Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.66; N, 6.06. Found: C, 67.64; H, 5.71; N, 6.04.

Treatment of 1.0 g (6.5 mmol) of **1c** with ethylene oxide in acetic acid as described above followed immediately by basic hydrolysis (1 equiv of NaOH in aqueous CH_3OH at room temperature for 2 h) yielded directly after workup 1.22 g (99%) of alcohol **6a**, mp 113–115 °C.

10b*H*-Oxazolo[3,2-*a*]quinoline (7). A solution of 1.0 g (7.70 mmol) of quinoline and 10 mL (200 mmol) of ethylene oxide in 50 mL of acetic acid was allowed to sit at room temperature overnight. Workup in the usual fashion yielded 1.34 g (100%) of **7** as a mobile yellow oil: NMR ($CDCl_3$) δ 7.30–6.40 (m, 5, including H-5), 5.75 (dd, 1, J = 3 and 9 Hz, H-4), 5.50 (d, 1, J = 3 Hz, H-10b), 3.50 (br s, 4, NCH_2CH_2O); IR ($CHCl_3$) 3000, 2900, 1650, 1600, 1500, 1465 cm^{-1}.

Acknowledgments. We thank Dr. Catherine Costello (MIT) for the aquisition and interpretation of the high resolution mass spectrum for **3b**, Professor Arthur C. Watterson (University of Lowell) for assistance in interpreting the ^{13}C NMR spectrum of **3b**, and Professor Jack E. Baldwin (MIT) for an invaluable discussion regarding the mechanisms of the transformations discussed herein. This investigation was supported in part by the National Cancer Institute, Contract 1-CM-53741.

Registry No.—**1b**, 53055-08-6; **1c**, 1198-30-7; **3b**, 68152-19-2; **6a**, 68152-20-5; **6b**, 68152-21-6; **7**, 68152-22-7; ethylene oxide, 75-21-8; quinoline, 91-22-5; 1-cyano-1,2-dihydro-2-(phenylsulfonyl)isoquinoline, 1035-19-4.

References and Notes

(1) Presented in part at the Eighth Northeast Regional Meeting of the American Chemical Society, Boston, Massachusetts, June, 1978, Abstract ORGN-57.
(2) New England Nuclear, Boston, Massachusetts 02118.
(3) Author to whom correspondence should be addressed.
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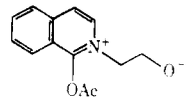
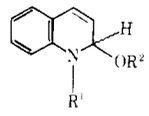
(7) Professor Jack E. Baldwin.(MIT) has kindly pointed out to us that, although these results do suggest the intermediacy of **2c**, they do not unambiguously implicate intermediate **3c** [formed from a 5-endo-trig ring closure: (J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976)] in the conversion of **1c** to **6a** and **6b**. Intermolecular attack of solvent on **2c** could compete with intramolecular ring closure (either 5-endo-trig yielding **3c** or 6-exo-dig yielding lactone **4**) to give intermediate i shown below. Our results do not exclude the intermediacy of i in the conversion of **1c** to mixture **6a** and **6b**, but do show that the formation of these isoquinolones through whatever mechanism is more favored than lactone **4**.



i

(8) Although several alcohols (R^2 = H) and ethers (R^2 = alkyl) of general structure ii, a quinoline pseudobase, have been described (N. Campbell in "Rodd's Chemistry of Carbon Compounds", 2nd ed, Vol. IV, Part F, S. Coffey, Ed., Elsevier, Amsterdam, 1976, p 271, and references cited therein), the preparation of **7** represents the first example of a cyclic derivative of ii.



ii

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Transannular Cyclizations of 1-Aza-4-cyclooctene[1]

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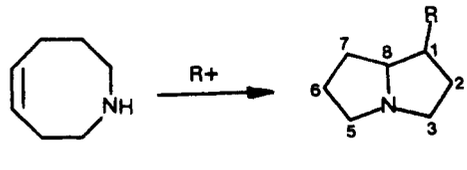
The stereospecific, transannular cyclizations of 1-aza-4-cyclooctene (1) are described. Compound **1** reacts with electrophiles (Br_2, I_2, $HgCl_2$, PhSBr, PhSeBr) to produce 1-substituted pyrrolizidines **6**. The stereochemistry of the bromine-induced cyclization was determined by X-ray crystallography. The reaction proceeds via transannular reaction of the nitrogen with the corresponding "onium" ion. There is no evidence of through-space (transannular) interaction of the amine and the double bond by PES.

Most naturally occurring pyrrolizidine alkaloids[3] contain substitution at the C-1 position. Thus, an approach to this bicyclic ring system which would enable simultaneous substitution at the 1 position would allow for the greatest flexibility in the synthesis of these natural products (eq 1). The

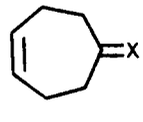


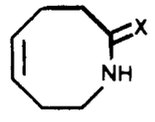
(1)

1 2

synthetic pathway described herein results in the stereospecific formation of C-1 substituted pyrrolizidines via transannular cyclization. Intramolecular cyclizations of medium ring systems are common.[4,5] We have reported recently our results in the azacyclononene series.[6]

Preparation of 1-Aza-4-cyclooctene (1). Amine **1** was prepared by the following series of reactions. Formation of oxime **3** of 4-cycloheptenone[7] followed by treatment with *p*-toluenesulfonyl chloride and pyridine yielded tosylate **4**. Tosyl oxime **4** underwent a facile Beckmann rearrangement[8] to give lactam **5**. Compound **5** was a white crystalline material





3 X = NOH **5** X = O

4 X = NOTs **1** X = H_2

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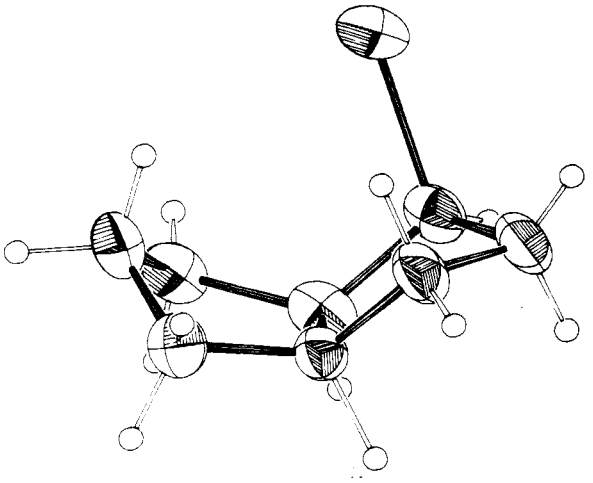
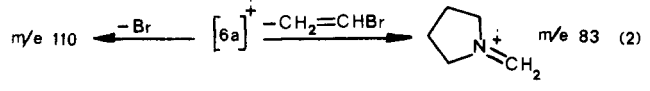


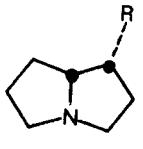
Figure 1. ORTEP drawing of $(C_7H_{13}NBr)^+ Br^-$.

which displayed the normal carbonyl absorption band at 1645 cm^{-1} typical of an eight-membered ring lactam.[9] Reduction of **5** with lithium aluminum hydride afforded amine **1**. Amine **1** was subsequently treated with various electrophiles to determine which agents facilitate the desired ring closure.

Transannular Cyclizations. Reaction of **1** with bromine[5b] in methylene chloride afforded a salt, which showed a single peak by GLC analysis of the free base. The NMR spectrum showed the absence of any olefinic protons but a one hydrogen multiplet at δ 4.43 consistent with a proton α to bromine. The mass spectrum showed a fragmentation pattern typical of the pyrrolizidine ring[10] system (eq 2) and a molecular ion at *m/e*

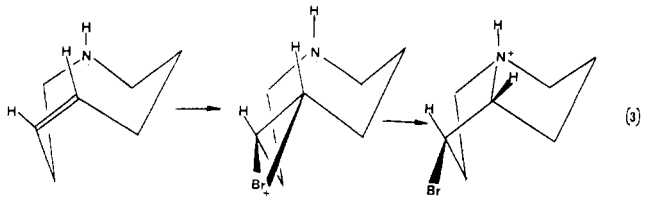


191 and 189. Elemental analysis of the hydrochloride and picrate salts confirmed the presence of a compound with an empirical formula $C_7H_{12}NBr$. The stereochemistry of the product **6a** was confirmed by an X-ray structure determina-



6a R = Br
6b R = H
6c R = HgCl
6d R = SePh
6e R = SPh
6f R = I

tion (Figure 1) on the HBr salt.[11] Figure 2[23] shows the numbering scheme used for all tables. Structural parameters are collected in Tables III–VII.[23] The stereochemical consequences of this reaction are displayed in eq 3.



It is important to note that the transannular cyclization yields a product with a substituent at C-1 which could in principle be further modified and that the ring closure is

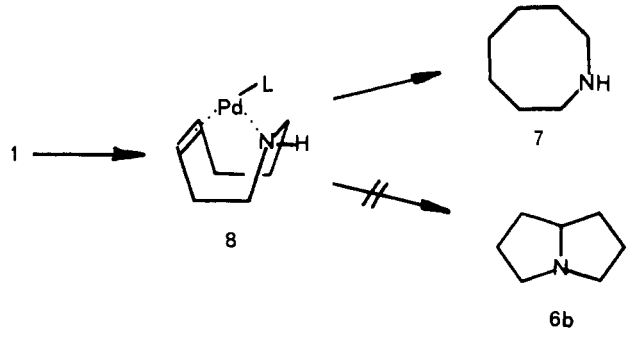
Table I. Transannular Cyclizations of 1-Aza-4-cyclooctene

electrophile	registry no.	product	registry no.	% yield
Br_2	7726-95-6	**6a**	65113-03-0	85
$HgCl_2$	7487-94-7	**6c**	68201-03-6	91
PhSeBr	34837-55-3	**6d**	68201-04-7	63
PhSBr	28074-23-9	**6e**	68201-05-8	71
I_2	7553-56-2	**6f**	68201-06-9	71

stereospecific. Both of these factors are important in a pyrrolizidine alkaloid synthesis. Reduction of **6a** with lithium aluminum hydride affords the pyrrolizidine nucleus **6b.**[2]

An aminomercuration reaction[5c] was observed when amine **1** was treated with mercuric chloride in tetrahydrofuran. The mercurial **6c** was reduced with sodium borohydride to again yield pyrrolizidine **6b.** Studies[12] have shown that the aminomercuration reaction proceeds with complete trans stereospecificity. Thus, the stereochemistry depicted for **6c** is consistent with the initial formation of the intermediate mercuronium ion followed by nucleophilic attack of the amine.

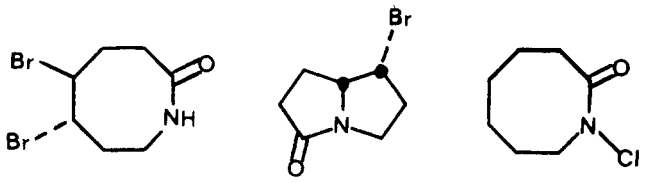
Hegedus[13] has reported a palladium-assisted intramolecular amination leading to indoles. It was anticipated that under similar conditions **1** would cyclize with the appropriate palladium complex and subsequent oxidative cleavage could yield C-1 substituted alkaloids. Addition of **1** to a tetrahydrofuran solution of $PdCl_2(PhCN)_2$[14] afforded a yellow-brown precipitate. Addition of triethylamine to the reaction mixture yielded a clear black solution with the slow formation of a black precipitate. Reduction of the mixture with potassium borohydride afforded the saturated product **7** and *no* pyrrolizidine. Apparently the formation of complex **8** prevents transannular cyclization.



Both selenium[15] and sulfur[16] electrophiles induce the transannular ring closure. Treatment of amine **1** with benzeneselenyl bromide[17] afforded the transannular product **6d** in good yield. Reaction of **1** with benzenesulfenyl bromide yielded the ring-closed product **6e** as well as a small amount of **6a.** Both **6d** and **6e** displayed the expected fragmentation pattern in the mass spectrum for the pyrrolizidine nucleus (base peak *m/e* 83) and had similar NMR spectra.

To complete the series of electrophiles which might induce cyclization, amine **1** was treated with iodine and the iodide **6f** was obtained in good yield. Thus, a novel group of 1-substituted pyrrolizidines are readily available (Table I).

Amides have also demonstrated their ability to participate in transannular ring closures.[6,18] Attempts were made to induce cyclization of lactam **5** under reaction conditions similar to those that would be employed in the cyclization of amine **1.** Treatment of **5** with bromine in methylene chloride yielded a compound whose NMR spectrum indicated the absence of olefinic protons. The infrared spectrum of the product, however, showed a carbonyl absorption at 1650 cm^{-1} consistent with compound **9** but not **10;** elemental analysis indicated that



9 10 11

the product formed was the dibromolactam **9** with no trace of cyclized lactam **10**.

Mechanistic Considerations. The reaction of electrophiles with amino olefins has only recently[5a] been recognized as a facile cyclization methodology. Such addition reactions with bromine proceed by either of two mechanistic pathways: (1) formation of a bromonium ion intermediate followed by ring closure, or (2) initial formation of a dibromide which subsequently cyclizes with elimination of hydrogen bromide. The reaction conditions employed in this cyclization imply a mechanism that is consistent with the opening of a bromonium ion intermediate: fast electrophile (Br_2), good nucleophile (amine). The stereochemistry of adduct **6a** is also that derived via the bromonium ion pathway (eq 3). Formation of dibromide followed by cyclization would lead to the alternative stereochemistry. In addition, we reasoned that the unusual constraints of the eight-membered ring, particularly the proximity (<3 Å) of the nitrogen lone pair to the double bond, would allow for ready cyclization.

In order to determine whether there is through-space interaction between the nitrogen lone pair and the transannular π electrons, photoelectron spectra of azacyclooctane **7** and azacyclooctene **1** were obtained[20] (Table II) and compared with suitable reference compounds. Although Morishima[22] has seen interactions in smaller rings, the spectra clearly show that there is *no* transannular interaction; the lone pair ionization potential of **1** is the same as that for **7** within experimental error (±0.4 eu).

Thus, the electrophilic cyclizations in this series are similar to those of the nine-membered rings; conformational properties of the system will dictate when transannular cyclization is favorable. Edwards[18b] has examined the transannular cyclization of medium ring *N*-chloroamides and found that the compound **11** does not cyclize for geometric reasons. The π electrons of a planar amide cannot overlap with the rear lobe of the C–Cl bond. In our case, bromination of lactam **5** leads only to dibromide because the amide function is a much poorer nucleophile (relative to Br). Reaction with an external nucleophile is more rapid than the conformational changes in **5** necessary to bring the nitrogen lone pair in position for cyclization since models indicate that amide overlap cannot be maintained in the process.

Experimental Section

General. Melting points were measured in capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on Varian HR-220 and T-60A spectrometers. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane. 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, KBr pellets, or on neat samples using a Perkin-Elmer 137 Infracord. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Mich. Gas chromatography was performed with a Varian Model 3700 gas chromatograph with an FID detector on a 1.5% OV-101 on Chromasorb G column (5 ft × ⅛ in. glass column) with helium carrier gas. 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-Cycloheptenone Oxime (3). Into a 100-mL flask equipped with a reflux condenser was added 1.7 g (0.015 mol) of 4-cycloheptenone 7, 50 mL of methanol, 2 g (0.029 mol) of hydroxylamine hydrochloride, and 2 g of sodium bicarbonate. The mixture was heated to reflux for 4 h and after cooling was poured into 50 mL of water. The solution was extracted several times with chloroform, and the organic layers were combined and dried over sodium sulfate. Evaporation of the solvent left a heavy oil which crystallized slowly on standing under vacuum to yield **3** as white crystals: 1.7 g, 88% yield; mp 56–58 °C; IR ($CHCl_3$) 3250 and 1650 cm^{-1}; NMR ($CDCl_3$) δ 9.40 (broad s, 1 H, =NOH), 5.70 (m, 2 H), 2.1–2.9 (m, 8 H); mass spectrum, *m/e* (relative intensity) 125 (7, M^+), 108 (22), 107 (24), 106 (35), 98 (17), 93 (17), 81 (25), 80 (52), 79 (100), 77 (19), 67 (99).

Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.06; H, 8.85; N, 11.15.

4-Cycloheptenone Oxime Tosylate (4). Oxime **3** (1.2 g, 9.6 mmol) was dissolved in 150 mL of methylene chloride and cooled to −10 °C with an ice–salt slush bath. After the addition of 2 mL of pyridine, 2.2 g (11.6 mmol) of *p*-toluenesulfonyl chloride in 50 mL of methylene chloride was added dropwise over 1 h. The reaction mixture was allowed to slowly warm to room temperature and was stirred overnight. The yellow solution was poured into 50 mL of 10% HCl, extracted with chloroform, and washed with saturated sodium bicarbonate solution, and the organic layer was dried over sodium sulfate. Evaporation of the solvent at room temperature afforded the crude tosylate as a brown oil which was recrystallized from chloroform–pentane to yield **4** as white crystals: 2.05 g, 77% yield; mp 83–84 °C; IR ($CHCl_3$) 1600 cm^{-1}; NMR ($CDCl_3$) δ 7.92 (d, 2 H, J = 8 Hz), 7.40 (d, 2 H, J = 8 Hz), 5.70 (m, 2 H), 2.47 (s, 3 H, Ar–CH_3), 2.1–2.9 (m, 8 H); mass spectrum, *m/e* (relative intensity) 155 (24), 109 (14), 108 (19), 94 (20), 91 (62), 67 (27).

Anal. Calcd for $C_{14}H_{17}NSO_3$: C, 60.19; H, 6.13; N, 5.01; S, 11.48. Found: C, 60.07; H, 6.11; N, 5.01; S, 11.50.

1-Aza-2-ketocyclooct-5-ene (5). A solution containing 1 g (3.58 mmol) of tosyl oxime **4**, 50 mL of water, 400 mg of potassium carbonate, and 50 mL of tetrahydrofuran was stirred overnight at room temperature. The mixture was extracted several times with chloroform, and the organic extracts were washed with saturated sodium bicarbonate. After drying over sodium sulfate, the solvent was evaporated, leaving crude lactam which was recrystallized from methylene chloride–pentane to yield **5** as white crystals: 406 mg, 91% yield; mp 88–89 °C; IR ($CHCl_3$) 3400 and 1645 cm^{-1}; NMR ($CDCl_3$) δ 7.05 (broad s, 1 H, –NH), 5.73 (m, 1 H), 5.52 (m, 1 H), 3.45 (q, 2 H, J = 5 Hz, $-CH_2NH-$), 2.66 (m, 2 H), 2.45 (m, 4 H); mass spectrum, *m/e* (relative intensity) 125 (27, M^+), 96 (86), 69 (16), 68 (61), 67 (23), 54 (100).

Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.23; H, 8.74; N, 11.09.

1-Aza-2-keto-5,6-dibromocyclooctane (9). To a solution containing 50 mg (0.4 mmol) of lactam **5** and 10 mL of methylene chloride was added 212 mg (1.3 mmol) of bromine in 10 mL of methylene chloride over 15 min. The resulting red solution was stirred for 1 h at room temperature and poured into 50 mL of water. The aqueous layer was discarded, and the organic layer was washed with saturated sodium bicarbonate (20 mL) and water (20 mL) and dried over sodium sulfate. Evaporation of the solvent afforded **9** as light yellow crystals: 87 mg, 76% yield; mp 111–114 °C dec; IR ($CHCl_3$) 3400 and 1650 cm^{-1}; NMR ($CDCl_3$) δ 7.00 (broad s, 1 H, –NH), 4.80 (m, 2 H, CHBr–CHBr–), 3.65 (m, 2 H, $-CH_2NH-$), 2.3–3.0 (m, 6 H); mass spectrum, *m/e* (relative intensity) 285 (1, M^+), 206 (66), 204 (68), 124 (74).

Anal. Calcd for $C_7H_{11}NOBr_2$: C, 29.50; H, 3.89; N, 4.91; Br, 56.08. Found: C, 29.61; H, 3.92; N, 4.86; Br, 55.99.

1-Azacyclooct-4-ene (1). Lactam **5** (135 mg, 1.08 mmol) dissolved in 5 mL of tetrahydrofuran was added dropwise to a solution containing 150 mg (3.9 mmol) of lithium aluminum hydride in 50 mL of ether. The reaction mixture was heated to reflux for 4 h and stirred overnight. After quenching with water, the solution was filtered to remove the salts and amine **1** was distilled, affording a clear liquid: 75 mg, 63% yield; bp 80–90 °C (20 mm); IR (neat) 3300 cm^{-1}; NMR ($CDCl_3$) δ 5.75 (m, 2 H), 2.80 (m, 4 H), 2.10 (m, 6 H), 1.60 (m, 1 H, –NH); mass spectrum, *m/e* (relative intensity) 111 (30, M^+), 83 (11), 82 (43), 70 (12), 68 (18), 67 (15), 57 (40), 56 (28), 54 (21), 44 (100).

Table II. Ionization Potentials

compd	IP, eu	ref
piperidine	8.64 (n)	19
7	8.47 (n)	20
1	8.44 (n), 9.06 (π)	20
cyclooctene	8.98 (π)	21

Anal. Calcd for $C_7H_{13}N$: M_r = 111.1049. Found: M_r = 111.1059.

The picrate was recrystallized from ethanol to yield yellow needles, mp 148–149 °C.

Anal. Calcd for $C_{13}H_{16}N_4O_7$: C, 45.89; H, 4.74; N, 16.46. Found: C, 45.90; H, 4.55; N, 16.43.

***trans*-1-Bromopyrrolizidine (6a).** A solution containing 75 mg (0.47 mmol) of bromine in 5 mL of methylene chloride was added dropwise to a mixture of 44 mg (0.40 mmol) of amine 1 in 25 mL of methylene chloride. The resulting yellow solution was stirred overnight at room temperature and the solvent evaporated, leaving the HBr salt as a crude red oil (104 mg, 97% yield) recrystallized from acetonitrile–ether: mp 120–130 °C; IR ($CHCl_3$) 2250–2700 cm^{-1}; NMR ($CDCl_3$) δ 1.0–5.0 (broad m, 13 H); mass spectrum, *m/e* (relative intensity) 191 (5), 189 (7), 149 (19), 110 (18), 83 (100), 82 (34), 80 (11), 55 (26).

Anal. Calcd for $C_7H_{13}NBr_2$: C, 31.02; H, 4.84; N, 5.17; Br, 58.97. Found: C, 31.04; H, 4.81; N, 5.21; Br, 59.11.

Ether was added to the red oil obtained above, and 1 N NaOH was added to completely dissolve the HBr salt. The ether layer was dried over potassium carbonate and evaporated, leaving **6a** as a yellow oil: 64 mg, 85% yield; NMR ($CDCl_3$) δ 4.43 (m, 1 H, –CHBr–), 3.66 (m, 1 H), 1.8–3.2 (m, 10 H); mass spectrum, *m/e* (relative intensity) 191 (9, M^+, ^{81}Br), 189 (9, M^+, ^{79}Br), 110 (33), 108 (14), 83 (100), 82 (46), 55 (57). The picrate was recrystallized from ethanol to yield yellow crystals, mp 224–226 °C.

Anal. Calcd for $C_{13}H_{15}N_4O_7Br$: C, 37.25; H, 3.61; N, 13.37; Br, 19.06. Found: C, 37.32; H, 3.71; N, 13.05; B_r, 18.92.

Crystallography. Crystals of **6a**·HBr were obtained by evaporation from ether solution. An irregularly shaped crystal of approximate dimensions 0.12 × 0.10 × 0.09 mm was used for the X-ray study. The crystal was mounted on a glass fiber using silicone grease and placed directly on the goniostat which was equipped with a gaseous nitrogen cooling system,[24] and the sample was maintained at −160 ± 5 °C throughout characterization and data collection. The diffractometer used was locally constructed[25] and consisted of a Picker four-circle goniostat interfaced to a Texas Instruments 980B minicomputer. The source was a molybdenum target monochromatized by means of a graphite crystal (002 plane), and the source–sample and sample–aperture distances were 23.5 and 22.5 cm, respectively. The receiving aperture dimensions were 2.5 mm wide and 4.0 mm in height. An ultrastable goniometer designed to minimize frosting and interference was used to hold the sample.

The sample was characterized using a systematic search procedure in which all reflections located in a limited region of reciprocal space were located and centered. A model of the reciprocal lattice was then constructed and examined for symmetry and systematic extinctions.[24] Based on such a procedure, the crystal was found to be monoclinic with extinctions corresponding to $P2_1/n_1$ (nonstandard setting of $P2_1/a$). Twelve reflections were centered in both positive and negative regions of 2θ using an automated top/bottom–left/right slit assembly (which was the basis of the goniostat alignment), and the angular data from these reflections were refined to yield the final cell dimensions of a = 10.068 (12) Å, b = 13.469 (9) Å, c = 7.135 (3) Å, and β = 97.30°. The calculated density based on four molecules per unit cell was 1.32 gm/cm^3, and the linear absorption coefficient was 41.7 cm^{-1} [λ (Mo Kα) = 0.71069 Å].

All data in the $+h$, $+k$, $+l$ quadradant were collected for the range $4.0 > 2\theta > 50.0$, and a limited sphere of complete data was collected to compare symmetry equivalent data and check for systematic errors. A standard θ–2θ scan technique was used with a speed of 3.0°/min over a range symmetrically disposed 1.0° on either side of the calculated positions of the $K\alpha_1$ and $K\alpha_2$ peaks, and 10-s background counts were recorded at each extreme of the scan. During the data collection, three reflections were monitored after every 100 measurements and examined for systematic trends. The intensities of the three showed only random fluxuations and no systematic trends.

The data were corrected for background, Lorentz, and polarization effects using formulas which have been given previously.[26] Based on prior experience, an "ignorance factor" of 0.03 was used in calculating the standard errors based on counting statistics. The final data set consisted of 896 unique structure amplitudes of which 852 had $I > 0.0$. For the purpose of least-squares refinement, only those amplitudes with $I > 0.0$ were utilized.

Direct methods were used to locate all nonhydrogen atoms. Anisotropic refinement rapidly converged, and a difference Fourier was then examined in an attempt to locate the hydrogen atoms. It was possible to locate peaks in positions which were chemically reasonable for all hydrogens. Isotropic refinement of hydrogens converged with the exception of the hydrogen on the nitrogen atom [H(16)], which tended to shift to a position 1.6 Å from the nitrogen and had excessively large thermal parameters. For the final refinements, fixed positional parameters for H(16) were taken from a difference Fourier synthesis and an isotropic B of 3.0 Å^2 was assigned.

Final residuals were $R(F)$ = 0.0387 and $R_w(F)$ = 0.0350 with the goodness of fit for the last cycle being 1.124, and the largest Δ/σ for a nonhydrogen parameter was 0.02.

All computations were performed on a CYBER 172-CDC6600 computer using the IUMSC XTEL interaction program library. The programs were based in part on A. C. Larson's Los Alamos code and J. A. Ibers' Northwestern University code. All relevant structural data are gathered in Tables III–VII.[23]

Reaction of 1 with Mercuric Chloride. Amine 1 (75 mg, 0.68 mmol) in 1 mL of tetrahydrofuran was added dropwise to a solution containing 187 mg (0.69 mmol) of mercuric chloride in 5 mL of tetrahydrofuran with the immediate formation of a white precipitate. After stirring for 1 h, the mixture was filtered and the filter cake washed with 5 mL of fresh THF. The white crystals were dried overnight under vacuum, leaving **6c:** 235 mg, 91% yield; mp 125–135 °C; IR (KBr) 2250–2700 cm^{-1}; NMR [$(CD_3)_2SO$] δ 1.5–4.5 (broad m, 13 H); mass spectrum, *m/e* (relative intensity) 274 (6), 273 (1), 272 (11), 271 (5), 270 (7), 269 (4), 268 (2), 202 (8), 201 (3), 200 (6), 199 (4), 198 (2), 111 (12), 110 (33), 109 (52), 108 (100), 83 (28), 82 (51), 81 (22), 80 (41).

Anal. Calcd for $C_7H_{13}NHgCl_2$: C, 21.97; H, 3.42; N, 3.66; Hg, 52.42; Cl, 18.53. Found: C, 19.04; H, 2.89; N, 2.87; Hg, 57.60; Cl, 17.03.

Pyrrolizidine (6b). Method A. Into a 50-mL flask equipped with a reflux condenser was added 200 mg (5.26 mmol) of lithium aluminum hydride, 135 mg (0.71 mmol) of *trans*-1-bromopyrrolizidine (**6a**), and 35 mL of ether. The solution was heated to reflux overnight, quenched with water, and filtered, and the solvent was evaporated to afford pyrrolizidine (**6b**) as a light yellow liquid, 42 mg, 53% yield. The picrate was recrystallized from ethanol to yield yellow crystals, mp 234–235 °C (lit.[27] mp 245 °C).

Anal. Calcd for $C_{13}H_{16}N_4O_7$: C, 45.89; H, 4.74; N, 16.46. Found: C, 45.95; H, 4.64; N, 16.29.

Method B. A suspension containing 160 mg (0.42 mmol) of **6c** in 7 mL of tetrahydrofuran was treated with excess sodium borohydride solution (0.5 M $NaBH_4$ in 3.0 M NaOH) and stirred for 30 min. The solution was centrifuged, affording 80 mg of Hg, 95% yield. The organic layer was decanted and dried over potassium carbonate. The solvent was evaporated, leaving pyrrolizidine (**6b**) as a light yellow liquid. This material was found to be identical with the pyrrolizidine prepared previously. The picrate was recrystallized from ethanol to yield yellow crystals, mp > 230 °C dec.

Reaction of 1 with Iodine. To a solution containing 50 mg (0.45 mmol) of amine 1, 10 mL of ether, and 10 mL of methylene chloride was added 135 mg (0.53 mmol) of iodine in 10 mL of methylene chloride. The purple solution was stirred at room temperature overnight and the solvent evaporated, leaving a purple oil. After washing with ether, the oil was dissolved in 1 M NaOH and extracted several times with ether. The ether extracts were dried over potassium carbonate and the solvent evaporation, leaving **6f** as a yellow oil: 76 mg, 71% yield; NMR ($CDCl_3$) δ 4.45 (m, 1 H, –CHI–), 3.41 (m, 1 H), 3.14 (m, 2 H), 2.77 (m, 2 H), 2.36 (m, 2 H), 1.6–2.0 (m, 4 H); mass spectrum, *m/e* (relative intensity) 237 (41, M^+), 236 (5), 110 (58), 109 (10), 108 (13), 83 (100), 82 (24), 55 (19).

Anal. Calcd for $C_7H_{12}NI$: M_r = 237.0015. Found: M_r = 237.0019.

Reaction of 1 with Benzeneselenyl Bromide. Bromine (187 mg, 1.17 mmol) in 1 mL of tetrahydrofuran was added to a stirred solution containing 422 mg (1.35 mmol) of diphenyl diselenide in 10 mL of THF. The dark red solution was stirred for 30 min at room temperature, and 100 mg (0.90 mmol) of amine 1 in 2 mL of THF was added dropwise. After stirring for 2.5 h, the solvent was evaporated, leaving a red oil. The oil was washed with ether, and the yellow ether layer was discarded. Fresh ether was added, and 1 M NaOH was added dropwise till the oil completely dissolved. The ether layer was decanted, extracted with 10% HCl (3 × 5 mL), made basic with solid NaOH, and extracted with ether, and the ether extracts were dried over potassium carbonate. Evaporation of the solvent afforded **6d** as a light yellow oil: 150 mg, 63% yield; NMR ($CDCl_3$) δ 7.50 (m, 2 H), 7.23 (m, 3 H), 3.48 (m, 1 H, –CHSe–), 3.14 (m, 2 H), 2.93 (m, 1 H), 2.50 (m, 2 H), 2.0–2.3 (m, 2 H), 1.6–2.0 (m, 4 H); mass spectrum, *m/e* (relative intensity) 267 (4, M^+, ^{80}Se), 110 (12), 109 (33), 83 (100), 55 (18). The picrate was recrystallized from methanol, mp 120–130 °C.

Anal. Calcd for $C_{13}H_{17}N^{80}Se$: M_r = 267.0527. Found: M_r = 267.0523.

Reaction of 1 with Benzenesulfenyl Bromide. Bromine (94 mg, 0.59 mmol) in 1 mL of tetrahydrofuran was added to a solution containing 147 mg (0.67 mmol) of diphenyl disulfide in 10 mL of THF. After stirring for 30 min at room temperature, 50 mg (0.45 mmol) of

amine 1 in 1 mL of THF was added dropwise. The yellow mixture was stirred for 2.5 h and the solvent evaporated, leaving an orange oil. The oil was washed with ether and the ether discarded. The addition of fresh ether followed by 1 M NaOH (sufficient amount to dissolve the oil) left a yellow organic layer which was extracted with 10% HCl (3 × 5 mL), made alkaline with solid NaOH, and extracted again with ether, and the ether extracts were dried over potassium carbonate. The solvent was filtered and evaporated, leaving a yellow oil (70 mg, 71% yield) which by GLC analysis contained **6e** plus a small amount of **6a**. NMR ($CDCl_3$) for **6e:** δ 7.40 (m, 2 H), 7.25 (m, 3 H), 1.6–3.8 (m, 12 H). Mass spectrum, *m/e* (relative intensity) 219 (9, M^+), 110 (5), 109 (18), 108 (6), 84 (6), 83 (100), 55 (12).

Anal. Calcd for $C_{13}H_{17}NS$: M_r = 219.1082. Found: M_r = 219.1074.

Reaction of 1 with $PdCl_2(PhCN)_2$.[14] A solution containing 42 mg (0.38 mmol) of amine 1 in 5 mL of tetrahydrofuran was added dropwise to a mixture containing 150 mg (0.39 mmol) of $PdCl_2(PhCN)_2$ in 5 mL of THF at −40 °C with the immediate formation of a yellow precipitate. The yellow mixture was stirred for 1 h at room temperature, and triethylamine was added dropwise till the solution was clear with the formation of a black precipitate. After stirring for 2 h at room temperature, 25 mg (0.46 mmol) of potassium borohydride and 0.5 mL of 2 M NaOH were added and the solution was stirred for an additional 30 min. The clear solution was filtered from the palladium metal and extracted with 4 M HCl (3 × 5 mL). The aqueous layer was made alkaline with NaOH pellets and extracted with ether, and the ether extracts were dried over potassium carbonate. The sole product was determined by GLC to be **7** with identical spectral characteristics with those of azacyclooctane prepared by a separate route from cycloheptanone. No trace of either pyrrolizidine or starting material was observed.

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Registry No.—**1**, 57502-48-4; **3**, 65113-00-0; **4**, 65113-01-1; **5**, 65113-02-2; **6a**·HBr, 65113-05-5; **6a** picrate, 68225-94-5; **6b**, 643-20-9; **6d** picrate, 68201-07-0; **7**, 1121-92-2; **9**, 68201-08-1; diphenyl disulfide, 882-33-7; $PdCl_2(PhCN)_2$, 14220-64-5; diphenyl diselenide, 1666-13-3.

Supplementary Material Available: Figure 2 (numbering scheme for tables), Table III (fractional coordinates of atoms), Table IV (anisotropic thermal parameters), Table V (distances), Table VI (angles), and Table VII (torsion angles and structure factors) (6 pages). Ordering information is given on any current masthead page.

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Notes

Synthesis of 1,4,5,6-Tetrahydro-2-(hydroxymethyl)-4-oxo-3-pyridinecarboxylic Acid γ-Lactones

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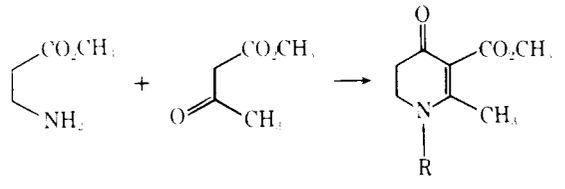
The tetrahydropyridine ring plays a central role in the construction of a variety of alkaloids.[1] Our own interest in the total synthesis of morphine alkaloids[2] required a practical synthesis of the previously unreported lactones **4a–c.** In this note, we describe an efficient synthesis of these and related compounds.

Using the method of Becker,[3] keto ester **1a** is easily pre-



1a, R = H
b, R = CH_3
c, R = CO_2CH_3

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