Several weeks at room temperature were required for the re-equilibration.

Hexafluoroacetone Dimethylhydrazone (4).—2,2,2-Trifluoro-1-(trifluoromethyl)ethylidenimine (11 ml) was bubbled into a chilled solution of 6.0 g of *N*,*N*-dimethylhydrazine in 25 ml of ether. After the addition was complete, the solution was warmed to room temperature and poured onto 30 g of phosphorus pentoxide.

Distillation gave only a trace of the desired hydrazone. The product was purified by gas chromatography on a 6 ft × 0.25 in. column of 20% silicone #200 on 60/80 Chromo "W." At 50° and 10 cc/min the retention time was 50 min; pmr (CCl_4) δ 3.24 (q, J = 1.2, q, J = 2.4 Hz).

Anal. Calcd for $C_5H_6F_6N_2$: mol wt, 208.0434. Found: mol wt, 208.0429 (high-resolution mass spectrum).

1-[1-(Trifluoromethyl)ethylidenehydrazono]-1-(trifluoromethyl)ethane.—To a stirred solution of 25 g of trifluoroacetone in 200 ml of ether at −30° was added dropwise 25 g of anhydrous hydrazine. An extremely exothermic reaction occurred. The solution was allowed to warm to room temperature and phosphorus pentoxide was added until further addition produced no change. The solution was distilled through a spinning-band column, giving 10 g of product as a pale yellow liquid: bp 58–62° (180 mm); ^{19}F nmr (CCl_4) δ −73.48 (s); pmr δ 1.5 (s); ir (CCl_4) 7.5, 8.3, 8.7, and 9.0 μ.

Anal. Calcd for $C_6H_6F_6N_2$: C, 32.8; H, 2.8. Found: C, 32.8; H, 3.0.

Trifluoroacetone Dimethylhydrazone.—To a solution of 11.2 g of trifluoroacetone in 25 ml of ether at −20° was added dropwise with stirring under nitrogen 6 g of *N*,*N*-dimethylhydrazine. The solution was stirred for 1 hr at room temperature after the addition was complete. Phosphorus pentoxide was added until no further exotherm was observed. The liquid was distilled through a small spinning-band column, giving 2.5 g of product as a colorless liquid: bp 100–103°; ir (CCl_4) 3.3, 3.45, 6.8, 6.9, 7.4, 8.3, 9.0, 9.8, 10.4, and 14.4 μ; pmr δ 2.00 (s, CCH_3), 2.67 (s, NCH_3).

Anal. Calcd for $C_5H_9F_3N_2$: mol wt, 154.0718. Found: mol wt, 154.0717 (high-resolution mass spectrum).

Registry No.—**1a** (X = NH_2), 34226-09-0; **1a** (X = OH), 34226-10-3; **1a** [X = $N(CH_3)_2$], 34226-11-4; **1a** [X = $N{=}C(CH_3)CF_3$], 34226-12-5; *cis*-**3**, 4639-94-5; *trans*-**3**, 4592-87-4; **4**, 34224-15-2.

7,8,9-Trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines. Configurational and Conformational Changes in Epimerization of N-Substituted Derivatives[1]

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Proton exchange 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 were studied by nmr. The hydrochloride salts of the *N*-methyl derivatives of the trans and cis isomers each crystallize to give only one epimeric form, **5a** and **6a**, respectively. In formic acid proton exchange and equilibration of epimers are relatively slow processes and the equilibration is catalyzed by sodium formate. Crystalline **5a** dissolved in formic acid is shown to have the cyclohexane and hetero rings in chair and half-chair conformations, respectively, with the *N*-methyl group in equatorial orientation and cis to H-4a. Epimerization of **5a** involves an inversion of the nitrogen without any change in conformations of the six-membered rings. The nmr data for the crystalline cis isomer **6a**, in formic acid, indicates chair and half-chair conformations of the two rings, with H-4a having an equatorial orientation relative to the cyclohexane ring and being axial relative to the hetero ring, with the *N*-methyl group equatorial and cis to H-4a. Epimerization to **6b** is associated with an inversion of conformation of the hetero and cyclohexane rings; thus the *N*-methyl group has an equatorial orientation in both epimers. Exchange processes were also investigated to a limited extent in other solvents, including chloroform-*d*, trifluoroacetic acid, and D_2O. The conformations of the free bases are also discussed.

7,8,9-Trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines and a number of N-substituted derivatives have been prepared by known methods from *trans*- and *cis*-2-(3,4,5-trimethoxyphenyl)cyclohexylamines[2] (**1** and **2**) for pharmacological evaluation.

Under conditions of slow proton exchange on the nmr time scale, the nmr spectra of the salts of the tertiary amines showed an equilibration between two geometrical isomers. This epimerization was studied more extensively in the hydrochloride salts of the *N*-methyl isomers **5** and **6**. The hydrochloride salts of **5** and **6** each crystallize in a single epimeric form, the form that is thermodynamically most stable in solution in each case. The nmr spectra of freshly prepared solutions of the crystalline salts of **5** or **6** dissolved in formic acid show the presence of only one epimer in each case (**5a** or **6a**), followed by a slow appearance of a second minor isomer (**5b** or **6b**). The rate of equilibration is enhanced by sodium formate. Melts of the salts give the spectra of the equilibrated systems.

Spectrum A, Figure 1, shows part of the nmr spectrum of a solution of the crystalline hydrochloride salt of **5** in 99% formic acid, and spectrum B is that of the equilibrated system after addition of sodium formate. Spectrum A indicates the presence of a single epimer. The most relevant signals are the *N*-methyl doublet at τ 6.83 (J_{NH-CH_3} = 5 Hz) and the signals of the diastereotopic hydrogens on C-6 which appear as sets of doublets of doublet with chemical shifts of τ 5.29 and 5.68. The C-6 hydrogen giving the lower field signal will be referred to as H-6 and the one giving the upper field signal as H-6′. The signals of H-6 and H-6′ yield the following coupling constants: $J_{6,6'}$ = 16 Hz, $J_{NH,6}$ = 4 Hz, and $J_{NH,6'}$ = 8.6 Hz. The difference of coupling constants between the ammonium proton and the two diastereotopic C-6 hydrogens is of importance in the assignment of configuration to epimer **5a** (*vide infra*). The spectrum of **5a** in trifluoroacetic acid has the same pattern as in formic acid (Table I)

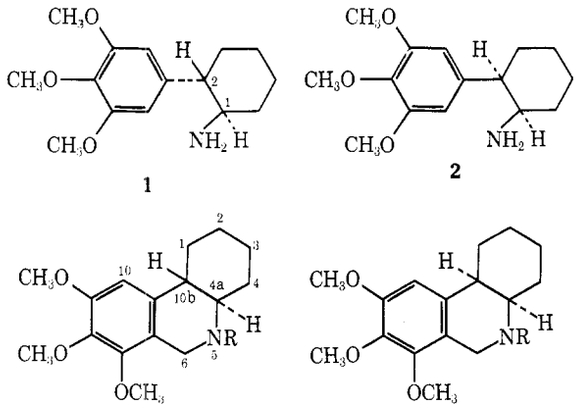
(1) This investigation was supported by Grant MH 12204 from the National Institute of Mental Health, U. S. Public Health Service. The compounds were submitted to Eli Lilly and Co. for pharmacological evaluation.

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

TABLE I
60-MHz NMR SPECTRAL DATA OF HYDROCHLORIDE SALTS

Solvent	Compd	Chemical shifts, τ (ppm) H-10	H-6	H-6′	NCH_3	NH	$J_{NH,6}$	$J_{NH,6'}$
HCOOH	**3** (trans)	3.13		~5.5[a]				
	5a (trans)	3.15	5.29	5.68	6.83		4.0	8.6
	5a, **5b** equil[b]	3.15	5.3	5.7	6.83			
				~5.4[a]	7.02			
	4 (cis)	3.18		~5.4[a]				
	6a (cis)	3.19	5.25	5.74	6.80		4.2	7.2
	6a, **6b** equil[b]	3.19						
		3.07		Complex	6.78			
CF_3COOH	**5a**	3.19	5.14	5.74	6.80	2.1	3.9	7.4
	6a	3.19	5.15	5.73	6.80	2.1	3.8	8.2
$CDCl_3$	**5a**, **6b** equil[b]	3.40	5.5	6.0	7.07	−2.25	~4.0	~8.0
		3.37		~5.75[a]	7.28	−2.72		

[a] Near equivalence of H-6 and H-6′. [b] Values from equilibrated systems.



1 **2**

3, R = H
5, R = CH_3
7, R = Et
8, R = $PhCH_2$
10, R = $HOCH_2CH_2$

4, R = H
6, R = CH_3
9, R = $PhCH_2$
11, R = $HOCH_2CH_2$

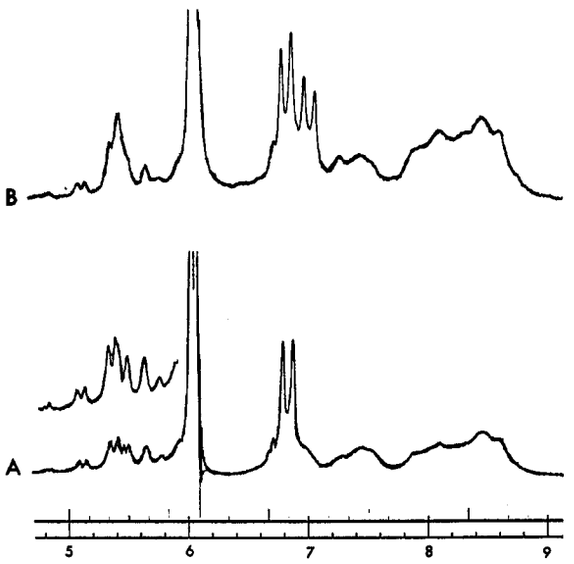


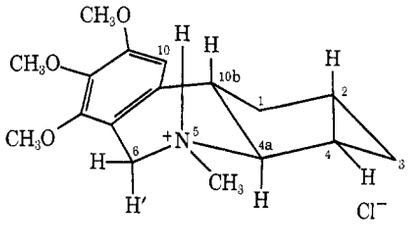
Figure 1.—Nmr spectra (60 MHz) of **5** HCl in 99% formic acid; spectrum A is prior to equilibration and B is after equilibration catalyzed by sodium formate.

but in addition it allows the detection of the signal of the ammonium proton as a broad signal at τ 2.1. Decoupling of the ammonium proton by strong irradiation at τ 2.1 caused a collapse of the *N*-methyl doublet to a singlet at τ 6.83 and it reduced the signals of H-6 and H-6′ to doublets ($J_{6,6'}$ = 16 Hz), thus confirming the assigned vicinal CH–NH^+ coupling.

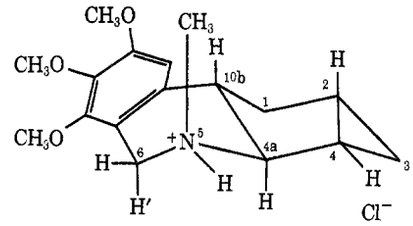
Spectrum B shows that the signal of the *N*-methyl group at τ 7.02 is at higher field for the minor epimer **5b** and that the chemical shifts of the C-6 hydrogens are more nearly equivalent, as seen from an enhancement of the signal in the region of τ 5.4. There is also a difference in the chemical shift of the aromatic hydrogen H-10 in the two epimers, τ 3.15 for **5a** and τ 3.13 for **5b**. The ratio of **5a** to **5b** is about 2:1 at equilibrium in formic acid. In the absence of sodium formate the equilibration required about one month at room temperature. In the presence of 2 equiv of sodium formate the equilibrium was reached in ~4 hr. Regeneration of the base from the equilibrated salt gave an nmr spectrum identical with that of the original base.

In deuterated chloroform, equilibration of the hydrochloride salt of **5** was established in less than 4 min, giving about equal amounts of the two epimers. An important feature of the spectrum is the presence of two ammonium proton signals of about equal intensities but of different widths which, taken together, integrate for one proton. The downfield signal at τ −2.72 has a width of about 15 Hz at 60 MHz and that at −2.25 is about 22 Hz wide. Irradiation of each NH^+ signal, in turn, decoupled only one NCH_3 doublet at a time, and showed that the low field NH^+ and the high field *N*-methyl signals are coupled, and vice versa. Equilibration between **5a** and **5b** in chloroform is fairly fast on an absolute time scale but still slow on the nmr time scale. The nmr spectrum of the hydrochloride salt of **5** in D_2O gives only one singlet for the *N*-methyl signal. This is indicative that in D_2O proton exchange and nitrogen inversion are fast processes on the nmr time scale and that the chemical shift of the *N*-methyl signal represents the weighted average of the shifts of the two epimers.

Configuration and Conformation of Salts 5a and 5b.—In the 4a,10b-trans compounds there is only one possible half-chair conformation of the hetero ring. A boat conformation is not ruled out *a priori*, but the nmr data are consistent with structures in which both **5a** and **5b** have the cyclohexane and hetero rings in chair and half-chair conformations, respectively (structures **5a** and **5b**), and where epimerization involves an inversion of the nitrogen with the methyl group occupying an equatorial position (cis to H-4a) in **5a** and an axial position (trans to H-4a) in **5b**. This assignment



5a



5b

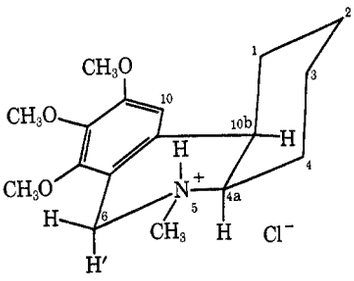
is supported by the observed chemical shifts and splitting patterns of the signals of H-6 and H-6′, based on the demonstrated dependency of CH–NH$^+$ spin–spin coupling constants on dihedral angle in a manner similar to the coupling between vicinal protons on carbon atoms.[3,4] The observed coupling constant for **5a** in formic acid of $J_{NH,6'}$ = 8.6 Hz and $J_{NH,6}$ = 4 Hz are consistent with the NH proton having an axial orientation and H-6′ and H-6 having pseudoaxial and pseudoequatorial orientations, respectively. The upfield chemical shift of H-6′ is also consistent with this assignment. For the hydrochloride salt of the corresponding secondary amine (**3**) under similar conditions, the chemical shifts of the C-6 hydrogens are nearly equivalent. The effect of the N–CH_3 bond will be to shield the C-6 hydrogen having a cis orientation to the *N*-methyl group.[3,5] The more nearly equivalent chemical shifts of H-6 and H-6′ in **5b** is consistent with this shielding effect of the *N*-methyl group where H-6 is shielded by the *N*-methyl group relative to H-6′. The higher field position of the signal of the methyl group in **5b** also supports the assigned structures. The effect of the magnetic anisotropy of the aromatic ring will be to deshield the in-plane methyl group in **5a** relative to the out-of-plane methyl in **5b**. If epimer **5b** had a predominance of the boat conformation, the methyl group would occupy an analogous position relative to the aromatic ring as in **5a**. The assigned structures are also confirmed by the nonequivalent ammonium proton signals in chloroform. Decoupling experiments showed that the lower field, narrower signal belongs to epimer **5b**. This is consistent with the assigned structures on the basis of shielding effects of the aromatic ring and of larger coupling constants in **5a** between the axial NH proton with axial H-4a and pseudoaxial H-6′ hydrogens than between the equatorial NH proton and the same adjacent hydrogens in **5b**.

Configuration and Conformation of Salts 6a and 6b.— In the 4a,10b-cis compounds there are two possible half-chair conformations of the hetero ring, each being associated with a given chair conformation of the

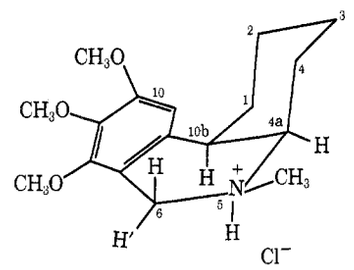
(3) H. Booth and J. H. Little, *Tetrahedron*, **23**, 291 (1967).

(4) (a) J. L. Sudmeier and G. Occupanti, *J. Amer. Chem. Soc.*, **90**, 154 (1968); (b) H. Booth, *Chem. Commun.*, 802 (1968); (c) J. I. Legg and D. W. Cooke, *Inorg. Chem.*, **5**, 594 (1966).

(5) H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Lett.*, 2553 (1964).



6a



6b

cyclohexane ring. The nmr spectrum of freshly prepared formic acid solution of crystalline hydrochloride salt of **6** is consistent with a single epimeric form (structure **6a**). The spectrum is characterized by well-defined sets of doublets of doublet for the diastereotopic hydrogens on C-6 at τ 5.25 and 5.74, one doublet for the *N*-methyl signal at 6.80, a single signal for H-10 at 3.19, and a fairly narrow envelope (<1.0 ppm) for the eight methylene protons on carbons 1–4. The coupling constants associated with H-6 and H-6′ are $J_{6,6'}$ = 16 Hz, $J_{NH,6}$ = 4.2 Hz, and $J_{NH,6'}$ = 7.2 Hz. The same pattern is obtained in trifluoroacetic acid. The spectra are consistent with structure **6a** where the hetero ring has a half-chair conformation and the ammonium proton has an axial orientation and is coupled with pseudoaxial H-6′ and pseudoequatorial H-6. The similarity of the chemical shift of the *N*-methyl group with that of **5a** implies an analogous orientation relative to the aromatic ring. The narrowness of the combined cyclohexane methylene signals implies that the hydrogens on C-1 do not fall in the deshielding region of the aromatic ring as is the case in **5a** and **5b** where their signals experience a downfield shift and are centered at about τ 7.4 (Figure 1). Equilibration in formic acid caused the appearance of a second aromatic H-10 signal at τ 3.07, an increase in the complexity of the H-6 and H-6′ signals, and a broadening of the envelope of the cyclohexane methylene signals. There was no appearance of a second *N*-methyl signal. The ratio of **6a** to **6b**, as obtained from the integration of the H-10 signals at equilibrium, was about 3:2. The results are consistent with structures **6a** and **6b**, each having the chair and half-chair conformations of the cyclohexane and hetero ring, respectively. In the thermodynamically most stable epimer (**6a**) H-4a has an equatorial orientation in relationship to the cyclohexane ring and an axial orientation with respect to the half-chair hetero ring and the *N*-methyl group is equatorial and cis to H-4a. Epimerization is associated with an inversion of conformation of the cyclohexane and the hetero ring to give structure **6b** where H-4a is axial in relationship to the cyclohexane ring and equatorial relative to the half-chair hetero ring and where the *N*-methyl group

is trans to H-4a but still occupies an equatorial orientation and has the same relative position to the aromatic ring, thus accounting in part for the identical chemical shifts of the *N*-methyl group in the two epimers. In **6b** the equatorial hydrogen on C-1 falls close to, and in the field of deshielding of, the aromatic ring.

Nmr Spectra and Conformation of Bases in the Trans and Cis Series.—The nmr spectra of the free bases of the 4a,10b-trans series, measured in deuteriochloroform and in pyridine, are consistent with structures having the cyclohexane and hetero rings in chair and half-chair conformations, respectively, and with a predominance of the structure where the N substituent occupies an equatorial orientation. For the secondary amine (**3**) the difference in chemical shift of the diastereotopic hydrogens 6 and 6′ is 0.16 ppm in chloroform and 0.20 ppm in pyridine. N-Alkylation brings a difference of about 0.7 ppm and the increase in nonequivalence is associated primarily with an upfield shift of the signal of H-6′. A shielding of the pseudoaxial H-6′ is expected by the *N*-alkyl bond when the *N*-alkyl group occupies an equatorial orientation on the half-chair hetero ring. This shielding parallels the pattern produced by alkylation of 4-methylpiperidine.[3] The geminal coupling $J_{6,6'}$ was found to be in the order of 16 Hz for the secondary and tertiary amine of the trans and cis series with the exception of the *N*-benzyl compounds where it was closer to 13 Hz. For compounds **5** and **7** the signal of H-6′ appears as doublets of doublet, $J_{6',6}$ = 16 Hz and J = 1.5 Hz. The small coupling is attributed to long-range coupling by H-4a. Examples of H–C–N–C–H coupling are known,[6,7] and, although the proposed geometry does not satisfy the planar requirement of the W rule in the H–C–C–C–H system,[8] the stereochemistry is analogous to that of a carbocyclic steroid in which long-range coupling has been reported through a nonplanar H–C–C–C–H system.[9] In the spectrum of **5** in pyridine the signals of H-4a and H-10b partially overlap with each other but centers of individual signals appear to be at about τ 7.4 and 7.6. Irradiation at τ 7.4 caused the four-peak multiplet of H-6′ to collapse to a doublet, $J_{6,6'}$ = 15.6 Hz. No decoupling occurred upon irradiating at τ 7.6. This supports the long-range coupling by H-4a because in every case where differentiation has been possible between the signals of H-4a and H-10b the former was found to be at lower field. No similar long-range coupling was observed in any of the cis isomers.

The spectra of the cis isomers show a nonequivalence of chemical shifts of H-6 and H-6′ and an upfield shift of the signal of H-6′ upon N-alkylation similar to what was seen for the trans compound. In addition, the signals of H-4a and H-10b in **4** are well separated in both solvents. In pyridine one signal occurs at τ 6.9 as a fairly narrow signal, $W_{1/2} \sim 7$ Hz, and the other as a wider unresolved multiplet at τ 7.5. In the methylated product **6** the narrow signal has been shifted upfield and the two signals overlap at about τ 7.6, and there has also been a similar upfield shift of 0.67 ppm of the signal of H-6′. The data suggest that the narrow signal at τ 6.9 is caused by H-4a having a similar relative position to the *N*-methyl group as H-6′ and that both these hydrogens are cis to the *N*-methyl group. The relative widths of the signal of H-4a and H-10b implies a chair conformation of the cyclohexane ring where H-10b is axial and H-4a is equatorial, for **4** as well as **6**. This conclusion is supported by the narrow range of the signals of the cyclohexane methylene hydrogens, which demonstrates the absence of deshielding of hydrogens on C-1 and indicates a structure where the C-10b–C-1 bond is perpendicular to the plane of the aromatic ring. The combined data are consistent with **6** having a predominance of the structure in which the hetero and cyclohexane rings have half-chair and chair conformations, respectively, where H-4a occupies an axial orientation with respect to the hetero ring and an equatorial orientation relative to the cyclohexane ring, and where the *N*-methyl group is equatorial and cis to H-4a. It is interesting to note that this is also the geometry of the thermodynamically most stable protonated form of **6**.

(6) D. H. R. Barton, R. H. Hesse, and G. W. Kirby, *J. Chem. Soc.*, 6379 (1965).

(7) T. Masamune, S. Ohuchi, S. Shimokawa, and H. Booth, *Tetrahedron*, **22**, 773 (1966).

(8) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 334.

(9) Y. Osawa and M. Neeman, *J. Amer. Chem. Soc.*, **85**, 2856 (1963).

Experimental Section

Melting points were determined on a Kofler hot stage unless otherwise indicated. The salts in the 7,8,9-trimethoxy-1,2,3,4,-4a,5,6,10b-octahydrophenanthridine series decomposed on heating and as a result melting points are a relatively poor criterion of purity. Most uniform results were obtained by placing samples on the hot stage within about 5–10° of the melting point. Owing to heat sensitivity it was also necessary to dry analytical samples at room temperature. Elemental analyses were performed by Alfred Bernhardt, Mülheim, Germany, and Huffman Laboratories, Wheatridge, Colo. Nmr spectra were recorded on Varian A-60 or Varian T-60 spectrometers operating at 33–35° with tetramethylsilane internal reference. Equilibrium studies were carried out at room temperature with periodic examination by nmr. Table I lists the nmr data for the hydrochloride salts. Ir spectra were determined on Beckman IR-5a or Beckman IR-20 spectrophotometers. Solid samples were determined in the solid phase as KBr pellets unless otherwise indicated. Strong methoxy absorption at 1110–1130 cm^{-1} was present in all compounds.

7,8,9-Trimethoxy-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (**3**).—A solution of 453 mg of 1 hydrochloride[2] (1.50 mmol) and 146 mg (~1.63 mmol) of aqueous 37% formaldehyde in 30 ml of ethanol was refluxed for 29 hr. The reaction mixture, from which considerable crystalline product had separated, was evaporated and the resulting crude solid crystallized from methanol, yielding 449 mg (95.2%) of **3** hydrochloride as colorless needles or plates, mp 262.5–263.5° dec, ir 2790 cm^{-1} (NH^+).

Anal. Calcd for $C_{16}H_{24}O_3NCl$: C, 61.23; H, 7.71; N, 4.46. Found: C, 61.54; H, 7.51; N, 4.51.

The amine **3** regenerated from the hydrochloride after crystallization from hexane–benzene had mp 76–78°; ir 3440 cm^{-1} (NH); nmr ($CDCl_3$) τ 3.36 (s, 1, H-10), 5.87 (d, 1, $J_{6,6'}$ = 16 Hz, H-6), 6.03 (d, 1, $J_{6,6'}$ = 16 Hz, H-6′), 8.51 (s, 1, NH).

The *p*-toluenesulfonate was prepared by addition of *p*-toluenesulfonic acid to a methanolic solution of **3** followed by removal of methanol under reduced pressure. Two crystallizations from methanol–water gave the hydrate, mp <100° with resolidification and remelting at 158.5–159.5° (Fisher-Johns). Azeotropic removal of water of hydration with chloroform followed by ethyl acetate crystallization afforded the salt as colorless needles, partially melting at 157.5–160°, regrowth to cubes at 160–167°, and complete melting by 169.5°. The melting behavior is probably a result of a mixture of polymorphic forms. Infrared NH^+ absorption occurred at 2800 cm^{-1}.

7,8,9-Trimethoxy-4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (**4**).—Treatment of 9.66 g (32.0 mmol) of **2** hydrochloride[2] with ~42 mmol of formaldehyde in 650 ml of refluxing ethanol for 24 hr afforded 9.93 g (98.8%) of **4** hydro-

chloride after crystallization from 2-propanol, mp 244–244.5° dec, ir 2780 cm^{-1} (NH^+).

Anal. Calcd for $C_{16}H_{24}O_3NCl$: C, 61.23; H, 7.71; N, 4.46. Found: C, 61.07; H, 7.54; N, 4.39.

The amine **4** crystallized from hexane and had mp 90.5–92.5°; ir 3440 cm^{-1} (NH); nmr ($CDCl_3$) τ 3.56 (s, 1, H-10), 5.85 (d, 1, $J_{6,6'}$ = 16.5 Hz, H-6), 6.08 (d, 1, $J_{6',6}$ = 16.5 Hz, H-6'), 8.46 (s, 1, NH).

5-Methyl-7,8,9-trimethoxy-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (5).—With cooling, 0.88 g of 88% formic acid (~16.8 mmol) was added to 1.061 g of **1** (4.00 mmol). Aqueous 37% formaldehyde (1.0 g, ~12.3 mmol) was added and the mixture was heated until gas evolution started. After vigorous gas evolution had subsided, heating on a steam bath was resumed overnight (total 18 hr). After cooling, the mixture was diluted with a small amount of water (2 ml), chilled, and made alkaline with KOH with stirring. The amine liberated was extracted with benzene (three 50-ml portions). The benzene extracts were dried (Na_2SO_4) and evaporated, giving the crude liquid amine. Conversion to the hydrochloride and crystallization from 2-propanol–ethyl acetate yielded 1.247 g (95.1%) of **5** hydrochloride, mp 209–210° dec, ir 2490 cm^{-1} (NH^+).

Anal. Calcd for $C_{17}H_{26}O_3NCl$: C, 62.28; H, 8.00; N, 4.27. Found: C, 61.99; H, 7.76; N, 4.26.

The liquid amine **5** regenerated from hydrochloride exhibited moderately strong absorption in the ir (liquid, neat) at 2760 cm^{-1} (NCH); nmr ($CDCl_3$) τ 3.43 (s, 1, H-10), 6.06 (d, 1, $J_{6,6'}$ = 15.6 Hz), 6.71 (d d, 1, $J_{6',6}$ = 15.6 Hz, $J_{6',4a}$ = 1.5 Hz, H-6'), 7.63 (s, 3, NCH_3).

The *p*-toluenesulfonate prepared as described for that of **3** above was freed of traces of *p*-toluenesulfonic acid by extraction of a benzene solution with water. The benzene extracts were dried (Na_2SO_4) and evaporated. Treatment with a small amount of ethyl acetate afforded crystals which on recrystallization from benzene–petroleum ether (bp 30–60°) gave needles, mp 171–172.5°, ir 2570 cm^{-1} (NH^+).

5-Methyl-7,8,9-trimethoxy-4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (6).—A solution of 1.57 g (5.65 mmol) of **4** and 5.0 ml of 37% formaldehyde in 100 ml of ethanol was hydrogenated in the presence of 500 mg of 10% Pd/C until hydrogen uptake ceased. Following removal of catalyst by filtration, the solution was treated with 5 ml of glacial acetic acid and evaporated. The residue was dissolved in 10 ml of water, chilled, and made alkaline with KOH. The liberated amine was extracted with benzene (four 50-ml portions) and the benzene extracts were dried (Na_2SO_4) and evaporated. The crude liquid amine was converted to the hydrochloride in the usual manner; crystallization from 2-propanol–ethyl acetate afforded 1.715 g (92.5%) of **6** hydrochloride, mp 204–206.5° dec, ir 2550 cm^{-1} (NH^+).

Anal. Calcd for $C_{17}H_{26}O_3NCl$: C, 62.28; H, 8.00; N, 4.27. Found: C, 62.34; H, 7.92; N, 4.20.

Clark–Eschweiler treatment of **2** as described for preparation of **5** afforded **6** hydrochloride in 84.9% yield. Physical and spectral properties of this product were identical with those of a sample prepared by the catalytic reductive methylation above.

Nmr of free base in $CDCl_3$: τ 3.53 (s, 1, H-10), 6.08 (d, 1, $J_{6,6'}$ = 15.8 Hz, H-6), 6.70 (d, 1, $J_{6',6}$ = 15.8 Hz, H-6'), 7.58 (s, 3, NCH_3).

5-Ethyl-7,8,9-trimethoxy-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (7).—Catalytic reductive alkylation of 2.08 g (7.50 mmol) of **3** using excess acetaldehyde (~3.31 g, ~75 mmol) according to the procedure described for **6** followed by crystallization from 2-propanol yielded 2.20 g (85.9%) of **7** hydrochloride as a microcrystalline solid, mp 210–210.5° dec, ir 2500 cm^{-1} (NH^+).

Anal. Calcd for $C_{18}H_{28}O_3NCl$: C, 63.24; H, 8.26; N, 4.10. Found: C, 63.17; H, 8.29; N, 4.24.

Nmr of free base in pyridine: τ 3.24 (s, 1, H-10), 5.83 (d, 1, $J_{6,6'}$ = 16.2 Hz, H-6), 6.43 (d d, 1, $J_{6',6}$ = 16.2 Hz, $J_{6',4a}$ = 1.5 Hz, H-6'), 7.40 (q, 2, NCH_2CH_3), 8.94 (t, 3, NCH_2CH_3).

5-Benzyl-7,8,9-trimethoxy-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (8).—A mixture of 277 mg (1.00 mmol) of **3**, 186 mg (4.0 mmol) of 99% formic acid, and 227 mg (2.14 mmol) of redistilled benzaldehyde was heated under reflux on a steam bath for 18 hr. Moderate to slow gas evolution occurred initially, but abated considerably after 2 hr. After cooling, the mixture was diluted with 5 ml of glacial acetic acid and 10 ml of 5% HCl. Excess benzaldehyde was removed by washing with carbon tetrachloride (three 5-ml portions). Carbon tetrachloride washings were extracted with an additional 10 ml of 5% HCl. Aqueous acidic solutions deposited some of the product hydrochloride on standing; resolubilization was effected by addition of methanol. The aqueous acidic portions were combined and evaporated under reduced pressure. Crystallization of the residue from methanol yielded 313 mg (77.5%) of the hydrochloride of **8** as colorless needles, mp 209–210° dec, ir 2500 cm^{-1} (NH^+).

Anal. Calcd for $C_{23}N_{30}O_3NCl$: C, 68.38; H, 7.49; N, 3.47. Found: C, 68.09; H, 7.55; N, 3.56.

5-Benzyl-7,8,9-trimethoxy-4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (9).—Heating of 1.387 g (5.00 mmol) of **4** with formic acid and benzaldehyde for 7 hr as described above and crystallization from ethyl acetate and 2-propanol produced 1.561 g (77.2%) crude **9** hydrochloride, mp 181–190° dec (Fisher-Johns). A pure sample crystallized from ethanol melted at 182.5–183° dec to a two-phase system, ir 2510 cm^{-1} (NH^+).

Anal. Calcd for $C_{23}H_{30}O_3NCl$: C, 68.38; H, 7.49; N, 3.47. Found: C, 67.99; H, 7.52; N, 3.70.

Nmr of free base in pyridine: τ 3.25 (s, 1, H-10), 5.93 (d, 1, $J_{6,6'}$ = 13 Hz, H-6), 6.50 (d, 1, $J_{6',6}$ = 13 Hz, H-6'), 6.2 (s, 2, NCH_2Ph). In $CDCl_3$ the signals of the benzylic hydrogens are nonequivalent and they overlap with the signals of the methoxy groups.

5-(2-Hydroxyethyl)-7,8,9-trimethoxy-4a,10b-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (10).—A solution of 838 mg (3.02 mmol) of **3** and ~5 mmol of ethylene oxide in 30 ml of absolute ethanol was heated at 75° in a small stainless steel Parr bomb for 24 hr. After cooling, the contents of the bomb were evaporated. Crystallization of the residue from acetone, then acetone–hexane, afforded 757 mg (77.9%) of **10**, mp 118.5–120.5° (Fisher-Johns). A sample purified for analysis by two further crystallizations from acetone followed by recrystallization from benzene–hexane had mp 120–121.5°; ir ($CHCl_3$) 3620 (w), 3420 cm^{-1} (OH); nmr (pyridine) τ 3.21 (s, 1, H-10), 5.68 (d, 1, $J_{6,6'}$ = 16.4 Hz, H-6), 6.22 (d, 1, $J_{6',6}$ = 16.4 Hz, H-6'), 6.1 (m, 2, $NHCH_2CH_2OH$), 7.13 (m, 2, $NHCH_2CH_2OH$).

Anal. Calcd for $C_{18}H_{27}O_4N$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.51; H, 8.58; N, 4.60.

The hydrochloride was prepared by treatment with 5% hydrochloride acid and isolated by chloroform extraction as described below for **11** hydrochloride. Crystallization from acetone gave colorless needles: mp 170.5–172° dec; ir 3330 (OH), 2530 cm^{-1} (NH^+).

5-(2-Hydroxyethyl)-7,8,9-trimethoxy-4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (11).—Hydroxyethylation of 693 mg (2.50 mmol) of **4** with ~6.2 mmol of ethylene oxide in 50 ml of absolute ethanol was carried out under the conditions employed for the *trans* isomer **10**. Evaporation of the reaction mixture gave crude **11** as a viscous oil which failed to crystallize. It was converted to the hydrochloride by shaking a benzene solution with 5% HCl (20 ml in three portions). The hydrochloride salt was extracted from the combined acid extracts with chloroform (50 ml total) and the chloroform extracts were dried (Na_2SO_4) and evaporated. Crystallization of the residue from acetone afforded 723 mg (80.7%) of **11** hydrochloride: mp 172–174° dec (Fisher-Johns); ir 3320 (OH), 2590 cm^{-1} (NH^+). An analytical sample prepared by three crystallizations from 2-propanol–ethyl acetate had mp 172.5–177.5° dec, with the melting point very dependent on heating rate.

Anal. Calcd for $C_{18}H_{28}O_4NCl$: C, 60.41; H, 7.89; N, 3.92. Found: C, 60.02; H, 7.92; N, 4.21.

Registry No.—**3**, 34035-48-8; **3** HCl, 34035-49-9; **3** tosylate, 34035-50-2; **4**, 34035-51-3; **4** HCl, 34035-52-4; **5**, 34035-53-5; **5** HCl, 34035-54-6; **5** tosylate, 34035-55-7; **6**, 34035-56-8; **6** HCl, 34035-57-9; **7**, 34035-58-0; **7** HCl, 34087-66-6; **8** HCl, 34035-59-1; **9**, 34035-60-4; **9** HCl, 34035-61-5; **10**, 34087-67-7; **10** HCl, 34035-62-6; **11** HCl, 34035-63-7.