Articles

Rigid Congeners of Dopamine Based on Octahydrobenzo[*f*]quinoline: Peripheral and Central Effects

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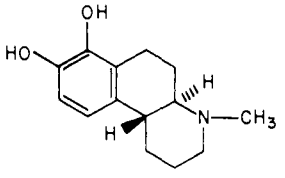
A series of *cis*- and *trans*-dihydroxyoctahydrobenzo[*f*]quinoline congeners of dopamine has been prepared, in which the N substituent is H, ethyl, or *n*-propyl. The trans isomers include the dopamine moiety held rigidly in an antiperiplanar disposition which is believed to be necessary for certain central and peripheral dopaminergic effects. The cis isomers are flexible molecules; the dopamine moiety lacks conformational integrity and it can exist in a conformation which is believed not to favor dopaminergic activity. The trans series of compounds was shown to possess a high level of central and peripheral dopaminergic effects, whereas the cis series was of low activity or was inert. These data further support previous proposals concerning stereochemical requirements for certain dopaminergic agonist activity.

A prior communication[1] described prominent dopamine-like effects of a *trans*-octahydrobenzo[*f*]quinoline system **1**. The present communication describes the



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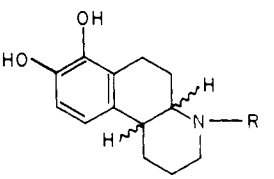
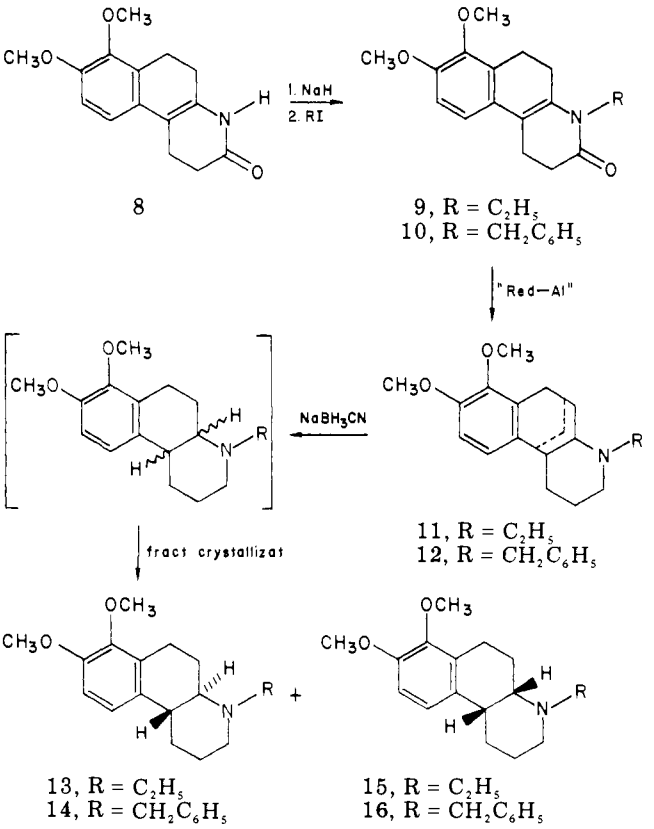


cis	trans
2, R = H	5, R = H
3, R = C_2H_5	6, R = C_2H_5
4, R = *n*-C_3H_7	7, R = *n*-C_3H_7

preparation and some biological effects of cis- and trans-fused isomers in which the N substituent has been varied (**2–7**). Preparation of the *trans*-octahydrobenzo[*f*]quinoline system, typified by **1**, has been described in detail,[1] and that portion of the sequence relevant to the present study is outlined in Scheme I. The cyclic enamine reduction product of **9** or **10** consists of an equilibrium mixture of two double-bond positional isomers[1,2] of **11** and **12**. Reduction of these types of enamine mixtures leads invariably to mixtures of cis- and trans-fused systems, regardless of the method of reduction employed.[1] It was found that the *N*-ethyl and *N*-benzyl cis–trans mixtures could be separated into pure cis and trans products by simple fractional crystallization. Catalytic N-debenzylation of **14** (Scheme II) provided the pure trans secondary amine **17** which is amenable to appropriate N-alkylation. While not all of the N-alkylated compounds in the present study were prepared by this sequence involving the *N*-benzyl derivative, the method is presented as a general one for preparation of variously N-alkylated pure *cis*- and *trans*-7,8-dimethoxylated octahydrobenzo[*f*]quinolines. In earlier work,[1] separation of cis and trans isomers of *N*-methyl homologues could be effected only by a laborious column chromatographic technique.

Scheme I. Preparation of *cis*- and *trans*-*N*-Ethyl and -*N*-Benzyl Systems



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9, R = C_2H_5
10, R = $CH_2C_6H_5$

11, R = C_2H_5
12, R = $CH_2C_6H_5$

13, R = C_2H_5
14, R = $CH_2C_6H_5$

15, R = C_2H_5
16, R = $CH_2C_6H_5$

The unsaturated lactam **8** (Scheme III) was reduced catalytically to the saturated lactam **19** which appeared to consist of a single isomer. The lactam **19** resisted reduction with lithium aluminum hydride or "Red-Al"; however, reduction with sodium borohydride–acetic acid[3]

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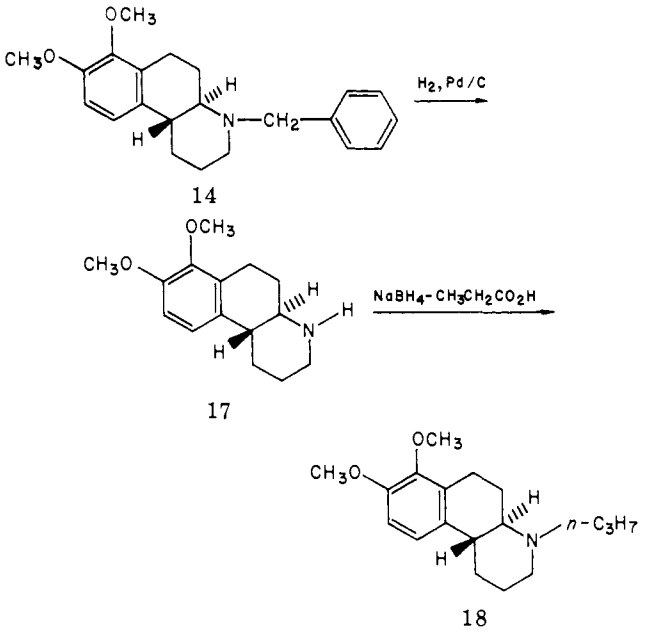
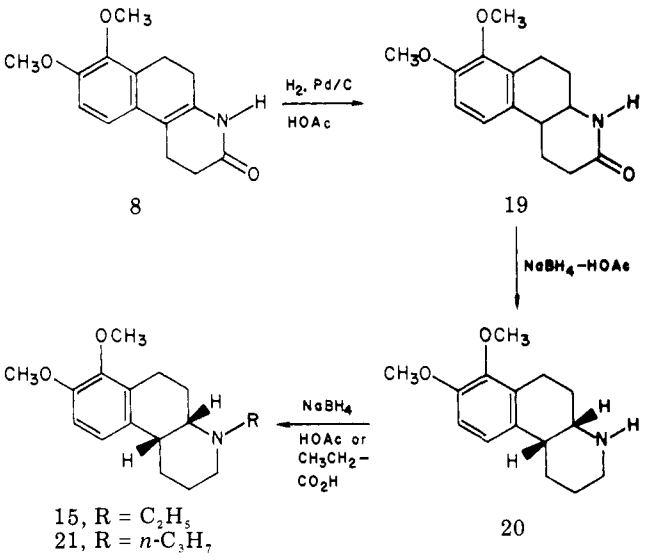
Scheme II. Preparation of Trans Secondary Amine and *N*-*n*-Propyl Systems



Scheme III. Preparation of *cis*-*N*-Ethyl and *cis*-*n*-Propyl Systems



gave a product for which GC and NMR data indicated the presence of a single isomeric component, which was subsequently shown, by comparison of IR spectra with those of authentic trans isomer, to be cis. Thus, it was inferred that the saturated lactam **19** was the pure cis-fused isomer.

The cis and trans secondary amines **20** and **17** (Schemes II and III) were appropriately N-alkylated using a sodium borohydride–carboxylic acid complex by the method of Marchini et al.[4]

The cis or trans geometry of the secondary amines **20** and **17** (Schemes II and III) and of the *N*-benzyl homologues **16** and **14** (Scheme I) was established on the basis of strong "Bohlmann bands" in the 2700–2900-cm^{-1} region of the infrared spectra of the trans isomers, as was described earlier[1] for *N*-methyloctahydrobenzo[*f*]quinoline systems. In these systems, the Bohlmann region in the infrared is highly diagnostic of the stereochemistry of ring fusion. The secondary amine **20** (Scheme III), which, on the basis of IR data, was assigned the cis geometry, was N-methylated to give a product (**22**) whose NMR spectrum was identical with that of an authentic sample of the *cis*-*N*-methyl isomer prepared by a literature[1] method. This experiment further confirms the correctness of the stereochemistry of the compounds described herein. The IR spectra of *cis*- and *trans*-*N*-ethyl and *n*-propyl systems could not be used to establish stereochemistry of ring fusion. However, since these N-alkylated congeners had been prepared from secondary amines of well-established stereochemistry, their geometry was known.

Walsh and Smissman[5] have described the NMR magnetic nonequivalence of N-$CH_2C_6H_5$ protons in octahydrobenzo[*g*]quinolines, and they have utilized the *N*-benzyl substituent as a probe for determining cis or trans configuration of these ring systems. The benzyl methylene proton signal of the cis isomer should appear as a singlet or as an AB quartet having a relatively small chemical-shift difference, whereas the benzyl methylene proton signal of the trans isomer should appear as an AB quartet having a large chemical-shift difference. In the present study of octahydrobenzo[*f*]quinolines, the compound **14** (Scheme I) which had been assigned the trans geometry exhibited an AB quartet centered at δ 3.72 (2 H, N-$CH_2C_6H_5$), $\Delta\nu$ = 48 Hz, whereas compound **16** (Scheme I) which had been assigned the cis geometry exhibited two sharp signals centered at δ 3.70 (2 H, N-$CH_2C_6H_5$), $\Delta\nu$ = 1 Hz. Thus, the NMR data are consistent with the assigned geometry of ring fusion of the isomers.

The ether linkages of the dimethoxy molecules were cleaved with HBr, and the free catechol systems were evaluated biologically as their HBr salts. Spectral (IR and NMR) data on all compounds prepared were consistent with their proposed structures.

Pharmacology. Results. Hyperactivity and Stereotyped Behavior Following Intracerebral Injection in the Rat. Dopamine injected into the nucleus accumbens causes a hyperactivity and stereotyped behavior characterized by continuous sniffing. Of the benzoquinoline derivatives tested, only the *trans*-*n*-propyl compound **7** induced both hyperactivity (comparable to that produced by dopamine) and a stereotyped behavior characterized by a periodic biting associated with a sniffing response (Figure 1). A biting behavior was never observed in animals treated with dopamine. The locomotor and stereotypic effects of dopamine and **7** were apparent 30–45 and 5–15 min, respectively, after injection, and they persisted for 5–6 h. A stereotyped behavior associated with some biting was also recorded for animals treated with the *trans*-*N*-ethyl compound **6**, but this agent failed to induce hyperactivity (Figure 2). In contrast, the *cis*-*N*-ethyl system **3** induced a moderate intensity hyperactivity but only weak stereotyped sniffing (Figure 2). Compounds **2**, **4**, and **5** were only weakly active or inactive in both test procedures (Table I, Figure 1). With the exception of dopamine and **7**, the onset of all drug effects was within 30–60 (hyperactivity) or 15–30 min (stereotypy), and the duration of all effects was 3–4$^+$ h.

Similar to observations following intraaccumbens injections, intracaudate dopamine caused both a hyperactivity and a stereotyped behavior characterized by repetitive sniffing and biting behavior (Table I). However, in this test procedure, both **6** and **7** caused a hyperactivity comparable to the dopamine response and a stereotyped behavior characterized by sniffing and some biting (Figures 1 and 2). Stereotyped biting was particularly marked following administration of **7** (Figure 1). Compounds **2** and **5** were inactive (Table I), while compound **3** caused only weak hyperactivity (Figure 2). However, of these three

Table I. Assessment of the Ability of Dopamine and Some Benzo[*f*]quinoline Derivatives to Induce Hyperactivity and Stereotyped Behavior Following Bilateral Intracerebral Injection into the Nucleus Accumbens and Caudate-Putamen of Rats ($N = 10$)

compd	hyperact of nucleus accumbens	stereotypy of nucleus accumbens	hyperact of caudate-putamen	stereotypy of caudate-putamen
2	inact[a]	inact	inact	inact
5	inact	inact	wk act.[b]	wk act.
dopamine	act. (6.25-50 μg)	wk act. (12.5-50 μg)	act. (6.25-25 μg)	act. (12.5-50 μg)

[a] Inactive at doses up to 25 μg. [b] Effect less than the maximum attainable (e.g., 70-80 counts/5 min for hyperactivity, score 4 for stereotypy; see Experimental Section).

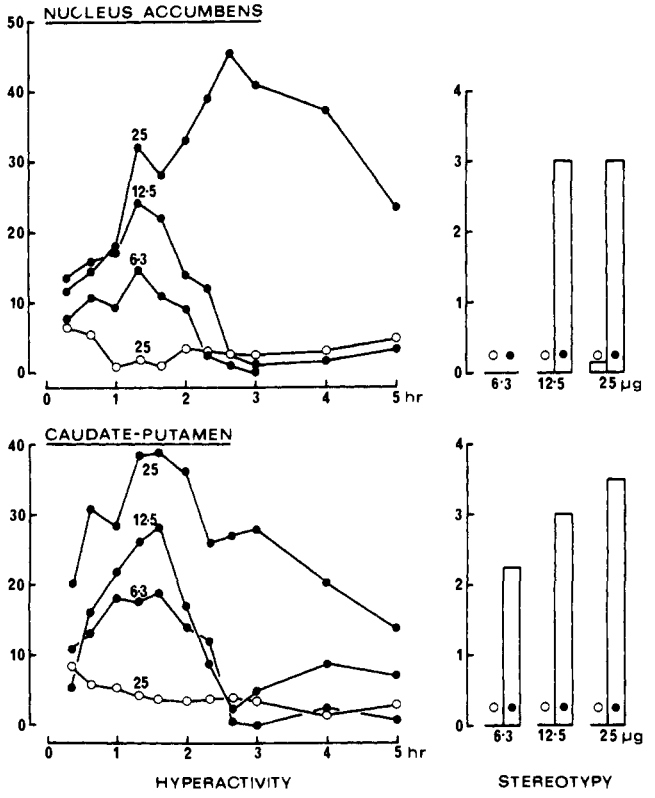


Figure 1. Hyperactivity and stereotyped behavior induced by some benzo[*f*]quinoline derivatives injected bilaterally into the nucleus accumbens or caudate-putamen. Hyperactivity is expressed in counts/5 min and stereotypy is scored (see Experimental Section): (●) compound 7; (○) compound 4 ($n = 6$–8; SEM < 19%). The mean maximum responses are given for stereotypy.

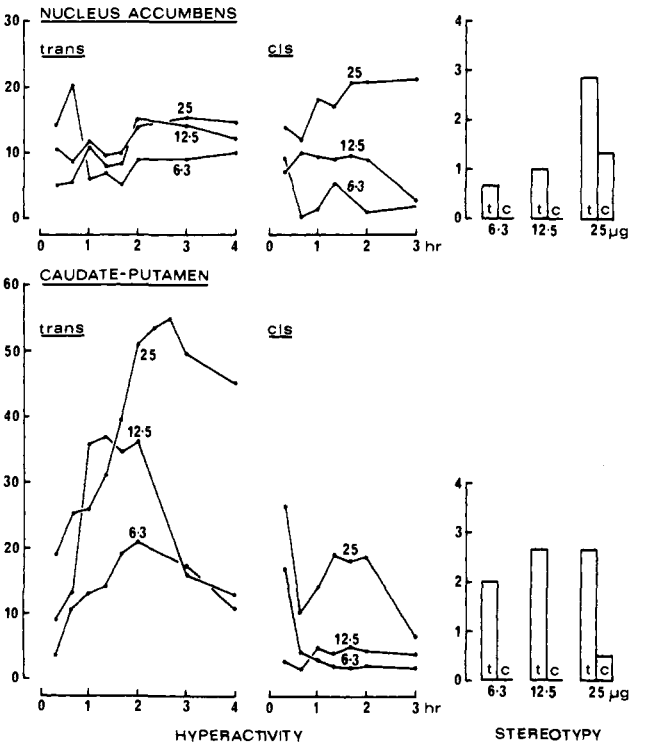


Figure 2. Hyperactivity and stereotyped behavior induced by some benzoquinoline derivatives injected bilaterally into the nucleus accumbens or caudate-putamen. Hyperactivity is expressed in counts/5 min and stereotypy is scored (See Experimental Section). Trans (t) and cis (c) represent compounds 6 and 3, respectively: $n = 6$–8; SEM < 16%. The mean maximum responses are given for stereotypy.

agents, only 5 induced a consistent stereotyped sniffing behavior. Compound 4 was inactive in both the hyperactivity and stereotypy tests (Figure 1). The hyperactivity observed after the direct injection into the caudate-putamen was generally slow in onset (30–45 min), in contrast to stereotypy which was apparent 5–15 min after injection. Both behavioral effects persisted for 5–6 h for dopamine, 6, and 7, but the duration of the effect of other active agents was generally less than 3 h.

Stereotyped Behavior Following Peripheral Injection in the Rat. The subcutaneous administration of 2, 3, or 4 failed to induce any consistent stereotyped response in the rat. However, apomorphine and 5–7 (Table II) induced both stereotyped sniffing and biting. The onset of action of each agent was within 10–15 min, and the duration ranged from 20–40 min at lower doses of the drug (which caused primarily sniffing) to 120$^+$ min at supramaximal doses (although the apomorphine response never persisted for longer than 90 min). The biting behavior caused by 0.05 mg/kg of 6 and 7 was recorded for 40–90 min.

Climbing, Circling, and Stereotyped Behavior in the Mouse. Apomorphine was shown to induce a dose-dependent climbing behavior in mice. Compounds 2–5 each failed to induce a climbing response at 10 mg/kg, but

Table II. Assessment of the Ability of Some Benzo[*f*]quinoline Derivatives to Induce a Stereotyped Behavior in the Rat and Mouse and to Induce Climbing and Circling Behavior in the Mouse Following Subcutaneous Administration ($N = 10$)

compd	stereotypy induction		induct of climbing	induct of ipsilateral circling
	in rats	in mice	in mice	in mice
5	1.0-10.0[a]	inact	inact	inact[d]
2	inact[b]	inact	inact	inact
6	0.025-0.05	1.0-2.0	0.25-1.0	0.5-2.0
3	inact[c]	inact	inact	inact
7	0.025-0.05	0.05-1.0	0.1-0.5	0.05-0.5
4	inact	inact	inact	inact
apomorphine	0.5-2.0	1.5-4.0	0.5-1.5	0.25-1.0

[a] Dose range indicates the threshold dose and that producing the maximum attainable response, in mg/kg sc. [b] Inactive at doses up to 10.0 mg/kg sc. [c] Periodic sniffing behavior in some animals at 0.5-4.0 mg/kg sc. [d] Very weak circling behavior. Maximum 2 revolutions/2 min, at 10 mg/kg sc only.

Table III. Various Biological Actions in Cats and Dogs of Some Octahydrobenzo[f]quinoline Derivatives

compd	emetic act. in Dogs[e]	pecking in pigeons[f]	cat cardioaccelerator nerve inhibn[g]
apomorphine	1.0[a]	1.0[b]	19 (11-30)[d]
2	0.024	inact	27 (19-42)
3	0.053	inact	inact
4	inact	inact	inact
5	4.5	c	0.7 (0.52-0.97)
6	4.9	0.39	0.5 (0.34-0.64)
7	2.7	0.32	0.3 (0.18-0.41)

[a] The ED_{50} for apomorphine hydrochloride administered subcutaneously to dogs was 0.14 μmol/kg. [b] The ED_{50} for apomorphine hydrochloride administered im to pigeons was 0.77 μmol/kg. The pecking response to 1.6 μmol/kg was used as the 100% response for the antagonist studies. [c] Antagonizes apomorphine. ED_{50} 0.6 μmol/kg. [d] 95% confidence limits of the ID_{50} dose. [e] Potency relative to apomorphine, $N = 8$. [f] Potency relative to apomorphine, $N = 10$. ID_{50}, iv, nmol/kg, $N = 15$.

6 and 7 induced climbing behavior (Table II). The intensity of this response was particularly marked for 7, the more potent of the two agents, and animals given 0.5 mg/kg of 7 climbed for more than 90% of the 30-min period following the first climb. This agent was, therefore, shown to be more potent and more effective than apomorphine (Table II).

A dose-dependent circling behavior, ipsilateral to the side of the lesion, was induced by apomorphine in mice having unilateral electrolesions of the caudate-putamen, but 2–5 were weakly active or inactive at doses of 10 mg/kg. However, both 6 and 7 induced dose-dependent ipsilateral circling behavior, with 7 again being the more potent and producing a circling response of intensity equal to that of apomorphine (Table II).

Similar to observations in the climbing and circling tests, only 6 and 7 mimicked the actions of apomorphine in the stereotypy test in the mouse, 7 being the more potent agent. Biting was periodic at lower doses but became continuous as the doses were increased (Table II). Compounds 2–5 were inactive in the stereotypy test in the mouse at 10 mg/kg doses (Table II).

The onset of the different behavioral effects of the benzoquinoline derivatives in the mouse was shown to differ. Thus, the onset of stereotyped biting occurred within 15–30 min, but circling and climbing developed within 10–15 min at all doses. The maximum stereotypic effects developed within 45–90 min of injection, but the maximum response was recorded for circling and climbing within 15–30 min of injection. Both circling and climbing behavior developed at lower doses of 6 and 7 than those required to induce stereotyped biting (Table II). The duration of the behavioral effects of 6 and 7 were generally apparent for 90–120+ min, although the stereotyped biting consistently persisted for longer periods than either climbing or circling.

Emesis in Dogs, Pecking in Pigeons, and Cardiac Effects in Cats. Table III summarizes the ability of the subject compounds to induce emesis in dogs, pecking in pigeons, and to inhibit positive chronotropic responses of cat hearts following electrical stimulation of the postganglionic right cardioaccelerator nerves. All of the trans isomers 5–7 were more potent than apomorphine in inducing emesis in dogs. The cis isomers 2–4 were very weak or inactive. A similar pattern of action was found for the compounds' ability to inhibit cardioaccelerator nerve stimulation. The trans isomers 5–7 were effective at a fraction of a nmol/kg. Compound 2 demonstrated considerable activity in this test, but the N-alkylated cis-homologues 3 and 4 were inactive. Compounds 3 and 4 increased heart rate both in vivo and in vitro.

The ability to induce pecking in pigeons was found to be maximal with the trans-N-alkyl derivatives 6 and 7. The trans secondary amine 5 was an antagonist of apomorphine-induced pecking. The N-alkyl cis isomers were inactive as agonists and antagonists.

Discussion

When evaluated in various models to assess dopamine-like action on cerebral dopamine systems, a consistent differentiation was obtained between the cis and the trans isomers. The trans systems 5–7 were effective stereotypic agents in the rat, whereas the cis isomers 2–4 were inactive. In the behavioral models of stereotypy, climbing, and circling induction in the mouse, all of which are highly predictive of dopamine agonist activity, only compounds with the trans geometry were active. However, in the mouse models, both the cis and trans secondary amines (2 and 5) demonstrated little or no activity. This may reflect a reduced ability of these two agents to pass the blood–brain barrier, and this is analogous to inactivity of primary amines in the 2-aminotetralin series.[6,7] However, it should be noted that 5 showed no significant dopamine-like action on direct injection into two areas of the brain (the nucleus accumbens and caudate-putamen), in direct contrast to the motor effects of hyperactivity and stereotypy observed with dopamine, 2-aminotetralin derivatives,[6,7] and the trans-N-alkylated compounds 6 and 7. Also, it is pertinent that 5 actually antagonized apomorphine pecking in pigeons, a response generally assumed to involve a striatal site of action; this indicates an effective penetration into cerebral tissue and suggests that the nature of the receptor interaction is that of a potential partial agonist/antagonist. Nevertheless, the interpretational problems associated with the data obtained using the trans secondary amine 5 do not obscure the essential differences between the cis- and trans-N-alkylated derivatives in the rat, mouse, and pigeon. Further, the greatly increased potency conferred by these N-alkyl substituents reflects that found in the 2-aminotetralin series.[6,8]

An assessment of drug action on the dopamine-sensitive emetic mechanism in the dog (a cerebral mechanism, but lying outside the blood–brain barrier in the area postrema) showed that this receptor system similarly exhibited a preferential sensitivity to all three trans compounds 5–7. However, when the emetic data are compared with those obtained in the behavior studies, a distinction is apparent. In the emesis model, the secondary amine 5 has a potent action which is not significantly increased (compound 6) or may even be decreased (compound 7) by N-alkylation. The essential observations using an in vivo model, based on the cardioaccelerator nerve experiments in the cat, are that an inhibition of adrenergic transmission occurs using 5–7, the compounds being at least 100 times more potent than apomorphine. The importance of the proper stereochemistry of the subject compounds was indicated by the inactivity (3 and 4) or weak activity (2) of the cis isomers. Again, as with the emetic mechanism in the dog, this dopamine neuroleptic-sensitive site showed little difference in sensitivity to the secondary amine or the N-alkylated derivatives.

Analysis of molecular models reveals that the *trans*-7,8-dihydroxyoctahydrobenzo[f]quinoline ring system holds the dopamine moiety rigidly in an antiperiplanar disposition in the "α" conformation (23), as illustrated (Figure 3) by the conformational drawing (24) and the

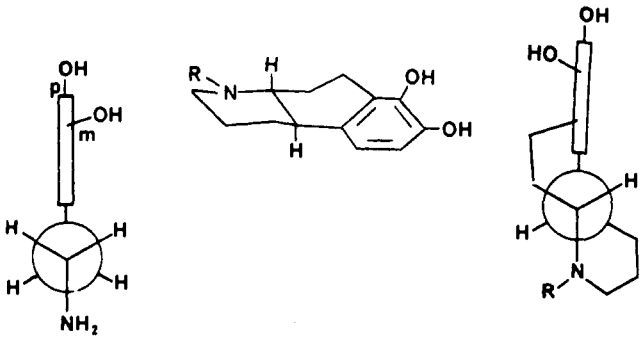


Figure 3. The α conformation of dopamine and stereochemistry of the *trans*-octahydrobenzo[*f*]quinoline system.

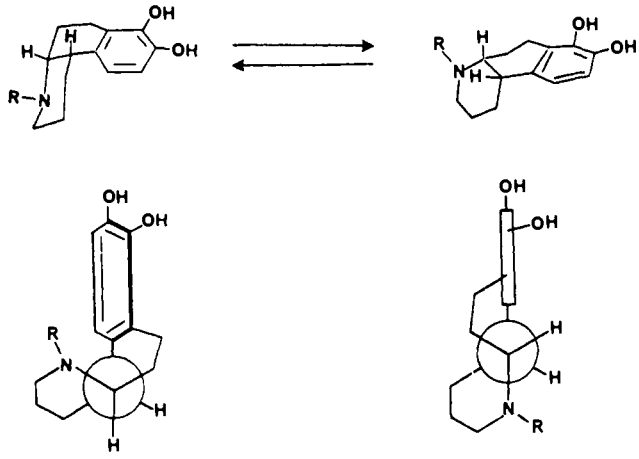


Figure 4. Stereochemistry of the *cis*-octahydrobenzo[*f*]quinoline system.

corresponding Newman projection (**25**), which has been proposed[9] to be significant in certain dopamine–receptor interactions. In contrast, the cis series (Figure 4) is only a semirigid system and it can exist in two interconvertible "flip" conformations. In one of these (**26**), the amino group and the catechol ring are gauche, and the catechol ring is not coplanar with the ethylamine side chain, as illustrated by **28**. In the other cis conformer (**27**), the dopamine moiety approaches the antiperiplanar disposition **29**, but this conformer, overall, is not a planar molecule, and the heterocyclic ring makes almost a right angle with the plane of the other two rings, which is proposed to be detrimental to dopamine-like effects. The work reported herein demonstrates that the conformational integrity of the trans isomers holds the molecules firmly in an optimum steric disposition with respect to the dopamine receptor(s).

It should be noted that the dopamine receptors involved in the central nervous system assays may be presynaptic or postsynaptic. The compounds that were active as inhibitors of the cat cardioaccelerator nerve preparations (presynaptic) were also active in preparations involving the CNS. However, this analogy does not establish the site of action.

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 programmed for a 2 °C/min rise and are uncorrected. 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 a Finnegan 1015 S/L spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated by the symbols of the elements, the analytical results were within ±0.4% of the theoretical values. Relative amounts of each component in isomeric mixtures were determined by relative peak heights of characteristic signals in the aromatic region of the NMR spectrum.

Pharmacology. Methods. Hyperactivity and Stereotyped Behavior Following Intracerebral Injection in the Rat. Rats (male, Sprague–Dawley, 250 ± 26 g) were prepared for bilateral intracerebral drug injection into the caudate-putamen and nucleus accumbens using the techniques described previously.[10] Guide cannulae (0.65-mm diameter stainless steel) were stereotaxically implanted with their tips at anterior 8.0, vertical +3.0, lateral +3.0 (caudate-putamen) and anterior 9.0, vertical +2.5, lateral +1.6 (nucleus accumbens)[11] and were kept patent by stainless-steel stylets (0.3-mm diameter). Animals were used for intracerebral injection 10–14 days after surgery when the stylets were replaced by injection units (also made of 0.3-mm stainless steel tubing) which extended 1.5 (caudate-putamen) or 2.5 mm (nucleus accumbens) below the guides to terminate at the center of the selected nuclei. After a nialamide pretreatment (100 mg/kg, ip, 2 h), rats were manually restrained and the drug was delivered bilaterally in a volume of 1–2 μL (Agla micrometer syringe) over a 60-s period. Rats were used once only; guide cannulae locations were then determined histologically. All locations were found to be within the correct area and to be indistinguishable from those previously reported.[10]

Hyperactivity was measured in cages (30 × 20 × 15 cm high) which were fitted with one photocell placed off center. The number of light-beam interruptions occurring in each 5-min period was recorded electromechanically and, at the same time, the animal's behavior was recorded from visual observation in order to eliminate counts due to behavior other than hyperactivity, for example, due to behavior characterized by repetitive, restricted head or limb movements (see ref 10 for details).

Stereotyped behavior was assessed separately using a simple scoring system: 0 = no stereotyped behavior; 1 = periodic sniffing and/or repetitive head and limb movements; 2 = continuous sniffing and/or repetitive head and limb movements; 3 = periodic biting, gnawing, or licking; 4 = continuous biting, licking, or gnawing.

Stereotyped Behavior Following Peripheral Injection in the Rat. Stereotyped behavior was assessed as indicated above when control and test agents were administered subcutaneously. All behavioral experiments were carried out between 08:00 and 18:00 h in sound-proofed, diffusely illuminated rooms maintained at a temperature of 21 ± 2 °C. Groups of 10 animals were used.

Climbing, Circling, and Stereotyped Behavior in the Mouse. The studies used male albino mice (20–25 g for peripheral studies, 30–35 g at the time of surgery). Climbing behavior was measured in perspex cages (20 × 15 × 15 cm) lined with 1-cm^2 wire mesh (2-mm diameter wire). Animals were classed as climbing when they held the wire with all four paws. During the period of climbing, a mouse moved consistently around the sides or top of the cage. Two different measures of climbing were determined: *climbing index*, which is the percentage of time spent climbing during the 30-min period following the first climb, and *maximum time*, which is the maximum time spent in a single climb throughout the duration of the drug effect.[12] Circling behavior was assessed in mice having a unilateral electrolesion of the caudate-putamen. The electrolesion was induced stereotaxically by placing a stainless-steel electrode (0.65-mm diameter, insulated except at the tip) 1.0 mm anterior to Bregma, 2.3 mm lateral to midline, and 3.5 mm from the skull surface. The lesion was caused by passing 1.5 mA for 15 s. Fourteen days were allowed for recovery; animals were then tested for circling using 1.0 mg/kg sc of apomorphine hydrochloride, and only those animals which circled 7^+ revolutions/2 min, ipsilateral to the side of the lesion, were used in subsequent studies (7-day recovery). Circling behavior was assessed manually as the number of complete revolutions in one direction only, after an animal was placed in a perspex cage (20 × 15 × 15 cm). On completion of the studies, the correct location of the lesions was confirmed using the atlas of Lehman[13] as a guide.

Emetic Activity in Dogs. Each compound was administered to at least five dogs by the subcutaneous route. The frequency of vomiting was recorded for 1 h. Doses of the compounds were varied by 0.3 log intervals. Antiemetic activity was evaluated by administering the compounds sc, and 15 min later administering apomorphine sc at a dose of 100 μg/kg and evaluating the ability

to decrease the frequency of vomiting. Activity relative to apomorphine was calculated by a parallel line bioassay.

Induction of Pecking in Pigeons. The compounds were administered im and the frequency of pecking was counted for 1 h. Doses were varied by 0.3 log intervals, and the pecking induced by 1.63 μmol of apomorphine hydrochloride was regarded as a 100% response.

Inhibition of the Postganglionic Cardioaccelerator Nerve in Cats. The preparation involved induction of anesthesia by intrathorax administration of sodium pentobarbital (30 mg/kg). The arterial pressure was measured from the right femoral artery using a Statham P23AA pressure transducer and recorded using a Beckman RS dynograph. The pulses were integrated and recorded by use of a cardiotachometer. The respiration was supported by a Harvard respiratory pump, and following a midline incision of the thorax bipolar platinum electrodes were placed on the right postganglionic cardioaccelerator nerves for stimulation using a Grass S4S stimulator. The frequency of stimulation was 2 Hz. The impulses were delivered for 20–30 s and a pulse duration of 5 ms was used. Supramaximal voltage was used. After the establishment of consistent controls, the compounds were administered in doses that were varied by 0.48 log intervals. The amount required to inhibit positive chronotropic responses by 50% were calculated.

Drugs. Dopamine hydrochloride (Koch-Light) was prepared for intracerebral injection in distilled water and was neutralized immediately before use with $NaHCO_3$. For peripheral administration (sc), apomorphine and **2**–**7** were dissolved in distilled water containing 0.1% sodium metabisulfite. For intracerebral administration, **2**–**7** were prepared in N_2-bubbled distilled water with a minimum quantity of *N,N*-dimethylformamide added when necessary. Appropriate solvent control injections were performed in each experiment; solvent alone failed to modify behavior. Doses are expressed as weight of the salt.

7,8-Dimethoxy-4-ethyl-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (9). A mixture of 4.0 g (0.015 mol) of 7,8-dimethoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (**8**),[1] 1.0 g (0.021 mol) of NaH, and 100 mL of anhydrous (distilled from $LiAlH_4$) dimethoxyethane was heated under reflux for 3 h. The mixture was cooled to room temperature, 9.6 g (0.0615 mol) of ethyl iodide was added, and the reaction mixture was heated under reflux for 2 h. Excess NaH was destroyed by addition of 5 mL of H_2O, and the resulting mixture was evaporated under reduced pressure. The residue was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 phase was evaporated under reduced pressure to leave a light yellow solid residue, which was recrystallized from EtOH–H_2O to give 4.28 g (96%) of white crystals, mp 116–118 °C. Anal. ($C_{17}H_{21}NO_3$) C, H, N.

7,8-Dimethoxy-4-benzyl-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (10). This was prepared from 5.1 g (0.019 mol) of **8**,[1] 1.25 g (0.025 mol) of NaH, 3.7 g (0.021 mol) of benzyl bromide, and 125 mL of anhydrous dimethoxyethane as was described for **9**. The crude product was recrystallized from EtOH–H_2O to give 4.0 g of pale yellow crystals. Evaporation of the mother liquor afforded an oil, which was chromatographed on alumina and eluted with CH_2Cl_2 to afford material which was recrystallized from EtOH–H_2O to give 2.0 g of crystals: total yield 6.0 g (87%); mp 113–115 °C. Anal. ($C_{22}H_{23}NO_3$) C, H, N.

7,8-Dimethoxy-4-ethylhexahydrobenzo[*f*]quinoline (11). To 5.3 g (0.018 mol) of **9** in 150 mL of dry benzene was added 20 g of a 70% solution 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 the dropwise addition of 5 mL of H_2O to the cooled solution, and the solid aluminum salts were dissolved by the addition of excess 50% KOH. The organic phase was separated, washed twice with 100-mL portions of H_2O, and dried (Na_2SO_4). Removal of volatiles under reduced pressure left an orange-red oil (4.8 g, 98%), which solidified on standing. This material was employed in the subsequent step without purification.

7,8-Dimethoxy-4-benzylhexahydrobenzo[*f*]quinoline (12). This was prepared from 4.0 g (0.01 mol) of **10**, 11 g of a 70% solution (0.04 mol) of Red-Al, and 120 mL of dry benzene, as was described for **11**. A quantitative yield (3.68 g) of an orange-brown oil was obtained, which crystallized on standing and was employed in the subsequent step without purification.

***cis*- and *trans*-7,8-Dimethoxy-4-ethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (15 and 13).** A mixture of 4.0 g (0.015 mol) of **11** and 1.26 g (0.02 mol) of $NaBH_3CN$ in 50 mL of MeOH was stirred for 16 h, and methanolic HCl was added from time to time as required to maintain the reaction mixture at approximately pH 6 (pH paper). The excess $NaBH_3CN$ was decomposed by the addition of 10 mL of concentrated HCl. Volatiles were then removed under reduced pressure, and the residual paste was taken up in H_2O. The aqueous solution was basified with KOH and was extracted with CH_2Cl_2. This extract was dried (Na_2SO_4) and evaporated to yield a brown oil which was taken up in dry Et_2O and treated with excess ethereal HCl. The resulting salt was taken up in MeOH, and Et_2O was carefully added in small portions at room temperature to the first traces of a cloud point. Upon cooling, colorless needles were deposited, which were collected and recrystallized from MeOH–Et_2O to give 0.88 g (21%) of the *trans*-**13** HCl: mp 150–151 °C; IR ($CHCl_3$) of the free base 2831, 2869 cm^{-1} (weak). Anal. ($C_{17}H_{26}ClNO_2$) C, H, N (and 2.83% H_2O).

Treatment of the mother liquor from the initial crystallization of the trans isomer **13** with additional Et_2O induced separation of a second solid, which was recrystallized from MeOH–Et_2O to afford 0.89 g (21%) of the *cis*-**15** HCl: mp 225–227 °C; IR ($CHCl_3$) of the free base 2839, 2828 cm^{-1} (weak). IR and NMR ($CDCl_3$) spectra of this material were identical with similar spectra recorded for a product prepared by N-ethylation of the authentic cis secondary amine **20** (vide infra).

***cis*- and *trans*-7,8-Dimethoxy-4-benzyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (16 and 14).** These were prepared from 3.8 g (0.011 mol) of **12** and 1.25 g (0.02 mol) of $NaBH_3CN$ in 20 mL of acetonitrile, as described for **15** and **13**, maintaining pH 6 by addition of acetic acid. The brown oily mixture of free-base products was converted to its HCl salt, which was fractionally crytallized from MeOH–Et_2O as described for the separation of **15** and **13**. The trans isomer separated first; it was recrytallized from MeOH–Et_2O to yield 0.63 g (17%) of crystals of the *trans*-**14** HCl: mp 262–264 °C; IR ($CHCl_3$) of the free base 2858, 2837, 2793, 2751 cm^{-1} (strong). Anal. ($C_{22}H_{28}ClNO_2$) C, H, N.

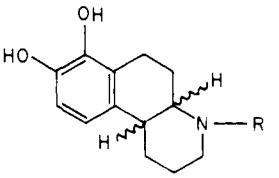
Treatment of the mother liquor from the initial crystallization of the trans isomer **14** with additional Et_2O induced separation of a second solid which was recrystallized from MeOH–Et_2O to give 0.99 g (26%) of the *cis*-**16** HCl: mp 241–244 °C; IR ($CHCl_3$) of the free base 2836, 2824, 2800 cm^{-1} (weak). Anal. ($C_{22}H_{28}ClNO_2$) C, H, N.

***trans*-7,8-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (17).** A mixture of 0.631 g (0.0017 mol) of **14** and 0.42 g of 5% Pd/C in 25 mL of MeOH was hydrogenated at an initial pressure of 25 psig for 16 h. The reaction mixture was filtered, and the filtrate was evaporated to leave a white solid, which was recrystallized from MeOH–Et_2O to give 0.418 g (87%) of product: mp 268–270 °C; IR ($CHCl_3$) of the free base 2860, 2838 cm^{-1} (strong). Anal. ($C_{15}H_{22}ClNO_2$) C, H, N.

7,8-Dimethoxy-1,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-3(2*H*)-one (19). 7,8-Dimethoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3-one (**8**)[1] (1.0 g, 0.0037 mol) was hydrogenated over 0.4 g of 5% Pd/C in 30 mL of acetic acid at an initial pressure of 40 psig. Uptake of H_2 was complete in 15 min. Filtration and evaporation of the filtrate left 0.9 g (90%) of a white solid which was used in the next step without purification. NMR and GC analysis indicated that this material consisted of a single component. An analytical sample was recrystallized from Me_2CO, mp 187–189 °C. Anal. ($C_{15}H_{19}NO_3$) C, H, N.

***cis*-7,8-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (20).** A procedure of Umino et al.[3] was used. A solution of 1.59 g (0.0266 mol) of acetic acid in 6 mL of dioxane was added over 10 min to 1.01 g (0.0266 mol) of $NaBH_4$ and 0.63 g (0.00266 mol) of **19** in 10 mL of dioxane, maintained at 10 °C. The mixture was then refluxed for 5.5 h. Volatiles were evaporated and the residue was decomposed with H_2O and extracted with $CHCl_3$. The organic extract was dried (Na_2SO_4) and evaporated to leave a yellow oil which solidified on standing. NMR spectra and GC analysis indicated that this material was composed of a single substance. It was treated with ethereal HCl, and the resulting solid was recrystallized from EtOH–Et_2O to yield 0.46

Table IV. *cis*- and *trans*-Octahydrobenzo[*f*]quinolines



compd	geometry of ring fusion	R	yield, %	mp, °C[a]	formula	anal.
2	cis	H	90	>300	$C_{13}H_{18}BrNO_2$	C, H, N
3	cis	C_2H_5	94	280-281	$C_{15}H_{22}BrNO_2$	C, H, N
4	cis	n-C_3H_7	99	275-276[b]	$C_{16}H_{24}BrNO_2$	C, H, N
5	trans	H	90	>300	$C_{13}H_{18}BrNO_2$	C, H, N
6	trans	C_2H_5	91	281-283	$C_{15}H_{22}BrNO_2$	C, H, N
7	trans	n-C_3H_7	95	260-262	$C_{16}H_{24}BrNO_2$	C, H, N

[a] Recrystallized from MeOH-Et_2O. [b] Decomposition.

g (67%) of a solid: mp 243–245 °C; IR ($CHCl_3$) of the free base 2860, 2838 cm^{-1} (weak). Anal. ($C_{15}H_{22}ClNO_2$) C, H, N.

***cis*-7,8-Dimethoxy-4-ethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (15). Method B.** $NaBH_4$ (0.374 g, 0.01 mol) was added in small portions to 2.52 g (0.034 mol) of acetic acid in 50 mL of dry benzene, maintaining the temperature below 20 °C. When H_2 evolution ceased, 0.494 g (0.002 mol) of the free base of **20** in 10 mL of dry benzene was added and the resulting mixture was refluxed overnight. The cooled mixture was shaken with excess 2 N NaOH. The organic layer was dried (Na_2SO_4) and evaporated, and the yellow oily residue was treated with ethereal HCl to give a solid. This was recrystallized from MeOH–Et_2O to give 0.555 g (89%) of a white solid: mp 225–227 °C; IR ($CHCl_3$) of the free base 2839, 2828 cm^{-1} (weak). Anal. ($C_{17}H_{26}ClNO_2$) C, H, N.

***cis*-7,8-Dimethoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (21).** This was prepared from 0.74 g (0.003 mol) of the free base of **20**, 3.78 g (0.051 mol) of propionic acid, 0.561 g (0.015 mol) of $NaBH_4$, and 50 mL of dry benzene by method B described for **15**. The HCl salt was recrystallized from MeOH–Et_2O to afford 0.89 g (91%) of a white solid: mp 245–246 °C; IR ($CHCl_3$) of the free base 2875, 2837 cm^{-1} (weak). Anal. ($C_{18}H_{28}ClNO_2$) C, H, N.

***trans*-7,8-Dimethoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (18).** This was prepared from 0.331 g (0.0013 mol) of the free base of **17**, 1.69 g (0.023 mol) of propionic acid, 0.255 g (0.0067 mol) of $NaBH_4$, and 30 mL of dry benzene by method B described for **15**. The HCl salt was recrystallized from MeOH–Et_2O to yield 0.41 g (90%) of a white solid: mp 178–180 °C; IR ($CHCl_3$) of the free base 2874, 2860, 2838, 2802 cm^{-1} (weak). Anal. ($C_{18}H_{28}ClNO_2$) C, H, N.

***cis*-7,8-Dimethoxy-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (22).** Compound **20** (0.10 g, 0.00035 mol), 0.4 mL (0.004 mol) of 37% aqueous formaldehyde solution, and 0.030 g (0.0005 mol) of $NaBH_3CN$ in 15 mL of MeOH were stirred at room temperature overnight in the presence of 2 g of 3 Å molecular sieves. The reaction was quenched by the addition of 10 mL of concentrated HCl; then the mixture was extracted repeatedly with $CHCl_3$. The combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated to afford a solid which was recrystallized from MeOH–Et_2O to give 0.074 g (73%) of white crystals, mp 136–139 °C. The free base of this product showed mp 79–80 °C, lit.[1] mp 81–82 °C. An NMR spectrum of the free base ($CDCl_3$) was superimposable upon a similar spectrum of an authentic sample[1] of **22**.

Ether Cleavage Reactions. The amine HCl (0.001 mol) was heated in 30 mL of 48% HBr under N_2 at 135–145 °C for 3 h. Volatiles were removed under reduced pressure, and the residue was recrystallized (see Table IV).

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