and cautiously treated with 15 mL of methanol. When the exothermic reaction was over, the solution was evaporated to a foam which was crystallized from 8 mL of 3% aqueous HBr and dried to afford 1.29 g of (±)-19·HBr·1.5H_2O: mp 251–253 °C dec; CI MS m/e 366 and 368 ($M^+ + 1$).

Anal. Calcd for $C_{16}H_{16}BrNO_4$·HBr·1.5H_2O: C, 40.52; H, 4.03; N, 2.95. Found: C, 40.24; H, 4.11; N, 2.73.

Reaction of (±)-1, (+)-1, and (−)-1 with (*S*)-(−)-α-Methylbenzyl Isocyanate. Formation of Diastereoisomers 20 and 21. Addition of 157 mg (0.5 mmol) of the appropriate crystalline base to 74–80 mg (0.50–0.54 mmol) of freshly distilled (*S*)-(−)-α-methylbenzyl isocyanate in 2.5 mL of $DCCl_3$ afforded a homogeneous solution after shaking for ~10 min. TLC (system C) after 0.5 h indicated only one spot at higher R_f than amine 1 for the urea derivative(s) **20** and **21** which were not separated in this TLC system. These solutions were utilized directly for the NMR analyses of optical purity described above. Resonances for the methyl doublets of **20**, **21**, and the isocyanate were centered at δ 1.26, 1.01, and 1.59, respectively.

Acknowledgment. We would like to thank Ms. Paula Parisius and Alice Wong for combustion analyses, Mr. William Landis and Noel Whittaker for mass spectral determinations, and Dr. W. E. Scott, Hoffmann-La Roche, Nutley, NJ, for large-scale preparation of an intermediate. Helpful discussions with Drs. W. C. Ripka, A. E. Jacobson, and E. L. May are gratefully acknowledged.

Registry No. (±)-**1**, 13168-51-9; (±)-1·TsOH, 72258-86-7; (±)-1·HCl, 72258-87-8; (+)-1, 57231-34-2; (+)-1·(+)-2′-BTA, 72264-50-7; (+)-1·HCl, 6507-35-3; (−)-1, 4781-58-2; (−)-1·(−)-2′-BTA, 72258-88-9; (−)-1·HCl, 6451-82-7; (±)-**2**, 1699-46-3; (+)-**2**, 485-19-8; (+)-**2**·$HClO_4$, 14199-16-7; (+)-**2**·HCl, 903-91-3; (−)-**2**, 3968-19-2; (−)-**2**·$HClO_4$, 72258-89-0; (−)-**2**·HCl, 1431-01-2; **7**, 554-52-9; **7**·HCl, 1477-68-5; **8**, 1131-94-8; **8**·NH_3, 72258-90-3; **9**, 21411-19-8; **10**, 72258-91-4; (±)-**11**, 55869-76-6; (±)-**12**, 72258-92-5; (+)-**12**, 72274-69-2; (−)-**12**, 72274-70-5; (±)-**13**, 72274-71-6; (±)-**14**, 72264-51-8; (±)-**16**, 58116-06-6; (±)-**16**·HCl, 63125-28-0; (±)-**17**, 72258-93-6; (±)-**17** picrate, 72264-52-9; (±)-**17**·HBr, 72258-94-7; (±)-**18**·HBr, 67200-79-7; (+)-**18**·HBr, 72072-53-8; (−)-**18**·HBr, 72072-54-9; (±)-**19**·HBr, 72258-95-8; **20**, 72258-96-9; **21**, 72258-97-0; (*S*)-(−)-α-methylbenzyl isocyanate, 14649-03-7.

Pavinan and Isopavinan Alkaloids. Synthesis of Racemic and Natural Thalidine, Bisnorargemonine, and Congeners from *N*-Norreticuline[1a]

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The isopavinan alkaloids thalidine and *O*-methylthalisopavine and the pavinan alkaloids bisnorargemonine and argemonine were synthesized as the racemates and natural isomers from the appropriate form of *N*-norreticuline. The sequence utilizing (*S*)-(−)-*N*-norreticuline afforded the natural alkaloids and confirmed the absolute stereochemistry previously assigned to these compounds by several methods. The tetracyclic skeleton of both alkaloids was readily constructed from the same intermediate, 4-methoxy-*N*-acyl-*N*-norreticuline. In the racemic series, oxidation of (±)-*N*-formyl-*N*-norreticuline with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in methanol at low temperature afforded the crystalline 4-methoxy-*N*-formyl derivative formally through 1,6-addition of methanol to an intermediate quinone methide. Facile entry into the isopavinan series via crystalline *N*-formyl-*N*-northalidine was accomplished by treatment of the 4-methoxy compound with a catalytic amount of methanesulfonic acid in acetonitrile. Thermolytic elimination of methanol from the 4-methoxy intermediate readily provided 3,4-dehydro-*N*-norreticuline which was cleanly cyclized under the same conditions to the pavinan, *N*-formyl-*N*-norbisnorargemonine. Hydrazinolysis of these *N*-formyl derivatives provided the corresponding secondary amines in high yield, and borane reduction of the *N*-formyl functionality efficiently afforded (±)-thalidine and (±)-bisnorargemonine. In the natural series, treatment of the readily available (*S*)-(−)-*N*-norreticuline with ethyl chloroformate gave the (+)-*N*-carbethoxy derivative which was subjected to a reaction sequence analogous to that employed for the (±)-*N*-formyl compound. The corresponding (+)-*N*-carbethoxy congeners of natural (−)-thalidine and (−)-bisnorargemonine thus obtained were reduced with lithium aluminum hydride to afford the optically pure natural alkaloids. Methylation of the racemic and natural phenolic alkaloids with diazomethane gave the corresponding forms of *O*-methylthalisopavine and argemonine. Each of the *N*-formyl and *N*-carbethoxy intermediates were shown by NMR to exist as rotomers resulting from hindered rotation about the amide bond, and in several cases these rotomers were separable by TLC.

The pavinan and isopavinan alkaloids[2-5] can be formally viewed as oxidatively cyclized 1-benzyl-1,2,3,4-tetrahydroisoquinolines (BTIQ). Most frequently acid-catalyzed cyclization of appropriately oxidized congeners of BTIQ has been employed as the key step for formation of these tetracyclic systems. In recent years, a number of studies[4-6] have revealed that acid-catalyzed cyclization of 3,4-dehydro derivatives of BTIQ (1,2-dihydroisoquinolines) favors pavinan formation while isopavinans are usually obtained by similar treatment of 4-oxygenated BTIQ.

(1) (a) Presented in preliminary form by W.C.R. at the American Chemical Society/Chemical Soceity of Japan Chemical Congress, Honolulu, Hawaii, Apr 4, 1979; Abstr. No. ORGN 291. (b) Guest worker on leave from the Central Research Department, E. I. duPont de Nemours and Co., Wilmington, DE 19898. (c) Guest worker on leave from Hoechst AG, Frankfurt 80, West Germany.

(2) T. Kametani, "The Chemistry of the Isoquinoline Alkaloids", Vol. 1, Elsevier, New York, 1969, pp 41, 235. See also, *ibid.*, Vol. 2, Kimkodo Publishing Co., Sendai, Japan, 1974, p 99.

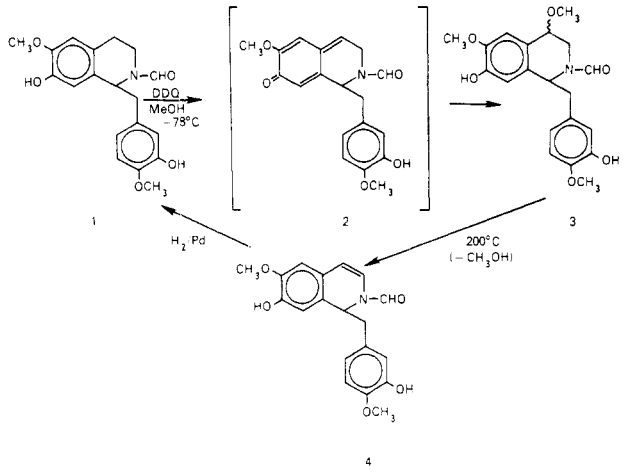
(3) It has been suggested by Soine and Stermitz [C.-C. Chen and T. O. Soine, *J. Pharm. Sci.*, 61, 55 (1972)] that the term pavinage be used for the skeleton of **6** and this was shortened to pavinan by Dyke.[9] Similarly, the skeleton of **9** will be referred to as isopavinan.

(4) M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, 1972, p 96.

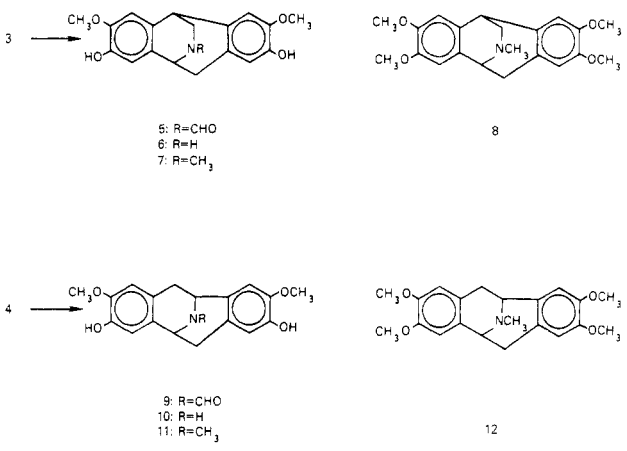
(5) M. Shamma and J. L. Moniot, "Isoquinoline Alkaloids Research: 1972–1977", Plenum Press, New York, 1978, p 61.

(6) S. F. Dyke, R. G. Kinsman, P. Warren, and A. W. C. White, *Tetrahedron*, 34, 241 (1978), and references cited therein.

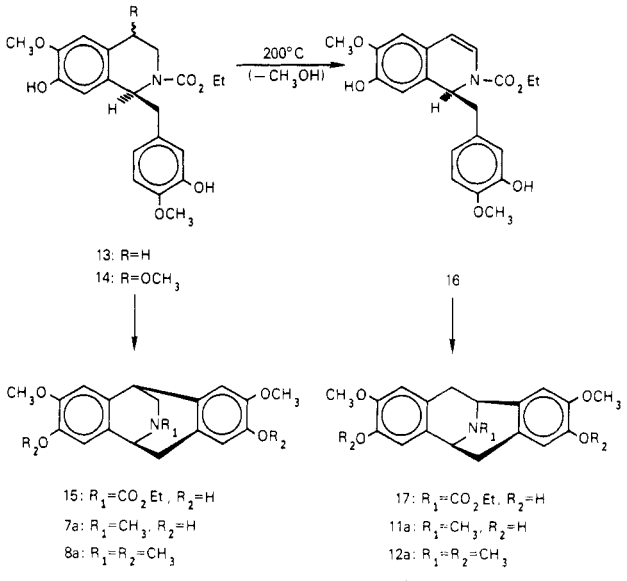
Scheme I



Scheme II



Scheme III



Complications are, however, inherent in the formation of both ring systems, and frequently these cyclizations result in low yields and product mixtures. Certain of these difficulties have been discussed by Dyke[6] and are predominately due to the instability of the basic precursors to the relatively severe acid treatment required for cyclization. As an example, the labile 4-hydroxy derivatives of BTIQ have been invoked[7,8] (but not isolated in a pure state to our knowledge) as intermediates in the frequently used amino acetal route to isopavinans and postulated to occur as biosynthetic intermediates[7,9] to both pavinans and isopavinans. These precursors have also been generated in situ;[10,11] however, mixtures of pavinans and isopavinans (which can be separated by column chromatography) are usually obtained along with other material in cyclizations involving 4-oxygenated BTIQ. Furthermore, the product distribution ratios obtained in these cyclizations are often difficult to predict since they depend on a number of factors as in the case of the 3,4-dehydro derivatives of BTIQ.[6] These problems have been exacerbated by the labile nature of the benzylic hydroxyl group in the 4-hydroxy derivatives of BTIQ and the fact that two diasteroisomeric alcohols are possible in this system,[11] which renders purification of the precursor BTIQ difficult and for the most part impractical.

We now report our results which circumvent a number of the difficulties described above and are, in principle, applicable to the synthesis of other naturally occurring pavinans and isopavinans (see below). This work deals with a novel synthesis of the *N*-acyl-4-methoxy derivatives of BTIQ and facile conversion of these compounds to either the isopavinan or pavinan ring system. In contrast to the 4-hydroxy derivatives of BTIQ, *N*-acyl-4-methoxy derivatives are stable and well-characterized compounds, readily prepared as illustrated for **3** in Scheme I. From these *N*-acyl-4-methoxy derivatives of BTIQ, efficient syntheses of the isopavinan (±)-thalidine (**7**),[10] its natural enantiomer (**7a**),[10] the pavinan (±)-bisnorargemonine (**11**),[12] and its natural enantiomer (**11a**)[13-18] were accomplished as shown in Schemes II and III.

Our syntheses of the racemic alkaloids **7** and **11** utilized (±)-*N*-formyl-*N*-norreticuline (**1**) as starting material, which is easily prepared[19] from the now readily available (±)-*N*-norreticuline. Oxidation of **1** in methanol at −78 °C with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded an intensely blue solution which probably contained the quinone methide **2**, since treatment of this solution with sodium borohydride discharged the blue color, leaving a clear yellow solution that contained only **1** (and DDQ hydroquinone), most likely regenerated by reduction of quinone methide **2**. When the blue methanolic solution obtained at −78 °C was mixed with dry silica gel and allowed to warm to room temperature, clean conversion of the putative **2** occurred to give (±)-4-methoxy-*N*-formyl-*N*-norreticuline (**3**) which could be isolated as a crystalline hydrate in 70–75% yield. The mass spectrum of **3** showed the expected molecular ion and fragmentation pattern. The 220-MHz ^{1}H NMR spectrum of **3** in $DCCl_3$ was unusually complex and revealed that the aliphatic methoxy

(7) D. W. Brown, S. F. Dyke, G. Hardy, and M. Sainsbury, *Tetrahedron Lett.*, 1515 (1969).
(8) M. Sainsbury, D. W. Brown, S. F. Dyke, and G. Hardy, *Tetrahedron*, **25**, 1881 (1969).
(9) S. F. Dyke, *Heterocycles*, **6**, 1441 (1977).
(10) M. Shamma, A. S. Rothenberg, S. S. Salgar, and G. S. Jayatilake, *Lloydia*, **39**, 395 (1976).
(11) S. F. Dyke and A. C. Ellis, *Tetrahedron*, **27**, 3803 (1971). For an example of separation of the two possible diasterisomers of a 1-methyl-4-hydroxytetrahydroisoquinoline see: G. Grethe, M. Uskokovic, T. Williams, and A. Brossi, *Helv. Chim. Acta*, **50**, 2397 (1967).
(12) C.-C. Chen, T. O. Soine, and K. H. Lee, *J. Pharm. Sci.*, **59**, 1529 (1970).
(13) L. B. Kier and T. O. Soine, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 187 (1960). In this report **11a** was referred to as rotundine. This name was later[14] changed to bisnorargemonine.
(14) L. B. Kier and T. O. Soine, *J. Pharm. Sci.*, **50**, 321 (1961).
(15) T. O. Soine and L. B. Kier, *J. Pharm. Sci.*, **52**, 1013 (1963).
(16) F. R. Stermitz, S. Y. Lo, and G. Kallos, *J. Am. Chem. Soc.*, **85**, 1551 (1963).
(17) F. R. Stermitz and J. N. Seiber, *J. Org. Chem.*, **31**, 2925 (1966).
(18) S. M. Kupchan and A. Yoshitake, *J. Org. Chem.*, **34**, 1062 (1969).
(19) K. C. Rice and A. Brossi, *J. Org. Chem.*, preceding paper in this issue.

group appeared as two closely spaced singlets in a ratio of slightly greater than 1:2 as did the two aromatic methoxy groups. The formyl proton also appeared as two lines in the same ratio; however, line separation was greater than in the case of the methoxy groups. This behavior is attributed to the presence of two rotomers resulting from hindered rotation (probably due to partial double bond character of the N–CHO bond) of the formyl group.[20] It does not seem likely that **3** is a diasterisomeric mixture since the 4-unsubstituted starting material **1**, in which only rotational and conformational isomers are possible, also shows the presence of two rotomers in the NMR.[19] In addition, the rigid (±)-*N*-formylisopavinan **5** and the corresponding (±)-pavinan **9** exist as distinct rotomers as discussed below.

The gross structure of **3** was further confirmed by a number of chemical transformations. Thermolytic elimination of methanol from **3** occurred smoothly at 200 °C and provided the crystalline (±)-3,4-dehydro compound **4**, which showed the expected spectral properties. The NMR spectrum of **4** also revealed the presence of two rotomers. Unlike **3**, the rotomers of **4** appeared as two spots on TLC. Catalytic hydrogenation of **4** readily afforded **1** as anticipated.

The key acid-catalyzed cyclization of (±)-**3** readily occurred in acetonitrile (25 °C) containing 1% (v/v) of methanesulfonic acid to produce predominately (±)-*N*-formyl-*N*-northalidine (**5**) which was easily isolated by crystallization. Thus, **3** behaves in a manner similar to that of the basic 4-acetoxy derivatives of BTIQ prepared by Umezawa.[21] That the isopavinan, and not the pavinan, carbon skeleton had been formed was clearly evident from the mass spectrum of **5**, that showed, in addition to the molecular ion, a major fragment resulting from loss of the CH_2=NCHO unit, expected to be characteristic[22] of *N*-formyl-*N*-norisopavinans but not the corresponding pavinans. The structure of isopavinan **5** was further confirmed by the chemical transformations described below. TLC of the filtrate from the crystallization of **5** indicated additional amounts of **5**, the isomeric pavinan **9**, and several unidentified minor products. The existence of rotomers in this series was again demonstrated for **5** by NMR and TLC, and one of the rotomers was isolated by crystallization in a state of near purity as shown by NMR and TLC.

When the (±)-3,4-dehydro compound **4** was cyclized under similar conditions, the crystalline (±)-*N*-formyl-*N*-norpavinan **9** was formed almost exclusively with little, if any, of the isopavinan present. Rotomers of **9** were again detected by TLC and NMR. The structure of **9** followed from spectral data and reduction to **11**, of established structure, as described below.

The very mildly acidic conditions utilized for cyclization of the neutral *N*-formyl derivatives **3** and **4** and the corresponding *N*-carbethoxy congeners **14** and **16** are in sharp contrast to the conditions which have generally been applied in classical synthesis of pavinans and isopavinans from basic precursors.[6] This observation may be partially explicable in terms of the involvement of doubly charged (protonated) intermediates, in the acid-catalyzed electrophilic cyclization of basic precursors, which may be energetically less favorable than those in the present case where cyclization of the neutral *N*-acyl compounds should proceed via a unipositive ion.[23]

Diborane reduction proved to be the method of choice for conversion of **5** and **9** to (±)-thalidine (**7**) and (±)-bisnorargemonine (**11**), respectively. By utilization of this reducing agent and the usual methanolic HCl workup for removal of boron as volatile trimethyl borate, the HCl salts of **7** and **11** were obtained directly, and the difficulties frequently encountered in the isolation of phenolic amines from lithium aluminium hydride (LAH) and similar metal hydride reductions were avoided.

The physical data collected for our samples of **7**[10] and **11**[12] agree well with the literature data for these compounds. Furthermore, methylation of **7** and **11** with diazomethane gave the fully O-methylated and well-characterized alkaloids (±)-*O*-methylthalisopavine (**8**)[11] and (±)-argemonine (**12**).[24] Hydrazinolysis of **5** and **9** smoothly afforded the corresponding (±)-*N*-nor congeners **6** and **10** in high yield and purity. The versatility of *N*-formyl as a protecting group in the acid-catalyzed cyclization above, as precursor to the *N*-methyl group, and as a readily removable function leading to the *N*-nor compounds is thus demonstrated.

Our work in the natural pavinan and isopavinan series utilized the now readily available[19] (*S*)-(–)-*N*-norreticuline which was converted directly to the foamy (+)-carbamate **13**[25] in essentially quantitative yield. Oxidation of **13** with DDQ in methanol as described for **1** gave the corresponding (+)-4-methoxy derivative **14** as a foam that contained traces of starting material by TLC. Direct cyclization of **14** with 1% (v/v) methanesulfonic acid in acetonitrile afforded crystalline (–)-*N*-carbethoxy-*N*-northalidine (**15**) in 66% isolated yield from (*S*)-(–)-*N*-norreticuline. Natural (–)-thalidine (**7a**), obtained by LAH reduction of **15**, gave physical data which are in good agreement with those reported by Shamma for this alkaloid.[10] Thermolysis of chiral **14** afforded the corresponding 3,4-dehydro compound **16** as a foam, which was cyclized directly to the *N*-carbethoxy-*N*-norpavinan **17**. Reduction of **17** with LAH then afforded crystalline (–)-bisnorargemonine (**11a**) with physical data in agreement with those reported.[13-18] The optically active synthetic alkaloids **7a** and **11a** were identical with their racemic counterparts except for optical rotation and melting point as were the fully O-methylated (–)-*O*-methylthalisopavine (**8a**)[18] and (–)-argemonine (**12a**).[13] The physical data collected for our samples of **8a** and **12a** were in agreement with those reported. The synthetic relationships now established with the conversion (*S*)-(–)-*N*-norreticuline of known absolute configuration[26] to (–)-thalidine (**7a**), (–)-bisnorargemonine

(20) For examples of isolable rotomers resulting from restricted rotation about amide bonds, see: (a) R. R. Fraser and K. Taymaz, *Tetrahedron Lett.*, 4573 (1976); (b) H. Volter and G. Helmchen, *ibid.*, 1251 (1978). For examples of rotomers in the morphinan series, see: (c) H. C. Beyerman, E. Buurman, T. S. Lie, and L. Maat, *Recl. Trav. Chim. Pays-Bas*, **95**, 43 (1976); (d) H. C. Beyerman, L. van Bommet, L. Maat, and C. Olieman, *ibid.*, **95**, 312 (1976); (e) C. Olieman, L. Maat, K. Waliszewski, and H. C. Beyerman, *J. Chromatogr.*, **133**, 382 (1977).

(21) O. Hoshino, M. Taga, and B. Umezawa, *Heterocycles*, 1, 223 (1973).

(22) For a discussion of the mass spectral fragmentation of pavinans and isopavinans see ref 4, p 110, and references cited therein.

(23) In a similar case involving the electrophilic Grewe cyclization of appropriately substituted 1-benzyl-1,2,3,4,5,6,7,8-octahydroisoquinolines to the 2- and 4-hydroxymorphinan system, *N*-formyl derivatives cyclize many times faster than the corresponding secondary amine (E. Mohacsi and W. Leimgruber, Hoffmann-La Roche, Inc., Nutley, NJ, unpublished results).

(24) A. R. Battersby and R. Binks, *J. Chem. Soc.*, 2888 (1955).

(25) We employed the *N*-carbethoxy derivative of (*S*)-(–)-*N*-norreticuline for synthesis of **7a** early in this study and have reported the syntheses of the natural alkaloids **7a** and **11a** via this intermediate. In our opinion, however, the *N*-formyl congeners of BTIQ are generally more tractable in terms of providing crystalline intermediates, ease of cleavage of the *N*-acyl group, and reduction to the *N*-methyl compounds. We would therefore employ the appropriate optical isomer of *N*-formyl-*N*-norreticuline[19] for any further synthetic work in this area.

(26) A. R. Battersby, R. Southgate, J. Staunton, and M. Hirst, *J. Chem. Soc. C*, 1052 (1966).

(11a), and (-)-argemonine (12a) provide direct confirmation of the absolute configuration of these alkaloids, previously proven in other ways.[4,5,10]

Although the transformation of 1 to the corresponding 4-methoxy derivative 3, which appears to result from 1,6-addition of methanol to quinone methide 2, has not been studied in detail, it can be speculated that certain *N*-acyl-7(or 5)-hydroxy derivatives of BTIQ could undergo analogous quinone methide formation and that addition of nucleophiles other than methanol could be accomplished in these systems. Indeed, Schwartz[27] has recently reported a valuable preparative method for (2- and 4-hydroxyphenyl)acetonitriles which seems to involve addition of cyanide ion to a quinone methide. Extension of this type of oxidation—nucleophilic addition to benzylic functionalization of *N*-acyl phenethylamines, polycyclic isoquinolines, and other alkaloidal systems capable of quinone methide formation—can thus readily be envisioned.

The general approach reported in this study should prove to be of value in syntheses of a variety of racemic and chiral pavinans, isopavinans, and their congeners, considering the potential availability of the required phenolic precursor BTIQ from sequences similar to those in the preceding report. Since methylenedioxy groups have been cleaved in the presence of methoxy groups,[28-30] the reverse also being true,[31] considerable latitude exists for manipulation of the oxygenation substitution in these (and other) alkaloidal systems. The methods available for removal of undesired phenolic hydroxyl groups[32] and the availability of the *N*-norpavinans and isopavinans as previously described extend the possibility of structural variation in these systems even further.

Experimental Section

Melting points (corrected) were determined in open capillary tubes by using a Thomas-Hoover apparatus. Elemental analyses were performed by the Section on Microanalytical Services and Instrumentation of this laboratory. IR spectra were recorded on a Perkin-Elmer 257 or Beckman IR 4230 instrument. Optical rotations were measured by using a Perkin-Elmer Model 141 polarimeter with the solvents and concentrations specified. NMR spectra were determined by using a Varian HR-220 spectrometer with Me_4Si as the internal reference. Chemical-ionization (CI) mass spectra were obtained by using a Finnigan 1015D spectrometer with a Model 6000 data collection system, and electron-ionization (EI) mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E spectrometer (70 eV). Silica gel GF analytical and preparative thin-layer chromatography (TLC) plates used throughout this work were purchased from Analtech, Inc. Silica gel 60 (70–230 mesh) and Silicar CC-7 (No. 7087) were purchased from EM Laboratories and Mallinckrodt, Inc., respectively. The solvent systems used for TLC were as follows: (A) 4.75 mL of EtOAc, 0.25 mL of MeOH, 2 drops of concentrated aqueous NH_3; (B) 89 mL of $CHCl_3$, 10 mL of MeOH, 1 mL of concentrated aqueous NH_3; (C) 5 mL of MeOAc, 4 drops of concentrated aqueous NH_3; (D) 5 mL of EtOAc, 2 drops of concentrated aqueous NH_3; (E) 80 mL of $CHCl_3$, 18 mL of MeOH, 2 mL of concentrated aqueous NH_3; (F) Et_2O. The rotomer ratios reported below were determined by integration of the appropriate NMR spectrum.

(±)-4-Methoxy-*N*-formyl-*N*-norreticuline (3). (±)-*N*-Formyl-*N*-norreticuline (1;[19] 10.29 g, 30.0 mmol) was heated to solution in 770 mL of methanol and cooled to −78 °C. The clear solution was treated dropwise with a solution of 7.63 g (33.0 mmol) of 98% DDQ in 50 mL of methanol during 10 min to afford an intensely blue solution. After being stirred 1.5 h at −78 °C, the reaction mixture at −78 °C was added to 800 g of Silicar CC-7 at ambient temperature. After the mixture was mixed thoroughly (color change from blue to red) and allowed to stand 1.5 h, the silica was placed on a filter and washed well with ethyl acetate (10 × 420 mL). The washings were evaporated to a semisolid, which was dissolved in 800 mL of ethyl acetate and washed successively with saturated aqueous $NaHCO_3$ (2 × 100 mL), H_2O (2 × 100 mL), and brine (100 mL). The solution was dried ($MgSO_4$) and evaporated to a foam which was dissolved in 30 mL of propionitrile and treated with 0.75 mL of H_2O. Crystallization of hydrated 3 occurred rapidly, and when crystallization was complete (cooling to −10 °C), the light tan solid was washed with 25 mL of propionitrile at −10 °C and Et_2O (2 × 10 mL) and dried to give 7.35 g of hydrated 3, mp 106–110 °C (froth), that showed traces of 1 on TLC (system A). Evaporation of the filtrate and washings left a residue that was dissolved in 10 mL of 95:5 ethyl acetate–methanol and filtered through 20 g of silica gel 60. After the silica was washed well with ethyl acetate, the filtrate and washings were evaporated to give residue that was crystallized from 6 mL of propionitrile containing 0.25 mL of H_2O to give a second crop of 1.01 g of 3, mp 106–110 °C (froth), of a purity similar to that of the first crop. The total yield was 8.35 g (70%), calculated as $3 \cdot 1.5H_2O$. A sample of the first crop from a similar run which was recrystallized from methanol–H_2O and air-dried gave a satisfactory analysis for $3 \cdot 1.5H_2O$ (homogenous in TLC system A): mp 114–117 °C (froth); CI MS (NH_3) *m/e* 374 ($M^+ + 1$), 359 (342 + NH_3), 342 ($M^+ - MeOH + 1$): EI MS *m/e* 373 (M^+, weak), 204 (base); IR ($CHCl_3$) 3543 (OH), 1652 cm^{-1} (C=O); NMR ($CDCl_3$) for the mixture of rotomers (dried by distillation with $CHCl_3$ and then in vacuo) δ 2.70–3.18 (m, 3 H), 3.32 and 3.43 (2 s, 3 H, 4-OCH_3), 3.81, 3.85, 3.88, and 3.90 (4 s, 6 H, 2 ArOCH_3's), 6.48–6.89 (m, 5 H, ArH), 7.59 and 8.02 (2 s, 1 H, CHO). The ratio of rotomers in this sample was ~2:1.

Anal. Calcd for $C_{20}H_{23}NO_6 \cdot 1.5H_2O$: C, 59.99; H, 6.55; N, 3.50. Found: C, 59.61; H, 6.18; N, 3.16.

(±)-3,4-Dehydro-*N*-formyl-*N*-norreticuline (4). A 100-mL flask containing 1.173 g (2.93 mmol) of $3 \cdot 1.5H_2O$ was evacuated under high vacuum, and filled with argon (4×), evacuated to ~200 mm, and heated at 200–210 °C (bath temperature) for 1 h. The resulting amber glass (969 mg) was heated to solution in 10 mL of ethyl acetate and filtered through 3.0 g of silica gel 60 which was washed well with ethyl acetate. Evaporation of the filtrate and washings left a foam that was crystallized from 5 mL of butyronitrile (cooling to 0 °C) to give 692 mg of 4, mp 176.5–178 °C. An additional 182 mg of 4 was obtained as a second crop, mp 176–177.5 °C. The total yield was 87%. The two rotomers of 4, which were observed in the NMR spectrum (see below), could be partially separated with one development in TLC systems C and D and appeared as two closely running spots. Recrystallization of the first crop from a similar run from propionitrile gave an analytical sample: mp 178.5–180 °C; EI MS *m/e* 341 (M^+), 204 (base); IR ($CHCl_3$) 3550 (OH), 1675 cm^{-1} (CHO); UV λ_{max} 310 nm (ε 12 470), 290.5 (10 900), 235.5 (24 490), 211 (23 570); NMR (Me_2SO-d_6) for the mixture of rotomers δ 2.45–2.73 (m, 2 H, CH_2), 3.59–3.87 (3 lines, 6 H, OCH_3), 4.18–5.00 and 5.27–5.45 (2 m, 1 H, C-1 H), 5.89 and 6.14 (2 d, 1 H, *J* = 8 Hz, olefinic H), 6.32 and 6.51 (2 br d, 1 H, *J* = 8 Hz, olefinic H), 7.41 and 8.36 (2 s, 1 H, CHO), 8.98 (br s, 2 H, OH). The ratio of rotomers in this sample was ~1:2.

Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.89; H, 5.68; N, 4.25.

Catalytic Hydrogenation of 4. A solution of 100 mg (0.29 mmol) of 4 in 100 mL of methanol containing 80 mg of 5% Pd/C catalyst was shaken with hydrogen at 60 psig for 2 h. The mixture was filtered through Celite, evaporated to a foam, and crystallized from 2-propanol to give 63 mg of 1, mp 184–185.5 °C (lit.[19] mp 184–185.5 °C). The IR spectrum and TLC behavior of this material were identical with an authentic sample of 1. An additional 18 mg of 1 was obtained as a second crop, mp 182.5–184 °C.

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(±)-*N*-Formyl-*N*-northalidine (5). To a stirred solution of 50 mL of acetonitrile and 0.5 mL of CH_3SO_3H at 25 °C was added 1.20 g (3.0 mmol) of **3**·1.5H_2O. The solid dissolved rapidly, and after 80 min, 1.5 mL of concentrated aqueous NH_3 was added. Evaporation of the solvent left a residue that was partitioned between 50 mL of $CHCl_3$ and 20 mL of H_2O (hot). The $CHCl_3$ was separated, and the aqueous phase was reextracted with 20 mL of $CHCl_3$. The combined $CHCl_3$ extracts were washed with 20 mL of H_2O and evaporated to a foam which was heated to solution in 10 mL of propionitrile. When the solution was cooled, a gellike substance separated. The mixture was boiled for ~5 min while the side of the container was rubbed with a glass rod, and crystalline material separated as the gellike material dissolved. When crystallization was complete at 25 °C, the solid was filtered, washed with 8 mL of propionitrile, and dried to give 650 mg (64%) of **5**, mp 284.5–286 °C dec, which consisted of two rotomers that appeared as closely running spots in TLC systems B and C. TLC of the filtrate showed the presence of **9**, rotomers of **5**, and several minor, unidentified byproducts. In a similar experiment, the lower R_f rotomer[33] (TLC system C) of **5** was obtained as a second crop that, by NMR, contained only ~5% of the higher R_f rotomer. An analytical sample of **5** was prepared by dissolving a portion of the first crop in warm Me_2SO and diluting it with several volumes of H_2O: mp 285–287 °C dec; EI MS *m/e* 341 (M^+), 284 ($M^+ - CH_2{=}NCHO$,[22] base); IR (KBr) 3400, 3250 (OH), 1655 cm^{-1} (CHO); NMR (Me_2SO-d_6; for the mixture of rotomers) δ 2.68–3.05 (m, 1 H), 3.11–3.63 (m, 3 H), 3.77 (s, sh, 6 H, 2 OCH_3), 3.87–4.11 (m, 1 H), 5.07 and 5.32 (2 br s, 1 H), 6.41 and 6.43 (2 s, 1 H, ArH), 6.80, 6.84, 6.86, and 6.92 (4 s, 3 H, ArH), 8.16 and 8.36 (2 s, 1 H, CHO), 8.79, 8.91, and 8.96 (3 s, 2 H, exchange with D_2O, OH). The ratio of rotomers in this sample was ~1:1.3.

Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.60; H, 5.83; N, 3.94.

(±)-*N*-Northalidine (6). A mixture of 5.0 mL of 64% aqueous hydrazine, 5.0 mL of 95% hydrazine, and 461 mg (1.35 mmol) of **5** was heated to solution under argon behind a safety shield, refluxed 2.0 h, cooled, and evaporated to a semisolid. The residue was heated to solution in 5.0 mL of 10% aqueous 2-propanol and cooled to 20 °C. The crystalline solid that separated was filtered, washed with 8.0 mL of H_2O, and dried to directly afford 409 mg (97%) of analytically pure **6**·H_2O which showed one spot in TLC system E: mp 227–229 °C (softens at 170.5–174.5 °C, loses H_2O); EI MS *m/e* 313 (M^+), 312 ($M^+ - 1$), 284 ($M^+ - CH_2{=}NH$,[22] base); IR (KBr) 3530, 3440 (OH), 3310 cm^{-1} (NH); NMR (1:3 $DCCl_3$–Me_2SO-d_6) δ 2.73–2.91 (m, 1 H), 3.00–3.25 (m, 2 H), 3.27–3.45 (m, 1 H), 3.64–3.73 (m, 1 H), 3.72–3.77 (2 s, 6 H, 2 OCH_3), 3.95–4.09 (m, 1 H), 6.40 (s, 1 H, ArH), 6.62 (s, 1 H, ArH), 6.71 (s, 1 H, ArH), 6.75 (s, 1 H, ArH).

Anal. Calcd for $C_{18}H_{19}NO_4$·H_2O: C, 65.24; H, 6.39; N, 4.23. Found: C, 64.95; H, 6.38; N, 4.01.

(±)-Thalidine (7). To a stirred solution of 40 mL of 1 M BH_3 in THF under argon was cautiously added 341 mg (1.0 mmol) of **5**. When H_2 evolution was complete, the mixture was refluxed 4.0 h, cooled, and treated cautiously with 7.0 mL of methanol. Evaporation of the solvents left the boron-containing intermediate as a gum that was dissolved in 30 mL of methanol, rendered strongly acidic with HCl gas, and refluxed until TLC in system B showed conversion of the higher R_f intermediate to **7** was essentially complete (~3.5 h). The cooled mixture was evaporated, and methanol (3 × 25 mL) was added and evaporated from the residue. The residue from the final evaporation was partitioned between 15 mL of H_2O and 30 mL of Et_2O. The aqueous phase was filtered, and the Et_2O was washed with H_2O (2 × 5 mL) which was used to rinse the filter. Evaporation of the combined aqueous filtrates left a solid that was recrystallized from 5 mL of H_2O (with cooling to 0 °C) to give 313 mg (82%) of analytically pure **7**·HCl·H_2O, mp 268–269.5 °C dec, after washing with 1 mL of H_2O at 0 °C and air-drying. A solution of 200 mg (0.52 mmol) of **7**·HCl·H_2O was heated to solution in 3 mL of 20% aqueous 2-propanol and treated with 5 drops of concentrated aqueous NH_3 to give 158 mg (92% recovery) of **7**: mp 237.5–239.0 °C dec (lit.[10] mp 219–221 °C); EI MS *m/e* 327 (M^+), 326 ($M^+ - 1$), 284 ($M^+ - CH_2{=}NCH_3$,[22]), 190 (base). In a similar run, 55 mL of 20% MeOH in $CHCl_3$ was added to the aqueous solution of crude **7**·HCl. The aqueous phase was rendered alkaline to pH 9–9.5 with concentrated aqueous NH_3 while stirring. The $CHCl_3$ was removed, and the aqueous phase extracted with $CHCl_3$ (2 × 25 mL). The combined $CHCl_3$ extracts were washed with 10 mL of H_2O and evaporated to afford 317 mg (97%) of **7**, mp 232–234 °C dec, which was homogenous on TLC in system B.

Anal. Calcd for $C_{19}H_{21}NO_4$·H_2O·HCl: C, 59.75; H, 6.33; N, 3.67. Found: C, 59.70; H, 6.26; N, 3.30.

(±)-*O*-Methylthalisopavine (8). A solution of 100 mg (0.31 mmol) of **7** in 20 mL of methanol was treated with excess ethereal CH_2N_2 until TLC (system B) indicated complete conversion of **7** and an intermediate spot to a higher R_f single spot. Sufficient acetic acid was added to destroy excess CH_2N_2. Evaporation of the solvents left a residue that was partitioned between 10 mL of 5% aqueous NaOH and 80 mL of Et_2O. The Et_2O was separated, dried (Na_2SO_4), and evaporated to a foam that was crystallized from methanol–2-propanol to afford 38 mg (35%) of **8**: mp 164.5–166.5 °C (lit.[11] mp 165–166 °C); EI MS *m/e* 355 (M^+), 312 ($M^+ - CH_2{=}NCH_3$), 204 (base).

(±)-*N*-Formyl-*N*-norbisnorargemonine (9). To a stirred solution of 0.75 mL of CH_3SO_3H in 75 mL of acetonitrile was added 2.39 g (7.0 mmol) of **4**. The mixture was heated to 60 °C until the **4** dissolved, stirred at ~25 °C for 6.5 h, and treated with 5 mL of concentrated aqueous NH_3. Evaporation of the solvent left a semisolid that was partitioned between 90 mL of H_2O and 125 mL of $CHCl_3$. The $CHCl_3$ was separated, washed with 50 mL of H_2O, and evaporated to an orange foam which was heated to solution in 12 mL of 2-propanol containing 1.0 mL of H_2O. Crystallization was allowed to proceed overnight at 25 °C to afford 1:80 g (75%) of **9**, mp 216.5–218.5 °C. TLC in system C revealed only traces of **5** in the mother liquor from **9**. Partial separation of the rotomers of **9** could be accomplished on TLC in system D. An analytical sample was prepared by warming the material to solution in DMF (2 mL/g), diluting it with 3 volumes of H_2O, filtering of the resulting material, washing the solid successively with 1:3 DMF–H_2O, 2-propanol, and ether, and air-drying: mp 217.5–219.5 °C; EI MS *m/e* 341 (M^+), 204 (base); IR (KBr) 3400 (OH), 1650 (C=O) cm^{-1}; NMR (Me_2SO-d_6; for the mixture of rotomers) δ 2.41–2.89 (m, 2 H), 2.98–3.32 (m, 2 H), 3.65 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 4.91–5.14 (m, 1 H), 5.36–5.61 (m, 1 H), 6.39 (s, 1 H, ArH), 6.52 (s, 1 H, ArH), 6.65 and 6.69 (2 s, 1 H, ArH), 6.82 and 6.89 (2 s, 1 H, ArH), 8.24 and 8.25 (2 s, 1 H, CHO), 8.86 (br s, 2 H, OH). The ratio of rotomers in this sample was ~1:3.

Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.58; H, 5.87; N, 3.80.

(±)-*N*-Norbisnorargemonine (10). A stirred mixture of 5.0 mL of 64% aqueous hydrazine, 5.0 mL of 95% hydrazine, and 500 mg (1.47 mmol) of **9** was heated to solution under argon and then refluxed 2.0 h behind a safety shield. The mixture was cooled and evaporated to a foam to which was added 5.0 mL of 50% aqueous 2-propanol. The mixture was rendered acidic with 37% aqueous HCl, heated to solution, and immediately rendered alkaline to pH 9–9.5 with concentrated aqueous NH_3. Crystalline material separated rapidly, and after the solution was cooled to 0 °C and diluted with 5.0 mL of H_2O and the solid washed well with H_2O and air-dried, 462 mg (98%) of analytically and chromatographically (TLC, system E) pure **10**·0.5H_2O was obtained directly: mp 249–250.5 °C; EI MS *m/e* 313 (M^+), 312 ($M^+ - 1$), 176 (base); IR (KBr) 3420 (OH), 1598, 1499, 1260 cm^{-1}; NMR (1:3 $CDCl_3$–Me_2SO-d_6) δ 2.35–2.66 (m, 2 H), 2.98–3.25 (m, 2 H), 3.66 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 4.05–4.27 (m, 2 H), 6.32 (s, 1 H, ArH), 6.43 (s, 1 H, ArH), 6.52 (s, 1 H, ArH), 6.66 (s, 1 H, ArH), 8.32 (br s, ~2 H, OH).

Anal. Calcd for $C_{18}H_{19}NO_4$·0.5H_2O: C, 67.06; H, 6.25; N, 4.35. Found: C, 67.16; H, 6.38; N, 4.04.

(±)-Bisnorargemonine (11). To a stirred solution of 30 mL of 1 M BH_3 in THF (30 mmol) under argon was added 341 mg (1.0 mmol) of **9**. When H_2 evolution subsided, the mixture was

(33) A small sample of this material was heated below the melting point in a test tube without solvent over a small flame. TLC (system C) of the resulting material indicated nearly equal amounts of the two rotomers. After the sample had been allowed to stand at ambient temperature for about two weeks, the NMR spectrum (Me_2SO-d_6) of the original sample of the lower R_f rotomer showed an increased amount of the higher R_f material. The rotomers of **5** and related compounds will be studied in more detail, and the results of this investigation will be reported in due course.

refluxed overnight, cooled, treated cautiously with 8 mL of methanol (H_2O), and evaporated. The residue was dissolved in 30 mL of methanol, saturated with HCl gas at the boiling point, refluxed 4 h, and evaporated, and methanol (3 × 25 mL) was added and evaporated to give a residue which was partitioned between 10 mL of H_2O and 15 mL of Et_2O. The H_2O was removed and reextracted with 15 mL of Et_2O. The combined Et_2O extracts were washed with H_2O (2 × 5 mL) and discarded. The combined H_2O extracts were rendered alkaline to pH 9–9.5 with concentrated aqueous NH_3, and the precipitated base was extracted into 25 mL of $CHCl_3$. The aqueous phase was reextracted with 10 mL of $CHCl_3$, and the combined $CHCl_3$ extracts were evaporated, dissolved in 5 mL of 1:1 $CHCl_3$–methanol, and filtered through 7.0 g of silica gel 60 which was washed well with TLC system B. The solvent was evaporated to a foam which was crystallized from 5.0 mL of butyronitrile to afford 252 mg of **11**: mp 233.5–235.0 °C (lit.[12] mp 231.5–232.5 °C); EI MS *m/e* 327 (M^+), 326 (M^+ – 1), 190 (base). Concentration of the filtrate and washings to ~0.75 mL gave an additional 34 mg of **11**, mp 231.5–233 °C, for a total yield of 87%.

(±)-Argemonine (12). Methylation of 100 mg (0.31 mmol) of **11** as described above for **7** gave a foam that was crystallized from 1 mL of Et_2O containing a few drops of CH_2Cl_2 to give 68 mg (63%) of **12**: mp 138–140 °C (lit.[24] mp 135–140 °C); EI MS *m/e* 355 (M^+), 354 (M^+ – 1), 204 (base).

(+)-*N*-Carbethoxy-*N*-norreticuline (13). A stirred mixture of 3.69 g (10.0 mmol) of (–)-*N*-norreticuline·HCl·H_2O,[19] 40 mL of H_2O, and 100 mL of $CHCl_3$ was treated with 4.20 g (50.0 mmol) of $NaHCO_3$ in one portion and warmed to 50 °C until two homogenous phases were obtained. The rapidly stirred mixture was cooled to 25 °C, treated dropwise with 1.63 g (15.0 mmol) of redistilled ethyl chloroformate during 10 min, and then stirred 2.5 h at 20–25 °C. The $CHCl_3$ was separated, washed with 40 mL of 5% HCl, dried ($MgSO_4$), and evaporated to give 4.28 g (~100%) of **13** (that still contained $CHCl_3$) as a homogenous (TLC system F) foam which was identical (TLC system F, IR) to the crystalline racemic material previously described;[19] EI MS *m/e* 387 (M^+), 250 (base). A sample of **13** from a similar preparation which had been exhaustively dried showed $[\alpha]^{24}_D$ +66.3° (*c* 0.39, MeOH).

(+)-4-Methoxy-*N*-carbethoxy-*N*-norreticuline (14). A stirred solution of 4.27 g (~10 mmol) of the **13** from above in 400 mL of methanol at –75 °C was treated dropwise during 5 min with a solution of 2.50 g (10.8 mmol) of 98% DDQ in 20 mL of methanol. After being stirred for 1.5 h at –75 °C, the solution was mixed directly with 400 g of Silicar CC-7 and allowed to stand 45 min, and the silica was then washed on a filter with ethyl acetate (5 × 500 mL). The combined washings were concentrated to ~40 mL, diluted with 200 mL of CH_2Cl_2, and washed with 200 mL of H_2O, leaving some solid material in the H_2O phase. The CH_2Cl_2 extract was washed with 100 mL of 5% aqueous $NaHCO_3$, and H_2O (2 × 100 mL), dried ($MgSO_4$), and evaporated to afford 4.10 g (98%) of **14** as foam which showed traces of **13** by TLC (system F): EI MS *m/e* 417 (trace, M^+), 385 (M^+ – CH_3OH), 280 (M^+ – benzyl, base), 248 (M^+ – benzyl – CH_3OH); NMR ($CDCl_3$; for the mixture of rotomers) δ 0.86–1.18 (2 t, 3 H, *J* = 7 Hz, CCH_3), 3.41 and 3.48 (2 s, 3 H, aliphatic OCH_3), 3.86 (s, sh, 3 H, $ArOCH_3$), 3.91 (s, sh, 3 H, $ArOCH_3$), 5.75 and 5.86 (br s, 2 H, OH, exchange with D_2O), 6.52–6.91 (m, 5 H, ArH). The ratio of rotomers in this sample was ~1:3. A homogenous (TLC system F) sample of foamy **14**, obtained chromatographically, showed $[\alpha]^{23}_D$ +42.1° (*c* 0.7, MeOH).

(–)-*N*-Carbethoxy-*N*-northalidine (15). A mixture of the 4.10 g of foamy **14** from above, 75 mL of acetonitrile, and 0.75 mL of CH_3SO_3H was stirred for 2.75 h at 20–25 °C, treated with 3.0 mL of concentrated aqueous NH_3, and evaporated, and the residue was partitioned between 50 mL of H_2O and 100 mL of $CHCl_3$. The $CHCl_3$ was separated, washed with H_2O (2 × 50 mL), dried ($MgSO_4$), and evaporated to give 3.96 g of brown foam which was crystallized from 20 mL of ethyl acetate (with cooling to –10 °C) to give 2.25 g of pure (TLC system F) **15**, mp 196.5–198 °C. A second crop of 290 mg of **15** was obtained; mp 196.5–198 °C. The total yield was 2.54 g (66%) based on (–)-*N*-norreticuline·HCl·H_2O. Recrystallization from ethyl acetate afforded an analytical sample: mp 198.5–200 °C; EI MS *m/e* 385 (M^+), 284 (M^+ – CH_2=NCO_2Et,[22] base); IR ($CHCl_3$) 3543 (OH), 1680 (C=O) cm^{-1}; $[\alpha]^{23}_D$ –153.3° (*c* 0.42, MeOH); NMR ($CDCl_3$; for the mixture of rotomers) δ 1.20 and 1.30 (2 t, 3 H, *J* = 7 Hz), 2.87 and 2.93 (2 br s, 1 H), 3.32–3.66 (m, 2 H), 3.66–3.70 (m, 1 H), 3.86 (s, sh, 6 H, OCH_3), 3.93–4.32 (m, 3 H), 5.20 and 5.36 (2 br s, 1 H), 5.74, 5.84, and 5.94 (3 br s, exchange with D_2O, OH), 6.59 (s, sh, 1 H, ArH), 6.68 (s, 1 H, ArH), 6.75 (s, 1 H, ArH), 6.85 (s, sh, 1 H, ArH). The ratio of rotomers in this sample was ~1.0:1.5.

Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.01; N, 3.63. Found: C, 65.36; H, 6.30; N, 3.72.

(–)-Thalidine (7a). A solution of 1.54 g (4.0 mmol) of **15** in 12 mL of dry THF was added dropwise to a stirred refluxing solution of 380 mg (10.0 mmol) of LAH in 150 mL of THF. The suspension of white solid was refluxed 18 h, cooled, cautiously treated with 3 mL of concentrated aqueous NH_3, stirred 30 min, and filtered. The bluish gray solid was dissolved in 50 mL of 10% aqueous NaOH and rendered acidic to pH 1 and then alkaline to pH 9–9.5 with concentrated aqueous NH_3. The mixture was shaken with 100 mL of $CHCl_3$, and the resulting emulsion was filtered through 15 g of Celite. The Celite was washed with $CHCl_3$ (2 × 50 mL), stirred with 100 mL of $CHCl_3$, filtered, and washed with 100 mL of $CHCl_3$. The combined $CHCl_3$ extracts were separated, washed with 40 mL of H_2O, dried (Na_2SO_4), and evaporated to give a solid that was recrystallized from 6 mL of butyronitrile to give 567 mg of off-white **7a**, mp 219.5–221 °C. Concentration of the filtrate and washings to ~3 mL afforded an additional 145 mg of **7a**, mp 216–218 °C. The total yield was 712 mg (54%). For final purification, 520 mg of **7a** from above was dissolved in the minimum volume of warm 1:1 $CHCl_3$–MeOH and filtered through 7.0 g of silica gel 60 which was washed well with TLC system E. The filtrate and washings were evaporated to a light yellow foam which was heated to solution in 2.0 mL of methanol and diluted with 0.5 mL of H_2O. After the solution was cooled to 0 °C, the white crystalline **7a** was collected, washed with cold 1:3 H_2O–MeOH, and air-dried to afford 410 mg of pure (TLC system B) **7a**: mp 222–223 °C; $[\alpha]^{23}_D$ –172.1° (*c* 0.7, MeOH) [lit.[10] mp 205–207 °C; $[\alpha]^{23}_D$ –172° (*c* 0.7, MeOH)]. The chromatographic (TLC systems A and B) and spectral properties (IR, EI MS) of **7a** were identical with those of the racemate **7**.

(–)-*O*-Methylthalisopavine (8a). Methylation of **7a** as described above for the racemate **7** afforded a foam that was crystallized from isopropyl ether to afford 46 mg (43%) of **8a**: mp 92–94 °C (lit.[18] mp 91–92 °C). The chromatographic (TLC systems A and B) and spectral (IR, EI MS) properties of **8a** were identical with those of the racemate **8**.

(+)-3,4-Dehydro-*N*-carbethoxy-*N*-norreticuline (16). Crude **14** (2.92 g) prepared exactly as described above from 2.58 g (7.0 mmol) of (–)-*N*-norreticuline·HCl·H_2O was dissolved in 10 mL of 1:1 Et_2O–ethyl acetate and filtered through 30 g of silica gel 60 which was washed well with Et_2O. Evaporation of the solvents left 2.72 g (~100%) of purified, foamy **16**. The flask containing this material was evacuated under high vacuum and refilled with argon (4×), evacuated to ~200 mm, and heated at 190–200 °C for 1 h. The resulting material was purified by filtration through 30 g of silica gel 60 as described above for **14** to give 2.18 g (81%) of foamy **16** which was nearly homogenous on TLC (system F). A homogenous (TLC system F) sample of **16** was obtained by preparative TLC (system F): EI MS *m/e* 385 (M^+), 248 (M^+ – benzyl, base); IR ($CHCl_3$) 3547 (OH), 1698 (C=O) cm^{-1}; $[\alpha]^{23}_D$ +209.2° (*c* 0.32, $CHCl_3$); NMR ($CDCl_3$; for the mixture of rotomers) δ 1.16 and 1.26 (2 t, 3 H, *J* = 7 Hz, CH_2CH_3), 2.55–2.95 (m, 2 H, benzylic CH_2), 3.78–3.93 (4 s, 6 H, 2 OCH_3), 3.98–4.32 (m, 2 H, CH_2CH_3), 5.18–5.32 and 5.32–5.43 (2 m, 1 H, C-1 H), 5.61 (br s, 2 H, exchanges with D_2O), 5.73 and 5.86 (2 d, 1 H, olefinic H), 6.25–6.93 (m, 6 H, ArH + 1 olefinic H). The ratio of rotomers in this sample was ~1:1.

(–)-*N*-Carbethoxy-*N*-norbisnorargemonine (17). A solution of 2.00 g (5.19 mmol) of **16** from above was dissolved in 75 mL of acetonitrile containing 0.75 mL of CH_3SO_3H, kept at 25 °C for 1.5 h, treated with 2.0 mL of concentrated aqueous NH_3, and evaporated to give a residue that was partitioned between 200 mL of Et_2O and 50 mL of H_2O. The small amount of red tar that did not dissolve was triturated with boiling Et_2O (2 × 50 mL). The combined Et_2O extracts were washed with 50 mL of H_2O and 50 mL of 5% aqueous HCl, dried ($MgSO_4$), evaporated to a foam, dissolved in 10 mL of 4:1 $CHCl_3$–ethyl acetate, and filtered through 50 g of silica gel 60 which was washed well with ethyl acetate. The filtrate and washing were evaporated to afford 1.61 g (81%) of

17 as a foam which was nearly homogenous on TLC (system F). A sample obtained by preparative TLC (system F) showed the following: EI MS m/e 385 (M^+), 384 ($M^+ - 1$), 248 ($M^+ - C_8H_9O_2$, base[22]); IR ($CHCl_3$) 3546 (OH), 1686 (C=O) cm^{-1}; $[\alpha]^{23}_D$ -57.3° (c 0.15, $CHCl_3$); NMR ($CDCl_3$; for the mixture of rotomers) δ 1.28 (t, 3 H, CH_2CH_3, J = 8 Hz), 2.64-2.91 (m, 2 H), 3.24-3.50 (m, 2 H), 3.77, 3.83, and 3.86 (3 s, 6 H, 2 OCH_3), 4.09-4.32 (m, 2 H, CH_2CH_3), 5.32-5.55 (m, 2 H), 5.60 (br s, 2 H, OH, exchanges with D_2O), 6.41 and 6.44 (2 s, 1 H, ArH), 6.51 and 6.53 (2 s, 1 H, ArH), 6.65 (s, 1 H, ArH), 6.73 (s, 1 H, ArH). The ratio of rotomers in this sample was ~1:1.

(-)-Bisnorargemonine (11a). A solution of 750 mg (1.95 mmol) of 17 in 25 mL of dry THF was added dropwise to a stirred, refluxing solution of 500 mg (13.2 mmol) of LAH in 200 mL of dry THF. The mixture was refluxed 18 h, cooled, and cautiously treated dropwise with 40 mL of concentrated aqueous NH_3. When the addition was completed, the mixture was allowed to stand 10 min, and then the clear THF (which contained only traces of **11a**) was decanted and discarded. To the gellike precipitate which adhered to the sides of the flask were added 50 mL of H_2O and sufficient 37% aqueous HCl to dissolve the inorganic material and acidify the aqueous phase to pH <1 (Hydrion paper). The aqueous was removed, and the small amount of brown tarry material remaining in the flask was triturated with boiling H_2O (2 × 25 mL). The combined, stirred aqueous phase was treated with 100 mL of $CHCl_3$ and rendered alkaline to pH 9-9.5 with concentrated aqueous NH_3, and the resulting emulsion was filtered through Celite. The filter was washed with $CHCl_3$ (2 × 50 mL), and the aqueous was separated and extracted with $CHCl_3$ (5 × 50 mL). The Celite and inorganic material was slurried with boiling methanol (2 × 50 mL) and filtered, and the methanol was evaporated. The residue was triturated with 50 mL of boiling $CHCl_3$ and filtered. The combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated to afford 526 mg of a foam which was crystallized from 2.0 mL of cold methanol to afford 206 mg (32%) of off-white **11a**, mp 248.5-249.5 °C dec. Preparative TLC of a portion of this material (system B) followed by recrystallization from MeOH provided pure **11a**: mp 252-253 °C dec; $[\alpha]^{23}_D$ -222.7° (c 0.3, $CHCl_3$) [lit.[17] mp 243-246 °C, $[\alpha]^{27}_D$ -222° (c 0.3, $CHCl_3$)]. The chromatographic (TLC systems A and B) and spectral properties (IR, EI MS) of **11a** were identical with those of the racemate **11**.

(-)-Argemonine (12a). Methylation of 100 mg of **11a** as described above for **7** gave a foam that crystallized from aqueous 2-propanol to afford 45 mg (41%) of hydrated **12a**: mp 129-134 °C (lit.[17] mp 125-135 °C). Drying this material overnight at 100 °C afforded anhydrous **12a**, mp 152.5-153.5 °C (lit.[13] mp 151-151.5 °C). The chromatographic (TLC systems A and B) and spectral properties (IR, EI MS) of **12a** were identical with those of the racemate **12**.

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Registry No. 1, 72258-92-5; 3, 72258-98-1; 4, 72258-99-2; 5, 72259-00-8; 6, 72259-01-9; 7, 63162-85-6; 7·HCl, 72300-71-1; 7a, 63110-83-8; 8, 33579-95-2; 8a, 18944-92-8; 9, 72259-02-0; 10, 72259-03-1; 11, 29944-24-9; 11a, 6808-63-5; 12, 18831-00-0; 12a, 6901-16-2; 13, 24192-18-5; 14, 72264-53-0; 15, 72259-04-2; 16, 72259-05-3; 17, 72259-06-4; (-)-N-norreticuline·HCl, 6451-82-7.

Synthetic Study of (+)-Nootkatone from (-)-β-Pinene

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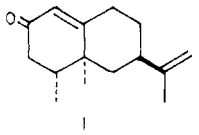
A facile stereoselective synthesis of (+)-nootkatone (1) has been achieved starting with (+)-nopinone (**2b**). The key step was the conjugate addition of methallyltrimethylsilane (**20b**) to *trans*-3-ethylidenenopinone (**16**), which was obtainable from **2b** on the cross condensation with acetaldehyde followed by acid treatment, giving an adduct with the desired stereochemistry, **24a**, as the predominant product. Dione **23**, obtained from the adduct on methylation followed by ozonization, afforded nootkatone hydrochloride (**26**) on treatment with hydrogen chloride. Regioselective dehydrochlorination of the hydrochloride yielded 1. An alternative route in which allyltrimethylsilane was used is also described.

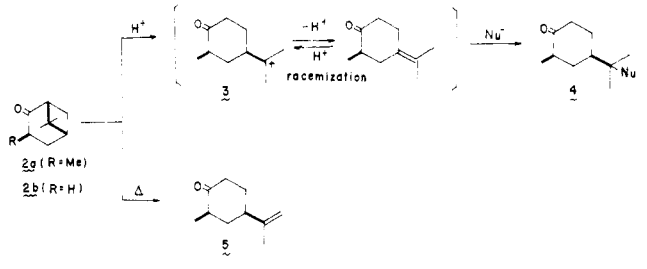
(+)-Nootkatone (1) is an eremophilanoid isolated first from the heartwood of Alaska yellow cedar (*Chamaecyparis nootkatensis*).[1] MacLeod found this ketone in the peel oil of grapefruit (*Citrus paradisi*), revised the structure proposed,[2] and recognized it as the constituent that most powerfully contributed to grapefruit flavor.[3] His results undoubtedly stimulated synthetic efforts toward nootkatone.



1

The stereoselective synthesis of (±)-1 has been accomplished by annulation reactions of substituted cyclohexanones[4] or by acid cleavage-cyclization of a bicyclo-

Scheme I



[2.2.2]octyl derivative.[5] Only the (+)-enantiomer of this ketone, however, possesses the intrinsic scent of grapefruit peel oil.[6] This fact has prompted the synthesis of the

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