spectrum, m/e (relative intensity)[31] 279 (1.0, M + 2), 278 (9, M + 1), 277 (58, M), 276 (100, M - 1), 138 (20), 135 (28), 116 (39), 92 (21), 89 (19), 77 (71).

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.89; H, 5.54; N, 5.05.

Product analyses for reactions involving variable amounts of cinnamonitrile and BF_3·Et_2O were perfomed by analytical LC on a Waters Associates Model ALC/GPC instrument using a 30-cm Porasil column and 5% methylene chloride in hexane buffered with 0.3% triethylamine.

Preparation of Annuloline (3). α-Diazo-*p*-methoxyacetophenone (0.366 g, 2.03 mmol) dissolved in 5.0 mL of methylene chloride was slowly added over a 5-min period to a rapidly stirred solution of 0.56 g of BF_3·Et_2O (3.94 mmol) and 1.89 g of 3,4-dimethoxycinnamonitrile (10.0 mmol of a 67:33 trans–cis mixture) in 15 mL of methylene chloride. The previously described procedure was followed and, after evaporation of the organic solvent, the resulting orange-red oil was dissolved in 50 mL of anhydrous ethanol. The ethanolic solution was then treated with a saturated picric acid solution until no more precipitate deposited from the solution. After the mixture cooled, the yellow precipitate was filtered and recrystallized from ethanol to yield the picrate derivative of **3** in 48% yield, mp 219–221 °C (lit.[21] mp 216–218 °C). The hydrochloride derivative of **3** was produced in alternate experiments but proved to be more difficult to form and resulted in lower yields of the isolated product: mp 176–178 °C (lit.[21] mp 174–177 °C). Annuloline was liberated from its hydrochloride salt with dilute ammonium hydroxide. Alternatively, annuloline was isolated from the crude reaction mixture by column chromatography on a 10-cm silica gel column using hexane–ether mixtures: ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J_o = 9.0 Hz, 2 H), 7.48 (d, J_{trans} = 16.5 Hz, 1 H), 7.24 (s, C_4-H), 7.03 (d, J_m = 2 Hz, 1 H), 6.96 (d, J_o = 9.5 Hz, 1 H), 6.91 (d, J_o = 9.0 Hz, 2 H), 6.82 (d of d, J_o = 9.5 Hz, J_m = 2 Hz, 1 H), 6.78 (d, J_{trans} = 16.5 Hz, 1 H), 3.91 (s, OCH_3), 3.87 (s, OCH_3), 3.82 (s, OCH_3); mass spectrum, m/e (relative intensity)[31] 339 (1, M + 2), 338 (11, M + 1), 337 (58, M), 336 (80, M - 1), 175 (12), 169 (12), 149 (20), 136 (10), 137 (100), 132 (12), 107 (13), 92 (28), 89 (26), 77 (68).

Reactions of α-Diazoacetophenone with Nitriles in the Presence of Antimony Pentafluoride. The handling of SbF_5 and reactions that employed this acid were performed in a glovebag in a dry atmosphere. In a typical procedure, SbF_5 (0.43 g, 2.0 mmol) was combined with 0.123 g of acetonitrile (3.0 mmol) in 5 mL of methylene chloride and the reaction flask was cooled to either −15 or −35 °C. α-Diazoacetophenone (0.299 g, 2.0 mmol) in 5 mL of methylene chloride was added dropwise to the cooled reaction solution over a 30-min period. The color of the reaction solution changed to orange and gas evolution was slow. After gas evolution was complete, 20 mL of 20% aqueous sodium hydroxide was added to the reaction solution, and the reaction mixture was allowed to warm to room temperature. The resulting mixture was extracted with 100 mL of ether, the ether layer was washed with 100 mL of water, and the aqueous extracts were washed with 50 mL of ether. The combined ether solution was dried over anhydrous magnesium sulfate, and ether and methylene chloride were distilled under reduced pressure. Reactions performed at −78 °C involved the sequential addition of acetonitrile and α-diazoacetophenone to SbF_5 in methylene chloride.

Acknowledgment. We gratefully acknowledge the financial support of the National Science Foundation for this work. We extend our appreciation to John T. De Jong, Christie L. Funckes, and Burton A. Leland for their extensive efforts in the preparation of oxazoles.

Registry No. 1a, 69163-82-2; **1b**, 74185-52-7; **1c**, 74185-53-8; **1d**, 68395-78-8; **1e**, 3969-09-3; **1f**, 68395-79-9; **1g**, 74195-08-7; **1h**, 68395-80-2; **1i**, 92-71-7; **1j**, 68395-81-3; **1k**, 74185-54-9; **1l**, 74185-55-0; **1m**, 74185-56-1; **1n**, 68395-82-4; **1o**, 68395-83-5; **1p**, 32595-70-3; **1q**, 74185-57-2; **2**, 74185-58-3; **3**, 3988-51-0; **3** picrate, 74185-59-4; **3** hydrochloride, 74185-60-7; bisoxazole 2,2′-dimethylene-5,5′-diphenylbisoxazole, 31995-37-6; p-$CH_3OC_6H_4COCHN_2$, 6832-17-3; $C_6H_5COCHN_2$, 3282-32-4; $(CH_3)_3CCOCHN_2$, 6832-15-1; $CH_3(CH_2)_5COCHN_2$, 58237-58-4; $N_2CHCO(CH_2)_8COCHN_2$, 55349-59-2; $CH_3CH_2OCOCHN_2$, 623-73-4; malononitrile, 109-77-3; *trans*-cinnamonitrile, 1885-38-7; *trans*-3,4-dimethoxycinnamonitrile, 37629-85-9; *cis*-3,4-dimethoxycinnamonitrile, 37627-42-2; CH_3CN, 75-05-8; $H_2C{=}CHCN$, 107-13-1; $H_2C{=}C(CH_3)CN$, 126-98-7; $(CH_3)_3CCN$, 630-18-2; C_6H_5CN, 100-47-0; $C_6H_5CH_2CN$, 140-29-4; $NCCH_2CH_2CN$, 110-61-2; $C_6H_5COCH_2Cl$, 532-27-4; p-$CH_3OC_6H_4COCH_2Cl$, 2196-99-8; $C_6H_5COCH_2F$, 450-95-3; p-$CH_3OC_6H_4COCH_2F$, 73744-44-2.

Supplementary Material Available: Physical and spectral (^{1}H NMR, mass spectra, and elemental analyses) data for oxazoles **1a–1o**; full ^{13}C NMR data for compounds **1a**, **1e**, **1h**, **1j**, and **1k** (5 pages). Ordering information is given on any current masthead page.

Extension of a Nuphar Piperidine Synthesis to Quinolizidines and an Indolizidine

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Nuphar quinolizidines (±)-nupharolutine and (±)-7-epinupharolutine and a (±) Nuphar indolizidine were synthesized from cyclopentanones that were appropriately substituted at the C-2 and C-3 positions. Four cyclopentanones were prepared. Each possessed a terminal double bond incorporated in a C-2 side chain of variable length. These side chains were 2-propenyl, 3-butenyl, 3-methyl-3-butenyl, and 4-pentenyl. The carbocyclic ring of the four C-2-substituted cyclopentanones was expanded, with simultaneous incorporation of nitrogen, by the Beckmann rearrangement. Thereby, 6-substituted 2-piperidones were obtained. Epoxidation of the terminal double bond and subsequent treatment of the resulting epoxypiperidone with sodium hydride gave useful bicyclic products when the piperidone side chains were 3,4-epoxybutyl and 3-methyl-3,4-epoxybutyl. The presence of the 3,4-epoxybutyl group resulted in the formation of a (hydroxymethylene)indolizidone while the presence of the 3-methyl-3,4-epoxybutyl group resulted in the formation of a tertiary hydroxyquinolizidone. These bicyclic lactams were elaborated upon to complete the alkaloid syntheses. Thus the control of the ring size in the ring-formation step rested on the epoxy side chain length and substitution pattern. The measure of steric control rested in part on thermodynamics at the cyclopentanone stage.

Anhydronupharamine (1) and the nupharolutines, **2a** and **2b**, are typical of the stereochemical group of Nuphar piperidines and quinolizidines having only equatorial substituents attached to the furan-bearing ring. In a

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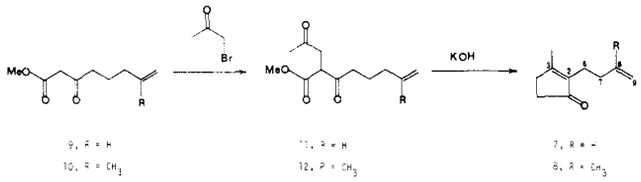
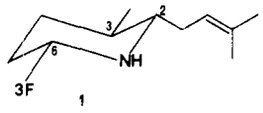
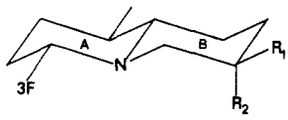
Scheme I. Formation of α,β-Unsaturated Cyclopentenones Employed in Nuphar Quinolizidine and Indolizidine Syntheses



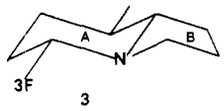
second stereochemical group, all the attachments are equatorial except the ring-A methyl, which is axial.[1]



1



2a, R_1=OH; R_2= CH_3
2b, R_2=OH; R_1=CH_3



3

Earlier we prepared 1 by a synthesis that originated with an appropriately 2,3-disubstituted cyclopentanone and proceeded through the expansion of the five-membered ring, with the simultaneous incorporation of nitrogen, to form a piperidone, the introduction of the 3-furyl group, and the reduction of the 3-furyl-bearing carbon.[2] The measure of steric control at C-2 and C-3 rested on the greater stability of a trans 2,3-disubstituted cyclopentanone relative to the cis isomer. We wished to extend this synthesis to Nuphar quinolizidines **2a** and **2b** and the indolizidine **3**. A Nuphar indolizidine, apparently the only one known, was obtained from castoreum[3] in a quantity sufficient only for mass spectral examination,[4] which indicated the gross structure corresponding to **3**. While the stereochemistry of the castoreum indolizidine remains unknown, the extension of the synthesis to the all-equatorial series of indolizidine was of interest nevertheless in testing the versatility of the trans-2,3-cyclopentanone approach.

The plan for modifying the original synthesis in a manner appropriate for the formation of the second ring entailed the incorporation of a C-2 side-chain epoxide which functioned as the electrophile in reacting with an anionic amide nitrogen. However, the principal problem in utilizing this approach concerned the chain length and the epoxide substitution pattern required to obtain the desired ring size and the appropriately located ring substituents. The results obtained in seeking a solution to this particular problem are included in this report, which presents in total the syntheses according to the following sequence: the preparation of the cyclopentanones; formation of the epoxypiperidones; formation of the bicyclic systems; quinolizidine and indolizidine formation. This division of results corresponds to the four distinct phases of synthesis according to the trans 2,3-disubstituted cyclopentanone approach.

(1) Piperidines belonging to the all-equatorial stereochemical group have the 2*S*, 3*R*, 6*S* configuration while those possessing the C-3 axial methyl have the 2*S*, 3*S*, 6*S* configuration. Quinolizidines belonging to the two stereochemical groups have the same configurations as piperidines at corresponding chiral centers.

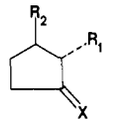
(2) R. T. LaLonde, N. Muhammad, and C. F. Wong, *J. Org. Chem.*, **42**, 2113 (1977).

(3) Castoreum, an article of commerce used in perfumery, is the dried scent glands of the Canadian beaver.

(4) B. Mauer and G. Ohloff, *Helv. Chim. Acta*, **59**, 1169 (1976).

Results

Cyclopentanone Syntheses. The cyclopentanones necessary for the study of bicyclic ring formation required α hydrocarbon chains in which a terminal double bond was separated from the ring by one, two, and three methylenes. The first of these, 2-allylcyclopentanone (**4**) was prepared through the thermolysis of an allyl ketal of cyclopentanone according to the procedure of Lorette and Howard.[5]



4, X = O; R_1 = $CH_2CH=CH_2$; R_2 = H
5, X = O; R_1 = $(CH_2)_2CH=CH_2$; R_2 = CH_3
6, X = O; R_1 = $(CH_2)_2C(CH_3)=CH_2$; R_2 = CH_3
13, X = O; R_1 = $(CH_2)_3CH=CH_2$; R_2 = H
14, X = NOH; R_1 = $CH_2CH=CH_2$; R_2 = H
15, X = NOH; R_1 = $(CH_2)_2CH=CH_2$; R_2 = CH_3
16, X = NOH; R_1 = $(CH_2)_2C(CH_3)=CH_2$; R_2 = CH_3
17, X = NOH; R_1 = $(CH_2)_3CH=CH_2$; R_2 = H

The cyclopentanones **5** and **6**, possessing two methylenes interposed between the side chain terminal double bond and the ring, also contained the C-3 methyl and were the cyclopentanones which led ultimately to the Nuphar quinolizidines and indolizidine. These cyclopentanones were obtained by the lithium in liquid ammonia reduction of the corresponding α,β-unsaturated cyclopentanones, **7** and **8**, which were prepared essentially by the method of La Forge et al.[6] as shown in Scheme I. The only deviation from the La Forge procedure occurred in initiating the synthesis of the cyclopentenone (**8**) containing the side-chain methyl. In this case, the β-keto ester **10** was obtained directly by the base-promoted acylation of 6-methyl-6-hepten-2-one with dimethyl carbonate while the La Forge approach leading to **9** began with the acylation of ethyl acetoacetate by 5-hexenoyl chloride followed by sodium methoxide promoted deacetylation of the resulting 3-carbethoxy-8-nonene-2,4-dione.

Lithium in liquid ammonia reduction and equilibration of the cis and trans isomers in the course of the workup produced the 2,3-disubstituted cyclopentanones **5** and **6** both in 75% yield from the cyclopentenone. According to GC analysis, the cyclopentanone possessing the 3-butenyl side chain contained 11% of the cis isomer while the cyclopentanone with the 3-methyl-3-butenyl side chain contained 12% of the cis isomer. In comparison, the corresponding γ,γ-dimethylallyl-substituted cyclopentanone, used in the synthesis of anhydronupharamine (**1**), contained 8% of the cis isomer.[2] The comparison of cis isomer compositions is of interest at this point in the syntheses in evaluating the influence of the C-2 side chain on the thermodynamic control of stereochemistry. The cis isomers were carried through to the end of the syntheses.

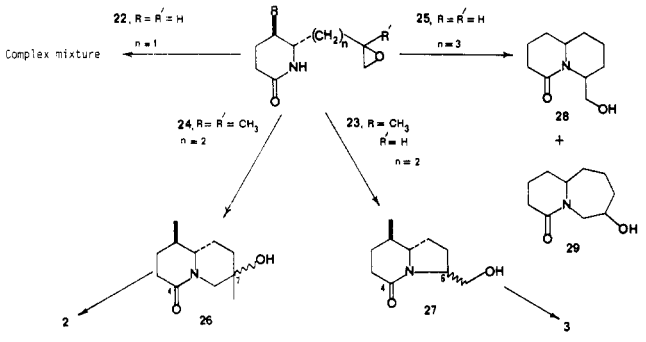
Cyclopentanone **13**, in which the ring and the side-chain terminal double bond were separated by three methylenes, was prepared by alkylation of the sodium enolate of 2-(carbomethoxy)cyclopentanone and subsequent saponification and decarboxylation.

Epoxypiperidone Formation. The cyclopentanones were converted to their oximes **14**–**17**, which in their turn

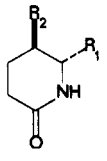
(5) N. B. Lorette and W. L. Howard, *J. Org. Chem.*, **26**, 3112 (1961).

(6) F. B. La Forge, N. Green, and W. A. Gersdorf, *J. Am. Chem. Soc.*, **70**, 3707 (1948).

Scheme II. Summary of Results Obtained When Various Piperidones, Containing Side-Chain Epoxides, Were Treated with Sodium Hydride in Benzene



were treated with PCl_5 in ether or with *p*-TsCl in pyridine to effect the Beckmann rearrangement to the 6-alkenylpiperidones **18–21** in yields ranging from 45 to 68%. The



18, R_1 = $CH_2CH{=}CH_2$; R_2 = H

19, R_1 = $(CH_2)_2CH{=}CH_2$; R_2 = CH_3

20, R_1 = $(CH_2)_2C(CH_3){=}CH_2$; R_2 = CH_3

21, R_1 = $(CH_2)_3CH{=}CH_2$; R_2 = H

22, R_1 = $CH_2CH(O)CH_2$; R_2 = H

23, R_1 = $(CH_2)_2CH(O)CH_2$; R_2 = CH_3

24, R_1 = $(CH_2)_2C(CH_3)(O)CH_2$; R_2 = CH_3

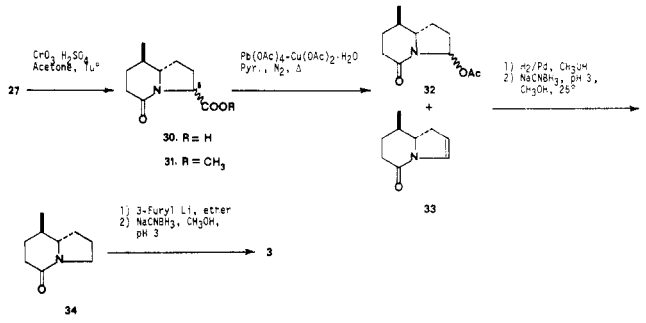
25, R_1 = $(CH_2)_3CH(O)CH_2$; R_2 = H

observation of a single-proton multiplet within the range 2.8–3.7 ppm in the ^1H NMR and the results of the GLC analyses indicated that only the more highly substituted carbon had migrated as expected. Epoxidation of the alkenyl side chain with *m*-chloroperbenzoic acid gave the crude epoxides **22–25** in yields ranging from 50 to 65%. These epoxides were employed directly in the ring-formation step since attempts to purify **23** by distillation and **24** by alumina elution chromatography resulted in degradation and consequent loss of material.

Formation of the Bicyclic Lactams. Scheme II summarizes the course of the ring forming reactions, which were promoted by heating benzene solutions of the epoxypiperidines in the presence of NaH. Products potentially useful as intermediates were obtained when two methylene groups separated the piperidone ring and epoxide group. Importantly, the size of the newly formed ring was determined not only by chain length but also by the absence or presence of the side-chain methyl group; its absence resulted in the formation of the indolizidone **27** while its presence resulted in the formation of the quinolizidone **26**. The ^1H NMR of the latter revealed a singlet methyl resonance at the downfield position of δ 1.25, which indicated the involvement of this methyl group in a tertiary alcohol. Moreover, a two-proton resonance attributable to CH_2OH was lacking in the δ 3.7 region where indolizidone **27** and quinolizidone **28** revealed their CH_2OH methylenes.

A GC/MS examination of the quinolizidone product showed four chromatographic peaks, two major and two minor, whose spectra were virtually identical, but none

Scheme III. Transformation of (Hydroxymethylene)indolizidone 27 to the Nuphar Indolizidine Alkaloid 3



revealed an *m/e* value corresponding to the loss of CH_2OH from the molecular ion. Such fragmentation results in the base peak which dominates the mass spectrum of indolizidone **27** and quinolizidone **28**. The presence of the four isomers was taken to mean that these had resulted from the newly formed chiral center at C-7 and the presence of 12% of the cis 2,3-disubstituted cyclopentanone formed at the cyclopentanone stage of the synthesis.

Formation of the indolizidone **27** from epoxypiperidone **23** was indicated by the dominance of *m/e* 152 in the mass spectrum. Also the ^1H NMR showed a two-proton multiplet at δ 3.66 attributable to CH_2OH, a one-proton multiplet at δ 3.10 attributable to the C-6 hydrogen, and a second one-proton multiplet at δ 4.26 attributable to hydrogen at the bridgehead carbon (C-9). Subsequent oxidation to a carboxylic acid confirmed the presence of the primary alcohol function. Two indolizidone isomers, present in 30 and 70%, respectively, were observed by GC.

A complex mixture of products, containing no less than nine components, resulted from the piperidone **22**, where the epoxide function was separated from the ring carbon by a single methylene. Consequently, this type of piperidone epoxide did not appear useful in forming indolizidines, especially in view of the previous success, and was abandoned. Extending the side chain to include three interposed methylenes resulted in the formation, in poor yield, of a mixture of two components isolated in the ratio of 1:3. According to the spectral data, the minor component proved to be the quinolizidone **28**, the product resulting from ring formation in the exo mode.[7] A similar examination revealed the major component, **29**, was the one resulting from ring formation in the endo mode. The results of this limited experimentation in forming quinolizidones and indolizidones from piperidone epoxides indicated the direction to proceed, and thus the alkaloid syntheses were pursued accordingly.

Nuphar Quinolizidine and Indolizidine Formation. Completion of the Nuphar quinolizidine alkaloid synthesis involved attachment of the 3-furyl group at the carbonyl carbon and subsequent reduction. Thus quinolizidine **26** was treated with an excess of 3-furyllithium and then immediately reduced. The best yield of nupharolutines was 26% although minor variations in the procedure were attempted. Elution chromatography produced pure nupharolutine (**2a**) and 7-epinupharolutine (**2b**) in a ratio of 1:9. The TLC and mass, ^1H NMR, and IR spectra were identical with those of the authentic samples.[8]

Completion of the indolizidine synthesis required the removal of the hydroxymethylene from **27**, the addition of the 3-furyl group to the carbonyl carbon, and reduction. Scheme III summarizes the transformations, the reagents,

(7) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976).
(8) R. T. LaLonde, C. F. Wong, and K. C. Das. *J. Am. Chem. Soc.*, **94**, 8522 (1972).

and the conditions involved.

Decarboxylation of **30**, formed in 69% yield from **27**, produced a mixture of acetoxyindolizidone **32** and enamide **33**. The presence of the acetoxy group in **32** was evident from the ^1H NMR and IR spectra of the mixture while the olefinic double bond in **33** was suggested from the presence of a more mobile UV-absorbing spot on the TLC plate. This spot persisted even after the mixture was treated with sodium cyanoborohydride but disappeared when hydrogenation over palladium followed the treatment with sodium cyanoborohydride. Thus when the two-step reduction–hydrogenation was used, the indolizidonecarboxylic acid **30** was converted to indolizidone **34** in 88% yield.

The Nuphar indolizidine **3** was obtained in 25% yield by treatment of indolizidone **34** with a excess of 3-furyllithium, subsequent reduction of the product with sodium cyanoborohydride at pH 3, and elution from a column. The mass spectrum of **3** was virtually identical with that published for the indolizidine isolated from castoreum. When compared with the spectra of deoxynupharidine, nupharolutine, and 7-epinupharolutine, the intensity of the IR Bohlmann bands and the ^1H NMR chemical shift and splitting values for the C-4 axial and C-1 methyl protons indicated a trans-fused indolizidine, **3**, containing equatorial 3-furyl and C-1 methyl groups. The ^{13}C NMR was also consistent with this stereochemistry.

Discussion

In the evaluation of the 2,3-disubstituted-cyclopentanone approach to the synthesis of Nuphar piperidines, quinolizidines, and indolizidines, the following points should be made. First, the structural variation of the C-2 side chain has some minor influence on the degree of stereocontrol since the 2,3-disubstituted cyclopentanones leading to **2** and **3** contained slightly more of the undesired cis isomer than the similar cyclopentanone utilized in the synthesis of the piperidine alkaloid **1**. Noteworthy also in regard to stereocontrol is the preponderance of equatorial 3-furyl introduction when the sodium cyanoborohydride reduction is performed. Thus both steps controlling stereochemistry are working together to favor the formation of the all equatorially substituted ring A.

Second, good control of ring size can be achieved in forming the bicyclic systems by appropriately choosing the chain length and substitution pattern of the epoxide side chain. However, the method requires the degradative removal of carbon to obtain indolizidines free of substitution in the five-membered ring.

Third, it is the terminal step, the reaction of a lactam (in the case of **2** and **3**) or an *O*-methyl lactim (in the case of **1**) with 3-furyllithium which handicaps the cyclopentanone approach the most. In fact, the completion of the synthesis of **1** could not be achieved at all through the direct introduction of a 3-furyl group but required an indirect approach entailing four additional steps via the 3-furoyl route. However, the overall percentage yield for all of the additional steps amounted to 27%, which is virtually the same as the single low-yield step in which the syntheses of **2** and **3** are completed.

Experimental Section

Spectra were determined as follows: infrared (IR), neat and in $CDCl_3$, as indicated, on a Perkin-Elmer 137 spectrometer (s, m, w, and br refer to strong, medium, weak, and broad, respectively); ^1H nuclear magnetic resonance (NMR) spectra, samples in $CDCl_3$ solution in 5-mm tubes (1% Me_4Si at δ 0.00), on a Varian A60A operating at a radio frequency of 60.0 MHz or, as indicated otherwise , on a Varian XL-100-15 operating at a radio frequency of 100 MHz in the FT absorption mode and with the field-frequency lock established on $CDCl_3$ (m, s, d, t, q, q', and br refer to multiplet, singlet, doublet, triplet, quartet, quintet, and broad, respectively); fully ^1H noise and off-resonance decoupled ^{13}C NMR spectra, on an XL-100-15 operating in the FT absorption mode at 25.2 MHz, samples in $CDCl_3$ solution in 5-mm tubes, the $CDCl_3$ also furnishing the field-frequency lock and reference (77.2 ppm from Me_4Si at δ 0.0) signals; mass spectra, on a Hitachi Perkin-Elmer RMU6E with a chamber temperature of 200 °C and at 70 eV; combined gas–liquid chromatography/mass spectrometry (GC/MS), on a LBK 9000 equipped with columns A and C (see GC below) which were employed at conditions indicated elsewhere. High-resolution mass spectra were performed by the Cornell University Mass Spectrometry Center. Gas–liquid chromatography (GLC) was performed at the column temperature and flow rate or back-pressure indicated on the following columns: 200 cm × 2 mm glass column packed with 2.5% OV-17 on Chromosorb WHP (column A); 5 ft × 1/4 in. stainless-steel column packed with 3.0% OV-225 on Chromosorb GHP (column B); 6 ft × 1/4 in. glass column packed with 15.5% SE-30 on Chromosorb WHP (column C). Unless indicated otherwise, thin-layer chromatography (TLC) was performed on microscope slides coated uniformly with 250 μm of SiO_2 or Al_2O_3. Chromatograms were developed with the solvents indicated. Spots were visualized with I_2, ultraviolet radiation, or Dragendorff–Munier reagent. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Solvents were removed at reduced pressure on a rotary evaporator. Elemental analyses were performed by Galbraith Analytical Laboratories and the Analytical Department of Bristol Laboratories.

Methyl 7-Methyl-3-oxo-7-octenoate (10). To a suspension of 87.3 g of NaH (2.0 mol, 55% oil dispersion) in 1 L of dry ether under N_2 was added 180 g of dimethyl carbonate (2.0 mol). The resulting mixture was heated to reflux, and 126 g of 6-methyl-6-hepten-2-one (1.0 mol, BASF, West Germany) was added over 5 h to the heated mixture. The mixture was heated to reflux for another 2 h, cooled to 25 °C, and poured onto crushed ice containing 125 mL of acetic acid. The ether solution was separated, washed with dilute aqueous $NaHCO_3$, and dried ($MgSO_4$). Removal of the ether at reduced pressure left an oil which was distilled to give 120 g of **10**: 65%; bp. 97–98 °C (1.2 mm); IR (neat) 3180, 1650 and 890, 1850, 1720 cm^{-1}; ^1H NMR δ 4.72 (s, 2 H, C-8 H), 3.72 (s, 3 H, OCH_3), 3.45 (s, 2 H, C-2 H), 2.55 (t, 2 H, C-4 H), 2.23–1.82 (m, 4 H, C-5 and C-6 H), 1.72 (s, 3 H, CH_3); GLC (column A, 125 °C, flow rate 74 mL/min) R_t = 2.4 min. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.77. Found: C, 65.43; H, 8.90.

4-(Carbomethoxy)-9-decene-2,5-diones 11 and 12. To a stirred suspension of NaH in dioxane under N_2 was added dropwise the solution of the 3-oxo-7-octenoate in dioxane. The resulting mixture was stirred until no effervescence was observed. The mixture was cooled to −25 °C, and a solution of bromoacetone in dioxane was added with vigorous stirring. The mixture was heated to reflux for 30 min and cooled to 25 °C, and the solvent was removed. The yellow pasty mixture was poured onto crushed ice. The pH was adjusted to 4–6 with 25% aqueous H_2SO_4. The aqueous solution was extracted repeatedly with ether. The extracts were combined and dried ($MgSO_4$). Removal of the ether yielded crude **11** and **12** which were used in the next step without further purification due to their instability during distillation.

4-(Carbomethoxy)-9-decene-2,5-dione (**11**): yield 43.0 g (86%) from 5.8 g of NaH (0.24 mol), 38 g of methyl 3-oxo-7-octenoate, (**9**, prepared by the method of La Forge et al.[6]), and 0.26 mol of bromoacetone in 125, 60, and 50 mL, respectively, of dioxane; IR (neat) 3065, 1640 and 910, 1740, 1720 cm^{-1}; GLC (column B, 175 °C, back-pressure 16 psi) R_t = 5.4 min.

4-(Carbomethoxy)-9-methyl-9-decene-2,5-dione (**12**): yield 78.3 g (60%) from 13.0 g of NaH, 100 g of methyl 7-methyl-3-oxo-7-octenoate (**10**), and 74.33 g of bromoacetone (0.54 mol) in 250, 50, and 50 mL, respectively, of dioxane; IR (neat) 3065, 1640 and 910, 1740, 1720 cm^{-1}; GLC (column B, 175 °C, back-pressure 16 psi) R_t = 5.4 min.

2-(3-Alkenyl)-3-methyl-2-cyclopentenones 7 and 8. Solutions of the 4-(carbomethoxy)-9-decene-2,5-diones in 3% aqueous NaOH were stirred at 70 ± 2 °C for 3 h and thereafter cooled to 25 °C. The pH was adjusted to 4.0 with 25% aqueous H_8O_4, and the liberated ketone was extracted repeatedly with ether. The combined ether extracts were washed with brine and dried

($MgSO_4$). Removal of ether and distillation of the residue gave the cyclopentenones **7** and **8**.

2-(3-Butenyl)-3-methyl-2-cyclopentenone (**7**): yield 15.0 g (51%) from 42 g of **11** in 700 mL of NaOH; bp 77–78 °C (0.4 mm) [lit.[6] bp 115–118 °C (16 mm)]; IR (neat) 3065, 1640, 910, 1695, 1645 cm^{-1}; ^1H NMR δ 6.18–5.47 (m, 1 H, C-8 H), 5.07 (m, 1 H, C-9 H), 4.83 (m, 1 H, C-9 H), 3.55–2.15 (m, 8 H, C-4, C-5, C-6, and C-7 H), 2.05 (s, 3 H, CH_3); GLC (column B, 150 °C, back-pressure 14 psi) R_t = 2.8 min.

2-(3-Methyl-3-butenyl)-3-methyl-2-cyclopentenone (**8**): yield 32 g (62%) from 75 g of **12** in 1200 mL of NaOH; bp 77–78 °C (0.4 mm); IR (neat) 3165, 1650 and 885, 1695, 1645 cm^{-1}; ^1H NMR δ 4.60 (s, 2 H, C-9 H), 2.60–1.83 (m, 8 H, C-4, C-5, C-6 and C-7 H), 2.03 (s, 3 H, CH_3), 1.73 (s, 3 H, CH_3); GLC (column A, 125 °C, flow rate 74 mL/min) R_t = 2.1 min. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.32; H, 9.99.

***trans*-2-(3-Alkenyl)-3-methylcyclopentanones 5 and 6.** Solutions of the 3-methyl-2-(3-alkenyl)-2-cyclopentanones in 100 mL of ether were added to liquid NH_3 in a flask at −78 °C. Small pieces of lithium wire were added over a period of 3 min with vigorous stirring. The blue reaction mixture was stirred an additional 10 min. Solid NH_4Cl was added and vigorous stirring continued for 15 min, and to the resulting white slurry was added slowly 100 mL of water. The flask was removed from the cooling bath and kept at 35–40 °C until the bulk of the NH_3 had evaporated. The ether layer was separated, the aqueous layer was extracted repeatedly with ether, and the combined extracts and original ether were dried ($MgSO_4$). Removal of the ether and distillation gave the cyclopentenones **5** and **6**.

trans-2-(3-Butenyl)-3-methylcyclopentanone (**5**): yield 10.6 g (75%) from 14.0 g of **7**, 1 L of liquid NH_3, and 5.0 g of Li wire (0.705 mol); bp 65–66 °C (2.8 mm); IR (neat) 3065, 1640 and 910, 1740 cm^{-1}; ^1H NMR δ 6.20–5.47 (m, 1 H, C-8 H), 5.08 (m, 1 H, C-9 H), 4.86 (m, 1 H, C-9 H), 2.50–1.28 (m, 10 H, $(C)_3CH$, $(C)_2CH_2$), 1.15 (d, 3 H, CH_3); GLC (column A, 125 °C, back-pressure 14 psi) R_t(trans isomer) = 3.3 min, R_t (cis isomer) = 4.2 min. Anal. Calcd for $C_{10}H_{16}O$: C, 78.88; H, 10.61. Found: C, 78.79; H, 10.65.

trans-2-(3-Methyl-3-butenyl)-3-methylcyclopentanone (**6**): 7.35 g (73%) from 10 g of **8**, 800 mL of liquid NH_3, and 3.4 g of Li wire (0.24 mol); bp 62–63 °C (2.0 mm); IR (neat) 3080, 1650 and 890, 1740 cm^{-1}; ^1H NMR δ 4.70 (s, 2 H, C-9 H), 2.50–1.33 (m, 10 H, $(C)_3CH$, and $(C)_2CH_2$), 1.70 (s, 3 H, CH_3), 1.15 (d, 3 H, CH_3); GLC (column A, 100 °C, flow rate 15 mL/min) R_t (trans isomer) = 2.4 min, R_t (cis isomer) = 3.4 min. Anal. Calcd for $C_{11}H_{18}O$: C, 79.44; H, 10.98. Found: C, 79.60; H, 10.93.

2-Allylcyclopentanone (4). The title compound was prepared according to a published procedure:[5] bp 78–79 °C (22 mm); IR (neat) 1724 (s), 1634 (m), 990 (m), 9.17 cm^{-1} (s); ^1H NMR δ 4.8–5.3 (m, 2 H, C=CH_2), 5.4–6.2 (m, 1 H, CH=C).

2-(Carbomethoxy)-2-(4-pentenyl)cyclopentanone. A 56.9-g sample of freshly distilled 2-(carbomethoxy)cyclopentanone (0.4 mol; Aldrich Chemical Co.) was added under N_2 over a period of 45 min to a rapidly stirred mixture of 20.2 g of ether-washed 57% NaH (oil dispersion) in 600 mL of benzene. The resulting white paste was heated under N_2 to reflux for 14 h, thereafter 78.5 g of 1-iodo-4-pentene was added at reflux, and the resulting mixture was heated an additional 12 h. The mixture was cooled to 50 °C, and 300 mL of THF was distilled from NaH directly into the reaction mixture, which was heated an additional 4 days. The mixture was cooled, and the pH was adjusted to 2 with 10% aqueous HCl. The organic layer was diluted with 200 mL of ether, washed successively with water, aqueous 5% $NaHCO_3$, water, and brine, and dried over $MgSO_4$. Removal of the solvents gave 91 g of a pale yellow oil which when distilled afforded 52 g of the title compound: bp (0.05 mm) 78–82 °C; IR ($CHCl_3$) 1754 (s), 1724 (s), 1639 cm^{-1} (m); ^1H NMR δ 2.0 (m, 2 H, CH_2CO), 3.60 (s, 3 H, $COOCH_3$), 5.0 (m, 2 H, C=CH_2), 5.7 (m, 1 h, C=CH).

2-(4-Pentenyl)cyclopentanone (13). A solution of 21 g of KOH in 190 mL of water was added slowly to a solution of 50 g of 2-(carbomethoxy)-2-(4-pentenyl)cyclopentanone (0.24 mol) in 150 mL of EtOH heated to reflux. Additional EtOH was added from time to time to dissolve the precipitate that formed. The solution was heated for 4 h, cooled to 25 °C, and stirred rapidly, and 50% H_2SO_4 was added slowly to pH 2. After the foaming subsided, the mixture was extracted with ether (4 × 50 mL). The combined organic extracts were washed successively with water, saturated aqueous $NaHCO_3$, and brine and dried over $MgSO_4$. The solvents were removed and the residual oil was distilled through a long glass column at atmospheric pressure to obtain 17 g of **13**: bp 223–228 °C; IR ($CDCl_3$) 1724 (s), 1639 (w), 910 cm^{-1} (m); ^1H NMR δ 5.0 (m, 2 H, C=CH_2), 5.7 (m, 1 H, C=CH). Anal. Calcd for $C_{10}H_{16}O$: C, 76.92; H, 10.53. Found: C,77.08; H, 10.42.

Cyclopentanone oximes 14–17. A solution of H_2NOH·HCl in EtOH–water (1:1) was added to a solution of the cyclopentanone in dry pyridine. The mixture was heated to reflux for 15–30 min and cooled to 25 °C, and the reaction flask was evacuated at 60 °C to form an oil which was extracted repeatedly with small portions of ether. The combined ether extract was dried ($MgSO_4$), and the ether was removed to give an oil which was distilled.

2-Allylcyclopentanone oxime (**14**): yield 6.77 g (75%) from 8.06 g of 2-allylcyclopentanone (**4**) in 20 mL of pyridine and 5 g of H_2NOH·HCl in 20 mL of solvent; bp 83–85 °C (1.0 mm); IR (neat) 3448 (s, br), 1669 (w), 1637 cm^{-1} (w); ^1H NMR δ 4.8–5.3 (m, 2 H, C=CH_2), 5.5–6.2 (m, 1 H, CH=C), 9.00 (br s, 1 H, NOH). Anal. Calcd for $C_8H_{13}NO$: C, 69.06; H, 9.35; N, 10.07. Found: C, 69.24; H, 9.41; N, 10.11.

2-(4-Pentenyl)cyclopentanone oxime (**17**): yield 11 g (77%) from 13 g of 2-(4-pentenyl)cyclopentanone (**13**) in 22 mL of pyridine and 6.5 g of H_2NOH·HCl in 12 mL of solvent; bp 92–94 °C (0.15 mm); IR (neat) 3279 (br s), 1666 (w), 1631 (w), 910 cm^{-1} (s); ^1H NMR δ 4.8–5.3 (m, 2 H, C=CH_2), 5.4–6.3 (m, 1 H, CH=C), 9.13 (br s, 1 H, NOH). Anal. Calcd for $C_{10}H_{17}NO$: C, 71.86; H, 10.18; N, 8.38. Found: C, 71.91; H, 10.01; N, 8.46.

trans-2-(3-Butenyl)-3-methylcyclopentanone oxime (**15**): yield 10.7 g (98%) from 10 g of **5** in 20 mL of pyridine and 5 g of H_2NOH·HCl in 10 mL of solvent; bp 91–92 °C (0.2 mm); IR (neat) 3280, 3065, 1640, 910 cm^{-1}; ^1H NMR δ 6.20–5.45 (m, 1 H, C-8 H), 5.08 (m, 1 H, C-9 H), 4.86 (m, 1 H, C-9 H), 2.80–1.16 (m, 10 H, $(C)_3CH$, $(C)_2CH_2$), 1.03 (d, 3 H, CH_3); GLC (column B, 150 °C, back-pressure 15 psi) R_t (trans isomer) = 3.0 min, R_t (cis isomer) = 3.4 min. Anal. Calcd for $C_{10}H_{17}NO$: C, 71.80; H, 10.26; N, 8.38. Found: C, 71.85; H, 10.30; N, 8.29.

trans-2-(3-Methyl-3-butenyl)-3-methylcyclopentanone oxime (**16**): yield 5.35 g (98%) from 5 g of **6** in 10 mL of pyridine and 2.5 g of H_2NOH·HCl in 10 mL of solvent; bp 94–95 °C (0.2 mm); IR (neat) 3200, 3060, 880, 1650; ^1H NMR δ 4.70 (s, 2 H, C-9 H), 2.83–1.20 (m, 10 H, $(C)_3CH$, $(C)_2CH_2$), 1.70 (s, 3 H, CH_3); GLC (column A, 125 °C, flow rate 74 mL/min) R_t (trans isomer) = 2.5 min, R_t (cis isomer) = 3.0 min. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.86; H, 10.58; N, 7.72. Found: C, 72.75; H, 10.65; N, 7.76.

6-Alkenyl-2-piperidones 19–21. A quantity of PCl_5 was added to the oxime in ether, and the resulting slurry was stirred at the temperature and for the period indicated below. The cold reaction mixture was poured onto crushed ice in 10 N NaOH. The mixture was stirred, the phases were separated, and the aqueous phase was extracted repeatedly with CH_2Cl_2. The combined extracts were dried ($MgSO_4$), and the solvent was removed at reduced pressure to give an oil which was purified.

6-(4-Pentenyl)-2-piperidone (**21**; yield 4.5 g 45%) was obtained as follows: 15.4 g of PCl_5 and 10 g of oxime **17** in 1 L of ether were stirred at −5 °C for 2 h and at 25 °C for 12 h, and the CH_2Cl_2 solution was poured into 200 mL of 10 N NaOH–ice. Purification was accomplished by chromatography on SiO_2 (activity 1) with elution first with 1.2 L of hexane–ether (80:20) and then with hexane–ether–CH_3OH until TLC showed no further elution of the piperidone. The latter solvent yielded **21**: IR ($CDCl_3$) 3030 (w), 1667 (s), 910 cm^{-1} (s); ^1H NMR δ 1.0–2.5 (5 H, CH_2), 3.1–3.6 (m, 1 H, C-6 H), 4.8–5.2 (m, 2 H, C=CH_2), 5.2–6.3 (m, 1 H, C=CH), 6.8 (br s, 1 H, NH); mass spectrum, *m/e* (relative intensity) 167 (5, M^+), 124 (30), 111 (30), 99 (31), 98 (100), 55 (82). Anal. Calcd for $C_{10}H_{17}NO$: C, 71.86; H, 10.18; N, 8.38. Found: C, 71.74; H, 10.34; N, 8.36.

trans-6-(3-Butenyl)-5-methyl-2-piperidone (**19**; yield 5.7 g, 60%) was obtained as follows: 14.2 g of PCl_5 and 9.5 g of oxime **15** in 600 mL of ether were stirred at 25 °C for 20 h and the CH_2Cl_2 solution was poured into 100 mL of 10 N NaOH–ice. Purification by sublimation gave **19**: mp 30–31 °C; IR (neat) 3005 and 910, 1645; ^1H NMR δ 6.66 (br, 1 H, NH), 6.23–5.48 (m, 1 H, >C=C-(9)H), 5.11 (m, 1 H, C=C(10)H), 4.88 (m, 1 H, C=C(10)H), 3.5–2.8 (m, 1 H, C-6 H), 3.53–1.20 (m, 9 H, $(C)_3CH$, $(C)_2CH_2$), 1.03 (d,

3 H, CH_3); GLC (column B, 175 °C, back-pressure 18 psi) R_t = 7.6 min. Anal. Calcd for $C_{10}H_{17}NO$: C, 71.80; H, 10.26; N, 8.38. Found: C, 71.86; H, 10.31; N, 8.40.

trans-6-(3-Methyl-3-butenyl)-5-methyl-2-piperidone (**20**; yield 3.4 g, 68%) was obtained as follows: 10.0 g of PCl_5 and 5.0 g of oxime **16** in 400 mL of ether were stirred at −78 °C for 1 h, and the CH_2Cl_2 solution was poured into 100 mL of 10 N NaOH–ice. Purification by chromatography on SiO_2 (grade 62), eluting with hexane–ether–methanol (5:4:1), gave **20**: IR (neat) 3060 and 880, 1650 cm^{-1}; ^1H NMR δ 6.33 (s, 1 H, NH), 4.73 (s, 2 H, >C=CH_2), 3.13 (m, 1 H, C-6 H), 2.67–1.73 (s, 3 H, CH_3), 1.17 (m, 9 H, $(C)_3CH$, $(C)_2CH_2$), 1.03 (d, 3 H, CH_3); GLC (column C, 180 °C, flow rate 30 mL/min) R_t (trans isomer) = 13.0 min, R_t (cis isomer) = 11.8 min; TLC (Brinkman Polygram precoated Sil G/UV 254, 250 μm; hexane–ether–MeOH, 5:4:1) R_f 0.0196. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.86; H, 10.58; N, 7.72. Found: C, 72.90; H, 10.65; N, 7.68.

6-Allyl-2-piperidone (18). To 5 g of oxime **14** in 20 mL of dry pyridine at 0 °C and under N_2 was added 7.59 g of *p*-TsCl. After the resulting solution was stirred at 0 °C for 1 h, the temperature was allowed to rise to 25 °C and was held there for 15 h. Thereafter the solution was diluted with 300 mL of $CHCl_3$ and extracted with 2 N HCl (3 × 25 mL). The aqueous layers were combined and extracted with $CHCl_3$ (2 × 50 mL). The combined $CHCl_3$ extracts were dried (Na_2SO_4). Removal of the $CHCl_3$ gave 5 g of brown oil, which was chromatographed on SiO_2 (10% H_2O) by elution with $CHCl_3$ in three successive 100-mL fractions and one final 500-mL fraction. The second and third fractions combined yielded 1 g of colored **18** while the last fraction yielded 2.52 g of clear **18**: IR ($CHCl_3$) 3424 (w), 1623 (s), 926 cm^{-1} (s); ^1H NMR δ 1.0–3.0 (9 H, CH_2 and CH_3), 3.2–3.7 (m, 1 H, C-6 H), 4.9–5.4 (m, 2 H, C=CH_2), 5.5–6.4 (m, 1 H, C=CH), 6.8 (br s, 1 H, NH). Anal. Calcd for $C_8H_{13}NO$: C, 69.06; H, 9.35; N, 10.07. Found: C, 69.29; H, 9.18; N, 10.01.

6-(Epoxyalkyl)-2-piperidones 22–25. To a solution of the 6-alkenyl-2-piperidone in CH_2Cl_2 was added *m*-chloroperbenzoic acid (mcpba) (85%) in small portions over 5–10 min. The mixture was stirred at 25 °C for 1–3 days. The mixture was filtered to remove insoluble mcba. The filtrate was first washed two or three times with portions of 10% aqueous sodium sulfite and then with portions of 10% aqueous sodium bicarbonate. The CH_2Cl_2 solution was dried ($MgSO_4$). Removal of the CH_2Cl_2 at reduced pressure yielded epoxides which were used in the next step without further purification.

6-(2,3-Epoxypropyl)-2-piperidone (**22**): yield 1.6 g (55%) from 5 g of mcpba and 2.52 g of piperidone **18** in 20 mL of CH_2Cl_2; IR ($CHCl_3$) 3436 (m), 1647 (s), 1259 cm^{-1} (m); ^1H NMR δ 1.1–2.7 (9 H), 2.77 (t, $J \approx 4$ Hz, 1 H, epoxide CC(O)H), 3.05 (m, 1 H, epoxide CC(O)(C)H), 3.52 (m, 1 H, CONCH), 7.58 (br d, 1 H, $J \approx 10$ Hz, CONH, disappears on addition of D_2O).

6-(4,5-Epoxypentyl)-2-piperidone (**25**): yield 1.55 g (50%) from 3.25 g of mcpba and 1.8 g of piperidone **21** in 25 mL of CH_2Cl_2; IR ($CDCl_3$) 3030 (w), 1639 (s), 1250 cm^{-1} (m); ^{1} H NMR δ 2.47 (dd, J = 5, 2.5 Hz, 1 H, epoxide CC(O)H), 2.73 (t, J = 6 Hz, 1 H, epoxide CC(O)H), 2.92 (m, 1 H, epoxide CC(O)(C)H), 6.89 (m, 1 H, CONH).

trans-6-(3,4-Epoxybutyl)-5-methyl-2-piperidone (**23**): yield 700 mg (64%) from 1.82 g mcpba and 1.0 g of piperidone **19** in 15 mL of CH_2Cl_2; IR (neat) 3200, 3020, 1650, 1280, 835 cm^{-1}; ^1H NMR δ 6.88 (br, 1 H, NH), 3.33–1.16 (m, 13 H, $(C)_3CH$, $(C)_2CH_2$), 1.05 (d, 3 H, CH_3).

trans-6-(3-Methyl-3,4-epoxybutyl)-5-methyl-2-piperidone (**24**): yield 1.09 g (65%) from 2.06 g of mcpba and 1.55 g of piperidone **20** in 25 mL of CH_2Cl_2; IR (neat) 3020, 1645, 845, 790 cm^{-1}; ^1H NMR δ 6.98 (br s, 1 H, NH), 9325–1.33 (m, 12 H, $(C)_3CH$, $(C)_2CH_2$), 1.25 (s, 3 H, CH_3), 0.95 (br, 3 H, CH_3).

Attempted Conversion of 6-(2,3-Epoxypropyl)-2-piperidone (22) to Bicyclic Lactams. A stirred 0.02 M solution of 159 mg of **22** in 50 mL of dry benzene was treated under N_2 with 37 mg of NaH for 60 h at 25 °C and for 0.5 h at 80 °C. A 1.54-mL quantity of aqueous HCl was added to bring the pH to 1. The benzene layer was separated, and the aqueous layer was extracted with 5 mL of $CHCl_3$. The combined organic layers were dried (Na_2SO_4). Removal of the solvent yielded 130 mg of brown residue, 90 mg of which was chromatographed on a column of Al_2O_3 (activity 3) with the following: $CHCl_3$ (50 and 25 mL successively, fractions 1 and 2), 6% EtOH in $CHCl_3$ (10, 5, and 25 mL successively, fractions 3, 4, and 5), 20% EtOH in $CHCl_3$ (50 mL, fraction 6). All fractions were analyzed by mass spectroscopy. The spectra of all fractions showed the presence of high-molecular-weight (m/e >155) material, but only the mass spectrum of impure fraction 4 (8.5 mg, 6.5%) revealed an indication of bicyclic lactam presence by exhibiting peaks at m/e 155, 138, 137, and 124, which would result from an indolizidone formed in the endocyclic mode. When ring closure was attempted at higher concentrations, relatively greater amounts of high molecular weight material were formed.

Conversion of Piperidone 25 to 28 and 29. To a stirred mixture of 1.38 g of NaH (57% oil dispersion, 0.0327 mol) and 85 mL of benzene under N_2 was added slowly 1.0 g of piperidone **25** (0.00545 mol) in 20 mL of benzene. After 1 h, when the foaming had subsided, the mixture was refluxed at 90 °C for 30 h. The mixture was cooled at 0 °C, about 5 mL of water was added slowly, and then 25% aqueous H_2SO_4 was added until the pH was 2–3. The organic layer was separated, and the water layer was extracted with $CHCl_3$ (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$), and the solvents were removed. The residue was chromatographed on SiO_2 with hexane until TLC indicated that the eluant contained no solute and then with hexane–ether–methanol (60:30:10) until TLC showed no solute in the eluant. From the latter solvent system was obtained 500 mg of oil of which 164 mg was chromatographed on Al_2O_3 (activity 2) with 300 mL of $CHCl_3$–ethyl acetate (8:2), at which point no solute remained in the eluant. The 55 mg of product obtained was rechromatographed on SiO_2 with acetone: 50 mL (F1, 0 mg), 50 drops (F2, 0 mg), 26 samples of 10 drops (F3, combined 40 mg), 15 samples of 10 drops (F4, combined 2.4 mg), 20 samples of 0.5 mL (F5, combined 13.8 mg). F3 was **29**: IR ($CHCl_3$) 3448 (s and sharp), 1613 cm^{-1} (s); ^1H NMR (100 MHz) δ 2.38 (m, 2 H, CH_2CON), 2.97 (dd, ABX, J = 15, 2 Hz, 1 H, NCHCOH), 3.5 (7, 1 H, NCH), 4.02 (m, 1 H, NCCHOH), 4.47 (dd, ABX, J = 15, 2 Hz, 1 H, NCHCOH); ^{13}C NMR δ 18.2 (t), 19.2 (t), 29.0 (t), 31.3 (t), 36.0 (t), 36.3 (t), 52.5 (t), 59.2 (d), 70.4 (d), 173.4 (s); mass spectrum, m/e (relative intensity) 183 (53, M^+), 165 (23), 154 (63), 152 (4), 140 (32), 126 (30), 113 (91), 112 (100), 98 (54), 83 (33).

The residue from F5 was dissolved in $CHCl_3$ and passed through Al_2O_3. Removal of the $CHCl_3$ gave 11.5 mg of oily quinolizidone **28**: IR ($CHCl_3$) 3390 (w, br, bonded OH), 1613 cm^{-1} (s); ^1H NMR (100 MHz) δ 2.39 (m, 2 H, CHCON), 3.39 (m, 1 H, NCH), 3.64 (dd, ABX, J = 15, 7 Hz, 2 H, CH_2OH), 4.69 (s, 1 H, OH), 5.44 (m, 1 H, NCH, X of ABX); ^1C NMR δ 19.2 (t), 19.4 (t), 25.3 (t), 31.1 (t), 33.3 (t), 34.0 (t), 47.0 (d), 52.7 (d), 65.7 (t), 170.0 (s); mass spectrum, m/e (relative intensity) 183 (5, M^+), 165 (10), 152 (100), 138 (21), 124 (16), 98 (16), 83 (21).

***trans*-1-Methyl-6-(hydroxymethyl)-4-indolizidone (27).** To a suspension of 0.4 g of ground NaH (0.016 mol) in 30 mL of dry benzene under N_2 was added 0.6 g of epoxypiperidone **23** in 10 mL of benzene. The heterogeneous mixture was refluxed for 14 h, cooled to 25 °C, and poured onto crushed ice. The pH of the mixture was adjusted to 4.0 with 25% aqueous H_2SO_4. The benzene solution was separated, and the aqueous phase was extracted repeatedly with CH_2Cl_2. Benzene and CH_2Cl_2 extracts were combined, the resulting solution was dried ($MgSO_4$), and the solvent was removed to give an oil which was chromatographed on SiO_2 (grade 62) by using ether–methanol (10:1) to give 0.41 g of **27** (69%): IR (neat) 3320, 1620 cm^{-1}; ^1H NMR δ 5.60 (br, 1 H, OH), 4.26 (br, 1 H, C-9 H), 3.66 (m, 2 H, CH_2OH), 3.10 (br, 1 H, C-6 H), 2.66–1.16 (m, 9 H, $(C)_3CH$, $(C)_2CH_2$), 1.05 (br, 3 H CH_3); mass spectrum, m/e (relative intensity) 183 (10, M^+), 153 (50), 152 (100), 124 (51), 82 (22), 68 (38), 55 (33); GLC (column A, 150 °C, flow rate 40 mL/min) R_t (major isomer) = 9.2 min, R_t (second isomer) = 10.0 min; TLC (Brinkmann Polygram precoated Sil G/UC 254, 250 μm; ether–methanol, 5:1) R_f 0.41. Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.53; H, 9.37; N, 7.64. Found: C, 65.60; H, 9.40; N, 7.60.

***trans*-1-Methyl-7-methyl-7-hydroxy-4-quinolizidone (26).** To a suspension of 0.5 g of ground NaH (0.02 mol) in 25 mL of dry benzene under N_2 was added 1.0 g of epoxypiperidone **24** (0.005 mol) in 15 mL of benzene. The heterogeneous mixture was refluxed for 14 h, cooled to 25 °C, and poured onto crushed ice. The pH of the mixture was adjusted to 4.0 with 25% aqueous H_2SO_4. The benzene layer was separated, and the aqueous phase was extracted repeatedly with CH_2Cl_2. The benzene and CH_2Cl_2

extracts were combined, the resulting solution was dried ($MgSO_4$), and the solvent was removed at reduced pressure to obtain an oil which was chromatographed on SiO_2 (grade 62) by using hexane–ether–methanol (4:4:1) to obtain 0.76 g of **26**: 70%; IR (neat) 3400, 1620 cm^{-1}; ^1H NMR δ 4.68 (1 H, d, C-10 H), 3.50–1.33 (12 H, m, $(C)_3CH$, $(C)_2CH_2$, OH), 1.25 (3 H, s, CH_3), 1.0 (3 H, br, CH_3); mass spectrum, m/e (relative intensity) 197 (28, M^+), 154 (20), 127 (65), 126 (100), 112 (35), 70 (30), 55 (56); GLC (column A, flow rate 55 mL/min) R_t of isomers = 4.85 (29%), 5.2 (5%), 6.8 (56%), 8.1 min (10%); TLC (Brinkmann Polygram precoated Sil G/UV 254, 250 μm; hexane–ether–MeOH, 5:4:1) R_f 0.25. Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.95; H, 9.72; N, 7.10. Found: C, 66.90; H, 9.80; N, 7.15.

Nupharolutine (2a) and 7-Epinupharolutine (2b). To a solution of 1.55 g of *n*-butyllithium (0.024 mol) in 9.7 mL of hexane at −78 °C was added dropwise with stirring a solution of 3.19 g of 3-bromofuran (0.024 mol) in 40 mL of dry ether over 30 min, and stirring was continued for 30 min. To this solution was added a solution of 600 mg of quinolizidone 26 (0.003 mol) in 10 mL of ether. The mixture was stirred at −78 °C for 4 h and at 25 °C overnight. The solvent was removed and the residue was taken up in 50 mL of CH_2Cl_2. The mixture was poured onto crushed ice containing 10 mL of 25% H_2SO_4. The aqueous layer was separated and washed with 25 mL of CH_2Cl_2. The aqueous layer was cooled, was made basic with addition of potassium carbonate, and was extracted repeatedly with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried ($MgSO_4$), and the solvent was removed to obtain a residue which was dissolved in 20 mL of absolute ethanol. The resulting solution was stirred with 300 mg of $NaBH_4$ under N_2 for 6 h at 25 °C. The solvent was removed, the residue was dissolved in 25 mL of CH_2Cl_2, 5 mL of H_2O was added, the two phase system was stirred for 10 min, the phases were separated, the aqueous phase was extracted repeatedly with CH_2Cl_2, and all CH_2Cl_2 solutions were combined and dried ($MgSO_4$). Removal of the CH_2Cl_2 afforded 450 mg of an oil of which an 83-mg sample was chromatographed repeatedly on columns of SiO_2 (10% H_2O) and Al_2O_3 to give 1 mg of nupharolutine (**2a**) and 9.4 mg of 7-epinupharolutine (**2b**).

Indolizidonecarboxylic Acid 30 and Methyl Ester 31. A solution of 94 mg of (hydroxymethylene)indolizidone **27** (0.51 mmol) in 10 mL of acetone was cooled to 5–10 °C, and 3.5 mL of 2.68 M CrO_3 in H_2SO_4–water (Jones reagent) was added over 2.5 h. Thereafter, 5 drops of CH_3OH were added to destroy excess chromic acid, the solvents were evaporated at 40 °C, and to the residue was added 5 mL of water. The resulting mixture was extracted continuously with ether for 24 h, the solvent was removed, the residue was dissolved in acetone, and the solution was treated with 250 mg of $NaHCO_3$. The acetone was removed, and to the residue was added 10 mL of water. The mixture was extracted continuously for 1 h. The ether solution was dried (Na_2SO_4), and the solvent was removed to give 23 mg of neutral material.

The aqueous solution remaining was acidified with 5 mL of 1 N HCl, and the resulting solution was extracted continuously with ether for 24 h. Removal of the ether afforded 70 mg of crystalline solid **30**: 69%; mp 161–180 °C; IR ($CHCl_3$) 2703–2222 (m), 1724 (s), 1608 cm^{-1} (s); ^1H NMR 1.05 (m, 3 H), 8.4 (br s, 1.4 H).

An ethereal solution of 21 mg of indolizidonecarboxylic acid **30** was treated with CH_2N_2 in ether until a yellow color persisted. Removal of the slight excess of CH_2N_2 and ether gave 26 mg of colorless oil which was chromatographed on a column of SiO_2 with 50 mL of $CHCl_3$, giving fraction 1, and five 0.5-mL portions of $CHCl_3$–acetone (94:6), giving fractions 2–6. Fractions 2–6 were combined to give 14 mg of methyl ester **31**: TLC (SiO_2; $CHCl_3$–acetone, 9:1) R_f 0.3; IR ($CHCl_3$) 1748 (s), 1631 cm^{-1} (s); ^1H NMR δ 1.08 (CH_3CH, m, 3 H), 3.77 and 3.78 ($COOCH_3$, 2 s, 3 H). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.35; H, 7.94; N, 6.65.

Acetoxyindolizidone 32 and Enamide 33. A 54-mg sample of indolizidonecarboxylic acid **30** (0.27 mmol), 11.6 mg of $Cu(OAc)_2 \cdot H_2O$ (0.056 mmol), and 14 mg of C_5H_5N (0.17 mmol) in 5 mL of dry benzene were stirred under N_2, and to the resulting mixture was added 526 mg of $Pb(OAc)_5$ (1.19 mmol). After being stirred at 25 °C, the mixture was refluxed for 1 h. The mixture was cooled at 25 °C, 10 mL of saturated aqueous $NaHCO_3$ was added, the aqueous mixture was extracted with $CHCl_3$ (4 × 10 mL), the $CHCl_3$ solution was dried (Na_2SO_4), and the solvent was removed to give 51 mg of a light brown oil: TLC (SiO_2–acetone) R_f 0.61 (UV and I_2 active), R_f 0.47 (I_2 active) (compared to indolizidonecarboxylic acid **30**, R_f 0.36); ^1H NMR δ 6.7 (m, 0.4 H), 2.08 (2 s, 3 H).

Indolizidone 34. A solution of 51 mg of acetoxyindolizidone **32** and enamide **33** in 0.3 mL of MeOH was put under N_2, acidified to an initial pH of 3 with 2 N aqueous HCl, treated portionwise with a total of 100 mg of $NaCNBH_3$ at 25 °C, and then allowed to stand at 25 °C for 14 h, during which time the pH was periodically adjusted to 2–3. The MeOH was removed, 10 mL of water was added to the residue, the mixture was extracted with $CHCl_3$ (4 × 10 mL), and the organic extract was dried (Na_2SO_4). The solvent was removed to obtain 48 mg of light brown oil: TLC (SiO_2; $CHCl_3$–acetone, 9:1) R_f 0.88 (UV and I_2 active).

The 48-mg mixture was dissolved in 5 mL of MeOH, 10 mg of 10% Pd/C was added, and the mixture was shaken under 1 atm of H_2 at 25 °C for 1 h. Removal of the 10% Pd/C by filtration and the solvent by evaporation left 46 mg of crystalline solid which was chromatographed on a column of Al_2O_3 (activity 2) by elution with $CHCl_3$–acetone (95:5) in 25-, 35-, 10-, 1-, and 30-mL fractions. The 10- and 1-mL fractions contained 22.7 and 6.2 mg of pure indolizidone **34**, respectively, and were combined. The 35-mL fraction contained 10.7 mg of product which in MeOH at pH 2 was treated again with $NaCNBH_3$. Elution chromatography (Al_2O_3, activity 2) with $CHCl_3$–acetone (95:5) produced an additional 8.5 mg which was combined with the 22.7- and 6.2-mg portions, thus giving a total of 37.4 mg of indolizidone **34** (88%): TLC (Si_2O_3; $CHCl_3$–acetone, 9:1) R_f 0.44; IR ($CHCl_3$) 2941–2857 (m), 1618 (s), 1460 cm^{-1} (m); ^1H NMR (100 MHz) δ 3.50 (m, 2 H, CH_2N), 2.98 (m, 1 H, CHN), 1.02 (d, J = 6 Hz, 2 H, CH_3CH); high-resolution mass spectrum calcd for $C_9H_{15}NO$, m/e 153.1152; found, m/e 153.1154.

Nuphar Indolizidine 3. A solution of 3-furyllithium in ether–hexane was prepared by adding under N_2 0.06 mL of commercial 1.6 M butyllithium in hexane to 170 mg of 3-bromofuran in 1 mL of anhydrous ether at −40 °C and stirring the resulting mixture for 1 h. To this solution at −40 °C was added with vigorous stirring a solution of 36 mg of indolizidone **34** in 0.5 mL of anhydrous ether. The resulting mixture was allowed to stand at −40 °C for 3 h and at 5 °C for 14 h, at the end of which time 1 mmol of 2 N HCl was added at 0 °C. The solid obtained was dissolved in 2 mL of MeOH, the pH was adjusted to 2 with 2 N HCl, and 50 mg of $NaCNBH_3$ was added. The pH was periodically lowered to 2–3 with 2 N HCl over 2 h while the reduction was allowed to proceed at 25 °C. A second 50-mg portion of $NaCNBH_3$ was added, and the pH again was maintained at 2–3 for a period of 2 h. Thereafter, the MeOH was removed, the residue was shaken with 10 mL of water and 10 mL of $CHCl_3$, the aqueous layer was extracted repeatedly with 10-mL portions of $CHCl_3$, and the combined $CHCl_3$ solution was dried (Na_2SO_4). Removal of $CHCl_3$ yielded 38 mg of dark brown oil whose TLC (SiO_2; $CHCl_3$–acetone, 95:5) indicated nearly equal amounts of a mobile component (R_f 0.8) and origin material, which was removed by filtering a CH_2Cl_2 solution of the 38 mg of oil through a 1-cm column of Al_2O_3 and thereafter rinsing the latter with 25 mL of CH_2Cl_2. The CH_2Cl_2 was removed to obtain 15 mg of yellow oil which was chromatographed on Al_2O_3 with hexane–ether (94:6) in four 1-mL fractions (1–4), one 2-mL fraction (5), and one 1-mL fraction (6). Fractions 3, 4, and 6 each yielded 1 mg of impure material while fraction 5 yielded 7.9 mg of indolizidine **3**: TLC (Al_2O_3; $CHCl_3$–acetone, 95:5) R_f 0.8; IR ($CHCl_3$) 2932 (s), 2778 (m, Bohlmann band), 866 cm^{-1} (s, 3-furyl); mass spectrum, m/e (relative intensity) 205 (26, M^+), 195 (10), 176 (9), 162 (12), 150 (7), 149 (8), 148 (8), 136 (22), 121 (11), 108 (8), 107 (7), 94 (100), 81 (15), 70 (35); ^1H NMR (100 Hz) δ 0.89 (d, J = 6 Hz, 3 H, CH_3CH), 3.52 (dd, J = 8.0, 6.0 Hz, 1 H, 3-furyl CHN), 6.45 (m, 1 H, β 3-furyl H), 7.36 (m, 2 H, α 3-furyl H); ^{13}C NMR 18.2 (q), 20.2 (t), 29.2 (t), 34.1 (t), 34.4 (t), 36.5 (d), 53.3 (t), 60.0 (d), 71.6 (d), 139.7 (d), 143.1 (d); high-resolution mass spectrum calcd for $C_{13}H_{19}NO$, m/e 205.1457; found, m/e 205.1467.

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Registry No. 2a, 73789-08-9; **2b**, 73789-09-0; **3**, 74282-88-5; **4**, 55038-60-3; *cis*-**5**, 74282-89-6; *trans*-**5**, 74282-90-9; *cis*-**6**, 74282-91-0; *trans*-**6**, 74282-92-1; **7**, 60924-91-6; **8**, 4868-25-1; **9**, 71203-69-5; **10**, 71203-75-3; **11**, 74282-93-2; **12**, 74282-94-3; **13**, 42988-47-6; **14**, 74282-95-4; *cis*-**15**, 74282-96-5; *trans*-**15**, 74282-97-6; *cis*-**16**, 74282-98-7; *trans*-**16**, 74282-99-8; **17**, 74283-00-4; **18**, 74283-01-5; **19**, 74298-03-6; *cis*-**20**, 74283-02-6; *trans*-**20**, 74283-03-7; **21**, 74283-04-8; **22**, 74298-04-7; **23**, 74283-05-9; **24**, 74283-06-0; **25**, 74283-07-1; **26** isomer 1, 74283-08-2; **26** isomer 2, 74283-09-3; **27** isomer 1, 74283-10-6; **27** isomer 2, 74311-05-0; **28**, 74283-11-7; **29**, 74283-12-8; **30**, 74283-13-9; **31**, 74283-14-0; **32**, 74283-15-1; **33**, 74283-16-2; **34**, 74283-17-3; dimethyl carbonate, 616-38-6; 6-methyl-6-hepten-2-one, 10408-15-8; bromoacetone, 598-31-2; 2-(carbomethoxy)-2-(4-pentenyl)cyclopentanone, 74283-18-4; 2-(carbomethoxy)cyclopentanone, 53229-93-9; 1-iodo-4-pentene, 7766-48-5; 3-bromofuran, 22037-28-1.

Hindered Amines. Synthesis of Hindered Acyclic α-Aminoacetamides[1]

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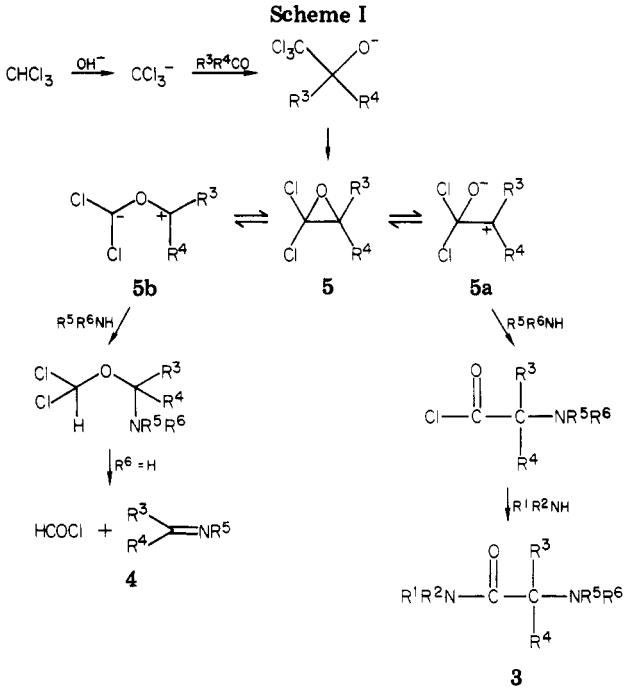
Hindered amines and their nitroxyl radicals are useful in spin-label studies as nonnucleophilic bases and as stabilizers for polymers against UV degradation. Hindered acyclic α-aminoacetamides (**3**, R^5 = aryl, *tert*-butyl; R^6 = H) can be synthesized from amines, ketones, and chloroform with 50% sodium hydroxide solution in phase-transfer-catalyzed reactions. Nucleophilic secondary amines will undergo the same reactions while bulky ones fail. Mixed **3** can be prepared from different amines according to their nucleophilicities. 1,1-Dialkyl-2,2-dichlorooxirane (**5**) is believed to be the reactive intermediate. Imines are sometimes formed as byproducts through the opening of a carbon–carbon bond in the oxirane ring by amines. Thus, *tert*-butylcyclohexylamine (**7**) is obtained in 62% yield after hydrogenation of the crude imine from *tert*-butylamine, cyclohexanone, and chloroform.

Hindered amines are versatile compounds. Their lithio salts attract considerable synthetic interest as strong and nonnucleophilic bases.[2] Their nitroxyl radicals have been used extensively as spin labels in biological studies.[3] Their *N*-chloro derivatives regioselectively chlorinate alkanes at the 2-position in acidic media.[4] Industrially, hindered amines are able to prolong polymer life against UV light.[5] We described[1a] a novel synthesis of 1,3,3,5,5-pentasubstituted 2-piperazinones from N^1,2,2-trisubstituted 1,2-ethanediamines, chloroform, and ketones in phase-transfer-catalyzed (PTC) reactions.[6] We now report the synthesis of several types of acylic hindered amines (**3**) by extending these reactions to monoamines (**1** and **2**), chloroform, and ketones under similar conditions.

$$\underset{\mathbf{1}}{R^1R^2NH} + CHCl_3 + R^3R^4CO + \underset{\mathbf{2}}{R^5R^6NH} \xrightarrow[NaOH]{PTC} \underset{\mathbf{3}}{R^1R^2NC(O)CR^3R^4NR^5R^6}$$

When aniline and its para-substituted derivatives (**1**, **2** = substituted anilines) are subjected to these reaction conditions, α-anilinoacetanilide derivatives[7] (**3a–e**) are formed in generally good yields. However, when *o*-toluidine or ketones other than acetone are used, a large amount of Schiff bases[8] (**4f–h**) is observed in addition to

Scheme I



(1) (a) Part 2 of a series; for part 1, see: Lai, J. T. *J. Org. Chem.* **1980**, *45*, 754. (b) Presented in part at the 179th American Chemical Society National Meeting, Phase Transfer Catalysis Symposium, Houston, TX, March 25, 1980.

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