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Centrally Acting Emetics. 10. Rigid Dopamine Congeners Derived from Octahydrobenzo[*f*]quinoline[1]

Joseph G. Cannon,* Gerard J. Hatheway,

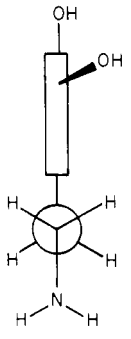
Division of Medicinal Chemistry and Natural Products, College of Pharmacy

John Paul Long, and Fouad M. Sharabi

Department of Pharmacology, College of Medicine, The University of Iowa, Iowa City, Iowa 52242. *Received February 6, 1976*

In a study of conformational requirements for certain dopaminergic agonist molecules, a series of conformationally predictable dopamine congeners related to *cis*- and *trans*-octahydrobenzo[*f*]quinoline was prepared. The complexity and equivocal character of the reduction of variously substituted 4-methyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinolines were demonstrated and studied. It was shown that several literature methods for reduction of these systems were in error regarding the stereochemical nature of the product(s). It has been concluded that geometrically specific and predictable reductions of these hexahydrobenzo[*f*]quinolines seem unlikely to attain, and a plausible rationalization for this conclusion has been proposed. Pharmacologic data on the compounds prepared are consistent with our earlier proposals of a biologically significant conformation of dopamine for emesis, the pecking syndrome in pigeons, and other physiological effects.

Prior communications[2] have proposed a biologically significant conformer **1** for dopamine, based upon studies



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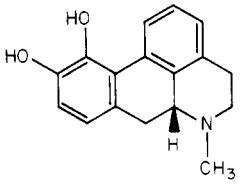

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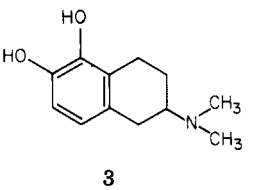

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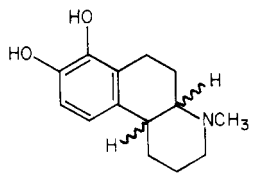

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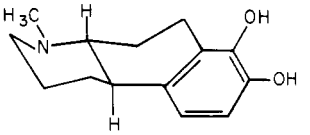

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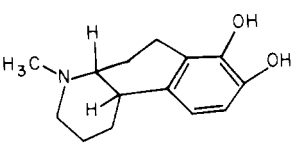
on 6a-(*R*)-apomorphine (**2**) and certain 2-aminotetralin derivatives related to "M-7" (**3**). In an investigation designed further to evaluate systems possessing this type of antiperiplanar dopamine disposition, the 1,2,3,4,4a,-5,6,10b-octahydrobenzo[*f*]quinoline system (**4**) was utilized as a means of attaining conformationally discrete dopamine-like systems. This structure is capable of existing as cis or trans isomers about the fusion of the B and C rings. The trans isomer **5** is a rigid molecule, in which the dopamine portion is held rigidly in the antiperiplanar conformation **1**. In addition, the entire molecule of **5** is planar, like the apomorphine and the aminotetralin **3**. The cis isomer of **5** is not a completely rigid molecule, and Dreiding models suggest that it can exist in two "flip" conformations, **6** and **7**.



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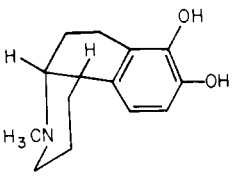

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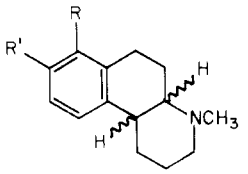
In **7**, the catechol ring and the amino group of the dopamine moiety are in a gauche disposition, which has been concluded[2] to be unfavorable for dopaminergic effects. The other cis conformational extreme (**6**) presents the catechol ring and the amino group in an anti orientation. However, it (like **7**) is a nonplanar molecule with the plane of the C ring almost perpendicular to that of the A and B rings. It was predicted that the geometries of both cis conformations would be unfavorable for emetic and other dopaminergic effects and that the rigidly held geometry of the trans isomer **5** would favor activity.

In addition to the cis and trans isomers of **4**, a series of nonoxygenated and monohydroxylated cis and trans

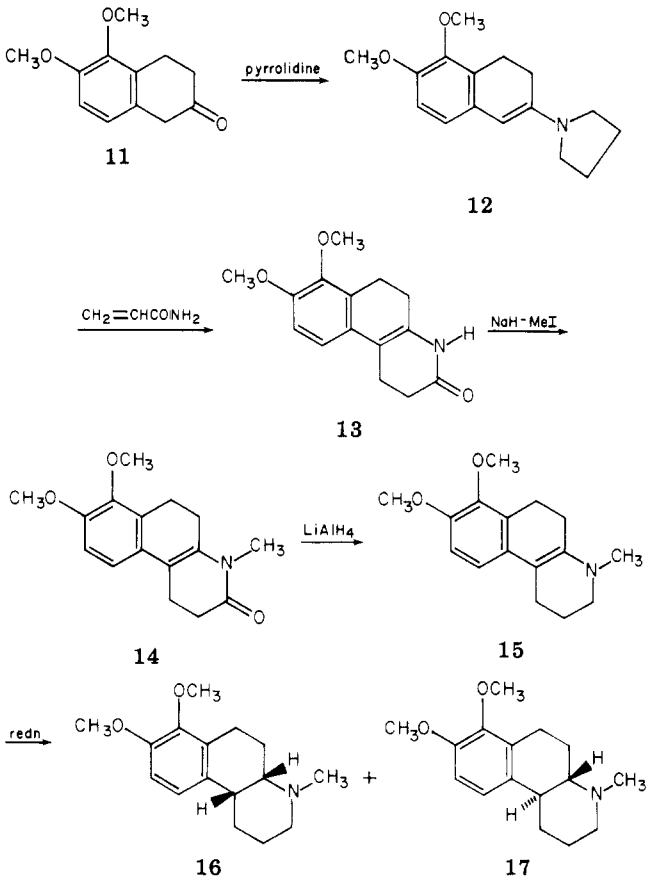
isomers 8–10 was selected for preparation, for further study of the contribution of phenolic groups to biological activity.



8, R = H; R′ = OH
9, R = OH; R′ = H
10, R = R′ = H

The compounds were prepared utilizing a modification of a method of Ninomiya et al.[3] as illustrated in Scheme I for the dioxygenated system **4**. The methyl ethers of the phenolic systems were cleaved and the resulting free phenols were submitted for biological study in the form of their hydrohalide salts.

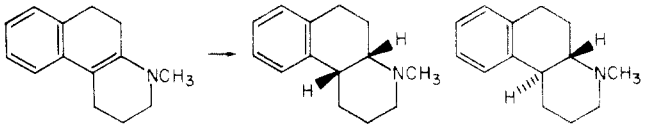
Scheme I. Preparation of 1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinolines



Pinder et al.[4] postulated that the emetic action of apomorphine in dogs is dopaminergically mediated, and the mechanism of action is postulated to be by direct dopamine receptor stimulation. McGeer[5] has also stated that Dopa may cause emesis by stimulation of the chemoreceptor trigger zone. Dopamine, Dopa, and apomorphine have been shown to suppress the positive chronotropic response induced by cardiac stimulation, by blocking sympathetic transmission in the heart.[6–10] These characteristic dopaminergic effects were used as models to evaluate the compounds described herein for possible dopaminergic effects.

Chemical Discussion. Attempts to reduce the amide carbonyl of the unsaturated lactam **13** (Scheme I) or of its congeners **23** and **25** resulted in isolation of unidentified substances. However, the N-methylated lactams (e.g., **14**) could be reduced to the hexahydro systems (**15**) in high yields with $LiAlH_4$ or "Red-Al". An attempt to prepare an *N*-methyl lactam (analogous to **14**) directly by treatment of the pyrrolidineenamine of 6-methoxy-2-tetralone with *N*-methylacrylamide provided a 7% yield of the desired product, and this one-step preparation was abandoned.

Nelson et al.[11] reported that hydrogenation of the hexahydrobenzo[*f*]quinoline **18** with PtO_2 in ethanol provided an 89% yield of the cis isomer **19**. However, no rigorous proof for the cis geometry was presented. In the



18 **19** **20**

present study, hydrogenation of **18** under these conditions resulted in a 70% yield of an octahydro product, for which gas chromatographic analysis indicated the presence of two components, in a ratio of approximately 6:1. The major component was assumed to be the cis isomer **19**, consistent with the conclusion of the Nelson group[11] which was based upon the premise that catalytic hydrogenation proceeds exclusively by cis addition across the C–C double bond. Horii and co-workers[12] found that reduction of **18** with $NaBH_4$ gave a 1:1.5 mixture of cis–trans isomers, and the Horii group and Smissman and co-workers[13] concluded that reduction of **18** with lithium in liquid ammonia gave a pure trans-fused product (**20**). Further, Horii et al.[14] have reported that reduction of 2-methyl-**18** with BH_3 in THF gave a mixture of isomers in which the trans predominated (83:17). Masamune and Koshi[15] found that hydrogenation of 1,2,3,4-tetrahydrobenzo[*f*]quinoline with PtO_2 in acetic acid gave equal but extremely low yields of *cis*- and *trans*-1,2,3,4,4a,5,6,10b-octahydro products. These workers conceded that they had not presented rigid proof to support their assignment of respective geometries to the cis and trans isomers. In the present work, treatment of **18** with lithium in liquid ammonia gave a product which was shown by gas chromatographic analysis to consist of a 1:1.45 mixture of products which, on the basis of work described subsequently, we concluded to be the ratio of cis–trans isomers. The NMR spectrum of this mixture exhibited sharp NCH_3 signals at δ 2.40 and 2.35. Catalytic hydrogenation of **18** in acetic acid and reduction with BH_3 in THF resulted in mixtures consisting predominantly of the cis (cis–trans ratios of 1.7:1 and 3.2:1, respectively). NMR data on these mixtures were similar to those obtained for the product of the lithium–ammonia reduction, except for variations in relative intensities of the two NCH_3 signals.

The mixture of isomers **19** and **20** could be separated by column chromatography and the chromatographed products were shown by GC to be homogeneous. The NMR spectrum of each isomer exhibited one NCH_3 (one at δ 2.40 and the other at 2.35), and mass spectra showed that the two compounds had identical molecular weights (201 mass units). The ir spectrum of the isomer with the NCH_3 signal at δ 2.35 was identical with a similar spectrum of the trans isomer **20** reported by Masamune and Koshi,[15] and the ir spectrum of the δ 2.40 isomer was identical with a similar spectrum of the cis isomer **19** reported by these workers. Thus, contrary to the earlier literature, it is concluded that neither chemical nor catalytic reduction of **18** gives rise to a single, predictable product, but rather, variable mixtures of cis and trans isomers are formed. Dyke[16] has concluded that, if their structures permit,

Table I. Agonist and Antagonist Properties of Congeners of Octahydrobenzo[f]quinoline

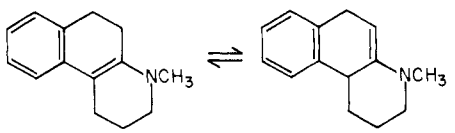
Compd	Cis or trans isomer	Rel emetic act. in dogs	Antagonism of apomorphine-induced emesis in dogs, ED_{50}, μmol/kg	Rel potency to inhibit apomorphine-induced pecking in pigeons, μmol/kg for ED_{50}	Hypothermia in mice, °C decrease in rectal temp induced by 10 mg/kg sc
Apomorphine		1.0[a]	N[c]	P[d]	−3.6
16	t	I[b]	N	1.0 (1.7)	N[c]
17	c	I	N	0.11 (15.1)	N
19	c	I	8.8	0.61 (2.7)	−1.6
20	t	I	4.1	0.74 (2.2)	−2.6
35	c	I	6.0	0.44 (3.8)	0.0
36	t	0.03	N	0.76 (2.2)	−1.4
37	c	I	10.0	0.10 (16.5)	−2.3
38	t	I	4.3	0.18 (9.0)	−2.4
39	c	0.02	N	0.20 (8.3)	−1.6
40	t	6.1	N	P[d]	−4.4

[a] ED_{50} = 0.144 μmol/kg based on the assumption that 0.32 μmol/kg of apomorphine produced maximal response. [b] I = inactive. [c] N = not tested. [d] P = induces pecking in pigeons. Compound **40** is 0.44 times as active as apomorphine.

Table II. Effect of Octahydrobenzo[f]quinolines on Positive Chronotropic Response Induced by Cardiac Nerve Stimulation in the Cat at 2 Hz Frequency

	In vitro (transmural stimulation of right atrium)		In vivo (stimulation of right cardioaccelerator nerve)	
Compd	Amt of drug causing 50% inhibn of control Δ in heart rate, estd ID_{50}, μM	Amt of drug causing 50% potentiation of control Δ in heart rate, μM	Amt of drug (μmol/kg) causing 50% inhibn of control change in heart rate	Amt of drug (μmol/kg) causing 50% potentiation of control Δ in heart rate
40	3.2×10^{-3}		5.2×10^{-3}	
39	4.7×10^{-2}		5.9×10^{-1}	
36	1.0×10^{-1}		>2.1	
35		9.0×10^{-1}		>3.3
38		12.7		Up to 3.3 (no effect)
37		3.9		Up to 3.3 (no effect)
20		7.8		Up to 3.5 (no effect)
19		1.6		Up to 3.5 (no effect)

enamines may participate in tautomeric equilibria involving two different C=C moieties, and that the relative amounts of each tautomer depend upon several steric and electronic factors. In the case of the hexahydrobenzo[f]quinoline system, an equilibrium between **18** and **21** may be operative. Catalytic hydrogenation of such an equi-



18 **21**

librium mixture (involving exclusive cis addition of hydrogen) would result in a mixture of cis- and trans-fused octahydro products, **19** and **20**, with the geometry of the products of **21** being determined by the approach of the hydrogen relative to the C-10b proton.

Horii et al.[17] have described and discussed "Bohlmann bands" in the ir spectra of variously substituted 1,2,3,-4,4a,5,6,10b-octahydrobenzo[f]quinolines. These bands are said to be characteristic of aliphatic C–H stretching in nitrogen heterocycles which have at least two hydrogens on carbons attached to nitrogen, both of which are oriented trans axial to the nonbonded electron pair on the nitrogen.[18] The N electron pair in the trans isomer **20** is flanked by two rigidly held trans-axial hydrogens, and its ir spectrum would be expected to exhibit strong absorption in the Bohlmann region. Indeed, the compound with the NCH_3 signal at δ 2.35 showed an intense band at 2850 cm^{-1}, whereas its isomer (NCH_3 δ 2.40) did not exhibit this band.

Reductive procedures on 7- and 8-methoxy and 7,8-dimethoxy analogues of **18** gave mixtures of products analogous to those described for **18**. In each instance, cis or trans stereochemistry of the pure components was assigned on the basis of the position of the NCH_3 signal in the NMR (δ 2.35 for trans; 2.40 for cis) and on the presence of a Bohlmann band at 2850 cm^{-1} for trans and complete absence of this band for cis isomers.

Pharmacology. Results. As indicated in Tables I and II, compounds in the series appear to possess both dopamine receptor agonist and antagonist properties. Compound **40**, the 7,8-dihydroxy trans system (Table I), was six times more potent than apomorphine as an emetic agent in dogs. Its cis isomer (**39**) was much less active, and none of the remaining compounds, at doses up to 5 mg/kg, induced emesis nor did they appear to induce any behavioral changes. Compounds **19**, **20**, **35**, **37**, and **38** antagonized apomorphine hydrochloride induced emesis in the dog. In the pigeon, all of the compounds except **40** demonstrated considerable antagonism to apomorphine-induced pecking. The ED_{50} for **16** (the most potent member of the series in this assay) was 0.44 mg/kg. The rectal temperature did not change after compound **35** and the most active compounds in this assay were apomorphine hydrochloride and **40**, which demonstrated hypothermic activity. The remaining compounds appeared to be intermediate in their ability to lower rectal temperature in mice.

In vivo and in vitro cardioaccelerator nerve experiments (Table II) demonstrated that **36**, **39**, and **40** were effective inhibitors of adrenergic transmission. **40** was effective at less than 1.0 μg/kg administered intravenously. The inhibitory actions of these compounds following cardioaccelerator nerve stimulation in the cat were prevented by prior iv administration of haloperidol (100 μg/kg). In the in vitro experiments, **19**, **20**, **35**, **37**, and **38** produced potentiation of adrenergic stimulation. Since this potentiation was not observed in vivo, no attempt was made

to evaluate the possible mechanism of action.

Discussion

Members of the series demonstrate highly potent agonist and antagonist properties when evaluated on various models for dopamine receptor interactions. In this series, it appears that the catechol substitution pattern is needed to produce maximal emetic activity in the dog. The *trans*-monohydroxy derivatives **36** and **38** were much less active than **40**. The antagonistic action of certain compounds on apomorphine-induced emesis was an unexpected response, and no structure–activity correlations were apparent in comparing the active agents. Likewise, in the pigeon, apomorphine-induced pecking was inhibited by all of the compounds except **40**. This marked antagonist action is also suggestive of the ability of these compounds to inhibit dopamine receptors, as was described for some related systems by Cheng and co-workers.[19] The hypothermia in mice which was produced by the antagonist compounds was not marked and was considerably less than would be obtained with haloperidol or chlorpromazine in similar doses. Likewise, the in vitro and in vivo cardioaccelerator nerve experiments in the cat demonstrated that the compounds that were highly effective in inhibiting transmission in these preparations were also effective emetics in the dog. With respect to antagonist activities, cis–trans isomerism about the B and C ring fusion does not seem to be important. However, for agonist activity, dramatic potency changes were observed between cis and trans isomers, e.g., emetic effects for **39** and **40**. It appears that the structural specificity for agonist activities in this series is much greater than the structural requirements for the apparent dopamine blocking activity. The biological results on the compounds in this series offer further support for our proposal of the prime import of the dopamine antiperiplanar conformer **1** for certain dopaminergic activities.

Experimental Section

Boiling points are uncorrected. Melting points were determined in open capillaries using a Thomas-Hoover Uni-Melt apparatus or a Mettler FP-5 automated melting point apparatus and are corrected. Ir spectra were obtained with a Beckman IR-10 instrument, and NMR spectra were recorded with a Varian Associates T-60 instrument (Me_4Si). Mass spectra were recorded on Finnegan 1015 S/L and Perkin-Elmer Hitachi RMU-66 spectrometers. GC was performed with a Hewlett-Packard 5750B instrument with a flame ionization detector. A glass column (6 ft × $^1/_8$ in. i.d.) packed with 3% OV-17 on 80–100 mesh Supelcoport (Supelco, Inc.) was used throughout. Flow rates were carrier gas (He), 70 ml/min (50 psig); H_2, 40 ml/min (13 psig); air, 440 ml/min (30 psig). Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and the Microanalytical Service, College of Pharmacy, University of Iowa. Where analyses are indicated by symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

The relative amounts of each component in isomeric mixtures were determined by relative peak heights of the NCH_3 signals in the NMR and relative peak areas in GC. Parallel results were obtained by each method.

Pharmacology. Methods. The compounds were evaluated for possible agonist and antagonist interactions with dopamine receptors. The dose–response curves for emetic activity were obtained using mongrel dogs, five dogs per dose, and the doses were varied by 0.3 log intervals. Apomorphine hydrochloride was used as the reference standard. All compounds were administered subcutaneously and the frequency of emesis was counted for 1 h following administration of the compounds. Dogs were also used to evaluate the ability to antagonize apomorphine hydrochloride induced emesis. The compounds were administered subcutaneously 15 min prior to the subcutaneous administration of 100 μg/kg of apomorphine hydrochloride. The frequency of emesis for 1 h was recorded and compared with the control value obtained with apomorphine hydrochloride in the same dogs (see Table I).

The ability of the compounds to induce or antagonize pecking in pigeons was evaluated. The frequency of pecking was recorded for 1 h following the intramuscular administration of the test compound. Apomorphine hydrochloride was the reference standard. The ability to antagonize pecking induced by apomorphine hydrochloride (1.6 μmol/kg) was quantified using the method of Cheng et al.[19] The compounds were administered intramuscularly 15 min prior to the intramuscular injection of apomorphine hydrochloride. The dose–response curves were obtained with five pigeons for each dose, and three separate doses of antagonists were varied by 0.3 log intervals (see Table I). The ability of the compounds to lower rectal temperature in mice was evaluated and measured every 15 min following the subcutaneous administration of 10 mg/kg of the test compound. The values reported in Table I represent the maximal temperature decrease, and it occurred 30–45 min following administration of the compounds. Values for each compound were the average responses obtained from three mice. Control animals showed a steady decrease of no more than 1.5 °C over a period of 3 h. The ability of the compounds to inhibit transmural stimulation of right atria of cats using in vitro and in vivo experiments was evaluated. In the in vitro experiments, field stimulation with a frequency of 2 Hz was used. The pulse duration was 5 ms and the voltage was maximal. Stimulation (10 s) was applied every 5 min and was used to activate the adrenergic nerve terminals.[20] Following the establishment of the control values for increase in heart rate, the compounds were added to the Feigan's solution and 5 min later the influence on transmural stimulation was determined. Both antagonism and potentiation of responses to nerve stimulation were observed. The in vivo preparations of the right cardioaccelerator nerves were the same as previously described.[21] In this preparation, inhibition of the positive chronotropic response to 2 Hz stimulation was evaluated. None of the compounds tested in this preparation demonstrated potentiation of the heart rate responses to cardioaccelerator nerve stimulation (see Table II).

3,4-Dihydro-2(1*H*)-naphthalenone (22). A procedure of Sims et al.[22] was employed, using 105 g (0.685 mol) of phenylacetyl chloride and 183 g (1.37 mol) of $AlCl_3$: yield, 63 g (68%); bp 100–102° (0.25 mm) [lit.[23] bp 140–143° (19 mm)].

1,4,5,6-Tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (23). Compound **22** (10.2 g, 0.07 mol), 7.5 g (0.105 mol) of pyrrolidine, and a catalytic amount of *p*-TsOH were refluxed in 200 ml of benzene under N_2 in a Dean-Stark apparatus for 3 h. Volatiles were evaporated under N_2 and 14.0 g (0.21 mol) of acrylamide was added. The resulting mixture was stirred for 1 h at 80° and then for 0.5 h at 130° to polymerize excess acrylamide. Addition of 100 ml of H_2O resulted in separation of a dark solid which was collected on a filter. Three recrystallizations from Et_2O (charcoal) gave 9.7 g (70%) of a white crystalline product: mp 179–180° (lit.[24] mp 176–177°).

4-Methyl-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (24). Compound **23** (10.0 g, 0.05 mol) and 13.0 g (0.055 mol) of NaH were refluxed in 200 ml of anhydrous dimethoxyethane for 3 h. MeI (28.6 g, 0.2 mol) was added to the cooled mixture and the resulting solution was refluxed for 3 h and stirred overnight at room temperature. Excess NaH was destroyed by addition of 5 ml of H_2O and the resulting mixture was evaporated on a steam bath under reduced pressure. Addition of 100 ml of benzene to the residue caused separation of NaI which was removed by filtration. Evaporation of the filtrate followed by azeotroping of residual H_2O with benzene left a viscous residue which crystallized from Me_2CO–hexane to give 10.0 g (93%) of crystalline material: mp 106.2° (lit.[13] mp 106–107°).

4-Methyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline (18). To 6.1 g (0.0285 mol) of **24** in 100 ml of dry benzene was added 24.8 g of a 70% solution (0.0855 mol) of sodium bis(2-methoxyethoxy)-aluminum hydride in benzene ("Red-Al") and the resulting solution was refluxed for 6 h. Excess hydride was destroyed by dropwise addition of 5 ml of H_2O to the cooled solution, and the solid Al salts were dissolved by addition of excess 50% KOH. The organic phase was separated, washed twice with 100-ml portions of H_2O, and dried ($MgSO_4$). Removal of volatiles left an oily residue which was distilled to give 4.3 g (85%) of a pale yellow oil: bp 114–116° (0.15 mm) [lit.[11] bp 119–125° (0.2 mm)]; NMR ($CDCl_3$) δ 2.70 (s, 3 H, NCH_3), 1.76–3.13 (m, 10 H, $-CH_2-$),

6.83–7.35 (m, 4 H, ArH). A MeI salt was recrystallized from MeOH–Et_2O: mp 200–203° (lit.[11] mp 186.5° dec).

Reduction of 4-Methyl-1,2,3,4,5,6-hexahydrobenzo[f]quinoline (18). Preparation of *cis*- and *trans*-4-Methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline (19 and 20). Method A. This was a variation of the method of Nelson et al.[11] Compound 18 (1.0 g, 0.005 mol) in 50 ml of anhydrous EtOH was hydrogenated at 50 psig in the presence of 0.04 g of PtO_2. Uptake of 1 equiv of H_2 was complete in 0.5 h. Removal of the catalyst and evaporation of volatiles gave an oil which was distilled at 85–90° (0.01 mm) to give 0.7 g (70%) of a pale yellow liquid: lit.[11] bp 90–92° (0.15 mm); NMR ($CDCl_3$) δ 1.72–3.15 (m, 12 H, $-CH_2-$, >CH–), 2.40 (s, 3 H, NCH_3). Anal. ($C_{15}H_{21}NO$) C, H, N. The ratio of cis–trans isomers in this material was estimated by GC to be 5.7:1.

Method B (H_2–PtO_2–AcOH). This was a variation of a method of Horii et al.[25] Compound 18 (0.7 g, 0.0035 mol) in 30 ml of glacial AcOH was hydrogenated at 15 psig in the presence of 0.55 g of PtO_2. Hydrogenation was complete in 0.5 h. The catalyst was removed and the reaction mixture was treated with excess saturated $NaHCO_3$ and was extracted with hexane. The extract was dried ($MgSO_4$) and evaporated to give 0.55 g (80%) of a yellow oil: NMR ($CDCl_3$) δ 1.52–3.08 (m, 12 H, $-CH_2-$, >CH–), 2.35, 2.40 (d, 3 H, NCH_3), 7.01–7.18 (m, 4 H, ArH). The ratio of cis–trans isomers in the material was estimated by GC and NMR to be 1.7:1.

Method C (Li–NH_3). This was carried out by the method of Horii et al.[12] Compound 18 (2.0 g, 0.0256 mol) in 10 ml of anhydrous Et_2O was added to 1.25 g (0.18 g-atom) of Li wire in 500 ml of liquid NH_3 and the resulting mixture was stirred for 5 h. Small portions of NH_4Cl were then added cautiously to the stirred solution until the deep blue color was discharged. The NH_3 was evaporated and the residual white mass was treated with 50 ml of H_2O and 50 ml of Et_2O. The organic phase was separated and the aqueous phase was extracted with four 50-ml portions of Et_2O. The combined Et_2O extracts were dried ($MgSO_4$) and evaporated to leave a yellow oil which was distilled at 97–104° (0.22 mm) to afford 1.5 g (75%) of a pale yellow liquid: NMR ($CDCl_3$) δ 1.52–3.08 (m, 12 H, $-CH_2-$, –CH–), 2.35, 2.40 (d, 3 H, NCH_3), 7.01–7.18 (m, 4 H, ArH). The ratio of cis–trans isomers in this material was estimated by GC and NMR to be 1:1.45.

Method D (B_2H_6–THF). To 1.0 g (0.005 mol) of 18 in 40 ml of anhydrous THF at 0° was added 9.0 ml of a 1 M solution (0.009 mol) of BH_3 in THF and the resulting solution was stirred for 1 h at room temperature. The solution was then refluxed for 1 h with 35 ml of glacial AcOH. After cooling, the reaction mixture was made basic to litmus with saturated $NaHCO_3$ and was extracted with three 50-ml portions of Et_2O. The combined organic phases were dried ($MgSO_4$) and evaporated. The residual oil was distilled, bp 85–90° (0.1 mm), to give 0.875 g (85%) of a pale yellow oil. The ratio of cis–trans isomers in this material was estimated by GC to be 3.22:1.

Separation of *cis*- and *trans*-4-Methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline (19 and 20). GC operating conditions were column temperature, 145°; injection port temperature, 210°; detector temperature, 265°. Retention times of 11.6 and 12.2 min were observed for the cis and trans isomers, respectively. Column chromatographic separation of 3.8 g of a 1:1.45 cis–trans mixture, obtained from method C, was accomplished with 1.0 kg of neutral alumina (Fischer 80–100 mesh, activated by heating at 160° for 24 h) in a 100 × 4.5 cm column wrapped in Al foil. The column was eluted with 4:1 benzene–$CHCl_3$ at a rate of 25 drops/min, collecting 11-ml fractions. A total of 2650 fractions was taken and their composition was monitored by GC, using the 1:1.45 cis–trans mixture as the external standard. Fractions 1810–2229 contained a single compound; they were pooled and evaporated under reduced pressure to give a yellow liquid which was distilled at 84–86° (0.05 mm). The clear distillate crystallized on standing, mp 35–37°, to give 1.5 g (38% from 18) of the trans isomer **20**. GC and NMR analysis indicated that this material was homogeneous: ir (film) 2780, 2850, 2940 cm^{-1} (aliphatic CH stretch); NMR ($CDCl_3$) δ 2.35 (s, 3 H, NCH_3), 1.70–3.02 (m, 12 H, $-CH_2-$, –CH–), 7.03–7.30 (m, 4 H, ArH). A mass spectrum exhibited a parent ion at *m/e* 201, corresponding to $C_{14}H_{19}N$. A HBr salt was recrystallized from EtOH: mp 228–230°. Anal. ($C_{14}H_{20}BrN$) C, H, N.

Fractions 2390–2600 were pooled and evaporated under reduced pressure to give a yellow oil which was distilled at 83–85° (0.15 mm) to give 0.8 g (20% from 18) of the cis isomer **19**, a clear oil which was shown by GC and NMR to be homogeneous: ir (film) 2780, 2940 cm^{-1} (aliphatic CH stretch); NMR ($CDCl_3$) δ 2.40 (s, 3 H, NCH_3), 1.55–3.11 (m, 12 H, $-CH_2-$, –CH–), 6.98–7.25 (m, 4 H, ArH). A mass spectrum exhibited a parent ion at *m/e* 201, corresponding to $C_{14}H_{19}N$. A HBr salt was recrystallized from EtOH, mp 204–206°. Anal. ($C_{14}H_{20}BrN$) C, H, N.

8-Methoxy-1,4,5,6-tetrahydrobenzo[f]quinolin-3(2*H*)-one (25). 6-Methoxy-3,4-dihydro-2(1*H*)-naphthalenone[22] (31.8 g, 0.18 mol), 21.2 g (0.3 mol) of pyrrolidine, a catalytic amount of *p*-TsOH, and 400 ml of benzene were treated as described for **23**. Treatment of the reaction mixture with 250 ml of H_2O caused separation of a dark solid which was collected on a filter. Three crystallizations from Me_2CO (charcoal) gave 19.0 g (44%) of white crystals: mp 205–207°; ir (KBr) 1650, 1670 cm^{-1} (C=O), 3100, 3200 (NH stretch); NMR ($CDCl_3$) δ 2.23–3.03 (m, 8 H, $-CH_2-$), 3.8 (s, 3 H, OCH_3), 6.66–7.10 (m, 3 H, ArH). Anal. ($C_{14}H_{15}NO_2$) C, H, N.

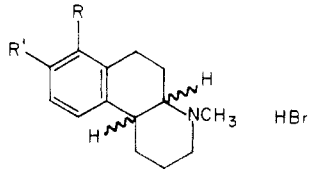
8-Methoxy-4-methyl-1,4,5,6-tetrahydrobenzo[f]quinolin-3(2*H*)-one (26). Compound **25** (22.9 g, 0.1 mol), 6.0 g (0.25 mol) of NaH, and 57.5 g (0.4 mol) of MeI in 400 ml of anhydrous dimethoxyethane were treated as described for **24**. The crude product was distilled to give 21.0 g (87%) of material: bp 182–184° (0.2 mm). This oil crystallized on standing: mp 73–76°; NMR ($CDCl_3$) δ 3.11 (s, 3 H, NCH_3). Anal. ($C_{15}H_{17}NO_2$) C, H, N.

4-Methyl-8-methoxy-1,2,3,4,5,6-hexahydrobenzo[f]quinoline (27). Compound **26** (20.6 g, 0.085 mol) in 400 ml of benzene was treated with 73.0 g of a 70% solution (0.252 mol) of sodium bis(2-methoxyethoxy)aluminum hydride as described for 18: yield, 16.6 g (85%) of a pale yellow oil; bp 149–151° (0.2 mm). Anal. ($C_{15}H_{19}NO$) C, H, N. A MeI salt was recrystallized from Me_2CO–MeOH: mp 226–228°. Anal. ($C_{16}H_{22}INO$) C, H, N.

Reduction of 4-Methyl-8-methoxy-1,2,3,4,5,6-hexahydrobenzo[f]quinoline (27). Preparation of *cis*- and *trans*-4-Methyl-8-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline (28 and 29). Compound **27** (10.25 g, 0.045 mol) and 1.8 g (0.047 mol) of $NaBH_4$ were stirred in 100 ml of anhydrous EtOH at room temperature for 6 h. Excess hydride was destroyed by careful addition of AcOH to the cooled solution. The solution was then made basic to litmus with 5% KOH and 100 ml of Et_2O and 100 ml of H_2O were added. The organic phase was separated and the aqueous layer was extracted with three 50-ml portions of Et_2O. The combined organic solutions were dried ($MgSO_4$) and evaporated, and the residual oil was distilled to give 8.2 g (79%) of a pale yellow oil: bp 154–156° (0.3 mm). The ratio of cis–trans isomers in this material was estimated by GC and NMR to be 1:1: NMR ($CDCl_3$) δ 1.45–3.13 (m, 12 H, $-CH_2-$, >CH–), 2.35, 2.40 (d, 3 H, NCH_3), 3.76 (s, 3 H, OCH_3), 6.63–7.28 (m, 3 H, ArH).

Separation of *cis*- and *trans*-4-Methyl-8-methoxy-1,2,3,-4,4a,5,6,10b-octahydrobenzo[f]quinoline (28 and 29). GC operating conditions were column temperature, 182°; injection port temperature, 250°; detector port temperature, 250°. Retention times of 10.2 and 10.8 min, respectively, were observed for the cis and trans isomers. Column chromatographic separation of 6.0 g of a 1:1 cis–trans mixture was carried out as described for **19** and **20**. The column was eluted with 1:1 benzene–$CHCl_3$ at a rate of 28–30 drops/min, collecting 11-ml fractions. A total of 830 fractions was taken, and their composition was monitored by GC, using the 1:1 cis–trans mixture as the external standard. Fractions 170–350 contained a single component; 351–620 contained a mixture; and 621–830 contained a single component. Pooled fractions 170–350 were evaporated under reduced pressure to give a yellow oil which was distilled at 112–115° (0.01 mm). The clear distillate crystallized upon standing, mp 45–48°, to give 1.0 g (17%) of **29**. This was shown by GC to be homogeneous: ir (film) 2780, 2850, 2940 cm^{-1} (aliphatic CH stretch); NMR ($CDCl_3$) δ 1.67–3.00 (m, 12 H, $-CH_2-$, >CH–), 2.35 (s, 3 H, NCH_3), 3.76 (s, 3 H, OCH_3), 6.63–7.27 (m, 3 H, ArH). A mass spectrum exhibited a parent ion at *m/e* 231, corresponding to $C_{15}H_{21}NO$. Fractions 621–830 were pooled and evaporated under reduced pressure to give a pale yellow oil. Distillation at 105–107° (0.01 mm) gave 0.95 g (16%) of a clear oil. This material was shown

Table III. Phenolic 1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinoline Salts



Compd	R	R	Geometry of ring fusion	Yield, %	Mp, °C[a]	Formula	Analyses
35	OH	H	Cis	79	264 dec	$C_{14}H_{20}BrNO$	C, H, N
36	OH	H	Trans	82	318 dec	$C_{14}H_{20}BrNO$	C, H, N
37	H	OH	Cis	85	266-268	$C_{14}H_{20}BrNO$	C, H, N
38	H	OH	Trans	70	315-320	$C_{14}H_{20}BrNO$	C, H, N
39	OH	OH	Cis	88	274-276	$C_{14}H_{20}BrNO_2$	C, H, N
40	OH	OH	Trans	78	294-296	$C_{14}H_{20}BrNO_2$	C, H, N

[a] Recrystallized from EtOH-Et_2O.

by GC to be homogeneous: ir (film) 2780, 2940 cm^{-1} (aliphatic CH stretch); NMR ($CDCl_3$) δ 1.67–3.00 (m, 12 H, $-CH_2-$, –CH–), 2.40 (s, 3 H, NCH_3), 3.76 (s, 3 H, OCH_3), 6.63–7.18 (m, 3 H, ArH). A mass spectrum exhibited a parent ion at *m/e* 231, corresponding to $C_{15}H_{21}NO$.

7-Methoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (30). 5-Methoxy-3,4-dihydro-2(1*H*)-naphthalenone (35.0 g, 0.2 mol), 29.4 g (0.3 mol) of pyrrolidine, 21.2 g (0.3 mol) of acrylamide, a catalytic amount of *p*-TsOH, and 400 ml of benzene were treated as described for **23**. The crude product was washed with two 25-ml portions of Et_2O to yield 22.7 g (54%) of a white powder: mp 247.6°. Anal. ($C_{14}H_{15}NO_2$) C, H, N.

7-Methoxy-4-methyl-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (31). Compound **30** (19.0 g, 0.083 mol) was treated with 2.2 g (0.091 mol) of NaH and 47.5 g (0.332 mol) of MeI in 300 ml of anhydrous dimethoxyethane as described for **24**. The initially formed crystalline product (18.2 g, 90%) was analytically pure: mp 173.7°; NMR ($CDCl_3$) δ 3.13 (s, 3 H, NCH_3). Anal. ($C_{15}H_{17}NO_2$) C, H, N.

4-Methyl-7-methoxy-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline (32). Compound **31** (15.2 g, 0.063 mol) in 500 ml of anhydrous benzene was treated with 54.5 g of a 70% solution of Red-Al as described for **18**. The crude product was recrystallized from hexane to give 13.4 g (93%) of a solid: mp 62–64°. Anal. ($C_{15}H_{19}NO$) C, H, N.

Reduction of 4-Methyl-7-methoxy-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline (32). Preparation of *cis*- and *trans*-4-Methyl-7-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (33 and 34). Compound **32** (7.0 g, 0.033 mol) was reduced with 1.1 g (0.03 mol) of $NaBH_4$ in 100 ml of anhydrous EtOH as described for reduction of **27**. The crude product consisted of 7.1 g (94%) of an oily white solid. The ratio of cis–trans isomers in this material was estimated by GC and NMR to be 1.47:1: NMR ($CDCl_3$) δ 1.43–3.20 (m, 12 H, $-CH_2-$, –CH–), 2.35, 2.40 (d, 3 H, NCH_3), 3.78 (s, 3 H, OCH_3), 6.50–7.22 (m, 3 H, ArH).

Separation of *cis*- and *trans*-4-Methyl-7-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (33 and 34). GC operating conditions were column temperature, 200°; injection port temperature, 230°; detector temperature, 265°. Retention times of 5.8 and 6.08 min, respectively, were observed for the cis and trans isomers. Column chromatographic separation of 5.2 g of a 1.47:1 cis–trans mixture was accomplished as described for **19** and **20**. The column was eluted with 1:1 benzene–$CHCl_3$ at a rate of 18–25 drops/min, collecting 10-ml fractions. A total of 1030 fractions was taken, and their composition was monitored by GC, using the 1.47:1 cis–trans mixture as the external standard. Fractions 710–829 contained a single component, 830–899 contained a mixture, and 900–1030 contained a single component. Pooled fractions 710–829 were evaporated under reduced pressure to give a solid which was recrystallized from hexane to give 1.0 g (19%) of white crystals of **34**, mp 84–86°. This material was shown by GC to be homogeneous: ir (KBr) 2750, 2830, 2920 cm^{-1} (aliphatic CH stretch); NMR ($CDCl_3$) δ 1.23–3.17 (m, 12 H, $-CH_2-$, >CH–), 2.35 (s, 3 H, NCH_3), 3.78 (s, 3 H, OCH_3), 6.58–7.32 (m, 3 H, ArH). A mass spectrum exhibited a parent ion at *m/e* 231, corresponding to $C_{15}H_{21}NO$. Anal. ($C_{15}H_{21}NO$) C, H, N. Pooled fractions 900–1030 were evaporated under reduced pressure to give a solid which was recrystallized from hexane to give 2.0 g (38%) of white crystals of **33**, mp 51–53°. This material was shown by GC to be homogeneous: ir (KBr) 2880, 2940 cm^{-1} (aliphatic CH stretch); NMR ($CDCl_3$) δ 1.43–3.17 (m, 12 H, $-CH_2-$, –CH–), 2.40 (s, 3 H, NCH_3), 3.78 (s, 3 H, OCH_3), 6.57–7.25 (m, 3 H, ArH). A mass spectrum exhibited a parent ion at *m/e* 231, corresponding to $C_{15}H_{21}NO$. Anal. ($C_{15}H_{21}NO$) C, H, N.

7,8-Dimethoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (13). 5,6-Dimethoxy-3,4-dihydro-2(1*H*)-naphthalenone[26] (16.0 g, 0.079 mol), 8.25 g (0.115 mol) of pyrrolidine, 8.25 g (0.115 mol) of acrylamide, a catalytic amount of *p*-TsOH, and 250 ml of benzene were treated as described for **23**. The crude product was recrystallized three times from Me_2CO(charcoal) to give 6.6 g (33%) of white crystals, mp 233–236°. Anal. ($C_{15}H_{17}NO_3$) C, H, N.

7,8-Dimethoxy-4-methyl-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (14). Compound **13** (8.5 g, 0.033 mol) was treated with 0.850 g (0.036 mol) of NaH and 18.9 g (0.132 mol) of MeI in 200 ml of anhydrous dimethoxyethane as described for **24**. The crude product was recrystallized from Me_2CO to give 7.2 g (82%) of white crystals: mp 142–144°; NMR ($CDCl_3$) δ 3.13 (s, 3 H, NCH_3). Anal. ($C_{16}H_{19}NO_3$) C, H, N.

4-Methyl-7,8-dimethoxy-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline (15). Compound **14** (6.0 g, 0.022 mol) in 250 ml of anhydrous benzene was treated with 19.0 g of a 70% solution (0.066 mol) of sodium bis(2-methoxyethoxy)aluminum hydride as described for **18**. The crude product was recrystallized from hexane to give 4.55 g (80%) of pink crystals, mp 91.3°. Anal. ($C_{16}H_{21}NO_2$) C, H, N. A MeI salt was recrystallized from Me_2CO–MeOH: mp 178° dec. Anal. ($C_{17}H_{24}INO_2$) C, H, N.

Reduction of 4-Methyl-7,8-dimethoxy-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline (15). Preparation of *cis*- and *trans*-4-Methyl-7,8-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (16 and 17). Compound **15** (7.6 g, 0.292 mol) in 200 ml of glacial AcOH was hydrogenated at 15 psig in the presence of 3.5 g of 10% Pd/C. The reduction was complete in 1.5 h. The catalyst was removed by filtration and the filtrate was evaporated on a steam bath under reduced pressure. The residue was taken up in 10% NaOH and the resulting solution was extracted with three 100-ml portions of Et_2O. The combined extracts were dried ($MgSO_4$) and evaporated to give a solid which was recrystallized from hexane to give 6.0 g (79%) of material, mp 66–74°. The ratio of cis–trans isomers in this material was estimated by GC and NMR to be 2:1: NMR ($CDCl_3$) δ 2.35, 2.40 (d, 3 H, NCH_3), 1.6–3.02 (m, 12 H, $-CH_2-$, >CH–), 3.80, 3.82 (d, 6 H, OCH_3), 6.63–6.97 (m, 2 H, ArH).

Separation of *cis*- and *trans*-4-Methyl-7,8-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (16 and 17). GC operating conditions were column temperature, 200°; injection port temperature, 230°; detector temperature, 265°. Retention times of 10.2 and 11.0 min, respectively, were observed for the cis and trans isomers. Column chromatographic separation of 5.2 g of a 2:1 cis–trans mixture was accomplished as described for **19** and **20**. The column was eluted with $CHCl_3$ at a rate of 40 drops/min, collecting 10-ml fractions. A total of 379 fractions was collected, and their composition was monitored by GC using

the 2:1 cis-trans mixture as the external standard. Fractions 235–282 contained a single component; 283–309 contained a mixture; and 310–379 contained one component. Pooled fractions 235–282 were evaporated under reduced pressure to give a solid which was recrystallized from hexane to give 0.4 g (8%) of white crystals of **17**, mp 87–89°. This material was shown by GC to be homogeneous: ir (KBr) 2780, 2830, 2920 cm^{-1} (aliphatic CH stretch); NMR ($CDCl_3$) δ 1.67–3.07 (m, 12 H, $-CH_2-$, –CH–), 2.36 (s, 3 H, NCH_3), 3.82, 3.85 (d, 6 H, OCH_3), 6.68, 6.82, 6.95, 7.10 (q, 2 H, ArH). A mass spectrum exhibited a parent ion at *m/e* 261, corresponding to $C_{16}H_{23}NO_2$. Anal. ($C_{16}H_{23}NO_2$) C, H, N. Fractions 310–379 were pooled and evaporated under reduced pressure to give a solid which was recrystallized from hexane to give 1.2 g (23%) of white crystals of **16**, mp 81–82°. This material was shown by GC to be homogeneous: ir (KBr) 2870, 2930 cm^{-1} (aliphatic CH stretch); NMR ($CDCl_3$) δ 1.47–3.13 (m, 12 H, $-CH_2-$, –CH–), 2.42 (s, 3 H, NCH_3), 3.87, 3.88 (d, 6 H, OCH_3), 6.70, 6.85, 6.90, 7.03 (q, 2 H, ArH). A mass spectrum exhibited a parent ion at *m/e* 261, corresponding to $C_{16}H_{23}NO_2$. Anal. ($C_{16}H_{23}NO_2$) C, H, N.

Ether Cleavage Reactions. The appropriate methyl ether (0.5 g) was heated in 16 ml of 48% HBr under N_2 at 125–130° for 4 h. After removal of volatiles under reduced pressure, residual H_2O was azeotroped with EtOH, and the solid residue was recrystallized. See Table III.

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