7; **29a**, 17037-67-1; **29b**, 57606-79-8; **30a**, 766-17-6; **30b**, 10066-29-2; **30b** picrate, 57606-80-1; **31**, 5809-41-6; **32**, 764-59-0; *syn*-**33**, 57606-81-2; *anti*-**33**, 57606-82-3; **34**, 57606-83-4; **36**, 57606-84-5; **38**, 57606-85-6; **39**, 57606-86-7; *syn*-**41**, 57606-87-8; *anti*-**41**, 57606-88-9; **42**, 57606-89-0; **43**, 57606-90-3; **44**, 10276-09-2; **45**, 4181-07-1; **46**, 57606-91-4; **50**, 57606-92-5; **51**, 57606-93-6; ethyl acetoacetate, 141-97-9; 4-bromo-1-butene, 5762-44-7.

References and Notes

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