g (27.3 mmol) of hydroxylamine hydrochloride, 3.78 g (27.3 mmol) of potassium carbonate and 60 mL of methanol were combined and refluxed overnight. TLC indicated the presence of starting material so another equivalent each of hydroxylamine hydrochloride and potassium carbonate were added, and the reaction mixture was again refluxed overnight. After the mixture was cooled to 25 °C and concentrated in vacuo, the residue was extracted with acetonitrile. Concentration gave 3.69 g of oil which was chromatographed on silica gel. A purple band was isolated and concentrated to give 620 mg of product **38**. (The sample may have decomposed on the column according to TLC.)

Method K. Scheme VI, Preparation of 39 and 40. A 5.0-g (32.0 mmol) quantity of 2-chlorohydroxamoyl chloride was dissolved in 100 mL of methanol and immediately cooled in an ice bath. To this solution was added 4.69 g (32.0 mmol) of *N*-methyl-*N'*-*n*-butylthiourea (addition time ca. 15 min). The reaction mixture was stirred at 0 °C for ca. 10 min before 5.38 g (64.1 mmol) of sodium bicarbonate was slowly added. The reaction was stirred overnight at 25 °C, filtered, and concentrated in vacuo. The residue was extracted with ethanol. Concentration of the ethanol solution gave a crude residue that was chromatographed on silica gel (gravity column) to give 3.5 g (48%) of a mixture of **39** and **40**. This mixture was treated with methyl isocyanate under standard conditions, and the resulting product was chromatographed on low-pressure LC to give **39a** and **40a** as pure compounds.

Method L. Preparation of 2-Oximido-4-thioxo-3,5,5-trimethylthiazolidine (42). A mixture of 3,5,5-trimethyl-2-(*n*-butylimino)thiazolidine-4-thione (500 mg, 2.17 mmol), hydroxylamine hydrochloride (470 mg, 6.72 mmol), pyridine (531 mg, 6.72 mmol), and ethanol (10 mL) was refluxed for 2.5 h. The reaction mixture was cooled to 25 °C and concentrated in vacuo to give a residue which was extracted with chloroform. Concentration of the chloroform gave an oil which was stirred in petroleum ether overnight. The ether was decanted off, the residue was dissolved in ethanol (2 mL), and water was added until the solution became cloudy. The precipitate was collected and dried to give 150 mg (36%) of **42**.

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Supplementary Material Available: Infrared, NMR, and analytical data (6 pages). Ordering information is given on any current masthead page.

Synthesis and Characterization of Stereoisomeric 11-Hydroxy-1,2,3,4,4a,5,6,11a-octahydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]-pyridines

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The four stereoisomeric 11-hydroxy-1,2,3,4,4a,5,6,11a-octahydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridines are prepared by reduction of 5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (**1**) either by catalytic reduction to give **3a** and **3b** or by sodium borohydride in boiling 2-propanol to give **3c** and **3d**. An intermediate borate complex, **6**, is proposed to account for reduction of the pyridine ring of **2** by sodium borohydride.

We have discovered an unprecedented total reduction of a pyridine ring to a piperidine derivative upon treatment of 5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (**1**)[2] with sodium borohydride. These results and the catalytic reduction of **1**, which together afford the four possible stereoisomeric amino alcohols, **3a–d**, are the subject of this report.

When **1** was treated with sodium borohydride in ethanol, an exothermic reaction to 40 °C occurred, and alcohol **2**[3] was isolated in 57% yield (Scheme I). Fractional crystallization of the mother liquor residue from **2** gave **3c**, a hexahydro derivative of **2** (13% yield). This was subsequently assigned trans, anti stereochemistry. When the reaction was repeated using a large excess of sodium borohydride in boiling 2-propanol for several hours, a 20% recrystallized yield of **3c** was obtained. Fractional crystallization of the mother liquor residue gave 3% of the trans, syn isomer, **3d**. The remaining product was **2**. Catalytic reduction of **1** or **2** in ethanol and hydrochloric acid[4] gave the two isomeric cis-ring-fused amino alcohols **3a** (55%) and **3b** (2.3%), which were isolated and separated by fractional crystallization.

Assignment of stereochemistry to the isomeric amino alcohols **3a–d** was readily accomplished from the 100-MHz ^{1}H NMR spectra by analysis of coupling constants and use of double-resonance techniques. The two isomers where H_{11} and H_{11a} are anti, **3b** and **3c**, show doublets for H_{11} at δ 4.88 (J = 8.5 Hz) and δ 4.82 (J = 9.0 Hz), respectively. Irradiation of H_{11} in **3c** simplifies the doublet of doublets (J = 9 Hz, J = 9 Hz) at δ 2.15 assigned to H_{11a} which is coupled to H_{11} and H_{4a}. Isomer **3c** was thus assigned trans, anti stereochemistry. The resonance signal for H_{11a} of **3b** could not be defined by the use of double-resonance or shift-reagent techniques.

Similarly, the isomers where H_{11} and H_{11a} are syn, **3a** and **3d**, have doublets for H_{11} at δ 4.98 (J = 2 Hz) and δ 4.61 (J = 2 Hz), respectively. For **3a**, irradiation of H_{11}

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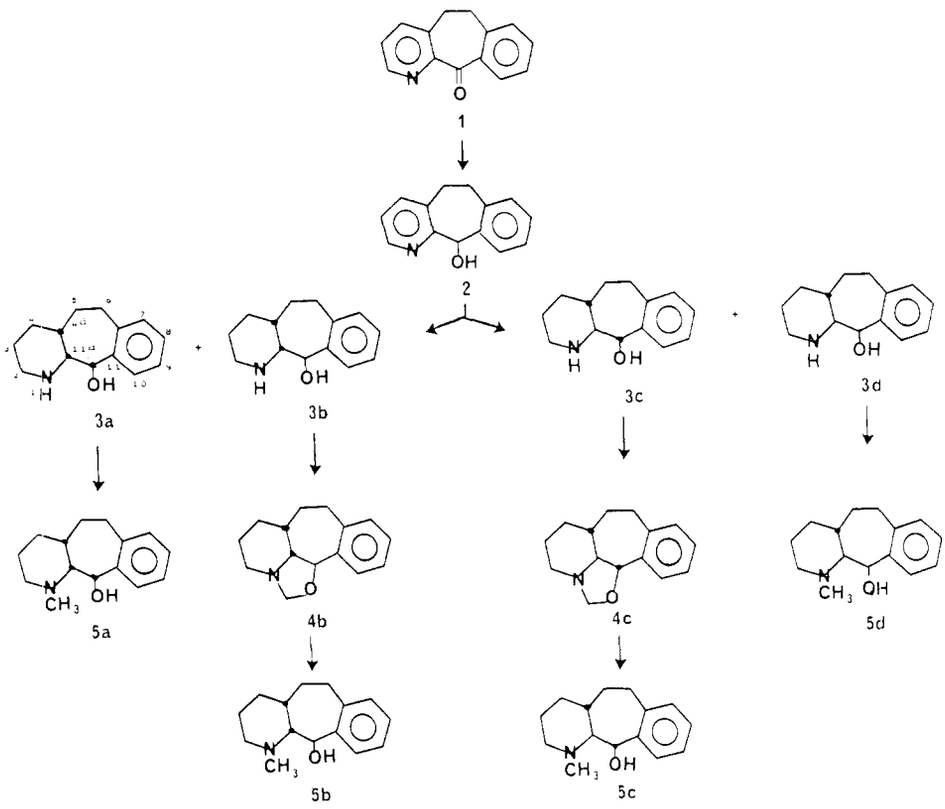
Scheme I



simplifies the doublet of doublets at δ 3.28 (J = 2 Hz, J = 2 Hz) due to coupling of H_{11a} to H_{11} and H_{4a} to a doublet (J = 2 Hz). Irradiation of H_{11} in **3d** simplifies the doublet of doublets at δ 2.48 (J = 2 Hz, J = 10 Hz) assigned to H_{11a} to a doublet (J = 10 Hz). These experiments define the ring stereochemistry in **3a** and **3d** as cis and trans, respectively. From the method of synthesis (catalytic reduction)[4] and by elimination, **3b** has cis ring stereochemistry.

The isomeric amino alcohols **3a–d** were treated with formic acid–formaldehyde under Eschweiler–Clarke conditions.[5] Different results were obtained, depending upon the stereochemistry of the amino alcohol: **3b** and **3c**, wherein H_{11} and H_{11a} are anti, afforded the oxazolidines **4b** and **4c**, which were stable to reduction by formic acid under the reaction conditions. Conversely, **3a** and **3d**, wherein the H_{11} and H_{11a} are syn, gave only the methylamino alcohols **5a** and **5d**, respectively. The Eschweiler–Clarke reaction of **3d** required 15 h for completion. During this period, TLC indicated the formation of an intermediate product which was converted to **5d**. This was presumably an oxazolidine which was unstable to the reduction conditions. No intermediate product was observed in the conversion of **3a** to **5a**. Treatment of the oxazolidines **4b** and **4c** with lithium aluminum hydride gave the isomeric methylamino alcohols **5b** and **5c** corresponding in stereochemistry to their precursors.

The methylene resonances in the ^1H NMR spectra of the oxazolidines **4b** and **4c** are considerably different. These methylene protons of **4b** show fortuitous magnetic equivalence, appearing as a singlet at δ 4.53. Conversely, the oxazolidine methylene protons of **4c** are nonequivalent, resonating at δ 3.95 (doublet of doublets, J = 0.5 Hz, J = 1 Hz) and at δ 4.80 (doublet, J = 1 Hz). The resonance at δ 3.95 is assignable to the proton α to the plane of the molecule. Inspection of a Dreiding model of **4c** indicates that this proton is synperiplanar with H_{11a}, which may account for the long-range (four-bond) coupling observed.

Discussion

Literature descriptions of the reduction of tertiary pyridine bases with borohydride are few. Kikugawa et al.[6] reported the sodium borohydride in ethanol reduction of a series of substituted pyridines activated by electronegative substituents on the 3- and 3,5-positions usually to give tetrahydropyridines. Only 3-nitropyridine was reduced to 3-nitropiperidine.[6] There are no references to the reduction of *unactivated* pyridines by borohydride.

The literature pertaining to the complex metal hydride reduction of quaternary pyridinium compounds is well documented.[7] In general, reduction of these activated pyridines with borohydride leads to the 1,2,3,6-tetrahydropyridines. The mechanism of the reduction leading to tetrahydropyridines has been shown by Lyle and coworkers[8] to involve initial 1,2 hydride addition to the activated pyridine nucleus, ultimately leading to a tetrahydropyridine. Increasing the steric bulk of the *N*-alkyl substituent leads to the formation of piperidine derivatives by initial 1,4 hydride addition.[8c]

In the present example, a seemingly unactivated pyridine ring is reduced to a piperidine derivative by sodium borohydride. A plausible explanation for this anomalous result is the initial formation of an internal borate complex, **6**, which activates the pyridine to hydride addition. Since the "N-substituent" is bulky, hydride adds initially to the

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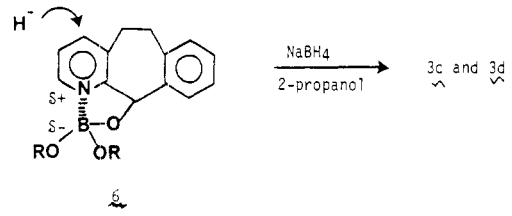
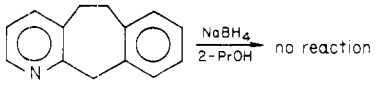


6

4-position, ultimately affording the piperidines **3c** and **3d**.

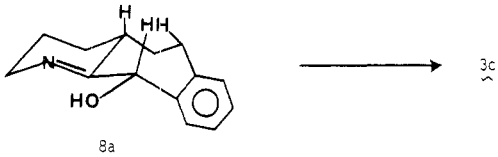
When 5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*a*]-pyridine (**7**)[9] was treated with five portions of sodium borohydride (4 molar excess each) in refluxing 2-propanol over 3 days, no reduction of the pyridine ring occurred, and **7** was recovered from the reaction mixture unchanged.



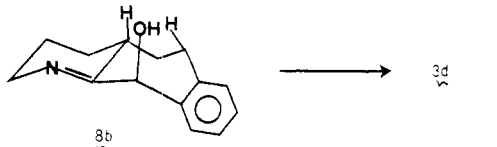
7

This evidence supports our hypothesis that the hydroxyl group provides a center for coordination, as depicted in structure **6**, so that pyridine ring reduction can occur.

The cis or trans ring stereochemistry in compounds **3a–d** is determined by the reducing agents. As expected, catalytic reduction gives the two cis-ring-fused stereoisomers, **3a** and **3b**.[4] The final step in the sodium borohydride reduction is assumed to be hydride addition to the imine bond in **8a** and **8b**. The pseudo-trans-diaxial arrangement



8a

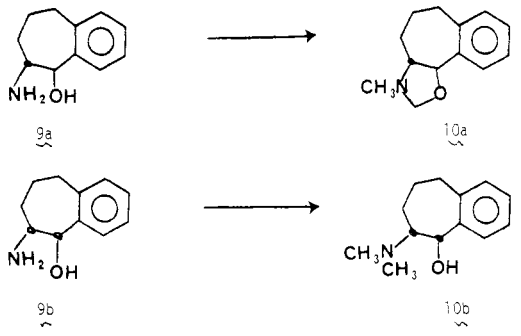


8b

of H_{4a}, H_6, and H_{11a} in **8a** would direct hydride addition in an anti fashion to give **3c**. Similar arrangements of H_{4a}, H_6, and OH in **8b** would afford **3d**.

The formation of the stable oxazolidines **4b** and **4c** is due to the syn relationship between the hydroxyl group and the methyleneimmonium Eschweiler–Clarke intermediate. The proximity of the hydroxyl group to the immonium function allows oxazolidine formation to occur before reduction of the intermediate by formic acid.

The stereochemical dependence of N-methylation vs. oxazolidine formation under Eschweiler–Clarke conditions is precedented by a recent report by Hirata et al.,[10] wherein the *trans*-aminobenzocycloheptanol **9a** gave only the oxazolidine **10a**, while the cis isomer, **9b**, gave the expected *N,N*-dimethyl derivative, **10b**. The corresponding five- and six-membered rings behaved normally. It should be noted that the geminal oxazolidine protons in **10a** resonate as an AB quartet (J = 2 Hz) at δ 4.07 and 4.77, which compare favorably with the corresponding protons in **4c**. Furthermore, **4c** has characteristic Bohlmann bands[11] at 2850, 2780, and 2740 cm^{-1} in its IR spectrum whereas **4b** lacks these bands.[12]



9a 10a

9b 10b

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Varian T60A, CFT 20, or XL-100-15 Fourier transform spectrometers, and chemical shift values are reported in parts per million downfield from internal Me_4Si. IR spectra were recorded on a Perkin-Elmer 221 spectrophotomer, and mass spectra were obtained with a Varian MAT CH5 spectrometer. All distillative concentrations of solvents were done with a rotary evaporator under reduced pressure. Yields were not optimized and are reported for recrystallized or analytically pure material.

***trans,anti*-11-Hydroxy-1,2,3,4,4a,5,6,11a-octahydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (3c).** $NaBH_4$ (2.1 g, 0.055 mol) was added to a stirred mixture of 23 g (0.11 mol) of **1** in 150 mL of 2-PrOH. After 0.25 h at ambient temperature, the reaction mixture was heated on a steam bath. Three portions of $NaBH_4$ were added to the hot reaction mixture after it had been heated for 0.5 h (2.1 g), 1.25 h (2.1 g), and 2 h (4.15 g). After being heated for 3.5 h, the mixture was allowed to cool to room temperature and was stirred overnight. An additional 4.15 g of $NaBH_4$ was added followed by 100 mL of 2-PrOH, and the reaction mixture was heated on a steam bath for 4 h. After cooling, it was diluted with H_2O, and the solid product was collected, washed with H_2O, and dried to give 15.3 g of a three-component mixture containing **2**, **3c**, and **3d** by TLC (30:10:1 $CHCl_3/CH_3OH/NH_4OH$ on silica). Recrystallization of this product mixture from 160 mL of 1,2-dimethoxyethane gave 5.0 g (20%) of the trans,anti isomer **3c**. A second recrystallization from CH_3OH afforded pure **3c**: mp 199–203 °C; IR (Nujol) 3285, 2700, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.15 (dd, J = 9, 9 Hz, 1, H_{11a}), 4.82 (d, J = 9 Hz, 1, H_{11}); mass spectrum, m/e 217.

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.51; H, 8.98; N, 6.38.

***trans,syn*-11-Hydroxy-1,2,3,4,4a,5,6,11a-octahydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (3d).** Concentration of the mother liquor from the recrystallization of **3c** to 75 mL gave 0.7 g (3%) of **3d**: mp 169–172 °C; IR (Nujol) 3255, 3245, 2700, 1445 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.48 (dd, J = 2, 10 Hz, 1, H_{11a}), 4.61 (d, J = 2 Hz, 1, H_{11}); mass spectrum, m/e 217.

Anal. Found: C, 77.00; H, 9.10; N, 6.59.

***cis,syn*-11-Hydroxy-1,2,3,4,4a,5,6,11a-octahydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (3a).** A mixture of 75 g (0.36 mol) of 1, 3 g of PtO_2, 60 mL of 37% HCl, and 1400 mL of EtOH was catalytically hydrogenated on a Parr apparatus at 40–45 psi of H_2 for 28 h. The mixture was filtered, and the filtrate was concentrated. The residual material was repeatedly diluted with three 200-mL portions of EtOH and concentrated. The residue was triturated in H_2O and rendered basic with 15% NaOH. The resulting solid was extracted three times with a total of 700 mL of CH_2Cl_2. The CH_2Cl_2 was cooled to 0 °C to give 43 g (55%) of **3a**: mp 160–162 °C; IR (Nujol) 3255, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.28 (dd, J = 2 Hz, 1, H_{11a}), 4.98 (d, J = 2 Hz, 1, H_{11}); mass spectrum, m/e 217.

Anal. Found: C, 77.11; H, 8.62; N, 6.31.

***cis,anti*-11-Hydroxy-1,2,3,4,4a,5,6,11a-octahydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (3b).** Concentration of the CH_2Cl_2 from **3a** and recrystallization of the 22-g residue from 125 mL of EtOAc followed by a second recrystallization from 300 mL of diisopropyl ether gave 1.8 g (2.3%) of **3b**: mp 156–158 °C;

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IR (Nujol) 3280, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.88 (d, J = 8.5 Hz, 1, H_{11}); mass spectrum, m/e 217.

Anal. Found: C, 77.65; H, 8.80; N, 6.39.

***cis,syn*-*N*-Methyl-11-hydroxy-1,2,3,4,4a,5,6,11a-octahydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (5a).** A mixture of 10.0 g (0.046 mol) of **3a**, 20 mL of 37% CH_2O, and 40 mL of HCO_2H was heated on a steam bath for 6 h and then concentrated. The residue was diluted with H_2O and then rendered acidic with 6 N HCl. The acidic solution was washed with EtOAc, rendered basic with 15% NaOH, and extracted with CH_2Cl_2. The CH_2Cl_2 was concentrated, and the residue (10.8 g) was recrystallized from 100 mL of CH_3CN to give 7.6 g of (72%) of **5a**: mp 166.5–170 °C; IR (Nujol) 3100, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (s, *N*-CH_3), 4.95 (d, J = 1 Hz, 1, H_{11}); mass spectrum, m/e 231.

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.25; H, 9.36; N, 6.04.

***trans,syn*-*N*-Methyl-11-hydroxy-1,2,3,4,4a,5,6,11a-octahydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (5d).** Heating a mixture of **3d** (7.0 g, 0.032 mol) with HCO_2H and 37% CH_2O for 15 h followed by acid–base workup as in the synthesis of **5a** and finally column chromatography on 300 g of Merck Al_2O_3 (II/III) with 2% CH_3OH–98% CH_2Cl_2 gave 4.9 g (66%) of **5d**: mp 113–115 °C; IR (Nujol) 3130, 2790, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (s, *N*-CH_3), 5.13 (d, J = 1 Hz, 1, H_{11}); mass spectrum, m/e 231.

Anal. Found: C, 77.53; H, 8.82; N, 5.90.

***cis,anti*-4,5,6,6a,7,8,12b,12c-Octahydro-2*H*-benzo[4,5]cyclohepta[1,2,3-*gh*]oxazolo[3,4-*a*]pyridine (4b).** A mixture of **3b** (3.0 g, 0.014 mol), HCO_2H (15 mL), and 37% CH_2O (15 mL) was heated on a steam bath for 4.5 h. Nitrogen was passed over the hot mixture on the steam bath for 0.5 h, and the residue was diluted with H_2O and acidified with 6 N HCl. The acidic solution was washed with EtOAc, rendered basic with 15% NaOH, and extracted with CH_2Cl_2. Concentration of the CH_2Cl_2 gave an oil (3.0 g). This was dissolved in 35 mL of hot MeOH and treated with 1.5 g (0.013 mol) of fumaric acid. The hot solution was filtered and allowed to cool, giving 1.4 g (40%) of the hemifumarate of **4b**, mp 165–168 °C.

Anal. Calcd for $C_{15}H_{19}NO \cdot {}^1/_2C_4H_4O_4$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.10; H, 7.28; N, 4.81.

A sample of the hemifumarate was rendered basic with 15% NaOH and extracted into CH_2Cl_2. The CH_2Cl_2 was filtered and evaporated to give an oil (**4b**): IR (Nujol) 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.53 (s, 2, $H_{13\alpha,\beta}$), 5.16 (d, J = 9.5 Hz, 1, H_{11}); mass spectrum, m/e 229.

***trans,anti*-4,5,6,6a,7,8,12b,12c-Octahydro-2*H*-benzo[4,5]cyclohepta[1,2,3-*gh*]oxazolo[3,4-*a*]pyridine (4c). (a) Formalin–Methanol.** A solution of **3c** (12.0 g, 0.055 mol) and 100 mL of 37% CH_2O in 100 mL of MeOH was heated under reflux for 1.5 h. The solution was concentrated to remove the MeOH, and the aqueous residue was acidified with 6 N HCl and washed with EtOAc and Et_2O. The acidic solution was then rendered basic with 15% NaOH and extracted with Et_2O. The Et_2O was dried (Na_2SO_4) and concentrated to give 11.3 g (90%) of a light oil. A 3.0-g sample and 1.52 g of fumaric acid were combined in hot MeOH, and the solution was filtered and cooled to give 2.3 g of the fumarate of **4c**, mp 138–141 °C.

A 0.8-g sample of the fumarate was suspended in H_2O, rendered basic with 15% NaOH, and extracted into CH_2Cl_2. The CH_2Cl_2 was filtered and concentrated to give 0.45 g of **4c** as an oil which crystallized slowly: IR 2850, 2780, 2740, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.02 (dd, J = 9, 9 Hz, 1, H_{11a}), 3.95 (dd, J = 0.5, 1 Hz, 1, $H_{13\alpha}$), 4.80 (d, J = 1 Hz, 1, $H_{13\beta}$), 4.96 (d, J = 9.0 Hz, 1, H_{11}); mass spectrum, m/e 229.

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.25; H, 8.26; N, 6.11.

(b) Eschweiler–Clarke Conditions. Reaction of 0.5 g of **3c** with 1 mL of 37% CH_2O and 1.5 mL of 97% HCO_2H on a steam bath for 2.5 h gave a single main product by TLC. Workup as described for **4b** followed by column chromatography gave 0.15 g of **4c**.

***cis,anti*-*N*-Methyl-11-hydroxy-1,2,3,4,4a,5,6,11a-octahydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (5b).** A mixture of **4b** (1.1 g, 0.0048 mol) and $LiAlH_4$ (1.0 g) in 50 mL of THF was heated under reflux for 22 h. An additional 1.0 g of $LiAlH_4$ was added, and reflux was continued for 3 h. The reaction mixture was cooled and hydrolyzed by the successive dropwise addition of H_2O (2 mL), 15% NaOH (2 mL), and H_2O (6 mL). The mixture was filtered, and the salts were washed with THF. The filtrate and washings were concentrated to give 0.9 g of crude **5b**. Column chromatography on 100 g of Baker silica gel (80–200 mesh) with 2–4% MeOH/CH_2Cl_2 gave 0.5 g (45%) of **5b** as an oil: IR (Nujol) 3205, 1485, 1455 cm^{-1}; H^1 NMR ($CDCl_3$) δ 2.52 (s, 3, *N*-CH_3), 5.00 (d, J = 8 Hz, 1, H_{11}); mass spectrum, m/e 231.

Anal. Found: C, 78.13; H, 9.51; N, 5.97.

***trans*,anti-*N*-Methyl-11-hydroxy-1,2,3,4,4a,5,6,11a-octahydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (5c).** Reaction of 8.0 g (0.035 mol) of **4c** with $LiAlH_4$ (2.7 g, 0.07 mol) in 200 mL of boiling THF for 26.5 h followed by hydrolytic workup in the same manner as in the preparation of **5b** gave 3.3 g (41% from MeOH) of **5c**: mp 105–110 °C; IR (Nujol) 3300, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.46 (s, 3, *N*-CH_3), 4.70 (d, J = 8.5 Hz, 1, H_{11}); mass spectrum, m/e 231.

Anal. Found: C, 78.10; H, 9.33; N, 6.13.

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Registry No. 1, 3964-73-6; 2, 19370-08-2; **3a**, 74610-13-2; **3b**, 74645-06-0; **3c**, 74645-07-1; **3d**, 74645-08-2; **4b**, 74610-14-3; **4b**·hemifumarate, 74645-09-3; **4c**, 74645-10-6; **4c**·fumarate, 74708-06-8; **5a**, 74610-15-4; **5b**, 74645-11-7; **5c**, 74645-12-8; **5d**, 74645-13-9.