Synthetic and Structural Studies of the Lolium Alkaloids

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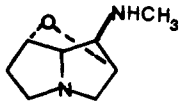
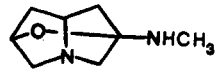
Application of transannular cyclizations to the synthesis of bridged pyrrolizidine alkaloids such as loline (1) is described. The general method involves bromination of 3-aza-9-oxabicyclo[4.2.1]non-7-ene (5), leading directly to the skeleton (12a) of the lolium alkaloids. Unsuccessful attempts to replace the bromine are described. The X-ray structure of the synthetic compound 12a as well as loline itself (1) and the biogenesis of lolium alkaloids are also discussed.

The loline alkaloids (1 and its relatives[2]) are members of a small group of norpyrrolizidine alkaloids whose common feature is a unique oxygen bridge. First isolated in 1955,[3] loline was assigned the erroneous structure 2 in



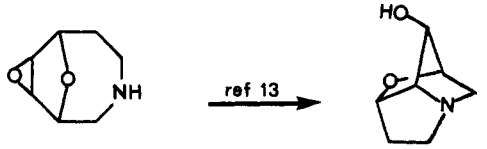
1 (Loline, Festucine)



2

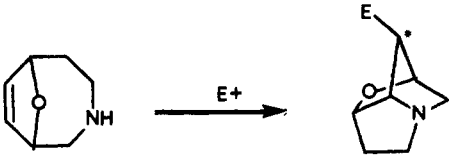
1960.[4a] In 1963 "festucine" (also 1) was isolated[4b] from tall Fescue and its structure assigned as 1. This caused some confusion in the literature even though the structure of loline was revised in 1965[5] and the identity of loline and festucine established by direct comparison in 1969.[6] An unpublished X-ray diffraction study[7] confirmed 1. The absolute configuration of the loline group of alkaloids was established in 1972.[8] Current views[9,10] conflict as to the actual pharmacological properties of these alkaloids, although loline shows weak antitumor activity.[11]

Recently, two syntheses of the loline ring system were reported.[12-14] Glass[13] was able to prepare the loline skeleton via an intramolecular cyclization of the amino epoxide 3 → 4. We provide the details[12] of our synthetic efforts in this area.



3 4

The synthetic strategy leading to the loline ring system is based on transannular cyclizations[12,15] of medium-ring amines. With the transannular ring closure established as a viable synthetic pathway leading to various alkaloid classes,[15] it was anticipated that reaction of amine with suitable electrophiles would lead to the tricyclic intermediate (eq 1). Inversion at this center (marked with an asterisk) would lead directly to the stereochemistry of the natural products.

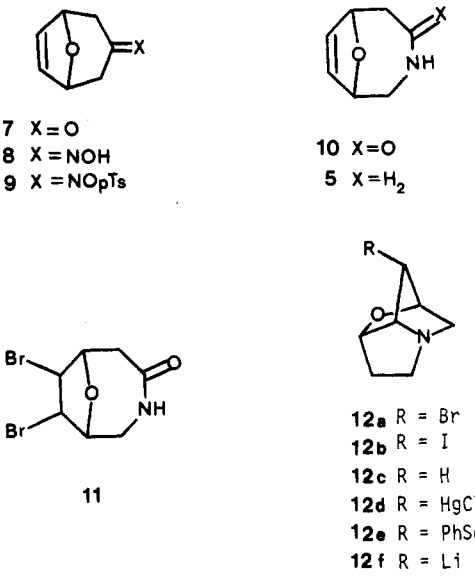


(1)

5 6

Preparation of Compound 5. The synthetic pathway leading to tricyclic 6 involved formation of the crucial intermediate 5. This bridged amine 5 could be prepared from the known ketone 7 (see Chart I), available by the interesting cycloaddition reactions of furan.[16,17] Treatment of 7 with hydroxylamine hydrochloride afforded oxime 8 which was subsequently converted to the oxime tosylate 9 with *p*-toluenesulfonyl chloride and pyridine. Due to the allylic nature of the oxygen bridge (also β to the C=N), mild conditions were employed (aqueous tetrahydrofuran

Chart I



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(2) For a somewhat dated review see: Tookey, H. L.; Yates, S. G. *An Quim.* **1972**, 921–935.

(3) Yunusov, S. Y.; Akramov, S. T. *J. Gen. Chem. USSR (Engl. Transl.)* **1955**, *25*, 1965–1971.

(4) (a) Yunusov, S. Y.; Akramov, S. T. *J. Gen. Chem. USSR (Engl. Transl.)* **1960**, *30*, 699–704, 705–710, 3105–3109. (b) Yates, S. G. *J. Chromatogr.* **1963**, *12*, 423–426.

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(9) The crude alkaloidal extract from tall fescue does not produce "fescue foot" symptoms when fed to a heifer.[10]

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and potassium carbonate) for the Beckmann rearrangement, and lactam **10** was obtained in good yield. Compound **10** was a white crystalline material (mp 133–134 °C) with a carbonyl absorption band at 1640 cm^{-1} typical of an eight-membered ring lactam.

Attempts to initiate direct ring closure of lactam **10** were unsuccessful; for example, reaction of **10** with bromine afforded dibromolactam **11** (isomers) and no cyclized material. These results are consistent with the poor nucleophilic character of the amide moiety.[15c]

Reduction of **10** with filtered[18] lithium aluminum hydride afforded the desired intermediate **5**. Reaction of **5** with bromine in methylene chloride induced transannular ring closure to bromide **12a**. This compound was identified by its mass spectrum which contained a parent ion at *m/e* 205 and an M + 2 peak at *m/e* 203 for $C_7H_{10}NO^{81}Br$ and $C_7H_{10}NO^{79}Br$ as well as an elemental analysis consistent with an empirical formula $C_7H_{10}NOBr$. The 220-MHz NMR spectrum showed a one proton doublet at 4.68 ppm (CHBr). The structure and stereochemistry of **12a** was confirmed by an X-ray diffraction experiment on the picrate salt[19] (Figure 1, supplementary material). The stereochemistry is consistent with the initial formation of a bromonium ion followed by nucleophilic attack by the nitrogen. The reaction thus provide the loline skeleton with a substituent at C-1.

Amine **5**, upon treatment with iodine, afforded iodide **12b**. This compound displayed an NMR spectrum similar to **12a** but containing a one proton signal at 4.73 ppm (CHI). The mass spectrum showed a parent ion at *m/e* 251 ($C^7H^{10}NOI$) with a fragmentation pattern, otherwise very similar to **12a**.

The aminomercuration reaction,[20a] which worked well in the unbridged pyrrolizidine system, was employed with surprising results. Under similar cyclization conditions, a mixture of amine **5** and mercuric chloride yielded a white crystalline material (elemental analysis: $C_7H_{11}NOHgCl_2$). Reduction with sodium borohydrode followed by the usual workup afforded only starting material **5** with no trace of the hemiloline **12c** expected from cyclization–reduction. It appeared that the addition of mercuric chloride yielded a salt and not the cyclized product **12d**.

The only difference between the starting amine **5** and 1-aza-4-cyclooctene (which cyclizes well under these conditions)[5c] was the presence of the oxygen bridge; however, this difference may be a crucial one. The oxygen may coordinate[20] with the mercury, forcing the molecule to assume a conformation that will not allow for ready cyclization.

Barrelle and Apparu,[20b] examining the aminomercuration of azirdines in cyclooctene systems, demonstrated the need for 2 equiv of a mercury salt. They suggested that the first mole attacked the nitrogen atom reversibly. The second mole initiates cyclization. In an attempt to induce cyclization, the mercuric chloride complex of **5** was dissolved in hexamethylphosphoramide (HMPA), and a second equivalent of mercuric chloride was added. The solution was stirred overnight and reduced with sodium borohydride. The product of the reaction was the starting amine **5**, with none of the cyclized product **12d** being observed.

Table I. Attempted Displacements of 12a,b[a]

nucleophile[b]	solvent[c]	reaction conditions
CH_3NH_2	CH_3CN	4 days, 125 °C
CH_3NH_2	CH_3CN	3 days, 100 °C, $AgBF_4$
CH_3NH_2	CH_3CN	3 days, 100 °C, AgO_2CCF_3
CH_3NH_2	CH_3OH	7 days, 150 °C
CH_3NH_2	CH_3OH	5 days, 100 °C, $AgBF_4$
NaN_3	$(CH_3)_2CO$, H_2O	4 days, reflux
NaN_3	CH_3CN, H_2O	2 days, reflux
NaN_3	HMPA	2 days, room temp
Bu_4NN_3	HMPA	2 days, 80 °C
CH_3SLi	HMPA	1 day, room temp

[a] All reactions afforded only starting material, either **12a** or **12b**. [b] Reactions using CH_3NH_2 were performed in sealed tubes under argon. [c] HMPA = hexamethylphosphoramide.

Aminopalladation was attempted with results similar to those obtained in the pyrrolizidine system. Reaction of amine **5** with $PdCl_2(PhCN)_2$ followed by reduction with potassium borohydride yielded the saturated amine **13** (picrate, mp 145–147 °C). These results were consistent with the formation of a palladium–olefin–amine complex which leads to **13** on reduction.

The final attempt to close the ring with a different electrophile involved the reaction of **5** with phenylselenyl bromide. The isolated product mixture consisted mostly of starting amine **5** and small amount (~10%) of the cyclized **12e** as evidenced by aromatic protons (SeAr) in the NMR spectrum as well as signal at 4.2 ppm (**CH**SePh).

Attempted Displacement at C-7. The stereospecificity of this reaction translates into a simple route alkaloids of this type. Conditions suitable of and S_N2 displacement at this center (C-1) by an appropriate nitrogen nucleophile would lead to inversion of stereochemistry, yielding the loline family of alkaloids. The obvious transformation leading directly to loline involved S_N2 displacement of the bromine in **12a** by methylamine. Treatment of **12a** with methylamine, however, under a variety of conditions (Table I), yielded only recovered starting material with no detectable trace of loline (**1**). When **12b** was treated with methylamine, starting material was also recovered, again with no detectable trace of loline. When either **12a** or **12b** was reacted with the more reactive nitrogen nucleophile, azide ion, only starting material was obtained. Lithium thiomethoxide[22] has been found to be a very powerful nucleophilic species; however, treatment of **12b** with lithium thiomethoxide yielded only starting material.

The results obtained in this study suggested that bromide was quite unreactive toward nucleophiles. Compound **12a** is a 7-norbornane system, and the paucity of substitution reactions at C-7 in the norbornane ring system is due to two factors:[23] first, the small C-1, C-7, C-4 bond angle (93°) makes substitution difficult; second, there is steric hindrance by the *exo*-hydrogens at C-5 and C-6 toward the incoming nucleophile. In this heterocyclic analogue, the X-ray structure revealed an even smaller angle (88°) between C-1, C-7, and C-4. Also, electron–electron repulsion between the lone-pair electrons on the bridgehead nitrogen and the incoming nucleophile may make displacement electronically unfavorable as well. The only "displacement" reaction of **12a** was the reduction with lithium aluminum hydride to hemiloline **12c**.[24]

(18) Unfiltered $LiAlH_4$ led to lower yields, possibly due to oxygen bridge cordination and ring opening by aluminum species.
(19) Huffman, J. C. Report No. 7604; Indiana University Molecular Structure Center: Bloomington, IN, 1976.
(20) (a) Roussel, J.; Perie, J. J.; Laval, J. P.; Lattes, A. *Tetrahedron* **1972**, *28*, 701. (b) Barrelle, M.; Apparu, M. *Tetrahedron* **1977**, *33*, 1309.
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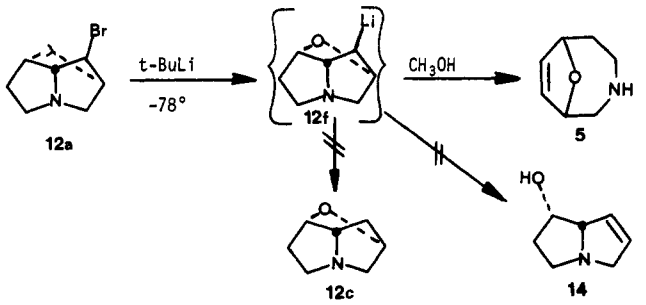
Scheme I



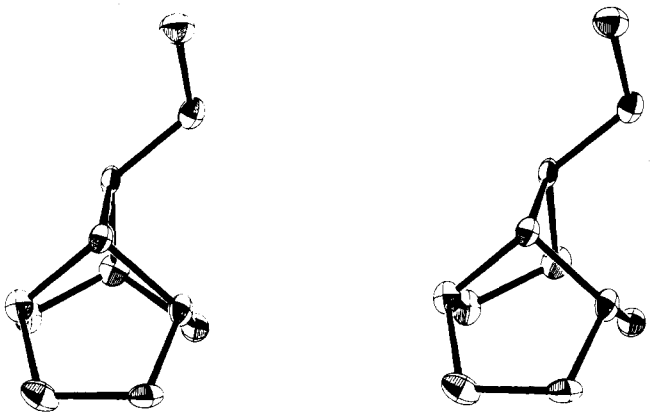


Figure 2. Stereoscopic view of molecule 1.

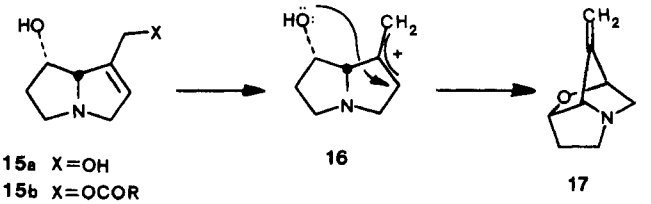
Treatment of **12a** with *tert*-butyllithium should yield the lithio derivation **12f** which might add to suitable electrophiles, giving an alternative route to loline (1). Reaction of **12a** with *tert*-butyllithium followed by hydrolysis afforded, however, neigher hemiloline **12c** (expected by simple hydrolysis) nor the unsaturated alcohol 14 but the starting amine **5** (Scheme I). The origin of **5** can be explained by formation of lithio compound **12f** followed by β elimination to the amine **5**.

X-ray Structure of Loline (1). Because the structure of loline (1) was never published and no errors were reported in the thesis,[7] we have repeated the X-ray diffraction experiment at low temperature to obtain more precise date for a structural comparison with synthetic model compounds. A single-crystal X-ray diffraction experiment confirmed structure 1 for loline (Figure 2).[25,26]

X-ray structures of 1 and **12a** are reported here, and the structure of 4 is reported by Glass.[27] The C(1)–C(7)–C(4) angles are 88°, 93°, 91.5°, respectively (the rather larger errors[35] in the structure of **12a** make a detailed comparison of these angles impossible). The very acute angle (~90 vs. 109.5° for normal sp^3) means that the transition state for the displacement reaction, which normally requires 120° or sp^2 geometry, looks very bad. This explains the remarkable stability of **12a** (which of course cannot eliminate HBr).

Biogenesis. It is interesting to speculate on the close relationship between loline 1 and retronecine **15a**. The toxicity of pyrrolizidine alkaloids has been attributed to the allylic ester[28] grouping which has been considered the essential feature for heptatoxic activity. A recently recognized[34] feature of structure/activity relationships in pyrrolizidine alkaloid hepatoxity appears to be the requirement that the alkaloid *not* possess a free (unesterified) 7-β hydroxyl group such as **15b** in (see Scheme II). Toxicity data[29] clearly indicates the presence of an unesterified 7β-hydroxyl dramatically reduces the toxicity. Consideration of the "electrophile" **16** derived from the allylic ester group (Scheme II) suggests that bridging by the free C-7 hydroxyl could lead directly to the loline type ring system **17**. Alkaloids of type **17** would be expected to be nontoxic. (A related in vivo detoxification of pyrrolizidine alkaloids by sheep rumen has been reported).[30] Implications are obvious for the biogenesis of the lolium alkaloids.

Scheme II



Experimental Section

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 or on neat samples by using a Perkin-Elmer 137 Infracord. Microanalysis were performed by Spang Microanalytical Laboratory. 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 × $^1/_8$ in. glass column) with helium carrier gas. Distillations were performed with a Buchi/Brinkmann standard microdistillation 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.

8-Oxabicyclo[3.2.1]oct-6-en-3-one (7). Into a 1-L, three-necked flask equipped with a mechanical stirrer and two dropping funnels and wrapped in aluminum foil were added 200 g of sodium carbonate, 150 mL of carbon tetrachloride, 50 mL of furan (dried by distillation from potassium carbonate), and 30 mL of a solution containing 55 g (~50%, 0.18 mol) of 2-methoxyallyl bromide[16] in 70 mL of carbon tetrachloride. The mixture was cooled to −10 °C with an ice–salt slush bath and stirred vigorously while the remaining 2-methoxyallyl bromide solution and a mixture containing 35 g (0.16 mol) of silver trifluoroacetate in 150 mL of furan were added. The solution was stirred 1 h after complete addition, poured into 250 mL of sodium chloride solution, and filtered to remove the salts. The filter cake was washed with 200 mL of ethyl acetate, and the aqueous layer was separated and discarded. The organic layer was dried over sodium sulfate and potassium carbonate and evaporated, leaving a yellow oil which was subject to column chromatography on silica gel with 1:3 to 3:1 ether/pentane as the elutant. Ketone 7 was isolated as light yellow crystals: 6.14 g (31% yield); mp 38–39 °C (lit.[16] mp 38 °C); IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 6.28 (s, 2 H), 5.07 (d, 2 H, J = 4 Hz), 2.1–3.0 (m, 4 H); mass spectrum, m/e (relative intensity) 124 (63, M^+), 82 (96), 81 (100), 54 (47), 53 (41); calcd for $C_7H_8O_2$ mol wt 124.0525, found 124.0531.

(24) Akramov, S. T.; Yunusov, S. Y. *Chem. Nat. Compd. (Engl. Transl.)* **1968**, *4*, 298.
(25) We thank Dr. S. G. Yates (USDA Northern Regional Research Laboratory, Peoria, IL) for a sample of loline (1).
(26) Huffman, J. C. Report No. 7828; Indiana University Molecular Structure Center: Bloomington, IN, 1979.
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(31) See paragraph at the end of this paper regarding supplementary material.

Table II. Crystal and Diffractometer Data

empirical formula	$C_8H_{16}N_2O^{2+},2Cl^-$ (1)	$C_7H_{11}ONBr^+C_6H_2O_7N_3^-$ (12a)	single bkgd time at extremes of scan, s	10	10
color of crystal	colorless				
crystal dimens (approximat), mm	0.3 × 0.3 × 0.4	0.6 × 0.4 × 0.3	aperture size, mm	3 × 3.5	3 × 3.5
space group	$P2_1P2_1P2_1$	$Pbca$	limits of data collection		
cell dimens (at −145 °C; 15 rflctns):			min 2θ, deg	4	4
a, Å	11.379 (6)	18.324 (9)	max 2θ, deg	50	45
b, Å	8.615 (4)	7.299 (4)	total reflctns collected	1203	
c, Å	10.770 (5)	23.620 (13)	no. of unique intensities	1097	2060
Z (molecules/cell)	4	8	no. with $F > 0.0$	1064	1870
vol, Å^3	1055.78	3159.10	no. with $F > \sigma(F)$	1060	
calcd density, g/cm^3	1.43	1.82	no. with $F > 2.33\sigma(F)$	1054	
wavelength, Å	0.710 69	0.710 69	final residuals: $R(E)$	0.0346	0.138[35]
mol wt	227.13	433.17	$R_w(F)$	0.0499	0.104
linear abs coeff, cm^{-1}	5.808	26.268	goodness of fit for the last cycle	1.56	1.90
detector to sample distance, cm	22.5	22.5	max δ/σ for last cycle	0.1	0.10
sample to source distance, cm	23.5	23.5			
takeoff angle, deg	2	2			
av ω-scan width at half-height, deg	0.25	1.5			
data collection	standard moving crystal–moving detector technique				
scan speed, deg/min	4	4			
scan width,	2.3 + dispersion	2.0 + dispersion			

8-Oxabicyclo[3.2.1]oct-6-en-3-one Oxime (8). A solution containing 2 g (16.1 mmol) of ketone **7**, 75 mL of methanol, 2.2 g (32.2 mmol) of hydroxylamine hydrochloride, and 2.2 g of sodium bicarbonate was heated to reflux for 5 h. The mixture was poured into 50 mL water and extracted several times with chloroform. The chloroform extracts were combined and dried over sodium sulfate, and the solvent was evaporated, leaving a yellow oil. Oxime **8** was crystallized from chloroform–pentane affording white crystals: 1.81 g (81% yield); mp 111–112 °C; IR ($CHCl_3$) 3300, 1650 cm^{-1}; NMR ($CDCl_3$) δ 9.64 (br s, 1 H, =NOH), 6.16 (s, 2 H), 4.84 (d, 2 H, J = 4 Hz), 2.95 (d, 1 H, J = 16 Hz), 2.57 (dd, 1 H, J = 4, 16 Hz), 2.32 (dd, 1 H, J = 4, 16 Hz), 2.20 (d, 1 H, J = 16 Hz); mass spectrum, m/e (relative intensity) 139 (33, M$^+$), 122 (55), 110 (10), 94 (26), 82 (36), 81 (100). Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.43; H, 6.35; N, 10.06.

8-Oxabicyclo[3.2.1]oct-6-en-3-one Oxime Tosylate (9). A flask containing 1.4 g (10.07 mmol) of oxime **8** in 100 mL of methylene chloride was cooled to −10 °C and 15 mL of pyridine added. A solution containing 3.4 g (17.8 mmol) of *p*-toluenesulfonyl chloride in 50 mL of methylene chloride was added dropwise over 1.5 h. After being stirred overnight at room temperature, the brown solution was poured into 25 mL of 10% HCl solution and the organic layer separated. After being washed with 25 mL of sodium bicarbonate solution, the organic layer was dried over sodium sulfate and the solvent evaporated at room temperature, leaving **9** as crude brown crystals (2.70 g, 91% yield) which were recrystallized from chloroform–pentane, affording **9** as white crystals: mp 98–99 °C; IR ($CHCl_3$) 1650, 1610 cm^{-1}; NMR ($CDCl_3$) δ 7.77 (d, 2 H, J = 8 Hz), 7.27 (d, 2 H, J = 8 Hz), 6.09 (s, 2 H), 4.84 (d, 1 H, J = 4 Hz), 4.80 (d, 1 H, J = 4 Hz), 2.93 (d, 1 H, J = 16 Hz), 2.57 (dd, 1 H, J = 4, 16 Hz), 2.43 (s, 3 H, $ArCH_3$), 2.36 (dd, 1 H, J = 4, 16 Hz), 2,27 (d, 1 H, J = Hz); mass spectrum, m/e (relative intensity) 155 (39), 139 (13), 110 (10), 107 (10), 91 (100), 82 (26), 81 (99), 68 (77). Anal. Calcd for $C_{14}H_{15}NSO_4$: C, 57.32; H, 5.12; N, 4.77; S, 10.93. Found: C, 57.22; H, 5.15; N, 4.77; S, 10.90.

3-Aza-4-oxo-9-oxabicyclo[4.2.1]non-7-ene (10). Oxime tosylate **9** (525 mg, 1.79 mmol) was added to a solution containing 50 mL of water and 200 mg of potassium carbonate. Tetrahydrofuran was added dropwise until all the tosyl oxime had dissolved (50 mL), and the mixture was stirred overnight at room temperature. The solution was extracted several times with methylene chloride. The aqueous layer was treated with ammonium chloride until saturation and extracted again with methylene chloride. All of the organic extracts were combined and after drying over sodium sulfate, and the solvent was evaporated, affording the crude lactam which was recrystallized from chloroform–pentane to yield **10** as white crystals: 212 mg (85% yield); mp 133–134 °C; IR ($CHCl_3$) 1640 cm^{-1}; NMR ($CDCl_3$) δ 7.30 (br s, 1 H, NH), 6.18 (d, 1 H, J = 6 Hz), 5.93 (d, 1 H, J = 6 Hz), 4.84 (s, 1 H), 4.70 (s, 1 H), 3.57 (d, 1 H, J = 14 Hz), 3.00 (dd, 1 H, J = 3, 14 Hz), 2.8–3.0 (m, 1 H), 2.50 (m, 1 H); mass spectrum, m/e (relative intensity) 139 (23, M$^+$), 110 (18), 81 (13), 68 (100), 43 (15). Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.47; H, 6.40; N, 9.98.

3-Aza-4-oxo-7,8-dibromo-9-oxabicyclo[4.1.1]nonane (11). Bromine (80 mg, 0.5 mmol) in 2 mL of methylene chloride was added to 64 mg (0.46 mmol) lactam **10** in 10 mL of methylene chloride. The resulting red solution was stirred overnight and the solvent evaporated, leaving a red oil which was crystallized from chloroform–pentane to yield **11** as light yellow crystals: 80 mg (58% yield), mp 150–160 °C; IR ($CHCl_3$) 1660 cm^{-1}; NMR ($CDCl_3$) δ 6.18 (br s, 1 H, NH), 4.75 (m, 2 H), 2.8–3.5 (m, 4 H); mass spectrum, m/e (relative intensity) 299 (1, M$^+$), 220 (36), 218 (38), 139 (22), 138 (100), 110 (56), 109 (45), 96 (23), 81 (19); calcd for $C_7H_9NO_2{}^{79}Br^{81}Br$ mol wt 298.8980, found 298.8954.

3-Aza-9-oxabicyclo[4.2.1]non-7-ene (5). A solution containing 300 mg (2.16 mmol) of lactam **11** in 10 mL of tetrahydrofuran was added dropwise to a mixture of 350 mg (9.21 mmol) of lithium aluminum hydride in 60 mL of ether. After being heated at reflux 5 h, the mixture was stirred overnight and quenched with water. The solution was filtered and amine **5** distilled at reduced pressure (20 mm) to yield a clear liquid: 175 mg (65% yield); bp 110–120 °C; IR (neat) 3400 cm^{-1}; NMR ($CDCl_3$) δ 6.07 (d, 1 H, J = 6 Hz), 5.91 (d, 1 H, J = 6 Hz), 5.91 (d, 1 H, J = 6 Hz), 4.98 (m, 2 H), 2.95 (m, 3 H), 2.68 (d, 1 H, J = 14 Hz), 1.95 (m, 1 H), 1.59 (m, 1 H), 1.48 (br s, 1 H, NH); mass spectrum, m/e (relative intensity) 125 (2, M$^+$), 96 (5), 69(9), 68 (12), 57 (26), 56 (17), 44 (100), 43 (63), 42 (19); calcd for $C_7H_{11}NO$ mol wt 125.0841, found 125.0831. The picrate was recrystallized from ethanol; mp 172–174 °C. Anal. Calcd for $C_{13}H_{14}N_4O_8$: C, 44.07; H, 3.98; N, 15.81. Found: C, 44.15; H, 4.03; N, 15.85.

1-Bromohemiloline (12a). Bromine (70 mg, 0.44 mmol) in 1 mL of methylene chloride was added dropwise to a solution of 50 mg (0.40 mmol) of amine **5** in 5 mL of ether and 5 mL of

methylene chloride. After complete addition, the resulting yellow solution and light yellow crystals were stirred overnight. Evaporation of the solvent left the HBr salt of **12a** as yellow crystals which were dried under vacuum: 113 mg (99% yield); mp 162–164 °C; mass spectrum, *m/e* (relative intensity) 205 (1), 203 (1), 124 (63), 95 (100), 82 (39), 81 (22), 80 (59), 67 (18). To the HBr salt obtained above were added 50 mL of ether and sufficient 1 M NaOH solution to completely dissolve the crystals. The ether layer was decanted, dried over magnesium sulfate, and evaporated, leaving **12a** as a light yellow oil: 69 mg (85% yield); NMR ($CDCl_3$) δ 4.68 (d, 1 H, J = 4 Hz, CHBr), 4.41 (d, 1 H, J = 1 Hz), 4.14 (s, 1 H), 3.39 (t, 1 H, J = 1 Hz), 3.30 (d, 1 H, J = 12 Hz), 3.02 (t, 2 H, J = 7 Hz), 2.45 (d, 1 H, J = 12 Hz), 2.14 (m, 1 H), 1.98 (m, 1 H); mass spectrum, *m/e* (relative intensity) 205 (1, M^+, ^{81}Br), 203 (1, M^+, ^{79}Br), 124 (51), 95 (100), 80 (15), 67 (22). The picrate was recrystallized from ethanol, yielding yellow needles, mp 185–186 °C. Anal. Calcd for $C_{13}H_{13}N_4O_8Br$: C, 36.05; H, 3.02; N, 12.93; Br, 18.45. Found: C, 36.25; H, 3.17; N, 12.93; Br, 18.51.

Experimental Crystallography. Low-temperature single-crystal studies were performed for 1 and **12a**. The diffractometer used was locally constructed[32] and consisted of a Picker goniostat interfaced to a T1980 minicomputer. The goniostat was equipped with an incident beam manocromator (highly oriented graphite crystal, 002 plane), and suitable crystals were mounted on a glass fiber with silicone grease and characterized directly on the goniostat by using reflection data obtained from a systematic search of reciprocal space. Cell dimensions and alignment were determined from angular data obtained with an automated top/bottom left/right slit assembly by using data in both the positive and negative regions of 2θ. Crystal and diffractometer data are listed in Table II for both compounds.

The structures were solved by direct methods and Fourier techniques[33] and refined by a full-matrix least-squares treatment by using all nonzero data. In both molecules hydrogen positions were located and refined isotropically.

1-Iodohemiloline (12b). To a stirred solution containing 100 mg (0.80 mmol) of amine **5**, 25 mL of ether, and 25 mL methylene chloride was added dropwise 250 mg (0.98 mmol) of iodine in 15 mL of methylene chloride. The dark red solution was stirred overnight, with formation of brown crystals. Evaporation of the solvent afforded black crystals which were washed with ether, and the ether was discarded. The resulting brown crystals were dried under vacuum, leaving the HI salt of **12b**: 292 mg (96% yield); mp 135–140 °C; mass spectrum, *m/e* (relative intensity) 128 (70), 127 (35), 124 (83), 95 (100), 80 (18), 67 (34). The crystals obtained above were dissolved in 5 mL of 1 M NaOH solution and extracted with ether. The ether extracts were dried over potassium carbonate, and the solvent was evaporated, leaving **12b** as a light yellow liquid: 117 mg (61% yield); NMR (CDCl) δ 4.73 (dd, 1 H, J = 5, 1 Hz, CHI), 4.32 (s, 1 H), 4.16 (s, 1 H), 3.45 (t, 1 H, J = 1 Hz), 3.32 (d, 1 H, J = 12 Hz), 3.09 (m, 2 H), 2.41 (d, 1 H, J = 12 Hz), 2.15 (m, 1 H), 2.02 (m, 1 H); mass spectrum, *m/e* (relative intensity) 251 (1, M^+), 124 (80), 95 (100), 81 (9), 80 (15), 67 (33). The picrate was recrystallized from ethanol to yield yellow needles, mp 167–169 °C. Anal. Calcd for $C_{13}H_{13}N_4O_8I$: C, 32.52; H, 2.73; N, 11.67; I, 26.43. Found: C, 32.61; H, 2.73; N, 11.58; I, 26.60.

Hemiloline (12c). A solution containing 60 mg (0.29 mmol) of bromide **12a** 30 mL of ether, and 150 mg (3.8 mmol) of lithium aluminum hydride was heated to reflux 8 h and stirred overnight. After being quenched with water, the mixture was filtered and the solvent evaporated, leaving **12c** as a clear liquid: 24 mg (65% yield); NMR ($CDCl_3$) δ 4.32 (m, 1 H), 4.23 (br s, 1 H), 3.36 (br s, 1 H), 3.18 (d, 1 H, J = 11 Hz), 2.98 (t, 2 H, J = 8 Hz), 2.34 (d, 1 H, J = 11 Hz), 1.8–2.2 (m, 4 H); mass spectrum, *m/e* (relative intensity) 125 (27, M^+), 97 (6), 96 (5), 86 (16), 84 (29), 83 (9), 82 (100), 55 (10); calcd for $C_7H_{11}NO$ mol wt 125.0841, found 125.0830.

Reaction of 5 with Mercuric Chloride. A solution of 50 mg (0.40 mmol) of amine **5** in 2 mL tetrahydrofuran was added dropwise to 130 mg (0.48 mmol) of mercuric chloride in 20 mL of tetrahydrofuran with the formation of a white precipitate after 5 min. The mixture was stirred 5 h and filtered. The white crystals were washed with 5 mL of fresh THF and dried under vacuum overnight, affording the mercuric chloride salt of **5**: 160 mg (100% yield); mp 157–160 °C; NMR ($(CD_3)_2SO$) δ 6.4 (br s, 1 H), 6.05 (s, 2 H, olefinic protons), 1.8–5.1 (m, 8 H); mass spectrum, *m/e* (relative intensity) 274 (14), 272 (27), 271 (13), 270 (18), 202 (12), 125 (4), 95 (7), 82 (7), 68 (17). Anal. Calcd for $C_7H_{11}NOHgCl_2$: C, 20; H, 2.80; N, 3.55; Hg, 50.57; Cl, 17.88. Found: C, 20.33; H, 2.42; N, 3.60; Hg, 47.08; Cl, 16.66.

The white crystals obtained above were suspended in 5 mL of THF, and 5 mL of hexamethylphosphoramide (HMPA) was added to completely dissolve the amine salt. A second equivalent (130 mg) mercuric chloride was added and the solution stirred overnight. The product was reduced with excess sodium borohydride solution, and the workup afforded amine **5** as the sole product (GLC and NMR were comparable to those prepared previously).

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Registry No. 1·2HCl, 25161-92-6; **5**, 69496-60-2; **5** picrate, 69973-28-0; **5**·$HgCl_2$, 78421-03-1; **7**, 40458-77-3; **8**, 69496-57-7; **9**, 69496-58-8; **10**, 69496-59-9; **11**, 78421-04-2; **12a**, 78478-34-9; **12a**·HBr, 78511-86-1; **12a** picrate, 78511-87-2; **12b**, 78478-35-0; **12b**·HI, 78511-88-3; **12b** picrate, 78511-89-4; **12c**, 29079-42-3; **12e**, 78435-88-8; furan, 110-00-9; 2-methoxyallyl bromide, 26562-24-3.

Supplementary Material Available: Figure 1 (ORTEP stereopair for molecule **12a**), Figures 3 and 4 (numbering schemes for Tables III–XI), Tables III–VI (crystallographic data for **12a**), Tables VII–XI (crystallographic data for 1) (18 pages). Ordering information is given on any current masthead page.

(32) All computations were performed on a CYBER 172-CDC6600 computer using the Indiana University Molecular Structure Center XTEL interactive program library. The programs were based in part on A. C. Larson's Los Alamos code and J. A. Ibers' Northwestern University programs. Molecular fitting was by S. C. Nyburg's BMFIT, and drawings were by C. Johnson's ORTEP.

(33) (a) Huffman, J. C.; Streib, W. E.; Sporleder, C. R., unpublished work. (b) Huffman, J. C. Ph.D. Thesis, Indiana University, 1974.

(34) (a) Crout, H. C. *Chimia* **1976**, *30*, 270. (b) Mattocks, A. R. "Phytochemical Ecology"; Harbone, J. B., Ed.; Academic Press: London and New York, 1972; p 179 ff.

(35) The poor quality of the structure determination (and resultant large residuals and estimated standard deviations) is due primarily to excessive mosaicity of the crystal as seen in the ω scan width (1.5° at half-height).