organic component. The net overall process may involve an activated complex that is similar to that for *p,p'*-DDT (see eq 12).

$$(p\text{-ClPh})_2CFCCl_3 + O_2^- \xrightarrow{RH} (p\text{-ClPh})_2C{=}CCl_2 + Cl^- + {}^1/_2H_2O_2 + {}^1/_2O_2 + RF \quad (14)$$

The ring–disc results from $HCCl_3$ (and possibly for *p,p'*-DDT and Methoxychlor) clearly show that superoxide ion is not as effective as $OH^-$ for the deprotonation of a carbon acid. This might be expected because superoxide ion does not react with benzaldehyde, but $OH^-$ does,[34] and $O_2^-$ is a weak base in water ($pK_a$ of $HO_2\cdot$ = 4.7). However, $O_2^-$ is an effective strong Brønsted base for the deprotonation of oxygen and nitrogen acids via its facile proton-induced disproportionation to $H_2O_2$ and $O_2$.[2] In general, proton exchange on carbon acids is much slower than exchange on oxygen or nitrogen acids, which reflects the generally higher activation energies for deprotonation of carbon acids.[35,36] Therefore, deprotonation of carbon acids is controlled more by kinetic factors than by equilibrium thermodynamics, and $O_2^-$ is a less effective base than $OH^-$ for such acids.

**Acknowledgment.** This work was supported by the National Science Foundation under Grant No. CHE-8212299. We also thank Professor Charles Wilkins and Ms. Carolyn Johlman for their assistance with the mass spectral analyses, Dr. Luciano Mueller of The Southern California Regional NMR Facility (NSF-supported at the California Institute of Technology) for his assistance with the $^{19}F$ NMR spectral determinations, Professor T. Roy Fukuto for a gift of a sample of F-DDT, and Professor Robert C. Neuman, Jr., for helpful discussions.

**Registry No.** $O_2$, 7782-44-7; $O_2^-$, 11062-77-4; $CCl_4$, 56-23-5; $FCCl_3$, 75-69-4; $HCCl_3$, 67-66-3; $CF_3CCl_3$, 354-58-5; $PhCCl_3$, 98-07-7; $CH_3CCl_3$, 71-55-6; $HOCH_2CCl_3$, 115-20-8; $CH_3CH(OH)CCl_3$, 76-00-6; $(p\text{-}ClC_6H_4)_2CHCCl_3$, 50-29-3; $(p\text{-}MeOC_6H_4)_2CHCCl_3$, 72-43-5; $(p\text{-}ClC_6H_4)_2CFCCl_3$, 1545-65-9; $(p\text{-}ClC_6H_4)_2C{=}CCl_2$, 72-55-9; $(Me_4N)O_2$, 3946-86-9; $:CCl_2$, 1605-72-7; $OH^-$, 14280-30-9; 2,3-dimethyl-2-butene, 563-79-1.

(34) Gibian, M. J.; Sawyer, D. T.; Ungermann, T.; Tangpoonpholvivat, R.; Morrison, M. M. *J. Am. Chem. Soc.* **1979**, *101*, 640.
(35) Crooks, J. E. "Proton-Transfer Reactions"; Caldin, E., Gold, V., Eds.; Chapman & Hall, Ltd.: London (Wiley: New York), 1975; Chapter 6.
(36) Reutov, O. A.; Beletskaya, I. P.; Butin, K. P. "CH-Acids"; Pergammon Press: New York, 1978.

# Diels–Alder Reactions of 1-Azadienes[1]

**Yea-Shun Cheng, Andrew T. Lupo, Jr., and Frank W. Fowler***

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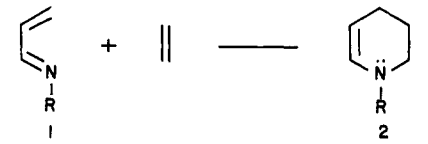
**Abstract:** *N*-Acyl-1-azadienes have been prepared by the thermal elimination of acetic acid from *o*-acetylhydroxylamine derivatives. These reactive compounds have been observed to undergo the intramolecular Diels–Alder reaction to give piperidine derivatives. Studies on substituted azadienes suggest that the reaction follows predominantly an exo stereochemical pathway.

The incorporation of the Diels–Alder reaction into a synthetic scheme for the preparation of carbocyclic rings has proven to be a powerful strategy in total synthesis. This is because in one step two carbon–carbon bonds are formed with potential control of stereochemistry at all four of the newly created tetrahedral centers. Few reactions can rival the Diels–Alder reaction in this respect.

Piperidine derivatives are a common structural feature in many goal compounds and, in principle, the Diels–Alder reaction can also be applied to the preparation of these nitrogen heterocycles[2] by substitution of one of the carbon atoms of the reacting $\pi$ system by nitrogen. The use of imines as dienophiles is well documented,[3] and the intramolecular version of this reaction has been effectively applied to the preparation of alkaloids.[4] Nitrogen-containing dienes are less common although the Diels–Alder reaction of 1- and 2-azadienes has been reported.[2] The Diels–Alder reaction of 1-azadienes, in principle, is particularly valuable for the synthesis of nitrogen heterocycles (Scheme I). Not only is a six-membered ring formed with potential control of stereochemistry at the tetrahedral centers but the product is an endocyclic enamine derivative. Because enamines are valuable for further structural elaboration[5] and are often postulated as key intermediates in alkaloid biosynthesis,[6] general methods for the preparation of

Scheme I




Scheme II


(1) A portion of this work has previously appeared as a communication to the editor: Cheng, Y.-S.; Fowler, F. W.; Lupo, A., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 2090.
(2) (a) Wollweber, H. *Methoden. Org. Chem.* (*Houben*-Weyl) **1970**, *Teil 3*, 1128–1137. (b) Hamer, J. "1,4-Cycloaddition Reactions"; Hamer, J., Ed.; Academic Press: New York, 1967. (c) Arbuzov, Y. A. *Russ. Chem. Rev.* (*Engl. Transl.*) **1964**, *33*, 407. (d) Onishenko, A. S. "Diene Synthesis"; Israel Program for Scientific Translators: Jerusalem, 1964. (e) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 211. (f) Needleman, S. B.; Changkuo, M. C. *Chem. Rev.* **1962**, *62*, 405. For a recent example see: Sainte, F.; Serckx-Poncin, B.; Hesbain-Frisque, A. M.; Ghosez, L. *J. Am. Chem. Soc.* **1982**, *104*, 1428.
(3) (a) Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949. (b) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*. 3087.
(4) (a) Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6387. (b) Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. *Ibid.* **1982**, *104*, 7065. (c) Bremmer, M. L.; Weinreb, S. M. *Tetrahedron Lett.* **1983**, 261.
(5) (a) Kuehne, M. E. *Synthesis* **1970**, 510. (b) "Enamines: Synthesis, Structure and Reactions"; Cook, A. G., Ed.; Marcel Dekker: New York, 1969.
(6) Cordell, G. A. "Introduction to Alkaloids: A Biosynthetic Approach"; Wiley-Interscience: New York, 1981.

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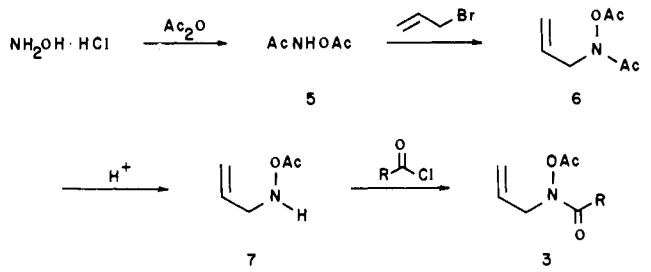
Scheme III



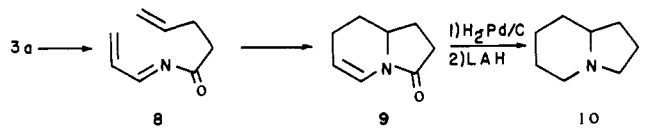
endocyclic enamines have long been sought by synthetic chemists.[7] Clearly, the Diels–Alder reaction of 1-azadienes would be a valuable method in heterocyclic syntheses. For this reason we have embarked on a research program with the goal of determining the conditions necessary to induce the Diels–Alder reaction of 1-azadienes.

There are only a few reports in the literature on the Diels–Alder reaction of 1-azadienes.[8] Most of these reactions do not appear to be general and are of limited synthetic interest. A possible and important exception was recently disclosed by Ghosez et al.,[9] who observed that *N*-amino-1-azadienes react with dienophiles to give Diels–Alder adducts.

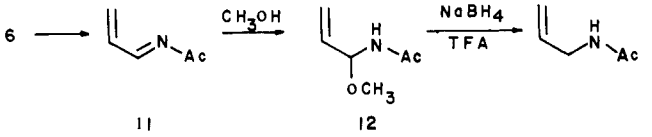
The scarcity[10] of known examples of 1-azadienes undergoing the Diels–Alder reaction is in sharp contrast to all carbon dienes[11] and even the 1-oxa analogues ($\alpha,\beta$-unsaturated carbonyl compounds) for which numerous examples are known.[12] In general, pericyclic reactions that result in the formation of a carbon–nitrogen single bond at the expense of a carbon–nitrogen double bond are relatively rare.[13]

The presence of electron-withdrawing groups on an imine is known to enhance its reactivity as a dienophile in the Diels–Alder reaction.[3] Since a carbonyl group appears to be particularly effective, we chose initially to investigate *N*-acyl-1-azadienes as possible reactants in the Diels–Alder reaction.[14]

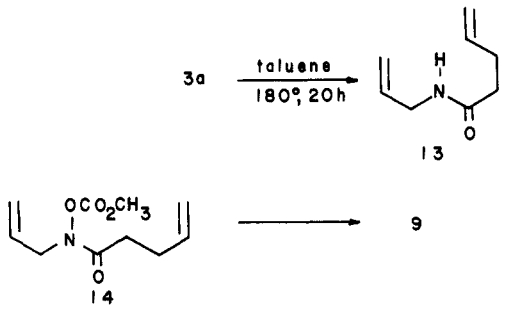
Scheme IV



Scheme V



Scheme VI



The literature reveals that *N*-acyl-1-azadienes are relatively rare compounds.[5] This is not a surprising situation since it is well-known that the simple *N*-acyl imines are very reactive. They are generally not isolated but generated in situ and used synthetically as transient intermediates.[3]

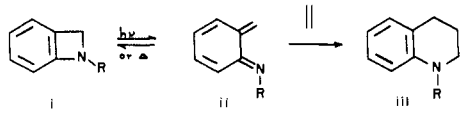
Our approach to the synthesis of *N*-acyl-1-azadienes was to explore methods that generated these compounds by a thermal reaction in the gas phase.[16] The absence of solvent would suppress unwanted ionic reactions, and the high dilution would suppress polymerization. For our initial studies we chose to investigate the intramolecular Diels–Alder reaction because preparation of the unstable azadiene and its Diels–Alder reaction would be unimolecular and could be accomplished under the same reaction conditions.

An old but effective method for the preparation of multiple bonds in the gas phase is acetate pyrolysis[17] (Scheme II). Suitable precursors for the required azadienes **4** could have the acetoxy function either on the nitrogen atom or on the carbon atom adjacent to the nitrogen atom. We initially chose to investigate the *N*-acetoxy amides (*O*-acetylhydroxamic acids) because we anticipated they would be synthetically more accessible.[18] An additional advantage of these compounds is that they can be prepared by a convergent synthesis from hydroxylamine. That is, the precursor diene and dienophile can be added as separate fragments to hydroxylamine. This is an important consideration in total synthesis as the complexity of the desired azadiene increases.

In principle there is some flexibility in the order of attachment of the three substituents to hydroxylamine. Our initial studies on this problem have used the method depicted in Scheme III.

(7) (a) Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193. (b) Wenkert, E. *Ibid.* **1968**, *1*, 78.

(8) One of the best known examples is the quinone methane imine ii



accessible from the benzoazetine i where the formation of the aromatic ring is probably an important factor. (a) Burgress, E. M.; McCullagh, L. *J. Am. Chem. Soc.* **1966**, *88*, 15–80. (b) Baydar, A. E.; Boyd, G. V.; Lindley, P. F.; Watson, F. *J. Chem. Soc., Chem. Commun.* **1979**, 178. (c) Mao, Y.-L.; Boehelheide, V. *J. Org. Chem.* **1980**, *45*, 1547. (d) Lancaster, M.; Smith, D. J. H. *J. Chem. Soc., Chem. Commun.* **1980**, 471. Although this reaction has been used mainly to characterize the quinone methane imines it has recently been applied to azasteroid synthesis: Ito, Y.; Satoru, M.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1981**, *103*, 5250.

(9) Serckx-Poncin, B.; Hesbain-Frisque, A. M.; Ghosez, L. *Tetrahedron Lett.* **1982**, 3261.

(10) Some of the earlier claims of 1-azadienes behaving as dienophiles in Diels–Alder reactions have been shown to be in error. For example, see: (a) Daniels, P. H.; Wong, J. L.; Atwood, J. G.; Canada, L. B.; Rogers, R D. *J. Org. Chem.* **1980**, *45*, 435. (b) Jung, M. E.; Shapiro, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 7862.

(11) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779 and references cited therein.

(12) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651.

(13) For example, the ene reaction is well-known for both carbon–carbon and carbon–oxygen double bonds (Hoffmann, H. m. R. *Angew. Chem. Int. Ed Engl.* **1968**, *8*, 556) but is essentially unknown for carbon–nitrogen double bonds. A single exception was recently reported for an activated *N*-sulfonyliminoacetate: (a) Achmatowicz, O., Jr.; Pietraszkiewicz, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2680. (b) Achmatowicz, O., Jr.; Pietraszkiewicz, M. *Tetrahedron Lett.* **1981**, 4323. (c) Tschaen, D. M.; Weinreb, S. M. *Tetrahedron Lett.* **1982**, 3015.

(14) There are two obvious roles that the carbonyl group can play in facilitating the cycloaddition reactions of imines. The amide functional group that is produced in these reactions possesses substantial stabilization energy (15 kcal/mol). It is reasonable to assume that part of this stabilization also occurs in the transition state of cycloaddition reaction. In addition, the presence of the carbonyl group would lower the energy of the azadiene LUMO allowing a larger stabilizing interaction with the HOMO of the dienophile.

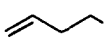
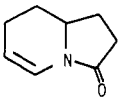
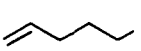
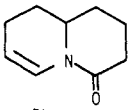
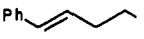
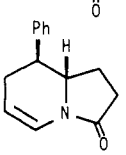
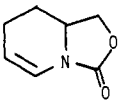
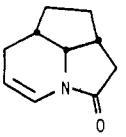
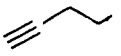
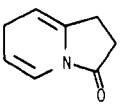
(15) Although *N*-acyl-1-azadienes have been postulated as reactive intermediates (e.g., see Oppolzer, W.; Frostl, W. *Helv. Chim. Acta* **1975**, *58*, 587), we are only aware of one example of the characterization of this function group: (Overman, L. E.; Clizbe, L. A.; Freerks, R. L.; Marlowe, C. K. *J. Am. Chem. Soc.* **1981**, *103*, 2807).

(16) (a) Wiersum, U. E. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 317. (b) Wiersum, U. E. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 365. (c) Brown, R. F. C. "Pyrolytic Methods in Organic Chemistry"; Academic Press: New York, 1980. (d) Seybold, G. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 365.

(17) (a) Smith, G. G.; Kelly, F. W. *Prog. Phy. Org. Chem.* **1971**, *8*, 75. (b) DePuy, C. H.; King, R. W. *Chem. Rev.* **1960**, *60*, 431.

(18) (a) Sandler, S. R.; Karo, W. "Organic Functional Group Preparations"; Academic Press: London, 1972; Vol. 3, Chapter 12. (b) Bauer, L.; Exner, O. *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 376.

Table I. Diels-Alder Reactions of *N*-Acyl-1-azadienes

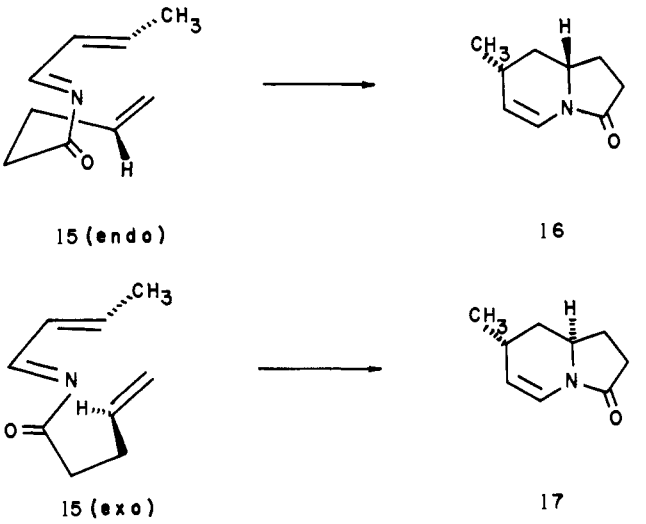
| Reactant | R | Product |
|---|---|---|
| 3a |  |  (75%) |
| 3b |  |  (69%) |
| 3c |  |  (74%) |
| 3d |  |  (70%) |
| 3e |  |  (69%) |
| 3f |  |  (90%) |

This synthesis of *N*,*O*-diacetyl-*N*-alkylhydroxylamine **6** was carried out analogous to a known method.[19] The reaction of *N*,*O*-diacetylhydroxylamine **5** with the allyl bromides gave *N*-alkylation.[20] The selective hydrolysis of the *N*-acyl substituent was accomplished readily under acidic conditions. Although the *O*-acylhydroxylamine derivatives are known to rearrange to the nitrogen-substituted isomers, this reaction proved to be slow compared to acylation with suitable acid chlorides.

Evaporation of hydroxylamine derivative **3a** through the hot reaction tube[21] produced the Diels–Alder adduct **9** (Scheme IV) and acetic acid as the predominant products. A 75% yield of the indolizidine **9** was obtained by passing the product mixture through a short column of solid potassium carbonate to remove the acetic acid.

The structure of indolizidine **9** was apparent from its spectral data and was confirmed by conversion to the known racemic δ-coniceine[4a] **10**.

Scheme VII




By a similar procedure, the hydroxylamine derivatives **3a–f** were converted to fused $\Delta^2$-piperideine (see Table I). These are stable compounds not possessing the high reactivity normally associated with the analogous enamines.[22] They have characteristic $^1$H NMR spectra showing the two olefinic and the saturated hydrogen $\alpha$ to nitrogen with three distinct chemical shifts. The olefinic hydrogen $\alpha$ to the nitrogen atom occurs at particularly low field. In addition to the electronegativity of the nitrogen atom the carbonyl group also causes a downfield shift of this nucleus.[23]

The azadienes (e.g., **8**) are only presumed intermediates. They have never been directly observed even with hydroxylamine precursors that do not contain a dienophile capable of undergoing the Diels–Alder reaction. For example, evaporating the *N*,*O*-diacetyl-*N*-allylhydroxylamine (Scheme V) through the hot reaction tube with benzene-$d_6$ and observing the product mixture immediately by $^1$H NMR spectroscopy did not show the presence of any absorptions expected for the azadiene **11**. If methanol was present in the receiver, then a quantity of the amide **12** could be isolated. This presumably arises by addition of methanol across the C=N bond of the acyl imine. Confirmation of structure **12** was obtained by $NaBH_4$–TFA reduction to the known *N*-allylacetamide.

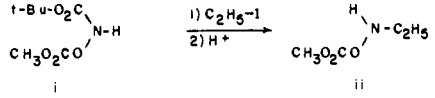
The *N*-acyl-1-azadienes are clearly very reactive compounds in condensed phase, and to date we have not observed the *intermolecular* Diels–Alder reaction of these dienes by trapping the azadiene **11** with potential dienophiles such as ethyl vinyl ether or maleic anhydride.

Attempts to produce the indolizidine **9** from **3a** in the condensed phase were not successful. Heating the hydroxylamine **3a** in toluene at 180 °C for hours induced loss of acetic acid, but none of the intramolecular Diels–Alder adduct **9** was detected. Surprisingly, the major product of this reaction was the amide **13** (Scheme VI).

The rate of double bond formation from ester pyrolysis is known to be sensitive to the structure of the ester. For example, carbonates and carbamates are known to undergo elimination at a lower temperature than the analogous acetates.[24] A similar result was obtained for the pyrolysis of diacylhydroxylamine **14**. The voltage required to induce elimination of the carbonate **14** corresponded to a drop in about 140 °C. This is a greater effect than observed for the preparation of carbon–carbon double bonds and

(19) Johnson, J. E.; Springfield, J. R.; Hwang, J. S.; Hayes, L. J.; Cunningham, W. C.; McClaugherty, D. L. *J. Org. Chem.* **1971**, *36*, 284.

(20) Less reactive alkylating agents react slowly and give predominantly O-alkylation. For these compounds an alternative procedure must be used. For example, alkylation of carbamate i (Zinner, G.; Nebel, G.; Hitze, M.




*Arch. Pharm.* (*Weinheim, Ger.*) **1970**, *303*, 316) with ethyl iodide followed by acidic hydrolysis gave hydroxylamine ii which readily reacted with acylating agents. The tendency of *N*-alkoxycarbonyl derivatives to undergo nitrogen rather than oxygen alkylation has been noted previously (Smith, P. A. S. "The Chemistry of Open-chained Nitrogen Compounds"; W. A. Benjamin: New York, 1966: Vol. 2, p 68–98) and has been taken advantage of in a recent synthesis of aerobactin (Maurer, P. J.; Miller, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 3096).

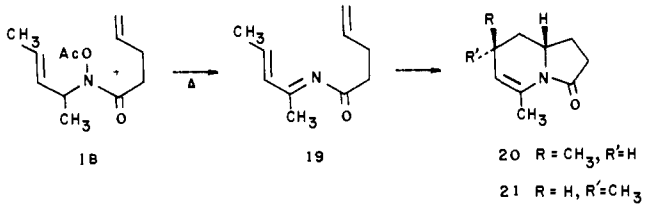
(21) This apparatus has been previously described: Beeken, P.; Bonfiglio, J.; Hasan, I.; Piwinski, J.; Weinstein, B.; Zollo, K.; Fowler, F. W. *J. Am. Chem. Soc.* **1979**, *101*, 6677.

(22) Endocyclic enamines that do not contain substituents on the double bond are very unstable with respect to dimerization. The simple *N*-methyl-$\Delta^2$-piperideine has only recently been isolated and rapidly dimerizes within minutes under neutral conditions (F. W. Fowler and P. Beeken *J. Org. Chem.* **1980**, *45*, 1336).

(23) LaLonde, R. T.; Donvito, T. N. *Can. J. Chem.* **1974**, *52*, 3778.

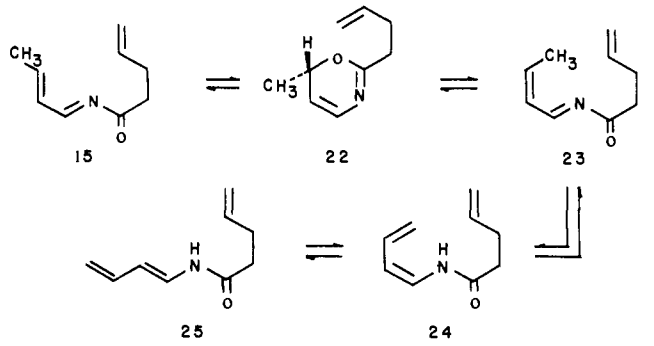
(24) O'Connor, G. L.; Nace, H. R. *J. Am. Chem. Soc.* **1953**, *75*, 2118.

Scheme VIII



18 19 20 R = $CH_3$, R'=H 21 R = H, R'=$CH_3$

Scheme IX



15 22 23 25 24

possibly reflects a weakening of the N–O bond due to an increase in lone pair–lone pair repulsion as well as an increase in the nucleophilicity of the carbonyl oxygen. The carbonates have the additional advantages in proceeding with higher yield, and the crude products contain less polymeric impurities. If the product is acid sensitive, it may also be an advantage that the other products are carbon dioxide and methanol rather than acetic acid.

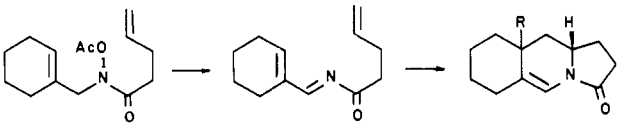
The stereochemical course of the intramolecular Diels–Alder reaction has been a problem of considerable current interest.[25] Usually the relative importance of the two stereochemical pathways, exo and endo, are apparent from the ratio of cis and trans fused products. However, this is not possible for the intramolecular Diels–Alder reaction of azadienes because the nitrogen atom lacks stereochemical integrity. In principle, this question can be answered by studying 4-substituted azadienes such as **15**. If the reaction proceeds through an exo transition state, then the hydrogens at positions 7 and 8a in the product will be trans. Alternatively, if the reaction is proceeding through an endo transition state, then the hydrogens at these positions will be cis to each other (Scheme VII). The Diels–Alder reaction of **15** actually gave a trans/cis ratio of 3, indicating that the reaction was proceeding predominantly but not exclusively through the exo transition state.

Support for the Diels–Alder reaction of azadienes proceeding predominantly through the exo transition state was also obtained from the Diels–Alder reaction of **19**. It has previously been noted that the exo–endo ratio of the intramolecular Diels–Alder reaction is sensitive to substitutions of the connecting chain between the diene and dienophile.[22] It would be predicted[30] that the endo transition state is less stable with respect to the reactant than the exo transition state because of a greater steric interaction between

Scheme X

26 27

Scheme XI



28 29 30 R=β-H 31 R=α-H

the allyl hydrogens of the diene and the substituent on position 2 of the dienophile[31] (see Scheme VIII). Evaporation of hydroxylamine derivative **18** through the reaction tube produced a mixture of indolizidines **20** and **21** that showed a small but real increase in the trans isomer (trans/cis = 4.5). The effect of the additional methyl group on the exo–endo ratio was small, but it was the same order of magnitude as analogous carbocyclic systems.[3]

Another mechanistic possibility for the formation of the *cis*- and *trans*-indolizidines became apparent when an attempt was made to produce the azadiene **15** from its hydroxylamine precursor at lower temperatures. Under these conditions the major products were not the indolizidines but a mixture of the amino dienes **24** and **25**. A reasonable mechanism (Scheme IX) for the formation of these amino dienes would involve isomerization of the trans azadiene to the cis azadiene **23** via the oxazine **22**. A 1,5-hydrogen shift of this cis azadiene would give the cis amino diene **24**. If the cis azadiene is the intermediate in the Diels–Alder reaction leading to the indolizidines, then the *trans*-indolizidine **17** would be the product of an endo rather than exo transition state.

Support for Scheme IX comes from studies on the rearrangement of propargyl imidates to amino dienes.[27] Azadienes were also postulated as intermediates in these reactions, and in the case of a highly substituted azadiene it and the isomeric oxazine were isolated and characterized.

It was somewhat surprising that the amino dienes **24** and **25** did not undergo the intramolecular Diels–Alder reaction to give the quinoline derivative **27** (Scheme X, R = H) since this is known to be a successful reaction if the nitrogen atom carries an ethyl substituent (R = $C_2H_5$).[29] Heating a mixture of the amino dienes in the gas phase resulted in producing a mixture of the indolizidines **16** and **17**, indicating the existence of an equilibrium, under the reaction conditions, among all of the species shown in Scheme IX.

In order to gain a more definitive answer regarding the question of stereochemistry of this reaction, the cycloaddition of **29** was studied. The carbon–carbon double bond of this azadiene is constrained by the ring and can only exist in the cis configuration. If the previous cycloaddition reactions were proceeding through both the *Z* and *E* azadienes, then the cycloaddition of **29** should give only one indolizidine. However, if the reaction proceeds through both exo and endo transition states, then the ratio of *cis*- and *trans*-indolizidines **30** and **31** should be about the same as observed previously (Scheme XI).

Heating hydroxylamine derivative **28** gave a 1:3 ratio of **30** and **31**. This conclusion was based primarily on the $^{13}C$ NMR spectrum which showed 22 absorptions.[33] These absorptions

(25) (a) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (b) Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 10. (c) Ciganek, E. *Org. React.*, in press.

(26) In the absence of any overriding structural constraint exo cycloaddition is usually the predominant stereochemical pathway followed by thermal intramolecular cycloaddition reactions (see ref 24).

(27) Overman, L. E.; Clizbe, L. A.; Freerks, R. L.; Marlowe, C. K. *J. Am. Chem. Soc.* **1981**, *103*, 2807. It was pointed out by a referee that **23** could be produced from **15** via the 1-azacyclobut-2-ene valence isomer. Presently, we can not rule out this possibility.

(28) Attempts to induce this reaction in solution were also unsuccessful (toluene, 190 °C).

(29) Oppolzer, W.; Frostl, W. *Helv. Chim. Acta* **1975**, *58*, 590.

(30) (a) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269. (b) Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033. (c) White, J. D.; Sheldon, B. G.; Solheim, B. A.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 2273.

(31) This steric interaction should be greatest for transition states in which the dienophile is reactant like and the bond distance between the carbon-to-nitrogen and the dienophile is short.

(32) (a) Taber, D. F.; Campbell, C.; Gunn, B. C.; Chiu, I-C. *Tetrahedron Lett.* **1981**, 5141. (b) Roush, W. R.; Peseckis, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6696.

(33) We assume that two of these absorptions each represents two rather than one carbon atoms to account for all 24 carbon atoms of **32** and **33**.

occurred in two groups according to their relative intensity. For example, in the olefinic region there are four absorptions, two weak and two strong in a 3:1 ratio. The absorption due to the carbon at position **8a** was also of value for assigning the structure to the major product. The larger of the two absorptions occurs upfield by 2.08 ppm. An upfield shift of this absorption would be anticipated for cis isomer **31** because of the gauche interaction of the N–CH carbon with the carbon atom attached to position 10.[22] Thus, the major isomer of this reaction is also the result of an exo transition state.

An underlying assumption in the previous discussion is that the product ratios are a result of kinetic control. It is possible that the Diels–Alder reactions are reversible and the product ratios simply reflect their relative thermodynamic stabilities. We believe this is not the situation since the major product **17** from the cycloaddition of **15** contains a pseudoaxial methyl group and would be anticipated to be less stable than **16** which contains a pseudoequatorial methyl group. Also, subjecting the minor product **16** to the reaction conditions does not result in conversion to the major product **17**.

We believe all the data strongly support competing exo and endo transition states for these cycloaddition reactions. Although both the *E* and *Z* azadienes are probably present, the *Z* azadiene is probably not an important reaction intermediate in these Diels–Alder reactions.

In addition to the normal preference for exo transition states in the intramolecular Diels–Alder reaction,[25c] this transition state for *N*-acyl-1-azadienes may receive some additional stabilization from the developing amide group. Molecular models of the product, with the amide fully developed, show that the exo transition state possesses less angle strain than the endo transition state.

In summary, *N*-acyl-1-azadienes have been prepared, as transient intermediates, by thermal elimination of acetic acid from the *N*-acyl-*N*-allyl-*O*-acetylhydroxylamines. The *N*-acyl-1-azadienes are very reactive compounds undergoing the intramolecular Diels–Alder reaction to give endocyclic enamides. The data on substituted azadienes suggest that these reactions primarily follow an exo stereochemical pathway. Because of the ease in preparing the prerequisite hydroxylamines and the degree of structural complexity present in the final Diels–Alder product, this reaction should provide to be of value in heterocyclic synthesis.

## Experimental Section[35]

**General Comments on the Synthesis of *N*-Allyl-*N*-acyl-*O*-acetylhydroxylamines.** The known *N*,*O*-diacetylhydroxylamine was the starting material for most of the syntheses.[36] N-Alkylation was most effectively performed in dimethylformamide using potassium carbonate as a base. In some cases, when indicated, sodium iodide was found to be an effective catalyst for accelerating the rate of the reaction. The greater reactivity of allylic halides is apparently responsible for suppressing O-alkylation, which can be a problem with less reactive alkylating agents. For less reactive alkylating agents an alternative procedure can be used.[20] At this point, two of the three desired substituents are in place. Selective acidic hydrolysis of the *N*-acetyl function gives the *N*-allyl-*O*-acetylhydroxylamines. These compounds are relatively unstable with respect to migration of the acetyl group from oxygen to nitrogen and are usually used directly in the next step. Since the next acylation step is a relatively rapid reaction the instability of the above hydroxylamine did not present a problem. All of the compounds up to this point were usually oils that had characteristic nuclear magnetic resonance and infrared spectra. The diacylhydroxylamines show two distinct carbonyl absorptions in the infrared spectrum. The acyl groups attached to nitrogen occur in the region of 1620–1675 $cm^{-1}$ whereas the acyl groups attached to oxygen occur in the region of 1790–1800 $cm^{-1}$. The carbonyl groups of *O*-acylhydroxylamines that do not have an *N*-acyl substituent (the hydrolysis products) are shifted to 1726–1740 $cm^{-1}$. In the proton NMR spectrum the allylic hydrogens of the diacylhydroxylamines always occur at lower field (ca. 0.6 ppm) than the *O*-acylhydroxylamines that do not have an *N*-acyl substituent. The *N*-acyl-*O*-acetylhydroxylamines usually do not show parent ions in the mass spectrum. The highest mass absorption is M – 59 (loss of $CH_3CO_2$).

***N*-Allyl-*N*,*O*-Diacetylhydroxylamine (6).** The procedure followed was analogous to that reported by Johnson et al.[19] To 0.103 mol (12.05 g) of *N*,*O*-diacetylhydroxylamine in 20 mL of dimethylformamide was added 1 equiv of allyl bromide and potassium carbonate. The reaction mixture was stirred 20 h at room temperature. The precipitate was filtered and the dimethylformamide was removed by a reduced pressure distillation. The resulting residue was chromatographed on silica gel (eluted with 1:1 ether/hexane) to afford 8.17 g (50%) of *N*-allyl-*N*,*O*-diacetylhydroxylamine: $^1H$ NMR ($CDCl_3$, HFT-80) $\delta$ 2.05 (s, 3 H), 2.20 (s, 3 H), 4.23 (d, $J$ = 7 Hz, 2 H), 5.0–6.2 (m, 3 H); IR (film) 1671 (s), 1795 (s), 1379 (s), 1180 (s), 1140 (m), 1040 (m), 1000 (m), 930 (m), 845 (m) $cm^{-1}$; MS, $m/z$ (relative intensity) 157 ($M^+$, 3.6), 56.1 (11.6), 73.1 (36.2), 115.0 (61.8), 43.1 (100).

Anal. Calcd for $C_7H_{11}NO_3$: C, 53.43; H, 7.12. Found: C, 53.49; H, 7.05.

***N*-Allyl-*O*-acetylhydroxylamine (7).** To 0.01 mol (1.57 g) of the *N*-allyl-*N*,*O*-diacetylhydroxylamine was added 10 mL of 6 N HCl. The reaction mixture was stirred at room temperature for 1 h and then the excess acid was neutralized with solid sodium carbonate. The reaction mixture was extracted with methylene chloride. The methylene chloride extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–ether, 1:1) to give **7** (54% yield). The *N*-allyl-*O*-acetylhydroxylamine is unstable, rearranging to the more stable *N*-acetyl-*N*-allylhydroxylamine isomer on standing at room temperature. Therefore, it is immediately used after purification: $^1H$ NMR ($CDCl_3$, HFT-80) $\delta$ 2.15 (s, 3 H), 3.50 (d, $J$ = 3 Hz, 2 H), 5.00–6.25 (m, 3 H); IR (film) 3260 (m), 1726 (s), 1641 (m), 1416 (m), 1371 (s), 1226 (s), 1000 (m), 931 (m) $cm^{-1}$; MS, $m/z$ (relative intensity) 115 ($M^+$, 9.8), 73 (25), 56 (48), 57 (61), 43 (100).

***O*-Acetyl-*N*-allyl-*N*-pent-4-enoylhydroxylamine (3a).** A solution containing 0.012 mol of $NEt_3$ and 0.01 mol of the *N*-allyl-*O*-acetylhydroxylamine in 2 mL of carbon tetrachloride was placed in a round-bottomed flask and cooled in an ice bath, the pent-4-enoyl chloride (0.012 mol) was carefully added, and the reaction mixture was allowed to be stirred at room temperature for 1 h. The carbon tetrachloride layer was washed with 1 mL of water. The aqueous layer was extracted with carbon tetrachloride, and the combined carbon tetrachloride layers were dried ($MgSO_4$). Evaporation of the carbon tetrachloride gave *N*-4-pentenoyl-*N*-allyl-*O*-acetylhydroxylamine (**3a**). The crude product could be further purified by chromatography on a silica gel column with ether/hexanes (1:2) to afford **3a** (86%). This compound does not show parent ion in the mass spectrum. The highest $m/z$ ion indicates the loss of acetic acid: $^1H$ NMR ($CDCl_3$, HFT-80) $\delta$ 2.17 (s, 3 H), 2.20–2.42 (m, 4 H), 4.40 (d, $J$ = 8 Hz, 2 H), 4.76–6.20 (m, 6 H); IR (film) 1790 (s), 1670 (s), 1635 (m), 1438 (s), 1390 (m), 1180 (s), 1140 (s), 1000 (m), 920 (m), 855 (m) $cm^{-1}$; MS, $m/z$ (relative intensity) 137 (M – 61, 21), 115 (23), 83 (77), 55 (100), 43 (40).

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67. Found: C, 60.72; H, 7.84.

**Hydroxamic Acid Derivatives 3b–f.** The same procedure as that described for compound **3a** was used for the preparation of the following compounds. Pure compounds were obtained from silica gel column chromatography (eluted with 50% ether–hexane solution).

***N*-5-Hexenoyl-*N*-allyl-*O*-acetylhydroxyamine (3b)**: 86%; $^1H$ NMR ($CDCl_3$, HFT-80) $\delta$ 1.40–2.50 (m, 2 H), 2.13 (s, 3 H), 4.18 (d, 2 H, $J$ = 6 Hz), 4.07–6.10 (m, 6 H); IR (film) 1790 (s), 1670 (s), 1400 (m), 1180 (s), 1000 (m), 920 (m), $cm^{-1}$; MS, $m/z$ (relative intensity) 152 (M – 59, 22), 115 (30), 97 (67), 69 (100), 55 (45), 43 (36).

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11. Found: C, 62.52; H, 8.20.

(34) Levy, G. C.; Nelson, G. S. "C-13 NMR for Organic Chemists"; Wiley-Interscience: New York, 1972.

(35) Melting points were recorded on a Fischer-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 727 spectrometer as either thin films or KBr solid solutions. The absorption intensities are described as being either strong (s), medium (m), or weak (w) and were all referenced to the 1601.4 absorption of polystyrene. Proton NMR spectra were recorded on either a Varian HFT-80 or a Nicolet NT-300 spectrometer. Carbon-13 NMR spectra were recorded on either a Varian CFT-20 or a Nicolet NT-300 spectrometer. All chemical shifts were reported in ppm (units) from tetramethylsilane as an internal standard. Low resolution mass spectra were recorded on a Hewlett-Packard 5980A spectrometer. High-resolution mass spectra were recorded on an AEI MS-30 spectrometer. Analytical gas chromatography was determined on a Hewlett-Packard 5830 chromatograph equipped with a flame ionization detector. Preparative gas chromatography were carried out on a Varian 920 chromatograph equipped with a hot-wire detector. Thin-layer chromatography was carried out with Silica Gel 60 PF254 (E. M. Merck). Liquid chromatography was carried out using 70–230-mesh Silica Gel 60 (E. M. Merck). All dry solvents were distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

(36) Exner, O.; Horak, M. *Collect. Czech. Chem. Commun.* **1959**, *24*, 2992.

**N-(5-Phenyl-4-pentenoyl)-N-allyl-O-acetylhydroxylamine (3c)**: 50%; $^1$H NMR ($CDCl_3$, HFT-80) δ 2.15 (s, 3 H), 2.15–2.75 (m, 4 H), 4.32 (d, 2 H, $J$ = 3 Hz), 5.05–6.40 (m, 5 H), 7.10–7.40 (m, 5 H); IR (film) 1800 (s), 1675 (s), 1500 (m), 1400 (s), 1180 (s), 1000 (m), 975 (s) cm$^{-1}$; MS, $m/z$ (relative intensity) 214 (M − 59, 4), 130 (52), 117 (100), 115 (40), 91 (27).

**Allyl N-Acetoxy-N-allylcarbamate (3d)**: 50%; $^1$H NMR ($CDCl_3$, HFT-80) δ 2.13 (s, 3 H), 4.23 (d of t, $J$ = 2 Hz, 7 Hz), 4.59 (d of t, $J$ = 2 Hz, 5 Hz), 5.00–6.15 (m, 6 H); IR (film) 1798 (s), 1722 (s), 1420 (m), 1375 (m), 1240 (m), 1192 (s) cm$^{-1}$; MS, $m/z$ (relative intensity) 199 (M$^+$, 1.5), 158 (8), 159 (100), 113 (26), 86 (25), 80 (23), 43 (28), 41 (24).

**N-(2-Cyclopentenylacetyl)-N-allyl-O-acetylhydroxylamine (3e)**: 65%; $^1$H NMR ($CDCl_3$, HFT-80) δ 0.70–1.75 (m, 3 H), 2.05–2.60 (m, 3 H), 2.18 (s, 3 H), 5.10–6.10 (m, 5 H); IR (film) 1795 (s), 1720 (m), 1660 (s), 1640 (m), 1400 (m), 1180 (s), 1000 (m), 920 (m), 845 (m), 720 (m) cm$^{-1}$; MS, $m/z$ (relative intensity) 164 (M-59, 10), 157 (9), 119 (15), 81 (26), 67 (100), 43 (17), 41 (13).

**N-4-Pentynoyl-N-allyl-O-acetylhydroxylamine (3f)**: 51%; $^1$H NMR ($CDCl_3$, HFT-80) δ 2.20 (s, 3 H), 2.45–3.10 (m, 5 H), 4.28 (d of d, 2 H, $J$ = 6 Hz), 5.0–6.20 (m, 3 H); IR (film) 1790 (s), 1662 (s), 1440 (s), 1400 (s), 1384 (s), 1190 (s) cm$^{-1}$; MS, $m/z$ (relative intensity) 195 (M$^+$, 2), 136 (22), 115 (24), 81 (100), 53 (65), 43 (35).

**Standard Thermolysis Procedure.** The procedure that we used is relatively simple and has been described previously.[21] The major change was that the heating element was 18-gauge Ni-Chrome wire and was wrapped inside the reaction tube. This modification simplified the construction and did not appear to alter the chemistry. The temperature of the reaction tube was controlled by varying the voltage across the heating element. The conditions required to induce a reaction were usually determined experimentally. That is, a sample just small enough for analysis was evaporated through the tube and the voltage was adjusted until the yield of the desired product was maximized. The temperature required to induce the reactions described below was estimated with a thermocouple to be approximately 650 °C and the contact time was estimated to be approximately 1 μs. The sample size was usually 50–200 mg although smaller and larger quantities (multigram) have successively been prepared with this method.

**1,7,8,8a-Tetrahydro-3(2H)-indolizinone (9).** By use of the standard thermolysis procedure, 52 mg of N-allyl-N-pent-4-enoyl-O-acetylhydroxylamine (**3a**) gave **9**, which was purified by chromatography on a silica gel column with ether as the eluent to afford 28 mg of **9** (75%): $^1$H NMR ($CDCl_3$, HFT-80) δ 1.15–2.60 (m, 8 H), 3.40–3.90 (m, 1 H), 4.90–5.20 (m, 1 H), 6.75 (d, 1 H, $J$ = 4 Hz); IR (film) 3100 (m), 2950 (s), 1700 (s), 1640 (s), 1420 (s), 1370 (s), 1320 (s), 1290 (s), 1050 (m) cm$^{-1}$; MS, $m/z$ (relative intensity) 137 (M$^+$, 66), 82 (100), 69 (30), 54 (25); high-resolution mass spectrum, $m/e$ 137.1865 ($C_8H_{11}NO$ requires 137.1840).

**δ-Coniceine (10).** To a suspension of 10% Pd/C (6 mg) in 2 mL of absolute ethanol was added 87 mg of **9** in 1 mL of ethanol. The mixture was stirred, cooled in an ice bath, and treated with a positive pressure of hydrogen (760 mmHg). Approximately 15 mL of hydrogen was absorbed over 20 h. The reaction mixture was then passed through a short column of Celite and concentrated in vacuo. The GLC and NMR spectra of the crude product showed high purity, and this was used directly for the following reduction without purification. A solution of this crude product (31 mg) in ether was added dropwise to a suspension of lithium aluminum hydride in ether. The reaction mixture was refluxed for 3 h and quenched with 0.5 mL of 20% NaOH. The water layer was extracted twice with either (5 mL). The combined ether solution was dried ($MgSO_4$), and the ether was removed in vacuo to give recemic δ-coniceine **10**. Mass spectrum of **10** matched with that of a standard sample.[37]

The standard thermolysis procedure was used to prepare the following indolizinones that are listed in Table I.

**1,2,3,8,9,9a-Hexahydro-4-quinolizinone**: 69%; $^1$H NMR ($CDCl_3$, HFT-80) δ 1.10–2.20 (m, 10 H), 3.21–7.60 (m, 1 H), 4.95–5.32 (m, 1 H), 6.20 (d, 1 H, $J$ = 4 Hz); IR (film) 2980 (s), 1640 (s), 1446 (s), 1310 (s), 1280 (s), 1185 (s), 1100 (s), 740 (m) cm$^{-1}$; high-resolution mass spectrum, $m/z$ 151.1989 ($C_9H_{13}NO$ requires 151.1997).

**1,7,8,8a-Tetrahydro-(8R*,8aS*)-8-phenyl-3(2H)-indolizinone**: 74%; $^1$H NMR ($CDCl_3$, HFT-80) δ 0.85–3.05 (m, 7 H), 3.40–4.05 (m, 1 H), 5.10–5.35 (m, 1 H), 6.70 (d, 1 H, $J$ = 4 Hz), 7.05–7.50 (m, 5 H); needle and colorless crystal, mp = 137–139 °C; IR (KBr) 1690 (s), 1650 (m), 1490 (w), 1450 (w), 1430 (m), 1410 (s), 1360 (m), 1320 (m), 1270 (m), 750 (s) cm$^{-1}$; MS, $m/z$ (relative intensity) 213 (M$^+$, 55), 129 (48), 128 (52), 130 (100), 116 (38), 115 (47); high-resolution mass spectrum, $m/e$ 213.1158 ($C_{14}H_{15}NO$ requires 213.1153).

(37) Heller, S. R. "EPA/NIH Mass Spectral Data Base"; Vol. 1, 218.

**1,7,8,8a-Tetrahydro-2-oxa-3(2H)-indolizinone**: 70%; $^1$H NMR ($CDCl_3$, HFT-80) δ 1.00–2.05 (m, 4 H), 3.95 (m, 3 H), 4.55 (s, 1 H), 5.05 (m, 1 H), 6.58 (d of t, $J$ = 8 Hz); IR (film) 1745 (s), 1645 (m), 1406 (s), 1308 (m), 1265 (s), 1065 (s) cm$^{-1}$; MS, $m/z$ (relative intensity) 139 (M$^+$, 100), 94 (64), 80 (18), 67 (47), 54 (36); high-resolution mass spectrum, $m/e$ 139.0623 ($C_7H_9NO_2$ requires 139.0633).

**1-Azatricyclo[5.3.1.0$^{4,11}$]undec-9-en-2-one**: 69%; $^1$H NMR ($CDCl_3$, HFT-80) δ 0.80–1.00 (m, 10 H), 3.80 (t, 1 H, $J$ = 2 Hz), 4.80–5.15 (m, 1 H), 6.75 (d, 1 H, $J$ = 4 Hz); IR (film) 2995 (m), 1670 (s), 1410 (s), 1375 (m), 1300 (m), 1240 (m) cm$^{-1}$; MS, $m/z$ (relative intensity) 163 (M$^+$, 49), 164 (6), 162 (12), 134 (15), 120 (10), 106 (16), 80 (100), 67 (19); high-resolution mass spectrum, $m/e$ 163.0987 ($C_{10}H_{13}NO$ requires 163.0997).

**1,7-Dihydro-3(2H)-indolizinone**: 90%; This compound is unstable at room temperature. It decomposed slowly into another unidentified product: $^1$H NMR ($CDCl_3$, HFT-80) δ 2.20–2.65 (m, 4 H), 2.85–3.25 (m, 2 H), 4.5–4.65 (m, 1 H), 4.90–5.20 (m, 1 H), 7.15 (d of d, 1 H, $J$ = 8 Hz); IR (film) 1690 (s), 1430 (s), 1283 (m), 1250 (m) cm$^{-1}$; MS $m/z$ (relative intensity) 135 (M$^+$, 40), 134 (100), 106 (83), 80 (15), 78 (29); high-resolution mass spectrum, $m/e$ 135.0671 ($C_8H_9NO$ requires 135.0684).

**N-(1-Methoxy-2-propenyl)acetamide (12).** By using of the standard thermolysis procedure with the receiver flask containing 150 μL of methanol, 80 μL (104 mg) of N-allyl-N,O-diacetylhydroxylamine **6** gave, after purification by column chromatography (ether as eluent), 59.1 mg of **12** (69.1%): $^1$H NMR ($CDCl_3$, HFT-80) δ 2.07 (s, 3 H), 3.37 (s, 3 H), 5.1–6.1 (m, 5 H); IR (film) 3300 (s), 1670 (s), 1638 (m), 1535 (s), 1440 (m), 1375 (s), 1275 (m), 1200 (m), 1160 (m), 1062 (s), 980 (m) cm$^{-1}$. The structure of **12** was confirmed by N-allylacetamide. A solution containing 132 mg of N-(1-methoxy-2-propenyl)acetamide (**12**) and 154 mg of sodium borohydride in benzene (0.5 mL) was cooled in an ice bath under a nitrogen atmosphere, and stirred for 5 min. Then 1 mL of trifluoroacetic acid was carefully added. The resulting mixture was diluted with another 1.5 mL of benzene, warmed to room temperature, and stirred for an additional 10 min. The reaction mixture was carefully neutralized with 1.5 mL of 2 N NaOH. The resulting mixture was centrifuged and extracted with $CH_2Cl_2$, dried ($K_2CO_3$), filtered, and concentrated to yield 110 mg of a yellow liquid. The crude material was purified with VPC (3% OV-101 at 70 °C and was identified as N-allylacetamide by comparison with an authentic sample.

**Solution Pyrolysis of 3a. N-Allyl-pent-4-enamide (13).** A solution of 25 μL (25.61 mg) of N-allyl-N-4-pentenoyl-O-acetylhydroxylamine (**3**) in toluene (425 μL) was put in a glass tube and sealed. The sealed tube was heated in an oven at 180 °C for 20 h. The reaction mixture was passed through potassium carbonate to remove acetic acid. Removal of toluene in vacuo afforded 11 mg crude **13** which was purified by column chromatography on silica gel (hexane–ether, 1:1) to afford pure **13** identical with an authentic sample prepared from N-allylamine and pent-4-enoyl chloride: $^1$H NMR ($CDCl_3$, HFT-80) δ 1.65 (m, 1 H), 2.28 (m, 4 H), 3.85 (t of t, $J$ = 2 Hz, $J$ = 6 Hz, 2 H), 5.90–6.07 (m, 6 H). IR (film) 3348 (s), 3105 (m), 2953 (m), 1663 (s), 1642 (s), 1543 (s), 1420 (m), 1263 (m), 983 (m) cm$^{-1}$; MS, m/z (relative intensity) 139 (M$^+$, 4), 138 (10), 84 (100), 57 (59), 56 (39), 55 (51).

**N-Allyl-N-4-pentenoyl-O-(methoxycarbonyl)hydroxylamine (14).** A solution of 1.92 g of N-allyl-N,O-diacetylhydroxylamine (**6**) in 50 mL of concentrated hydrochloric acid was heated at reflux on a steam bath for 3 h. After cooling, the reaction mixture was diluted with 2 mL of $CH_2Cl_2$ made basic with solid sodium hydroxide. The $CH_2Cl_2$ layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ many times. The combined extract was concentrated and the solid was formed. This crude product was recrystallized from an ether–pentane (1:1) solution to afford 0.228 g of white crystal (25.5%) of N-allylhydroxylamine, mp 33–35 °C. N-allylhydroxylamine was unstable at room temperature. The resulting compound was used without further purification. To a solution of N-allylhydroxylamine (0.206 g, 2.82 mmol) in $CCl_4$ (5 mL) was added 4-pentenoyl chloride (0.403 g, 3.408 mmol) and triethylamine (0.290 g, 2.87 mmol) in an ice bath. The resulting mixture was stirred at room temperature for 1 h. This solution was washed with 10% $Na_2CO_3$ aqueous solution (2 mL) and 2 mL of $H_2O$, and the separated $CCl_4$ layer was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by silica gel chromatography using ether as eluent to give 0.235 g of N-allyl-N-4-pentenoylhydroxylamine (54%): $^1$H NMR ($CDCl_3$, HFT-80) δ 2.92 (m, 4 H), 4.70 (d, $J$ = 5 Hz, 2 H), 4.75–6.00 (m, 6 H); IR (film) 3230 (s, br), 1620 (s), 1420 (m), 1170 (m), 920 (m) cm$^{-1}$. To a stirred solution of N-allyl-N-4-pentenoylhydroxylamine (1.61 g, 0.0105 mol) and triethylamine (1.07 g, 0.0106 mol) in carbon tetrachloride (10 mL) at 0 °C was carefully added methyl chloroformate (1.249 g, 0.0132 mol). This solution was allowed to stir at room temperature for 2 h. The mixture was poured into $H_2O$, and extracted thoroughly with $CCl_4$. The combined extracts were dried ($MgSO_4$),

filtered, evaporated, and separated on a silica gel column (eluted with 50% hexane ether solution) to afford 1.67 g (75%) of **14**: $^1$H NMR ($CDCl_3$, HFT-80) $\delta$ 2.35 (m, 4 H), 3.85 (s, 3 H), 4.25 (d, $J$ = 5 Hz, 2 H), 4.80–6.10 (m, 6 H); IR (film) 1800 (s), 1680 (s), 1442 (s), 1255 (s), 935 (s) cm$^{-1}$; MS, $m/z$ (relative intensity) 138 (M-75, 14), 131 (17), 83 (54), 55 (100).

**Flash Vacuum Pyrolysis of *N*-Allyl-*N*-4-pentenoyl-*O*-(methoxycarbonyl)hydroxylamine (14)**: When the standard thermolysis procedure was used, 525 mg of **14** gave 360 mg of a product which was purified with column chromatography using ether as an eluent giving 234 mg (65%) of **9**.

***O*-Acetyl-*N*-2-butenyl-*N*-4-pentenoylhydroxylamine.** This compound was prepared by an overall procedure similar to that previously described for **3a**. A solution containing *N*,*O*-diacetylhydroxylamine (11.79 g, 0.101 mol), potassium carbonate (13.80 g, 0.100 mol), 14.32 g of 1-bromo-2-butene (containing 20% of 3-bromo-1-butene), and 14.98 g of NaI in DMF (30 mL) was stirred at room temperature for 24 h. Then DMF was removed by a reduced pressure distillation. The resulting residue was chromatographed on a silica gel column with ether as an eluent to give 9.55 g (56%) of *N*-2-butenyl-*N*,*O*-diacetylhydroxylamine that was homogeneously by TLC. Without adding NaI, the yield of this reaction is 45%: $^1$H NMR ($CDCl_3$, HFT-80) $\delta$ 1.80 (d, $J$ = 6 Hz, 3 H), 2.15 (s, 3 H), 4.20 (d, $J$ = 8 Hz, 2 H), 5.6–6.0 (m, 2 H); IR (film) 1792 (s), 1662 (s), 1440 (m), 1390 (m), 1360 (m), 1180 (s), 960 (m) cm$^{-1}$; MS, $m/z$ (relative intensity) 112 (M - 59, 17), 87 (20), 70 (18), 55 (36), 43 (100). Hydrolysis of the above hydroxylamine derivative using a procedure similar to that described for **7** gave, after silica gel chromatography (ether), a 46% yield of *O*-acetyl-*N*-2-butenylhydroxylamine: $^1$H NMR ($CDCl_3$, HFT-80) $\delta$ 2.67 (d, $J$ = 6 Hz, 3 H), 2.05 (s, 3 H), 3.52 (d of d, $J$ = 4 Hz, 2 H), 5.20–5.90 (m, 2 H); IR (film) 3260 (m), 1737 (s), 1440 (m), 1367 (m), 1230 (s) cm$^{-1}$; MS, $m/z$ (relative intensity) 129 ($M^+$, 1), 56 (25), 55 (24), 43 (100), 39 (11); high-resolution mass spectrum, $m/e$ 129.0795 ($C_6H_{11}NO_2$ requires 129.0789).

The above hydroxylamine derivative was acylated with 4-pentenoyl chloride, by a procedure analogous to that for the preparation of **3a**, to give, after silica gel chromatography (1:1 hexane:ether), the product in 85% yield: $^1$H NMR ($CDCl_3$, HFT-80) $\delta$ 1.70 (d, $J$ = 4 Hz, 3 H), 2.17 (s, 3 H), 2.75–3.10 (m, 4 H), 4.22 (d, $J$ = 5 Hz, 2 H), 4.90–6.00 (m, 5 H); IR (film) 1790 (s), 1660 (s), 1180 (s) cm$^{-1}$; MS, $m/z$ (relative intensity) 152 (M - 59, 10), 87 (12), 83 (36), 55 (100), 43 (33).

**Flash Vacuum Pyrolysis of *O*-Acetyl-*N*-2-butenyl-*N*-4-pentenoylhydroxylamine.** With the standard thermolysis procedure, 99.8 mg of the hydroxylamine gave 33.8 mg of a product which was purified with flash column chromatgraphy using ether as an eluent giving 20.4 mg (40%) of **17** and 9.8 mg (20%) of **16**.

**1,7,8,8a-Tetrahydro-(7*R**,8a*R**)-7-methyl-3(2*H*)-indolizinone (17)**: $^1$H NMR ($CDCl_3$, NT-300) $\delta$ 1.04 (d, $J$ = 7 Hz, 3 H), 3.25–4.00 (m, 1 H), 5.07 (d of d, $J$ = 10 Hz, 6 Hz, 1 H), 6.75 (d, $J$ = 10 Hz, 1 H); IR (film) 1685 (s), 1620 (m), 1425 (s), 1285 (m) cm$^{-1}$; high-resolution mass spectrum, $m/e$ 151.0990 ($C_9H_{13}NO$ requires 151.0997).

**1,7,8,8a-Tetrahydro-(7*R**,8a*S**)-7-methyl-3(2*H*)-indolizinone (16)**: $^1$H NMR ($CDCl_3$, NT-300), $\delta$ 1.07 (d, $J$ = 7 Hz, 3 H), 3.30–4.00 (m, 1 H), 4.87 (d of t, $J$ = 10 Hz, 1 Hz, 1 H), 6.65 (d of d, $J$ = 10 Hz, 2 Hz, 1 H); IR (film) 1685 (s), 1620 (m), 1425 (s), 1285 (m) cm$^{-1}$; high-resolution mass spectrum, $m/e$ 151.0984 ($C_9H_{13}NO$ requires 151.0997); MS for isomeric mixtures **17** and **16**, $m/z$ (relative intensity) 151 ($M^+$, 59), 136 (100), 108 (51), 68 (22).

By use of the standard thermolysis procedure at a lower temperature (150 °C lower than the normal pyrolysis temperature), 105 mg of the hydroxylamine gave 71 mg of crude product which was purified with column chromatography on silica gel (hexane–ether, 1:1) to give 28 mg (37%) of **24**, 9 mg (12%) of **25**, and 22 mg (29%) of the mixture of **17** and **16**.

**(*Z*)-*N*-1,3-Butadienyl-4-pentenamide (24)**: mp 44–45 °C (from hexane); $^1$H NMR ($CDCl_3$, HFT-80), $\delta$ 6.72 (t, $J$ = 10 Hz, 1 H), 7.65 (br, 1 H), 6.65–5.00 (m, 7 H), 2.41 (m, 2 H); IR (NaCl, neat) 3350 (m), 1680 (m), 1645 (s), 1420 (s), 1400 (s), 1248 (m) cm$^{-1}$; MS, $m/z$ (relative intensity) 151 ($M^+$, 21), 69 (100), 68 (17), 55 (27); high-resolution mass spectrum, $m/e$ 151.0978 ($C_9H_{13}NO$ requires 151.0997).

**(*E*)-*N*-1,3-Butadienyl-4-pentenamide (25)**: mp 86–88 °C (from hexane); $^1$H NMR ($CDCl_3$, HFT-80) $\delta$ 6.98 (t, $J$ = 13 Hz, 1 H), 7.75 (br, 1 H), 6.80–4.80 (m, 7 H), 2.85 (m, 4 H); IR (neat, NaCl 3330 (m), 1648 (s) 1530 (m), 1228 (m) cm$^{-1}$; MS, $m/z$ (relative intensity) 151 ($M^+$, 21), 69 (100), 68 (17), 55 (27); high-resolution mass spectrum, $m/e$ 151.0995 ($C_9H_{13}NO$ requires 151.0997).

**Flash Vacuum Pyrolysis of 24 and 25**: With the standard thermolysis procedure, 53 mg of a mixture of **24** and **25** gave 44 mg of the cyclized products **17** and **16** (83%).

***N*-Pent-2-en-4-yl-*N*-pent-4-enoyl-*O*-acetylhydroxylamine (18).** This compound was prepared by an overall procedure analogous to that for the preparation of **3a**. A solution containing 1.94 g of 2-bromo-3-pentene (0.0130 mol, 1 equiv), 1.53 g of *N*,*O*-diacetylhydroxylamine (0.0130 mol, 1 equiv), and 1.80 g of $K_2CO_3$ (0.0103 mol, 1 equiv) in 5 mL of DMF was allowed to stir at room temperature for 24 h. The mixture was filtered and the DMF was removed by a reduced pressure distillation. The resulting residue was chromatographed on silica gel (eluted with 50% hexane–ether solution) to afford 191 mg (8%) of pure *N*-pent-2-en-4-yl-*N*,*O*-diacetylhydroxylamine: $^1$H NMR ($CDCl_3$, HFT-80) $\delta$ 1.24 (d, $J$ = 7 Hz, 3 H), 1.67 (d, $J$ = 5 Hz, 3 H), 2.00 (s, 3 H), 2.17 (s, 3 H), 4.80–6.00 (m, 2 H); IR (film) 1655 (s), 1795 (s), 1370 (m), 1180 (s) cm$^{-1}$; MS, $m/s$ (relative intensity) 126 (M - 59, 15) 68 (14), 69 (100), 43 (34). A mixture of 154 mg of the above hydroxylamine and 1.5 mL of 8 N HCl was stirred at room temperature for 3 h. The resulting mixture was neutralized with sodium carbonate, and extracted thoroughly with $CH_2Cl_2$. The combined extract was dried over $MgSO_4$, filtered, concentrated in vacuo, and chromatographed on silica gel (50% ether–hexane) to afford 31 mg (26%) of *O*-acetyl-*N*-(1-methyl-2-butenyl)-hydroxylamine: $^1$H NMR ($CDCl_3$, HFT-80) $\delta$ 1.75 (d, $J$ = 7 Hz, 3 H), 1.67 (d, $J$ = 5 Hz, 3 H), 2.08 (s, 3 H), 3.85–4.20 (m, 1 H), 5.15–5.80 (m, 2 H); IR (film) 3273 (w), 3003 (m), 2965 (m), 1740 (s), 1444 (m), 1385 (m), 1218 (s), 963 (m) cm$^{-1}$; MS, $m/z$ (relative intensity) 128 (18), 101 (17), 86 (17), 83 (71), 70 (33), 69 (100), 68 (78).

The above hydroxylamine was acylated with 4-pentenoyl chloride by a procedure analogous to that for the preparation of **3a** to give, after silica gel chromatography (1:1 hexane–ether), compound **18** in a 32% yield: $^1$H NMR ($CDCl_3$, HFT-80) $\delta$ 1.24 (d, $J$ = 6 Hz, 3 H), 1.40 (d, $J$ = 5 Hz, 3 H), 2.17 (s, 3 H), 2.32 (m, 4 H), 4.85–6.00 (m, 5 H); IR (film) 1795 (s), 1445 (m), 1380 (m), 1180 (s) cm$^{-1}$; MS, $m/z$ (relative intensity) 166 (M - 59, 30), 158 (10), 143 (11), 128 (17), 84 (20), 85 (36), 69 (100), 55 (21).

**Flash Vacuum Pyrolysis of 18.** By the standard thermolysis procedure, 30 mg of **18** gave 15 mg (68%) of product which was further purified by silica gel column chromatography (ether) to afford 13.8 mg of a mixture of **20** and **21**. This mixture showed only one spot by thin-layer chromatography: $^1$H NMR ($CDCl_3$, NT-300) $\delta$ 4.75 (d, $J$ = 6 Hz), 4.52 (m), 3.7 (m), 2.24 (m), 1.58 (m), 1.00 (d, $J$ = 6 Hz); IR (film) 3004 (m), 2950 (s), 1719 (s), 1414 (s), 1384 (m), 1284 (m) cm$^{-1}$; MS, $m/z$ (relative intensity) 165 ($M^+$, 32), 150 (100), 122 (56), 94 (17); high-resolution mass spectrum, $m/e$ 165.1149 ($C_{10}H_{15}NO$ requires 165.1153).

***O*-Acetyl-*N*-(cyclohexenylmethyl)-*N*-4-pentenoylhydroxylamine (28).** This compound was prepared by an overall scheme analogous to that for the preparation of **3a**. To 2.77 g (0.024 mol) of *N*,*O*-diacetylhydroxylamine in 10 mL of DMF was added 4.20 g (0.024 mol) of (1-bromomethyl)cyclohexene[38] and 3.27 g of potassium carbonate. The reaction mixture was stirred at room temperature for 20 h. The precipitate was filtered and the DMF was removed by reduced pressure distillation. The pure compound (3.29 g) was obtained from silica gel column chromatography (hexane–ether, 1:1) (65%): $^1$H NMR ($CDCl_3$, HFT-80), $\delta$ 2.05 (s, 3 H), 2.18 (s, 3 H), 1.58 (m, 4 H), 1.95 (m, 4 H), 4.15 (s, 1 H), 5.35 (m, 1 H); IR (film) 2995 (s), 1800 (s), 1680 (s), 1440 (m), 1400 (m), 1380 (m), 1240 (w), 1180 (s), 855 (m) cm$^{-1}$; MS, $m/z$ (relative intensity) 211 ($M^+$, 0.5), 152 (59), 110 (100), 93 (25), 95 (47).

A solution of 2.99 g of *N*,*O*-diacetyl-*N*-(cyclohexenylmethyl)-hydroxylamine in 15 mL of 6 N HCl was stirred at room temperature for 1 h and then neutralized with solid sodium carbonate. The resulting mixture was extracted with $CH_2Cl_2$ thoroughly. The combined extract was dried ($MgSO_4$), filtered, and concentrated to afford 0.765 g of the pure *O*-acetyl-*N*-(cyclohexenylmethyl)hydroxylamine (40%) which was quite unstable and was used for the following acylation without further purification: $^1$H NMR ($CDCl_3$, HFT-80) $\delta$ 1.60 (m, 2 H), 2.05 (m, 2 H), 2.07 (s, 3 H), 3.94 (s, 2 H), 5.65 (m, 1 H), 7.75 (br, 1 H); IR (film) 3280 (m), 2950 (s) 1740 (s), 1620 (m), 1440 (m), 1385 (m), 1220 (s) cm$^{-1}$.

The acylation procedure was the same as previously described for **3a**. Purification was achieved by silica gel column chromatography (eluted with hexane–ether, 2:1) to give **28** (74%): $^1$H NMR ($CDCl_3$, HFT-80), $\delta$ 1.57 (m, 2 H), 1.95 (m, 2 H), 2.15 (s, 3 H), 2.45 (m, 4 H), 4.15 (s, 2 H), 4.85–6.00 (m, 4 H). IR (film) 2995 (s), 1800 (s), 1670 (s), 1442 (m), 1386 (m), 1180 (s), 855 (m) cm$^{-1}$; MS, $m/z$ (relative intensity) 251 ($M^+$, 0.3), 192 (82), 110 (100), 95 (29), 55 (33).

With the standard thermolysis procedure, 76 mg of **28** gave 36 mg (63%) of **30** and **31**: $^1$H NMR ($CDCl_3$, HFT-80) $\delta$ 0.80–2.60 (m, 15 H), 3.30–3.85 (m, 1 H), 6.55 (s, 1 H); IR (film) 296 (s), 2885 (s), 1650 (s), 1445 (m), 1410 (s), 1300 (m) cm$^{-1}$; $^{13}$C NMR ($CDCl_3$, NT-300) $\delta$ 170.484, 127.536, 124.8, 115.187, 114.029, 55.209, 52.129, 39.251, 36.656, 36.353, 36.202, 35.797, 34.357, 32.941, 31.747, 31.180, 31.041, 29.423, 27.064, 26.891, 26.235, 25.960; MS, $m/z$ (relative intensity) 191

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(M+, 100), 190 (54), 162 (32), 108 (50), 84 (34); high-resolution mass spectrum, m/e 191.1318 ($C_{12}H_{17}NO$ requires 191.1310).

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**Registry No. 3a**, 77413-79-7; **3b**, 77413-80-0; **3c**, 87842-62-4; **3d**, 87842-63-5; **3e**, 77413-82-2; **3f**, 87842-64-6; **5**, 7340-09-2; **6**, 87842-65-7; **7**, 87842-66-8; (±)-**9**, 87842-67-9; (±)-**10**, 62279-67-8; **12**, 77413-86-6; **13**, 87842-68-0; **14**, 87842-69-1; **16**, 87842-70-4; **17**, 87842-71-5; **18**, 87842-72-6; **20**, 87842-73-7; **21**, 87842-74-8; **24**, 87842-75-9; **25**, 87842-76-0; **28**, 87842-77-1; **30**, 87842-78-2; **31**, 87842-79-3; 4-pentenoyl chloride, 39716-58-0; 1,2,3,8,9,9a-hexahydro-4-quinolizinone, 87842-80-6; *cis*-1,7,8,8a-tetrahydro-8-phenyl-3(2*H*)-indolizinone, 77413-85-5; 1,7,8,8a-tetrahydro-2-oxa-3(2*H*)-indolizinone, 87842-81-7; 1-azatricyclo[5.3.1.$0^{4,11}$]undec-9-en-2-one, 77413-84-4; *N*-allylacetamide, 692-33-1; *N*-allylhydroxylamine, 52716-05-9; *N*-allyl-*N*-(4-pentenoyl)hydroxylamine, 87842-83-9; *O*-acetyl-*N*-(2-butenyl)-*N*-(4-pentenoyl)hydroxylamine, 87842-84-0; 1-bromo-2-butene, 4784-77-4; *N*-(2-butenyl)-*N*,*O*-diacetylhydroxylamine, 87842-85-1; *O*-acetyl-*N*-(2-butenyl)hydroxylamine, 87842-86-2; 4-bromo-2-pentene, 1809-26-3; *N*-(2-penten-4-yl)-*N*,*O*-diacetylhydroxylamine, 87842-87-3; *O*-acetyl-*N*-(1-methyl-2-butenyl)hydroxylamine, 87842-88-4; *N*,*O*-diacetyl-*N*-(1-cyclohexenylmethyl)hydroxylamine, 87842-89-5; *O*-acetyl-*N*-(1-cyclohexenylmethyl)hydroxylamine, 87842-90-8; 1-bromomethylcyclohexene, 37677-17-1; allyl bromide, 106-95-6.

# Heterocycles as Masked Diamide/Dipeptide Equivalents. Formation and Reactions of Substituted 5-(Acylamino)oxazoles as Intermediates en route to the Cyclopeptide Alkaloids

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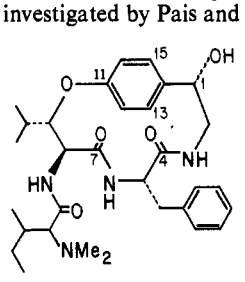
**Abstract:** A variety of novel 2,4-dialkyl-5-(acylamino)oxazoles have been prepared by using either amide nitriles or diamides/dipeptides as starting materials. Ring closure calls for the use of trifluoroacetic acid/trifluoroacetic acid anhydride or an acid halide in chlorinated solvents. The first examples of chiral systems have also been prepared incorporating both alkyl and protected amine substitutents at the C-2 methyl residue derived from the corresponding amino acids. Unmasking of these heteroaromatic moieties to their dipeptide equivalents is demonstrated. Both carbon and nitrogen alkylation chemistry is examined as model studies for subsequent elaboration to specific heterocyclophanes, potential precursors of numerous cyclopeptide alkaloids.

The cyclopeptide alkaloids ("phencyclopeptines") make up a rapidly expanding class of naturally occurring compounds that have been known for almost a century.[2] The first definitive structure elucidation, however, was not reported until 1966 when pandamine (**1**), was investigated by Pais and co-workers.[3] Since




**1**, Pandamine

this time the number of these bases isolated and of known structure continues to increase, there presently being over 80 members.[4]

Several characteristic features are common to the majority of these alkaloids. Generally they contain a 13-, 14-, or 15-membered ring, incorporating an aryl ether, which in turn is derived from a *p*-hydroxystyrylamine moiety and a β-hydroxyamino acid residue. A rather limited number of amino acids serve to complete the cyclic array, which tend to have hydrophobic side chains. These include phenylalanine, leucine, and isoleucine, although valine-, proline-, and tryptophane-derived species have been observed.[2]

Although the phencyclopeptines are found in the leaves and bark of a number of plants, extraction techniques usually afford highly complex mixtures containing as many as 20 components, rendering isolation of individual compounds an extremely tedious adventure.[2] From their common occurrence, however, has come a rich history of service in folk medicine. This tradition continues today among natives of central and southern Africa where natural sources of phencyclopeptines are used as remedies for diarrhea and dysentary.[2] Much of the modern medicinal interest in these cyclophanes, especially where the 14-membered ring series is concerned, stems from their potential as specific ion sequestering agents. Frangulanine (**2**) has been reported to induce swelling in rat liver mitochondria in 0.15 M KCl or RbCl solution but has no effect in aqueous solutions of NaCl or LiCl.[5] Similarly,

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