1140 (s) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.65 (s, 4 H), 3.00 (t, 4 H), 1.90 (m, 2 H); EI-MS (70 eV) m/e (rel intensity), 210 (39), 132 (100); UV (EtOH) λ_{max} 212 (ϵ 1280), 237 (ϵ 1500) nm. Anal. Calcd for $C_6H_{10}O_2S_3$: C, 34.26; H, 4.79. Found: C, 34.33; H, 4.85.

From 4 and Dimethylamine. Dimethylamine gas (2 bubbles/s) was passed through a stirred solution of **4** (4.0 g, 0.013 mol) in THF (250 mL) at 35 °C. Stirring was continued an additional 10 h at room temperature. The THF was removed to give a yellow oil which solidified to a white solid on standing at room temperature. It was washed with cold ethanol (100 mL). Recrystallization from ethanol gave white plates (1.2 g, 0.0057 mol, 44%): mp 139–140 °C; mmp with product from 3,3-dibromothietane 1,1-dioxide 136–138 °C. The infrared and ^1H NMR spectra were identical with that product.

Desulfurization of 6. A mixture of **6** (0.50 g, 0.0028 mol) and Raney nickel[23] (20 g) in ethanol (200 mL) was refluxed for 20 h. The nickel was removed by filtration, and the solution was concentrated to give a white product which was recrystallized from carbon tetrachloride to give white prisms of thietane 1,1-dioxide (0.15 g, 0.0014 mol, 50%): mp 75–76 °C (lit.[18] mp 75.5–76 °C). Its IR and ^1H NMR spectra were identical with those of an authentic sample.

Reaction of 3-Chlorothiete 1,1-Dioxide with Sodium Hydroxide. 3-Chlorothiete 1,1-dioxide (0.50 g, 0.0036 mol) was added to aqueous sodium hydroxide (0.28 g, 15 mL), and the mixture was heated for 10 min until the sulfone dissolved. The solution was cooled, acidified to pH 1 with 10% hydrochloric acid, and extracted with methylene chloride (3 × 50 mL). The methylene chloride solution was dried ($MgSO_4$) and the solvent was removed to give dimethyl sulfone (0.23 g, 0.0015 mol, 68%): mp 105–107 °C (lit.[24] mp 109 °C). Infrared and ^1H NMR spectra were identical with those reported previously.[25]

1-Chloro-7-thiabicyclo[4.2.0]-3-octene 7,7-Dioxide (7). 1,3-Butadiene (10 mL) was added to a solution of 3-chlorothiete 1,1-dioxide (4.0 g, 0.029 mol) and hydroquinone (0.75 g) in benzene (10 mL) in a Carius tube cooled in liquid nitrogen. The tube was sealed under vacuum at liquid nitrogen temperature and heated at 125 °C for 4 days. The tube was opened, and the benzene was removed to give a residue which was dissolved in methanol (50 mL). This solution was filtered and the methanol removed to give a white solid which was recrystallized from chloroform–hexane to give white crystals (2.2 g, 0.017 mol, 59%): mp 81–82 °C; ^1H NMR ($CDCl_3$) δ 6.10 (m, 2 H), 4.7–4.3 (m, 3 H), 2.7 (m, 4 H). The product was treated with bromine (2.6 g, 0.016 mol) in refluxing carbon tetrachloride (35 mL) for 1 h. The solvent was removed and the residue was dissolved in benzene (50 mL). Diazabicyclo[4.3.0]non-5-ene (4.1 g, 0.033 mol) was added, and the mixture was refluxed for 1 h. The solution was cooled and washed with aqueous 10% hydrochloric acid (3 × 10 mL). The benzene layer was dried ($MgSO_4$), and the benzene was removed to give a yellow oil. Pentane was added to give benzothiete 1,1-dioxide as a yellow solid (1.3 g, 0.0084 mol, 50%): mp 124–127 °C (lit.[5] mp 126–128 °C). Spectroscopic properties were identical with those of an authentic sample.

2a-Chloro-3,8-oxy-3,8-diphenyl-2a,3,8,8a-tetrahydro-2*H*-naphtho[2,3-*b*]thiete 1,1-Dioxide (8). A solution of 3-chlorothiete 1,1-dioxide (1.0 g, 0.0072 mol) and 1,3-diphenylisobenzofuran (2.1 g, 0.0073 mol) in *m*-xylene (10 mL) was refluxed for 24 h. The product precipitates on cooling the mixture to room temperature. It was recrystallized from chloroform (1.04 g, 0.0025 mol, 35%): mp 223–225 °C; IR (KBr) 1330 (s), 1140 (s); ^1H NMR ($CDCl_3$) δ 8.26–6.43 (m, 14 H), 5.10 (s, 1 H), 4.23 (s, 2 H). Anal. Calcd for $C_{23}H_{17}ClO_3S$: C, 67.56; H, 4.19. Found: C, 67.67; H, 4.13.

Registry No. 1, 90344-86-8; **2a**, 90344-91-5; **2b**, 90344-92-6; **3a**, 90344-93-7; **3b**, 90344-94-8; **4**, 90345-03-2; **6**, 85069-70-1; **7**, 90345-04-3; **8**, 90367-67-2; $CH_2(CO_2Me)_2$, 108-59-8; $CH_2(CO_2Et)_2$, 105-53-3; Me_2NH, 124-40-3; Et_2NH, 109-89-7; PhNHMe, 100-61-8; $HS(CH_2)_3SH$, 109-80-8; $MeSO_2Me$, 67-71-0; $(CH_2{=}CH)_2$, 106-99-0; thietane, 287-27-4; thietane 1,1-dioxide, 5687-92-3; 3-chlorothietane 1,1-dioxide, 15953-83-0; 3,3-dichlorothietane 1,1-dioxide, 90344-85-7; 3,3-dibromothietane 1,1-dioxide, 59463-73-9; 2,3-dibromothietane 1,1-dioxide, 90344-87-9; 2-bromothiete 1,1-dioxide, 90344-88-0; 3-bromothiete 1,1-dioxide, 59463-74-0; 2,3-dibromo-3-chlorothietane 1,1-dioxide, 90344-89-1; 2-bromo-3-chlorothiete 1,1-dioxide, 90344-90-4; 5,5-dimethyl-1,3-cyclohexanedione, 126-81-8; 1,3-cyclohexanedione, 504-02-9; thiete 1,1-dioxide, 7285-32-7; 3-[bis(ethoxycarbonyl)methyl]thietane 1,1-dioxide, 82299-32-9; ethyl acetoacetate, 141-97-9; 3-[[1-acetyl-1-(ethoxycarbonyl)]-methyl]thietane 1,1-dioxide, 90344-95-9; 3-(dimethylamino)thiete 1,1-dioxide, 1599-35-5; 3-(diethylamino)thiete 1,1-dioxide, 59514-12-4; 3-piperidinothiete 1,1-dioxide, 1623-62-7; 3-morpholinothiete 1,1-dioxide, 1599-38-8; 3-(*N*-methylanilino)thiete 1,1-dioxide, 1599-21-9; 3-(1-imidazolyl)thiete 1,1-dioxide, 90344-96-0; piperidine, 110-89-4; morpholine, 110-91-8; imidazole, 288-32-4; 3-*n*-butoxythiete 1,1-dioxide, 90344-97-1; 3-isobutoxythiete 1,1-dioxide, 90344-98-2; 3-isopropoxythiete 1,1-dioxide, 90344-99-3; 3-phenoxythiete 1,1-dioxide, 90345-00-9; 3,3-di-*n*-propoxythietane 1,1-dioxide, 90345-01-0; 3,3-bis(allyloxy)thietane 1,1-dioxide, 90345-02-1; 3,3-diethoxythietane 1,1-dioxide, 18487-59-7; 3,3-dimethoxythietane 1,1-dioxide, 10099-05-5; *n*-butyl alcohol, 71-36-3; isobutyl alcohol, 78-83-1; isopropyl alcohol, 67-63-0; phenol, 108-95-2; *n*-propyl alcohol, 71-23-8; allyl alcohol, 107-18-6; ethanol, 64-17-5; methanol, 67-56-1; benzothiete 1,1-dioxide, 16065-50-2; 1,3-diphenylisobenzofuran, 5471-63-6.

(23) Mozingo, R. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. III, p 181.
(24) Baumann, E.; Walter, G. *Ber.* **1893**, *26*, 1131.
(25) Pouchert, C. J.; Campbell, J. R. "The Aldrich Library of NMR Spectra"; Aldrich Chemical Co., Inc., 1974; Vol. 10, p 2C. Pouchert, C. J. "The Aldrich Library of Infrared Spectra", 2nd ed.; Aldrich Chemical Co., 1975; p 470A.

General Synthesis of Phenanthroindolizidine, Phenanthroquinolizidine, and Related Alkaloids: Preparation of (±)-Tylophorine, (±)-Cryptopleurine, (±)-Septicine, and (±)-Julandine[1]

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Received October 14, 1983

A general synthetic route to the pentacyclic phenanthro class and related indolizidine and quinolizidine alkaloids via β-amino ketone intermediates is reported. The synthesis of tylophorine, cryptopleurine, septicine, and julandine, in racemic forms, has been described. Synthetic steps in the preparations of these alkaloids involve 1,3-dipolar cycloadditions of the cyclic nitrones as a common feature followed by crucial ring closures by aldol reactions and photolyses.

There are biogenetic relationships between the phenanthroindolizidine and phenanthroquinolizidine groups of alkaloids, and they are characterized by their unique pentacyclic structure as well as interesting biological

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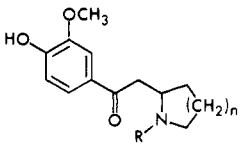
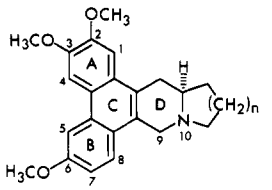
properties.[2] Among a number of biological and pharmacological activities associated with these groups of alkaloids, antitumor activity is most notable and, thus, is responsible for considerable recent synthetic attention.[2] These alkaloids have been suggested to be biogenetically formed via β-amino ketone intermediates, which is consistent with the fact that phyllostone (1) and pleurospermine (2) cooccur with antofine (3) and cryptopleurine (4),



1, n = 1; R = CH_3

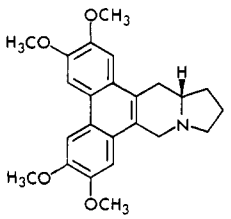
2, n = 2; R = H



3, n = 1

4, n = 2

respectively, in the same plant in each case.[2] This suggested to us that a new entry to the synthesis of these pentacyclic indolizidine and quinolizidine alkaloids by utilizing β-amino ketones as useful common building blocks could be evolved. With this in mind we planned to utilize isoxazolidines, available from the 1,3-dipolar cycloaddition of nitrones to olefins,[3] to serve as synthetic equivalents of β-amino alcohols and, thus, β-amino ketones. In this paper we describe a new, efficient route to the pentacyclic alkaloids (±)-tylophorine (5) and (±)-cryptopleurine (4) and their seco bases (±)-septicine (6) and (±)-julandine (7).



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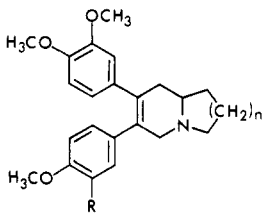
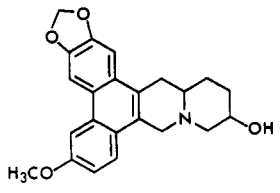


6, n = 1; R = OCH_3

7, n = 2; R = H

The key feature of the synthetic method involves the 1,3-dipolar cycloaddition reaction for the synthesis of β-amino alcohols, which were converted in subsequent steps (including intramolecular photocyclization) to the alkaloids containing the phenanthrene nucleus.

We first chose cryptopleurine (4) as a synthetic target, which constitutes together with cryptopleuridine (8) a rare



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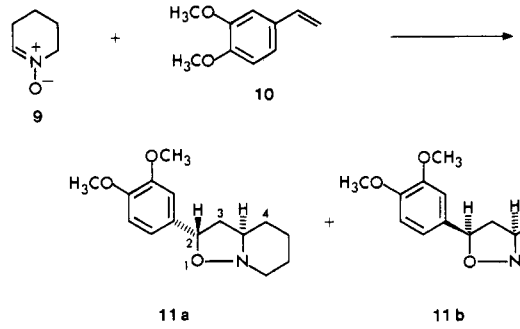
group of naturally occurring alkaloids with the trans-fused phenanthro[9,10-*b*]quinolizidine ring system. Cryptopleurine (4) has been reported to act as an antitumor agent[4] and to show highly specific and potent cytotoxic[5] and vesicant activities.[6] As a result of these interesting and unique biological activities and for the study structure–activity relationships, this alkaloids and the secophenanthroquinolizidine alkaloid, julandine (7) (for synthesis, see ref 7a,c), have recently received intense attention, and three syntheses of cryptopleurine involving oxidative coupling[7] have been reported.[8]

Our synthesis of alkaloids 4 and 7 began with the 1,3-dipolar cycloaddition reaction of 2,3,4,5-tetrahydropyridine 1-oxide (9) with 3,4-dimethoxystyrene (10), readily avail-

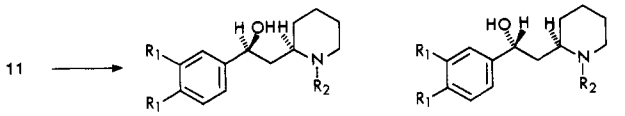


9 10

11a 11b

able by the Wittig reaction of 3,4-dimethoxybenzaldehyde with methylenetriphenylphosphorane. The reaction was carried out in boiling toluene for 5 h to give the cycloadduct 11 in 93% yield, which showed a single spot on TLC. The ^{13}C NMR spectrum of this product, however, indicated a pair of signals for each of the carbons in the molecule, suggesting two diastereomers, i.e., **11a** and **11b**. Actually, the product was shown to be a 20:1 mixture of trans and cis isomers **11a** and **11b** on the basis of the gas chromatographic mass spectral (GC/MS) analyses.[9] The preferential formation of the trans adduct **11a** is rationalized in terms of a preference for an exo-oriented transition state,[10] since secondary orbital interactions would not be a controlling factor in this case.[10]

On reductive N–O bond cleavage of 11 with zinc in aqueous acetic acid the amino alcohol **12a** was isolated in



12a, R_1 = OCH_3; R_2 = H 12b, R_1 = OCH_3; R_2 = H

13a, R_1 = H; R_2 = CH_3 13b, R_1 = H; R_2 = CH_3

90% yield.[11] Compound **12a** should have the configurations of C_2 and C_2, identical with those of the corresponding carbons, i.e., C_{3a} and C_2, respectively, in the trans

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(2) (a) Govindachari, T. R.; Viswanathan, N. *Heterocycles* **1978**, *11*, 587. (b) Bick, I. R. C.; Sinchai, W. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1981; Vol. XIX, Chapter 3.

(3) For recent reviews of synthetic applications of the [3 + 2] cycloaddition reactions of nitrones, see: Black, D. S. C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, 205. Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123. Oppolzer, W. *Ibid.* **1977**, *16*, 10. Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. Iida, H.; Kibayashi, C. *Yuki Gosei Kagaku Kyokai Shi* **1983**, *41*, 652.

(4) Gellert, E.; Rudzats, R. *J. Med. Chem.* **1964**, *7*, 361. Donaldson, G. R.; Atkinson, M. R.; Murray, A. W. *Biochem. Biophys. Res. Commun.* **1968**, *31*, 104. Hartwell, J. L.; Abbott, B. J. *Adv. Pharmacol. Chemother.* **1969**, *7*, 117.

(5) Farnsworth, N. R.; Hart, N. K.; Johns, S. R.; Lamberton, J. A.; Messmer, W. *Aust. J. Chem.* **1969**, *22*, 1805.

(6) de la Lande, I. S. *J. Exptl. Biol. Med. Sci.* **1948**, *26*, 181.

(7) (a) Paton, J. M.; Pauson, P. L.; Stevens, T. S. *J. Chem. Soc. C* **1969**, 1309. (b) Kotani, E.; Kitazawa, M.; Tobinaga, S. *Tetrahedron* **1974**, 3027. (c) Herbert, R. B. *J. Chem. Soc., Chem. Commun.* **1978**, 794.

(8) For earlier syntheses of cryptopleurine, see: (a) Bradsher, C. K.; Berger, H. *J. Am. Chem. Soc.* **1957**, *79*, 3287; **1958**, *80*, 930. (b) Marchini, P.; Belleau, B. *Can. J. Chem.* **1958**, *36*, 581.

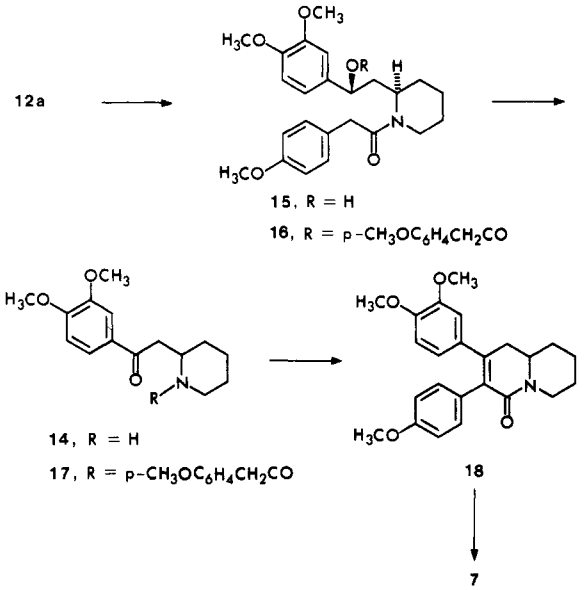
(9) Both isomers **11a** and **11b** had virtually identical mass spectra with *m/e* 263 (M^+) (see Experimental Section).

(10) Tufariello, J. J.; Asrof Ali, S. *Tetrahedron Lett.* **1978**, 4647.

(11) The other isomer **12b** which would have been expected to be formed from the minor cis adduct **11b** was not isolated in pure form in this procedure.

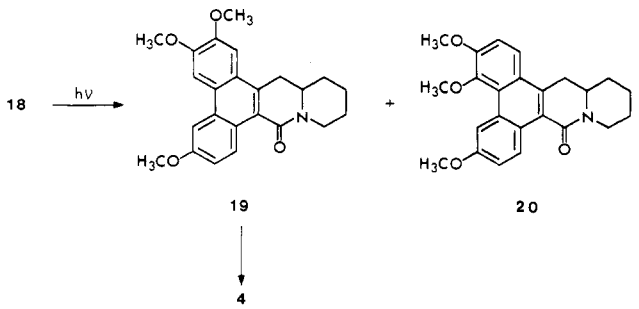
adduct **11a** which is the predominant component in the cycloadduct mixture. The stereochemical assignment for **12a** was due to its ^{1}H NMR signal for the benzylic proton, which appeared at δ 4.99 (dd, J = 8, 4 Hz), in good agreement with that reported for allosedamine (**13a**) (δ 5.04, dd, J = 10, 4 Hz) rather than that reported for sedamine (**13b**) (δ 4.84, dd, J = 9.5, 2.5 Hz).[10]

Since direct oxidation of the amino alcohol **12a** to the amino ketone **14** failed because of the lability of **12a** to various oxidants, **12a** was acylated with (*p*-methoxyphenyl)acetyl chloride to provide a chromatographycally separable mixture of the amide alcohol **15** and amide ester **16**. In practice, however, the crude mixture was without



separation subjected to subsequent partial hydrolysis of the ester group by brief treatment under alkaline conditions to produce **15** in 64% yield from **12**. Oxidation of **15** with Collins reagent yielded the keto amide **17** in 82% yield, which was then converted to the lactam **18** in 67% yield by intramolecular aldol condensation induced by sodium ethoxide. Lithium aluminum hydride reduction of **18** provided (±)-julandine (**7**) in 63% yield. Synthetic **7** exhibited the identical IR and ^{1}H NMR spectra with those of a natural sample of julandine and proved to be identical by TLC, melting point, and mixture melting point with an authentic sample of (±)-julandine.

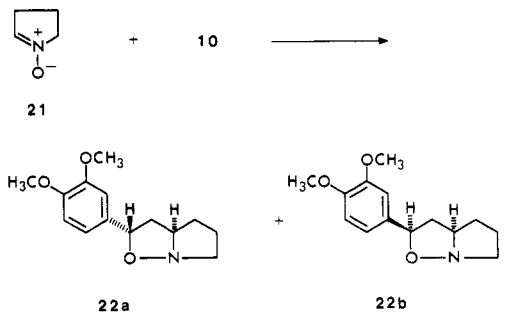
Irradiation of the lactam **18** using a Pyrex-filtered high-pressure mercury lamp in the presence of iodine yielded two fluorescent photocyclization products **19** and **20** in 48% and 14% yield, respectively. The structure of



each regioisomer was secured on the basis of its ^{1}H NMR spectrum. In the spectrum of **19** the C_4 aromatic proton on ring A appeared as a singlet at δ 7.81. In the spectrum of **20**, however, the two aromatic protons on ring A gave rise to an ortho-coupled AB quartet centered at δ 7.79 (C_1-H) and 7.30 (C_2-H) with J = 9 Hz. Furthermore the C_5 aromatic proton on ring B was remarkably shifted downfield owing to the proximity of the C_4 methoxy group on ring A. The major product **19** with the "proper" or "desired" methoxyl substitution mode was converted to (±)-cryptopleurine (**4**) by reduction with lithium aluminum hydride in 95% yield. The synthetic substance was found to be identical with natural (−)-cryptopleurine (**4**) by IR, ^{1}H NMR, TLC, and mass spectroscopy.

Next we planned to apply this methodology to the synthesis of tylophorine (**5**). Such alkaloids, which possess the phenanthroindolizidine ring system, have sometimes been designated as Tylophora alkaloids since they have mainly isolated from plants of the genus *Tylophora* and comprise a small group of alkaloids.[12] Tylophorine has been previously synthesized by several groups of workers.[13] All of these syntheses have been accomplished by utilizing synthetic routes starting from phenanthrene derivatives except for two routes[13d,f] involving oxidative coupling.

For the synthesis of tylophorine (**5**) and also the seco base septicine (**6**),[14] a sequence similar to that described above for the synthesis of the quinolizidine alkaloids cryptopleurine (**4**) and julandine (**7**) can be envisioned. Thus the cycloaddition reaction was performed between 1-pyrroline 1-oxide (**21**) and 3,4-dimethoxystyrene (**10**) in



boiling toluene to give the cycloadduct **22** which showed a single spot on TLC. One might however predict that the reaction proceeds via an exo-oriented transition state and an endo-oriented transition state, the latter of which would be disfavored because of steric interactions between the pyrrolidine ring hydrogen and the aromatic ring in analogy with the case of **11**. In fact, GC analysis of this product indicated a ratio of 5:2 favoring the trans isomer **22a** resulting from the exo-oriented transition state. In the ^{1}H NMR spectrum of the free base of the cycloadduct, however, no clear distinction between these isomers **22a** and **22b** could be made, but the spectrum of its picrate in pyridine-d_5 indicated two well-resolved pairs of singlets for the methoxyl groups in a ratio of 75:35, very similar to the ratio found by GC analysis as described above.

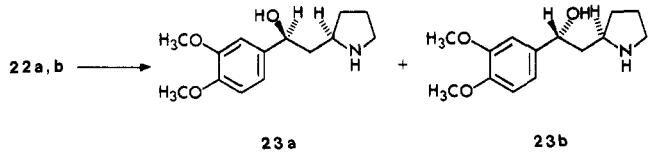
Catalytic hydrogenation of the inseparable mixture of diastereomers **22a** and **22b** resulted in N–O bond cleavage

(12) Govindachari, T. R. "The Alkaloids"; Academic Press: New York, 1967; Vol. IX, Chapter 13.

(13) (a) Govindachari, T. R; Lakshmikantham, M. V.; Rajadurai, S. *Tetrahedron* **1961**, *14*, 284. (b) Herbert, R. B.; Moody, C. J. *J. Chem. Soc. D* **1970**, 121. Cragg, J. E.; Herbert, R. B.; Jackson, F. B.; Moodey, C. J.; Nicolson, I. T. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2477. (c) Chauncey, B.; Gellert, E. *Aust. J. Chem.* **1970**, *23*, 2503. (d) Liepa, A. J.; Smmons, R. E. *J. Chem. Soc., Chem. Commun.* **1977**, 826. (e) Weinreb, S. M.; Khatri, N. A.; Shringarpure, J. *J. Am. Chem. Soc.* **1979**, *101*, 5073. Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *Ibid.* **1981**, *103*, 6387. (f) Mangla, V. K.; Bhakuni, D. S. *Tetrahedron* **1980**, *36*, 2489.

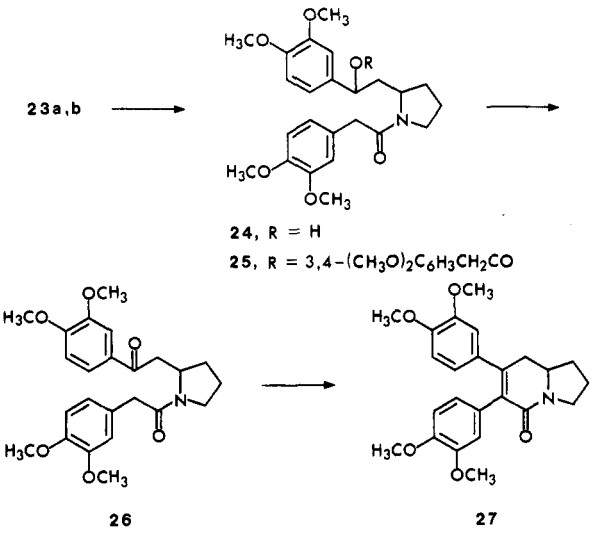
(14) For the synthesis of septicine, see: (a) Russel, J. H.; Hunziker, H. *Tetrahedron Lett.* **1969**, 4035. (b) Govindachari, T. R.; Viswanathan, N. *Tetrahedron* **1970**, *26*, 715. (c) Herbert, R. B.; Jackson, F. B.; Nicolson, I. T. *J. Chem. Soc., Chem. Commun.* **1976**, 450 and the latter paper in ref 13b. (d) Stevens, R. V.; Luh, Y. *Tetrahedron Lett.* **1977**, 979. (e) Iwashita, T.; Suzuki, M.; Kusumi, T.; Kakisawa, H. *Chem. Lett.* **1980**, 383.

to afford the amino alcohol **23** in 86% yield. The product

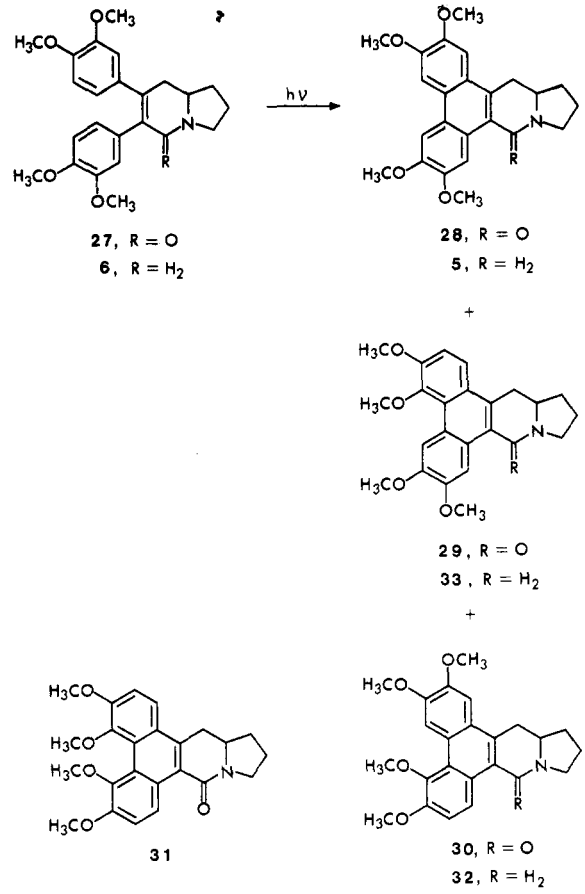


obtained was found to be a mixture of two diastereomers (**23a** and **23b**) resulting from the trans and cis adducts **22a** and **22b**, respectively. The major component **23a** could be separated after repeated recrystallizations from chloroform–hexane, where the melting point was raised from 154–156 to 160–161 °C. In analogy with the case in the piperidine analogue **12**, the stereostructure of this major alcohol **23a** was supported by the ^{1}H NMR absorptions of the benzylic proton which appeared as a doublet of doublets at δ 5.10 with J = 4 and 9 Hz, very similar to that observed in allosedamine (**13a**) rather than sedamine (**13b**) (vide supra). However, no effort was made to separate these isomers since our synthetic sequence involves an oxidation step which removes the chirality at the benzylic carbon.

Treatment of the amino alcohol **23** with (3,4-dimethoxyphenyl)acetyl chloride in chloroform in the presence of potassium carbonate afforded the amide alcohol **24** accompanied by a minor amount of the amide ester **25**.



The crude mixture of the products was hydrolyzed under alkaline conditions to produce **24** in 70% yield based on **23**. Oxidation with Collins reagent converted **24** into the keto amide **26** in 86% yield, which then gave lactam **27** in 95% yield by intramolecular aldol reaction induced by alcoholic potassium hydroxide. Irradiation of **27** followed by separation by preparative TLC yielded 9-oxotylophorine (**28**), 9-oxoisotylocrebrine (**29**), and 9-oxotylocrebrine (**30**) in 55%, 24%, and 4.3% yields, respectively. The positional isomers **28** and **29** could be readily discriminated by the signals in the ^{1}H NMR spectra for the two aromatic protons on ring A which occurred at δ 7.21 and 7.69 (or 7.70) as singlets in **28** and at δ 7.71 and 7.74 as doublets with an ortho coupling (10 Hz) in **29**. The remaining two aromatic protons on ring B in these isomers **28** and **29** gave rise to two singlets at δ 7.70 (or 7.69) and 9.02, and at δ 8.78 and 9.12, respectively. In the latter case the signal due to the "bay" proton[2b] (i.e., C_5-H) moved remarkably downfield (δ 8.78) relative to that for **2** (δ 7.70 (or 7.69)), owing to the close proximity of the C_4 methoxyl group. The location of the methoxyl groups in the last isomer could not be assigned by ^{1}H NMR data because of an insufficient quantity of the sample. To this product



either structure **30** or **31** could be alloted; however, Dreiding models indicated that the possibility of structure **31** might be ruled out because of serious nonbonding interaction between the C_4 and C_5 methoxyl groups, and therefore structure **30** would be preferred.

Transformation of 9-oxotylophorine (**28**) to tylophorine (**5**) with lithium aluminum hydride or diborane resulted in only the recovery of the starting material or very low yields of the product. Thus the lactam **27** in hand was reduced with the mixed hydride reagent from lithium aluminum hydride and aluminum chloride (3:1) in ether–THF to afford (±)-septicine (**6**) in 88% yield. Its identification was made by direct comparison by mixture melting point and TLC behavior and the spectra (IR and ^{1}H NMR) of an authentic sample of (±)-septicine. Irradiation of **6** followed by purification by high-performance liquid chromatography (HPLC) provided (±)-tylophorine (**5**) in 43% yield along with a minor amount of a less-polar component which was considered to be a mixture of tylocrebrine (**32**) and isotylocrebrine (**33**). Synthetic tylophorine (**5**) was found to be identical with natural (−)-tylophorine by IR, ^{1}H NMR, and mass spectra as well as TLC behavior.

We believe that this work demonstrates some general new methodology thoroughly applicable to the preparations of naturally occurring phenanthroindolizidine and phenanthroquinolizidine alkaloids as well as their biogenetically related congeners.

Experimental Section

General Procedures. Melting points were determined by using a Yanagimoto micro apparatus and are uncorrected. IR spectra were determined on a Hitachi 215 spectrophotometer. ^{1}H NMR spectra were recorded at 60 (Varian T-60), 90 (Varian EM-390), 100 (JEOL JNM-PS-100), and 270 MHz (JEOL JNM-FX 270) with tetramethylsilane as an internal standard and $CDCl_3$ as solvent unless otherwise noted. ^{13}C NMR spectra were mea-

sured with a JEOL JNM-FX 270 spectrometer at 67.8 MHz with tetramethylsilane as an internal standard and $CDCl_3$ as solvent. Mass spectra were obtained with Hitachi RMU-7L and M-80 (equipped with a Hitachi M-003 data processing system) double-focusing mass spectrometers at an ionizing potential of 70 eV. GC/MS analyses were performed with a Hewlett-Packard Model GC-5710A gas chromatograph by using a 1-ft column of Silicone DC 2% QF-1 on Chromosorb W AW DMCS (60–80 mesh) interfaced with a JEOL JMS-D 300 mass spectrometer (at 70 eV). Gas chromatographic analyses were conducted on a Shimazu GC-7AG instrument with a 1-m column of Silicone 5% OV-17 on Chromosorb W AW DMCS (60–80 mesh). HPLC was carried out by using a Kusama KP-6H micro pump with a Kusano CIG column (silica gel, 10-μm particle size, 15 mm i.d. × 30 cm). TLC was run on Merck precoated silica gel 60-F 254 plates. Merck silica gel 60 (230–400 mesh) was used for column chromatography.

Photochemical experiments were carried out with a 100-W Ushio high-pressure mercury lamp in a Pyrex immersion well apparatus. All drying operations were performed over anhydrous magnesium sulfate unless otherwise noted.

3,4-Dimethoxystyrene (10). To a stirred solution of *n*-butyllithium (170 mL of a 1.6 M solution in hexane, 0.26 mol) in ether (300 mL) was added in small portions (triphenylphosphonio)methyl bromide (93 g, 0.26 mol). This mixture was stirred at room temperature for 4 h. To the resulting mixture was added with stirring a solution of 3,4-dimethoxybenzaldehyde (36.5 g, 0.22 mol) in ether (200 mL) at such a rate that gentle refluxing occurred. After addition was complete, the reaction mixture was heated under reflux with stirring for 20 h and allowed to cool to room temperature. After removal of the precipitate by filtration, the ethereal filtrate was washed with water until neutral, dried over $CaCl_2$, and evaporated. The oily residue was distilled to give **10** (15.2 g, 42%): bp 92–95 °C (3 mmHg) (lit.[15] bp 113–115 °C (6–7 mmHg)); IR (neat film) 1620 cm^{-1}; ^1H NMR (60 MHz) δ 3.74 (s, 3 H), 3.78 (s, 3 H), 5.08 (dd, 1 H, J = 11, 2 Hz), 5.55 (dd, 1 H, J = 18, 2 Hz), 6.39–6.94 (m, 4 H).

2-(3,4-Dimethoxyphenyl)-3,3a,4,5,6,7-hexahydro-2*H*-isoxazolo[2,3-*b*]pyridine (11). A mixture of **9** (3.00 g, 18.3 mmol) and **10** (1.81 g, 18.3 mmol) in toluene (60 mL) was heated under reflux for 5 h. Removal of the solvent under reduced pressure and chromatography on silica gel (chloroform) gave a colorless oil (**11**) (4.45 g, 93%). GC/MS analysis of this product gave two peaks in a ratio of 20:1 and for the major component **11a** with a longer retention time gave m/e (relative intensity) 263 (M^+, 8), 164 (100), 149 (15) and for the minor component **11b** with a shorter retention time m/e 263 (M^+, 6), 164 (100), 149 (19). **11a**: ^{13}C NMR δ 24.5 (t), 25.5 (t), 30.0 (t), 43.7 (t), 55.8 (t), 56.2 (q), 67.8 (d), 78.6 (d), 111.5 (d), 112.5 (d), 120.1 (d), 135.4 (s), 150.2 (s). **11b**: ^{13}C NMR δ 19.2 (t), 24.8 (t), 26.0 (t), 39.5 (t), 50.7 (t), 56.2 (q), 61.1 (d), 79.6 (d), 111.1 (d), 112.5 (d), 119.8 (d), 136.2 (s), 150.0 (s). After a longer period the oily product was solidified. An analytical crystalline sample of **11a** was obtained from this material by recrystallization from hexane: mp 58–60 °C; ^1H NMR (270 MHz) δ 1.25–3.09 (unresolved, 9 H), 3.55 (br m, 1 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 5.00 (dd, J = 7, 4 Hz), 6.83 (d, 1 H, J = 8 Hz), 6.91 (br s, 2 H); exact mass calcd for $C_{15}H_{21}NO_3$ m/e 263.1521, found 263.1546.

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.29; H, 8.09; N, 5.32.

2-[2(*S)-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-piperidine (12a).** To a stirred solution of 11 (6.2 g, 23.6 mmol) in 50% aqueous acetic acid (200 mL) was added zinc dust (9 g) by several portions at room temperature. The reaction mixture was stirred for 2 h at 50 °C and filtered. The filtrate was basified with K_2CO_3 and extracted with chloroform. The organic layer was washed with water and recrystallized from benzene–hexane to give **12a** (5.6 g, 90%) as colorless fine needles: mp 149–150 °C (with sublimation); IR ($CHCl_3$) 3630–3150 cm^{-1}; ^1H NMR (270 MHz) δ 1.25–1.86 (unresolved, 8 H), 2.54 (br t, 1 H, J = 15 Hz), 2.79 (br s, 1 H), 3.07 (br d, 1 H, J = 15 Hz), 3.86 (s, 3 H), 3.89 (s, 3 H), 4.99 (dd, 1 H, J = 8, 4 Hz), 6.84 (s, 2 H), 6.96 (s, 1 H); ^{13}C NMR δ 24.5 (t), 26.3 (t), 31.9 (t), 44.2 (t), 46.7 (t), 54.5 (d), 55.8 (q), 55.9 (q), 71.5 (d), 108.9 (d), 110.9 (d), 117.6 (d), 138.2 (s), 147.8 (s), 148.8 (s); mass spectrum, m/e (relative intensity) 265 (M^+, 13), 247 ($M^+ - H_2O$, 4), 180 (4), 168 (7), 164 (8), 139 (9), 127 (9), 98 (18), 84 (100).

Anal. Calcd for $C_{15}H_{22}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 68.11; H, 9.02;, N, 5.29.

2-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-1-[(4-methoxyphenyl)acetyl]piperidine (15). To a mixture of **12a** (1.20 g, 4.53 mmol) and K_2CO_3 (0.62 g, 4.49 mmol) in acetonitrile (60 mL) was added dropwise with vigorous stirring and ice cooling a solution of *p*-methoxyphenylacetyl chloride (0.84 g, 4.53 mmol) in the same solvent (30 mL) over a period of 50 min. The reaction mixture was stirred at ambient temperature for another 1 h, after which the inorganic salts were filtered off and washed with acetonitrile. Solvent removal in vacuo left an oil which contained the *O,N*-diacyl compound **16** as a byproduct in 10–20% according to TLC analysis or separation by silica gel chromatography (chloroform), showing IR bands at 1725 and 1605 cm^{-1}. A mixture of the residual oil and K_2CO_3 (4 g) in 33% (v/v) aqueous methanol (30 mL) was heated under reflux for 2 h. Concentration in vacuo and dilution of the residue with water and ice gave an oil which was extracted with chloroform. The organic phase was washed with water, dried, and evaporated. The residue was purified by chromatography on silica gel (chloroform) and recrystallized from benzene–hexane to give **15** (1.45 g, 78%) as colorless fine needles: mp 133.5–135 °C; IR ($CHCl_3$) 3625 (sh), 3550 (sh), 3325, 1600 cm^{-1}; ^1H NMR (100 MHz) δ ~1.6 (br s, 6 H), 3.76, 3.84, and 3.86 (s, 3 H each, 2 H signals (AB q?) are included in this region), 6.74–6.87 (m, 4 H), 7.08–7.31 (m, 3 H); mass spectrum, m/e (relative intensity) 413 (M^+, 20), 274 (45), 244 (63), 233 (67), 232 (29), 148 (25), 128 (21), 126 (22), 121 (100); exact mass calcd for $C_{24}H_{31}NO_5$ m/e 413.2220, found 413.2197.

Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.97; H, 7.84; N, 3.31.

1-(3,4-Dimethoxyphenyl)-2-[1-[(4-methoxyphenyl)-acetyl]piperidin-2-yl]ethanone (17). To a stirred solution of Collins reagent (2.9 g) in dichloromethane (50 mL) was added a solution of **15** (1.10 g, 2.66 mmol) in the same solvent (10 mL). The orange-yellow solution was stirred at ambient temperature for 1 h. During the reaction the solution changed to deep red. The resulting dark tar was filtered off through a Celite pad and washed with dichloromethane. The combined filtrate and washings was washed with 5% HCl and then 5% NaOH and dried. Evaporation of the solvent and silica gel chromatography (benzene–ethyl acetate, 3:1, v/v) gave **17** (0.90 g, 82%) as a colorless gum: IR ($CHCl_3$) 1660, 1630 (sh), 1610 (sh), 1600, 1580 cm^{-1}; ^1H NMR (100 MHz) δ 1.59 (br s, 6 H), ~2.9–3.3 (m, 3 H), 3.55–3.76 (m, 4 H, with sharp singlet δ 3.64 and 3.76), 3.92 (s, 9 H), 6.68–7.81 (m, 7 H); mass spectrum, m/e (relative intensity) 411 (M^+, 33), 264 (19), 262 (50), 231 (13), 165 (100), 148 (36), 121 (60); exact mass calcd for $C_{24}H_{29}NO_5$ m/e 411.2024, found 411.2052.

2-(3,4-Dimethoxyphenyl)-1,6,7,8,9,9a-hexahydro-3-(4-methoxyphenyl)-4*H*-quinolizin-4-one (18). A solution of **17** (500 mg, 1.22 mmol) in ethanol (30 mL) containing sodium ethoxide prepared from 1.0 g of sodium was heated with reflux for 2 h and concentrated in vacuo. After the residue had been quenched by the addition of ice–water (30 mL), it was extracted with chloroform. The organic layer was washed with water, dried, and evaporated. Purification of the residue by silica gel chromatography (benzene–ethyl acetate–chloroform, 1:1:1, v/v) and recrystallization from ethyl acetate–hexane gave **18** (320 mg, 67%) as pale yellow fine needles: mp 142.5–143 °C (lit.[7a] mp 141–142 °C).

(±)-Julandine (7). To a stirred, cooled (0 °C) suspension of $LiAlH_4$ (450 mg, 11.9 mmol) in THF (120 mL) was added dropwise a solution of **18** (190 mg, 0.483 mmol) in THF (90 mL), and the mixture was heated with reflux for 1 h. The mixture was cooled to 0 °C and water was slowly added to quench the reaction. After inorganic material was filtered off through a pad of Celite, the filtrate was dried and evaporated. Purification of the residue by column chromatography (silica gel, benzene–diisopropyl ether, 2:1, v/v) followed by recrystallization from ethyl acetate–hexane afforded (±)-julandine (**7**) (115 mg, 63%) as colorless long needles: mp 139–140 °C (lit.[7a] mp 136–137 °C); ^1H NMR (100 MHz) δ ~1.2–3.2 (unresolved, 13 H), 3.52 (s, 3 H), 3.70 (s, 3 H), 3.78 (s, 3 H), 6.46 (s, 1 H), 6.64 (s, 2 H), 6.66 and 6.95 (AB q, 4 H, J =

(15) Frank, R. L.; Adams, C. E.; Allen, R. E.; Gander, R.; Smith, P. V. *J. Am. Chem. Soc.* **1946**, *68*, 1365.

9 Hz); mass spectrum, m/e (relative intensity) 379 (M^+, 95), 296 ($M^+ - C_5H_9N$, 87), 265 (100).

Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69. Found: C, 76.13; H, 7.74; N, 3.69.

The synthetic material was identical by IR and ^1H NMR spectrometry with natural julandine. Furthermore this material was identical with an authentic (±)-julandine (mp 139–140 °C, kindly provided by Dr. J. A. Lamberton) in TLC behavior and mixture melting point determination was undepressed.

Irradiation of 18. A solution of 18 (280 mg, 0.71 mmol) in dioxane (80 mL) containing iodine (15 mg) was irradiated with a high-pressure Hg lamp at ambient temperature for 20 h. The solvent was evaporated in vacuo, and the residue was dissolved in chloroform (70 mL), washed with water and aqueous $Na_2S_2O_3$, and dried. Evaporation of the solvent left a solid which was subjected to column chromatography (silca gel, benzene–diisopropyl ether, 10:1, v/v). The initially eluted component was recrystallized from ether–hexane to give **20** (40 mg, 14%) as yellow fine needles: mp 155–156 °C; ^1H NMR (100 MHz) δ ~1.3–2.2 (unresolved, 6 H), ~2.7–3.7 (unresolved, 4 H), 3.85 (s, 3 H), 3.95 (s, 3 H), 4.03 (s, 3 H), ~4.7 (br d, 1 H), 7.22 (dd, 1 H, J = 9, 3 Hz), 7.30 (d, 1 H, J = 9 Hz), 7.79 (d, 1 H, J = 9 Hz), 9.17 (d, 1 H, J = 3 Hz), 9.37 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.54; H, 6.16; N, 3.41.

Further elusion gave **19** (135 mg, 48%) as yellow crystals (from benzene–hexane): mp 194–196 °C (lit.[7a] mp 194–195 °C); ^1H NMR (100 MHz) δ ~1.3–2.2 (unresolved, 6 H), ~2.7–3.7 (unresolved, 4 H), 3.97 (s, 3 H), 4.01 (s, 3 H), 4.07 (s, 3 H), ~4.7 (br d, 1 H), 7.79 (d, 1 H, J = 3 Hz), 7.81 (s, 1 H), 9.53 (d, 1 H, J = 9 Hz).

(±)-Cryptopleurine (4). To a stirred mixture of $LiAlH_4$ (120 mg) in THF (60 mL) was gradually added a solution of **19** (50 mg, 0.13 mmol) in THF (25 mL) at room temperature. After 6 h of heating at reflux, the mixture was quenched by the addition of water under ice cooling. Removal of inorganic materials by filtration through a Celite pad and evaporation of the filtrate left a pale yellow solid which was recrystallized from acetone to give (±)-cryptopleurine (4) (46 mg, 95%) as colorless fine needles: mp 201–202 °C (lit.[8a] mp 199–200 °C); ^1H NMR (100 MHz) δ ~ 1.3–3.32 (unresolved, 11 H), 3.59 (br d, A part of AB q, 1 H, J = 16 Hz), 3.98 (s, 3 H), 4.03 (s, 3 H), 4.08 (s, 3 H), 4.41 (d, B part of AB q, 1 H, J = 16 Hz), 7.15 (dd, 1 H, J = 9, 3 Hz), 7.20 (s, 1 H), 7.75 (d, 1 H, J = 9 Hz), 7.85 (d, 1 H, J = 3 Hz), 7.87 (s, 1 H); mass spectrum, m/e (relative intensity) 377 (M^+, 35), 294 ($M^+ - C_5H_9N$, 100). Comparison of this product with authentic (±)-cryptopleurine showed them to have identical IR, ^1H NMR, and mass spectra as well as TLC behavior.

2-(3,4-Dimethoxyphenyl)-2,3,3a,4,5,6-hexahydropyrrolo[1,2-*b*]isoxazole (22). A mixture of **21** (1.3 g, 15 mmol) and **10** (2.5 g, 15 mmol) in toluene (50 mL) was heated under reflux for 3 h. The solution was washed with water, dried, and evaporated in vacuo. The residual pale yellow oil was purified by column chromatography (silica gel, chloroform) to give a colorless oil (**22**) (3.34 g, 88%): IR (neat film) 1590, 1515, 1260, 1235, 1140, 1025 cm^{-1}; ^1H NMR (100 MHz) δ ~1.4–2.6 (unresolved, 6 H), 3.21 (t, 2 H, J = 6 Hz), 3.83 (s, 3 H), 3.86 (s, 3 H), 4.95 (dd, 1 H, J = 9, 6 Hz), 6.72–69.4 (m, 3 H); exact mass calcd for $C_{14}H_{19}NO_3$ m/e 249–1364, found 249.1366. GC analysis of this product gave two peaks in a ratio of 5:2 for **22a** with longer retention time and **22b** with shorter retention time, respectively, at a column temperature of 150 to 170 °C and 3 °C/min elevating rate. Treatment of this oily product with an ethanolic solution of picric acid afforded the picrate of **22** as yellow crystals: mp 125–126 °C; ^1H NMR (270 MHz, pyridine-d_5) δ ~1.5–1.7 (m, 2 H), ~1.75–2.0 (m, 2 H), 2.28 (m, 1 H), 2.47 (m, 1 H), 3.26 (t, 2 H, J = 5 Hz), 3.71 (s), 3.74 (s) (δ 3.71/3.74 ratio of 5:2, total 3 H), 3.73 (s), 3.76 (s) (δ 3.73/3.76 ratio of 5:2, total 3 H), 5.07 (dd?), 5.16 (dd, J = 8, 5 Hz) (δ 5.16/5.07 ratio of 5:2, total 1 H).

Anal. Calcd for $C_{14}H_{19}NO_3 \cdot C_6H_3N_3O_6$: $C_6H_3N_3O_6$: C, 50.21; H, 4.64; N, 11.71. Found: C, 50.06; H, 4.64; N, 11.65.

2β-[2(*S)-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]pyrrolidine (23a).** To a solution of **22** (11.8 g, 47 mmol) in methanol (100 mL) was added 10% Pd/C (2.0 g), and the mixture was hydrogenated at 1 MPa of H_2 at room temperature. The mixture was filtered to remove the catalyst, and the filtrate was evaporated to leave a colorless solid which was washed with ether to give colorless crystals (10.2 g, 86%) having mp 155–157 °C. This product was repeatedly recrystallized from chloroform–hexane to give colorless fine needles (**24a**): mp 160–161 °C; IR ($CHCl_3$) 3375 cm^{-1}; ^1H NMR (90 MHz) δ ~1.55–2.5 (unresolved, 6 H), 3.25 (m, 2 H), 3.7 (br m, 1 H), 3.81 (s, 3 H), 3.85 (s, 3 H), 5.10 (dd, 1 H, J = 9, 4 Hz), 6.75 (d, 1 H, J = 8 Hz), 7.01 (dd, 1 H, J = 8, 3 Hz), 7.08 (d, 1 H, J = 3 Hz); mass spectrum, m/e (relative intensiy) 251 (M^+, 92), 233 ($M^+ - H_2O$, 35), 182 (26), 180 (28), 168 (35), 165 (42), 164 (100), 149 (26), 139 (33), 137 (25).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.67; H, 8.17; N, 5.50.

1-[(3,4-Dimethoxyphenyl)acetyl]-2-[2-(3,4-dimethoxyphenyl)-2-hydroxyethyl]pyrrolidine (24). To a stirred, cold (0 °C) mixture of **23** (1.20 g, 4.8 mmol) and K_2CO_3 (520 mg, 3.8 mmol) in dichloromethane (50 mL) was added dropwise a solution of (3,4-dimethoxyphenyl)acetyl chloride (1.1 g, 5.1 mmol) in the same solvent (20 mL) during 20 min. The mixture was stirred another 2 h at ambient temperature and filtered to remove inorganic materials. The filtrate was washed with water, dried, and evaporated. The oily residue was added to a solution of K_2CO_3 (5 g) in a 2:1 (v/v) methanol–water mixture (50 mL), and the reaction mixture was heated under reflux for 30 min. Removal of the solvent by evaporation in vacuo gave a brown oil which was extracted with chloroform and washed in the sequence of water, 5% NaOH, and 5% HCl. The organic layer was dried and evaporated to give a brown oil which was purified by column chromatography (silica gel, chloroform) to give **24** (1.44 g, 70%) as a pale yellow oil: IR ($CHCl_3$) 3320, 1600 cm^{-1}; ^1H NMR (90 MHz) δ ~1.5–2.2 (unresolved, 6 H), ~3.3–3.9 (m, 4 H with AB q (2 H) centered at δ 3.73), 3.88 (s, 6 H), 3.90 (s, 6 H), ~4.4–4.7 (m, 2 H), 6.84–6.98 (m, 6 H); mass spectrum, m/e (relative intensity) 429 (M^+, 12), 411 (30), 259 (59), 249 (38), 232 (42), 178 (100), 151 (91); exact mass calcd for $C_{24}H_{31}NO_6$ m/e 429.2151, found 429.2152.

1-(3,4-Dimethoxyphenyl)-2-[1-[(3,4-dimethoxyphenyl)acetyl]pyrrolidin-2-yl]ethanone (26). To a stirred solution of Collins reagent, prepared from 6.0 g (60 mmol) of CrO_3, in dichloromethane (100 mL) was added a solution of **24** (4.3 g, 10 mmol) in the same solvent (20 mL), and the mixture was stirred at ambient temperature for 2 h. After water (1 mL) had been added to the mixture, the mixture was stirred for 10 min and the organic phase was washed in the sequence of water, 5% HCl, and 5% NaOH. Drying and evaporation of the solvent left a pale yellow gum which was recrystallized from ethanol–hexane to give **26** (3.7 g, 86%) as colorless crystals: mp 98–99 °C; IR ($CHCl_3$) 1645 (sh), 1625 (sh), 1605 cm^{-1}; ^1H NMR (90 MHz) δ ~1.6–2.1 (unresolved, 4 H), 2.65 (dd, 1 H, J = 15, 11 Hz), ~3.4–3.9 (m, 5 H, with AB q (2 H) centered at δ 3.74), 3.88 (s, 6 H), 3.94 (s, 3 H), 3.96 (s, 3 H), ~4.3–4.7 (poorly resolved m, 1 H), 6.77–7.00 (m, 4 H), 7.69 (d, 1 H, J = 2 Hz), 7.89 (dd, 1 H, J = 9, 2 Hz); mass spectrum, m/e (relative intensity) 427 (M^+, 33), 248 (25), 178 (100), 165 (97), 151 (45).

Anal. Calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.83; N, 3.27. Found: C, 67.25; H, 6.82; N, 3.16.

6,7-Bis(3,4-dimethoxyphenyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (27). A solution of **26** (165 mg, 0.38 mmol) in 5% ethanolic KOH (30 mL) was heated under reflux for 1.5 h. The mixture was condensed in vacuo, diluted with water, and extracted with chloroform. The organic phase was washed with water and then 5% HCl and dried. Removal of the solvent by evaporation followed by purification by column chromatography (silica gel, chloroform–ethyl acetate, 20:1, v/v) gave **27** (150 mg, 95%) as a pale yellow oil: IR ($CHCl_3$) 1630 (sh), 1625, 1600 cm^{-1}; ^1H NMR (90 MHz) δ ~1.5–2.5 (unresolved, 4 H), 2.74 (d, 1 H, J = 8 Hz), 2.83 (d, 1 H, J = 2 Hz), ~3.4–4.3 (m, 3 H with s (3 H) at δ 3.51), 3.69 (s, 3 H), 3.80 (s, 6 H), 6.51 (s, 1 H), 6.70 (s, 2 H), 6.73 (s, 3 H); mass spectrum, m/e (relative intensity) 409 (M^+, 100), 340 ($M^+ - C_4H_7N$, 47), 312 (38), 309 (21), 195 (46), 165 (29), 149 (47); exact mass calcd for $C_{24}H_{27}NO_5$ m/e 409.1889, found 409.1874.

Irradiation of 27. A stirred solution of **27** (70 mg, 0.17 mmol) in dichloromethane (80 mL) containing iodine (5 mg) was irradiated with high-pressure Hg lamp at room temperature for 2.5 h. The mixture was washed in the sequence of water, 5% $Na_2S_2O_3$, and 5% KOH, dried, and evaporated. The residue was subjected to preparative TLC on silica gel (ethyl acetate–benzene, 6:1, v/v)

to give three components. The fastest moving band gave 9-oxotylocrebrine (**30**) (3 mg, 4.3%) as a pale yellow powder: mp 207 °C dec; ^{1}H NMR (100 MHz) δ 3.85 (s, 3 H), 4.02 (s, 3 H), 4.04 (s, 3 H), 4.06 (s, 3 H), no other signals were clearly assigned because of insufficiency of the sample in quantity; mass spectrum, *m/e* (relative intensity) 407 (M^+, 100), 392 (20), 338 ($M^+ - C_4H_7N$, 17), 310 (13), 295 (11), 248 (15), 221 (12), 295 (13), 168 (49), 165 (52), 164 (28), 151 (50).

The second component obtained from the middle band was recrystallized from chloroform–hexane to give 9-oxoisotylocrebrine (**29**) (17 mg, 24%) as colorless crystals: mp 237–238 °C dec; IR ($CHCl_3$) 1620 cm^{-1}; ^{1}H NMR (100 MHz) δ ~1.5–2.4 (unresolved, 4 H), 2.81 (dd, 1 H, *J* = 16, 13 Hz), 3.52 (dd, 1 H, *J* = 16, 4 Hz), ~3.7–4.1 (m, 3 H) with s (3 H) at δ 3.77, s (6 H) at δ 3.96, and s (3 H) at δ 3.98), 7.71 (d, 1 H, *J* = 10 Hz), 7.74 (d, 1 H, *J* = 10 Hz), 8.78 (s, 1 H), 9.12 (s, 1 H); mass spectrum, *m/e* (relative intensity) 407 (M^+, 100), 392 (17), 338 ($M^+ - C_4H_7N$, 20), 310 (20), 166 (44).

Anal. Calcd for $C_{24}H_{25}NO_5$: C, 70.75; H, 6.18; N, 3.44. Found: C, 70.42; H, 6.23; N, 3.43.

The slowest moving band gave 9-oxotylophorine (**28**) (38 mg, 55%) as colorless crystals (from chloroform–hexane): mp 280–281 °C dec; IR ($CHCl_3$) 1615 cm^{-1}; ^{1}H NMR (90 MHz) δ ~1.6–2.5 (unresolved, 4 H), 2.82 (dd, 1 H, *J* = 15, 13 Hz), 3.50 (dd, 1 H, *J* = 15, 5 Hz), ~3.7–4.2 (m, (3 H) with s (3 H) at δ 4.00, s (3 H) at δ 4.06, and s (6 H) at δ 4.08), 7.21 (s, 1 H), 7.69 (s, 1 H), 7.70 (s, 1 H), 9.02 (s, 1 H); mass spectrum, *m/e* (relative intensity) 407 (M^+, 100), 338 ($M^+ - C_4H_7N$, 37), 310 (26).

Anal. Calcd for $C_{24}H_{25}NO_5$: C, 70.75; H, 6.18; N, 3.44. Found: C, 70.70; H, 6.18; N, 3.42.

(±)-Septicine (6). To a stirred, cooled (0 °C) mixture of $AlCl_3$ (133 mg, 1.00 mmol) and $LiAlH_4$ (114 mg, 3.00 mmol) in ether (20 mL) was added a solution of **27** (200 mg, 0.49 mmol) in a 1:1 (v/v) solution of THF–ether mixture (50 mL). The mixture was stirred at ambient temperature for 1 h, decomposed by addition of water under ice cooling, and then basified (pH 11) with 30% KOH. The organic phase was dried and evaporated. Purification of the resulting residue by column chromatography (silica gel, chloroform) followed by recrystallization from ether afforded (±)-septicine (**6**) (170 mg, 88%) as colorless needles: mp 137–138 °C (lit.[14b] mp 135–136 °C); ^{1}H NMR (90 MHz) δ ~1.4–4.0 (unresolved (11 H) with s (3 H) at δ 3.57, s (3 H) at δ 3.60, and s (6 H) at δ 3.80), 6.55 (s, 2 H) 6.68 (s, 4 H); mass spectrum, *m/e* (relative intensity) 395 (M^+, 70), 326 ($M^+ - C_4H_7N$, 75), 295 (100), 264 (45). The synthetic alkaloids did not depress the melting point of an authentic specimen of (±)-septicine, and IR, ^{1}H NMR, and mass spectra were identical.

(±)-Tylophorine (5). A solution of (±)-septicine (**6**) (65 mg, 0.16 mmol) in dichloromethane (80 mL) containing iodine (5 mg) was irradiated in a Pyrex vessel with a high-pressure Hg lamp. After 21 h, the solution was washed with 5% KOH, dried, and evaporated. The residual mixture was separated by HPLC (silica gel, chloroform–ethanol, 50:1 v/v, 3 mL/min flow rate). The first fraction afforded (±)-tylophorine (**5**) (28 mg, 43%) as light tan crystals (from chloroform–hexane): IR ($CHCl_3$) 1620, 1600, 1520, 1470, 1260, 1250, 910 cm^{-1}; ^{1}H NMR (100 MHz) δ ~1.4–4.2 (?) (unresolved (10 H) with s (6 H) at δ 4.03 and s (6 H) at δ 4.10), 4.60 (d, 1 H, *J* = 15 Hz), 7.11 (s, 1 H), 7.26 (s, 2 H), 7.78 (s, 1 H); mass spectrum, *m/e* (relative intensity) 393 (M^+, 47), 324 ($M^+ - C_4H_7N$, 100). The synthetic sample was identical in TLC behavior and in IR, ^{1}H NMR, and mass spectra with natural tylophorine.

The second fraction contained a light tan solid (8 mg, 12%) indicating two chracteristically fluorescent spots on TLC which is considered to be a mixture of tylocrebrine (**32**) and isotylocrebrine (**33**). The final fraction contained the starting material (7 mg, 11%).

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Registry No. (±)-**4**, 23365-52-8; (±)-**5**, 25908-92-3; (±)-**6**, 26503-67-3; (±)-**7**, 23365-39-1; **9**, 34418-91-2; **10**, 6380-23-0; (±)-**11a**, 90171-73-6; (±)-**11b**, 90171-72-5; (±)-**12a**, 90243-11-1; (±)-**15**, 90171-74-7; (±)-**16**, 90171-75-8; (±)-**17**, 23367-75-1; (±)-**18**, 23367-76-2; (±)-**19**, 23365-51-7; (±)-**20**, 79228-21-0; **21**, 24423-88-9; (±)-**22a**, 86980-84-9; (±)-**22a**·picrate, 90194-63-1; (±)-**22b**, 86980-85-0; (±)-**22b**·picrate, 90245-06-0; (±)-**23a**, 86980-86-1; **24**, 90171-76-9; (±)-**26**, 76787-77-4; (±)-**27**, 76787-76-3; (±)-**28**, 86980-92-9; (±)-**29**, 86980-93-0; (±)-**30**, 86980-94-1; (±)-**32**, 30061-35-9; (±)-**33**, 90243-12-2; $(Ph)_3P{=}CHBr$, 39598-55-5; *p*-methoxyphenylacetyl chloride, 4693-91-8; 3,4-dimethoxybenzaldehyde, 120-14-9; 3,4-dimethoxyphenylacetyl chloride, 10313-60-7.

Constituents of Microbial Iron Chelators. Alternate Syntheses of δ-*N*-Hydroxy-L-ornithine Derivatives and Applications to the Synthesis of Rhodotorulic Acid

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δ-*N*-Hydroxy-L-ornithine derivatives, the key constituents of several microbial iron chelators, have been prepared from protected forms of L-glutamic acid. Reduction of α-*tert*-butyl *N*-Boc-glutamate (**3**) provided α-*tert*-butyl L-*N*-Boc-δ-hydroxynorvaline (**4**). Direct treatment of **4** with Cbz-*O*-benzylhydroxylamine (**5**) or trOC-*O*-benzylhydroxylamine (**6**) gave the protected δ-*N*-hydroxyornithine derivatives **7** and **8**, respectively. δ-N-Deprotection followed by acetylation provided α-*tert*-butyl-L-*N*-Boc-δ-*N*-acetyl-δ-*N*-benzyloxyornithine (**9**). Appropriate α-amino and α-carboxyl deprotections of **8** and **9** provided derivatives of δ-*N*-hydroxy-L-ornithine suitable for the synthesis of rhodotorulic acid (**24**) by two routes. The first route employed conventional peptide synthetic methods. The second synthesis of rhodotorulic acid involved the direct dimerization of Leuch's anhydrides **25** and **26** derived from the δ-*N*-acetyl- and δ-*N*-trOC-δ-*N*-benzyloxyornithines **11** and **16**.

Several microorganisms synthesize low molecular weight chelating agents (siderophores) to sequester and solubilize biologically essential ferric ion from their environment. Study of these siderophores has provided insight into the

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