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Articles

Congeners of the β Conformer of Dopamine Derived from *cis*- and *trans*-Octahydrobenzo[*f*]quinoline and *trans*-Octahydrobenzo[*g*]quinoline

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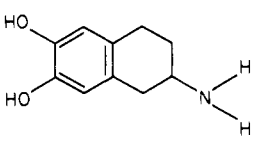
The so-called β conformer of dopamine has been proposed to be involved in agonist–receptor interactions at several sites in the dopaminergic nervous system. Further to evaluate this proposal, rigid congeners of the β conformer derived from linearly and angularly annelated octahydrobenzoquinolines have been synthesized. Certain N-alkylated trans-angularly annelated systems exhibited unusually potent and highly selective dopamine-like effects in an assay on a cardioaccelerator nerve preparation in the cat, but these compounds were inactive in a variety of assays for CNS effects. These compounds present a clear separation of CNS effects from some potent peripheral effects.

Investigation of agonist conformational requirements for effects on dopamine receptors in a variety of organs has led to the proposal that the so-called β conformation of dopamine, similar to that found in "A-6,7-DTN" (**1**), is



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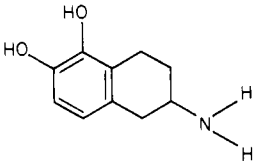

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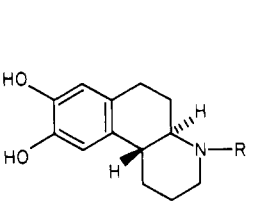
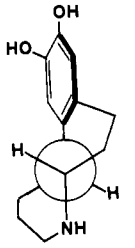
required for dopaminergic renal vascular activity.[1] It has been reported[2] that that **1** and certain of its N-alkylated homologues produce hyperactivity responses and stereotyped behavior in rats but that structure–activity correlations among members of the homologous series of N-alkylated compounds differ from those in similar homologous series based upon "A-5,6-DTN" (**2**), a congener of the α conformer of dopamine. Because the aminotetralin system is only semirigid and thus lacks complete conformational integrity, the present study was aimed at incorporation of the elements of the A-6,7-DTN molecule into a *trans*-octahydrobenzo[*f*]quinoline system (**3**), in which the dopamine moiety is locked into the antiplanar β conformer (**4**) and the benzene ring approaches coplanarity with the ethylamine side chain. Incorporation of the A-5,6-DTN moiety into a *trans*-octahydrobenzo[*f*]-quinoline system (**5**) has provided dopamine agonists of unusual potency.[3] The cis isomers of **3a–d** were prepared for verification of previous observations[3] that cis-fused compounds in this ring system exhibit low orders of dopamine-like activity. Preparation of **3a–d**, beginning with 6,7-dimethoxy-2-tetralone, paralled the previously described synthesis of the isomeric systems based upon **5**.[3] Separation of mixtures of cis- and trans-fused ring isomers was accomplished by fractional crystallization of the *N*-benzyl derivatives, and the geometry of ring fusion was established by the presence of strong "Bohlmann bands" in the 2700–2900-cm^{-1} region of the IR spectrum of the *trans*-*N*-benzyl isomer and by the large coupling constant of the *N*-benzyl protons (N-CH_2Ph) of the trans isomer,



3a, R = H
b, R = Me
c, R = Et
d, R = *n*-Pr



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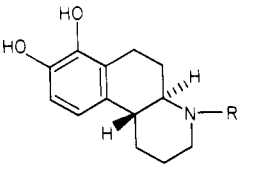

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(1) Volkman, P. H.; Kohli, J. D.; Goldberg, L. I.; Cannon, J. G.; Lee, T. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 3602.
(2) Cannon, J. G.; Lee, T; Goldman, H. D.; Costall, B; Naylor, R. J. *J. Med. Chem.* **1977**, *20*, 1111.
(3) Cannon, J. G.; Suarez-Gutierrez, C.; Lee, T.; Long, J. P.; Costall, B.; Fortune, D. H.; Naylor, R. J. *J. Med. Chem.* **1979**, *22*, 341.

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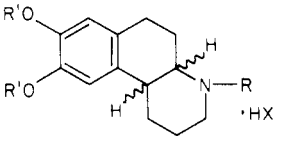
Table I. *cis*- and *trans*-1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinoline Derivatives

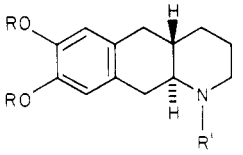


no.	R	R′	X	stereochem of ring fusion	meth of N-alkylation	mp, °C[a]	yield, %	formula	anal.
16	CH_3	CH_3	Cl	trans	A	249-251	86	$C_{16}H_{24}ClNO_2$	C, H, N
17	CH_3	CH_3	Cl	cis	A	222-225	78	$C_{16}H_{24}ClNO_2$	C, H, N
18	C_2H_5	CH_3	Cl	trans	B	284-285	91	$C_{17}H_{26}ClNO_2$	C, H, N
19	C_2H_5	CH_3	Cl	cis	B	175-178	73	$C_{17}H_{26}ClNO_2$	C, H, N
20	*n*-C_3H_7	CH_3	Cl	trans	C	238-241	79	$C_{18}H_{28}ClNO_2$	C, H, N
21	*n*-C_3H_7	CH_3	Cl	cis	C	239-241	93	$C_{18}H_{28}ClNO_2$	C, H, N
3a	H	H	Br	trans		300	89	$C_{13}H_{18}BrNO_2$	C, H, N
22	H	H	Br	cis		281-283	96	$C_{13}H_{18}BrNO_2$	C, H, N
3b	CH_3	H	Br	trans		302-303	94	$C_{14}H_{20}BrNO_2$	C, H, N
23	CH_3	H	Br	cis		247-250	76	$C_{14}H_{20}BrNO_2$	C, H, N
3c	C_2H_5	H	Br	trans		275-278	84	$C_{15}H_{22}BrNO_2$	C, H, N
24	C_2H_5	H	Br	cis		281-282	93	$C_{15}H_{22}BrNO_2$	C, H, N
3d	*n*-C_3H_7	H	Br	trans		286-288	79	$C_{16}H_{24}BrNO_2$	C, H, N
25	*n*-C_3H_7	H	Br	cis		259-261	82	$C_{16}H_{24}BrNO_2$	C, H, N

[a] Recrystallized from MeOH-Et_2O.

as has been discussed in detail in a prior article.[3] The *N*-benzyl systems were catalytically debenzylated, and the resulting secondary amines were appropriately N-alkylated by standard methods (see Table I).

Walsh and Smissman[4] have described the preparation of a *trans*-octahydrobenzo[*g*]quinoline system **6a** which



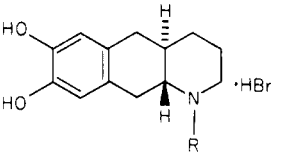
6a, R = Me; R′ = H
b, R = R′ = Me
c, R = Me; R′ = Et
d, R = Me; R′ = *n*-Pr

7a, R = R′ = H
b, R = H; R′ = Me
c, R = H; R′ = Et
d, R = H; R′ = *n*-Pr

is another rigid congener of the β conformer of dopamine and of the A-6,7-DTN system. Further chemical study and pharmacologic investigation of this benzoquinoline system have not been addressed in the literature since Professor Smissman's untimely death. Accordingly, an added goal of the work described herein was to complete a series of appropriately N-substituted systems having free catechol groups (**7a–d**) and to screen these compounds as potential dopaminergic agents (see Table II). Spectral (IR and NMR) data on all intermediates and final products were consistent with the proposed structures.

Pharmacology. Results. In mice, in the absence of any pretreatment, bilateral intra-accumbens administration of 100 μg of dopamine caused a weak hyperactivity (5–11 counts/5 min, $p > 0.05$, in the 30–90 min after injection); a 200-μg dose caused moderate hyperactivity (20–50 counts/5 min in the 30–200 min after injection, $p < 0.001$). A dose of 200 μg of intra-accumbens dopamine caused a weak stereotyped sniffing behavior. In contrast to dopamine, intra-accumbens injections of 3.125–50 μg of **7a–d**, **3a–d**, and **22–25** (Tables I and II), in the absence of any pretreatment, failed to cause hyperactivity of intensity greater than that observed for control animals receiving the same volumes (1 or 2 μL) of intra-accumbens solvent (5–15 counts/5 min only during the 30 min period

Table II. *trans*-7,8-Dihydroxy-1,2,3,4,5,5a,10,10a-Octahydrobenzo[*g*]quinoline Derivatives



no.	R	mp, °C[a]	yield, %	formula	anal.
7a	H	>310	84	$C_{13}H_{18}BrNO_2$	C, H, N
7b	CH_3	>300	86	$C_{14}H_{20}BrNO_2$	C, H, N
7c	C_2H_5	>300	89	$C_{15}H_{22}BrNO_2$	C, H, N
7d	*n*-C_3H_7	>310	86	$C_{16}H_{24}BrNO_2$	C, H, N

[a] Recrystallized from MeOH-Et_2O.

following injection). Indeed, after this exploratory phase, the animals appeared sedated, particularly those treated with **7c** and **7d**. Also, stereotyped behavior was not observed for any of the *trans*-octahydrobenzo[*g*]- or -[*f*]-quinolines (**7a–d** and **3a–d**) or for the *cis*-octahydrobenzo[*f*]quinolines (**22–25**) in these tests. The potential of dopamine to induce hyperactivity was enhanced in the presence of a monoamine oxidase inhibitor (nialamid). Under these conditions, 1–50 μg of dopamine caused dose-dependent hyperactivity responses (counts ranging from 10–20/5 min for a duration of 4 h at 1 μg to 30–75/5 min for 7+ h at 50 μg, onsets within 5–20 min).[5] A continuous sniffing behavior was also recorded at 25- and 50-μg doses of dopamine, although stereotyped gnawing, biting, and licking were never recorded. After nialamid pretreatment, only a 25-μg dose of **7a–d** was shown to cause a weak hyperactivity response in 50–60% of the animals tested (5–15 counts/5 min, developing after a delay of 60–90 min and persisting for only 2–3 h). This effect was not increased with increasing the dose to 50 μg. Even after nialamid, **7a–d** failed to cause any form of stereotyped behavior. Compounds **3a–d** and **22–25** were inactive in this preparation.

Climbing behavior, in which mice moved about the sides and top of the individual wire-lined cages, was induced by

(4) Walsh, D. A.; Smissman, E. E. *J. Org. Chem.* **1974**, *39*, 3705.

(5) Costall, B.; Naylor, R. J. *Eur. J. Pharmacol.* **1976**, *40*, 9.

Table III. Neural and Cardiovascular Properties of *cis*- and *trans*-1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinoline Derivatives

compd	N	inhibn of right cardioaccelerator nerves: ID_{50}, μmol/kg (95% CL)	antagonist	mean BP, mmHg ± SE		mean heart rate, beats/min ± SE	
				before drug	after ID_{50} dose	before drug	after ID_{50} dose
apomorphine	5	0.022 (0.017-0.031)	H[a]	109.5 ± 15.6	92.0 ± 13.8[c]	139.2 ± 12.8	128.9 ± 10.8
3b	7	0.0055 (0.0022-0.0093)	H	116.7 ± 10.2	95.6 ± 9.8	175.4 ± 9.5	160.9 ± 9.7[c]
3c	7	0.0009 (0.00052-0.0012)	H	115.4 ± 5.6	90.9 ± 4.3[c]	176.9 ± 10.8	161.3 ± 10.8[c]
3d	8	0.0013 (0.00053-0.0025)	H	116.4 ± 6.3	73.6 ± 5.7[c]	178 ± 12.6	156.9 ± 8.7[c]
23	6	0.31 (0.24-0.43)	P[b]	125.8 ± 9.1	95.4 ± 5.3[c]	174 ± 6.2	158.6 ± 9.9[c]
24	7	0.45 (0.25-4.5)	H	115.0 ± 9.7	89.8 ± 7.1[c]	183 ± 6.2	162.8 ± 13.9
25	4	0.26 (0.11-1.1)	H	114.9 ± 12.1	82.9 ± 12.0[c]	175.7 ± 9.3	165.0 ± 9.7[c]

[a] H = inhibition antagonized by haloperidol, 100 μg/kg. [b] P = inhibition antagonized by phentolamine, 2 mg/kg. [c] Significantly different from control values by paired Student's *t* test, $p < 0.05$.

subcutaneous apomorphine in doses of 0.5–1.5 mg/kg. Mice given 1.5 mg/kg sc of apomorphine climbed for a continuous period of up to 20 min (see ref 6). However, up to 40 mg/kg sc of **7a–d**, **3a–d**, and **22–25** failed to induce any climbing response. Similarly, although 1–4 mg/kg sc of apomorphine caused stereotyped biting behavior in the mouse, all of the benzoquinolines in this study were inactive at doses up to 40 mg/kg sc and no other form of stereotyped behavior was observed. Ipsilateral circling behavior was induced by apomorphine in mice with unilateral electrolesions of the caudate-putamen; 0.25–1 mg sc caused marked asymmetry and circling of intensity 3–12 revolutions/2 min, as measured manually (see ref 11 for details). Again, up to 40 mg/kg sc of all the benzoquinolines in this study failed to cause any circling response in animals shown to be capable of a maximum circling response to apomorphine. The animals selected exhibited 7+ revolutions/2 min when challenged with 1 mg/kg sc 7 days before testing with the benzoquinoline.

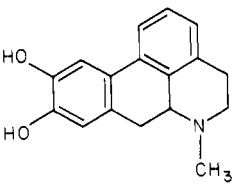
The cardioaccelerator nerve inhibiting actions and cardiovascular properties of the active octahydrobenzo[*f*]quinoline derivatives **3a–d** and **22–25** are shown in Table III. The marked potency of the trans derivatives (**3b–d**) is noteworthy, as is the relative decreased activity of the cis isomers (**23–25**). Both the cis and the trans compounds decreased arterial blood pressure and decreased heart rate at the dose that inhibited by 50% the positive chronotropic responses induced by stimulating the right cardioaccelerator nerve. The secondary amines (**3a** and **22**) demonstrated sympathomimetic activity. In seven cats, 0.01 μmol/kg of **3a** administered intravenously decreased the blood pressure 32.6 ± 2.6%. The compound was 0.55 times as active as norepinephrine when evaluated for its ability to increase heart rate in vivo. Compound **22** was a weak vasopressor (0.001 relative to norepinephrine) and positive chronotropic agent (0.007 relative to norepinephrine).

The *trans*-octahydrobenzo[*g*]quinoline derivatives **7a–d** were nearly inactive in lowering blood pressure, slowing resting heart rate, or inhibiting the right cardioaccelerator nerve. The compounds were evaluated using doses up to 400 μg/kg administered intravenously. The heart rate and blood pressure were altered less than 8%. Compound **7a** was most effective in inhibiting the cardioaccelerator nerve, but an average inhibition of only 24% was observed. The compounds **7a–d** did not elevate the blood pressure.

All of the compounds (**3a–d**, **7a–d**, and **22–25**) were inert in the renal blood-flow assay in the dog, in doses from 10 to 800 μg. In this assay, dopamine hydrochloride was active in a dose range of 10–50 μg. Compounds **3a** and **22** decreased renal blood flow with doses of 10–100 μg.

Discussion

While N-alkylated tetralin compounds derived from A-6,7-DTN (**1**) have both behavioral and biochemical activity as dopamine agonists,[2,7] the present study, which assessed the potential dopamine-like activity of the linearly and angularly annelated benzoquinoline derivatives **7a–d**, **3a–d**, and **22–25** to modify cerebral dopamine mechanisms involved in motor control after peripheral injection in the mouse, indicated that these compounds are inactive in doses up to 40 mg/kg sc. It is unlikely that this failure to modify behavioral effects reflects a failure to pass the blood–brain barrier, since the subject compounds also failed to induce a significant locomotor hyperactivity on direct injection into the nucleus accumbens. The induction of hyperactivity from this brain region of the rat is highly specific for dopamine and dopamine agonists and is markedly enhanced by prior inhibition of monoamine oxidase.[8] However, even after a nialamid pretreatment, all of the benzoquinoline derivatives in this study failed to induce a consistent locomotor hyperactivity. Likewise, compounds **7a–d** were nearly inactive in ability to alter the heart rate, blood pressure, or to inhibit stimulation of the cardioaccelerator nerves. It is therefore clear that, while the structures of **7a–d**, **3a–d** and **22–25** may superficially resemble the β conformer of dopamine and the 2-amino-6,7-dihydroxytetralins (**1**), the inclusion of the nitrogen atom into the fixed ring structure negates the potential to stimulate cerebral dopamine systems concerned with motor control and, moreover, that dopamine receptors in the kidney which respond to A-6,7-DTN are refractory toward these benzoquinoline systems. It is of interest that this inactivity reflects the behavioral and biochemical inactivity of "isoapomorphine" (**8**), as a dop-



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amine agonist,[9,10] a molecule which is also a congener of the β conformer of dopamine. The inactivity of the linear benzoquinolines (**7a–d**) in the renal blood-flow assay seems at variance with proposals of Goldberg et al.[12] who pos-

(6) Costall, B.; Naylor, R. J.; Nohria, V. *Eur. J. Pharmacol.* **1978**, *50*, 39.
(7) Cannon, J. G.; Costall, B.; Laduron, P.; Leysen, J.; Naylor, R. J. *Biochem. Pharmacol.* **1978**, *27*, 1417.
(8) Costall, B.; Naylor, R. J. *Eur. J. Pharmacol.* **1975**, *32*, 87.
(9) Costall, B.; Naylor, R. J.; Pinder, R. M. *J. Pharm. Pharmacol.* **1974**, *26*, 753.
(10) Grol, C. J.; Rollema, H. *J. Pharm. Pharmacol.* **1976**, *29*, 153.

tulated modes of binding of the active dopamine-like agents apomorphine and A-6,7-DTN (as well as dopamine itself) to the hypothetical renal vascular dopamine receptor. These workers suggested that the inactivity of isoapomorphine (8) in the renal vascular assay may be referrable to the unsubstituted aromatic ring which could inhibit proper alignment of the molecule at the receptor. Because compounds **7a–d** lack this unsubstituted aromatic ring, it might have been predicted on the basis of the Goldberg et al. diagrams for agonist–renal receptor interactions that these compounds would be biologically active. Some modification of the graphic representation of the renal vascular dopamine receptor–agonist interaction seems necessary to account for the inactivity of **7a–d**.

The CNS inactivity of the N-alkylated 8,9-dihydroxy-*trans*-octahydrobenzo[*f*]quinolines **3a–d** contrasts with the dopamine-like CNS activity of the isomeric 7,8-dihydroxy systems (**5**),[3] agents resembling the α-rotameric conformation of dopamine found in apomorphine.

In contrast to the inactivity found for the octahydrobenzo[*f*]quinoline derivatives (**3a–d** and **22–25**) in assays involving the CNS, some of these compounds (**3b–d** and **23–25**) demonstrated marked dopamine-like inhibitory activity on the peripheral cardioaccelerator nerves. The trans isomers **3b–d** are among the most potent agents yet reported in this assay. With most of the agents thus far evaluated in ongoing studies in our laboratories, a high correlation between central and peripheral actions has been found. Perhaps the variance in the present case of the octahydrobenzo[*f*]quinolines is a reflection of the type or site of dopamine receptor interaction within the CNS as contrasted with the periphery.

However, the reasons for this separation of selectivity between central and certain peripheral effects are not established and must await further studies.

The inhibition of the right cardioaccelerator nerve appeared to involve dopamine receptors, with the exception of compound **23**. This compound appeared to inhibit transmission by adrenergic α-receptor involvement, its effect being blocked by phentolamine. Although cats usually demonstrate dopaminergic receptor involvement with various series of test compounds, an apparent switch in type of inhibition within a series has not been observed before.

The trans secondary amine **3a** appears to be a potent β_1 and β_2 agonist. The blood-pressure decrease and positive chronotropic responses were inhibited by pretreatment with propranolol (2 mg/kg).

Experimental Section

Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer 267 instrument. NMR spectra were recorded with a Varian Associates T-60 instrument using tetramethylsilane as the internal standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated by the symbols of the elements, analytical results were within ±0.4% of the theoretical values.

Pharmacology. Methods. CNS Studies. Behavioral studies were carried out using Sprague–Dawley rats, 250 ± 25 g, and male albino B.K.W. mice, 20–25 g (30–35 g at the time of surgery). Potential to cause hyperactivity and stereotyped behavior was assessed in the rat following bilateral injection of the test and control (dopamine) agents into the nucleus accumbens (see ref 5 for details and methodology). Compounds **7a–d** were prepared for intraaccumbens injection in distilled H_2O containing 0.1% sodium metabisulfite, with the addition of minimum quantities of *N,N*-dimethylformamide. Compounds **3a–d**, **22–25**, and dopamine hydrochloride (Koch–Light) were prepared in N_2-bubbled H_2O containing 0.1% sodium bisulfite. In all experiments, control animals received intra-accumbens solvent and their behavior was assessed at the same time as the experimental animals receiving the drug. At least six rats received each dose or solvent injection. Rats were used on one occasion only and were then sacrificed for histological determination of injection sites. All injections were made into the area of the nucleus accumbens.[5]

Hyperactivity was measured in photocell cages, the interruptions of the light beam being recorded electromechanically and expressed in counts/5 min. The presence of stereotyped sniffing, head and/or limb movements, gnawing, biting, or licking was noted (see ref 5 for further details). Nialamid (Sigma) was prepared in a minimum quantity of concentrated HCl and was made to volume with H_2O; 100 mg/kg was given intraperitoneally 2 h before the intra-accumbens injections. Compounds **7a–d**, **3a–d**, **22–25**, and apomorphine hydrochloride (Macfarlan Smith) were prepared for mouse studies in distilled H_2O containing 0.1% sodium metabisulfite and were given in a volume of 1 mL/100 g of body weight. Throughout the study, doses were calculated as the free base.

Cat Right Cardioaccelerator Nerve Preparation. Each compound was evaluated in four to seven cats. Cats of either sex, 2.5–5 kg, were anesthetized by intraperitoneal injection of sodium pentobarbital (30 mg/kg). Respiration was supported, and blood pressure and heart rate were monitored by femoral artery cannula. All animals were pretreated with atropine sulfate (200 μg/kg, iv) and vagotomized. The right postganglionic cardioaccelerator nerve was exposed and placed on bipolar silver electrodes: 30-s stimulations were used and the parameters were 2-Hz, 3–5-ms duration, and maximal voltage 15–20 V.

Dog Renal Blood Flow. Each compound was evaluated in three dogs. Dogs of either sex, 10–15 kg, were anesthetized with sodium pentothal (15 mg/kg) and sodium barbital (200 mg/kg). Animals were respirated, and blood pressure and heart rate were monitored by femoral artery cannula. The left renal artery was exposed and renal blood flow was monitored with a flow probe, Carolina Squarewave Electromagnetic Flowmeter, Model 501. All dogs were pretreated with propranolol (2 mg/kg) and phenoxybenzamine (10 mg/kg). Doses were injected directly into the renal artery at volumes less than 0.3 mL and at doses that had no effect on systemic blood pressure.

Statistics. Statistical treatment of data in experiments where each preparation served as its own control was by the paired Student's *t* test.[15] The relative potency and 95% fiducial limits were calculated by a 2 × 2 parallel line bioassay.[16] ID_{50} values were determined by a nonquantal analysis described by Finney[16] (see Table III).

***trans*-7,8-Dimethoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydrochloride (6a).** This was prepared by the method of Walsh and Smissman:[4] mp ($MeOH–Et_2O$) 287–288 °C, lit.[4] ($Me_2CO–Et_2O$) 235 °C dec. Anal. ($C_{15}H_{22}ClNO_2$) C, H, N. Perchlorate salt: mp (2-PrOH) 287–288 °C, lit.[4] 279–281 °C.

***trans*-1-Methyl-7,8-dimethoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydrochloride (6b). Method A.**[17] A mixture of 0.5 g (0.002 mol) of the free base of **6a**, 0.25 g (0.004 mol) of $NaCNBH_3$, 1 mL of 37% aqueous formaldehyde solution (0.10 mol), 10 mL of MeCN, and 4 mL of MeOH was stirred overnight, and AcOH was added from time to time to maintain the pH at ca. 7 (pH paper). Excess concentrated HCl was added, and the resulting mixture was evaporated under reduced pressure. The residue was taken up in H_2O and washed twice with Et_2O. The aqueous layer was treated with excess NaOH and was ex-

(11) Costall, B.; Fortune, D. H.; Naylor, R. J.; Nohria, V. *Eur. J. Pharmacol.* **1979**, *56*, 207.
(12) Goldberg, L. I.; Kohli, J. D.; Kotake, A. N.; Volkman, P. H. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1978**, *37*, 82.
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tracted twice with $CHCl_3$. The dried (Na_2SO_4) extract was evaporated to leave a yellow oil, which was converted to its HCl salt. Recrystallization (MeOH–Et_2O) afforded 0.52 g (86%) of white crystals, mp 260–262 °C. Anal. ($C_{16}H_{24}ClNO_2$) C, H, N.

***trans*-1-Ethyl-7,8-dimethoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydrochloride (6c). Method B.** The procedure of Marchini et al.[13] was employed using 0.43 g (0.00174 mol) of the free base of **6a**, 0.405 g (0.0107 mol) of $NaBH_4$, 2.18 g (0.0364 mol) of AcOH, and 40 mL of benzene. The cooled reaction mixture was shaken with excess 2 N NaOH. The organic layer was dried (Na_2SO_4) and evaporated, and the yellow oily product was converted to its HCl salt. This was recrystallized from MeOH–Et_2O to give 0.478 g (88%) of a white granular solid, mp 241–242 °C. Anal. ($C_{17}H_{26}ClNO_2$) C, H, N.

***trans*-1-*n*-Propyl-7,8-dimethoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydrochloride (6d). Method C.** The method of Marchini et al.[13] was followed using 0.57 g (0.00231 mol) of the free base of **6a**, 0.437 g (0.01155 mol) of $NaBH_4$, 2.91 g (0.0393 mol) of propionic acid, and 40 mL of benzene. The reaction mixture was worked up as described for **6c**. The oily orange product was converted to its HCl salt and this was recrystallized from MeOH–Et_2O to give 0.633 g (94%) of a very pale yellow solid, mp 235–236 °C. Anal. ($C_{18}H_{28}ClNO_2$) C, H, N.

8,9-Dimethoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3-(2*H*)-one (9). This was prepared in 48% yield from 8.2 g (0.04 mol) of 6,7-dimethoxy-2-tetralone[2] and 4.55 g (0.064 mol) of acrylamide using the method of Cannon and Hatheway,[14] mp 264–266 °C. Anal. ($C_{15}H_{17}NO_3$) C, H, N.

8,9-Dimethoxy-4-benzyl-1,4,5,6-tetrahydrobenzo[*f*]-quinolin-3(2*H*)-one (10). A mixture of 5.19 g (0.02 mol) of **9**, 0.55 g (0.023 mol) of NaH, and 100 mL of dimethoxyethane (freshly distilled from $LiAlH_4$) was heated under reflux for 2 h. Benzyl bromide (3.77 g, 0.022 mol) in 25 mL of dimethoxyethane was then added and refluxing was continued for 3 h. The reaction mixture was stirred at room temperature overnight; then it was treated with excess H_2O. Volatiles were removed under reduced pressure, and the residue was partitioned between $CHCl_3$ and H_2O. From the $CHCl_3$ layer, a yellow oil was obtained which was crystallized from MeOH–H_2O to give a very pale yellow solid: mp 121–123 °C; yield 5.6 g (80%). Anal. ($C_{22}H_{23}NO_3$) C, H, N.

8,9-Dimethoxy-4-benzylhexahydrobenzo[*f*]quinoline (11). A mixture of 4.45 g (0.013 mol) of **10**, 24.5 mL of "Red-Al" (70% in benzene), and 120 mL of benzene was heated under reflux for 6 h, and then was stirred at room temperature overnight. The orange mixture was hydrolyzed with a minimum amount of H_2O, and sufficient 100% NaOH was added to dissolve the aluminum salts. The organic layer was washed three times with H_2O, dried (Na_2SO_4), and evaporated to leave an orange oil which soon solidified. This was used in the next step without purification: IR ($CHCl_3$) 1610 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.7–3.3 (m, 10 H), 3.77 (2 s, 6 H), 4.21 (s, 2 H), 6.48 (s, 2 H), 7.21 (s, 5 H).

***cis*- and *trans*-8,9-Dimethoxy-4-benzyl-1,2,3,4,4a,5,10,10b-octahydrobenzo[*f*]quinoline Hydrochloride (12 and 13).** A mixture of 4.1 g (0.0122 mol) of **11** and 1 g (0.0156 mol) of $NaCNBH_3$ in 50 mL of MeOH was stirred at room temperature overnight, adding AcOH from time to time to maintain a neutral pH (pH paper). The reaction mixture was treated with excess concentrated HCl, and volatiles were removed under reduced pressure. The residue was treated with H_2O, this mixture was washed with Et_2O, and the aqueous layer was treated with excess NaOH. The resulting mixture was extracted repeatedly with Et_2O. The pooled extracts were dried (Na_2SO_4) and filtered, and the Et_2O was removed. The residual brown oil was converted to its HCl salt and this was fractionally crystallized from MeOH–Et_2O. The first crop, 1.2 g (29%), mp 223–225 °C, was the trans-isomer **13**: IR ($CHCl_3$) of the free base 2858, 2834, 2798 cm^{-1} (strong, Bohlmann bands); NMR ($CDCl_3$) of the free base δ 1.2–3.2 (m, 12 H), 3.73 (AB quartet, $\Delta\nu$ = 44 Hz, J = 14 Hz, 2 H), 3.87 (s, 6 H) 6.58 (d, $\Delta\nu$ = 13 Hz, 2 H), 7.30 (s, 5 H). The second and third crop of crystals, 1.36 g (33%), mp 225–227 °C, were the cis-isomer **12**: IR ($CHCl_3$) of the free base 2867, 2855, 2833, 2798 cm^{-1} (weak, Bohlmann bands); NMR ($CDCl_3$) of the free base δ 0.9–3.5 (m, 12 H), 3.75 (AB quartet, $\Delta\nu$ = 4 Hz, 2 H), 6.53 (d, $\Delta\nu$ = 3 Hz, 2 H), 7.28 (m, 5 H). Anal. ($C_{22}H_{27}NO_2$) C, H, N.

***trans*-8,9-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo-[*f*]quinoline Hydrochloride (14).** A mixture of 0.631 g (0.0017 mol) of **13** 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 crystallized from MeOH–Et_2O to give 0.40 g (84%) of product: mp 297–298 °C; IR ($CHCl_3$) of the free base 2858, 2832 cm^{-1} (strong, Bohlmann bands). Anal. ($C_{15}H_{22}ClNO_2$) C, H, N.

***cis*-8,9-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]-quinoline Hydrochloride (15).** This was prepared in 97% yield from 0.7 g (0.0018 mol) of **12** by the method described for **14**: mp 268–270 °C (MeOH–Et_2O); IR ($CHCl_3$) of free base 2858, 2830 cm^{-1} (medium Bohlmann bands). Anal. ($C_{15}H_2ClNO_2$) C, H, N.

Ether Cleavage Reactions. The HCl salt of the amine (0.001 mol) was heated under N_2 with 6 mL of 48% HBr at 110–120 °C for 3 h. Volatiles were removed under reduced pressure and the residue was recrystallized (see Tables I and II).

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