Reaction of 5 with Hydroxide Ion.—Aqueous sodium hydroxide (1%, 50 ml) was added to a solution of 2.62 g (8.78 mmol) of **5** in 100 ml of acetonitrile. The solution became green and a green solid precipitated. Extraction with chloroform and repeated chromatography of the chloroform soluble material on silica columns gave 300 mg (1.5 mmol, 17%) of phenothiazine, 210 mg (0.53 mmol, 6%) of 3,10′-biphenothiazine, and 24 mg (0.11 mmol, 1.3%) of 3-phenothiazone. At least four other products were present but were not identified.

Registry No.—**1**, 21299-20-7; **2**, 2362-50-7; **3**, 34874-72-1; **5**, 34874-73-2; **7**, 34874-74-3; phenothiazine, 92-84-2.

7,8,9-Trimethoxy-1,2,3,4,4a,5,6,10b-octahydro- and 7,8,9-Trimethoxy-1,2,3,4,4a,10b-hexahydrophenanthridines. Synthesis and Stereochemistry of Certain 6-Substituted and 5,6-Disubstituted Derivatives[1]

BETTY R. LOWRY AND ALAIN C. HUITRIC*

College of Pharmacy, University of Washington, Seattle, Washington 98105

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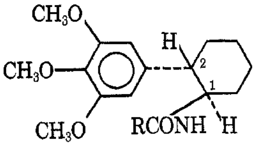
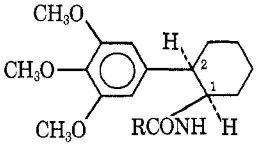
The diastereomers of 6-methyl and of 6-*o*-hydroxyphenyl derivatives of 7,8,9-trimethoxy-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine, obtained by the Pictet–Spengler reaction, were characterized by nmr. 7,8,9-Trimethoxy-4a,10b-*trans*-1,2,3,4,4a,10b-hexahydrophenanthridine (**7**), its 6-methyl derivative **9**, and the 4a,10b-cis isomer **8** and its methyl derivative **10** were prepared by the Bischler–Napieralski reaction from the appropriate amides **3–6**. Conformations of **8** and **10** were established by nmr in deuteriochloroform and rotational isomerism of the amides is discussed. Catalytic hydrogenation of **9** and **10** yielded only the isomer having the methyl group trans to H-4a in each case, compounds **11** and **15**, respectively. The conformation of the cis compound **15** was established by nmr. Epimerization studies of the hydrochloride salts of the *N*-methyl derivatives of **11** and **12** (compounds **16** and **17**, respectively) in formic acid showed that for **16** the equilibrium is essentially in the direction of a single epimer having the two methyl groups trans to each other, while at equilibrium **17** shows a mixture with at least 75% of the epimer having the methyl groups trans.

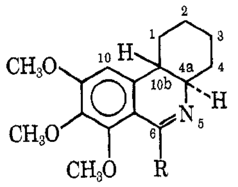
In a preceding paper[2] we have discussed the stereochemistry and epimerization of salts of N-substituted 7,8,9-trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines prepared from *trans*- (**1**) and *cis*-2-(3,4,5-trimethoxyphenyl)cyclohexylamine[3] (**2**) *via* the Pictet–Spengler reaction. The present paper deals with the stereochemistry of 6-substituted and 5,6-disubstituted derivatives and their preparation by the same route and by the Bischler–Napieralski cyclodehydration of the appropriate amides of **1** and **2**. The 7,8,9-trimethoxy-1,2,3,4,4a,10b-hexahydrophenanthridine intermediates of the Bischler–Napieralski reaction were of interest from a pharmacological standpoint in addition to being potential sources of specific stereoisomers of the 6-substituted octahydro series because of probable stereoselectivity in the catalytic hydrogenation step, as was actually shown to be the case (*vide infra*).



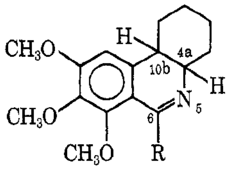
3, $R = H$
5, $R = CH_3$



4, $R = H$
6, $R = CH_3$



7, $R = H$
9, $R = CH_3$



8, $R = H$
10, $R = CH_3$

Results and Discussion

7,8,9-Trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,4,4a,10b-hexahydrophenanthridines and 6-Methyl Derivatives.—A wide variety of condensing agents and solvents have been used in the Bischler–Napieralski reaction.[4] In the present study yields of better than 90% of the hydrochloride salts of **7**, **8**, **9**, and **10** were obtained by use of phosphorus oxychloride in chlorobenzene with the appropriate amides **3–6**.

The nmr spectra of amides **3**, **4**, and **6** show the presence of amide C–N bond rotational isomers, but no evidence of two isomers was found in **5**. The ratio of isomers, estimated from the integration of the signals of the aromatic hydrogens which give a singlet for each isomer, was found to be about 6:1 for **3**, 5:4 for **4**, and 7:1, or more, for **6**. Published data on isomerism of secondary amides[5] indicate a usual predominance of the isomer having a trans orientation of the N substituents and the R or H on the carbonyl carbon. Our results are in agreement with this. In the formamides **3** and **4** the signal of the formyl hydrogen of the major isomer in each case gives a doublet with a coupling constant of 2 Hz between the formyl and NH protons, while the doublet for the minor isomer has a coupling constant of 12 Hz, consistent with a trans orientation of the coupled hydrogens in the minor isomer. This assignment is also supported by the fact that the signal of the formyl hydrogen, or the acyl methyl group, of the minor isomer is at higher field than that of the major isomer in each case. Molecular models in-

[1] This investigation was supported by Grant MH 12204 from the National Institute of Mental Health, U. S. Public Health Service. The compounds were submitted to Eli Lilly and Company for pharmacological evaluation.

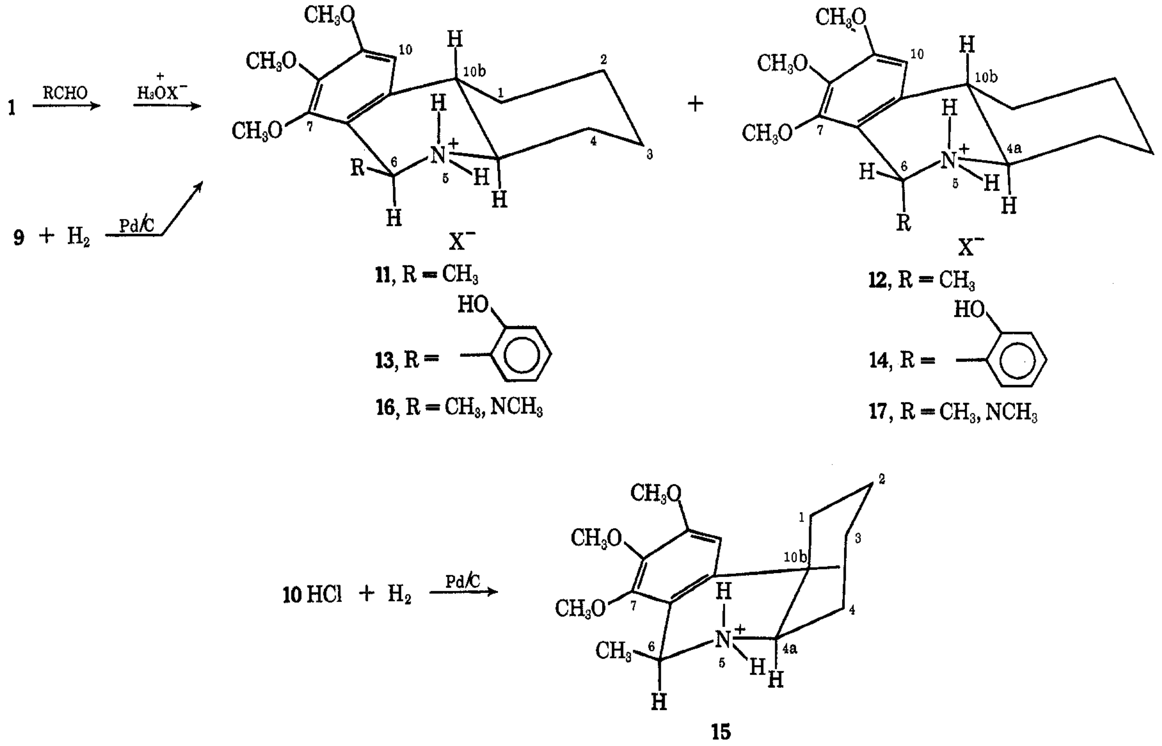
[2] B. R. Lowry and A. C. Huitric, *J. Org. Chem.*, submitted for publication.

[3] W. F. Trager and A. C. Huitric, *J. Pharm. Sci.*, **54**, 1552 (1965).

[4] W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 74 (1951).

[5] W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1971).

Scheme I



dicate that these groups should experience a greater shielding effect from the magnetic anisotropy of the aromatic ring when the groups have a cis orientation to the N substituent.

There is more conformational mobility in the *cis*-hexahydrophenanthridines **8** and **10**, where inversion of the cyclohexane ring is possible, than in the trans isomers **7** and **9** where only one chair form of the cyclohexane ring is possible. The nmr data indicate that in deuteriochloroform the cis compounds **8** and **10**, as well as their hydrochloride salts, have a predominance of that chair conformation of the cyclohexane ring in which H-4a has an axial orientation and H-10b is equatorial. This conclusion is based on a comparison of the spectra of the cis compounds with those of the corresponding trans isomers. For any of the cis compounds in the conformation where H-4a is axial and H-10b is equatorial the hydrogen H-10b has the asme relative position to the aromatic ring as in the trans isomer, but H-4a lies essentially in the plane, and in the deshielding region, of the imine double bond and the aromatic ring. In the inverted chair conformation it is H-4a that has the same relative position to the imine and aromatic groups as in the trans isomer while H-10b now lies in the deshielding region of the aromatic ring. For every cis compound the chemical shift of H-4a is from 0.6 to 0.7 ppm downfield from the position for the corresponding trans isomer, while the chemical shift of H-10b is downfield by about 0.1 to 0.3 ppm compared to the trans isomer. The patterns of the signals of the methylene hydrogens of the cyclohexane ring for the cis compounds are also consistent with a predominance of the conformation having H-4a axial and H-10b equatorial. The signals of these hydrogens give a fairly narrow envelope ($W_{1/2} \cong$ 15–19 Hz) accounting for seven protons which is centered at τ 8.5 for the free bases **8** and **10** and at τ 8.3 for their hydrochloride salts, and in each case there is a downfield signal accounting for one hydrogen in the region of τ 7.8–7.9 for the free bases and slightly lower for the salts. This downfield signal is attributed to the equatorial proton on C-1, which in the proposed conformation falls in the deshielding region of the aromatic ring. In the trans isomers both protons on C-1 experience a deshielding effect from the aromatic ring and the signal of the remaining six methylene protons give a broad envelope spread over a region of about 50 Hz.

Allylic coupling of about 3 Hz occurs between H-6 and H-4a in **7** and **8**, and of about 2 Hz in their hydrochloride salts. Homoallylic coupling[6] of about 2 Hz is seen between H-4a and the C-6 methyl protons in **9** and **10**, and of about 1.8 Hz in the salts following deuterium exchange with D_2O.

7,8,9-Trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,-4,4a,5,6,10b-octahydrophenanthridines and Derivatives. —In the preparation of 7,8,9-trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines, good yields were obtained by refluxing the hydrochloride salts of **1** and **2** with formaldehyde in ethanol.[2] This method was not so successful with other aldehydes. The best yields of the cyclization product of **1** with acetaldehyde, and salicylaldehyde, were obtained by preformation of the imines followed by treatment with acid. With acetaldehyde the ratio of H-6,4a-cis and H-6,4a-trans isomers varied with temperature. Treatment of the imine with 20% aqueous sulfuric acid at room temperature yielded **11** and **12** in ratio of about 2:1, while at 80° about equal amount of the two isomers was obtained (Scheme I). With salicylaldehyde, heating the imine to reflux in 10% sulfuric acid in 50% aqueous methanol gave **13** and **14** in a ratio of about 17:2. The ratio of **11** and **12** was estimated from the intensities of the nmr C-6 methyl

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[6] L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, pp 326, 327.

signals of the free bases which, in pyridine in the presence of slight amount of D_2O, appear as doublets at τ 8.40 for **11** and τ 8.46 for **12**. In the absence of D_2O the two signals overlap at τ 8.46. Since the signals appear in the region of the cyclohexane envelope absorption, only an estimate of the ratio of isomers is possible.

Separation of **11** and **12** was accomplished by fractional crystallization of the *p*-toluenesulfonate salts from methanol. Progress of the separation was followed by melting points and by nmr in 1:1 formic acid–deuterium oxide solution. The head fraction (**12**) was characterized by higher melting point and higher field 6-CH_3 doublet, τ 8.30 compared to τ 8.27 for isomer **11** enriched in the mother liquors.

The assignment of configurations to **11** and **12** is based on the nmr spectra of the hydrochloride salts in deuteriochloroform and supported by the fact that catalytic hydrogenation of **9** yielded almost exclusively **11**. The nmr spectra of the hydrochloride salts of **11** and **12** differ mostly in the chemical shifts of the C-6 methyl signals and the ammonium protons. The chemical shift of H-6 is essentially the same in both isomers. The chemical shift of 6-CH_3 is at lower field (τ 8.10) for **11** than for **12** (τ 8.24). In view of the long-range effects of the magnetic anisotropy of the aromatic ring,[7] and assuming that the half-chair is the predominant conformation of the heterocyclic ring, the data are consistent with a pseudoequatorial orientation of the methyl group in **11** and a pseudoaxial orientation in **12**. This assignment is supported by the chemical shifts of the ammonium protons which are equivalent at τ 0.00 in the hydrochloride salt **12** but are at τ -0.50 and $+0.63$ in the hydrochloride **11**. The chemical shifts of the ammonium protons in **12** remained equivalent upon addition of trifluoroacetic acid, showing that the equivalence in **12** is not the result of a more rapid proton exchange than in **11**. The effect of a methyl group on C-6 will be to shield the H-5 proton cis to the methyl,[2] causing an upfield shift of the axial H-5 in **11** and thus causing an increase in the difference between the chemical shifts of these two protons. In **12** the effect is to shield the equatorial ammonium proton and thus decrease the difference between the chemical shifts of the two protons.

Separation of **13** and **14** was accomplished by taking advantage of a significant solubility of the hydrochloride salt of **14** in benzene. The assignment of configuration is based on the difference of the nmr signals of the methoxy groups in the two isomers. The spectrum of the free base of the minor isomer **14** in deuteriochloroform shows the overlapping of the signals of two methoxy groups at τ 6.11 and the signal of the third group at τ 6.20. Under the same conditions there is a considerable upfield shift of the signal of one of the methoxy groups in the spectrum of the major isomer **13**, where the chemical shifts of the methoxy groups are τ 6.16, 6.20, and 6.62. In the parent compound,[2] unsubstituted at C-6, two of the signals overlap at τ 6.15 and the third is at τ 6.17. Infrared studies of chloroform and carbon tetrachloride solutions showed intramolecular hydrogen bonding of the phenolic hydrogen in both isomers. Molecular models indicate that for intramolecularly hydrogen bonded conformations, a greater shielding of the C-7 methoxy group by the phenolic atomatic ring is expected in isomer **13** than in isomer **14**.

Catalytic reductive alkylation[2] of **11** with formaldehyde yielded 5,6-dimethyl-7,8,9-trimethoxy-H6,4a-*cis*-4a,10b-*trans*-1,2,3,4,4a,5,6-10b-octahydrophenanthridine (**16**), and, correspondingly, **12** gave 5,6-dimethyl-7,8,9-trimethoxy-H6,4a-*trans*-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (**17**), both in good yields. It was of interest to compare the epimerization of the salts of the tertiary amines **16** and **17** with the results obtained by nmr with the 6-nor analogs[2] under conditions of slow proton exchange. The results indicate that the hydrochloride salts of **16** and **17**, obtained from crystallization from a mixture of ethyl acetate and 2-propanol, each had crystallized in a single epimeric form.

The nmr spectrum of the hydrochloride salt of **16** in formic acid exhibits a single NCH_3 signal which appears as a doublet (J_{NHCH_3} = 5 Hz) at τ 6.83, and a single C-6 methyl signal which appears as a doublet (J_{CHCH_3} = 6.6 Hz) at τ 8.22. Addition of sodium formate to catalyze the equilibration of N epimers did not cause the appearance of either a second NCH_3 doublet, as was the case with the 6-nor analog,[2] nor a second 6-CH_3 signal. This indicates that in formic acid the thermodynamic equilibrium for protonated **16** is far in the direction of a single epimer. From steric consideration this is expected to be the isomer with the methyl groups trans to each other (structure **11** with an equatorial NCH_3 group). In this epimer the NCH_3 group is gauche to only two groups, the C-6 methyl and C-4 methylene groups, while in the other epimer it is gauche to four groups and experiences 1,3-diaxial repulsion from the C-4 and C-10b hydrogens. This assignment is substantiated by the chemical shift of the NCH_3 signal, which is identical with that of the NCH_3 group of the epimer of the 6-nor analog having the equatorial NCH_3 in formic acid.[2] The coupling between H-6 and NH, as measured from the signal of H-6, is only about 4 Hz, while a value of at least 8 Hz is expected between the pseudoaxial CH and adjacent axial NH protons. This suggests a reduction of the dihedral angle which could result from a deformation of the half-chair conformation due to repulsion of the adjacent methyl groups, or it could result from an equilibrium between the half-chair and a boat conformation.

The nmr spectrum of the hydrochloride salt of **17** in formic acid exhibits a single NCH_3 signal as a doublet ($J_{NHCH_3} \cong 5$ Hz) at τ 7.02, and a single C-6 methyl signal as a doublet (J_{CHCH_3} = 6.6 Hz) at τ 8.18. There was no sign of epimerization after standing for 2 days, but the addition of sodium formate caused the gradual appearance of a second NCH_3 doublet at τ 6.91 and a second C-6 methyl doublet at τ 8.33. Equilibration appeared complete within 6 hr. An accurate estimate of the ratio of epimers was not possible because the doublets overlap other signals, but at equilibrium there appeared to be at least 75% of the original epimer. Prior to equilibration the signal of H-6 appears as a quartet (J_{CHCH_3} = 6.6 Hz). There is no evidence of coupling between H-6 and the adjacent NH. This implies a dihedral angle of about 90° between H-6 and NH. This is approximately what is expected for a structure with the hetero ring in a half-chair confor-

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(7) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

mation and with the C-6 methyl in a pseudoaxial orientation and the NCH_3 group in an axial orientation. The downfield position of the NCH_3 signal of the minor epimer implies an isomerization from an axial to an equatorial position. The upfield position of the 6-CH_3 signal in the minor epimer could result from repulsion between the cis methyl groups causing the 6-CH_3 group to be further out of the plane of the aromatic ring.

Catalytic hydrogenation of the hydrochloride salt of **10** yielded only one product. Cis addition to the imine double bond is expected to give the H-6,4a-cis isomer **15**. This structure is supported by nmr data of the hydrochloride salt in deuteriochloroform. The chemical shift of the C-6 methyl group and the nonequivalence and patterns of the signals of the ammonium protons are consistent with the half-chair, chair conformation shown by structure **15** where the C-6 methyl group has a pseudoequatorial orientation. In this conformation H-4a and H-10b have equatorial and axial orientations, respectively, in relation to the cyclohexane ring. The 6-CH_3 signal appears as a doublet at τ 7.92. The chemical shift implies a similar orientation of the methyl group to the aromatic ring as in **11**. The signal of one of the ammonium protons is at τ -1.10 and the other at τ 1.47. This large difference in chemical shifts supports structure **15** where the effect of the C-6 methyl group is to shield the axial H-5 proton cis to the methyl, thus increasing the difference in chemical shifts between the equatorial and axial NH protons. The upper field signal is considerably broader than the signal at τ -1.10, and this is consistent with the signal at τ 1.47 belonging to axial H-5 coupled with axial H-4a and pseudoaxial H-6. In the spectrum of the free base in deuteriochloroform the signal of H-4a occurs as a fairly narrow, unresolved multiplet, $W_{1/2} = 8$ Hz, at τ 6.99 and the signal of H-10b occurs at τ 7.62 as a much broader signal. This implies an equatorial orientation of H-4a and an axial orientation of H-10b in relationship to the cyclohexane ring, and the same predominant conformation in chloroform as for the hydrochloride salt.

Experimental Section

Microanalyses were performed by Alfred Berhardt, Mulheim, Germany, and Huffman Laboratories, Wheatridge, Colo. Melting points were determined on a Kofler hot stage unless otherwise indicated. Heat sensitivity of most of the salts necessitated placement of samples on the hot stage within about 5–10° of the melting point for most consistent results.

Nuclear magnetic resonance spectra were recorded in the presence of an internal tetramethylsilane standard on Varian A-60 or T-60 spectrometers operating at temperatures of about 33–35°. Infrared spectra of solids and neat liquids were determined on a Beckman IR-5a spectrophotometer and solution spectra were recorded on a Beckman IR-20 spectrophotometer. Matched cells (0.1 and 1 mm) were used for solution spectra in chloroform. The dilute sample of **13** in carbon tetrachloride was determined using a Beckman variable path cell at 3 mm, without reference cell. Spectral grade solvents were used.

***trans*-2-(3,4,5-Trimethoxyphenyl)cyclohexylformamide (3).**—A mixture of 531 mg (2.0 mmol) of **1**, 1.00 g (*ca.* 22 mmol) of 99% formic acid, and 35 ml of benzene was heated under gentle reflux for 21 hr. Water azeotrope was collected as formed in a water separator. After cooling, an additional 20 ml of benzene was added and the unreacted amine was removed by extraction with 5% HCl (15 ml in two portions). Upon work-up, these acid extracts produced 60 mg (11%). The benzene solution was washed neutral with 5% $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated under reduced pressure. The viscous crude product, 0.50 g, was chromatographed on 15 g of silica gel using dry column technique starting with ethyl ether and progressing to a 3:1 ether–acetone mixture. Product fractions were combined and crystallized from ethyl ether with gradual addition of hexane at room temperature, yielding 432 mg (74%) of formamide **3** as colorless cubes: mp 101–102°; ir (solid, KBr) 3360 (NH), 1660 cm^{-1} (C═O); nmr ($CDCl_3$) τ 2.10 (d, <1, J = 2 Hz, CHO, major), 2.33 (d, <1, J = 12 Hz, CHO, minor), 3.55 (s, <2, ArH, major), 3.61 (s, <2, ArH, minor), 4.33 (m, <1, NH, major), ~6.2 (m, <1, H-1, major), ~7.7 (m, ~1, H-2).

Anal. Calcd for $C_{16}H_{23}O_4N$: C, 65.51; H, 7.90; N, 4.78. Found: C, 65.40; H, 7.75; N, 4.74.

***cis*-2-(3,4,5-Trimethoxyphenyl)cyclohexylformamide (4).**—Application of the above formylation procedure to **2** regenerated from 2.11 g (7.00 mmol) of the hydrochloride, with the reflux period extended to 60 hr, gave crude crystalline product directly upon evaporation of the benzene solution. Recrystallization from benzene yielded 1.833 g (89%) of **4** as colorless crystals, mp 177.5–180.5°. A sample recrystallized from acetone for analysis gave colorless cubes: mp 176.5–179°; ir (KBr, solid) 3240 (NH), 1680 cm^{-1} (C═O); nmr ($CDCl_3$) τ 2.00 (d, <1, J = 2 Hz, CHO, major), 2.60 (d, <1, J = 12 Hz, CHO, major), 3.53 (s, <2, ArH, major), 3.60 (s, <2, ArH, minor), ~2.9 (m, <1, NH, minor), 3.86 (m, <1, NH, major), 5.5 (m, <1, H-1), 6.3 (m, <1, H-1), 7.2 (m, ~1, H-2).

Anal. Calcd for $C_{16}H_{23}O_4N$: C, 65.51; H, 7.90; N, 4.78. Found: C, 65.58; H, 8.00; N, 5.12.

***trans*-2-(3,4,5-Trimethoxyphenyl)cyclohexylacetamide (5).**—A cold solution of 1.061 g (4.00 mmol) of **1** in 20 ml of pyridine was treated with 1.0 g (10 mmol) of acetic anhydride with stirring, and then the reaction flask was protected with a drying tube and left at room temperature for 91 hr. After the reaction mixture was rechilled and treated with 5 ml of methanol to destroy excess acetic anhydride, it was evaporated under reduced pressure. The residue was dissolved in 100 ml of benzene and the resulting solution was washed successively with 5% HCl, water, 5% $NaHCO_3$ solution, and water to neutrality, then dried (Na_2SO_4) and evaporated. Crystallization of the residue from benzene afforded 1.213 g (98%) of **5** as fine, colorless needles: mp 141–141.5°; ir (KBr, solid) 3320 (NH), 1640 cm^{-1} (C═O); nmr ($CDCl_3$) τ 3.57 (s, 2, ArH), 4.37 (d, 1, J = 8 Hz, NH), 6.0 (m, 1, H-1), 7.6 (m, 1, H-2), 8.28 (s, 3, $COCH_3$).

Anal. Calcd for $C_{17}H_{25}O_4N$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.18; H, 8.10; N, 4.71.

***cis*-2-(3,4,5-Trimethoxyphenyl)cyclohexylacetamide (6).**—N-Acetylation of **2**, as described above, followed by crystallization from benzene, gave 94% of acetamide **6**: mp 157.5–159.5°; ir (solid, KBr) 3320 (NH), 1630 cm^{-1} (C═O); nmr ($CDCl_3$) τ 3.51 (s, <2, ArH, major), 3.58 (s, <2, ArH, minor), 3.85 (d, <1, J = 8 Hz, NH, major), 5.65 (m, <1, H-1, major), ~7.2 (m, ~1, H-2), 8.17 (s, <3, $COCH_3$, major), 8.53 (s, <3, $COCH_3$, minor).

Anal. Calcd for $C_{17}H_{25}O_4N$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.15; H, 8.13; N, 4.60.

Bischler–Napieralski Cyclization of *cis*- and *trans*-2-(3,4,5-Trimethoxyphenyl)cyclohexylamides.—Reagent grade chlorobenzene and phosphorus oxychloride were used without purification. Removal of traces of moisture from the apparatus, solvent, and starting amide was accomplished simultaneously by distillation of a few milliliters of the chlorobenzene. The resulting dry amide–chlorobenzene solution was then cooled prior to $POCl_3$ addition. The operations described below for **7** are typical of procedures applied in all cases. In cognate preparations, reaction times of 2–3 hr were allowed, although the vigorous HCl evolution during the initial heating period suggested that cyclization is quite rapid. A large excess (7–9 equiv) of $POCl_3$ was used in all instances.

7,8,9-Trimethoxy-4a,10b-*trans*-1,2,3,4,4a-10b-hexahydrophenanthridine (7) Hydrochloride.—With stirring at room temperature, 3.0 ml (*ca.* 33 mmol) of $POCl_3$ was added to a dry solution of 1.027 g (3.50 mmol) of **3** in 40 ml of chlorobenzene. The stirred mixture was slowly heated to gentle reflux for 3 hr. After cooling, the mixture was treated dropwise with 10 ml of water at a rate slow enough to prevent vigorous exothermic reaction with excess $POCl_3$. The resulting warm two-phase system was cooled, the aqueous layer was separated, and the chlorobenzene solution was extracted with two 5-ml portions of 5% HCl solution. The combined aqueous acid extracts were washed with three 10-ml portions of carbon tetrachloride and cooled in an ice bath. With stirring, the solution was made basic with KOH and the hexahydrophenanthridine was extracted with a total of 125 ml of benzene. The benzene solution was dried (Na_2SO_4) and concentrated to about 25 ml, diluted with 100 ml of petroleum ether (bp 30–60°), and saturated with HCl gas. Removal of solvents under reduced pressure and crystallization of the residue from 2-propanol–ethyl acetate gave 987 mg (90%) of the hydrochloride of **7** as nearly colorless crystals: mp 184–185° dec (with gas evolution); ir (solid, KBr) 2670, broad (NH$^+$), 1640 cm^{-1} (C═N); nmr (CDCl$_3$), **7** HCl, τ −4.5 (1, NH), 1.18 (dd, 1, H-6, $J \cong$ 8.5 and 2 Hz), 3.22 (s, 1, H-10), 5.87 (s, 6, OCH$_3$), 6.11 (s, 3, OCH$_3$), $\sim$6.4 (m, 1, H-4a), $\sim$7.2–7.3 (m, 3, H-10b and H-1); free base **7**, τ 1.48 (d, 1, H-6, $J \cong$ 3 Hz), 3.38 (s, 1, H-10), 6.03 (s, 3, OCH$_3$), 6.08 (s, 3, OCH$_3$), 6.13 (s, 3, OCH$_3$), $\sim$7.0 (m, 1, H-4a), $\sim$7.6 (m, 3, H-10b and H-1).

Anal. Calcd for $C_{16}H_{22}O_3NCl$: C, 61.63; H, 7.11; N, 4.49. Found: C, 61.58; H, 7.23; N, 4.55.

7,8,9-Trimethoxy-4a,10b-*cis*-1,2,3,4,4a,10b-hexahydrophenanthridine (8) Hydrochloride.—The hydrochloride of **8** was obtained in 95.1% yield as long plates, mp 177.5–178° dec (with gas evolution), after crystallization from 2-propanol–ethyl acetate: ir (solid, KBr), 2670, broad (NH$^+$), 1640 cm^{-1} (C═N); nmr (CDCl$_3$), **8** HCl, τ −4.4 (1, NH), 1.13 (dd, 1, H-6, $J \cong$ 7.5 and 2 Hz), 3.15 (s, 1, H-10), 5.85 (s, 3, OCH$_3$), 5.88 (s, 3, OCH$_3$), 6.10 (s, 3, OCH$_3$), $\sim$5.85 (m, 1, H-4a), $\sim$6.9 (m, 1, H-10b), $\sim$7.5 (m, 1, H-1); free base **8**, τ 1.33 (d, 1, H-6, $J \cong$ 3 Hz), 3.53 (s, 1, H-10), 6.03 (s, 3, OCH$_3$), 6.10 (s, 3, OCH$_3$), 6.14 (s, 3, OCH$_3$), $\sim$6.3 (m, 1, H-4a), $\sim$7.4 (m, 1, H-10b), $\sim$7.8 (m, 1, H-1).

Anal. Calcd for $C_{16}H_{22}O_3NCl$: C, 61.63; H, 7.11; N, 4.49. Found: C, 61.39; H, 7.08; N, 4.76.

6-Methyl-7,8,9-trimethoxy-4a,10b-*trans*-1,2,3,4,4a,10b-hexahydrophenanthridine (9) Hydrochloride.—2-Propanol–ethyl acetate crystallization of the Bischler–Napieralski cyclization product of **5** gave the hydrochloride of **9** in 94% yield: mp 182.5–183.5° dec; ir (KBr, solid) 2680, broad (NH$^+$), 1630 cm^{-1} (C═N); nmr (CDCl$_3$), τ −4.13 (1, NH), 3.22 (s, 1, H-10), 5.95 (s, 6, OCH$_3$), 6.15 (s, 3, OCH$_3$), $\sim$6.7 (m, 1, H-4a), 6.97 (b s, 3, 6-CH$_3$), $\sim$7.3 (m, 3, H-10b and H-1).

Anal. Calcd for $C_{17}H_{24}O_3NCl$: C, 62.66 H, 7.42 N, 4.30. Found: C, 62.47; H, 7.44; N, 4.40.

The free amine **9**, obtained from base treatment of the hydrochloride salt, was crystallized from hexane: mp 113–115° ir (solid, KBr) 1610 cm^{-1} (C═N); nmr (CDCl$_3$), τ 3.38 (s, 1, H-10), 6.10 (s, 6, OCH$_3$), 6.15 (s, 3, OCH$_3$), 7.55 (d, 3, 6-CH$_3$, $J \cong$ 1.7 Hz), 7.3 (m, 1, H-4a), $\sim$7.6 (m, 3, H-10b and H-1).

6-Methyl-7,8,9-trimethoxy-4a,10b-*cis*-1,2,3,4,4a,10b-hexahydrophenanthridine (10) Hydrochloride.—Bischler–Napieralski cyclization of **6** produced the hydrochloride of **10**, mp 173–175° (Fisher-Johns), in 94% yield upon crystallization from 2-propanol–benzene. Recrystallization from 2-propanol–ethyl acetate gave small cubes: mp 171–172° dec (with gas evolution); ir (solid, KBr) 2720, broad (NH$^+$), 1630 cm^{-1} (C═N); nmr (CDCl$_3$), τ −4.4, (1, NH), 3.22 (s, 1, H-10), 5.93 (s, 6, OCH$_3$), 6.13 (s, 3, OCH$_3$), $\sim$6.0 (m, 1, H-4a), 6.92 (d, 3, 6-CH$_3$, $J \sim$ 1.8 Hz), $\sim$7.2 (m, 2, H-10b and H-1).

Anal. Calcd for $C_{17}H_{24}O_3NCl$: C, 62.66 H, 7.42; N, 4.30. Found: C, 62.64; H, 7.52; N, 4.58.

A sample of the amine **10**, prepared by base treatment of its hydrochloride salt, and recrystallization from hexane, had mp 97–98°; ir (solid, KBr) 1610 cm^{-1} (C═N); nmr (CDCl$_3$), τ 3.50 (s, 1, H-10), 6.10 (s, 6, OCH$_3$), 6.17 (s, 3, OCH$_3$), 6.65 (m, 1, H-4a), 7.52 (d, 3, 6-CH$_3$, $J \cong$ 2.2 Hz), $\sim$7.6 (m, 1, H-10b), $\sim$7.9 (m, 1, H-1).

6-Methyl-7,8,9-trimethoxy-4a-6*H*-*cis*- and -4a,6*H*-*trans*-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines (11 and 12).—Excess acetaldehyde was bubbled through a stirred solution of 5.31 g (20.0 mmol) of **1** in 100 ml of benzene under nitrogen. The solution became turbid, then water separated. When no turbidity remained, the benzene solution was dried (Na_2SO_4) and evaporated under reduced pressure. The azomethine produced was a nearly colorless oil. This intermediate was cooled in an ice bath and dissolved in 50 ml of 20% H_2SO_4. After 4 days at room temperature partial crystallization occurred from the aqueous mixture. The sulfate salts were extracted with chloroform (200 ml in three portions), and the chloroform extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was redissolved in 25 ml of water and washed with CCl$_4$ and benzene to remove any nonbasic impurities. The free base mixture was regenerated by treatment of the cold, stirred aqueous solution with excess KOH, and was extracted with benzene (175 ml in four portions). Drying (Na_2SO_4) and evaporation to constant weight gave 5.56 g (95%) of a crude liquid mixture of **11** and **12**. This material, upon examination by nmr in pyridine containing a small amount of D$_2$O, exhibited two doublets at τ 8.40 and 8.46 (6-methyl) in a ratio of about 2:1.

Separation of 11 and 12 *via* *p*-Toluenesulfonic Acid Salts.—A cooled solution of the crude mixture of **11** and **12** free bases was treated with a methanolic solution of 3.80 g (20 mmol) of *p*-toluenesulfonic acid hydrate. The resulting acidic solution was evaporated under reduced pressure. Crystallization of the residue from methanol and water, followed by filtration, washing of the crystals with water to remove excess *p*-toluenesulfonic acid, and drying, afforded a quantitative yield of impure salts. The nmr of this mixture in 1:1 formic acid–deuterium oxide exhibited two 6-methyl doublets at τ 8.27 and 8.30 in an approximate ratio of 2:1. Recrystallization from methanol gave 6.7 g of a mixture of crystalline **11** and **12** *p*-toluenesulfonates, a 73% yield based on **1**. Extensive fractional crystallization from methanol with periodic recovery of the more soluble isomer from mother liquors with ethyl acetate afforded 1.76 g of **12** *p*-toluenesulfonate as head fractions, mp >260° (Fisher-Johns), 1.41 g of **11** *p*-toluenesulfonate as tail fraction, mp >204°–206° (Fisher-Johns), and 1.94 g of intermediate crystalline fractions in various stages of separation. Crystallization was continued to constant melting point for each isomer. Examination of separated *p*-toluenesulfonates of **11** and **12** by nmr in 1:1 formic acid–deuterium oxide in the τ 8.3 region indicated no contamination. By this separation procedure, the **11** isomer predominating in the Pictet–Spengler reaction was isolated in smaller amounts than **12** due to losses resulting from its markedly greater solubility in crystallization solvents.

6-Methyl-7,8,9-trimethoxy-4a,6*H*-*trans*-4a,10b-*trans*-1,2,3,4,-4a,5,6,10b-octahydrophenanthridine (12).—An analytical sample of **12** *p*-toluenesulfonate crystallized from methanol gave rocklike crystals, mp 264.5–266.5° dec.

Anal. Calcd for $C_{24}H_{33}O_6NS$: C, 62.18; H, 7.18; N, 3.20. Found: C, 62.04; H, 7.12; N, 3.17.

Amines were recovered from the respective *p*-toluenesulfonates by passage over a base-treated ion exchange column. A large excess of Amberlite IRA-401 was placed in a column with methanol. Excess methanolic KOH was passed over the resin, which was then washed with methanol until no longer basic to phenolphthalein.

A methanolic solution of **12** *p*-toluenesulfonate was passed over a column prepared as described above followed by methanol until no more product eluted. Evaporation, resolubilization in benzene, drying (Na_2SO_4), and reevaporation gave a quantitative yield of the liquid amine **12**: ir (liquid, neat) 3310 cm^{-1} (NH); nmr (pyridine + D$_2$O) τ 8.46 (d, 3, 6-CH$_3$, J = 6.5 Hz).

The hydrochloride of **12** was prepared in 93% yield by passage of a methanolic solution of **12** *p*-toluenesulfonate over a large excess of Amberlite IRA-401 ion exchange resin. The column was washed with methanol until no more material eluted. Addition of a small amount of HCl to the methanol solution improved the yield. Evaporation of the methanol solution and crystallization of the residue from methanol and ethyl acetate afforded **12** hydrochloride which was identical with a sample prepared from the amine **12**: mp 281–282.5° dec; ir (solid, KBr) *ca.* 2745 cm^{-1} (NH$_2$$^+$); nmr (CDCl$_3$) τ 0.0 (2, NH$_2$$^+$), 3.43 (s, 1, H-10), 5.25 (m, 1, H-6), 6.03 (s, 3, OCH$_3$), 6.17 (s, 6, OCH$_3$), 8.24 (d, 3, 6-CH$_3$, J = 6.8 Hz).

6-Methyl-7,8,9-trimethoxy-4a,6*H*-*cis*-4a,10b-*trans*-1,2,3,4,4a,-5,6,10b-octahydrophenanthridine (11).—Pure **11** *p*-toluenesulfonate crystallized from methanol as plates: mp 204–205.5° dec; ir (solid, KBr) *ca.* 2800 cm^{-1} (broad, NH$_2$$^+$).

Anal. Calcd for $C_{24}H_{33}O_6NS$: C, 62.18; H, 7.18; N, 3.02. Found: C, 62.34; H, 7.25; N, 2.95.

Passage of **11** *p*-toluenesulfonate over basic ion exchange resin as described for **12** also afforded **11** in high yield by the ion-exchange method described for **12** hydrochloride. This product and a sample prepared from the amine gave identical nmr spectra and melting points upon crystallization from methanol and ethyl acetate: mp 257–258.5° dec; ir (solid, KBr) *ca.* 2780 cm^{-1} (broad, NH$_2$$^+$); nmr (CDCl$_3$), τ −0.50 (1, 5-H$_e$), 0.63 (1, 5-H$_a$), 3.40 (s, 1, H-10), 5.25 (m, 1, H-6), 6.10 (s, 3, OCH$_3$), 6.15 (s, 6, OCH$_3$), 8.10 (d, 3, 6-CH$_3$, J = 6.6 Hz).

5,6-Dimethyl-7,8,9-trimethoxy-4a,6*H*-*trans*-4a,10b-*trans*-1,2,3,-4,4a,5,6,10b-octahydrophenanthridine (17).—A solution of **12** prepared from 1.39 g (3.00 mmol) of **12** *p*-toluenesulfonate by ion exchange was dissolved in 75 ml of ethanol and treated with a large excess (*ca.* 35 mmol) of 37% formaldehyde. This solution was hydrogenated at room temperature in the presence of 300 mg of 10% palladium on carbon at an initial hydrogen pressure of 30 psi. Hydrogen uptake was rapid for about 15 min, and no uptake was observed after 3 hr. The filtrate was acidified with glacial acetic acid and evaporated under reduced pressure. The residue was dissolved in 5 ml of water and the crude amine **17** was regenerated with excess KOH with cooling and stirring. Extraction with benzene, drying (Na_2SO_4), and evaporation gave crude **17** as a nearly colorless oil. Preparation of the hydrochloride and crystallization from ethyl acetate and 2-propanol yielded 929 mg (90%) of **17** hydrochloride, mp 245–256° dec with rapid sublimation. A sample recrystallized from 2-propanol gave mp 236–238° dec; ir (solid, KBr) 2480 cm^{-1} (broad, NH^+); nmr (HCOOH) τ 3.16 (s, 1, H-10), 5.27 (q, 1, H-6, J = 6.6 Hz), 6.00 (s, 3, OCH_3), 6.08 (s, 3, OCH_3), 6.10 (s, 3, OCH_3), 7.02 (d, 3, NCH_3, J = 5.2 Hz), 8.18 (d, 3, 6-CH_3, J = 6.6 Hz). After equilibration, doublets of the minor epimer appeared at τ 6.91 and 8.33 for the NCH_3 and 6-CH_3 groups, respectively.

Anal. Calcd for $C_{18}H_{28}O_3NCl$: C, 63.24; H, 8.26; N, 4.10. Found: C, 63.24; H, 8.13; N, 4.08.

5,6-Dimethyl-7,8,9-trimethoxy-4a,6*H*-*cis*-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (16).—Compound **11** prepared from 1.39 g (3.00 mmol) of **11** *p*-toluenesulfonate by ion exchange was methylated according to the catalytic reductive alkylation procedure described for **17**. Conversion of the crude **16** product to the hydrochloride and crystallization from ethyl acetate and 2-propanol gave 830 mg (81%) of **16** hydrochloride: mp 191–193.5° dec with sublimation; ir (solid, KBr) 2610 cm^{-1} (NH^+); nmr (HCOOH) τ 3.17 (s, 1, H-10), 5.23 (dq, 1, H-6, J = 6.6 and 4.0 Hz), 6.02 (s, 3, OCH_3), 6.08 (s, 3, OCH_3), 6.10 (s, 3, OCH_3), 6.83 (d, 3, NCH_3, J = 5.0 Hz), 8.22 (d, 3, 6-CH_3, J = 6.6 Hz).

Anal. Calcd for $C_{18}H_{28}O_3NCl$: C, 63.24; H, 8.26; N, 4.10. Found: C, 63.27; H, 8.23; N, 4.06.

Catalytic Hydrogenation of 6-Methyl-7,8,9-trimethoxy-4a,10b-*trans*-1,2,3,4,4a,10b-hexahydrophenanthridine (9).—A solution of 200 mg (0.691 mmol) of **9**, mp 113–115°, in 30 ml of ethanol was hydrogenated in the presence of 100 mg of 10% palladium on carbon at an initial pressure of 25 psi at room temperature. Hydrogen uptake slowed after about 20 min. After 1.5 hr, catalyst was filtered and washed with methanol. Evaporation of the filtrate under reduced pressure, addition of toluene, and reevaporation gave 189 mg of a slightly discolored oil. The nmr of this material in pyridine was identical with that of **11** and indicated the presence essentially of only one isomer, *p*-toluenesulfonate salt, mp 200–204°.

6-Methyl-7,8,9-trimethoxy-4a,6*H*-*cis*-4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (15).—A solution of 180 mg of the hydrochloride salt of **10** in 20 ml of ethanol was hydrogenated in the presence of 60 mg of 5% palladium on carbon for 45 min at an initial pressure of 25 psi at room temperature. The product was crystallized from absolute ethanol acidified with HCl gas, and then from absolute ethanol: mp 235–238° dec; nmr ($CDCl_3$) τ −1.10 (1, 5-H_e), 1.47 (1, 5-H_a), 3.57 (s, 1, H-10), 5.23 (m, 1, H-6), 6.11 (s, 3, OCH_3), 6.17 (s, 6, OCH_3), 7.92 (d, 3, 6-CH_3, J = 6.7 Hz).

Anal. Calcd for $C_{17}H_{26}O_3NCl$: C, 62.28; H, 8.00; N, 4.27. Found: C, 62.11; H, 8.12; N, 4.29.

6-(*o*-Hydroxyphenyl)-7,8,9-trimethoxy-4a,6*H*-*cis*- and -4a,6*H*-*trans*-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines.—A nitrogen atmosphere was maintained throughout the preparation of **13** and **14**. A mixture of 1.061 g (4.00 mmol) of **1** and 0.743 g (6.08 mmol) of redistilled salicylaldehyde was stirred and heated without solvent for 30 min, then 5 ml of benzene was added and distilled to azeotrope the water and drive the azomethine formation to completion. The resulting bright yellow residue was diluted with methanol (20 ml) and treated with 30 ml of 20% sulfuric acid. Addition of acid caused a rapid loss of the characteristic color. After 1 hr at reflux, the mixture had become essentially colorless. Heating was continued for a total of 24 hr. The reaction mixture was evaporated under reduced pressure until excess salicylaldehyde azeotroped. The concentrated solution partially crystallized on cooling, and was extracted with 60 ml of 5:1 chloroform and methanol, diluted with water (20 ml), and reextracted with chloroform. The crude salt of **1** (95 mg) was recovered from the aqueous phase. The combined chloroform extracts were dried (Na_2SO_4) and evaporated. The residue was redissolved in 30 ml of hot water, filtered, cooled, and washed with petroleum ether. The resulting aqueous solution was saturated with sodium carbonate, then extracted with benzene. Drying and evaporation gave 1.251 g of a cream-colored crystalline residue. A homogeneous sample of this material in deuteriochloroform was examined by nmr. After D_2O exchange, integration of signals for H-6 (**13**, **14**), total methoxy protons (**1**, **13**, **14**), and shielded methoxy (**13**) protons indicated 87% of cyclized products **13** and **14** in a ratio of 17:2. The proportion of cyclized products to **1** in the mixture, estimated from H-6 and the total aromatic proton signals, was in good agreement (86%) with that above, as was the estimation (85%) based on integrals for aromatic protons of **1** which are shielded with respect to all aromatic protons in **13** and **14**.

Crystallization of the mixture from benzene removed the more soluble starting material **1** and yielded 1.02 g (69%) of a mixture of **13** and **14**. The hydrochloride salts were prepared by bubbling HCl gas in a solution of the amines in benzene. The higher solubility of the hydrochloride of **14** in benzene allowed good separation of the two isomers.

The free base **13** was obtained from the hydrochloride salt and recrystallized from methanol and from a benzene–hexane mixture, to yield long, fine, colorless needles: mp 172–174°; ir ($CHCl_3$, 0.03 *M*) 3320 (NH), ~3100 cm^{-1} (broad) (bonded OH); ir (CCl_4, 0.01 *M*) 3320 (NH), ~3040 cm^{-1} (broad) (bonded OH); nmr ($CDCl_3$) τ 4.38 (s, 1, H-6), 6.16 (s, 3, OCH_3), 6.20 (s, 3, OCH_3), 6.62 (s, 3, OCH_3).

Anal. Calcd for $C_{22}H_{27}O_4N$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.46; H, 7.38; N, 3.99.

The hydrochloride of **13**, crystallized from a 2-propanol–benzene mixture, had mp 244–246° dec, and *p*-toluenesulfonate, crystallized from a methanol–water mixture, had mp 230–232° dec.

The free base of **14**, crystallized from benzene, gave colorless, dense crystals: mp 231–233°; ir ($CHCl_3$, 0.015–0.03 *M*), 3300 (NH), ~3080 cm^{-1} (bonded OH); nmr ($CDCl_3$) τ 4.41 (s, 1, H-6), 6.11 (s, 6, OCH_3), 6.20 (s, 3, OCH_3).

Anal. Calcd for $C_{22}H_{27}O_4N$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.40; H, 7.36; N, 3.76.

The *p*-toluenesulfonate of **14**, crystallized from a benzene–hexane mixture, had mp 234–236° dec.

Registry No.—**3**, 34913-46-7; **4**, 34913-47-8; **5**, 34913-48-9; **6**, 34913-49-0; **7** HCl, 34910-03-7; **8** HCl, 34910-04-8; **9**, 34910-05-9; **9** HCl, 34910-06-0; **10**, 34910-07-1; **10** HCl, 34910-08-2; **11**, 34910-09-3; **11** *p*-toluenesulfonate, 34910-10-6; **12**, 34910-11-7; **12** HCl, 34910-12-8; **12** *p*-toluenesulfonate, 34910-13-9; **13**, 34910-14-0; **13** HCl, 34910-15-1; **13** *p*-toluenesulfonate, 34910-16-2; **14**, 34910-17-3; **14** *p*-toluenesulfonate, 34910-18-4; **15** HCl, 34910-19-5; **16** HCl, 34910-20-8; **17** HCl, 34910-21-9; 7,8,9-trimethoxy-1,2,3,4,4a,5,6,10b-octahydrophenanthridine, 34910-22-0; 7,8,9-trimethoxy-1,2,3,4,4a,10b-hexahydrophenanthridine, 34910-23-1.