Indolizine Derivatives Related to Ergoline. Derivatives of 7*H*-Pyrrolo[3,2,1-*i*,*j*]quinoline, 7*H*-Naphtho[1,2,3-*h*,*i*]indolizine, and 7*H*-Pyrrolo[3,2,1-*g*,*h*]-4,7-phenanthroline

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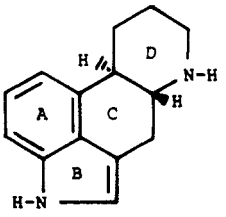
The synthesis and structure elucidations of several indolizine analogues of ergoline are reported. Reaction of 5,6,7,8-tetrahydroquinoline, 5,6,6a,7,8,9,10,10a-octahydrobenzo[*f*]quinoline (**6**), and *trans*-4-acetyl-1,2,3,4,4a,5,6,10b-octahydro-4,7-phenanthroline (**19**) with bromoacetone and cyclization of the acetonyl derivatives gave 1-methyl-8,9-dihydro-7*H*-pyrrolo[3,2,1-*i*,*j*]quinoline (**3**), 6-methyl-7a,8,9,10,11,11a-hexahydro-7*H*-naphtho[1,2,3-*h*,*i*]indolizine (**8**), and *trans*-6-methyl-8-acetyl-7a,8,9,10,11,11a-hexahydro-7*H*-pyrrolo[3,2,1-*g*,*h*]-4,7-phenanthroline (**22**), respectively. Hydrogenation of 4,7-phenanthroline in trifluoroacetic acid yielded the trans and cis isomers at junction C_{4a}–C_{10b} of 1,2,3,4,4a,5,6,10b-octahydro-4,7-phenanthrolines **13** and **14**. Their structures were established by spectroscopic methods.

Ergot alkaloids have as a main basic structural feature an ergoline ring (**1**). For many years attention has been



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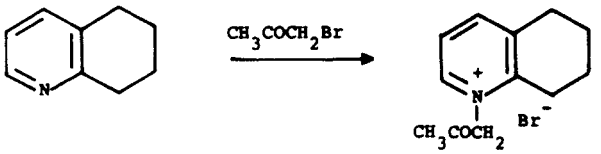

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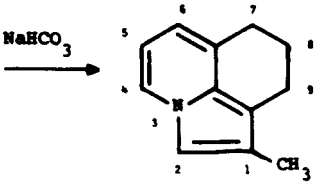

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focused on their central and peripheral pharmacological effects, including serotonin antagonism, vasoconstriction, and oxytocic and psychotropic activity.[1] More recently, ergot alkaloids and semisynthetic derivatives of ergoline as dopamine agonists have been shown to be potent inhibitors of the pituitary hormone prolactin; such an activity may be useful in the treatment of human breast cancer.[2] Other ergoline derivatives such as bromocriptine and lergotrile have shown promising effects in the treatment of dopamine-deficient parkinsonism.[3]

Considerable effort has been devoted to the synthesis of structural and simplified analogues of ergoline in order to assess the effects of structural changes on biological activity.[4-7]

This paper reports the synthesis of ergoline analogues in which the indole has been replaced by the indolizine nucleus. In investigations on biological activities of indolizine derivatives,[8] some indolizinylalkylamines and hydrazides of indolizinecarboxylic acids have shown pharmacological activities similar to those of indole analogues. These results suggest that the NH group of indole is not critical for pharmacological activity and that the indolizine nucleus may be considered as a basic system for biologically active compounds.

The first approach toward the synthesis of ergoline analogues with an indolizine nucleus involves the preparation of 1-methyl-8,9-dihydro-7*H*-pyrrolo[3,2,1-*i*,*j*]-quinoline (**3**). This compound is comparable with the tricyclic partial ABC structure of ergoline.

The synthesis was achieved from 5,6,7,8-tetrahydroquinoline and bromoacetone; the *N*-acetonyl-5,6,7,8-tetrahydroquinolinium bromide (**2**) was cyclized by sodium bicarbonate to **3**. The structure of **3** was confirmed by its NMR spectrum, which shows a singlet at δ 6.65 (H-2), and signals at δ 7.35–7.05 (m, H-4) and 6.15–5.9 (m, H-5,6), typical of the indolizine nucleus. A further approach, catalytic hydrogenation of benzo[*f*]quinoline according to Eliel's method,[9] with platinum oxide in trifluoroacetic acid and subsequent treatment with acetic anhydride, gave 4-acetyl-1,2,3,4,7,8,9,10-octahydro- (**4**), 7,8,9,10-tetrahydro- (**5**), and 5,6,6a,7,8,9,10,10a-octahydrobenzo[*f*]quinoline (**6**). Compound **4** was isolated as a solid by diluting the acetylation mixture with water; **5** and **6** were separated by column chromatography. Melting point of **5**, recrystallized from petroleum ether, was 55–56 °C, while Braun and Gruber[10] gave 158 °C; the picrate and hydrochloride have the same melting points reported in the literature.[10] Compound **5**, resynthesized according to the Braun and Gruber method, shows a melting point of 55 °C. The reaction of **6** with bromoacetone and sodium bicarbonate

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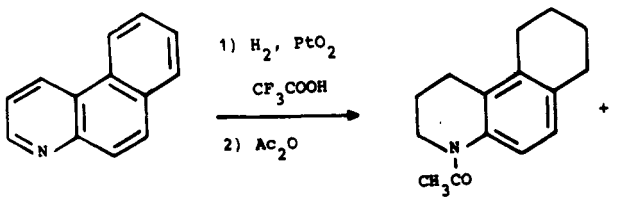

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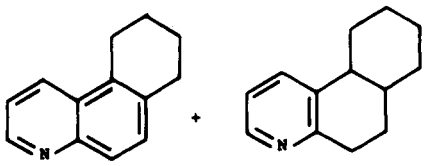

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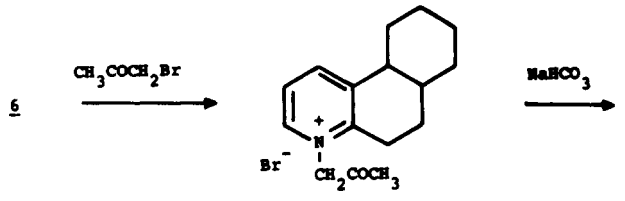
afforded 6-methyl-7a,8,9,10,11,11a-hexahydro-7*H*-naphtho[1,2,3-H,*i*]indolizine (8).



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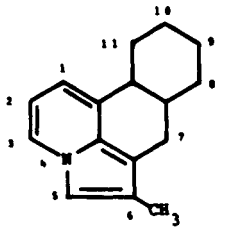

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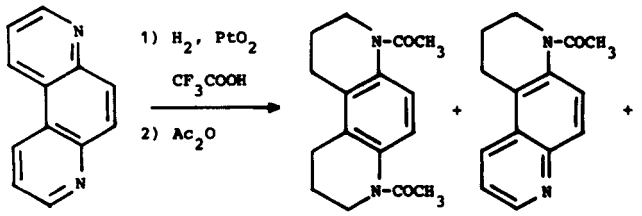
In order to obtain an indolizine structure more closely related to the ergoline system, 4-acetyl-1,2,3,4,4a,5,6,10b-octahydro-4,7-phenanthroline (12) was synthesized by



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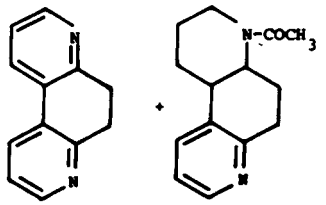


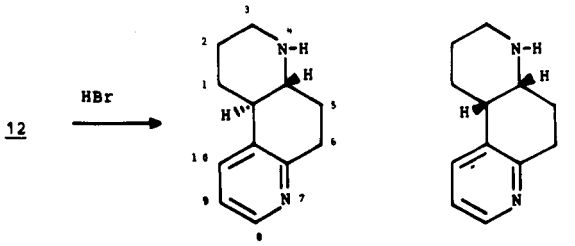
11 12

hydrogenation of 4,7-phenanthroline with platinum oxide in trifluoroacetic acid at 50 psi of H_2. By this method, acetylation of the reaction mixture gave 4,7-diacetyl-1,2,3,4,7,8,9,10-octahydro- (9), 4-acetyl-1,2,3,4-tetrahydro- (10), and 5,6-dihydro-4,7-phenanthroline (11) and 12.

The mixture of compounds 9–12 was separated by column chromatography.

When the same hydrogenation was carried out at 1 atm of hydrogen, the same compounds were formed, but the yields of compounds 11 and 12 were increased. According to Eliel,[9] heterocyclic compounds containing nitrogen atoms condensed with benzene nuclei are reduced preferentially in the benzo ring in acidic medium with platinum oxide and hydrogen at 50 psi. In this case, at a lower pressure the hydrogenation of the benzene ring is more selective. Furthermore, it can be assumed that compounds 10 and 11 are intermediates in the formation of 12. In fact, after reduction of 1,2,3,4-tetrahydro-4,7-phenanthroline under the same conditions, only 9 and 12 were obtained.

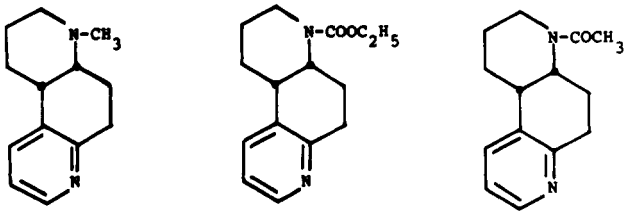
Hydrolysis of 12 with concentrated hydrobromic acid gave, after column chromatography, two products which proved to be the trans (13) and cis (14) isomers at the



13 14

C_4–C_{10b} junction of the free base. In fact, both isomers presented the same UV spectra, an identical elemental analysis, and the same molecular peak at *m/e* 188 in the mass spectra.

In order to establish the correct configuration, the *N*-methyl (15, 16), *N*-ethoxycarbonyl (17, 18), and *N*-acetyl (19, 20) derivatives of both isomers were prepared. The



15: trans 17: trans 19: trans

16: cis 18: cis 20: cis

cis or trans geometry of the methyl derivatives 15 and 16 was established by means of strong "Bohlmann bands" in the 2700–2900-cm^{-1} region of the IR spectrum of the trans isomer.[11] The N electron pair in the trans isomer 15 is flanked by two rigidly held trans-axial hydrogens, and its IR spectrum would be expected to exhibit strong absorption in the "Bohlmann region". The solid isomer 15 shows two intense bands at 2795 and 2860 cm^{-1}, whereas its liquid isomer 16 exhibits a weak absorption at 2795 and 2880 cm^{-1}; the IR spectra were recorded in chloroform at the same concentration. On this basis, 15 and 16 were assigned the trans and cis configurations, respectively; consequently,

(11) (a) E. L. Eliel, N. L. Allinger, S. J. Angual, and G. A. Morrison, "Conformational Analysis", Wiley, New York, 1968, pp 253–4; (b) F. W. Vierhapper and E. L. Eliel, *J. Org. Chem.*, 44, 1081 (1979); (c) Z. Horii, T. Kurihara, and I. Ninomiya, *Chem. Pharm. Bull.*, 17, 1733 (1969); (d) J. G. Cannon, G. J. Hatheway, J. P. Long, and F. M. Sharabi, *J. Med. Chem.*, 19, 987 (1976).

13 and 14 also have, respectively, the trans and cis structure.

The configuration of 13 and 14 was confirmed by IR and NMR spectra of their *N*-ethoxycarbonyl and *N*-acetyl derivatives. In fact, the IR spectrum of 17 shows a carbonyl absorption at higher frequency than that of 18 (1705 and 1675 cm^{-1}, respectively), thus indicating that in 17 there is a weak conjugation between the nitrogen N_4 and the carbonyl. The ethoxycarbonyl group, because of steric hindrance with the equatorial hydrogen atom at C_5, is forced into a position of weak conjugation. In derivative 18, instead, as seen with molecular models, there is no steric hindrance. The NMR spectrum of 17 shows in the region δ 4.35–3.7 a complex signal corresponding to three protons; the quartet for O–CH_2, centered at δ 4.1 (J = 7.5 Hz), is partially overlapped with a multiplet centered at δ 3.92; the latter is attributed to the axial hydrogen on C_{4a}, deshielded by the anisotropic effect of the carbonyl group scarcely conjugated to the nitrogen. NMR spectrum of 18 shows in the region δ 4.8–3.75 the signal of the quartet for O–CH_2, centered at δ 4.12 (J = 7.5 Hz) and partially overlapped with a complex multiplet between δ 4.8 and 4.35. The area of the signal corresponds to four protons attributed to the O–CH_2 group and to two hydrogens at C_3, deshielded by the carbonyl group conjugated to the nitrogen.

N-Acetyl derivatives present similar behavior as far as the absorption of the carbonyl group in the IR (19, 1635 cm^{-1}; 20, 1620 cm^{-1}). However, in 19 the acetyl group, on account of its smaller steric hindrance with respect to that of the ethoxycarbonyl group, can assume a conformation which does not show any hydrogen atom deshielded. This is confirmed by the NMR spectrum which does not present any signal above δ 3.7.

Instead, the NMR spectrum of 20 shows a very broad multiplet, corresponding to two protons, in the region δ 5.25–3.5. In this case the carbonyl group conjugated to the nitrogen deshields the two protons on C_3, as in 18.

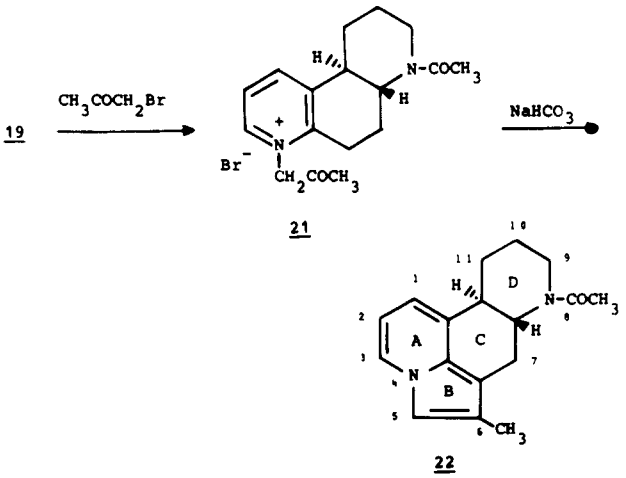
The different conjugation of the carbonyl to the nitrogen and the deshielding effects in compounds 17–20 can clearly be shown by Dreiding models of these molecules; so a trans junction for 17 and 19 and a cis junction for 18 and 20 are confirmed.

^{13}C NMR spectra of compounds 13 and 14, recorded on naturally abundant isotopic samples with off-resonance and complete proton decoupling, clearly confirmed the above statements. As to 13 and 14, the chemical shifts of the carbon atoms were assigned on the basis of values given in the literature[12-14] for *trans*- and *cis*-decahydroquinolines. In both isomers 13 and 14, the carbon atoms next to nitrogen, C_3 and C_{4a}, show signals at the lowest field. The signals corresponding to carbons C_{4a} and C_{10b} were assigned through off-resonance decoupling. In the case of 14 the signals of carbons C_{10b}, C_{4a}, and C_3 are all shifted upfield with respect to the signals of the same carbons in isomer 13, according to the data given in the literature for *cis*- and *trans*-decahydroquinoline and to the different β and γ effects.

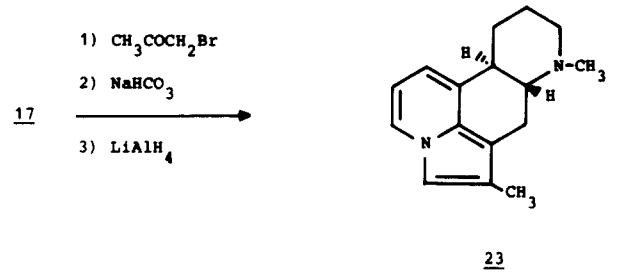
In fact, Dreiding models show that in the case of cis isomer 14 the C_{10b} is under the influence of $1_{\beta_{eq}} + 2_{\beta_{ax}}$ effects, while C_{4a} is influenced by $2_{\beta_{eq}} + 2_{\beta_{ax}}$ effects and C_3 by 2_{γ_g} effects, whereas in the trans isomer 13 the effects are respectively $3_{\beta_{eq}}$ for C_{10b}, $4_{\beta_{eq}}$ for C_{4a}, and $1_{\gamma_g} + 1_{\gamma_a}$ for C_3.

(12) H. Booth, and D. V. Griffiths, *J. Chem. Soc., Perkin Trans. 2*, 842 (1973).
(13) E. L. Eliel and F. W. Vierhapper, *J. Org. Chem.* **41**, 199 (1976).
(14) F. W. Vierhapper and E. L. Eliel, *J. Org. Chem.*, **42**, 51 (1977).

The reaction of 19 with bromoacetone and the cyclization with sodium bicarbonate of the corresponding N-acetonyl bromide (21) gave *trans*-6-methy-8-acetyl-7a,8,9,10,11,11a-hexahydro-7*H*-pyrrolo[3,2,1-*g*,*h*]-4,7-phenanthroline (22).



Compound 17 gave, by the same reactions and by reduction of the ethoxycarbonyl group with lithium aluminum hydride, *trans*-6,8-dimethyl-7a,8,9,10,11,11a-hexahydro-7*H*-pyrrolo[3,2,1-*g*,*h*]-4,7-phenanthroline (23).



Compounds 22 and 23, with a trans junction between the C and D rings, are strictly related to ergoline; their NMR spectra display the characteristic signals of the indolizine ring.

Experimental Section

The melting points were measured with a Büchi apparatus and are uncorrected. The NMR spectra were taken with a Varian EM-390 90 MHz spectrophotometer with Me_4Si as an internal standard. The IR spectra were run on a Perkin-Elmer Model 297 spectrometer. The UV spectra were determined with a Perkin-Elmer Model 575 spectrophotometer. Column chromatography was carried out with Merck Kieselgel 60 (70–230 mesh).

General Procedure for Synthesis of Acetonyl Derivatives 2, 7, and 21. Bromoacetone (2.2 mL, 25 mmol) in acetone (10 mL) was added dropwise to a stirred solution of 5,6,7,8-tetrahydroquinoline, 5,6,6a,7,8,9,10,10a-octahydrobenzo[*f*]quinoline (6), or *trans*-4-acetyl-1,2,3,4,4a,5,6,10b-octahydro-4,7-phenanthroline (19) (25 mmol) in acetone (15 mL). The mixture was refluxed under a nitrogen atmosphere for 2 h and then stirred at room temperature overnight. The solid was filtered, washed with acetone, and recrystallized.

1-Acetonyl-5,6,7,8-tetrahydroquinolinium bromide (2): mp 134–136 °C (from acetone); IR (Nujol) 1725 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_{16}BrNO$: C, 53.36; H, 5.97; N, 5.18. Found: C, 53.17; H, 6.05; N, 5.24.

4-Acetonyl-5,6,6a,7,8,9,10,10a-octahydrobenzo[*f*]-quinolinium bromide (7): mp 173–175 °C (from acetone); IR (Nujol) 1730 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{22}BrNO$: C, 59.28; H, 6.84; N, 4.32. Found: C, 59.31; H, 6.71; N, 4.26.

***trans*-4-Acetyl-7-acetonyl-1,2,3,4,4a,5,6,10b-octahydro-4,7-phenanthrolinium bromide (21):** mp 202–204 °C (from isopropyl alcohol–ethyl acetate); IR (Nujol) 1730 (C–CO–C), 1615 (N–CO–C) cm^{-1}. Anal. Calcd for $C_{17}H_{23}BrN_2O_2$: C, 55.60; H,

6.31; N, 7.62. Found: C, 55.53; H, 6.41; N, 7.75.

1-Methyl-8,9-dihydro-7*H*-pyrrolo[3,2,1-*i,j*]quinoline (3). A suspension of $NaHCO_3$ (5 g) in ethanol (60 mL) containing bromide **2** was refluxed for 1.5 h. After cooling, the solution was filtered and the filtrate evaporated in vacuo. The residue was suspended in water and extracted several times with ether. The ether extracts were dried and evaporated, and the oily residue was distilled under vacuum to give **3**: 2.13 g (75%); bp 87 °C (0.2 mmHg); NMR (CCl_4) δ 7.35–7.05 (m, 1 H, H-4), 6.65 (s, 1 H, H-2), 6.15–5.9 (m, 2 H, H-5,6), 2.65 (t, 4 H, H-7,9), 2.18 (s, 3 H, 1-CH_3), 2.1–1.65 (m, 2 H, H-8). Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 83.94; H, 7.75; N, 8.13. Picrate, mp 127–128 °C (from ethyl acetate). Anal. Calcd for $C_{18}H_{16}N_4O_7$: C, 54.0; H, 4.03; N, 14.0. Found: C, 54.09; H, 3.92; N, 14.06.

Hydrogenation of Benzo[*f*]quinoline. A mixture of benzo[*f*]quinoline (8.96 g, 50 mmol) and PtO_2 (0.75 g) in CF_3COOH (40 mL) was hydrogenated at 50 psi of H_2 in a Parr shaker. After 20 h, when the pressure had dropped 18 psi, the catalyst was filtered off, and the solution was diluted with water, chilled in ice, made basic with concentrated NaOH, and extracted with ether. The ether solution was dried over KOH and the solvent removed in vacuo. The crude residue was stirred with acetic anhydride (2.41 mL, 25.4 mmol) at 100 °C for 5 h. After cooling, the mixture was diluted with water (100 mL), concentrated HCl (15 mL) was added, and the solution was extracted with ether. The ether extracts were dried over KOH and evaporated under reduced pressure to give 4-acetyl-1,2,3,4,7,8,9,10-octahydrobenzo[*f*]quinoline (**4**): 3.51 g (31%); mp 68–69 °C [lit.[15] mp 68.5–69 °C (from chloroform)] IR (Nujol) 1650 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 6.95 (br s, 2 H, H-5,6), 3.7 (t, J = 6 Hz, 2 H, H-3), 2.9–2.3 (m, 6 H, H-1,7,10), 2.2 (s, 3 H, CH_3), 2.12–1.2 (m, 6 H, H-2,8,9).

The aqueous solution was chilled in ice, made basic with concentrated NaOH, and extracted with petroleum ether. The organic extracts were dried over KOH and evaporated under reduced pressure to give 4.96 g of dark oil. The oily residue was chromatographed on silica gel (500 g) and eluted with a mixture of benzene/acetone (6/4). The first-collected fractions contained 7,8,9,10-tetrahydrobenzo[*f*]quinoline (**5**): 1.74 g (19%); mp 55–56 °C (petroleum ether) (lit.[10] mp 158 °C); NMR (CCl_4) δ 8.7–8.5 (m, 1 H, H-3), 8.2–7.6 (m, 2 H, H-1,2), 7.2 (d, J = 9 Hz, 1 H, H-5) 7.15 (d, J = 9 Hz, 1 H, H-6), 3.15–2.45 (m, 4 H, H-7,10), 2.15–1.35 (m, 4 H, H-8,9); picrate mp 206–7 °C (lit.[10] mp 207 °C).

From the second-eluted fractions was recovered a mixture of compounds **5** and **6**. The last-eluted fractions, after removal of the solvent, gave 5,6,6a,7,8,9,10,10a-octahydrobenzo[*f*]quinoline (**6**): 4.4 g (47%); mp 146–147 °C (from absolute ethanol); NMR (CCl_4) δ 8.35–8.07 (m, 1 H, H-3), 7.37–6.72 (m, 2 H, H-1,2), 3.05–2.25 (m, 3 H, H-5,10a), 2.2–1.05 (m, 11 H, H-6,6a,7,8,9,10). Anal. Calcd for $C_{13}H_{17}N$: C; 83.37; H, 9.15; N, 7.48. Found: C, 83.19; H, 9.31; N, 7.32. Picrate, mp 146–147 °C (from absolute ethanol). Anal. Calcd for $C_{19}H_{20}N_4O_7$: C, 54.8; H, 4.84; N, 13.46. Found: C, 54.72; H, 4.78; N, 13.36.

6-Methyl-7a,8,9,10,11,11a-hexahydro-7*H*-naphtho[1,2,3-*h,i*]indolizine (8). $NaHCO_3$ (5 g), bromide **7** (2.54 g, 7.8 mmol), and ethanol (60 mL) were refluxed under N_2 for 3 h. After cooling, the solution was filtered and the filtrate evaporated in vacuo. The oily residue was distilled [bp 95 °C (0.1 mmHg)] and crystallized from petroleum ether: 1.57 g (88%); mp 47–48 °C; NMR (CCl_4) δ 7.5–7.2 (m, 1 H, H-3), 6.77 (s, 1 H, H-5), 6.25–5.95 (m, 2 H, H-1,2), 3–2.45 (m, 3 H, H-7,11a), 2.4–2 (m, 4 H, H-7a, CH_3), 1.85–1.2 (m, 8 H-8,9,10,11). Anal. Calcd for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 85.38; H, 8.46; N, 6.29. Picrate, mp 111–112 °C (from ethyl acetate–ethyl ether). Anal. Calcd for $C_{22}H_{22}N_4O_7$: C, 58.14; H, 4.88; N, 12.38. Found: C, 58.06; H, 4.93; N, 12.37.

Hydrogenation of 4,7-Phenanthroline. 4,7-Phenanthroline (5 g, 27.7 mmol) was dissolved in CF_3COOH (35 mL), PtO_2 (0.75 g) was added, and the mixture was hydrogenated at 50 psi of H_2 in a Parr shaker. After 10 h, when the pressure had dropped 8.6 psi (111 mmol of H_2), the catalyst was filtered off, and the solution was diluted with water. The aqueous solution was chilled in ice, made basic with concentrated NaOH, and extracted with chloroform. The organic solution was dried over Na_2SO_4 and the solvent distilled off. The crude residue (5.63 g) was stirred with acetic anhydride (8 mL) at 100 °C for 5 h. The solution was diluted with water and the solid formed was collected. Purification by column chromatography (SiO_2; chloroform/acetic acid, 95/5) afforded 4,7-diacetyl-1,2,3,4,7,8,9,10-octahydro-4,7-phenanthroline (**9**): 3.12 g; mp 184–185 °C (from ethyl acetate) (lit.[16] mp 181–182 °C); NMR ($CDCl_3$) δ 7.07 (br s, 2 H, H-5.6), 3.75 (t, J = 6 Hz, 4 H, H-3.8), 2.62 (t, J = 6 Hz, 4 H, H-1.10), 2.22–1.7 (m, 10 H, CH_3 and H-2,9).

The aqueous filtrate was made basic with concentrated NaOH and extracted with chloroform, and the organic phase was dried on Na_2SO_4 and evaporated. The residue, chromatographed on a silica gel column eluted with a mixture of ethyl acetate, acetone, methanol, and acetic acid (45:45:7:3), afforded the following compounds in order of elution. (a) First eluted was **9**. (b) 4-Acetyl-1,2,3,4-tetrahydro-4,7-phenanthroline (**10**): mp 119–120 °C (from benzene–petroleum ether) (lit.[17] mp 121 °C); NMR ($CDCl_3$) δ 8.77 (dd, J_{8-9} = 4.5 Hz, J_{8-10} = 1.5 Hz, 1 H, H-8), 8.15 (dd, J_{10-9} = 9 Hz, J_{10-8} = 2.2 Hz, 1 H, H-10), 7.87 (d, J_{6-5} = 9 Hz, 1 H, H-6), 7.65 (d, J_{5-6} = 9 Hz, 1 H, H-5), 7.5–7.17 (m, 1 H, H-9), 3.8 (t, J_{3-2} = 6 Hz, 2 H, H-3), 3.05 (t, J_{1-2} = 9 Hz, 2 H, H-1), 2.4–1.8 (m, 5 H, CH_3 and 2-H). (c) 5,6-Dihydro-4,7-phenanthroline (**11**): mp 129 °C (from ligroin) (lit.[18] mp 129.5–130.5 °C); NMR ($CDCl_3$) δ 8.36 (dd, J_{2-3} = J_{8-9} = 4.5 Hz, J_{1-3} = J_{8-10} = 1.5 Hz, 2 H, H-3.8), 7.8 (dd, J_{1-2} = J_{9-10} = 7.5 Hz, J_{1-3} = J_{8-10} = 1.5 Hz, 2 H, H-1,10), 7.25–6.95 (m, 2 H, H-2,9), 3.12 (s, 4 H, H-5,6). (d) 4-Acetyl-1,2,3,4,4a,5,6,10b-octahydro-4,7-phenanthroline (**12**) was obtained as an isomeric mixture. The total yields of reduced compounds were as follows: **9**, 44%; **10**, 4%; **11**, 5%; **12**, 39%.

The reduction of 4,7-phenanthroline was carried out also at atmospheric pressure and at room temperature by using the same reagents. The hydrogenation was carried out until the theoretical amount of hydrogen had been consumed (51 h). After filtration of the catalyst, the solution was worked up as described above. The total yields of reduced compounds were as follows: **9**, 18%; **10**, 2%; **11**, 22%; **12**, 46%.

***trans*- and *cis*-1,2,3,4,4a,5,6,10b-Octahydro-4,7-phenanthroline (13, 14).** A solution of **12** (2 g, 8.6 mmol) in HBr 48% (24 mL) was refluxed for 14 h. After cooling, the solution was made basic with concentrated NaOH and extracted with chloroform. The organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was chromatographed on a silica gel column with methanol/concentrated ammonium hydroxide (97/3) as the eluent to give, in the order of elution and after evaporation of solvent, *trans*-1,2,3,4,4a,5,6,10b-octahydro 4,7-phenanthroline [**13**: 1.06 g (69%); mp 71–72 °C (from cyclohexane)] and the cis isomer **14** as a liquid: 0.48 g (29%); bp 112 °C (0.25 mmHg).

For trans isomer **13**: IR (Nujol) 3280 (NH) cm^{-1}; NMR ($CDCl_3$) δ 8.5–8.3 (m, 1 H, H-8), 7.7-7.45 (m, 1 H, H-10), 7.25–6.95 (m, 1 H, H-9), 3.3–1 (m, 13 H); UV λ_{max} (EtOH), 207 nm (log ϵ 3.75); 268 (3.64), 276 (3.53); mass spectrum, m/e 188 (M^+); ^{13}C NMR ($CDCl_3$) δ 156.3 (s, C-6a), 146.7 (d, C-8), 133.8 (s, C-10a), 133 (d, C-10), 120.9 (d, C-9), 58.5 (d, C-4a), 46.8 (t, C-3), 42.5 (d, C-10b), 31.9 (C-1), 30.3 (C-5), 29 (C-6), 26.6 (t, C-2). Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.49; H, 8.62; N, 15.06.

For cis isomer **14**: IR (Nujol) 3280 (NH) cm^{-1}; NMR ($CDCl_3$) δ 8.5-8.3 (m, 1 H, H-8); 7.6–7.4 (m, 1 H, H-10), 7.2–6.9 (m, 1 H, H-9), 3.4–0.9 (m, 13 H); UV λ_{max} (EtOH), 207 nm (log ϵ 3.75), 268 (3.64), 276 (3.52); mass spectrum, m/e 188 (M^+); ^{13}C NMR ($CDCl_3$) δ 156.5 (s, C-6a), 146.6 (d, C-8), 135.3 (d, C-10), 134.5 (s, C-10a), 52.5 (d, C-4a), 43.5 (t, C-3), 37.9 (d, C-10b), 30.2 (C-1), 29 (C-5), 26.1 (C-6), 23.9 (t, C-2). Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.62; H, 8.50; N, 14.63.

***trans*- and *cis*-4-Methyl-1,2,3,4,4a,5,6,10b-octahydro-4,7-phenanthroline (15, 16).** Compound **13** or **14** (0.1 g, 0.53 mmol), 99% formic acid (0.14 mL), and 40% aqueous formaldehyde (0.12 mL) were stirred at room temperature overnight and then heated on a steam bath for 2 h. Concentrated HCl (0.8 mL) was added, and the excess of formic acid and formaldehyde were distilled off. The residue was dissolved in water, made alkaline with strong

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NaOH, and extracted with ether. The extracts were dried (Na_2SO_4), and after evaporation of the solvent they gave an oil, 0.1 g, (92%). In the case of trans isomer **15** the oil was recrystallized from petroleum ether; mp 47 °C. The cis isomer **16** was distilled, bp 124 °C (0.4 mmHg).

For trans isomer **15**: IR ($CHCl_3$, c = 0.048 g/mL) 2945, 2860, 2795 (strong aliphatic C–H stretching), 1575 cm^{-1}; NMR ($CDCl_3$) δ 8.5–8.3 (m, 1 H, H-8), 7.72–7.5 (m, 1 H, H-10), 7.28–7 (m, 1 H, H-9), 3.3–1 (m, 12 H), 2.4 (s, 3 H, CH_3). Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.21; H, 8.89; N, 13.81.

For cis isomer **16**: IR ($CHCl_3$, c = 0.048 g/mL) 2940, 2880, 2795 (weak aliphatic C–H stretching), 1575 cm^{-1}; NMR ($CDCl_3$) δ 8.5–8.2 (m, 1 H, H-8), 7.65–7.3 (m, 1 H, H-10), 7.2–6.9 (m, 1 H, H-9), 3.32–1.1 (m, 12 H), 2.35 (s, 3 H, CH_3). Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.11; H, 8.92; N, 13.75.

***trans*- and *cis*-4-(Ethoxycarbonyl)-1,2,3,4,4a,5,6,10b-octahydro-4,7-phenanthroline (17, 18).** To a solution of **13** or **14** (0.85 g, 4.5 mmol) and pyridine (0.37 mL, 4.58 mmol) in chloroform (15 mL), cooled at 0 °C, was added ethyl chloroformate (0.6 mL, 6.2 mmol) in chloroform (10 mL) with stirring which was continued for 24 h at room temperature. The solvent was evaporated in vacuo, and the residue was treated with water. The solution, after neutralization with 2 N NaOH, was extracted with chloroform. The organic layer, after being dried on Na_2SO_4 and after evaporation of the solvent in vacuo, gave a residue, yield 93%.

Trans isomer **17**: mp 66–67 °C (from petroleum ether); IR (Nujol) 1705 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 8.5–8.2 (m, 1 H, H-8), 7.65–7.35 (m, 1 H, H-10), 7.2–6.8 (m, 1 H, H-9), 4.35–3.7 (m, 3 H, OCH_2, H_{ax}-4a), 4.1 (q, J = 7.5 Hz, 2 H, OCH_2), 3.5–1.52 (m, 11 H), 1.25 (t, J = 7.5 Hz, 3 H, CH_3). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.32; H, 7.81; N, 10.82.

Cis isomer **18**: mp 65–67 °C (from petroleum ether); IR (Nujol) 1675 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 8.5–8.2 (m, H-8), 7.5–7.2 (m, 1 H, H-10), 7.15–6.8 (m, 1 H, H-9), 4.8-3.75 (m, 4 H, OCH_2, H-3), 4.15 (q, J = 7.5 Hz, 2 H, OCH_2), 3.25–1.45 (m, 10 H), 1.25 (t, J = 7.5 Hz, 3 H, CH_3). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.12; H, 7.79; N, 10.9.

***trans*- and *cis*-4-Acetyl-1,2,3,4,4a,5,6,10b-octahydro-4,7-phenanthroline (19, 20).** A solution of **13** or **14** (0.5 g, 2.6 mmol) in acetic anhydride (3 mL) was refluxed for 5 h, cooled, diluted with water, neutralized with strong NaOH, and extracted with chloroform. The organic layer, after being dried on Na_2SO_4 and after evaporation of the solvent, gave a residue which was recrystallized; yield 98%.

Trans isomer **19**: mp 150–151 °C (from ethyl acetate); IR (Nujol) 1635 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 8.42–8.2 (m, 1 H, H-8), 7.6–7.32 (m, 1 H, H-10), 7.2–6.85 (m, 1 H, H-9), 3.7–1.1 (m, 15 H), 2.1 (s, 3 H, CH_3). Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 73.11; H, 7.95; N, 12.26.

Cis isomer **20**: mp 189–190 °C (from ethyl acetate); IR (Nujol) 1620 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 8.45–8.2 (m, 1 H, H-8), 7.5–7.22 (m, 1 H, H-10), 7.2–6.85 (m, 1 H, H-9), 5.25–3.5 (m, 2 H, H-3), 3.3–1.2 (m, 12 H), 2.12 (s, 3 H, CH_3). Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 72.96; H, 7.92; N, 12.23.

***trans*-6-Methyl-8-acetyl-7a,8,9,10,11,11a-hexahydro-7*H*-pyrrolo[3,2,1-*g*,*h*]-4,7-phenanthroline (22).** A suspension of $NaHCO_3$ (3 g) in anhydrous ethanol (25 mL) containing bromide **21** (1 g, 2.7 mmol) was stirred under N_2 at 50 °C for 5 h and then refluxed for 1 h. After cooling, the solution was filtered, and the filtrate was evaporated in vacuo. The residue, suspended in water, was extracted several times with chloroform. The extracts, filtered through silica gel, were evaporated, and the residue was recrystallized: yield 55%; mp 228–229 °C (from benzene); IR (Nujol) 1630 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 7.7–7.4 (m, 1 H, H-3), 7 (s, 1 H, H-5), 6.45–6.1 (m, 2 H, H-1,2), 4.15–3.7 (m, 2 H, H_{ax}-9, H-7a), 3.4–1.1 (m, 7 H, H-7,9e,10,11), 2.2 (s, 3H, 6-CH_3), 2.1 (s, 3 H, $COCH_3$). Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 76.07; H, 7.56; N, 10.32.

***trans*-6,8-Dimethyl-7a,8,9,10,11,11a-hexahydro-7*H*-pyrrolo[3,2,1-*g*,*h*]-4,7-phenanthroline (23).** To a solution of **17** (1.25 g, 4.8 mmol) in ethyl acetate (20 mL) was added dropwise bromoacetone (5 mL) in ethyl acetate (10 mL). The mixture was heated at 60 °C under N_2 for 4 h. After the mixture cooled, the yellow precipitate was filtered and washed with ethyl acetate: 1.81 g (94%); mp 169 °C. The precipitate was dissolved in absolute ethanol containing $NaHCO_3$ (2 g). The suspension was refluxed for 2 h under N_2 and then filtered. The filtrate was evaporated, and the residue was poured into water (20 mL) and extracted with chloroform. The organic extracts were dried (Na_2SO_4) and then filtered through a short column of neutral alumina. After evaporation of the solvent, the oily residue was dissolved in anhydrous ether (15 mL) and added dropwise under N_2 to a stirred suspension of $LiAlH_4$ (0.5 g) in dry ether (15 mL). The reaction mixture was refluxed for 3 h and cooled. The excess of $LiAlH_4$ was destroyed with ethanol and 2 N NaOH and filtered. The solvent was evaporated, and the crude residue, dissolved in chloroform, was filtered through a short column of neutral alumina. The solution was washed with 2 N NaOH, dried ($CaSO_4$), and evaporated. The residue was recrystallized from hexane: mp 97–99 °C, (0.6 g, 56%); NMR ($CDCl_3$) δ 7.7–7.5 (m, 1 H, H-3), 7 (s, 1 H, H-5), 6.4–6.15 (m, 2 H, H-1,2), 3.4-1 (m, 16 H), 2.47 (s, 8-CH_3), 2.25 (s, 6-CH_3). Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 79.80; H, 8.41; N, 11.57.

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Registry No. 2, 80028-79-1; **3**, 80028-80-4; **3** picrate, 80028-81-5; **4**, 80028-82-6; **5**, 80028-83-7; **5** picrate, 80028-84-8; **6**, 80028-85-9; **6** picrate, 80028-86-0; **7**, 80028-87-1; **8**, 80028-88-2; **8** picrate, 80028-89-3; **9**, 80028-90-6; **10**, 80028-91-7; **11**, 80028-92-8; **12** (isomer 1), 80028-93-9; **12** (isomer 2), 80028-94-0; **13**, 80028-95-1; **14**, 80028-96-2; **15**, 80028-97-3; **16**, 80028-98-4; **17**, 80028-99-5; **18**, 80029-00-1; **21**, 80029-01-2; **22**, 80029-02-3; **23**, 80029-03-4; bromoacetone, 598-31-2; 5,6,7,8-tetrahydroquinoline, 10500-57-9; benzo[*f*]quinoline, 85-02-9; 4,7-phenanthroline, 230-07-9; *trans*-7-acetonyl-4-(ethoxycarbonyl)-1,2,3,4,4a,5,6,10b-octahydro-4,7-phenanthrolinium bromide, 80029-04-5.