Thermal Rearrangement of Cyclopropyl Imines. IV. Total Synthesis of *dl*-Mesembrine[1,2]

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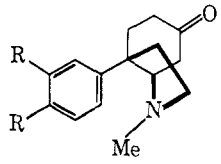
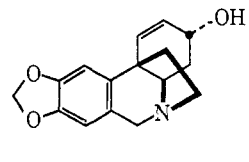
Abstract: The acid-catalyzed, thermally induced rearrangement of cyclopropyl imines has been further exploited as a general device for the synthesis of 3-aryl-Δ^2-pyrrolines. A unique annelation of these intermediates with methyl vinyl ketone provided a simple five-step total synthesis of the racemic form of the *Aizoaceae* alkaloid mesembrine (**1b**).

The *Aizoaceae* alkaloid (−)-mesembrine (**1b**) was first isolated from *Mesembryanthemum tortuosum* in 1957.[4] The gross structural features and *cis* ring fusion assigned to the octahydroindole nucleus of the natural base were derived from degradative and synthetic evidence.[5] From a general synthetic viewpoint these features are also found in certain *Amaryllidaceae* alkaloids such as crinine (**2**). A lengthy 21-step synthesis of *dl*-mesembrine has been reported.[6,7]



1a, R = H
b, R = OMe



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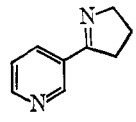

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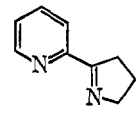

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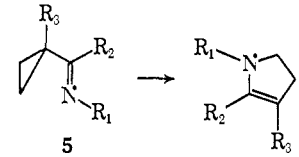
Our interest in the total synthesis of mesembrine (**1b**) arose simultaneously with the exploitation of the thermally induced, acid-catalyzed rearrangement of cyclopropyl imines as a general method of pyrroline synthesis.[8] This effort lead initially to efficient syntheses of the pyridine alkaloids myosmine (**3**) and apoferrorosamine (**4**).[8,9] The present study was therefore initiated to more clearly define the generality of the crucial rearrangement step **5** to **6** and to further express the utility of pyrrolines obtained in this manner as useful intermediates in the total synthesis of naturally occurring bases. We selected as our initial goal the mesembrine model **1a**.[1,2]



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1-Phenylcyclopropanecarbonitrile (**8a**) was prepared by the sodium amide induced bis alkylation of phenylacetonitrile with ethylene bromide.[10] Partial reduction of the nitrile function with limited quantities of lithium aluminum hydride at low temperature gave satisfactory yields of the corresponding aldehyde **9a**[11] which was separated from starting material by careful distillation. Conversion of this aldehyde to aldimine **10a** was accomplished in 96% yield by stirring a magnesium sulfate suspension with excess methylamine in benzene for 5 hr at room temperature. An extensive study of reaction conditions for inducing the rearrangement of **10a** to the Δ^2-pyrroline **11a** was obviated when it was discovered that more than adequate quantities of the latter material could be secured by precipitation of the aldimine as a rather hygroscopic hydrobromide from an ethereal solution and, without isolation of the salt, the ether and excess HBr removed. A 59% yield of analytically pure pyrroline was obtained by carefully heating the resultant solid hydrobromide, which melted at 65–67°, to 120° over the course of 1 hr and subsequent basification, ether extraction, and sublimation. Although quite satisfactory for the present investigation, a rather more efficient and effective procedure evolved later in our work wherein catalytic amounts of acid were employed, and the rearranged product was distilled directly from the reaction vessel. Although not applied to the present case, we are confident that this modification would be fully applicable.

With the obtention of the Δ^2-pyrroline **11a** we were now in a position to take advantage of the nucleophilic properties associated with the β-carbon of this endocyclic enamine. We had envisaged the Michael addition of this base with methyl vinyl ketone to proceed *via* the stages outlined below. Should the initial alkylation step proceed at all, then we anticipated a possible

(1) For a preliminary account of a portion of this work see: R. V. Stevens and M. P. Wentland, *Tetrahedron Letters*, 2613 (1968).

(2) A portion of the material in this paper was first presented by R. V. Stevens at the 23rd Southwest Regional Meeting of the American Chemical Society, Little Rock, Ark., Dec 8, 1967.

(3) U. S. Public Health Service Predoctoral Research Fellow, 1967 to present.

(4) K. Bodendorf and W. Krieger, *Arch. Pharm.*, **290**, 441 (1957).

(5) A. Popelak, G. Lettenbauer, E. Haack, and H. Spingler, *Naturwissenschaften*, 47, 231 (1960).

(6) M. Shamma and H. Rodriguez, *Tetrahedron Letters*, 4847 (1965).

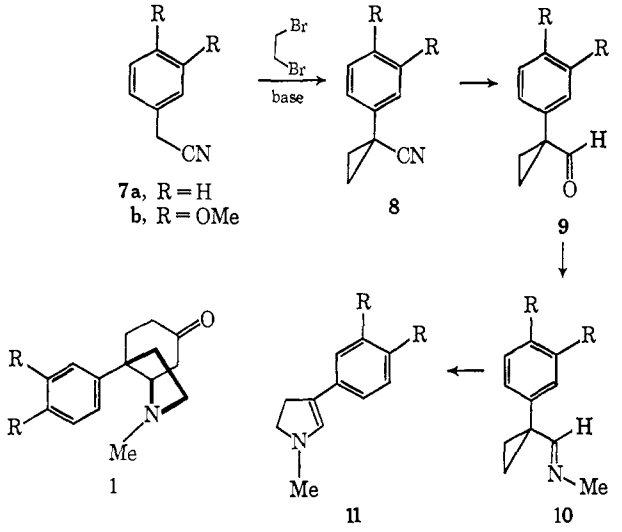
(7) Professor C. Tahk of Kent State University has kindly informed us prior to publication of his independent synthesis of mesembrine. The results of these two studies are simultaneously offered here by mutual agreement. After this manuscript had been submitted a communication appeared [T. J. Curphey and H. L. Kim, *ibid.*, 1441 (1968)] describing the total synthesis of *dl*-mesembrine. The final step of this synthesis employed the MVK annelation of endocyclic enamine **11b**.

(8) Part III: R. V. Stevens, M. C. Ellis, and M. P. Wentland, *J. Am. Chem. Soc.*, **90**, 5576 (1968).

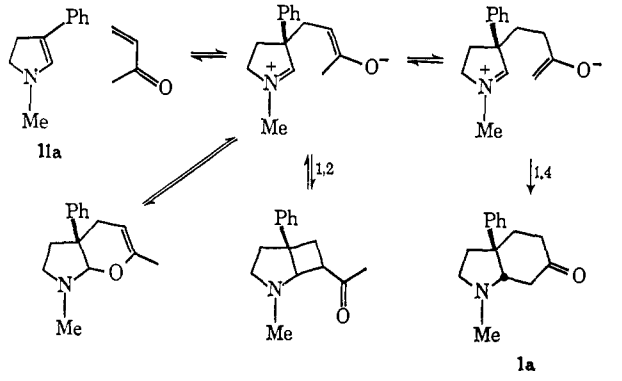
(9) R. V. Stevens and M. C. Ellis, *Tetrahedron Letters*, 5185 (1967).

(10) C. Dupin and R. Fraisse-Jullien, *Bull. Soc. Chim. France*, 1993 (1964).

(11) D. I. Schuster and J. D. Roberts, *J. Org. Chem.*, 27, 51 (1962).



menacing divergence between the 1,2- and 1,4-addition processes. Since the 1,2-addition process and dihydropyran formation are known, except in special cases, to be thermally reversible,[12] we anticipated the nature of the proton-transfer process required for 1,4 addition to be crucial. Although the required proton transfer is potentially intramolecular, we reasoned that employment of polar hydroxylic solvents should help favor the critical prototropic transfer. Although our initial experiments were inconclusive, they were instrumental in the ultimate satisfactory solution of this problem. Pyrroline **11a** was refluxed in a nitrogen-purged ethanolic solution with methyl vinyl ketone until the pyrroline could no longer be detected by tlc. The reaction mixture was then concentrated and further purification attempted by distillation. We were at first surprised to discover that a major portion of the distillate was the starting enamine **11a** since this had been judged by tlc to be absent. This result suggested that under the conditions employed the reaction had proceeded largely *via* either 1,2 addition or dihydropyran formation. The attempted distillation at a relatively higher temperature had apparently therefore served only to reverse this process. Indeed, methyl vinyl ketone was secured from the vacuum trap. Although low yields of the desired product **1a** could be isolated from this reaction by preparative layer chromatography,



the above interpretation suggested that employment of higher reaction temperatures might accelerate the decomposition of the (postulated) thermally labile addition product thus freeing the starting materials for the desired 1,4 combination. No effort was made to further corroborate these assumptions when it was discovered that employment of hot ethylene glycol as a solvent resulted in an effective yield of **1a**. The structural and stereochemical assignment was easily made by comparing the pmr spectrum of the model (Figure 1) with that of the natural base (Figure 2). Supporting evidence included the expected infrared spectrum and a correct combustion analysis of a picrate. Although the annelation of exocyclic enamines with methyl vinyl ketone finds a prominent role in organic synthesis, its employment here with an endocyclic enamine is apparently unique. We are convinced that this synthetic method will find an expanding role in alkaloid synthesis, and are currently investigating this possibility.

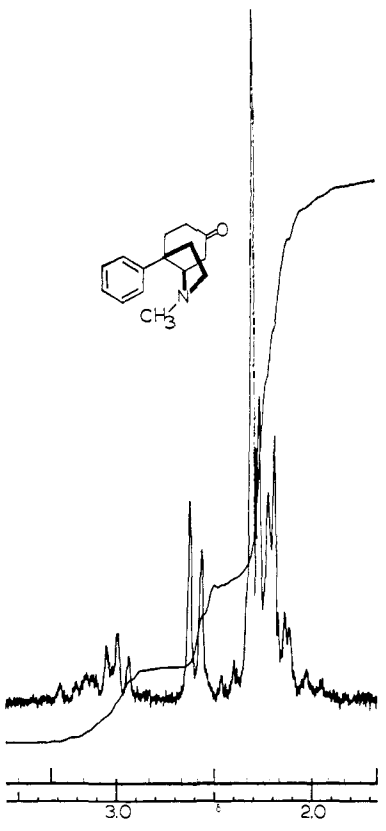


Figure 1.

The stereochemical course of the methyl vinyl ketone annelation had been anticipated. Thus, inspection of models reveals that maximum overlap of the termini of the π-orbital systems is most readily achieved *via* perpendicular attack as illustrated in expression **12**. The maintenance of similar geometry in the sterically more demanding substrate **13** has been recently reported,[13] and the application of this principle to intramolecular conjugate addition has been emphasized.[14] The experience gained in these experiments was next applied to the total synthesis of the natural base.

In contrast to 1-phenylcyclopropanecarbonitrile (**7a**), the corresponding dimethoxy isomer **7b** could not be

(12) J. Szmuszkovicz, *Advan. Org. Chem.*, 4, 39 (1963); I. Fleming and M. H. Karger, *J. Chem. Soc., C*, 226 (1967). We are grateful to a referee for directing our attention to the latter reference.

(13) R. B. Woodward, Abstracts, 20th National Organic Symposium of the American Chemical Society, Burlington, Vt., June 1967, p 104.

(14) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, p 314.

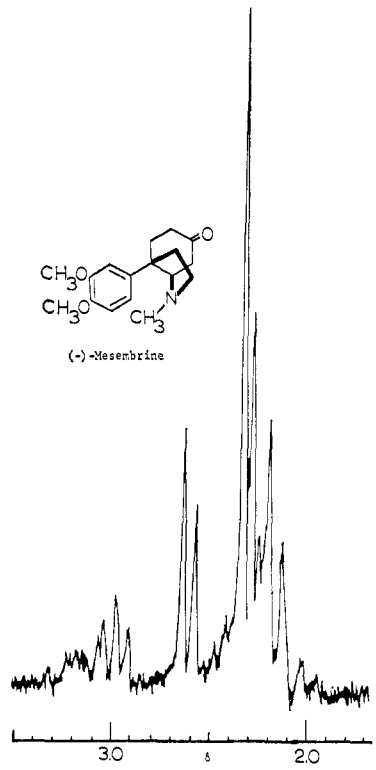
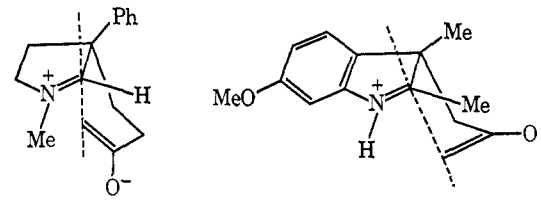


Figure 2.

induced to react with ethylene bromide under the conditions employed for the former substrate ($NaNH_2$, Et_2O). Although electronically understandable this result was nevertheless annoying. While searching for an alternative solution a communication was discovered,[15] wherein the formation of the dilithiated derivative **14a** was demonstrated. The expected greater covalent character revealed by this experiment immediately attracted our attention as a logical solution to the problem at hand. Indeed, exposure of **7b** to 2 equiv of *n*-butyllithium and rapid quenching in D_2O gave greater than 97% dideuterio derivative **14b** (pmr analysis). In order to verify the formulation of **14c** as the intermediate in the reaction medium it was desirable to rule out deuterium exchange during the work-up procedure. Although base (10% NaOH–THF) does equilibrate the dideuterio derivative **14b** to **7b**, this process is quite slow and could not be a significant factor in the quenching procedure employed.[16] When these results were applied to the synthesis of **8b** an adequate yield of this intermediate was obtained without extensive investigation of the reaction conditions.



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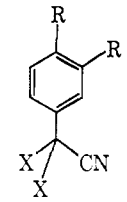

14a, R = H; X = Li
b, R = OMe; X = D
c, R = OMe; X = Li
d, R = H; X = D

With the proper cyclopropanecarbonitrile (**8b**) in hand and with the experience gained in our model studies[1] we turned our full attention to the ultimate goal of the present investigation. The previously employed selective hydride reduction of **8b** to the aldehyde **9b** was, amusingly, marred only by the crystallinity of both substances, thus creating a separation problem. This was easily overcome by treating the crude reduction mixture with saturated sodium bisulfite and extraction of the nitrile. Pure crystalline aldehyde was then regenerated directly from the bisulfite solution. A 91% yield of analytically pure aldimine **10b** was obtained by treating a benzene solution of aldehyde with a tenfold excess of methylamine in the presence of suspended magnesium sulfate for 20 hr at room temperature. As noted above, the thermally induced, acid-catalyzed rearrangement of cyclopropyl imines is best achieved by employing only catalytic amounts of acid. In the present case a 76% yield of analytically pure pyrroline **11b** was obtained from a 20-min, 148° run using the hydrobromide salt of **10b** as catalyst.

Racemic mesembrine (**1b**) was secured *via* the methyl vinyl ketone annelation procedure described above. Preparative layer chromatography of the crude reaction mixture gave ultimately a 56% yield of pure material whose solution infrared spectrum was identical with the natural base.[17] The rather characteristic pmr spectrum[17] of natural mesembrine (Figure 2) is perhaps as good a diagnostic tool and was identical with our synthetic material. Finally, combustion analysis of a picrate agreed with the required formulation.

Experimental Section[18]

1-Methyl-3-phenyl-2-pyrroline (11a). Anhydrous hydrogen bromide was slowly introduced to a solution of 0.667 g of N-methyl-1-phenylcyclopropanecarboxaldimine[8] in 10 ml of dry ether until precipitation was complete under nitrogen. The resulting white slurry was heated to 55° to expel solvent and the white crystalline residue, which melted at 65–67°, was carefully heated to 120° in the course of 1 hr. The resulting clear yellow melt was dissolved in dilute acid and nonbasic materials were extracted with ether. Basification of the aqueous acid portion followed by extraction with

(15) E. Kaiser and C. Hauser, *J. Am. Chem. Soc.*, **88**, 2348 (1966).

(16) Although convincing evidence for the formation of the dilithiated species **14a** has been offered[15] our results concerning the deuterium exchange in aqueous base–THF do not parallel those reported for **14d**. The formulation of these dilithiated species as a single resonance structure is not intended to imply their relative importance to the resonance hybrid.

(17) The authors are indebted to Professor P. Jeffs of Duke University for providing us with these spectra, and to Professor W. C. Wildman of Iowa State University for a sample of the natural base.

(18) Infrared spectra were obtained on a Beckman IR-8 spectrophotometer; ultraviolet spectra are of 95% ethanol solutions and were taken on a Cary Model 14 spectrophotometer. Proton magnetic resonance spectra were recorded in dilute deuteriochloroform solutions containing tetramethylsilane as internal standard on a Varian A-56/60A spectrometer operating at 60 Mc. Melting and boiling points are uncorrected. Microanalyses were secured from the Elek Microanalytical Laboratory, Torrance, Calif. Preparative layer chromatography operations employed Brinkmann precoated 20 × 20 cm plates of silica gel F-254, 2 mm thick.

ether afforded crude yellow crystalline pyrroline **11a**. Sublimation at 40° (0.1 mm) provided 0.393 g (59%) of analytically pure **11a**: mp 61–61.5°; ir ($CHCl_3$) 1613 cm^{-1}; uv_{max} (95% EtOH) 306.5 mμ (ε 11,390); pmr δ 7.09 (s, 5 H), 6.32 (t, 1 H, J = 1.4 cps), *ca.* 2.99 (m, 4 H), and 2.57 ppm (s, 3 H).

Anal. Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80. Found: C, 83.02; H, 8.22; N, 8.63.

(±)-Desdimethoxymesembrine (1a). 1-Methyl-3-phenyl-2-pyrroline (**11a**), 0.702 g (0.0044 mol), and 0.344 g (0.0049 mol) of methyl vinyl ketone were stirred under nitrogen in 25 ml of ethylene glycol at 80° for 2.5 hr and 150° for 1 hr. The ethylene glycol was then removed *in vacuo*, and the resulting red oil was dissolved in dilute acid, and nonbasic materials were extracted with ether. Basification of the aqueous acid portion followed by extraction with ether and removal of solvent provided a maroon oil from which 0.473 g (47%) of mesembrine model was secured in crude form by preparative layer chromatography. Rechromatography and subsequent vacuum distillation yielded a pure sample by tlc of the mesembrine model **1a**: bp 109° (bath temperature) (0.1 mm); ir (neat) 1719 cm^{-1}; pmr δ 7.31 ppm (m, 5 H), see Figure 1 for remainder of spectrum.

Mesembrine model **1a** was analyzed as its picrate (*i*-PrOH–H_2O): mp 168–170° dec.

Anal. Calcd for $C_{21}H_{22}N_4O_8$: C, 55.02; H, 4.84. Found: C, 55.00; H, 4.94.

1-(3,4-Dimethoxyphenyl)cyclopropanecarbonitrile (8b). A solution of 35.44 g (0.2 mol) of 1-(3,4-dimethoxyphenyl)acetonitrile in 500 ml of dry tetrahydrofuran was added dropwise under nitrogen and with stirring to 282 ml (0.45 mol) of a 1.6 *M* solution of *n*-butyllithium in hexane. A pale yellow solid precipitated during addition and a mild reflux was noted. The mixture was stirred for 2 hr until butane evolution ceased. The resulting brown slurry was cooled to −76° in a Dry Ice–acetone bath and 37.44 g (0.2 mol) of ethylene bromide in 500 ml of tetrahydrofuran was added dropwise. The resulting red slurry was warmed to room temperature in the course of 2 hr and stirred for an additional 5 hr at 26°. Water (500 ml) was then added cautiously to the reaction mixture, and the layers were separated. The solvents were removed from the organic portion on the rotary evaporator, and the resulting red oil was treated with water and the crude nitrile extracted with several portions of chloroform. The combined chloroform extracts were dried and the solvent was removed on the rotary evaporator. Vacuum distillation (*ca.* 130° (0.1 mm)) of the resulting red viscous oil provided 9.56 g (24%) of pure nitrile **8b** which slowly crystallized upon standing. Analytically pure compound was obtained through four recrystallizations (petroleum ether (bp 30–60°)–CCl_4) and vacuum sublimation (61° (0.1 mm)): mp 68–69°; ir (KBr) 2227 cm^{-1}; pmr δ 6.80 (unsymmetrical t, 3 H), 3.86 (s, 3 H), 3.82 (s, 3 H), and 1.48 ppm (sym m, 4 H).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.92; H, 6.59; N, 7.11.

1-(3,4-Dimethoxyphenyl)cyclopropanecarboxaldehyde (9b). This aldehyde was prepared by modification of the Roberts' procedure.[11] A solution of 0.06 g (0.0015 mol) of lithium aluminum hydride in 50 ml of dry ether was rapidly added, under nitrogen, to a stirred solution of 1.02 g (0.005 mol) of **8b** in 50 ml of dry ether and 20 ml of dry tetrahydrofuran at −76°. The tan slurry was warmed to room temperature in the course of 4 hr and stirred for an additional 4 hr at 26°. Dilute HCl, 40 ml, was then slowly added to the reaction mixture, and the layers were separated. The aqueous acid portion was washed with ether, the combined ethereal extracts were dried, and the solvent was removed on the rotary evaporator providing 0.40 g (38%) of crude aldehyde **9b**. Admixture of a solution of the crude aldehyde in ether with a saturated solution of sodium bisulfite, followed by separation of the layers, decomposition of the bisulfite solution with base, and extraction with ether, yielded pure crystalline aldehyde.

Analytically pure **9b** was secured by vacuum sublimation (65° (0.1 mm)): mp 60–61°; ir (KBr) 1711, 2743, and 2696 cm^{-1}; pmr δ 9.33 (s, 1 H), 6.72 (s, 3 H), 3.78 (s, 3 H), 3.76 (s, 3 H), and 1.32 ppm (sym m, 4 H).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.93; H, 6.78.

N-Methyl-1-(3,4-dimethoxyphenyl)cyclopropanecarboxaldimine (10b). A mixture of 0.983 g (0.0048 mol) of **9b**, 30 ml of a solution of 1.55 *M* methylamine in benzene (0.046 mol of CH_3NH_2), and 0.5 g of anhydrous $MgSO_4$ was stirred for 20 hr at 26°. The inorganic salts were filtered off and the benzene removed on the rotary evaporator yielding crude aldimine **10b**. This green oil was vacuum distilled (102–104° (0.1 mm)) providing 0.952 g (91%) of analytically pure aldimine, which slowly crystallized upon standing: mp 54–56°; ir (neat) 1662 cm^{-1}; pmr δ 7.56 (q, 1 H, J = 1.3 cps), 6.82 (s, 3 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 3.21 (d, 3 H, J = 1.3 cps), and 1.18 ppm (sym m, 4 H).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.46; H, 7.85; N, 6.42.

1-Methyl-3-(3,4-dimethoxyphenyl)-2-pyrroline (11b). A mixture of 0.126 g of **10b** and 3 mg of freshly prepared aldimine hydrobromide was stirred under nitrogen for 20 min at 148°. Upon cooling the yellow melt solidified. Pyrroline **11b** was extracted from resinous materials with hexane; subsequent removal of solvent and vacuum sublimation (100° (0.15 mm)) provided 0.096 g (76%) of white crystalline pyrroline. Analytically pure **11b** had mp 72° after two recrystallizations from hexane: ir ($CHCl_3$) 1619 cm^{-1}; $uv_{max}^{95\%\ EtOH}$ 305 mμ (ε 14,270); pmr δ 6.73 (m, 3 H), 6.27 (t, 1 H, J = 1.3 cps), 3.86 (s, 3 H), 3.82 (s, 3 H), *ca.* 2.90 (m, 4 H), and 2.62 ppm (s, 3 H).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81. Found: C, 71.50; H, 7.78.

(±)-Mesembrine (1b). A mixture of 0.106 g (0.000484 mol) of **11b**, 0.041 g (0.000581 mol) of methyl vinyl ketone, and 9 ml of ethylene glycol was stirred under nitrogen for 2.5 hr at 57° and 1 hr at 119°. The ethylene glycol was removed from the deep red reaction mixture by several extractions with water from an ethereal solution. Removal of the ether on the rotary evaporator provided a dark red oil from which pale yellow mesembrine was secured by preparative layer chromatography. Removal of resinous impurities by column chromatography provided 0.078 g (56%) of pure (±)-mesembrine whose ir (CCl_4) and nmr ($CDCl_3$) were identical with those of natural mesembrine: ir (CCl_4) 1722 cm^{-1}; pmr δ 6.88 (narrow m, 3 H), 3.89 (s, 3 H), and 3.87 ppm (s, 3 H), see Figure 2 for remainder of spectrum. A picrate of mp 171.5–172.5° (EtOH–EtOAc) was analyzed.

Anal. Calcd for $C_{23}H_{26}N_4O_{10}$: C, 53.28; H, 5.06. Found: C, 53.51; H, 5.20.

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