Novel Transformations Leading to 3-Benzylindolizidin-2-ones

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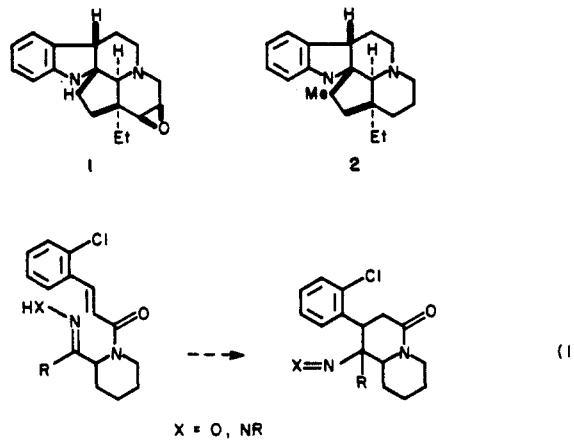
Received June 26, 1986

Several derivatives of keto amide **10** have been prepared and their cyclization reactions investigated. Oxime **11** and 2,4-dinitrophenylhydrazone **12** cyclize to give isoxazolidine **16** and pyrazolidine **17**, respectively, under acidic conditions (Scheme II). Oxime **11** also yields **16** when heated in acetonitrile, but 2,4-dinitrophenylhydrazone **12** is unreactive under these conditions. When heated in dimethylformamide oxime **11** and 2,4-dinitrophenylhydrazone **12** cyclize to give isoxazolidines **16** and **18** and pyrazolidines **17** and **19**, respectively. It is proposed that the cyclizations leading to **16–19** occur by a 1,3-dipolar cycloaddition mechanism. Similar cyclizations, leading to pyrazolidines **20** and **21**, occur when phenylhydrazone **13** and *tert*-butylhydrazone **14** are heated with pyridinium *p*-toluenesulfonate in hot ethanol (Scheme III). Dimethylhydrazones **15** and **34** cyclize to indolizidines **30** and **36** when heated in acetonitrile, presumably via a similar 1,3-dipolar cycloaddition mechanism (Scheme V and VI). A related reaction occurs when oxime **11** is oxidized with trifluorperoxyacetic acid; the intermediate *aci*-nitro compound undergoes cyclization to a product that is further oxidized to the nitroindolizidinone **42** (Scheme VII). In contrast, phenylhydrazone **13** and *tert*-butylhydrazone **14** cyclize upon being refluxed in acetonitrile to azo lactams **22** and **23**, respectively. It is proposed that these thermal reactions occur by an intramolecular ene mechanism. Finally, compounds **13** and **14** give both types of cyclization when heated in dimethylformamide (Scheme IV). Structures have been established by single-crystal X-ray analysis (compounds **16**, **24**, and **36**) and by NMR correlation.

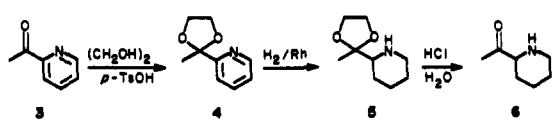
In connection with a project aimed at the total synthesis of 3*H*-indoline alkaloids [e.g., andrangine (**1**),[1] vallesamidine (**2**)[2]] we have investigated the possible transformation depicted in eq 1, in which an oxime or hydrazone



(1)

might serve as the nucleophilic partner in an intramolecular Michael addition, leading to a quinolizidone. Although we did not find a way to accomplish the transformation of eq 1, we have observed and characterized two alternative reactions of these substrates, leading to interesting indolizidinone systems. In this paper, we report the results of this investigation.

The starting material for our study, 2-acetylpiperidine (**6**), was prepared from the commercially available 2-acetylpyridine (**3**) as shown in eq 2. Ketalization of **3**

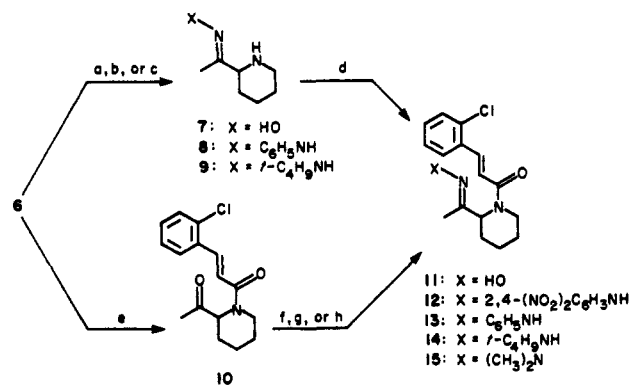


(2)

followed by catalytic hydrogenation of the pyridine ring provides amino ketal **5**. Because of the buffering effect of the basic nitrogen, compound **5** is unusually resistant to acidic hydrolysis; incomplete hydrolysis results after being dissolved in 2 N hydrochloric acid at room temperature for several hours. However, hydrolysis is smoothly accomplished by treatment of **5** with 6 N hydrochloric acid at room temperature for 24 h. Because amino ketone **6** is somewhat unstable, it is best stored in the form of its hydrochloride salt.

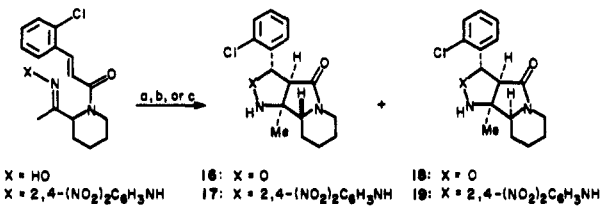
The derivatives of amino ketone **6** that were employed were prepared as shown in Scheme I. Reaction of **6** with hydroxylamine, phenylhydrazine, or *tert*-butylhydrazine provides oxime **7** or hydrazones **8** or **9**. Acylation of these

Scheme I[a]



[a] (a) $H_2NOH{\cdot}HCl$, C_5H_5N, EtOH; (b) $C_6H_5NHNH_2{\cdot}HCl$, HOAc; (c) $t\text{-}C_4H_9NHNH_2{\cdot}HCl$, HOAc; (d) *o*-chlorocinnamoyl chloride, Et_3N, CH_2Cl_2, −78 °C; (e) *o*-chlorocinnamoyl chloride, Et_3N, toluene, 25 °C; (f) $H_2NOH{\cdot}HCl$, *i*-PrOH, 25 °C; (g) 2,4-$(NO_2)_2C_6H_3NHNH_2{\cdot}HCl$, MeOH; (h) Me_2NNH_2, HOAc.

Scheme II[a]



[a] (a) CH_3CN, reflux; (b) PPTs, EtOH, 25 °C or reflux; (c) DMF, 110–120 °C.

(1) (a) Kan, C.; Das, B. C.; Husson, H.-P.; Potier, P. *Bull. Soc. Chim. Fr.* **1974**, *12*, 2839. (b) Bruneton, J.; Bouquet, A.; Cave, A. *Phytochemistry* **1974**, *13*, 1963. (c) Cave, A.; Bruneton, J. *Tetrahedron Lett.* **1973**, 51, 5081.

(2) (a) Walser, A.; Djerassi, C. *Helv. Chim. Acta* **1965**, *48*, 391. (b) Brown, S. H.; Djerassi, C.; Simpson, P. G. *J. Am. Chem. Soc.* **1968**, *90*, 2445. (c) Levy, J.; Mauperin, P.; Maindreville, M. D.; LeMen, J. *Tetrahedron Lett.* **1971**, *15*, 1003.

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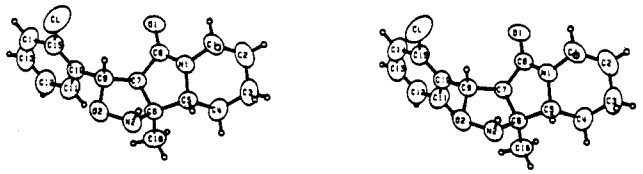


Figure 1. ORTEP representation of the X-ray structure of compound **16**.

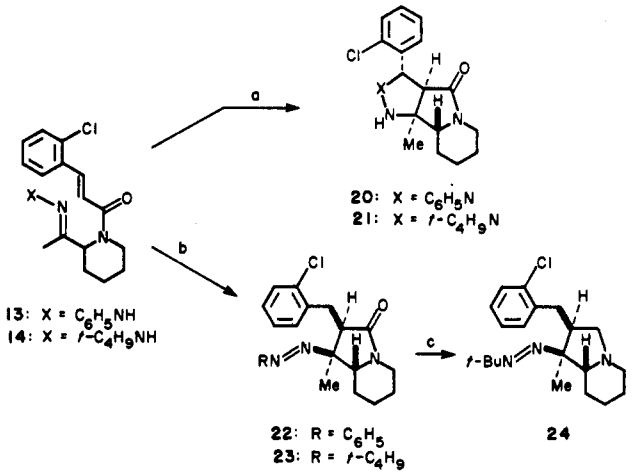
three compounds with *o*-chlorocinnamoyl chloride gives derivatives **11**, **13**, or **14**. Alternatively, amino ketone **6** may be acylated first to obtain keto amide **10**. Treatment of this compound with hydroxylamine, 2,4-dinitrophenylhydrazine, or 1,1-dimethylhydrazine gives derivatives **11**, **12**, or **15**.

Treatment of oxime **11** with PPTS in ethanol or in refluxing acetonitrile yields isoxazolidine **16** as a white, crystalline material, mp 146–148 °C (Scheme II). The highest yield of **16** (92%) is obtained by simply heating an acetonitrile solution of **11** at reflux for 30 h. Compound **16** is also obtained directly when keto amide **10** is treated with hydroxylamine hydrochloride and pyridine in refluxing ethanol. However, when oxime **11** is heated in DMF, the reaction is not stereospecific and a 1:1 mixture of diastereomic isoxazolidines **16** and **18** is obtained. The structure of isoxazolidine **16** was elucidated by single-crystal X-ray analysis (Figure 1).

A similar cyclization is observed when the 2,4-dinitrophenylhydrazone **12** is treated with PPTS in hot ethanol (Scheme II). When heated in a solution of dimethylformamide 2,4-dinitrophenylhydrazone **12** cyclizes to give a 9:1 mixture of pyrazolidines **17** and **19**, respectively. However, compound **12** is recovered unchanged from refluxing acetonitrile solution. The structure of pyrazolidine **17** was assigned on the basis of ^{1}H NMR decoupling experiments and by correlation of its NMR spectral data with that of isoxazolidine **16**. The structures of compounds **18** and **19** were assigned by correlation of their NMR spectral data with pyrazolidines **25** and **26** (vide infra).

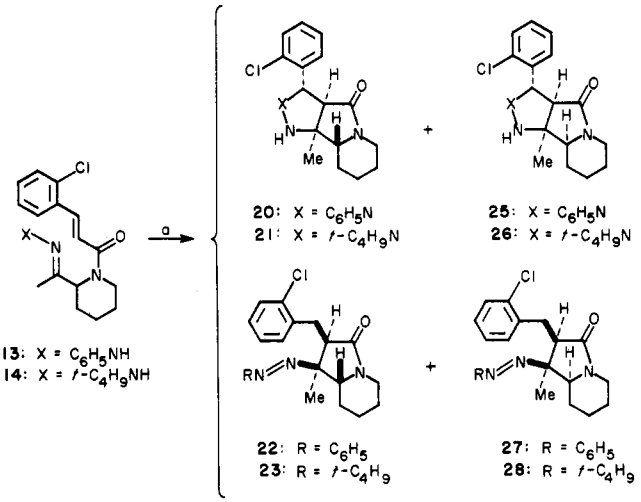
Compounds **16–19** presumably arise from intramolecular 1,3-dipolar cycloaddition of the oxime or hydrazone functions to the α,β-unsaturated amide double bond. Several reports dealing with similar cycloadditions of oximes and hydrazones have been described in the literature. The reaction appears to have been first discovered by Ochiai and co-workers, who reported in 1967 that formaldoxime reacts as a 1,3-dipole in cycloaddition reactions with alkenes and alkynes.[3] The intramolecular version of the oxime cyclization was employed as a step in Wildman's 6-hydroxybuphanidrine and 6-hydroxypowelline syntheses.[4] Grigg and co-workers reported in 1978 that arylhydrazones undergo the same reaction[5] and have subsequently published several other reports of investigations of X=YZH systems as potential 1,3-dipoles.[6] Hamelin and co-workers have examined the Brønsted and Lewis acid catalyzed cycloadditions of hydrazones, both of the inter- and intramolecular variety.[7] Hydrazone cycloadditions have also been investigated by Shimizu and co-workers[8] and by Wilson and Rekers.[9] In addition

Scheme III[a]



[a] (a) PPTS, EtOH, reflux; (b) CH_3CN, reflux; (c) $LiAlH_4$, THF, reflux.

Scheme IV[a]



[a] (a) DMF, 110–120 °C.

relevant reports on oxime cycloadditions have also been made by Lablache-Combier and Villaume[10] and by Winterfeldt and Krohn.[11]

Whereas **11** and 2,4-dinitrophenylhydrazone **12** react solely by the 1,3-cycloaddition mode, if at all, the phenylhydrazone and *tert*-butylhydrazone derivatives **13** and **14** show more complex behavior. Under acidic conditions, **13** and **14** behave like **11** and **12**, giving pyrazolidine derivatives **20** and **21**, identified by comparison of their ^{1}H and ^{13}C NMR spectra with those of the corresponding pyrazolidine **17** and isoxazolidine **16** (Scheme III). In sharp contrast, when heated in acetonitrile, **13** and **14** are transformed cleanly into azo lactams **22** and **23**, respectively. The mechanism for formation of **22** and **23** may be an intramolecular ene reaction. Compound **23** was identified by single-crystal X-ray analysis of the picric acid salt of **24**, the azo amine obtained by reduction of **23** with lithium aluminum hydride in refluxing THF. The ORTEP

(3) Ochiai, M.; Obayashi, M.; Morita, K. *Tetrahedron* **1967**, *23*, 2641.
(4) Wildman, W. C.; Slabaugh, M. R. *J. Org. Chem.* **1971**, *36*, 3202.
(5) Grigg, R.; Kemp, J.; Thompson, N. *Tetrahedron Lett.* **1978**, *31*, 2827.
(6) (a) Grigg, R.; Gunaratne, H. Q.; Kemp, J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 41. (b) Grigg, R.; Jordan, M.; Tangthongkum, A. *Ibid.* **1984**, 47. (c) Grigg, R.; Thianpantangul, S. *Ibid.* **1984**, 653.
(7) (a) LeFevre, G.; Sinabanhit, S.; Hamelin, J. *Tetrahedron* **1979**, *35*, 1821. (b) Fouchet, B.; Houcla, M.; Hamelin, J. *Tetrahedron Lett.* **1981**, *22*, 1333. (c) LeFevre, G.; Hamelin, J. *Ibid.* **1979**, *20*, 1757.
(8) (a) Shimizu, T.; Hayashi, Y.; Nakano, M.; Teramura, K. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 134. (b) Shimizu, T.; Hayashi, Y..; Ishikawa, S.; Teramura, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2456.
(9) Wilson, R. M.; Rekers, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 4005.
(10) Lablache-Combier, A.; Villaume, M. L. *Tetrahedron Lett.* **1968**, *24*, 6951.
(11) Winterfeldt, E.; Krohn, W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 709.

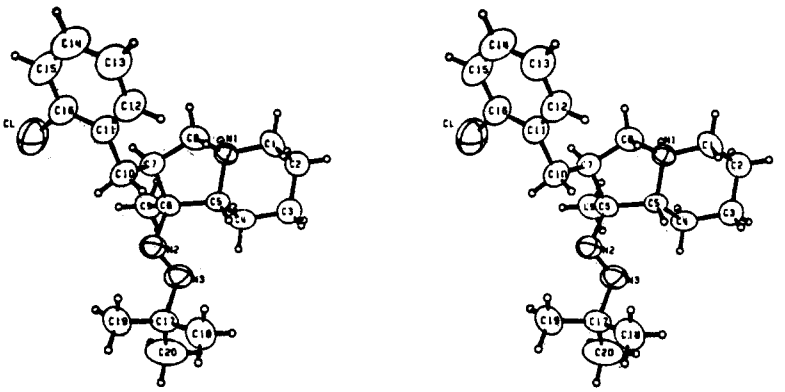
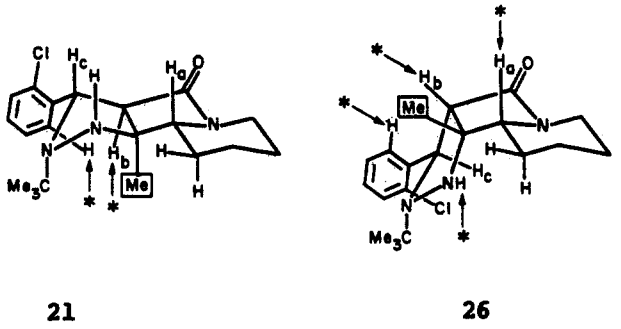


Figure 2. ORTEP representation of the X-ray structure of compound **24**.



21 **26**

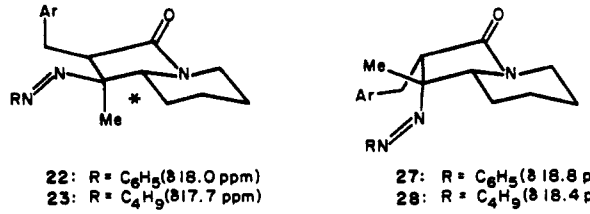
Figure 3. Nuclear Overhauser enhancement studies on pyrazolidines **21** and **26**. In each isomer, irradiation of the angular methyl resonance resulted in enhancement of the resonances from the protons indicated by *.

representation of this salt (with the picrate unit omitted for clarity) is shown in Figure 2.

To complicate the picture even more, **13** and **14** give both types of reaction when heated in DMF (Scheme IV). Furthermore, these reactions are not stereospecific; both the pyrazolidine and azo lactam products are obtained as diastereomeric mixtures. Phenylhydrazone **13** gives pyrazolidines **20** and **25** and azo lactams **22** and **27** in a ratio of 1:1:2:1 (87% yield). *tert*-Butylhydrazone **14** affords pyrazolidines **21** and **26** and azo lactams **23** and **28** in a ratio of 1:2:1:1 (56% yield).

The stereostructure of pyrazolidine **21** and **26** were rigorously established by difference nuclear Overhauser enhancement (NOE) studies. As shown in Figure 3, irradiation of the angular methyl group resonances (δ 1.30 and 1.26, respectively) produced enhancement of several other proton resonances in each case. The most significant result of this study is the observation of enhancement of the H_a signal in isomer **26** but not in isomer **21**. That the bicyclo[3.3.0]octane unit is cis in both isomers is shown by the observation of enhancement in the H_b signal in both **21** and **26**. The angular methyl and *o*-chlorophenyl groups are shown to be cis in both isomers by the observation of enhancement of the ortho aromatic proton and the absence of an enhancement in the H_c resonance in both isomers.

The relative stereostructures of azolactam pairs **22**/**27** and **23**/**28** are shown by the ^{13}C NMR chemical shifts of the angular methyl resonances in each case. In both series,



22: R = C_6H_5 (δ 18.0 ppm)
23: R = C_4H_9 (δ 17.7 ppm)

27: R = C_6H_5 (δ 18.8 ppm)
28: R = C_4H_9 (δ 18.4 ppm)

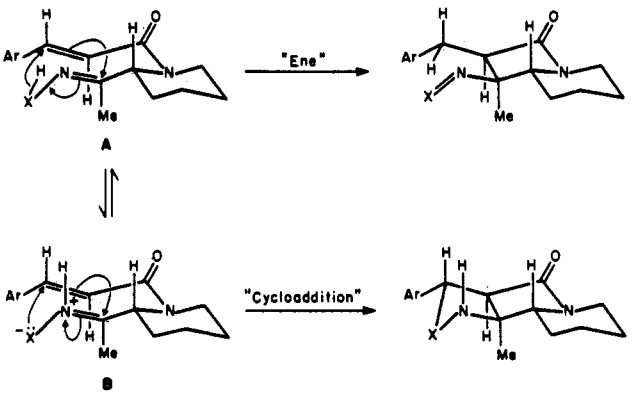


Figure 4. Mechanistic scheme for transformations of oxime **11** (X = O) and hydrazones **12**–**14** (X = NR) under neutral and acidic conditions.

Table I. Reaction Pathways for Oxime 11 and Hydrazones 12–14

compd	PPTS, EtOH reflux	conditions CH_3CN reflux	DMF, 110–120 °C[a]
11	cycloaddition[b]	cycloaddition	cycloaddition
12	cycloaddition	no reaction	cycloaddition
13	cycloaddition	ene	cycloaddition + ene
14	cycloaddition	ene	cycloaddition + ene

[a] Not stereospecific. [b] 25 °C.

the stereoisomer formed under conditions of refluxing acetonitrile (**22** and **23**) shows an angular methyl resonance that is 0.7–0.8 ppm upfield of corresponding resonance in the new isomer produced under conditions of refluxing DMF. This shift is nicely explained by the additional gauche interaction (marked by *) in **22** and **23**.

The perplexing spectrum of reactivity of oxime **11** and hydrazones **12**–**14** is summarized in Table I. We do not have a convincing mechanistic rationale that explains all of these observations. As shown in Figure 4, the major stereoisomers produced by both the 1,3-dipolar cycloaddition and ene mechanisms are those expected to arise from the more reasonable transition-state conformation. The results show that, when heated in acetonitrile, the most acidic derivatives (oxime **11** and hydrazone **12**) react by the 1,3-dipolar cycloaddition path while the least acidic derivatives (hydrazones **13** and **14**) react by the ene mechanism. If we assume an obligatory zwitteronic intermediate (B) in the 1,3-dipolar cycloaddition mechanism, this would make sense. Under acidic catalysis, the rate of formation of B would be increased and subsequently all four derivatives react by the dipolar cycloaddition mechanism. The results obtained with the use of DMF as the solvent might also be interpreted in a similar manner (i.e.,

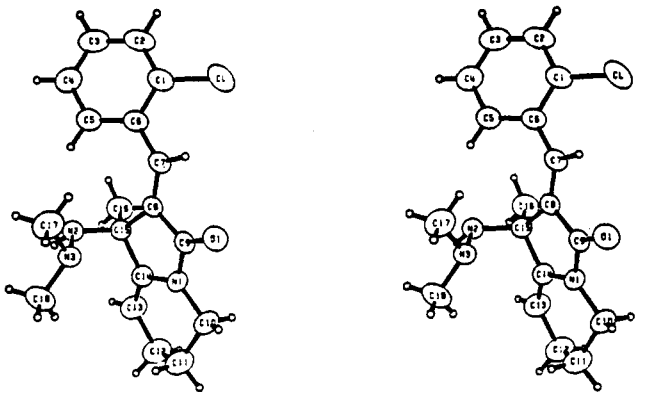
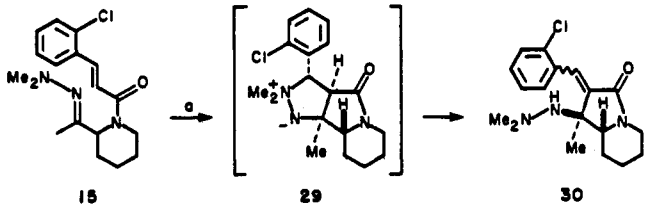


Figure 5. ORTEP representation of the X-ray structure of compound **36**.

Scheme V[a]



[a] (a) CH_3CN, reflux.

formation of B via a thermal tautomeric equilibrium). Under these conditions, equilibrium is apparently more facile than in refluxing acetonitrile giving rise to a mixture of A and B, and therefore competing reactions occur. However, this interpretation does not explain the lack of stereospecificity under these conditions. That the isomeric products in these two reactions do not arise from equilibration subsequent to the initial reactions was verified by a control experiment. Pyrazolidine **20** and azo lactam **22** were both recovered unchanged after being heated in DMF.

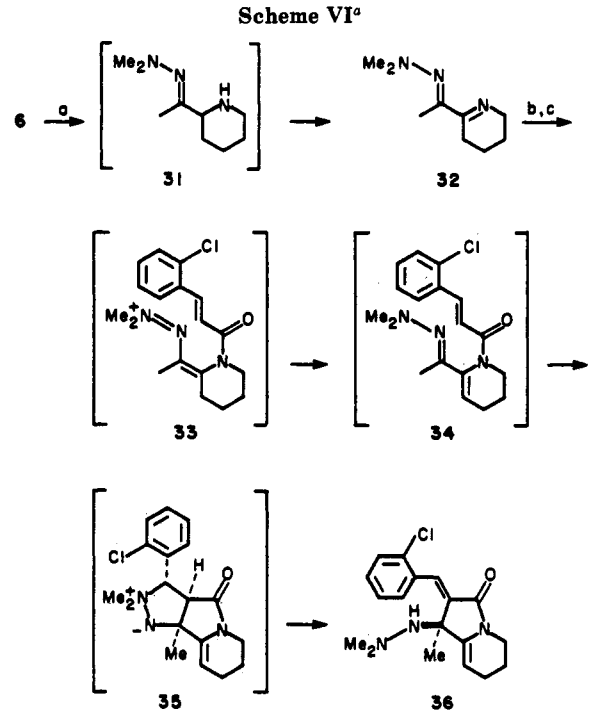
Baldwin and co-workers have studied the reactions of lithiated hydrazones with aldehydes, ketones, and alkyl halides.[12] We had hoped that the analogous but unknown Michael alkylation of the conjugate base derived from **12**, **13**, or **14** would lead to the desired quinolizidine ring system. However, we have seen no evidence of this reaction. In fact, the lithium salt of phenylhydrazone **13**, formed by treatment of **13** with *n*-butyllithium reacts at 0 °C to give pyrazolidines **20** and **25** in a ratio of 9:1 (57% yield).

In an attempt to prevent both the ene reaction and the dipolar cycloaddition from occurring, dimethylhydrazone **15** was prepared (Scheme I). However, heating this hydrazone in refluxing acetonitrile leads only to the cyclic product **30**, presumably by way of the zwitterionic 1,3-dipolar cycloaddition product **29** (Scheme V). The structure of **30** was assigned by correlation of its NMR spectra with a related lactam of unambiguous structure (vide infra).

An alternative attempt to prepare and cyclize dimethylhydrazone **15** (Scheme VI) led unexpectedly to enamide **36**, whose structure was shown by single-crystal X-ray analysis (Figure 5). A suggested mechanism for the formation of **36** is set forth in Scheme VI. It is proposed that the initial hydrazone **31** undergoes facile air oxidation, giving the unsaturated derivative **32**. Intermediate **32** may

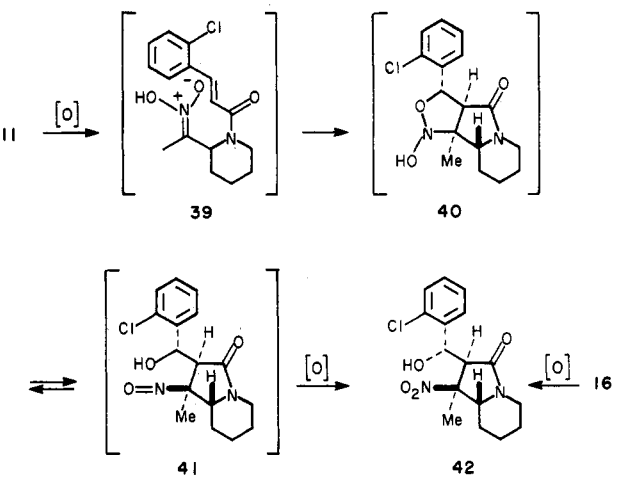
(12) (a) Adlington, R. M.; Baldwin, J. E.; Battaro, J. C.; Perry, M. W. D. *J. Chem. Soc., Chem. Commun.* **1983**, 1040. (b) Baldwin, J. E. Bottaro, J. C.; Kolhe, J. N.; Adlington, R. M. *Ibid*, **1983**, 22.

Scheme VI[a]



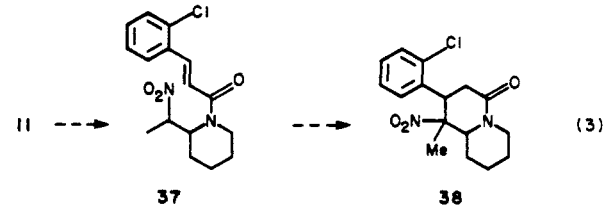
[a] (a) Me_2NNH_2, HOAc; (b) *o*-cinnamoyl chloride, Et_3N, CH_2Cl_2, −78 °C; (c) CH_3CN, reflux.

Scheme VII



be isolated as an unstable orange oil, which may be partially purified by bulb-to-bulb distillation. Support for its assigned structure rests principally on its ^{13}C NMR spectrum, which shows two imine-type resonances, with δ 161.0 and 167.4. We further propose that acylation of **32** occurs on the ring nitrogen to provide the delocalized cation **33**, which eliminates a proton to give **34**. This material was obtained only in an impure state and was not characterized. Upon being heated in acetonitrile, **34** undergoes the same transformation as its dihydro analogue, **15**, leading via zwitteronic **35** to the observed product **36**.

In one final attempt to bring about the desired cyclization, we investigated the oxidation of oxime **11**. We expected to obtain nitro amide **37**, which might be induced to undergo base-catalyzed intramolecular Michael addition, providing the desired quinolizidone **38** (eq 3). Again, however, our attempts were thwarted by the intervention of the ubiquitous 1,3-dipolar cycloaddition. As shown in Scheme VII, the sole product obtained when **11** is treated with trifluoroperoxyacetic acid, albeit in poor yield, is the crystalline nitro lactam **42**. The structure of **42** was as-



37 38 (3)

signed on the basis of its spectra and was confirmed by the observation that it is also produced by oxidation of isoxazolidine **16** with trifluoroperoxyacetic acid. A proposed mechanism for the formation of **42** is shown in Scheme VII. It is suggested that initial oxidation of the oxime provides **39**, the *aci*-nitro compound. This substance probably undergoes the 1,3-dipolar cycloaddition reaction, giving **40**, which is in equilibrium with the nitroso alcohol tautomer **41**. Further oxidation of the latter compound could then provide the observed nitro alcohol. Alternatively, **42** may arise from the initial dipolar cycloaddition of oxime **11** followed by oxidation of the resulting isoxazolidine.

In summary, derivatives of keto amide **10** show a pronounced predilection for formation of the 3-benzylindolizidin-2-one skeleton. Compounds of this basic type result from 1,3-dipolar cycloaddition reactions of oxime **11**, 2,4-dinitrophenylhydrazone **12**, phenylhydrazone **13**, *tert*-butylhydrazone **14**, and dimethylhydrazones **15** and **34** and from some intermediate in the oxidation of **11**. Similar substances arise from intramolecular ene reactions of hydrazones **13** and **14**.

Experimental Section

General. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Benzene and tetrahydrofuran (THF) were distilled from sodium/benzophenone immediately prior to use. Toluene, dimethylformamide (DMF), triethylamine, pyridine, and acetonitrile were distilled from calcium hydride prior to use. Dichloromethane was dried over the distilled from phosphorus pentoxide. All reactions involving air- or moisture-sensitive compounds were performed under a nitrogen atmosphere. Glassware, syringes, and needles employed were oven-dried and cooled in a desiccator prior to use.

Infrared (IR) spectra were determined with a Perkin-Elmer Model 1420 ratio recording infrared were determined with a Perkin-Elmer Model 1420 ratio recording infrared spectrometer. ^{1}H NMR spectra were determined with the followed spectrometers: UCB 250 or BVX 300 (superconducting, FT instruments operating at 250 or 300 MHz, respectively). ^{13}C NMR spectra were measured at 75.48 MHz with the BVX 300 spectrometer. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H NMR data are reported in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons and coupling constants in hertz. ^{1}H and ^{13}C NMR data observed for minor diastereomers are given in brackets and parentheses, respectively. X-ray crystallographic analyses were performed by the X-ray Crystallographic Laboratory; elemental analyses were performed by the Microanalytical Laboratory, both operated by the College of Chemistry, University of California, Berkeley, CA.

***o*-Chlorocinnamoyl Chloride.** Into a 250-mL round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser were placed *o*-chlorocinnamic acid (9.13 g, 0.05 mol), dry benzene (150 mL), and thionyl chloride (11.9 mL, 0.10 mol). The mixture was stirred under reflux for 2.5 h; the cloudy white solution slowly became clear as the reaction proceeded. The reflux condenser was replaced by a distillation apparatus, and the benzene and excess thionyl chloride were removed by distillation. The orange residue was purified by simple distillation under reduced pressure to afford 7.22 g (72%) of *o*-chlorocinnamoyl chloride as a light pink solid, bp 91–93 °C (0.23 torr). IR ($CDCl_3$): 1780 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.67 (d, 1, J = 15.6), 7.40 (m, 3), 7.66 (dd, 1, J = 8.2, 2.5), 8.29 (d, 1, J = 15.6). ^{13}C NMR ($CDCl_3$): δ 124.5, 127.3, 128.0, 130.4, 131.1, 132.6, 136.9, 146.0, 165.9. Anal. Calcd for $C_9H_6OCl_2$: C, 53.77; H, 3.01. Found: C, 53.74; H, 2.97.

2-Acetylpyridine Ethylene Ketal (4). Into a 100-mL round-bottomed flask equipped with a magnetic stirring bar and a Dean–Stark trap were placed 2-acetylpyridine (**3**), (2.00 g), ethylene glycol (4.50 mL), *p*-toluenesulfonic acid (0.18 g), and benzene (50.0 mL). The reaction mixture was heated under reflux for 32 h, and 20.0 mL of the benzene–water azeotrope was drained off. Additional portions of ethylene glycol (2.00 mL) and benzene (20.0 mL) were added, and the solution was heated under reflux for an additional 48 h. The collected azeotrope (20 mL) was drained and fresh benzene (20 mL) was added. After an additional 72 h the solution was cooled to room temperature, washed in succession with 1 N NaOH (80 mL), saturated $NaHCO_3$ (60 mL), water (60 mL), and brine (60 mL). The benzene solution was dried over $MgSO_4$ and filtered. The solvent was removed with a rotary evaporator to give 2.22 g of a yellow oil. Purification by bulb-to-bulb distillation afforded 2.14 g (80%) of **4** as a colorless liquid, bp 91–95 °C (0.80 torr). IR (film): 1590, 1210, 1050 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.74 (s, 3), 3.88 (m, 2), 4.11 (m, 2), 7.22 (ddd, 1, J = 7.4, 4.8, 1.2), 7.55 (dt, 1, J = 7.7, 0.9), 7.69 (dt, 1, J = 7.7, 1.7), 8.65 (dq, 1, J = 4.8, 0.9). ^{13}C NMR ($CDCl_3$): δ 25.1, 64.6, 108.3, 119.1, 122.5, 136.2, 149.1, 160.7. Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.17; H, 6.54; N, 8.40.

2-Acetylpiperidine Ethylene Ketal (5). 2-Acetylpyridine ethylene ketal (1.86 g, 11.2 mmol), absolute ethanol (5.0 mL), and 5% rhodium on alumina (0.25 g) were placed into a 25-mL round-bottomed flask equipped with a magnetic stirring bar. The reaction mixture was stirred under a hydrogen atmosphere for 9 days. The solution was filtered through a plug of Celite, and the solvent was removed with a rotary evaporator to give 1.79 g of crude product. Purification by bulb-to-bulb distillation at reduced pressure afforded 1.76 g (92%) of **5** as a colorless liquid, bp 55–60 °C (0.28 torr). IR (film): 3340, 1450 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.28 (m, 2), 1.30 (s, 3), 1.57 (m, 1), 1.74 (m, 1), 1.82 (br s, 2), 2.54 (dd, 1, J = 6.7, 2.5), 2.62 (dt, 1, J = 11.6, 2.9), 3.11 (d, quintet, 1, J = 11.6, 1.9), 3.97 (br s, 4). ^{13}C NMR ($CDCl_3$): 19.8, 24.4, 25.8, 26.9, 46.9, 62.8, 64.4, 64.6, 110.3. Anal. Calcd for $C_9H_{27}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 62.86; H, 9.96; N, 8.26.

2-Acetylpiperidine (6) and Its Hydrochloride Salt. A mixture of 2-acetylpiperidine ethylene ketal (1.58 g, 9.23 mmol) and 20 mL of 6 N HCl was stirred at room temperature for 24 h. The reaction mixture was made basic with solid NaOH, and the resulting basic solution was extracted with ether (4 × 10 mL). The organic extracts were dried over Na_2SO_4, filtered, and reduced in volume to approximately 10 mL. Gaseous HCl was bubbled through the solution. The solvent was removed with a rotary evaporator to give 1.21 g (80%) of hydrochloride salt as white powder, mp 225-28 °C dec. This material was used without further purification. ^{1}H NMR (Me_2SO-d_6): δ 1.60 (m, 6), 2.24 (s, 3), 2.30 (m, 1), 2.83 (m, 1), 3.24 (br, d, 1, J = 12.8), 4.05 (m, 1). The free base (**6**) was obtained as a light yellow oil by basification with K_2CO_3 and extraction into ether or ethyl acetate immediately prior to use. ^{1}H NMR ($CDCl_3$): δ 1.44 (m, 5), 1.95 (m, 3), 2.16 (s, 3), 2.63 (dt, 1, J = 11.0, 2.9), 3.12 (dm, 1, J = 12.3), 3.31 (dd, 1, J = 10.6, 2.9).

2-Acetylpiperidine Oxime (7). 2-Acetylpiperidine hydrochloride (0.60 g) was dissolved in saturated aqueous K_2CO_3, and the free amine was extracted into ether. The organic extract was dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator to give 2-acetylpiperidine (0.407 g, 3.20 mmol). Pyridine (1.0 mL), absolute ethanol (5.0 mL), and hydroxylamine hydrochloride (0.410 g, 5.90 mmol) were added. The light orange solution quickly turned cloudy as the reaction proceeded. The reaction mixture was stirred at room temperature for 3 h, and the solvent was removed with a rotary evaporator to give a light yellow solid. The crude product was taken up in aqueous K_2CO_3 and extracted with ether (2 × 25 mL) and ethyl acetate (2 × 25 mL). The organic extracts were combined, dried over $MgSO_4$, and filtered. The solvent was removed with a rotary evaporator to give 0.403 g (89%) of **7** as a white solid; mp 103–105 °C. IR ($CHCl_3$): 3595, 3960 (br), 1735, 1655 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.42 (m, 4), 1.58 (m, 1), 1.72 (m, 1), 1.89 (s, 3), 2.67 (dt, 1, J = 11.5, 2.9), 3.13 (d, 1, J = 11.5), 3.22 (dd, 1, J = 10.5, 2.6). ^{13}C NMR

($CDCl_3$): δ 10.5, 24.2, 25.3, 29.4, 46.2, 60.8, 158.2. Anal. Calcd for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.70. Found: C, 58.98; H, 9.87; N, 19.49.

2-Acetylpiperidine Phenylhydrazone (8). 2-Acetylpiperidine hydrochloride (2.0 g) was dissolved in saturated aqueous K_2CO_3 and extracted with ether. The ether extract was dried over $MgSO_4$ and filtered, and the solvent was reduced in volume to give the free amine (0.246 g, 1.93 mmol). Phenylhydrazine hydrochloride (0.310 g, 2.10 mmol, 1.1 equiv) in acetic acid (10 mL) was added, and the resulting brown solution was stirred at room temperature for 2.5 h. The phenylhydrazine hydrochloride slowly went into solution as the reaction proceeded. Most of the acetic acid was removed with a rotary evaporator and saturated K_2CO_3 was added slowly. The aqueous solution was extracted with ethyl acetate (4 × 5 mL). The organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed with a rotary evaporator to give 0.325 g (77%) of **8** as a yellow oil as a mixture of isomers. This crude product could be used without further purification or purified by bulb-to-bulb distillation under reduced pressure, bp 143–145 °C (0.54 torr). IR ($CHCl_3$): 3375, 3190, 1605, 1510 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.46 (m, 3), 1.61 (m, 1), 1.78 (m, 2), 1.87 (s, 3), [1.96 (s, 3)], [2.58 (dt, 1, J = 11.6, 3.0)], 2.72 (dt, 1, J = 11.6, 2.8), 3.15 (br dd, 1, J = 10.8, 1.7), 3.30 (dd, 1, J = 10.3, 2.8), [3.40 (dd, 1, J = 11.0, 3.0)], 6.82 (tt, 2, J = 7.3, 1.0), 6.97 (m, 1), 7.05 (dd, 1, J = 8.7, 1.0), 7.23 (dd, 2, J = 8.1, 7.0). ^{13}C NMR ($CHCl_3$): δ 11.5, (22.5), (24.3), 24.4, (25.7), (25.9), 25.9, 30.1, (46.3), 46.5, (60.4), 62.9, (111.8), 112.8, (118.2), 119.4, (128.8), 128.9 (144.8), 145.4, (145.7), 147.4.

2-Acetylpiperidine *tert*-Butylhydrazone (9). 2-Acetylpiperidine hydrochloride (0.30 g, 1.83 mmol), *tert*-butylhydrazine hydrochloride (0.399 g, 2.02 mmol, 1.1 equiv), and acetic acid (2.0 mL) were added to a 10-mL round-bottomed flask equipped with a magnetic stirring bar. The reaction mixture was stirrred at room temperature for 24 h, and the solvent was removed with a rotary evaporator to give a brown oil. This crude residue was dissolved in saturated aqueous K_2CO_3 and extracted with ether (2 × 20 mL) and ethyl acetate (2 × 20 mL). The organic extracts were combined, dried over $MgSO_4$, and reduced in volume with a rotary evaporator to give **9** as a yellow oil. This product could be used in the subsequent step without further purification; however, distillation affords the best results. The crude material was purified by bulb-to-bulb distillation at reduced pressure, bp 100–105 °C (0.50 torr) to give 0.287 g (79%) of **9** as a colorless oil. IR (film): 3280, 1712, 1640 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.18 (s, 9), 1.50 (m, 5), 1.72 (s, 3), 1.85 (m, 1), 2.70 (dt, 1, J = 11.6, 2.8), 3.11 (br d, 1, J = 10.5), 3.18 (dd, 1, J = 10.4, 2.8). ^{13}C NMR ($CDCl_3$): δ 11.1, 24.3, 26.0, 28.3, 30.1, 46.4, 52.9, 63.0, 147.6.

***N*-(*o*-Chlorocinnamoyl)-2-acetylpiperidine (10).** 2-Acetylpiperidine hydrochloride (0.32 g) was dissolved in saturated aqueous K_2CO_3, and the free amine was extracted into ether. The organic extract was dried over $MgSO_4$, filtered, and reduced in volume to give 2-acetylpiperidine (0.193 g, 1.52 mmol). Triethylamine (0.184 g, 0.26 mL, 1.82 mmol) and dry toluene (5.00 mL) were added immediately to the free amine, and the solution was stirred under nitrogen. In a 10-mL Erlenmeyer flask *o*-chlorocinnamoyl chloride (0.306 g, 1.52 mmol) solution was dissolved in dry toluene (5.0 mL). The acid chloride was added rapidly, whereupon the solution turned dark red-brown. The reaction mixture was stirred at room temperature for 1.5 h, quenched with water (20 mL), and extracted with ethyl acetate (20 mL). The aqueous phase was separated and extracted with two additional portions of ethyl acetate (2 × 10 mL). The organic extracts were combined, washed with 5% HCl (2 × 20 mL), and dried over $MgSO_4$. The light orange solution was filtered, and the solvent was removed with a rotary evaporator to give 0.445 g of a dark orange oil. This crude product was purified by chromatography on silica gel (18 g), with 2:1 hexanes/ethyl acetate as eluant to yield 0.403 g (91%) of **10** as a light yellow oil. IR ($CHCl_3$): 1725, 1645, 1605 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.43 (m, 2), 1.68 (m, 3), 2.17 (s, 3), 2.25 (m, 1), 3.25 (dt, 1, J = 12.7, 2.4), 4.03 (d, 1, J = 12.7), 5.29 (d, 1, J = 3.4), 7.02 (d, 1, J = 15.5), 7.26 (m, 2), 7.38 (m, 1), 7.64 (m, 1), 8.05 (d, 1, J = 15.5). ^{13}C NMR ($CDCl_3$): δ 20.2, 24.6, 25.1, 26.4, 43.8, 59.1, 119.6, 126.5, 127.1, 129.5, 130.0, 132.9, 133.9, 138.1, 165.7, 206.2. Mass spectrum (70 eV): m/z 291 (parent), 84 (base). HRMS Calcd for $C_{16}H_{18}NO_2Cl$: 291.1026. Found: 291.1040.

***N*-(*o*-Chlorocinnamoyl)-2-acetylpiperidine Oxime (11). (a) From *N*-(*o*-Chlorocinnamoyl)-2-acetylpiperidine (10).** Hydroxylamine hydrochloride (0.100 g, 1.37 mmol), isopropyl alcohol (2.0 mL), and keto amide **10** (0.100 g, 0.343 mmol) were placed into a 10-mL round-bottomed flask and stirred at room temperature for 32 h. Product formation was monitored by TLC. Approximately 0.5 g of silica gel was added to the reaction mixture, and the solvent was removed with a rotary evaporator. The crude product, adsorbed on silica gel, was purified by chromatography on silica gel (9 g) with 3:1 hexanes/ethyl acetate as eluant to yield 0.035 g (33%) of **11** as a white solid, mp 131–134 °C. IR ($CDCl_3$): 3580, 3300, 1685, 1625 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.25 (m, 1), 1.68 (m, 4), 1.86 (s, 3), 2.21 (m, 1), 3.20 (m, 1), 3.95 (br d, J = 15.0), 5.50 (br s, 1), 6.89 (d, 1, J = 15.6), 7.27 (m, 2), 7.41 (m, 1), 7.61 (m, 1), 8.00 (d, 1, J = 15.6), 8.20 (br s, 1). ^{13}C NMR (Me_2SO-d_6): δ 11.5, 19.7, 25.3, 26.0, 52.0, 107.5, 121.5, 127.5, 128.2, 129.8, 130.9, 132.8, 133.3, 136.6, 153.1, 164.7. Anal. Calcd. for $C_{16}H_{19}N_2O_2Cl$: C, 62.64; H, 6.24; N, 9.13. Found: C, 62.80; H, 6.21; N, 8.85.

(b) From 2-Acetylpiperidine Oxime (7). Into a 10-mL round-bottomed flask flushed with nitrogen were placed 2-acetylpiperidine oxime (**7**) (0.107 g, 0.753 mmol), CH_2Cl_2 (2.0 mL), and triethylamine (0.140 mL, 0.099 g, 0.978 mmol, 1.3 equiv). A solution of *o*-chlorocinnamoyl chloride (0.179 g, 0.828 mmol, 1.1 equiv) in CH_2Cl_2 (2.0 mL) was added in one portion. The reaction mixture was stirred at room temperature for 30 min. Approximately 0.5 g of silica gel was added, and the solvent was removed with a rotary evaporator. The crude product was purified by chromatography on silica gel (9 g) with 3:1 hexanes/ethyl acetate as eluant to yield 0.203 g (88%) of **11** as a white solid, identical spectrally with the sample prepared by method a.

***N*-(*o*-Chlorocinnamoyl)-2-acetylpiperidine 2,4-Dinitrophenylhydrazone (12).** Into a 25-mL Erlenmeyer flask were placed 2,4-dinitrophenylhydrazine (0.0800 g, 0.4038 mmol) and methanol (8.0 mL). Concentrated HCl (5 drops) was added slowly, and the mixture was warmed with a steam bath to dissolve the orange solid. Keto amide **10** (0.1108 g, 0.3797 mmol) in methanol (1 mL) was added to the hydrazine reagent, and the mixture was heated with a steam bath for 2 min. The solution was allowed to cool to room temperature and then further cooled in an ice–water bath. Water (1.0 mL) was added, and the orange crystals were filtered and washed with cold water to give 0.1324 g of a yellow-orange solid. A second crop of crystals yielded 0.0229 g, to afford a total of 0.1544 g (86%) of **12** as yellow-orange crystals, mp 160–162 °C. IR ($CHCl_3$): 3325, 1645, 1620 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.62 (m, 1), 1.77 (m, 4), 2.07 (s, 3), 2.39 (br d, 1, J = 7.6), 3.24 (m, 1), 4.08 (br d, 1, J = 1.6), 5.62 (br s, 1), 6.97 (d, 1, J = 14.9), 7.30 (m, 2), 7.43 (m, 1), 7.62 (m, 1), 7.88 (d, 1, J = 9.5), 8.04 (d, 1, J = 14.9), 8.33 (dd, 1, J = 9.5, 2.4), 9.14 (d, 1, J = 2.4), 11.14 (s, 1). ^{13}C NMR ($CDCl_3$): δ 3.8, 19.9, 25.4, 26.0, 43.7, 54.5, 112.6, 116.3, 120.1, 123.3, 126.9, 127.5, 129.3, 130.1, 130.5, 133.4, 134.5, 137.9, 138.9, 145.0, 155.1, 166.2. Anal. Calcd. for $C_{22}H_{22}N_5O_5Cl$: C, 56.00; H, 4.70; N, 14.84. Found: C, 55.77; H, 4.51, N, 14.91.

***N*-(*o*-Chlorocinnamoyl)-2-acetylpiperidine Phenylhydrazone (13).** To a solution of 2-acetylpiperidine phenylhydrazone (**8**) (0.275 g, 1.26 mmol) in CH_2Cl_2 (2.0 mL), under nitrogen, was added triethylamine (0.153 g, 0.210 mL, 1.52 mmol, 1.2 equiv). The resulting solution was cooled to −78 °C with a dry ice/acetone bath and a solution of *o*-chlorocinnamoyl chloride (0.279 g, 1.39 mmol, 1.1 equiv) in CH_2Cl_2 (2.0 mL) was added in one portion. The reaction mixture was stirred at −78 °C for 5 min and allowed to warm to room temperature. The solvent was removed with a rotary evaporator to give a sticky brown solid. The crude material was taken up in CH_2Cl_2, 1.0 g of flash silica gel was added, and the solvent was removed with a rotary evaporator. The crude product, adsorbed on silica gel, was purified by column chromatography on flash silica gel (18 g) with 4:1 hexanes/ethyl acetate as eluant to yield 0.409 g (85%) of **13** as a light yellow solid. Recrystallization from ethyl acetate gave a white powder, mp 156–158 °C. IR ($CHCl_3$): 3420, 1645, 1605 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.71 (m, 4), 1.84 (s, 3), 2.05 (m, 1), 2.43 (br d, 1, J = 11.1), 3.23 (br t, 1, J = 12.2), 3.95 (br d, 1, J = 12.2), 4.78 (m, 1), 5.56 (br s, 1), 6.89 (m, 2), 7.08 (m, 2), 7.27 (m, 4), 7.42 (m, 1), 7.63 (br s, 1), 8.02 (d, 1, J = 15.4). ^{13}C NMR ($CDCl_3$): δ 12.2, 19.8, 25.4, 26.4, 43.3, 53.9, 112.7, 119.5, 120.7, 126.8, 127.4, 129.0, 129.9, 130.1, 133.6, 134.3, 138.1, 142.3, 145.5, 165.7. Anal.

Calcd for $C_{22}H_{24}N_3OCl$: C, 69.19; H, 6.33; N, 11.00. Found: C, 69.19; H, 6.29; N, 10.95.

***N*-(*o*-Chlorocinnamoyl)-2-acetylpiperidine *tert*-Butylhydrazone (14).** 2-Acetylpiperidine *tert*-butylhydrazone (9) (0.287 g, 1.46 mmol), triethylamine (0.243 mL, 0.177 g, 0.175 mmol, 1.2 equiv), and CH_2Cl_2 (2.0 mL) were placed into a 10-mL round-bottom flask. The reaction mixture was cooled to −78 °C and *o*-chlorocinnamoyl chloride (0.323 g, 1.60 mmol, 1.1 equiv) in dichloromethane (2.0 mL) was added to the stirring solution in one portion. After 10 min at −78 °C the light yellow solution was allowed to warm to room temperature. The crude product was adsorbed on flash silica (1.0 g) and purified by chromatography on flash silica gel (18 g) with 3:1 hexanes/ethyl acetate as eluant to yield 0.496 g (94%) of **14** as a light yellow oil. IR ($CHCl_3$): 3320, 1643, 1600 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.19 (s, 9), 1.25–1.75 (m, 5), 1.67 (s, 3), 2.31 (d, 1, J = 9.6), 3.17 (br t, 1, J = 13.6), 3.90 (d, 1, J = 13.0), 4.58 (m, 1), 5.42 (br s, 1), 7.49 (d, 1, J = 15.1), 7.28 (m, 2), 7.40 (m, 1), 7.59 (br s, 1), 7.98 (d, 1, J = 15.1). ^{13}C NMR ($CDCl_3$): δ 11.9, 19.8, 25.4, 26.4, 28.5, 43.2, 53.3, 54.0, 120.9, 126.7, 127.4, 129.8, 130.0, 133.7, 134.3, 137.7, 143.1, 165.6. Mass spectrum (70 eV): m/z 361 (parent), 57 (base). HRMS Calcd for $C_{20}H_{28}N_3O^{35}Cl$: 361.1923. Found: 361.1907. Calcd for $C_{20}H_{28}N_3O^{37}Cl$: 363.1893. Found: 363.1890.

***N*-(*o*-Chlorocinnamoyl)-2-acetylpiperidine Dimethylhydrazone (15).** *N*-(*o*-Chlorocinnamoyl)-2-acetylpiperidine (0.0549 g, 0.188 mmol) was taken up in acetic acid (0.70 mL), and 1,1-dimethylhydrazine (0.016 mL, 0.012 g, 0.207 mmol, 1.1 equiv) was added in one portion. The reaction mixture was stirred at room temperature over nitrogen for 3 h, and an additional portion of 1,1-dimethylhydrazine (0.016 mL, 0.012 g, 0.207 mmol, 1.1 equiv) was added. The solution was stirred for an additional 6 h at room temperature. Most of the acetic acid was removed with a rotary evaporator. The sample was placed under high vacuum and heated gently to remove the remainder of the acetic acid to give 0.072 g of a yellow oil. The crude product was purified by chromatography on silica gel (3.5 g) with 2:1 hexanes/ethyl acetate as eluant to give 0.034 g (54%) of **15** as a viscous, light yellow oil. IR ($CHCl_3$): 1645, 1605, 1430 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.65 (m, 5), 1.91 (s, 3), 2.29 (br d, 1, J = 10.2), 2.47 (s, 6), 3.23 (br t, 1, J = 12.2), 3.92 (br d, 1, J = 10.2), 4.62 (br s, 1), 5.40 (br s, 1), 6.90 (d, 1, J = 15.6), 7.26 (m, 2), 7.40 (m, 1), 7.60 (br s, 1), 7.98 (d, 1, J = 15.6). ^{13}C NMR ($CDCl_3$): δ 14.9, 19.8, 47.2, 121.2, 126.8, 127.6, 130.0, 130.1, 133.9, 134.5, 137.9, 163.0, 170.4. Anal. Calcd for $C_{18}H_{24}N_3OCl$: C, 64.76; H, 7.25; N, 12.59. Found: C, 64.5; H, 7.1; N, 12.3.

Isoxazolidine 16. (a) From *N*-(*o*-Chlorocinnamoyl)-2-acetylpiperidine (10). Keto amide **10** (0.2464 g, 0.8445 mmol), hydroxylamine hydrochloride (0.0587 g, 0.8445 mmol), absolute ethanol (2.0 mL), and pyridine (0.50 mL) were placed into a 10-mL round-bottomed flask. The stirring reaction mixture was heated at reflux for 4.0 h. The ethanol was removed with a rotary evaporator and distilled water (5.0 mL) was added to the light orange oil. The solution was heated to dissolve the sticky material until only solid remained. The mixture was cooled and filtered, and the collected solid was washed with cold water. The filtrate was reduced in volume to give an oily residue, which was combined with the powdery solid obtained in the filtration. The total product was purified by chromatography on silica gel (11 g) with 2:1 hexanes/ethyl acetate as eluant to afford 0.1777 g (69%) of **16** as a white solid. Crystals, mp 146–148 °C, were grown from ethyl acetate for X-ray crystallographic analysis. IR ($CDCl_3$): 1690, 1450 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.10–1.60 (m, 3), 1.37 (s, 3), 1.71 (br, d, 1, J = 13.2), 1.95 (m, 2), 2.75 (dt, 1, J = 12.5, 3.5), 3.20 (d, 1, J = 3.1), 3.38 (br d, 1, J = 12.5), 4.23 (dd, 1, J = 13.2, 4.6), 5.50 (br s, 1), 5.61 (d, 1, J = 3.1), 7.30 (m, 2), 7.45 (m, 2). ^{13}C NMR ($CDCl_3$): δ 18.5, 23.9, 24.3, 28.2, 40.7, 62.7, 62.8, 68.6, 84.8, 126.8, 129.4, 130.5, 130.6, 133.7, 136.4, 170.4. Anal. Calcd. for $C_{16}H_{19}N_2O_2Cl$: C, 62.64; H, 6.24; N, 9.13. Found: C, 62.81; H, 6.31; N, 9.16.

(b) From *N*-(*o*-Chlorocinnamoyl)-2-acetylpiperidine Oxime (11) in Acetonitrile. Oxime **11** (0.0220 g, 0.717 mmol) was added to a 0.5-mL Wheaton vial with 0.50 mL of dry acetonitrile and placed over an N_2 atmosphere. The reaction mixture was heated in an 88–93 °C oil bath for 30 h, and the solvent was removed with a rotary evaporator to give 23.5 mg of crude material. The product was purified by column chromatography on silica gel (1.1 g) with 2:1 hexanes/ethyl acetate as eluant to afford 0.0202 g (92%) of **16** as a white solid, identical spectrally with that prepared by method a.

(c) From *N*-(*o*-Chlorocinnamoyl)-2-acetylpiperidine Oxime (11) under Acidic Conditions. Oxime **11** (0.030g, 0.098 mmol) was dissolved in absolute ethanol (0.5 mL), and pyridinium *p*-toluenesulfonate (0.010 g, 0.040 mmol) was added. The solution was stirred at room temperature for 50 h. The ethanol was removed with a rotary evaporator to give an oily yellow solid. The crude product was purified by chromatography on silica gel (1 g) with 3:1 hexanes/ethyl acetate as eluant to give 0.014 g (69% based on recovered starting material) of **16** as a white solid, identical spectrally with that prepared by method a.

Isoxazolidines 16 and 18. Oxime **11** (0.0280 g, 0.0913 mmol), and dry DMF (0.25 mL) were added to a 0.5-mL Wheaton vial, and the solution was heated in an oil bath at 120 °C for 24 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 × 5 mL). The organic extracts were dried over $MgSO_4$, filtered, and reduced in volume with a rotary evaporator to give a crude orange oil. The crude material was purified by chromatography on flash silica gel (1.1 g) with 2:1 hexanes/ethyl acetate as eluant to give 0.0165 g (59%) of isoxazolidines **16** and **18** as a white solid. The spectral data for isomer **16** were identical with those prepared by method a. Observed resonances which are unique to isomer **18** are as follows. ^1H NMR ($CDCl_3$): δ 1.42 (s, 3), 2.68 (m, 1), 3.29 (dd, 1, J = 11.5, 3.6), 3.35 (br s, 1), 4.42 (m, 1), 5.45 (s, 1). ^{13}C NMR ($CDCl_3$): δ 22.8, 23.8, 24.2, 40.5, 84.1, 126.5, 126.7, 129.5, 136.2.

Pyrazolidine 17. To a 0.5-mL Wheaton vial was added 2,4-dinitrophenylhydrazone **12** (0.0140 g, 0.0297 mmol), pyridinium *p*-toluenesulfonate (0.0080, 0.0318 mmol), and absolute ethanol (0.50 mL). The solution was heated for 18 h under nitrogen in a 110 °C oil bath. The solvent was removed with a rotary evaporator, and the resulting residue was purified by column chromatography on silica gel (1.0 g) with 3:1 hexanes/ethyl acetate as eluant to afford 8.1 mg (58%) of **17** as an orange solid. Recrystallization from ethyl acetate and hexanes provided an analytically pure sample, mp 238–240 °C dec. IR ($CDCl_3$): 3695, 1695, 1610, 1525, 1340 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.21 (m, 3), 1.29 (s, 3), 1.70 (m, 2), 1.90 (br d, 1, J = 12.8), 2.60 (dt, 1, J = 12.8, 3.6), 3.16 (m, 1), 3.17 (d, 1, J = 3.4), 4.09 (dd, 1, J = 13.2, 4.1), 4.61 (s, 1), 5.64 (d, 1, J = 3.4), 6.85 (d, 1, J = 9.4), 7.35 (m, 3), 7.50 (m, 1), 8.12 (dd, 1, J = 9.4, 2.6), 8.52 (d, 1, J = 2.6). ^{13}C NMR ($CDCl_3$): δ 19.5, 23.5, 24.1, 27.6, 40.9, 61.1, 64.4, 66.6, 66.8, 114.0, 122.8, 127.3, 127.4, 127.8, 130.0, 131.2, 132.5, 135.3, 136.5, 137.7, 144.3, 169.5. Mass spectrum (70 eV): m/z 471 (parent, base). Anal. Calcd for $C_{22}H_{22}N_5O_5Cl$: C, 56.00; H, 4.70; N, 14.84. Found: C, 55.75; H, 4.65; N, 14.63.

Pyrazolidines 17 and 19. The 2,4-dinitrophenylhydrazone **12** (0.0273 g, 0.0579 mmol) was dissolved in dry DMF (0.25 mL), heated with an oil bath at 110–120 °C for 18 h, quenched with saturated aqueous NH_4Cl (3.0 mL), and extracted with ethyl acetate (10 mL). The organic extracts were washed with distilled water (3 × 5 mL) and dried over $MgSO_4$. The solvent was removed with a rotary evaporator to give 0.0211 g of crude dark orange product. The residue was purified by chromatography on silica gel (1 g) with 3:1 hexanes/ethyl acetate as eluant to give 0.0137 g (50%) of pyrazolidines **17** and **19** in a 9:1 ratio as an orange solid. The spectral data for isomer **17** were identical with those obtained previously. Observed resonances which are unique to isomer **19** are as follows. ^1H NMR ($CDCl_3$): δ 1.27 (s, 3), 3.35 (s, 1), 4.34 (s, 1), 5.88 (s, 1), 6.96 (d, 1, J = 9.3), 8.57 (d, 1, J = 2.4).

Pyrazolidine 20. *N*-(*o*-Chlorocinnamoyl)-2-acetylpiperidine phenylhydrazone (**13**) (0.0572 g, 0.150 mmol), pyridinium *p*-toluenesulfonate (0.0376 g, 0.150 mmol), and absolute ethanol (0.50 mL) were added to a 0.5-mL Wheaton vial and placed under N_2. The solution was heated in a 120 °C oil bath for 12 h. As the solution was heated, the solids slowly dissolved. The solvent was removed with a rotary evaporator to give 93.8 mg of crude material. This residue was purified by column chromatography on silica gel (4.0 g) with 5:1 hexanes/ethyl acetate as eluant to give 0.0416 g of **20** as a white solid. Recrystallization from ethyl acetate provided analytically pure crystals, mp 188–190 °C. IR($CHCl_3$): 3460, 1685, 1600 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.25 (m, 2), 1.32 (s, 3), 1.67 (m, 2), 1.90 (m, 2), 2.53 (dt, 1, J = 12.7, 3.6), 3.03 (d, 1, J = 3.6), 3.30 (dd, 1, J = 11.8, 3.1), 4.07 (dd, 1, J = 12.7, 4.1), 4.17

(br s, 1), 5.24 (d, 1, J = 3.6), 6.77 (t, 1, J = 7.3), 6.90 (d, 2, J = 7.7), 7.20 (m, 4), 7.44 (m, 2). ^{13}C NMR ($CDCl_3$): δ 19.3, 23.7, 24.1, 27.4, 40.5, 63.2, 63.5, 66.6, 68.5, 113.1, 118.6, 127.2, 128.0, 128.7, 128.8, 130.6, 132.5, 138.9, 149.1, 170.8. Anal. Calcd for $C_{22}H_{24}N_3OCl$: C, 69.19; H, 6.33; N, 11.00. Found: C, 68.86; H, 6.35; N, 10.84.

Pyrazolidine 21. *tert*-Butylhydrazone **14** (0.590 g, 0.163 mmol), pyridinium *p*-toluenesulfonate (0.0410 g, 0.163 mmol), and absolute ethanol (0.50 mL) were added to a 0.5-mL Wheaton vial and placed under N_2. The reaction mixture was heated for 12 h in a 110 °C oil bath. The solvent was removed with a rotary evaporator to give a crude yellow oil. The crude material was taken up in ethyl acetate and washed with saturated aqueous K_2CO_3. The organic extract was dried over $MgSO_4$ and filtered, and the solvent was removed to give 40.2 mg of crude material, which was solely pyrazolidine **21** according to ^{1}H NMR data. The crude product was purified by chromatography on flash silica (2.0 g) with 3:1 hexanes/ethyl acetate as eluant to provide 0.0238 g (41%) of pyrazolidine **21** as a light yellow oil. IR ($CHCl_3$): 3420, 1680 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.98 (s, 9), 1.03–1.51 (m, 3), 1.30 (s, 3), 1.65 (dm, 1, J = 12.7), 1.82 (dd, 1, J = 12.6, 3.2), 1.94 (br d, 1, J = 10.4), 2.69 (dt, 1, J = 12.7, 3.5), 2.76 (d, 1, J = 3.1), 3.29 (dd, 1, J = 12.2, 3.1), 3.47 (br s, 1), 4.22 (dd, 1, J = 13.0, 4.7), 4.68 (d, 1, J = 3.1), 7.14 (dq, 1, J = 7.5, 1.8), 7.22 (dd, 1, J = 7.5, 1.5), 7.32 (dd, 1, J = 7.7, 1.4), 7.81 (dd, 1, J = 7.7, 1.7). ^{13}C NMR ($CDCl_3$): δ 21.4, 24.3, 24.7, 26.7, 29.0, 40.5, 56.1, 62.9, 63.9, 64.1, 65.2, 126.4, 127.7, 129.2, 129.6, 132.6, 142.9, 171.3. Mass spectrum (70 eV): m/z 361 (parent), 84 (base). HRMS: Calcd for $C_{20}H_{28}N_3O^{35}Cl$: 361.1923. Found: 361.1929. Calcd for $C_{20}H_{28}N_3O^{37}Cl$: 363.1893. Found: 363.1905.

Pyrazolidines 20 and 25. Dry THF (0.20 mL) and *N*-(*o*-chlorocinnamoyl)-2-acetylpiperidine phenylhydrazone (**13**) (0.0539 g, 0.141 mmol) were placed in a 10-mL round-bottomed flask equipped with a magnetic stirring bar. The solution was placed under N_2 and cooled to 0 °C with an ice bath. To the light yellow solution was added *n*-BuLi (0.102 mL of a 1.53 M solution in hexanes, 0.155 mmol, 1.1 equiv) dropwise. Immediately upon this addition, the reaction mixture turned a dark red-rust color. The solution was allowed to stir at 0 °C for 10 min, and the reaction was quenched with distilled water (0.25 mL). The mixture immediately became a light yellow color with the addition of the water. The solution was extracted with ethyl acetate (2 × 5 mL). The organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed with a rotary evaporator to give 49.9 mg of a light yellow solid. The crude product was purified by column chromatography on silica (2.2 g) with 3:1 hexanes/ethyl acetate as eluant to give 0.0306 g (57%) of **20** and **25** as a light yellow solid as a 9:1 mixture of diastereomers as determined by integration of the doublets at 5.24 and 5.41 ppm, respectively. The spectral data for both diastereomers were identical with those obtained previously.

Azo Lactam 22. To a 0.5-mL Wheaton vial was added *N*-(*o*-chlorocinnamoyl)-2-acetylpiperidine (0.0251 g, 0.0657 mmol) and dry acetonitrile (0.25 mL). The solution was placed under nitrogen and heated in a 110 °C oil bath for 12 h. The solvent was removed with a rotary evaporator to give 27.3 mg of a yellow oil. The crude product was purified by column chromatography on silica gel (1.2 g) with 3:1 hexanes/ethyl acetate as eluant to afford 0.0221 g (88%) of **22** as a light yellow oil. IR ($CHCl_3$): 1685, 1455 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.14 (s, 3), 1.38 (m, 3), 1.67 (br t, 2, J = 13.6), 1.98 (br d, 1, J = 12.5), 2.74 (dt, 1, J = 12.5, 3.1), 3.10 (dd, 1, J = 9.4, 3.5), 3.22 (m, 2),3.40 (dd, 1, J = 11.8, 2.9), 4.23 (dd, 1, J = 13.0, 4.1), 7.10 (m, 2), 7.27 (m, 2), 7.48 (m, 3), 7.73 (m, 2). ^{13}C NMR ($CDCl_3$): δ 18.0, 24.2, 24.9, 27.2, 29.4, 40.8, 50.4, 63.5, 74.8, 122.4, 126.3, 127.6, 129.0, 129.3, 130.8, 132.4, 133.7, 137.7, 151.5, 172.7. Anal. Calcd for $C_{22}H_{24}N_3OCl$: C, 69.19; H, 6.33; N, 11.00. Found: C, 69.22; H, 6.37; N, 10.79.

Azo Lactams 22 and 27 and Pyrazolidines 20 and 25. In a 0.5-mL Wheaton vial were placed *N*-(*o*-chlorocinnamoyl)-2-acetylpiperidine (0.0254 g, 0.066 mmol) and dry DMF (0.50 mL). The solution was heated under N_2 in an oil bath at 120 °C for 22 h. The reaction was quenched with satd aqueous NH_4Cl and extracted with ethyl acetate (3 × 5 mL). The extracts were combined, dried over $MgSO_4$, and filtered. The solvent was removed with a rotary evaporator to give 26.3 mg of crude material, which was a mixture of azo lactams and pyrazolidines in a ratio of 1.5:1. The products were separated and purified by column chromatography on flash silica gel (2.5 g) with 4:1 hexanes/ethyl acetate as eluant to give a total of 22.1 mg (87%) of products.

Azo lactams **22** and **27** [13.3 mg (52% yield)] were isolated in a 2:1 ratio as a light yellow oil. The spectral data for isomer **20** were identical with those obtained previously. Observed resonances which are unique to isomer **27** are as follows. ^{1}H NMR ($CDCl_3$): δ 0.92 (m, 1), 1.19 (s, 3), 3.44 (dd, 1, J = 11.7, 3.6), 4.25 (m, 1). ^{13}C NMR ($CDCl_3$): δ 18.8, 23.6, 23.8, 23.9, 28.9, 40.5, 52.0, 65.1, 74.9, 126.2, 129.0, 137.4.

Pyrazolidines **20** and **25** [8.8 mg (34% yield)] were isolated in a 1:1 ratio as white crystals. The spectral data for isomer **18** were identical with those obtained previously. Observed resonances which are unique to isomer **25** are as follows. ^{1}H NMR ($CDCl_3$): δ 3.16 (d, 1, J = 1.7), 3.23 (dd, 1, J = 11.7, 3.6), 3.94 (br s, 1), 4.03 (dd, 1, J = 13.2, 4.5), 5.41 (d, 1, J = 1.7). ^{13}C NMR ($CDCl_3$): δ 23.6, 23.8, 23.9, 25.9, 40.4, 62.5, 64.3, 64.9, 65.9, 113.4, 118.8, 126.9, 127.5, 130.7, 132.9, 138.1, 148.1, 171.2.

Azo Lactam 23. A solution of 2-acetylpiperidine *tert*-butylhydrazone, (**9**), (2.00 g, 0.0101 mol) triethylamine (1.70 mL, 1.23 g, 0.0122 mol, 1.2 equiv), and CH_2Cl_2 (15.0 mL) was cooled to −78 °C. To this solution was added *o*-chlorocinnamoyl chloride (2.23 g, 0.011 mol, 1.1 equiv) in CH_2Cl_2 (15.0 mL) over a 10-min period with a syringe pump. The reaction mixture was stirred for 0.5 h at −78 °C, and the solvent was removed with a rotary evaporator to give **14** as a brown sticky solid. The crude *tert*-butylhydrazone amide **14** was taken up in acetonitrile (25.0 mL) and the resulting solution heated to 90 °C for 12 h. The crude product was adsorbed on silica gel and flushed through silica gel (15 g, 40–63 μm, 400–230 mesh) to give 1.77 g of a dark orange oil. The residue was purified by chromatography to yield 1.16 g (58%) of **23** as a light yellow oil. IR ($CHCl_3$): 1685 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.99 (s, 3), 1.08–1.55 (m, 5), 1.20 (s, 9), 1.62 (br d, 1, J = 12.3), 1.95 (br d, 1, J = 11.9), 2.68 (dt, 1, J = 12.5, 3.0), 3.08 (m, 3), 3.25 (dd, 1, J = 11.9, 3.0), 4.19 (dd, 1, J = 13.2, 4.9), 7.28 (m, 4). ^{13}C NMR ($CDCl_3$): δ 17.7, 24.0, 24.7, 26.6, 26.9, 29.0, 40.5, 49.9, 62.7, 67.6, 73.0, 126.1, 127.4, 129.1, 132.2, 133.6, 138.0, 172.6. Mass spectrum (70 eV): m/z 362 (M + 1), 57 (base). HRMS Calcd for $C_{20}H_{29}N_3O^{35}Cl$: 362.2002. Found: 362.2008. Calcd for $C_{20}H_{29}N_3O^{37}Cl$: 364.1972. Found: 364.1977.

Azo Lactams 23 and 28 and Pyrazolidines 21 and 26. *N*-(*o*-chlorocinnamoyl)-2-acetylpiperidine *tert*-butylhydrazone (**14**) (0.0584 g, 0.161 mmol) was taken up in dry DMF (0.50 mL) and placed in a 0.5-mL Wheaton vial under N_2, and the solution was heated in an oil bath at 110–120 °C for 15 h. The solution was allowed to cool to room temperature, the reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed with a rotary evaporator to give 44.0 mg of azo lactams and pyrazolidines in a 1:1 ratio as determined by integration of the corresponding *tert*-butyl singlets in the ^{1}H NMR. The products were separated and purified by column chromatography on silica gel (2.0 g) with 4:1 hexanes/ethyl acetate as eluant to give a total of 32.8 mg (56%) of products.

Azo lactams **23** and **28** [14.3 mg (24% yield)] were isolated as a 1:1 mixture of diastereomers as determined by the integration of the corresponding *tert*-butyl singlets. The spectral data for the isomer **21** were identical with those obtained previously. The spectral resonances unique to diastereomer **28** are as follows. ^{1}H NMR ($CDCl_3$): δ 1.13 (s, 3), 1.26 (s, 9), 3.36 (dd, 1, J = 11.7, 3.4). ^{13}C NMR ($CDCl_3$): 18.4, 23.6, 24.0, 26.8, 27.2, 28.4, 40.3, 51.7, 64.6, 126.3, 127.5, 129.2, 132.3, 132.4, 174.4.

Pyrazolidines **21** [10.6 mg (18%)] and **26** [7.9 mg (14%)] were isolated as light yellow oils. The spectral data for the minor diastereomer are identical with those of **21** obtained under acidic conditions. The spectral resonances unique to the major diastereomer **26** are as follows. ^{1}H NMR ($CDCl_3$): δ 1.00 (s, 9), 1.10 (m, 2), 1.26 (s, 3), 1.35 (m, 2), 1.72 (m, 2), 1.97 (m, 1), 2.61 (br t, 1, J = 11.7), 2.81 (s, 1), 3.11 (dd, 1, J = 9.4, 5.7), 3.35 (br s, 1), 4.14 (br d, 1, J = 11.7), 4.80 (s, 1), 7.28 (m, 3), 7.94 (d, 1, J = 7.6). ^{13}C NMR ($CDCl_3$): δ 23.5, 23.9, 24.4, 25.1, 26.5, 40.1, 56.8, 61.3, 63.1, 63.6, 63.8, 126.2, 127.7, 129.6, 132.5, 143.1, 172.3.

Azo Amine 24 and Its Picrate Salt. Into a 10-mL round-bottomed flask were placed azo lactam **23** (0.1163 g, 0.3213 mmol) and dry THF (1.0 mL). Lithium aluminum hydride (1 M in THF) (1.61 mL, 1.61 mmol, 5.0 equiv) was added slowly to this solution

at room temperature. The reaction mixture was heated at reflux for 24 h, cooled in an ice bath, and quenched with distilled water (0.15 mL), 10% NaOH (0.2 mL), and distilled water (0.4 mL). The solids were filtered and washed with ether. The organic layer was separated, dried over $MgSO_4$, filtered, and reduced in volume to give 0.0994 g of a crude oil. The crude material was purified by chromatograph on silica gel (4 g) with 4:1 hexanes/ethyl acetate as eluant to yield 0.042 g (38%) of **24** as a colorless oil. IR ($CHCl_3$): 1480, 1453 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.12 (s, 3), 1.17 (m, 2), 1.19 (s, 9), 1.38 (m, 1), 1.48 (m, 1), 1.62 (d, 1, J = 12.3), 1.79 (d, 1, J = 5.6), 2.04 (dt, 1, J = 11.5, 3.1), 2.25 (m, 2), 2.53 (m, 1), 2.64 (dd, 1, J = 13.4, 11.5), 2.85 (dd, 1, J = 13.5, 3.8), 2.94 (dd, 1, J = 8.7, 6.5), 3.09 (br d, 1, J = 10.7), 7.15 (m, 3), 7.31 (m, 1). ^{13}C NMR ($CDCl_3$): δ 20.3, 24.4, 25.3, 25.7, 26.9, 33.0, 49.2, 54.1, 60.9, 67.1, 70.1, 75.7, 126.4, 127.2, 129.5, 130.4, 133.9, 139.2. Anal. Calcd for $C_{20}H_{30}N_3Cl$: C, 69.04; H, 8.69; N, 12.08. Found: C, 69.31; H, 8.80; N, 11.98.

To a solution of 0.117 g (0.337 mmol) of compound **24** in 3.0 mL of 95% ethanol was added 2.5 mL of a saturated solution of picric acid in 95% ethanol. The yellow mixture was heated to boiling and allowed to slowly cool to room temperature. The solvent was removed with a rotary evaporator to give an orange oil. The oily residue was taken up in methanol and cooled in an ice bath to yield 0.066 g (34%) of the picrate as yellow crystals, mp 126–127 °C. Recrystallization by slow evaporation from methanol provided crystals suitable for X-ray crystallographic analysis. IR ($CHCl_3$): 1635, 1620, 1570, 1550, 1380, 1320 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.09 (s, 1), 1.25 (s, 9), 1.40 (s, 3), 1.50 (m, 1), 1.68 (d, 1, J = 15.7), 2.07 (m, 3), 2.59 (dd, 1, J = 13.8, 11.2), 2.79 (m, 3), 3.03 (dd, 1, J = 13.8, 3.8), 3.47 (m, 1), 3.69 (dd, 1, J = 8.1, 7.3), 3.84 (d, 1, J = 11.6), 7.25 (m, 4), 8.87 (s, 2), 10.46 (br s, 1). ^{13}C NMR ($CHCl_3$): 19.7, 22.5, 22.9, 23.5, 26.8, 31.3, 47.9, 54.2, 57.9, 68.4, 71.8, 74.4, 126.6, 127.3, 128.1, 129.9, 130.1, 133.6, 136.3, 141.6, 161.7. Anal. Calcd for $C_{26}H_{33}N_6O_7Cl$: C, 54.12; H, 5.76; N, 14.56. Found: C, 53.97; H, 5.78; N,14.43.

Lactam 30. A solution of *N*-(chlorocinnamoyl)-2-acetylpiperidine dimethylhydrazone (0.0203 g, 0.0608 mmol) in 1.0 mL of dry acetonitrile was heated at reflux for 4 days. The solvent was removed with a rotary evaporator to give a crude orange residue, which was a 3:1 ratio of diastereomers as determined by integration of the dimethylamine singlets in the ^1H NMR spectrum. This crude material was purified by chromatography on silica gel (1.5 g) with 2:1 hexanes/ethyl acetate as eluant to give a total of 0.013 g (64%) of **30** as two diastereomeric products as light yellow oils.

High R_f diastereomer (R_f 0.36 in 1:1 hexanes/ethyl acetate); 3.5 mg. IR ($CHCl_3$): 1685 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.22 (s, 3), 1.42 (m, 3), 1.73 (m, 2), 1.95 (m, 1), 2.35 (s, 6), 2.73 (dt, 1, J = 12.7, 3.6), 3.06 (dd, 1, J = 11.2, 3.2), 4.02 (dm, 1, J = 14.4), 7.26 (m, 2), 7.39 (m, 1), 7.54 (s, 1), 7.97 (m, 1).

Low R_f diastereomer (R_f 0.26 in 1:1 hexanes/ethyl acetate); 5.7 mg. IR ($CHCl_3$): 1685 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.08 (s, 3), 1.25–2.05 (m, 6), 2.41 (s, 6), 2.80 (dt, 1, J = 12.6, 3.6), 3.44 (dd, 1, J = 11.9, 3.0), 4.33 (dm, 1, J = 13.1), 5.12 (br s, 1), 7.24 (m, 2), 7.38 (m, 1), 7.63 (s, 1), 7.95 (m, 1). ^{13}C NMR ($CDCl_3$): 18.0, 24.2, 24.7, 28.7, 41.2, 50.6, 62.7, 63.4, 125.8, 129.1, 129.3, 131.7, 131.8, 134.0, 134.1, 138.7, 166.6. Mass spectrum (70 eV): m/z 333 (parent), 59 (base). HRMS: Calcd for $C_{18}H_{24}N_3OCl$: 333.1610. Found: 333.1598.

Hydrazone Imine 32. A mixture of 1,1-dimethylhydrazine (0.766 mL, 0.606 g, 10.08 mmol, 1.1 equiv) and 2-acetylpiperidine hydrochloride (1.52 g, 9.17 mmol) in 10 mL of acetic acid was stirred at room temperature for 2 h. Most of the acetic acid was removed with a rotary evaporator and saturated K_2CO_3 was added slowly. The basic solution was extracted with ethyl acetate (3 × 10 mL). The organic extracts were dried over $MgSO_4$, and the solvent was removed with a rotary evaporator to give 1.17 g (76%) of **32** as a dark orange oil. Although this product was used without further purification, a small amount was purified by bulb-to-bulb distillation under aspirator pressure to give a light yellow oil. IR ($CHCl_3$): 3460, 1670, 1640 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.63 (m, 4), 2.08 (s, 3), 2.50 (m, 3), 2.59 (s, 6), 3.16 (m, 1), 3.75 (m, 2). ^{13}C NMR ($CDCl_3$): δ 13.4, 19.2, 22.0, 25.0, 47.0, 49.9, 161.0, 167.4.

Enamide 36. To a mixture of compound **32** (0.175 g, 1.05 mmol) and dry triethylamine (0.190 mL, 0.138 g, 1.36 mmol, 1.3 equiv) in 2.0 mL of CH_2Cl_2, under nitrogen, was added 0.253 g (1.26 mmol) of *o*-chlorocinnamoyl chloride in 2.0 mL of CH_2Cl_2. The reaction mixture was allowed to stir at room temperature for 3 h, and the solvent was removed with a rotary evaporator to give a sticky brown solid. The crude material was taken up in dry acetonitrile (5.0 mL), and the solution was heated at reflux for 12 h. The solvent was removed with a rotary evaporator to give a brown solid which was dissolved in 50% hydrochloric acid. The acidic solution was washed with ethyl and basified with NaOH. The basic solution was extracted with ethyl acetate. The organic extract was dried over $MgSO_4$ and reduced in volume to give 0.200 g (58%) of a brown-orange solid, pure by ^1H NMR spectroscopy. The crude material was purified by chromatography on silica gel (9 g) with 3:1 hexanes/ethyl acetate as eluant to yield 0.088 g (25%) of **36** as a yellow solid. Crystals, mp 142–144 °C, were grown by slow evaporation from methanol for X-ray crystallographic analysis. IR ($CHCl_3$): 3440, 1705, 1680, 1650 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.24 (s, 3), 1.84 (m, 2), 2.20 (dt, 2, J = 5.9, 4.1), 2.39 (s, 6), 2.64 (br s, 1), 3.62 (ddd, 1, J = 13.0, 8.0, 4.7), 3.81 (ddd, 1, J = 13.0, 6.4, 4.8), 4.91 (t, 1, J = 4.1), 7.25 (dd, 2, J = 5.8, 3.5), 7.39 (dd, 1, J = 5.8, 3.5), 7.80 (s, 1), 8.68 (dd, 1, J = 5.8, 3.5). ^{13}C NMR ($CDCl_3$): δ 19.6, 20.2, 21.4, 38.9, 49.7, 60.4, 95.7, 125.8, 129.1, 129.5, 129.7, 132.7, 132.8, 134.9, 136.5, 143.8, 166.3. Mass spectrum (70 eV, 160 °C): m/z 331 (parent), 59 (base). Anal. Calcd for $C_{18}H_{22}N_3OCl$: C, 65.15; H, 6.68; N, 12.66. Found: C, 65.23; H, 6.71; N, 12.61.

Nitro Lactam 42. (a) From Oxime 11. Acetonitrile (0.2 mL) and 90% hydrogen peroxide (0.022 mL, 0.027 g, 0.81 mmol) were placed in a 10-mL Erlenmeyer flask equipped with a magnetic stirring bar and a rubber septum. The solution was cooled to 0 °C, trifluoracetic anhydride (TFAA) (0.137 mL, 0.972 mmol) was added dropwise, and the mixture was stirred for 10 min. To a 10-mL round-bottomed flask equipped with a magnetic stirring bar were added oxime **11** (0.124 g, 0.405 mmol), urea (0.008 g, 0.133 mmol), disodium hydrogen phosphate (0.310 g), and acetonitrile (0.80 mL). The trifluoroperoxyacetic acid (TFPAA) solution was added to this suspension over a 5–10 min period. Upon this addition, the reaction mixture turned light blue. The solution was stirred for 3 h at 25 °C. As the reaction proceeded, the mixture turned a light yellow color. An additional portion of TFPAA was prepared as described above and added to the reaction mixture followed by acetonitrile (0.4 mL) and disodium hydrogen phosphate (0.310 g). The reaction mixture was stirred for 2 h at 25 °C. The solution was filtered and the solids were washed with CH_2Cl_2. The solvent was removed with a rotary evaporator to give 0.44 g of a crude yellow-orange oil. This material was purified by chromatography on silica gel with 1:1 hexanes/ethyl acetate as eluant to obtain 0.0382 g (28%) of **42** as a white solid, mp 165–168 °C. IR ($CHCl_3$): 3400, 1700 (br) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.10–1.75 (m, 4), 1.59 (s, 3), 1.81 (dd, 1, J = 12.4, 3.0), 2.00 (br d, 1, J = 13.5), 2.49 (d, 1, J = 4.5), 2.81 (dt, 1, J = 12.9, 3.5), 3.34 (d, 1, J = 6.6), 3.78 (dd, 1, J = 12.1, 3.2), 4.20 (dd, 1, J = 12.9, 4.9), 5.64 (dd, 1, J = 6.6, 4.5), 7.32 (m, 3), 7.56 (dd, 1, J = 7.4, 1.6). ^{13}C NMR ($CDCl_3$): δ 20.2, 23.9, 24.2, 27.6, 29.7, 40.7, 54.9, 64.1, 68.6, 89.9, 127.0, 129.2, 129.5, 132.0, 137.8, 167.7. Anal. Calcd for $C_{16}H_{19}N_2O_4Cl$: C, 56.72; H, 5.65; N, 8.27. Found: C, 56.70; H, 5.62; N, 8.19.

(b) From Isoxazolidine 16. Trifluoroperoxyacetic acid was prepared by the addition of trifluroacetic anhydride (0.137 mL, 0.972 mmol) to 90% hydrogen peroxide (0.027 g, 0.810 mmol) in acetonitrile (0.2 mL) at 0 °C. To a 10-mL round-bottomed flask equipped with a magnetic stirring bar were added isoxazolidine **16** (0.0854 g, 0.278 mmol), disodium hydrogen phosphate (0.3120 g), urea (0.008 g), and acetonitrile (0.6 mL). The TFPAA solution was added dropwise to the isoxazolidine solution. The reaction mixture turned a bright baby blue upon this addition. In 30–60 s, the blue color dissipated, and the solution turned a light yellow color. The reaction mixture was stirred for 1 h at 25 °C. The solution was filtered, and the solids were washed with CH_2Cl_2. The solvent was removed with a rotary evaporator to give an orange oil. The crude residue was purified by chromatography on silica gel (8 g) with 1:1 hexanes/ethyl acetate as eluant to yield 0.0507 g (57%) of **42** as a white solid. Analytical and spectral data were identical with those previously obtained.

Acknowledgment. This work was supported by grants from the National Science Foundation (CHE-81-20864 and

CHE-84-18437). The X-ray structures of compounds 16, 24, and 36 were determined by Dr. Fred Hollander, of the Berkeley College of Chemistry X-Ray Facility.

Supplementary Material Available: X-ray crystallographic data for compounds 16, 24, and 36, including experimental details, general temperature factor expressions, thermal and positional parameters of non-hydrogen atoms, bond lengths, bond angles, and torsional angles (24 pages). Ordering information is given on any current masthead page.

On the Use of *N*-[(Trimethylsilyl)methyl]amino Ethers as Capped Azomethine Ylide Equivalents

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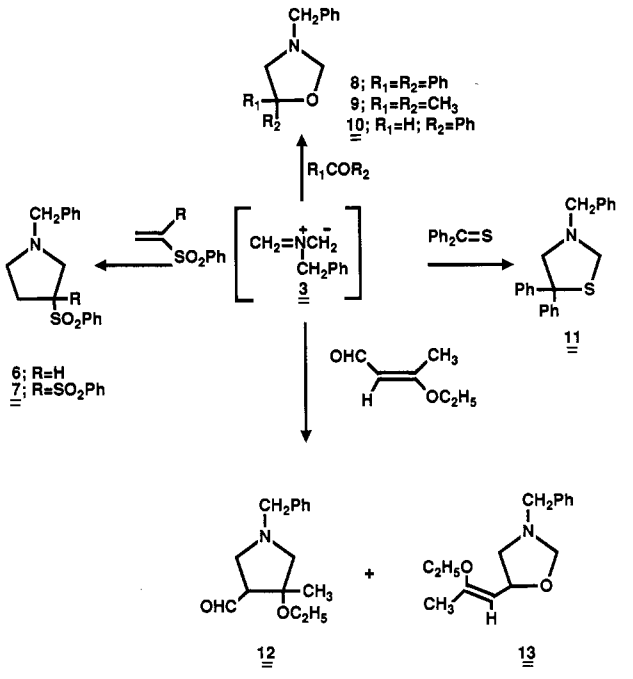
Received April 14, 1986

N-[(Trimethylsilyl)methyl]amino ethers have been found to act as azomethine ylide equivalents. Treatment of these compounds with lithium fluoride in the presence of a reactive dipolarophile afforded dipolar cycloadducts in high yield. The cycloaddition proceeded with complete stereospecificity with dimethyl fumarate and maleate. This result is consistent with the intermediacy of an azomethine ylide. The reaction of *N*-benzyl-*N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]amine afforded several silylated diamines when treated with zinc chloride or cesium fluoride in the absence of a trapping agent. This can be attributed to an initial loss of the methoxy group to give a transient iminium ion. This species reacts further with the azomethine ylide or undergoes hydrolysis to give a silylated amine. The cycloaddition behavior of several unsymmetrically substituted azomethine ylide precursors was also examined. Competitive rate studies showed that the cycloaddition is compatible with a HOMO-controlled process. The regiochemistry of the cycloaddition, however, is not easily rationalized by simple FMO considerations and may instead be related to the charge transfer interaction energy of the reaction.

The development of versatile methods for forming the five-membered pyrrolidine ring under mild conditions is a central objective of alkaloid synthesis.[1] Several years ago, the dipolar cycloaddition reaction of azomethine ylides attracted our attention as a particularly appealing method for pyrrolidine synthesis.[2-4] Studies conducted in these[5] and other laboratories[6-11] have show that the desilylation of α-trimethylsilyl onium salts represents a convenient method for azomethine ylide generation. More recently, we have described the use of α-(cyanomethyl)aminosilanes as convenient azomethine ylide precursors.[12] Exposure of these compounds to silver fluoride promotes a metal-assisted decyanation to an iminium salt[13,14] and a con-

Scheme I



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