solution and filtered through an alumina column using the same ammonium hydroxide solution for elution. The eluate was acidified to pH 4 with acetic acid and the precipitated acid was dried; 4.5 g (87% yield), mp 295° (lit.[9] mp 325°), λ_{max} 276 mμ (ε 12,600). *Anal.* Calcd for $C_{11}H_{12}O_5N_2 \cdot H_2O$: C, 48.9; H, 5.2; N, 10.4. Found: C, 48.8; H, 4.8; N, 10.5.

The **dimethyl ester XXIa** was prepared by treating a methanolic suspension of XXI with ethereal diazomethane; mp 207–211° from ethanol. *Anal.* Calcd for $C_{13}H_{16}N_2O_5$: C, 55.7; H, 5.7; N, 10.0. Found: C, 55.8; H, 5.6; N, 10.3.

5-Oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-*c*]pyridine-3-propionic Acid (Porphobilinogen Lactam) (XXV). Four grams of XXI was heated under reflux in 250 ml of water for 4 hr. The solution was evaporated to dryness and the residue was recrystallized from water; 2.67 g (87% yield); mp 295° (lit.[9] mp 280–283°); R_f 0.72; ν_{max} 3200, 1690, 1630 cm^{-1}. *Anal.* Calcd for $C_{10}H_{12}O_3N_2$: C, 57.7; H, 5.8; N, 13.4. Found: C, 57.5; H, 5.7; N, 13.3.

5-Oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-*c*]pyridine-3-acetic Acid (XXVI). One gram of XXII was decarboxylated by boiling in water as described above. The product was further purified by dissolving it in a dilute ammonium hydroxide solution and precipitating with acetic acid; 515 mg (68% yield), mp 255–260° dec, R_f 0.64. *Anal.* Calcd for $C_9H_{10}O_3N_2$: C, 55.7; H, 5.2; N, 14.4. Found: C, 55.8; H, 5.4; N, 14.6.

2-Aminomethyl-3-pyrroleacetic Acid (XXVII). The sublimed lactam XXIV (300 mg) was suspended in 2 ml of 4 *N* sodium hydroxide, 2 ml of ethanol was added, and the mixture was heated under reflux for 1 hr. The solution was then adjusted to pH 5 with acetic acid and 15% aqueous mercuric acetate was added until no more precipitate formed. The solid was centrifuged, the precipitate was suspended in water, and hydrogen sulfide was passed through the suspension until all of the mercuric salt was decomposed. The HgS was centrifuged and washed with water, and the pooled supernatant and wash were evaporated to dryness at 50° *in vacuo*. The crystalline residue was recrystallized by dissolving it in water and adding acetone; 190 mg (56% yield); mp 140° dec; δ (D_2O) 6.9 (d, H-5), 6.1 (d, H-4), 4.2 (CH_2CO_2H), 3.4 (CH_2NH_2). *Anal.* Calcd for $C_7H_{10}O_2N_2$: C, 54.5; H, 6.5; N, 18.2. Found: C, 54.3; H, 6.5; N, 18.0.

2-Aminomethyl-3,4-pyrrolediacetic Acid (XXIX). The lactam XXVI (200 mg) was dissolved in 2 ml of 2 *N* potassium hydroxide and the mixture was left at room temperature for 1 week. The solution was then adjusted to pH 4 with acetic acid and the pyrrolediacetic acid was isolated through its mercury salt as described above. It was recrystallized by dissolving it in water and adding methanol; mp 145° dec, R_f 0.42. *Anal.* Calcd for $C_9H_{12}O_4N_2 \cdot H_2O$: C, 47.0; H, 5.6; N, 12.2. Found: C, 46.8; H, 5.6; N, 12.1.

2-Aminomethyl-3-carboxymethyl-4-pyrrolepropionic Acid (Porphobilinogen, XXVIII). Two grams of porphobilinogen lactam XXV was dissolved in 6 ml of 2 *N* potassium hydroxide and the mixture was left at room temperature for 72 hr. The solution was then adjusted to pH 7 with 7 *N* acetic acid and cooled at 0° for 3 hr. The solid was further purified by dissolution in dilute ammonium hydroxide and precipitation with acetic acid; 1.94 g (83% yield) of porphobilinogen was obtained, mp 167° (lit.[9] mp 170–174°), R_f 0.50. *Anal.* Calcd for $C_{10}H_{14}O_4N_2 \cdot H_2O$: C, 49.2; H, 6.6; N, 11.5. Found: C, 49.4; H, 6.7; N, 11.5.

When ^{14}C-labeled porphobilinogen lactam XXV was used (0.93 mCi/mmole; the label was at C-2 of the propionic acid side chain) and the resulting porphobilinogen (0.95 mCi/mmole) was examined by paper chromatography no other radioactive spot could be detected. The porphobilinogen (XXVIII) had identical ir, R_f, and electrophoretic mobility as an authentic sample.

A Synthesis of Quebrachamine and 3,4-Dehydroquebrachamine[1]

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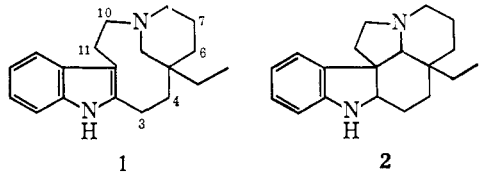
Contribution from the Sterling Chemistry Laboratory of Yale University, New Haven, Connecticut 06520. *Received December 13, 1968*

Abstract: A synthesis of quebrachamine (**1**) and 3,4-dehydroquebrachamine (**17**) has been achieved. The approach employs the alkylation of 1-benzyl-3-ethyl-1,4,5,6-tetrahydropyridine (**10**) with methyl haloacetates and subsequent cyclization to a nine-membered ring in high yield with polyphosphoric acid.

Quebrachamine (**1**) can be considered the parent base of that group of indole alkaloids having the aspidosperma[2] skeleton, whose other structural members are represented by aspidospermidine (**2**), kopsinine (**3**), and tuboxenine (**4**).



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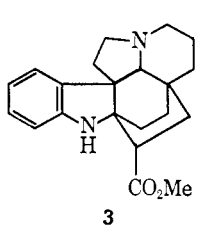

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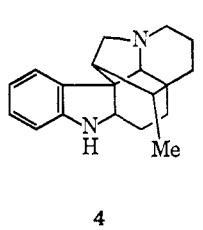

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Synthetic efforts in this area to date have culminated in syntheses of quebrachamine,[3] aspidospermine,[3] and aspidospermidine.[4] The conversion **1** → **2** has been achieved,[5] while the reverse process[6] (**2** → **1**) serves as the route to all but one of the reported syntheses of quebrachamine.[3d]

The most salient feature of the aspidosperma alkaloids is the presence of geminal diethyl substitution of the piperidine ring at C-5 which, along with the β-indolylethyl chain and varying degrees of oxidation level and substitution, *e.g.*, C-3 carbomethoxyl group, comprises the skeletal framework of these bases. Consequently it was anticipated that 1-benzyl-3-ethyl-1,4,5,6-tetrahydropyridine (**10**) would serve as a

(1) For a preliminary report see F. E. Ziegler and P. A. Zoretic, *Tetrahedron Lett.*, 2639 (1968).

(2) See (a) B. Gilbert, *Alkaloids*, **8**, 335 (1965); and (b) M. Hesse, "Indolalkaloide in Tabellen," Springer-Verlag, Berlin, 1964.

(3) (a) G. Stork and J. E. Dolfini, *J. Am. Chem. Soc.*, **85**, 2872 (1963); (b) Y. Ban, Y. Sato, I. Inoue, M. Nagai, T. Oishi, M. Terashima, O. Yonenitsu, and Y. Kanoaka, *Tetrahedron Lett.*, 2261 (1965); (c) M. E. Kuehne and C. Bayha, *ibid.*, 1311 (1966); (d) J. P. Kutney, N. Abdurahman, P. Le Quesne, E. Piers, and I. Vlattas, *J. Am. Chem. Soc.*, **88**, 3656 (1966); J. P. Kutney, K. K. Chan, A. Failli, J. M. Fromson, C. Gletsos, and V. R. Nelson, *ibid.*, 90, 3891 (1968).

(4) J. Harley-Mason and M. Kaplan, *Chem. Commun.*, 915 (1967).

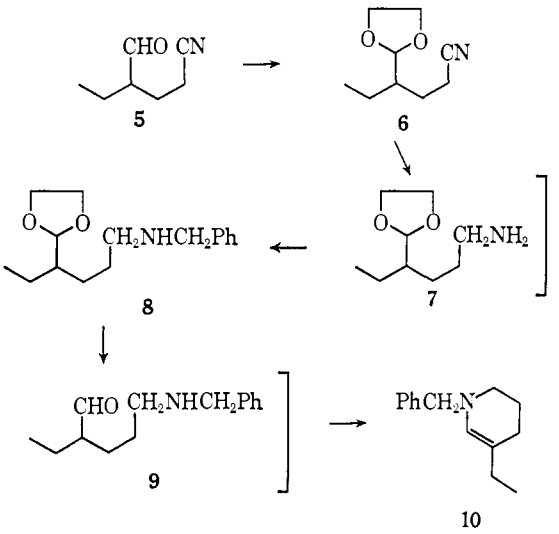
(5) A. Camerman, N. Camerman, J. P. Kutney, E. Piers, and J. Trotter, *Tetrahedron Lett.*, 637 (1965).

(6) K. Biemann and G. Spiteller, *ibid.*, 299 (1961).

versatile intermediate to the aspidosperma group. Such a species might be expected to undergo reactions characteristic of enamines,[7] *i.e.*, alkylation[8] and nucleophilic addition.[9]

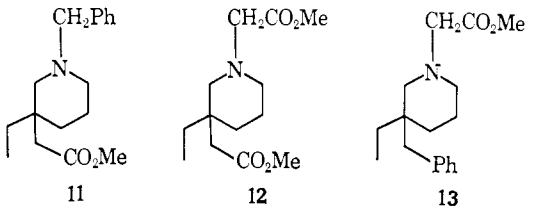
The synthesis of tetrahydropyridine **10** was dictated by the fact that it is a cyclic enamine, formally derived by intramolecular condensation of an aldehyde and a secondary amine. Accordingly, 1-piperidino-1-butene[10] was cyanoethylated in acetonitrile to afford 4-formylcapronitrile (**5**) in 77% yield. Since subsequent steps involved operations on the nitrile function which would prove fatal to the carbonyl, the latter was protected as its ethylene glycol acetal, affording the cyano acetal **6** in 88% yield (Scheme I). Reduction of

Scheme I



the cyano acetal to the amino acetal **7** was conveniently effected with ethereal lithium aluminum hydride. Without further purification the amino acetal was directly converted to its N-benzyl derivative **8** by reductive alkylation. No effort was made to preform the benzylidene Schiff base, but rather, it was allowed to form *in situ* during the hydrogenation. The crude benzylation product was subsequently hydrolyzed to liberate the aldehyde **9**. Examination of the crude hydrolysate, freed of neutral materials, indicated the presence of two different benzyl signals ($PhCH_2N$–) in the nmr spectrum at δ 3.50 and 3.75 along with aldehydic protons at 9.50. Traditional techniques for enamine formation, *i.e.*, refluxing benzene with azeotropic removal of water and refluxing toluene with *p*-toluenesulfonic acid or Amberlite 1R-120 sulfonic acid resin as catalysts, gave only slight shifts in the relative intensities of the benzyl signals. However, distillation at 130–190° at aspirator pressure thermally dehydrated the mixture, giving an immiscible mixture of enamine **10** and water. Separation of the components and redistillation afforded the pure enamine. In a rather fortuituous manner it was found that after drying an ethereal solution of the crude hydrolyzate over anhydrous magnesium sulfate for 24 hr it failed to eliminate water on distillation, but gave the enamine directly. Using this procedure, the enamine could be prepared from the cyano acetal **6** in 56% yield. The nmr spectrum clearly indicated that the signal at δ 3.75 was due to the enamine benzyl methylene (two protons), while a one-proton singlet at δ 5.60 fulfilled the requirement for a vinyl hydrogen.

With the requisite enamine in hand, it was now possible to investigate the introduction of an acetic acid moiety. The optimum conditions for alkylation were found to involve refluxing the enamine with 2 equiv of methyl halo ester in methanol followed by sodium borohydride reduction of the resultant immonium salts. Employing these conditions with methyl bromoacetate,[11] the sequence gave rise to three amines, **11**, **12**, and **13**, in 22, 2, and <1% yields, respectively, upon vpc analysis. Although methyl chloroacetate was ineffective as an alkylating agent, methyl iodoacetate afforded the same alkylation products in 44, 19, and 2% yields, respectively. The nmr



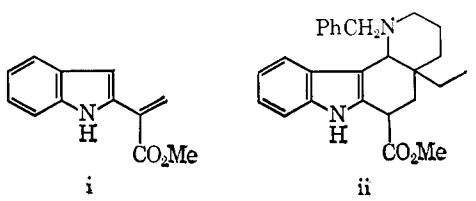
spectra served to characterize the alkylation products. The major component in each case was the desired amine, methyl 3-(1-benzyl-3-ethyl)piperidinoacetate (**11**), displaying a three-proton singlet at δ 3.50 (methyl ester) and a two-proton singlet at 3.35 (benzyl methylene), the latter value corresponding to that in N-benzylpiperidine. The diester **12**, methyl 3-(1-carbomethoxymethyl-3-ethyl)piperidinoacetate, gave rise to two three-proton singlets at δ 3.70 and 3.75 (2 methyl esters) and a two-proton singlet at 3.25 (N-acetic acid ester CH_2), while the minor component, methyl 1-(3-benzyl-3-ethyl)piperidinoacetate (**13**), displayed a three-proton singlet at δ 3.60 (methyl ester) and a two-proton singlet at 3.10 (N-acetic acid ester CH_2). The two proton singlets in the latter two compounds can be compared with methyl piperidinoacetate, which shows a three-proton singlet at δ 3.68 (methyl ester) and a two-proton singlet at 3.15 (N-acetic acid ester CH_2).

No attempts were made to elaborate the precise mode of formation of the minor components. The presence of methyl 1-(3-benzyl-3-ethyl)piperdinoacetate (**13**) is not without precedent since quaternization of N-isobutenyl-N-methylbenzylamine with methyl iodide affords α,α-dimethyldihydrocinnamaldehyde upon

(7) For a general review of cyclic enamines, see K. Bláha and O. Červinka, *Advan. Heterocyclic Chem.*, **6**, 146 (1966).

(8) In general, enamines of acyclic aldehydes are not effective in C alkylation: see G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963), and references cited therein. In some cases C alkylation can be effected: T. J. Curphey and J. C. Hung, *Chem. Commun.*, 510 (1967).

(9) It might be noted at this point that although the enamine reacted with methyl vinyl ketone, it failed to add to either acrylonitrile or methyl acrylate in either protic or aprotic solvents. In conjunction with other work, initial attempts to effect a reaction with methyl 2-α-(N-methylindolyl)acrylate (i) gave no cyclized product ii.

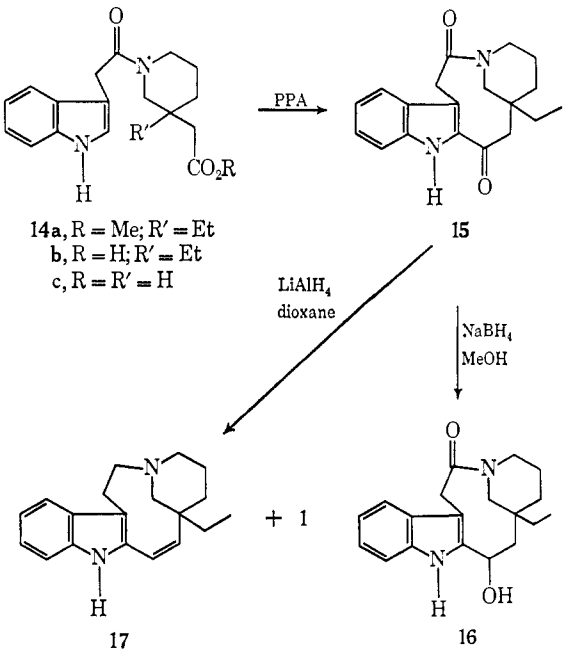


(10) C. Mannich and H. Davidsen, *Chem. Ber.*, **69**, 2106 (1936).

(11) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **87**, 1580 (1965).

hydrolysis.[12] The appearance of diester **12** can be envisaged as an exchange reaction of benzyl for methyl acetate on the N-alkylated enamine followed by further alkylation or debenzylation–realkylation of the immonium salt of ester **11**. The former process can serve as an alternate pathway for the formation of ester **13**. It is worthwhile noting that no bisbenzyl product was ever observed. This in no way eliminates either exclusive C-alkylation leading to isolable products or the absence of benzyl halide in solution, since such a product would be expected to be undetectable by vpc analysis due to the relatively large excess of halo ester in the reaction mixture.

Since only the desired ester was a benzylamine, the mixture of alkylation products could be directly hydrogenated over 10% palladium on charcoal to effect debenzylation of the major component. Direct condensation of the hydrogenation mixture with β-indolylacetyl chloride afforded the lactam ester **14a** and also served to permit the chemical separation of the minor alkylation products. Saponification of the



lactam ester afforded the corresponding lactam acid **14b** in 44% yield (based on **11**).

A recent study[13] involving the polyphosphoric acid catalyzed cyclization of β-indolealkanoic acids to cycloalkane[*b*]indolones has shown that a maximum yield of 95% was obtained in the seven-membered ring case, whereas the six- and eight-membered homologs formed in 55 and 30% yields, respectively. Upon heating lactam acid **14b** with polyphosphoric acid for 20 min at 90°, the desired cyclization occurred in 85% yield. The high yield clearly indicates that some special effects might be involved. When the desethyl lactam acid **14c** was prepared from methyl 3-piperidinoacetate in the manner described and cyclized, only polymeric material was obtained. If it is assumed that the piperidine ring exists in a chair conformation, the desethyl compound would exist with both the acetic acid and β-indolylacetyl chains equatorially disposed. However, the ethyl case **14b** should have two chair conformations of essentially equal ground-state energy, each having the β-indolylacetyl chain equatorial. One conformation would have an equatorial acetic acid chain and the other an axial one, since the nonbonded 1,3-diaxial interactions of the ethyl group should be of the same order of magnitude as for the acetic acid chain. With an axial acetic acid chain, the direction of the reaction is disposed toward intramolecular rather than intermolecular acylation, since the termini of the system are brought into closer proximity of one another. It is entertaining to speculate upon the nature of the transition state, *i.e.*, whether or not the reactive intermediate might involve participation of the amide nitrogen as in Figure 1, thereby invoking the cyclization of a six-membered ring, consequently reducing the entropy of the system.

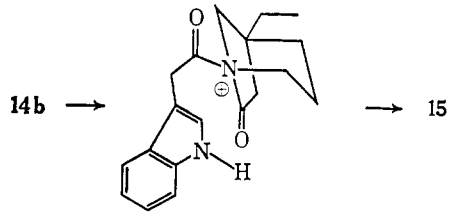


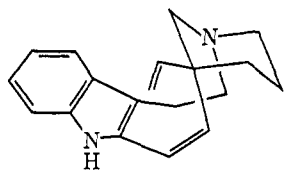
Figure 1.

The successful cyclization effected the appropriate contiguous arrangement of the skeletal framework of quebrachamine, leaving only the manipulation of undesirable functionality. The keto lactam was smoothly converted to a diastereomeric mixture of lactam alcohols **16** in 62% yield, from which one of the diastereomers could be crystallized. Reduction of the corresponding diastereomeric acetates or benzoates with lithium aluminum hydride[14] gave only trace amounts of quebrachamine along with a complex mixture of other products. Diborane, reportedly capable of reducing dialkylamides[15] as well as hydrogenolyzing 2-acylindoles,[16] was likewise ineffective. Direct reduction of the keto lactam with lithium aluminum hydride in refluxing tetrahydrofuran gave essentially the same results as with the acetate and benzoate of **16**; however, employing dioxane as a solvent, only two products were formed. Separation of the components by preparative thin layer chromatography afforded racemic quebrachamine (6%) as the minor reduction product in addition to a crystalline base in 57% yield.

The infrared spectrum of the major component indicated the lack of hydroxyl and carbonyl absorption. The mass spectrum displayed a molecular ion at *m/e* 280, 2 mass units less than that of quebrachamine (*m/e* 282). This difference indicated a single degree of unsaturation (assuming skeletal integrity) which was shown to be located at the 3,4 position by comparison of the intensity of the M − 29 peak in quebrachamine (Σ_{75} 3.0%) *vs.* 3,4-dehydroquebrachamine **17** (Σ_{75} 9.6%). The presence of the double bond favors the formation of the allylic

(12) K. C. Brannock and R. D. Burpitt, *J. Org. Chem.*, **26**, 3576 (1961).
(13) K. Ishizumi, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 863 (1967).
(14) L. J. Dolby and D. L. Booth, *J. Org. Chem.*, **30**, 1550 (1965).
(15) H. C. Brown and P. Heim, *J. Am. Chem. Soc.*, **86**, 3566 (1964).
(16) K. M. Biswas and A. H. Jackson, *Tetrahedron*, **24**, 1145 (1968).

cation as has been observed[17] in the case of 6,7-dehydroquebrachamine. The ultraviolet spectrum of 3,4-dehydroquebrachamine is of interest since it does not exhibit an extended chromophore,[18] but rather a typical 2,3-dialkylindole chromophore. Examination of Dreiding stereomodels indicates that the double bond must be *cis* and its plane must be orthogonal to the plane of the indole ring, thereby providing inhibition to resonance. In addition carbon chains C_3–C_4 and C_{10}–C_{11} must be 1,3-diaxial to the piperidine ring. This is confirmed by the lack of *trans* bands[19] in the 2800–2600-cm^{-1} region of the solution infrared spectrum, indicating that the electron pair of the piperidine nitrogen must be equatorially disposed to the piperidine ring. Consequently, 3,4-dehydroquebrachamine can be represented by **18**. In contrast quebrachamine can exist



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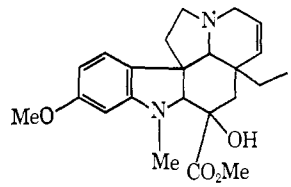

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with C_{10}–C_{11} equatorial and C_3–C_4 axial to the piperidine ring and accordingly the infrared spectrum shows *trans* bands at 2790, 2750, 2730, and 2680 cm^{-1}.

Although quebrachamine was obtained in low yield, it was felt that **17** might undergo reduction of the double bond. Catalytic hydrogenation over platinum oxide at atmospheric pressure gave only traces of side products (tlc) in addition to starting material, while palladium on charcoal catalyzed reduction at both atmospheric pressure and 50 psi left **17** untouched. In addition the double bond was inert to both diimide and diborane reduction. In view of the fact that the indole ring and the double bond are orthogonal to one another, it was not surprising that the "isolated" double bond could not be reduced *via* metal–ammonia reduction. Several attempts were made to add nucleophiles such as cyanide, carbon monoxide, and alcohol to the double bond, but all efforts in this area resulted in the recovery of unreacted 3,4-dehydroquebrachamine.

It is clear that the C_{10}–C_{11} chain inhibits approach of reagents to the *endo* face of the nine-membered ring double bond, whereas the ethyl group guards the *exo* face. The inertness of the double bond may be a foreboding sign for synthetic approaches to vindoline (**19**) which depend upon electrophilic addition to such an unsaturated center. The rigidity of 3,4-dehydroquebrachamine indicates that the same steric factors would be operable in a vindoline model.

Experimental Section

Melting point determinations were made on a Fisher-Johns apparatus and are corrected. Infrared spectra were recorded on both Perkin-Elmer 237B and 421 instruments. Ultraviolet spectra were obtained on a Cary *11S* recording spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer with tetramethylsilane as internal standard. Mass spectra were determined on an AEI-MS-9 mass spectrometer. Vapor phase chromatographic analyses were performed on a Wilkens Aerograph Model A-90-P employing a $^3/_8$ in. × 20 ft 20% SE-30 on Chromosorb W (45–60) column. Elemental analyses were determined by Galbraith Laboratories, Knoxville, Tenn., and Alfred Bernhardt Laboratories, Hohenweg, Germany. Anhydrous magnesium sulfate was employed as the drying agent unless otherwise stated. Preparative thin layer chromatography (tlc) was performed on Brinkman 20 × 20 cm silica gel F-254 plates.

4-Formylcapronitrile (5). The method of Stork[8] for the preparation of methyl 4-formylhexanoate was used, affording the cyano aldehyde in 77% yield on the same scale. The product had bp 109–111° (10 mm); ir (film) 2725 (aldehyde CH), 2250 (CN), and 1725 (C=O) cm^{-1}.

Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86. Found: C, 67.00; H, 8.90.

4-Formylcapronitrile 1,3-Dioxolane (6). A mixture of 110.7 g (0.88 mole) of 4-formylcapronitrile, 66.4 g (1.07 mole) of ethylene glycol, 16.8 g (0.088 mole) of *p*-toluenesulfonic acid monohydrate, and 1575 ml of benzene was refluxed, 12 hr being required to remove the theoretical amount of water by means of a Dean–Stark trap. The reaction mixture was cooled to room temperature, and the liquid portion was separated from insoluble catalyst by decantation, washed with 5% aqueous sodium hydroxide and saturated sodium chloride, dried, concentrated *in vacuo*, and distilled affording 131 g (88%) of the cyano acetal, bp 147–149° (20 mm), ir (film) 2250 cm^{-1} (CN).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94. Found: C, 63.99; H, 8.92.

1-Benzyl-3-ethyl-1,4,5,6-tetrahydropyridine (10). To a stirred suspension of 8.4 g (0.22 mole) of lithium aluminum hydride in 580 ml of ether was added 31.0 g (0.18 mole) of the cyano acetal **6** in 200 ml of ether at such a rate as to maintain a gentle reflux. After the addition had been completed, the reaction mixture was refluxed an additional 0.5 hr, cooled, decomposed with saturated aqueous sodium sulfate, filtered *in vacuo*, and dried. Filtration and concentration of the filtrate afforded 31 g of residue.

A mixture of the reduction product (*vide supra*), 36.8 g (0.35 mole, 37 ml) of benzaldehyde, and 3.1 g of 10% palladium on charcoal in 150 ml of ethanol was reduced on a Parr apparatus under 35–50 psi of hydrogen. After uptake of hydrogen had ceased, the mixture was filtered *in vacuo* on a pad of Celite, and the filtrate was concentrated *in vacuo*. The residual oil was treated with 200 ml of water, adjusted to pH 2 with concentrated hydrochloric acid, and extracted thoroughly with ether, and the aqueous layer was allowed to stand at room temperature overnight. The aqueous solution was basified with solid sodium carbonate, extracted thoroughly with ether, dried for 48 hr, filtered, concentrated *in vacuo*, and distilled affording 20.2 g (56%) of the enamine (97% pure by vpc): bp 91–94° (0.25 mm); ir (film) 1675 cm^{-1}; nmr (CCl_4) δ 0.95 (3 H, t, J = 7 Hz), 1.80 (6 H, m), 2.60 (2 H, m), 3.75 (2 H, s), 5.60 (1 H, s), and 7.20 (5 H, s).

Anal. Calcd for $C_{14}H_{19}N$ (vpc sample): C, 83.53; H, 9.51. Found: C, 83.26; H, 9.64.

Alkylation of Enamine 10 with Methyl Bromoacetate.[20] To a stirred, refluxing solution of 7.1 g (0.035 mole) of enamine **10** in 50 ml of methanol was added dropwise a solution of 10.7 g (0.07 mole) of methyl bromoacetate in 10 ml of methanol over a 15-min period. After the addition the reaction mixture was refluxed an additional 2.5 hr and cooled, and the solvent was removed *in vacuo*. The residual oil was triturated with ether to remove ether-soluble impurities, dissolved in 50 ml of methanol, cooled to 0°, and treated with 1.9 g (0.05 mole) of sodium borohydride, added in small portions. After stirring for 0.5 hr, the solvent was removed *in vacuo*, and the residue was diluted with 75 ml of water, thoroughly extracted with chloroform, dried, filtered, concentrated, and distilled affording 4.04 g of an oil, bp 100–144° (0.65 mm). The three components, separated by vpc in order of increasing retention time, were as follows.

Methyl 3-(1-carbomethoxymethyl)-3-ethylpiperidinoacetate (**12**, 2%): ir (CCl_4) 1735 cm^{-1}; nmr ($CDCl_3$) δ 0.85 (3 H, t, J = 7 Hz), 1.20–1.80 (6 H, m), 2.10–2.80 (6 H, m), 3.25 (2 H, s), 3.70 (3 H, s), and 3.75 (3 H, s). *Anal.* Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01. Found: C, 60.51; H, 9.19.

Methyl 3-(1-benzyl-3-ethyl)piperidinoacetate (**11**, 22%): ir (CCl_4) 1735 cm^{-1}; nmr ($CDCl_3$) δ 0.75 (3 H, t, J = 7 Hz), 1.20–1.70 (6 H, m), 1.80–2.50 (6 H, m), 3.35 (2 H, s), 3.50 (3 H, s), and

(17) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. I, Holden-Day, Inc., San Francisco, Calif., 1964, p 52.

(18) *Cf.* uleine, ref 2b, p 102.

(19) K. Nakanishi, T. Goto, and M. Ohashi, *Bull. Chem. Soc. Jap.*, 30, 403 (1957); F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

(20) Alkylation with methyl iodoacetate was conducted in the same manner, giving the yields stated in the discussion.

7.20 (5 H, m). *Anal.* Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15. Found: C, 74.16; H, 9.08.

Methyl 1-(3-benzyl-3-ethyl)piperidinoacetate (**13**, <1%): ir (CCl_4) 1750 cm^{-1}; nmr ($CDCl_3$) δ 0.90 (3 H, t. J = 7 Hz), 1.05–1.90 (6 H, m), 2.20 (2 H, s), 2.30–2.90 (4 H, m), 3.10 (2 H, s), 3.60 (3 H, s), and 7.15 (5 H, m). *Anal.* Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15. Found: C, 74.39; H, 9.27.

Debenzylation of Methyl 3-(1-Benzyl-3-ethyl)piperidinoacetate (11). Concentrated hydrochloric acid was added to a solution of 4.04 g of a mixture of tertiary amines (*vide supra*) in 20 ml of ethanol until the solution was adjusted to pH 3. The mixture was hydrogenated at atmospheric pressure over 900 mg of 10% palladium on charcoal. After uptake of hydrogen had ceased, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to yield an oil.

3-[1-(β-Indolylacetyl)-3-ethyl]piperidinoacetic Acid (14b). The above-mentioned oil from debenzylation was dissolved in 100 ml of methylene chloride and was added to a vigorously stirred solution of 11.0 g (0.104 mole) of anhydrous sodium carbonate dissolved in 70 ml of water at 0°. To this mixture was added 2.9 g (0.015 mole) of β-indolylacetyl chloride[21] in small portions over a period of 5 min and the resulting mixture was stirred an additional 1.5 hr. The layers were separated, the aqueous layer was thoroughly extracted with chloroform, and the organic portions were combined, washed with 5% aqueous sodium hydroxide and 10% aqueous hydrochloric acid, dried, filtered, and concentrated giving a gum: ir ($CHCl_3$) 1735, 1630 cm^{-1} (homogeneous by tlc). The residue was dissolved in 50 ml of methanol, treated with 60 ml of 5% aqueous sodium hydroxide, and refluxed under nitrogen for 2.5 hr. The reaction mixture was concentrated *in vacuo* to a low volume, washed with chloroform, acidified with 10% aqueous hydrochloric acid, extracted thoroughly with chloroform, dried, filtered, and concentrated *in vacuo* to afford 1.04 g (44% based on tertiary amines) of the lactam acid as a foam, ir ($CHCl_3$) 3600–2400 and 1710 cm^{-1}.

3,10-Dioxoquebrachamine (15). An intimate mixture of 500 mg (1.53 mmoles) of lactam acid **14b** and 50 g of polyphosphoric acid in a stoppered 200-ml round-bottom flask was constantly rotated while being heated on a steam bath at 90° (internal temperature 80°) for 20 min. The reaction mixture was cooled, decomposed with ice and water, thoroughly extracted with chloroform, dried, and concentrated to yield 412 mg (87%) of keto lactam: mp 231–233° (acetone): ir ($CHCl_3$) 1640 cm^{-1}; uv max (C_2H_5OH) 312 mμ (17,700) and 245 (12,450); mass spectrum (70 eV), *m/e* (relative intensity, >20% of base peak) 311 (23), 310 (100, Σ 13.7%), 226 (22), 158 (21), 157 (40), 154 (44), 143 (67), 130 (33), 129 (56), 128 (24), and 111 (24).

Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.72; H, 7.38; N, 8.82.

3-Hydroxy-10-oxoquebrach amine (16). To a stirred solution of 480 mg (1.55 mmoles) of keto lactam **15** in 10 ml of methanol maintained at 0° was added 750 mg (20 mmoles) of sodium borohydride. After 1.5 hr the solvent was removed *in vacuo*, and the residue was diluted with water, thoroughly extracted with chloroform, dried, filtered, and concentrated *in vacuo* to give 297 mg (62%) of a semisolid mixture of diastereomeric lactam alcohols by tlc. Fractional crystallization from ether–methanol afforded 72 mg (15%) of a single diastereomer: mp 228–230.5°; uv max (CH_3OH) 292 mμ (6040), 283 (7100), and 223 (35,000).

Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.04; H, 7.74; N, 8.97. Found: C, 73.26; H, 8.10; N, 8.82.

Quebrachamine (1) and 3,4-Dehydroquebrachamine (17). To a stirred, refluxing suspension of 600 mg (15.8 mmoles) of lithium aluminum hydride in 60 ml of dry dioxane maintained under a nitrogen atmosphere was added dropwise a solution of 347 mg (1.13 mmoles) of keto lactam **15** dissolved in 40 ml of dry dioxane. The reaction mixture was refluxed for 18 hr, cooled, decomposed with saturated aqueous sodium sulfate, and filtered on Celite *in vacuo*, and the filter cake was washed with hot tetrahydrofuran. The filtrate was dried, filtered, and concentrated. The residue was subjected to preparative thin layer chromatography using 3:1 benzene–methanol as eluent. The silica gel containing quebrachamine was extracted with methanol and concentrated giving a semisolid. Sublimation at 55° (1 μ) gave a solid, mp 98–106°. Recrystallization from aqueous ethanol yielded 20 mg (6%) of racemic quebrachamine, mp 109–110° (lit.[3a,22] 113–116°, mmp 109–111°). Both samples had superimposable solution infrared spectra, identical mass spectra, and identical R_f values and color (magenta with 1% ceric ammonium nitrate–phosphoric acid spray) on thin layer chromatography. The 3,4-dehydroquebrachamine was separated from the silica gel (*vide supra*) and sublimed at 75–80° (1 μ) affording 180 mg (57%) of 3,4-dehydroquebrachamine: mp 107–108°; ir ($CHCl_3$) 3480 (indole NH) and 3020 cm^{-1} (=CH); uv max (C_2H_5OH), 288 mμ (ε 6700), 279 (8000), and 226 (42,700); mass spectrum (70 eV), *m/e* (relative intensity, >20% of base peak) 280 (48), 279 (76), 251 (94), 239 (27), 238 (28), 237 (100, Σ_{75} 10.3%), 223 (29), 209 (27), 208 (32), 184 (48), 169 (24), and 156 (43).

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(21) E. Shaw and D. W. Woolley, *J. Biol. Chem.*, **203**, 979 (1953).

(22) We wish to thank Professor Stork for providing us with a sample of synthetic, racemic quebrachamine.