phenyl sulfide. The absence of *p*-nitro(methylthio)benzene in the products was confirmed. When hydrolysis of **16** was carried out in 1 N NaOH for 5 min at 100 °C, the reaction mixture was colored red and showed an intensive absorption at 400 nm. According to literature,[12] the color may have been due to formation of *p*-nitrophenolate ion and dimethyl sulfide.

Rates of Hydrolysis as Functions of pH and Buffer Concentrations. Hydrolysis studies of **1** were conducted at 1×10^{-4} M in the given buffer system[15] and summarized in Table I. Portions were taken at various times and read spectrometrically at the UV maximum at 350 nm due to forming *p*-nitro(methylthio)benzene. The difference between absorption intensities at infinite time and at any time indicates the amount of remaining **1**. Thus, the pseudo-first-order rate coefficients were calculated with a computer.

Acknowledgments. We thank Dr. Kusuo Horiki for his helpful suggestions and discussions and Miss Takako Nishiya for some of the syntheses.

Registry No.—**1**, 68258-47-9; **2**, 68258-48-0; **5**, 37620-72-7; **7**, 68258-49-1; **8**, 68330-61-0; **9**, 68258-50-4; **10**, 68258-51-5; **11**, 68258-52-6; **12**, 68258-53-7; **13**, 68258-54-8; **14**, 68258-55-9; **15**, 68258-56-0; **16**, 68330-63-2; **17**, 68330-64-3; 9-isopropylidenebenzonorbornene-*exo*-2-nitrile, 68258-57-1; 9-isopropylidenebenzonorbornene-*endo*-2-nitrile, 68330-65-4; 9-isopropylidenebenzonorbornene-*exo*-2-carboxylic acid, 68258-58-2; (9-ketobenzonorbornen-*endo*-2-yl)methyl *p*-nitrophenyl sulfide, 68330-66-5; 9-isopropylidenebenzonorbornadiene, 7350-72-3; 3,6-di(2′-pyridyl)-1,2,4,5-tetrazine, 1671-87-0; acrylonitrile, 107-13-1; silver tetrafluoroborate, 14104-20-2.

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(6) Papers by Tanida described in (a) H. Tanida, T. Irie, and T. Tsushima, *J. Am. Chem. Soc.*, **92**, 3404–3409 (1970); (b) C. J. Lancelot, D. J. Cram, and P. v. R. Schleyer, "Carbonium Ions", Vol. III, G. A. Olah and P. v. R. Schleyer, Eds., Wiley-Interscience, New York, N.Y., 1972, Chapter 27; (c) H. C. Brown and P. v. R. Schleyer, "The Nonclassical Ion Problem", Plenum Press, New York, N.Y., 1977.
(7) On the basis of Fieser–Drieding models, distances between the hydroxyl oxygen atom and the reacting carbon atom are 2.5 Å for **1** and 2.0 Å for **5**. This suggests the presence of serious nonbonded repulsive interaction, particularly in **5**.
(8) H. Tanida and T. Irie, *Bull. Chem. Soc. Jpn.*, **45**, 1999–2003 (1972).
(9) (a) H. Tanida, T. Tsuji, and H. Ishitobi, *J. Am. Chem. Soc.*, **86**, 4904–4912 (1964); (b) H. Tanida, *Farumashia*, **2** (6), 400–404 (1966).
(10) For a similar calculation, see E. R. Garrett, *J. Am. Chem. Soc.*, **80**, 4049–4056 (1958).
(11) If $k_{OH}[OH]$ is negligible, $k_H = (k_0 - k_{H_2O})/[H^+]$. With $k_0 = 5.13 \times 10^{-7}$ s^{-1}, assignments of k_0 at pH 4.65 and 5.22 (Table II) do not permit estimates of k_H, but that at pH 5.70 (5.45×10^{-7} s^{-1}) gives 1.6×10^{-2} M^{-1} s^{-1} for k_H. However, it would be more reasonable to say that $k_H[H^+]$ is absent in the pH area of the experiments.
(12) J. K. Coward and W. D. Sweet, *J. Org. Chem.*, **36**, 2337–2346 (1971).
(13) The calculation procedure and the value of $k_{H_2O}^{25°C}$ were reported,[5] but the value of $k_{OH}^{25°C}$ was not.
(14) Plots of $k_1^{25°C}$ (Table I) vs. [B] result in greater slopes with increasing pH values. Therefore, plots of k_B' vs. $[H^+]$ to obtain k_{HB} (slope) become negative.
(15) Refer to D. D. Perrin and B. Dempsey, "Buffers for pH and Metal Ion Control", Chapman and Hall, London, 1974.

Stereochemistry, Conformational Analysis, and Transannular Cyclizations of Nine-Membered Ring Azaolefins

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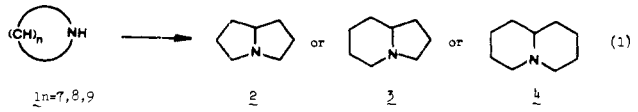
A transannular route to the indolizidine ring system (**3**) via an intramolecular cyclization of the appropriate azaolefins is described. Treatment of 1*H*-2,3,4,7,8,9-hexahydroazonine (**7b**) with either bromine or mercuric chloride affords, after reduction, the indolizidine alkaloid, δ-coniceine (**15**). The lactam analogue 1,3,4,7,8,9-hexahydro-2*H*-azonin-2-one (**7a**) also undergoes regiospecific ring closure when treated with a suitable electrophile (mercuric acetate) to yield the indolizinone skeleton **21**. Similar alkyl-substituted compounds were prepared and the products cyclized stereoselectively. The synthetic consequence of this reaction as well as the mechanistic implications are discussed.

Medium-ring compounds are often strained due to cross-ring interactions and undergo a variety of transannular reactions.[2] The transannular cyclization of medium-ring nitrogen compounds such as **1** would, in principle, provide a particularly interesting route to pyrrolizidine (**2**), indolizidine (**3**), or quinolizidine type alkaloids[3] (**4**) (eq 1). Transannular



(1)

1 n=7,8,9 2 3 4

reactions in heterocyclic systems were first reported in 1881[4] and many other transannular reactions in nitrogen heterocycles have been reported.[5] The transannular amine/carbonyl interaction has been carefully studied by Leonard,[6] who used such a route in a total synthesis of (±)-isoretronecanol.

We felt that the reaction of an amine or amide nitrogen with a remote (transannular) double bond possessed the most synthetic potential because: (1) additions to C–C double bonds are often stereospecific; and (2) the reaction leading to cyclized products would possess functionality where it is often found in naturally occuring alkaloids. The present paper reports our results on the chemistry of nine-membered ring lactams and amines.

Transannular Cyclizations. In previous communications[7a,b] we have shown that bromination[8] of 1-aza-4-cyclooctene (**5**), for example, leads to transannular ring closure to pyrrolizidines (**2**). The cyclization is stereospecific, yielding exclusively the product (**6**) expected from opening the bro-

5 6

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7a. X=O
7b. X=H_2

8a. X=O
8b. X=H_2

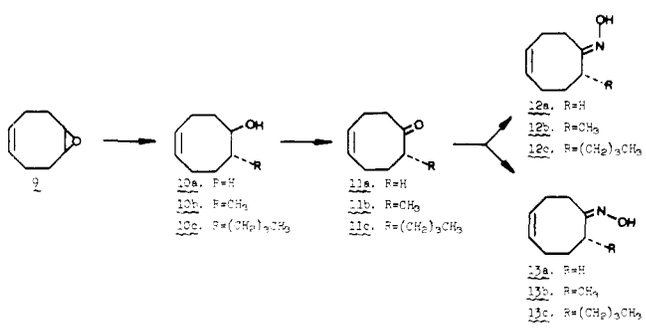
monium ion by nitrogen. Extension of this reaction to the synthesis of indolizidines (**3**) required the synthesis of amines **7b** and **8b.** Ketone **11a** was prepared[9] from 5,6-epoxycyclooctene **9** (Scheme I). Formation of the oxime of **11a** gave an inseparable mixture of syn/anti isomers **12a** and **13a,** which was carried on through the Beckmann rearrangement, yielding **7a** and **8a.** The isomeric lactams are expected by the mechanism of the Beckmann rearrangement, which results in bond migration anti to the leaving group. This result is substantiated by ^{13}C analysis of the mixture of lactams **7a** and **8a,** which showed a 15-line spectrum, the carbonyl carbon atom being equivalent.[10]

The mixture of lactams, which was inseparable by conventional separation techniques (TLC, GLC), was reduced with lithium aluminum hydride to yield the desired amines **7b** and **8b.** The amines were used as a mixture in the anticipation that the cyclized products would be more easily separated. The products *expected* from the intramolecular cyclization are shown in Scheme II. Amine **8b** can give at least two isomeric bromides, either a 6,5-system with the bromine atom on the five-membered ring or a 7,4-system with the bromine on the seven-membered ring. Amine **7b** should yield only the 6,5-system with the bromine on the six-membered ring.

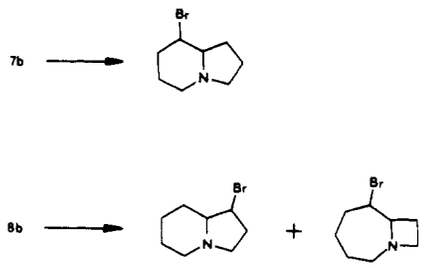
Treatment of amines **7b** and **8b** with bromine in methylene chloride (conditions suitable for ring closure)[7a,b] yielded only one major product, **14** (61% yield). The structure of **14** was confirmed by a single-crystal X-ray diffraction experiment on the picrate salt (Figure 1).[12]

The stereochemical consequences of this intramolecular cyclization reaction are interesting. Bromine-induced intramolecular cyclization reactions could proceed by two mechanistic pathways,[8a] formation of a bromonium ion intermediate followed by ring closure or initial formation of the dibromide, which subsequently cyclizes. The observed stereochemistry is consistent with formation of dibromide **16** (eq 2) followed by cyclization. The fate of the expected product from cyclization of **7b** is not clear. Reduction of **14** with lithium aluminum hydride in tetrahydrofuran afforded the indolizidine alkaloid (±)-δ-coniceine (**15,** 43%).[13] A more efficient procedure involves treatment of amines **7b/8b** with mercuric chloride in tetrahydrofuran followed by reduction with basic sodium borohydride to **15** (75% yield overall). Thus the transannular approach appears to be a useful route to indolizidine ring systems.

Scheme I



Scheme II



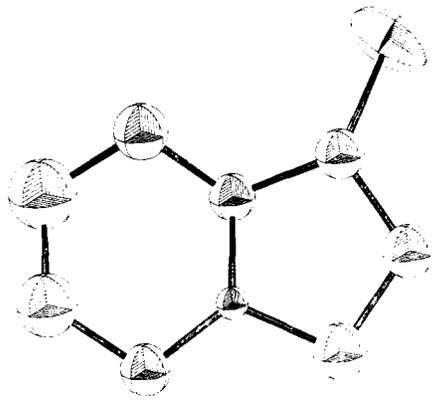
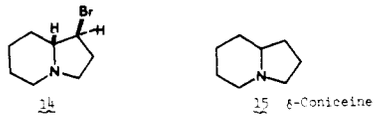
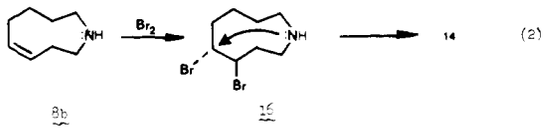


Figure 1.

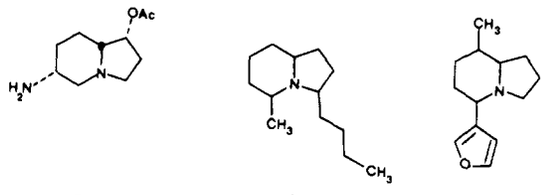


14 15 δ-Coniceine



8b 16 (2)

Preparation of Substituted Analogues. In an attempt to clarify the mechanistic aspects of these reactions and to demonstrate their synthetic utility in alkaloid synthesis, we undertook investigations of alkyl substitution on the lactam and amine precursors. Many indolizidine alkaloids contain relatively simple substitution on the ring, but their synthesis has been often quite tedious. Some examples include: slaframine (**17**), a metabolite isolated from the fungus *Rhizoctonia leguminicola*[14] which has been used as a medicinal agent in the treatment of the cystic fibrosis syndrome; 3-*n*-butyl-5-methyloctahydroindolizidine (**18**), a trail substance in the Pharoh ant;[15] and compound **19,** a recently isolated alkaloid from the scent gland of the Canadian beaver.[16]



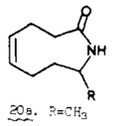
17 18 19

The synthesis of substituted indolizidines follows the synthetic pathway in Scheme I. Reaction of 5,6-epoxycyclooctene (**9**) with a dialkylcopperlithium reagent results in the formation of the substituted alcohols **10b,c.** Jones oxidation gives ketones **11b,c** which when treated with hydroxyamine lead to the formation of both syn and anti oxime isomers **12b,c** and **13b,c.** Separation of the oxime isomers was achieved by column chromatography on silica gel. (While the oxime isomers can be separated and identified, isomerization to the equilibrium mixture occurs after several days in chloroform or carbon tetrachloride solution.) NMR shift reagents allow for positive identification of the isomers. It is known that syn protons are shifted more strongly than the anti protons.[17] The CH_3 group which appeared as a doublet in the NMR spectrum

Table I. Shift Reagent Study of Syn/Anti Oximes 12b/13b

Eu(fod)$_3$, equiv	**12b** CH_3 doublet, δ	olefinic protons, δ	**13b** CH_3 doublet, δ	olefinic protons, δ
0.0	1.13	5.67	1.28	5.67
0.1	1.33	5.82	1.67	5.85
0.2	1.48	5.95	2.02	6.03
0.3	1.62	6.06	2.33	6.18
0.4	1.73	6.16	2.65	6.33
0.5	1.75	6.25	2.96	6.43

of **12b** and **13b** was used to distinguish the isomers (Table I). It was observed that the olefinic protons were also shifted more in the syn isomer than the anti isomer. It is also interesting to note that **11b** forms two oxime isomers, **12b** and **13b**, in a ratio of 60:40. Normally α-substituted ketones form a preponderance of the anti isomer (i.e., **12b**).[18] Clearly, the unique conformational properties of the cyclooctene ring allow relief of allylic strain in the syn isomer. Structural assignments of the *n*-butyl oximes **12c** and **13c** were based on similar arguments. Reaction of the oximes **12b,c** with *p*-toluenesulfonyl chloride followed by treatment with an aqueous tetrahydrofuran solution gave the Beckmann rearrangement products **20a,b**, respectively. The lactams were purified by



20a, R=CH_3
20b, R=$(CH_2)_3CH_3$

column chromatography on silica gel. The structures were assigned on the basis of spectral features such as amide carbonyl at 1660 cm^{-1} and assumed ring expansion anti to the leaving tosyl group.[19]

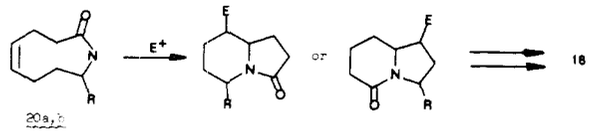
The synthetic strategy for the application of transannular cyclization to the Pharoah ant compound **18** is shown in Scheme III. It is apparent that a suitable precurser of **18** could be derived via *either* **20a** or **20b** depending on the selectivity of the cyclization. This question is now addressed.

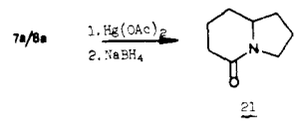
Regioselectivity of Amide Cyclizations. Amides have demonstrated their ability to cyclize via transannular ring closures,[20] although often reaction can occur on oxygen.[21] To further demonstrate the usefulness of this cyclization in the azacyclononenone system, the mixture of lactams **7a** and **8a** was reacted with an appropriate electrophile (mercuric acetate in aqueous tetrahydrofuran). An intramolecular cyclization resulted, giving lactam **21** (after sodium borohydride reduction). The reaction is regioselective: only the 5-indolizinone was observed.[22] The infrared spectrum of the product of cyclization showed a carbonyl frequency at 1640 cm^{-1} indicative of a six-membered ring amide and only one peak by GLC analysis. Reduction with lithium aluminum hydride gives (±)-δ-coniceine (**15**).

Molecular models indicate that the double bond character of the amide forces the molecule to assume a conformation allowing ring closure to occur with the formation of the six-membered ring lactam. Additional evidence which bears on this point is available from a study of the methylated analogue **20a**.

Yonemitsu and coworkers[23] have shown the existence of

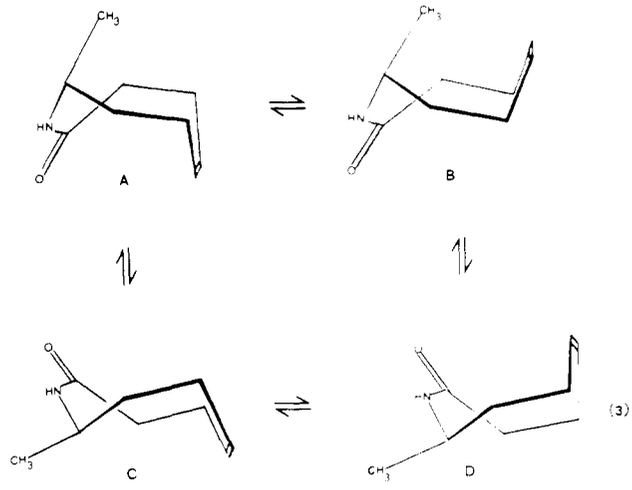
Scheme III





21

slow ring inversion of nine-membered ring lactams using NMR. The methyl lactams prepared above were studied to show the existence of this inversion. The NMR spectra of **20a** at 15 °C show two sets of doublets at δ 1.20 and 1.14 (J = 7 Hz) for the CH_3 group. This phenomenon can be explained by the equilibrium shown in eq 3.[24] The methyl group assumes either

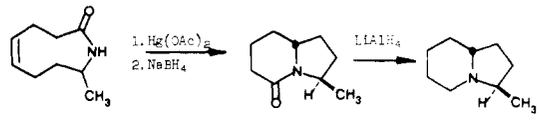


(3)

an axial or an equatorial position as the ring inverts. That the spectra were the result of slow ring inversion is shown by the following experiment. As the temperature was increased from 15 °C the doublets began to converge and at 80 °C there was only a single doublet centered at δ 1.07.

The regiochemical results obtained in the parent system (**7a/8a** → **21**) indicate that the cyclization should yield only the six-membered ring lactam. However, it was unclear what the stereochemistry of the alkyl substituent would be.

Compound **20a** upon treatment with mercuric acetate in aqueous tetrahydrofuran underwent a transannular cyclization. Reduction with sodium borohydride gave a single product **22**. IR evidence (C=O absorption at 1640 cm^{-1})



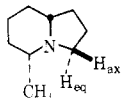
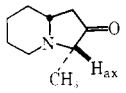
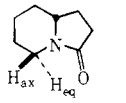
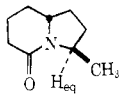
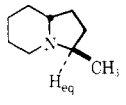
20a **22** **23**

verified the formation of a six-membered ring amide and the proton NMR spectrum showed only one doublet at 1.30 ppm, indicating the presence of a single isomer.[25]

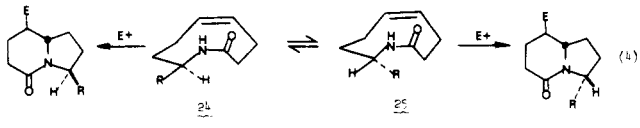
The stereochemistry of the methyl substituent was proven using the chemical shift data of the protons adjacent to the nitrogen atom. Cahill and Crabb used NMR to determine the stereochemistry of substituted indolizinones.[26] The chemical shifts of the axial and equatorial protons adjacent to the nitrogen atom may be used to assign structure. A comparison of their data (Table II) with the chemical shifts obtained from the spectra of **22** and **23** allows assignment of the stereochemistry of the cyclization. The signal observed at 4.14 ppm was assigned to the C-3 hydrogen based on a decoupling experiment. The downfield shift of the 3eq-H is due to the deshielding of the nitrogen lone pair of electrons and the amide moiety.

Thus the cyclization is stereospecific and allows for control of the stereochemistry at C-3. Molecular models of the two conformers (**24** and **25**) present at equilibrium (eq 4) reveal steric crowding due to the alkyl substituent "underneath" the

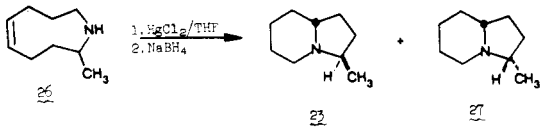
Table II. NMR Data for Indolizidines

compd	H_{ax}, δ	H_{eq}, δ	CH_3 doublet, δ	ref
	2.43	3.37	1.05	26
	2.36		1.06	26
	2.52	3.96		26
		4.14	1.30	this work
		3.30	0.89	this work

ring system in **25.** No twisting of bonds will allow for relief of this interaction. Conformer **24** shows no such interaction and leads to the observed product.



In an attempt to learn more about the factors controlling the stereochemistry of the transannular cyclization, lactam **20a** was reduced to the unsaturated amine **26** with lithium aluminum hydride. The NMR spectrum of amine **26** shows



only one doublet for the methyl group (δ 1.41, J = 7 Hz). Clearly, removal of the constraint of the amide moiety allows more rapid equilibration of conformers. Treatment of **26** with mercuric chloride in tetrahydrofuran followed by sodium borohydride led to cyclized products **23** and **27.** GLC comparison showed the major (70%) product to be **23,**[27] while the second compound (30%) of shorter retention time was the epimeric compound **27.**

The presence of two isomeric amines was confirmed by the NMR spectrum of the mixture. The spectrum showed two sets of doublets for the methyl group at 0.93 and 0.89 ppm (J = 7 Hz). The stereochemistry of the methyl group was also established by comparing Bohlmann band[28] differences in the region 2700–2900 cm^{-1}. All of the indolizidine alkaloids obtained in this study gave absorption in this region, indicating the presence of a trans-fused ring. The IR spectrum of the mixture **23** and **27** showed a marked increase in the Bohlmann band absorption, indicating the presence of an additional trans axial hydrogen in the isomer **27.**

In summary, we have examined several modes of transannular nine-membered ring closure which should be applicable to alkaloid synthesis. Currently, such work is underway and will be reported in due course.

Experimental Section

General. Melting points were measured in capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on Varian HR-220 and T-60A spectrometers. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Proton decoupled ^{13}C NMR spectra were recorded on a Varian XL-100A spectrometer using a Nicolet pulsed FT data collection system at an operating frequency of 25.2 MHz in either CCl_4 of $CHCl_3$ with tetramethylsilane as an internal standard. Mass spectra (70 eV) were obtained on Varian MAT CH-7 and AEI MS-9 spectrometers. IR spectra were obtained in solution cells with chloroform or on neat samples using a Perkin-Elmer 137 Infracord. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan. Analytical gas chromatography was performed with a Varian Aerograph Model 940 with FID detector on a 1.5% OV-101 on Chromasorb G column (5 ft × ⅛ in.) with helium carrier gas. Preparative gas chromatography was performed with a Varian Aerograph Model 920 on a 20% OV-101 on Chromasorb W column (5 ft × ¼ in.). Column chromatography work was done with MCB silica gel, 100–200 mesh, grade 923. Distillations were performed with a Büchi/Brinkmann Standard Micro distillation oven, Model KR, and boiling points reported are approximate. Both ether and tetrahydrofuran were dried by distillation from lithium aluminum hydride. All experiments were routinely done under an inert atmosphere.

4-Cyclooctenone Oxime (12a, 13a). Into a 250-mL flask equipped with a reflux condenser was added 1.3 g (10.5 mmol) of 4-cyclooctenone,[10] 100 mL of methanol, 2.5 g (36.0 mmol) of hydroxylamine hydrochloride, and 2.5 g of sodium bicarbonate. The solution was heated to reflux for 5 h and 50 mL of water was added. The mixture was extracted several times with chloroform and dried over sodium sulfate. Evaporation of the solvent left a heavy oil which slowly crystallized on standing under vacuum, leaving the oxime as white crystals: 1.35 g; 93% yield; mp 47–48 °C; IR (neat) 3250, 1640 cm^{-1}; NMR ($CDCl_3$) δ 7.7–7.9 (1 H, br s), 5.75 (2 H, m), 1.5–2.8 (10 H, m); mass spectrum m/e (% base) 139 (4), 122 (15), 120 (9), 94 (11), 81 (13), 79 (24), 67 (21). Anal. Calcd for $C_8H_{13}NO$: mol wt 139.0998. Found: mol wt 139.0998.

1,3,4,7,8,9-Hexahydro-2*H*-azonin-2-one (7a) and 1,3,4,5,8,9-Hexahydro-2*H*-azonin-2-one (8a). A solution containing 1.35 g (9.71 mmol) of 4-cyclooctenone oxime (**12a, 13a**), 100 mL of methylene chloride, and 3 mL of pyridine was cooled to −10 °C in an ice/salt slush bath and 2.3 g (12.1 mmol) of *p*-toluenesulfonyl chloride in 20 mL of methylene chloride was added dropwise over 1 h. After stirring overnight at room temperature the solution was poured into 10% HCl, extracted with methylene chloride, washed with saturated sodium bicarbonate, and dried over sodium sulfate. Evaporation of solvent afforded the crude tosylate as an oil which was recrystallized from chloroform/pentane to yield white crystals: 2.16 g; 76% yield; mp 86–87 °C; NMR ($CDCl_3$) δ 7.77 (2 H, d), 7.27 (2 H, d), 5.50 (2 H, m), 2.43 (3 H, s), 1.5–2.4 (10 H, m). The conversion of the tosylate to lactam was done in 500-mg batches by the following procedure. To a solution containing 500 mg (1.7 mmol) of tosylate, 15 mL of H_2O, and 200 mg of potassium carbonate was added enough tetrahydrofuran to completely dissolve the oxime tosylate. The reaction mixture was stirred overnight, extracted several times with chloroform, and dried over sodium sulfate. Evaporation of the solvent afforded a mixture of lactams which was recrystallized from chloroform/pentane to yield white crystals: 210 mg; 89% yield; mp 117–118 °C; IR ($CHCl_3$) 3400, 1660 cm^{-1}; NMR ($CDCl_3$) δ 7.00 (1 H, br s), 5.3–5.8 (2 H, m), 3.30 (2 H, m), 1.7–2.5 (8 H, m); mass spectrum m/e (% base) 139 (9), 111 (73), 110 (26), 82 (100), 81 (19), 67 (74), 54 (84). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.14; N, 10.06. Found: C, 69.09; H, 9.12; N, 10.05.

1*H*-2,3,4,7,8,9-Hexahydroazonine (7b) and 1*H*-2,3,6,7,8,9-Hexahydroazonine (8b). The mixture of lactams **7a** and **8a** (320 mg, 2.3 mmol) was dissolved in 10 mL of tetrahydrofuran and added dropwise to a solution containing 400 mg (10.5 mmol) of lithium aluminum hydride in 50 mL of ether. The solution was heated to reflux for 5 h and stirred overnight at room temperature. After quenching with water the mixture was filtered and the amines were distilled, yielding a clear liquid: 218 mg; 93% yield; bp 95–100 °C (20 mmHg); IR (neat) 3300 cm^{-1}; NMR ($CDCl_3$) δ 5.3–6.0 (2 H, m), 2.73 (4 H, m), 2.13 (5 H, m), 1.60 (4 H, m); mass spectrum m/e (% base) 125 (19), 110 (3), 96 (26), 82 (59), 70 (82), 68 (27), 43 (100). Anal. Calcd for $C_8H_{15}N$: mol wt 125.1205. Found: mol wt 125.1201. Picrate recrystallized from ethanol, mp 136–138 °C. Calcd for $C_{14}H_{18}N_4O_7$: C, 47.46; H, 5.12; N, 15.81. Found: C, 47.48; H, 5.10; N, 15.77.

***cis*-1-Bromooctahydroindolizine (14).** Into a 100-mL flask was added 240 mg (1.9 mmol) of the two isomeric amines **7b** and **8b,** 30 mL of ether, and 30 mL of methylene chloride. A solution containing 400 mg (2.5 mmol) of bromine in 5 mL of methylene chloride was added dropwise over 20 min. The resulting red solution was stirred overnight at room temperature. Evaporation of the solvent gave a dark red oil which was dried under vacuum. The resulting HBr salt was treated

with sodium hydroxide/ether and converted to the free base. The ether solution was dried over potassium carbonate and the solvent was evaporated, leaving a light red oil which was distilled, affording **14** as a clear liquid: 205 mg; 61% yield; bp 145–150 °C (20 mmHg); NMR ($CDCl_3$) δ 4.38 (1 H, m), 3.75 (1 H, m), 3.00 (2 H, m), 2.3–2.5 (2 H, m), 2.05 (4 H, m), 1.1–1.8 (4 H, m); mass spectrum *m/e* (% base) 205 (30), 204 (31), 203 (34), 202 (31), 124 (70), 122 (32), 97 (100), 96 (58), 81 (39), 69 (54). Anal. picrate recrystallized from ethanol, mp 165–166 °C. Calcd for $C_{14}H_{17}N_4O_7Br$: C, 38.83; H, 3.96; N, 12.93; Br, 18.44. Found: C, 38.89; H, 4.01; N, 12.84; Br, 18.35. The structure and stereochemistry of **14** were confirmed by a single-crystal X-ray analysis of the picrate.[12]

δ-Coniceine (15). Method A. Into a 100-mL three-neck flask fitted with a reflux condenser and a dropping funnel was added 300 mg (7.8 mmol) of lithium aluminum hydride and 60 mL of tetrahydrofuran. To this mixture was added 530 mg (2.6 mmol) of **14** in 20 mL of tetrahydrofuran dropwise over 10 min. The resulting mixture was heated to reflux overnight, quenched with water, and filtered to remove the salts. Distillation yielded δ-coniceine (**15**): 140 mg; 43% yield; bp 160–165 °C (lit.[13] bp 161 °C). Anal. Calcd for $C_8H_{15}N$: mol wt 125. Found: mol wt 125.1199.

Method B. Into a 25-mL test tube was added 10 mL of tetrahydrofuran and 389 mg (1.43 mmol) of mercuric chloride. A solution of 179 mg (1.43 mmol) of amines **7b/8b** in 5 mL of tetrahydrofuran was added dropwise with the immediate formation of a white precipitate. The mixture was stirred 15 min and filtered, and the crystals were washed with fresh tetrahydrofuran. The white crystals were dried under vacuum to yield the mercurial (HCl salt): 446 mg; 80% yield; mp 214–216 °C. Into a 15-mL test tube was added 220 mg (0.55 mmol) of the white solid and 4 mL of tetrahydrofuran. To this suspension was added 1 mL of a 0.5 M sodium borohydride solution in 3.0 M sodium hydroxide with the immediate formation of a mercury droplet. The mixture was stirred 15 min and centrifuged and the organic layer was separated, leaving 104 mg of mercury (94%). The organic layer was dried over potassium carbonate, and the solvent was distilled to yield **15**: 46 mg; 66% yield. The picrate was recrystallized from methanol, mp 224–228 °C (lit.[13] mp 225–228 °C). Anal. Calcd for $C_{14}H_{18}N_4O_7$: C, 47.46; H, 5.12; N, 15.81. Found: C, 47.39; H, 5.12; N, 15.84.

Method C. Lactam **21** (100 mg, 0.72 mmol) was dissolved in 2 mL of ether and added dropwise to a solution containing 100 mg (2.63 mmol) of lithium aluminum hydride in 20 mL of ether. After refluxing for 5 h the mixture was stirred overnight at room temperature. The reaction mixture was quenched with water and filtered and the solvent was evaporated, leaving **15** as a clear liquid: 74 mg; 82% yield. The picrate was recrystallized from methanol, mp 221–225 °C. Anal. Calcd for $C_8H_{15}N$: mol wt 125.1205. Found: mol wt 125.1211.

2-Methyl-5-cyclooctenol (10b). Into a 250-mL flask equipped with a dropping funnel was added 9.2 g (48.3 mmol) of cuprous iodide and 150 mL of ether. The solution was cooled to −10 °C with an ice/salt slush bath and 60 mL of methyllithium (1.6 M in ether, Alfa Products, 96 mmol) was added dropwise. After 30 min, 2 g (16 mmol) of 5,6-epoxycyclooctene[9] was added dropwise over 30 min and the solution was allowed to slowly warm to room temperature and stirred for 4 days. The mixture was quenched with saturated ammonium chloride and filtered to remove the salts. Evaporation of the solvent left a crude oil which was purified by column chromatography using 10:90 ether/pentane as the elutant. Distillation afforded pure alcohol (**10b**) as a clear liquid: 1.27 g; 56% yield; bp 140–150 °C (20 mmHg); IR (neat) 3450 cm^{-1}; NMR ($CDCl_3$) δ 5.57 (2 H, m), 3.60 (1 H, m), 0.8–2.4 (10 H, m), 1.00 (3 H, d); mass spectrum *m/e* (% base) 140 (4), 125 (2), 112 (33), 97 (79), 72 (63), 41 (100). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.98; H, 11.69.

2-Methyl-5-cyclooctenone (11b). A solution containing 2.54 g (18.1 mmol) of 2-methyl-5-cyclooctenol (**10b**) and 50 mL of acetone was cooled to 0 °C and Jones reagent (35 g of CrO_3, 30 mL of concentrated H_2SO_4 in 250 mL of H_2O) was added dropwise until the formation of a stable red color. The mixture was stirred 30 min and isopropyl alcohol was added to quench the excess reagent. Water was added to the green mixture to completely dissolve the salts and the mixture was extracted several times with ether. The ether extracts were dried over calcium chloride and magnesium sulfate and the solution was filtered. Evaporation of the solvent followed by distillation gave the ketone (**11b**) as a clear liquid: 2.05 g; 82% yield; bp 120–130 °C (20 mmHg); 2,4-DNP mp 137–138 °C; IR (neat) 1720 cm^{-1}; NMR ($CDCl_3$) δ 5.73 (2 H, m), 1.3–3.0 (9 H, m), 1.02 (3 H, d); mass spectrum *m/e* (% base) 138 (59), 123 (37), 96 (50), 81 (61), 68 (100). Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21; mol wt 138.1045. Found: C, 77.78; H, 10.14; mol wt 138.1059.

2-Methyl-5-cyclooctenone Oxime (12b, 13b). Into a 100-mL flask was added 1 g (7.25 mmol) of 2-methyl-5-cyclooctenone (**11b**) and 50 mL of anhydrous methanol. To this solution was added 850 mg (12.23 mmol) of hydroxylamine hydrochloride and 850 mg of sodium bicarbonate. The mixture was heated to reflux for 5 h, 50 mL of water was added, and the solution was extracted several times with chloroform. The chloroform extracts were dried over sodium sulfate and the solvent was evaporated, leaving a crude oil which contained both the syn and anti oxime isomers. The mixture was separated by column chromatography using 10:90 ether/pentane as the elutant to yield 813 mg (82% yield). Syn oxime isomer (**13b**): 280 mg; 38% yield; R_f 0.31 (50:50 ether/pentane); light yellow oil; IR (neat) 3200, 1650 cm^{-1}; NMR ($CDCl_3$) δ 8.40 (1 H, br s), 5.73 (2 H, m), 3.07 (2 H, m), 2.82 (1 H, m), 2.50 (2 H, m), 1.7–2.4 (4 H, m), 1.41 (3 H, d, J = 7 Hz); mass spectrum *m/e* (% base) 153 (13), 138 (19), 136 (39), 94 (28), 93 (45), 67 (60), 41 (100). Anal. Calcd for $C_9H_{15}NO$: mol wt 153.1154. Found: mol wt 153.1156. Anti oxime isomer (**12b**): 533 mg; 62% yield; R_f 0.41 (50:50 ether/pentane); white crystals, mp 50–53 °C; IR ($CHCl_3$) 3250 cm^{-1}; NMR ($CDCl_3$) δ 8.91 (1 H, br s), 5.64 (2 H, m), 3.20 (1 H, m), 1.6–2.5 (8 H, m), 1.14 (3 H, d, J = 7 Hz); mass spectrum *m/e* (% base) 153 (12), 138 (20), 136 (36), 111 (47), 67 (70), 41 (100). Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.60; H, 9.75; N, 9.09.

1,3,4,7,8,9-Hexahydro-9-methyl-2*H*-azonin-2-one (20a). A solution containing 200 mg (1.31 mmol) of oxime (**12b**) and 50 mL of methylene chloride was cooled to −10 °C with an ice/salt slush bath and 0.2 mL (2.5 mmol) of pyridine added. To this mixture was added dropwise over 15 min a solution of *p*-toluenesulfonyl chloride (400 mg, 2.1 mmol) in 10 mL of methylene chloride. The reaction mixture was allowed to slowly warm to room temperature, stirred for 5 h, poured into 20 mL of 10% HCl, extracted with methylene chloride, washed with saturated sodium bicarbonate, and dried over sodium sulfate. Evaporation of the solvent afforded the crude tosylate, which was not isolated. The tosylate was dissolved in 10 mL of tetrahydrofuran and added dropwise to a 50-mL flask containing 15 mL of water and 100 mg of potassium carbonate. The yellow solution was stirred overnight at room temperature and repeatedly extracted with chloroform. The chloroform extracts were dried over sodium sulfate, filtered, and evaporated, leaving the crude lactam (**20a**), which was purified by column chromatography using 10:90–20:80 ethyl acetate/ether as the eluant, leaving white crystals: 118 mg; 59% yield; mp 84–85 °C; IR ($CHCl_3$) 3250, 1660 cm^{-1}; NMR ($CDCl_3$) appears to be two conformational isomers δ 5.4–5.9 (2 H, m), 5.7 (½ H, br s), 5.09 (½ H, br), 4.32 (½ H, m), 3.5 (½ H, m), 1.5–2.5 (8 H, m), 1.20 (3/2 H, d, J = 7 Hz), 1.14 (3/2 H, d, J = Hz); on heating fractional resonances coalesce; mass spectrum *m/e* (% base) 153 (16), 138 (29), 96 (25), 84 (23), 44 (100). Anal. Calcd for $C_9H_{15}NO$: mol wt 153.1154. Found: mol wt 153.1140.

Hexahydro-5(1*H*)-indolizinone (21). Into a 50-mL pear-shaped flask was placed 887 mg (2.78 mmol) of mercuric acetate, 15 mL of water, and 15 mL of tetrahydrofuran. To this mixture was added 387 mg (2.78 mmol) of lactams **7a** and **8a** in 15 mL of tetrahydrofuran dropwise. The yellow mixture was stirred overnight at room temperature and the mercurial reduced with excess sodium borohydride solution (0.5 M $NaBH_4$ in 3.0 M NaOH). The solution was decanted from the metallic mercury formed, extracted several times with methylene chloride, and dried over sodium sulfate and the solvent was evaporated. The crude product was subjected to column chromatography using 10:90 methanol/ether as the eluant, yielding the product (**21**) as a clear liquid which was distilled: 328 mg; 85% yield; bp 120–125 °C (0.5 mmHg); IR (neat) 1640 cm^{-1}; NMR ($CDCl_3$) δ 3.3–3.6 (3 H, m), 1.1–2.5 (10 H, m); mass spectrum *m/e* (% base) 139 (36), 138 (20), 111 (20), 86 (62), 85 (25), 84 (100), 83 (76), 70 (38). Anal. Calcd for $C_8H_{13}NO$: C, 69.06; H, 9.35; N, 10.07; mol wt 139.0998. Found: C, 69.12; H, 9.45; N, 9.98; mol wt 139.1009.

***cis*-Hexahydro-3-methyl-5(1*H*)-indolizinone (22).** Into a 100-mL pear-shaped flask was added 750 mg (2.35 mmol) of mercuric acetate, 30 mL of tetrahydrofuran, and 30 mL of water. A solution containing 300 mg (1.96 mmol) of lactam (**20a**) in 5 mL of tetrahydrofuran was added dropwise over 15 min. The yellow solution became clear after 5 min and the mixture was stirred 2 h at room temperature. The alkyl mercurial formed was reduced with excess sodium borohydride solution and stirred 30 min. The clear solution was decanted from the metallic mercury and extracted several times with methylene chloride. The organic extracts were dried over sodium sulfate and the solvent was evaporated, leaving the crude lactam which was subjected to column chromatography using 10:90 methanol/ether as the eluant. Distillation of the isolated material afforded **22** as a clear liquid: 248 mg; 83% yield; bp 110–120 °C (0.5 mmHg); IR (neat) 1640 cm^{-1}; NMR ($CDCl_3$) δ 4.14 (1 H, m), 3.43 (1 H, m), 1.8–2.5 (6 H, m), 1.1–1.7 (4 H, m), 1.30 (3 H, d, J = 7 Hz); mass spectrum *m/e* (% base) 153 (36), 138 (100), 110 (16), 97 (16), 84 (17), 55 (24). Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.63; H, 9.92; N, 9.16.

***cis*-Octahydro-3-methylindolizine (23).** To a mixture containing 50 mg (1.31 mmol) of lithium aluminum hydride and 30 mL of ether was added dropwise a solution of 50 mg (0.33 mmol) of lactam **22** in 2 mL of ether. The solution was heated to reflux for 5 h and stirred overnight at room temperature. After quenching with water the solution was filtered and the solvent was evaporated, leaving amine **23** as a clear liquid; 43 mg; 96% yield; picrate mp 197–205 °C; IR (neat) 2780 cm^{-1} (weak); NMR ($CDCl_3$) δ 3.30 (1 H, m), 2.91 (1 H, m), 2.43 (2 H, m), 1.1–2.2 (10 H, m), 0.89 (3 H, d, J = 7 Hz); mass spectrum *m/e* (% base) 139 (18), 138 (20), 124 (100), 110 (8), 96 (10), 82 (5), 55 (10). Anal. Calcd for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47; N, 15.21. Found: C, 48.86; H, 5.35; N, 15.26.

2,3,4,7,8,9-Hexahydro-2-methyl-1*H*-azonine (26). Into a 50-mL flask equipped with a dropping funnel and a reflux condenser was placed 30 mL of ether and 180 mg (4.7 mmol) of lithium aluminum hydride. A mixture of 118 mg (0.8 mmol) of lactam **20a** in 2 mL of tetrahydrofuran was added dropwise over 15 min. The solution was heated to reflux for 5 h and stirred overnight at room temperature. After quenching with water the solution was filtered and the solvent was evaporated, leaving amine **26** as a clear liquid: 105 mg; 98% yield; bp 110–120 °C (20 mmHg); NMR [$(CD_3)_2CO$–picrate] δ 8.70 (2 H, s), 5.68 (2 H, m), 3.70 (1 H, m), 3.36 (2 H, m), 3.20 (2 H, br s), 2.41 (4 H, m), 1.91 (4 H, m), 1.41 (3 H, d, J = 7 Hz); mass spectrum *m/e* (% base) 139 (25), 124 (29), 110 (38), 96 (56), 84 (31), 70 (56), 57 (100). Anal. picrate mp 175–180 °C. Calcd for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47; N, 15.21. Found: C, 49.00; H, 5.48; N, 15.10.

Cyclization of Amine 26 with Mercuric Chloride. A solution containing 26 mg (0.187 mmol) of amine **26** in 2 mL of THF was added dropwise to 55 mg (0.20 mmol) of mercuric chloride and 3 mL of tetrahydrofuran with the immediate formation of a white precipitate. The mixture was stirred for 30 min after complete addition, filtered, and washed with fresh tetrahydrofuran, and the white crystals were dried under vacuum: 74 mg; 96% yield; mp 90–100 °C; mass spectrum *m/e* (% base) 374 (5), 373 (5), 372 (5), 371 (5), 359 (20), 358 (12), 357 (15), 356 (11), 210 (27), 200 (11), 199 (28), 198 (16), 139 (22), 138 (100), 137 (21), 123 (22), 122 (34), 110 (32), 96 (24). Anal. Calcd for $C_9H_{16}N^{202}Hg^{35}Cl$: mol wt 375.0678. Found: mol wt 375.0708.

Into a 20-mL centrifuge tube was placed 4 mL of tetrahydrofuran and 51 mg (0.124 mmol) of the hydrochloride salt obtained above. To this solution was added an excess of a sodium borohydride solution with the immediate formation of a mercury droplet. The mixture was stirred 30 min and the organic layer was decanted from the metallic mercury (17 mg of Hg, 68% yield). The mixture of amines was collected by preparative GLC (T = 160 °C). The mixture contained amine **27** and amine **22** in a ratio of 30:70, respectively, as shown by comparison with authentic amine **22** prepared previously: IR (neat) 2790 cm^{-1} (strong Bohlmann band); NMR ($CDCl_3$) δ 3.2–3.4 (1 H, m), 2.7–2.9 (1 H, m), 2.3–2.5 (2 H, m), 1.1–2.2 (10 H, m), two sets of doublets at 0.93 (3 H, d, J = 7 Hz) and 0.89 (3 H, d, J = 7 Hz); mass spectrum *m/e* (% base) 139 (22), 138 (21), 124 (100), 110 (11), 96 (35), 91 (13), 70 (11), 69 (11), 62 (15), 53 (13).

2-*n*-Butyl-5-cyclooctenol (10c). Into a 250-mL two-neck flask equipped with a dropping funnel was added 9.2 g (48.3 mmol) of cuprous iodide and 150 mL of ether. The solution was cooled to −78 °C and 60 mL (0.13 mol, 2.22 M in hexane, Alfa Products) of *n*-butyllithium was added dropwise over 30 min. The black solution was warmed to room temperature, allowed to stir 5 min, and cooled back to −78 °C. The epoxide (**9**, 2 g, 16 mmol) was added over 30 min. The resulting black mixture was stirred at −78 °C for 3 h and slowly warmed to room temperature. The solution was stirred overnight, quenched with saturated ammonium chloride solution, and filtered to remove the salts, and the solvent was evaporated to yield the crude alcohol. Column chromatography with 5:95–10:90 ether/pentane afforded the alcohol (**10c**), which was distilled: 0.82 g; 28% yield; bp 170–175 °C (20 mmHg); IR (neat) 3450 cm^{-1}; NMR ($CDCl_3$) δ 5.57 (2 H, m), 3.67 (1 H, m), 1.0–2.3 (15, H, m), 0.87 (3 H, m); mass spectrum *m/e* (% base) 182 (2), 164 (1), 121 (9), 119 (17), 117 (18), 84 (12), 55 (19), 40 (64), 32 (100). Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16; mol wt 182.1672. Found: C, 79.08; H, 12.03; mol wt 182.1669.

2-*n*-Butyl-5-cyclooctenone (11c). A solution containing 800 mg (4.4 mmol) of 2-*n*-butyl-5-cyclooctenol (**10c**) in 30 mL of acetone was cooled to 0 °C. Jones reagent was added dropwise until the appearance of a stable red color. The resulting mixture was stirred an additional 30 min and isopropyl alcohol was added dropwise until a stable green color. Water was added to completely dissolve the salts and the mixture was extracted several times with ether. The ether extracts were dried over calcium chloride/magnesium sulfate and filtered and the solvent was evaporated, leaving the crude ketone **11c** which was distilled: 675 mg; clear liquid; 85% yield; bp 125–130 °C (20 mmHg); 2,4-DNP derivative, mp 90–91 °C, recrystallized from ethanol; IR (neat) 1710 cm^{-1}; NMR ($CDCl_3$) δ 5.64 (2 H, m), 1.9–2.8 (6 H, m), 1.0–1.7 (9 H, m), 0.84 (3 H, t); mass spectrum *m/e* (% base) 180 (12), 124 (51), 109 (12), 96 (30), 95 (28), 83 (50), 67 (70), 55 (73), 54 (59). Anal. Calcd for $C_{12}H_{20}O$: mol wt 180.1515. Found: mol wt 180.1513. Calcd for 2,4-DNP derivative $C_{18}H_{24}N_4O_4$: C, 59.99; H, 6.71. Found: C, 59.99; H, 6.64.

2-*n*-Butyl-5-cyclooctenone Oxime (12c, 13c). A solution containing 650 mg (3.61 mmol) of 2-*n*-butyl-5-cyclooctenone (**10c**), 35 mL of methanol, 1.1 g (15.8 mmol) of hydroxylamine hydrochloride, and 1.1 g of sodium bicarbonate was heated to reflux for 5 h, poured into 50 mL of water, and extracted repeatedly with chloroform. The chloroform extracts were dried over sodium sulfate and the solvent was evaporated, leaving a crude mixture of the syn and anti oxime isomers. The resulting oxime isomers were separated by column chromatography on silica gel using 5:95–10:90 ether/pentane. The total yield of oxime was 519 mg (74% yield).

Anti isomer (**12c**): oil; 66% of product; 346 mg; R_f 0.45, 50:50 pentane/ether; IR (neat) 3270, 1650 cm^{-1}; NMR (CCl_4) δ 9.86 (1 H, s), 5.59 (2 H, m), 3.25 (1 H, m), 2.43 (4 H, m), 1.50 (6 H, m), 1.25 (4 H, m), 0.89 (3 H, t); mass spectrum *m/e* (% base) 195 (2), 178 (5), 160 (3), 139 (9), 111 (9), 85 (12), 81 (11). Anal. Calcd for $C_{12}H_{21}NO$: mol wt 195.1624. Found: mol wt 195.1638.

Syn isomer (**13c**): oil; 34% product; 173 mg; R_f 0.39, 50:50 pentane/ether); IR (neat) 3200, 1650 cm^{-1}; NMR (CCl_4) δ 9.57 (1 H, br s), 5.57 (2 H, m), 1.9–2.5 (8 H, m), 1.1–1.5 (7 H, m), 0.88 (3 H, t); mass spectrum *m/e* (% base) 195 (7), 178 (37), 152 (17), 139 (23), 138 (22), 122 (20), 111 (21), 110 (18), 98 (31), 94 (23), 85 (27), 81 (40), 69 (34), 67 (59), 55 (78), 41 (100). Anal. Calcd for $C_{12}H_{21}NO$: mol wt 195.1624. Found: mol wt 195. 1608.

1,3,4,7,8,9-Hexahydro-9-*n*-butyl-2*H*-azonin-2-one (20b). Into a 100-mL flask was added 200 mg (1.03 mmol) of anti oxime (**12c**) and 50 mL of methylene chloride. The solution was cooled to −10 °C and 0.2 mL of pyridine was added. A solution containing 300 mg (1.57 mmol) of *p*-toluenesulfonyl chloride in 5 mL of methylene chloride was added dropwise over 30 min. The mixture was allowed to stand overnight and the yellow solution was poured into 10% HCl. The organic layer was washed with saturated sodium bicarbonate and dried over sodium sulfate. Evaporation of the solvent afforded the crude tosylate as a yellow oil, which was dissolved in 10 mL of tetrahydrofuran and added dropwise to 10 mL of water and 100 mg of potassium carbonate. The reaction was stirred overnight and extracted several times with chloroform. The yellow organic layer was dried over sodium sulfate and evaporation of the solvent left the crude lactam **20b,** which was purified by column chromatography on silica gel eluting with 10:90–20:80 ethyl acetate/ether. The lactam was isolated as white crystals: 105 mg; 53% yield; mp 87–88 °C; IR ($CHCl_3$) 3250, 1660 cm^{-1}; NMR ($CDCl_3$) δ 6.64 (1 H, br s), 5.61 (2 H, m), 3.23 (1 H, m), 1.7–2.5 (6 H, m), 1.1–1.5 (8 H, m), 0.86 (3 H, m); mass spectrum *m/e* (% base) 195 (22), 138 (99), 126 (51), 125 (29), 110 (31), 96 (52), 86 (100), 82 (23), 68 (20), 41 (47). Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17; mol wt 195.1624. Found: C, 73.84; H, 10.72; N, 7.19; mol wt 195.1611.

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Registry No.—**7a,** 68344-49-0; **7b,** 68344-50-3; **7b** picrate, 68344-51-4; **8a,** 68344-52-5; **8b,** 68344-53-6; **8b** picrate, 68344-54-7; **9,** 19740-90-0; **10b,** 68344-55-8; **10c,** 68344-56-9; **11b,** 68344-57-0; **11b** 2,4-DNP, 68344-58-1; **11c,** 68344-59-2; **11c** 2,4-DNP, 68344-60-5; **12a,** 68344-65-0; **12a** tosylate, 68344-66-1; **12b,** 68344-61-6; **12b** tosylate, 68344-62-7; **12c,** 68344-63-8; **12c** tosylate, 68344-64-9; **13a,** 68344-35-4; **13a** tosylate, 68344-36-5; **13b,** 68344-28-5; **13c,** 68344-29-6; **14,** 68344-30-9; **14** picrate, 68344-31-0; **14** HBr, 68344-32-1; **15,** 62279-67-8; **15** picrate, 62318-95-0; **20a,** 68344-33-2; **20b,** 68344-34-3; **21,** 68344-37-6; **22,** 68344-38-7; **23,** 68344-39-8; **23** picrate, 68344-40-1; **26,** 68344-41-2; **26** picrate, 68344-42-3; **27,** 68344-43-4; 4-cyclooctenone, 31598-70-6.

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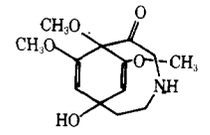

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Reaction of Crystalline Fluoro Olefins with Bromine Vapor. 2. Solid-State vs. Solution Stereospecificity for (*E*)- and (*Z*)-1-Substituted-2-chloro-*F*-ethene and -*F*-propene[1]

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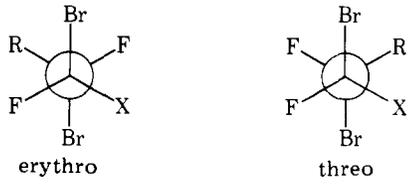
The addition of bromine to (*E*)- and (*Z*)-*p*-$HO_2CC_6H_4CF{=}CFX$ (X = Cl, CF_3) in solution and in the solid has been studied under ionic and radical conditions. For X = Cl, ionic addition leads to the *trans*-dibromo adduct in solution and in the solid–gas reaction. The radical solution reactions show stereoselective formation of the erythro isomer, while the radical solid–gas reactions may indicate a slight preference for cis addition. For X = CF_3, the *Z* isomer preferentially adds bromine cis in the solid state under either ionic or radical conditions. The *E* isomer also shows a preference for cis addition, but the solid-state reaction is complicated by competing mechanisms. The solution reactions for X = CF_3 are mainly nonstereoselective.

The addition of molecular bromine to a polyfluorinated olefin in solution is usually performed under radical conditions which quite often exhibit little stereochemical control over the products.[2] We were interested in the stereospecificity of the solid–gas reaction between a solid fluorinated olefin and bromine vapor to determine the change in stereochemistry due to reaction occurring in the solid state. We now report that the radical reaction between solid fluorinated olefins and bromine vapor shows a preference for cis addition of bromine. In addition, two paths have been observed for the ionic addition, an open cation and a bridged bromonium ion, with each leading to different reaction stereospecificity.

Hadjoudis and Schmidt have reported the ionic addition of bromine vapor to solid α,β-unsaturated acids, amides, and ketones to give the trans adducts.[3] However, this could be expected because of the intermediacy of a bromonium ion in the reaction. Previously it had shown that 2-substituted-*F*-propene derivatives add bromine only under radical conditions and that a carboxy group is necessary to prevent ex-

$$RCF{=}CFX \xrightarrow{Br_2} RCFBrCFBrX$$

1, X = Cl; R = 4-$HO_2CC_6H_4$–
2, X = CF_3; R = 4-$HO_2CC_6H_4$–



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