Conformationally Restricted Congeners of Dopamine Derived from Octahydrobenzo[*g*]quinoline and Octahydrobenzo[*f*]quinoline

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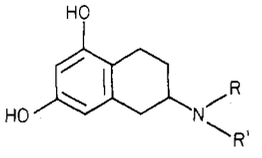
Series of N-alkylated derivatives of *trans*-octahydrobenzo[*g*]quinoline and of *cis*- and *trans*-octahydrobenzo[*f*]quinoline were prepared for pharmacological testing as congeners of 2-amino-5,7-dihydroxytetralin, which elicits dopaminergic effects in a variety of assays. Trans-fused compounds bearing *N*-ethyl or *N*-*n*-propyl displayed high potency/activity in inhibition of effect of stimulation of the cat cardioaccelerator nerve. Certain *N*-alkyl homologues in the octahydrobenzo[*f*]quinoline series showed high potency in binding studies in rat caudate homogenate.

Previous communications have described the synthesis and pharmacological properties of dopamine congeners having a resorcinol hydroxylation pattern, based upon a tetrahydronaphthalene ring (**1**)[1] and upon indan (**2**)[2] and benzocycloheptene (**3**)[2] rings. The present work addresses



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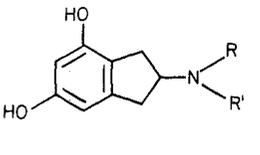

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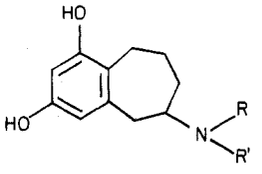

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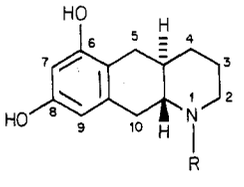
R, R′ = combinations of H, CH_3, C_2H_5, n-C_3H_7, and 2-C_3H_7

the synthesis and pharmacological evaluation of two rigid ring systems bearing a resorcinol-derived β-phenethylamine moiety, *trans*-6,8-dihydroxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (**4**) and *cis*- and *trans*-7,9-dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (**5**).



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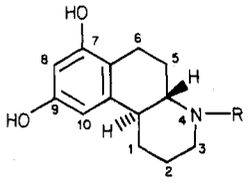
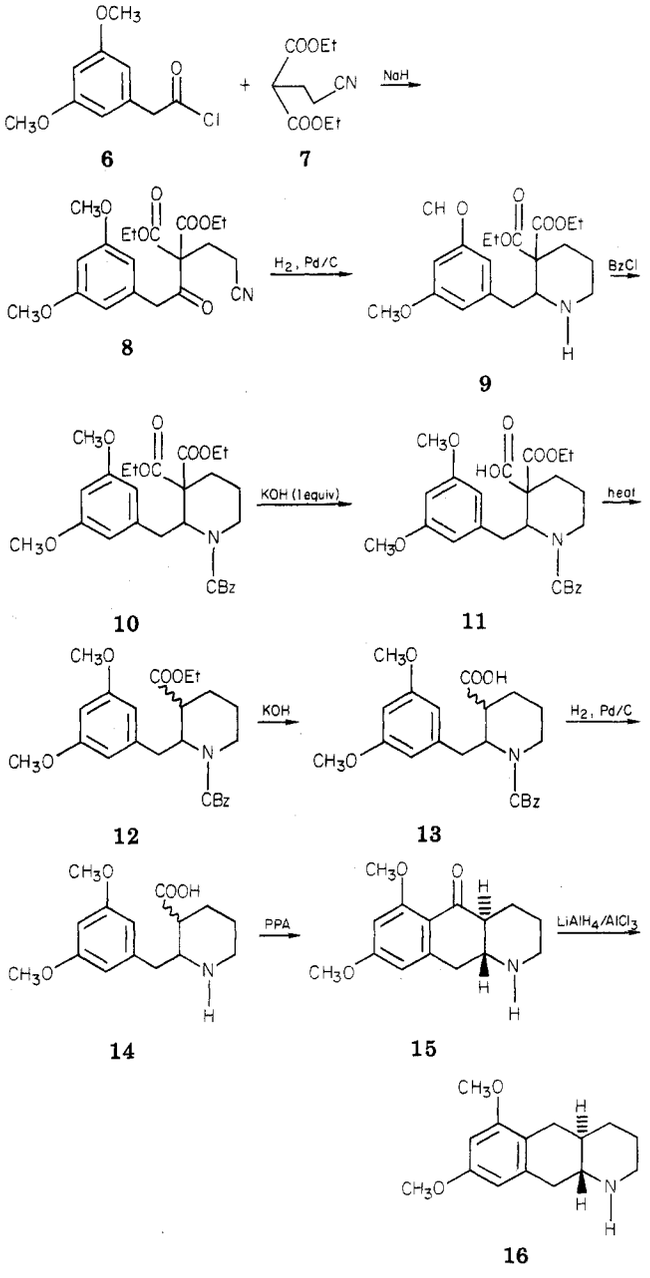


5

R = H, C_2H_5, n-C_3H_7

Chemistry. The ring system **4** was prepared by a modification of a sequence of Michne and Albertson[3] and is shown in Scheme I. Walsh and Smissman[4] reported that polyphosphoric acid mediated cyclizations to form octahydrobenzo[*g*]quinolines give rise to the trans-fused ring system exclusively (e.g., **14** → **15**, Scheme I). Reduction of the ketonic group of **15** to methylene could be effected with lithium aluminum hydride–aluminum chloride by a technique of Nystrom and Berger.[5] Catalytic hydrogenation was not successful in this step. Compound **16** exhibited strong absorption in the "Bohlmann region" of the infrared spectrum (2780 cm^{-1}), which is indicative of the trans geometry of ring fusion.[6,7] Further evidence for trans ring fusion was provided by the *N*-benzyl de-

Scheme I. Preparation of *trans*-6,8-Dimethoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline



rivative of **16** (**33**), which was shown by gas chromatographic analysis to be homogeneous and whose NMR

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(1) Cannon, J. G.; Brubaker, A. N.; Long, J. P.; Flynn, J. R.; Verimer, T.; Harnirattisai, P.; Costall, B.; Naylor, R. J.; Nohria, V. *J. Med. Chem.* **1981**, *24*, 149.

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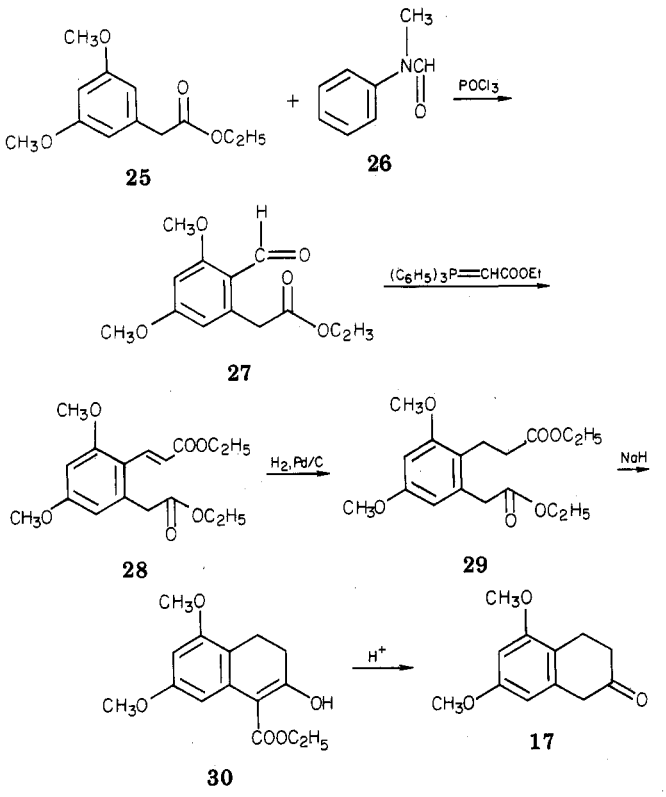
Scheme II. Preparation of 5,7-Dimethoxy-2-tetralone

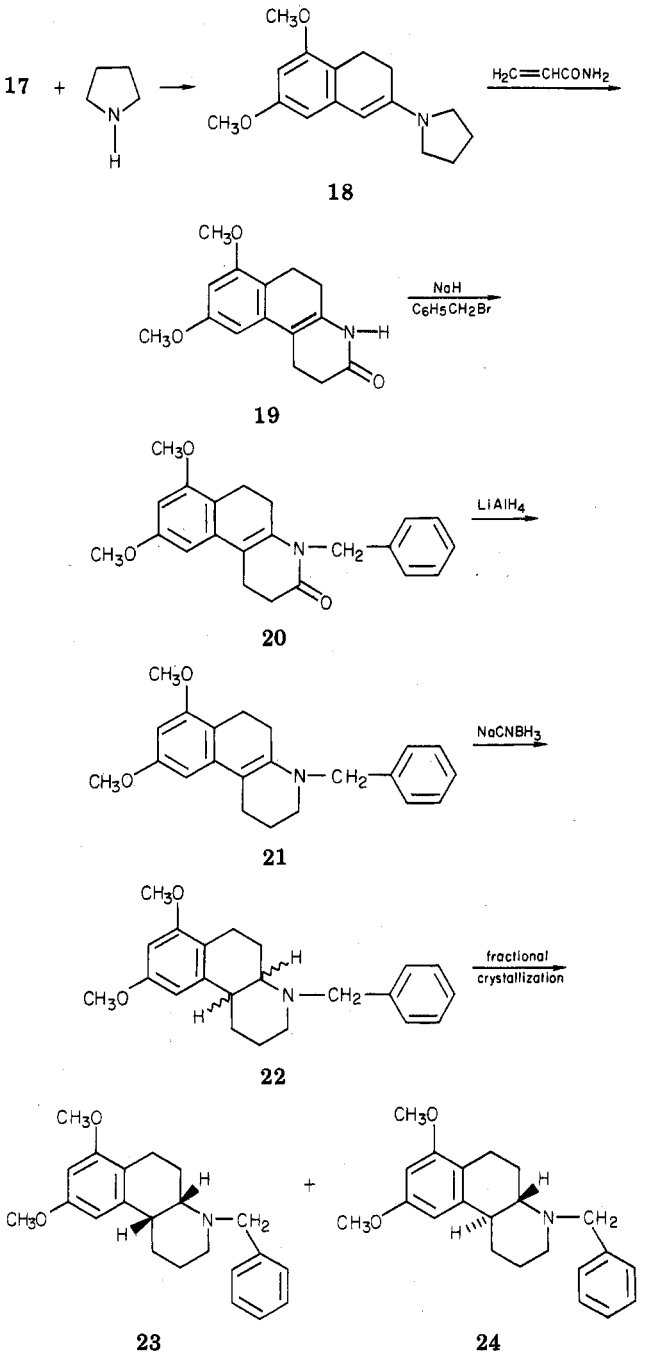


spectrum exhibited an AB system for the *N*-benzyl methylene protons, having a large (65 Hz) chemical-shift difference. These NMR data are characteristic of trans-fused octahydrobenzo[*g*]quinolines.[4]

Preparation of the ring system of **5** was based upon a sequence used in this laboratory previously.[8] As outlined in Scheme III, the proposed preparation of the angularly annulated target system **5** required sizeable amounts of 5,7-dimethoxy-2-tetralone (**17**). Attempts to prepare this compound in significant amounts by a variety of intramolecular benzene ring acylation or alkylation reactions failed.[1] Scheme II describes a more circuitous route to **17**, which, nevertheless, represents the first preparative method for this elusive compound. 2,4-Dimethoxy-6-methylbenzaldehyde is the sole product of a Gatterman reaction on 5-methylresorcinol dimethyl ether.[9] When ethyl (3,5-dimethoxyphenyl)acetate (**25**, Scheme II) was subjected to Gatterman reaction conditions, a large amount of polymeric material was formed, in addition to only a modest yield of the desired aldehydic product. Application of the mechanistically similar Vilsmeier-Haack reaction (which does not require as severe reaction conditions as the Gatterman reaction) gave a high yield of the desired aldehyde **27**.

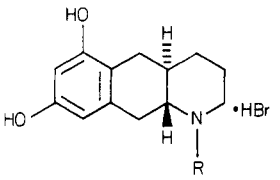
Stepanov et al.[10] prepared β-tetralone by a Dieckmann condensation on ethyl 1-[2-[(ethoxycarbonyl)methyl]-phenyl]propionate, but Shner and Przhiyaglovskaya[11] cited literature that stated that attempts to utilize the Dieckmann condensation to synthesize β-tetralone derivatives substituted in the aromatic ring were unsuccessful. In the present work, Dieckmann cyclization of **29** to give **30** (Scheme II) proceeded in excellent yield. NMR data indicated that the Dieckmann product exists in the enolic form, as shown. This product was not purified, but it was treated with hydrochloric acid to effect ester hydrolysis and subsequent decarboxylation. The overall yield of the substituted β-tetralone **17** from ethyl (3,5-dimethoxyphenyl)acetate was 53%.

Scheme III. Preparation of *cis*- and *trans*-7,9-Dimethoxy-4-benzyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline

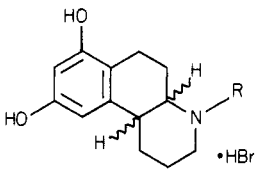


(2) Cannon, J. G.; Pease, J. P.; Hamer, R. L.; Ilhan, M.; Bhatnagar, R. K.; Long, J. P. *J. Med. Chem.*, following paper in this issue.
(3) Michne, W. F.; Albertson, N. F. *J. Med. Chem.* **1969**, *12*, 402.
(4) Walsh, D. A.; Smissman, E. E. *J. Org. Chem.* **1974**, *39*, 3705.
(5) Nystrom, R. F.; Berger, C. R. *J. Am. Chem. Soc.* **1958**, *80*, 2896.
(6) Horii, Z.; Kurihara, T.; Ninomiya, I. *Chem. Pharm. Bull.* **1969**, *17*, 1733.
(7) Eliel, E. L.; Allinger, N. L.; Angual, S. J.; Morrison, G. A. In "Conformational Analysis"; Wiley-Interscience: New York, 1968; pp 253–254.
(8) 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.
(9) Gatterman, L. *Justus Liebigs Ann. Chem.* **1907**, *357*, 313.
(10) Stepanov, F. N.; Iodko, M. O.; Vul'fson, N. S. *Ukr. Khim. Zh. (Russ. Ed.)* **1957**, *23*, 489; *Chem. Abstr.* **1958**, *52*, 6293c.
(11) Shner, V. F.; Przhiyaglovskaya, N. M. *Russ. Chem. Rev. (Engl. Transl.)* **1966**, *35*, 523.

Table I. Resorcinol Congeners of Dopamine Derived from Octahydrobenzo[*g*]quinoline and from Octahydrobenzo[*f*]quinoline



benzo[*g*]quinoline



benzo[*f*]quinoline

compd	ring system	geometry of ring fusion	R	mp, °C	yield, %	formula	anal.
42	*g*	trans	H	>300	82	$C_{13}H_{18}BrNO_2$	C, H, N
43	*g*	trans	C_2H_5	>300	70	$C_{15}H_{22}BrNO_2$	C, H, N
44	*g*	trans	*n*-C_3H_7	>300	42	$C_{16}H_{24}BrNO_2$	C, H, N
45	*f*	cis	H	>300	89	$C_{13}H_{18}BrNO_2$	C, H, N
46	*f*	cis	C_2H_5	>300	94	$C_{15}H_{22}BrNO_2$	C, H, N
47	*f*	cis	*n*-C_3H_7	297-299	71	$C_{16}H_{24}BrNO_2$	C, H, N
48	*f*	trans	H	>300	86	$C_{13}H_{18}BrNO_2$	C, H, N
49	*f*	trans	C_2H_5	301-303	85	$C_{15}H_{22}BrNO_2$	C, H, N
50	*f*	trans	*n*-C_3H_7	267-269	64	$C_{16}H_{24}BrNO_2$	C, H, N

Table II. Biological Potencies of Resorcinol Derivatives of Octahydrobenzo[*g*] and Octahydrobenzo[*f*]quinolines

compd	inhibn of cat cardioaccelerator nerve: ED_{50} μmol/kg (95% CL)	IC_{50}, μM,[f] – % of sp binding of rat caudate	
		[^{3}H]dopamine	[^{3}H]spiroperidol
42	I[a]	12.8	264
43	I[a]	0.44	32
44	1.74 (0.79-6.91)	0.37	15
45	>4.0[b,c]	11.1	113
46	>4.0[b]	0.43	10
47	>4.0[b]	1.7	11
48	NT[d]	1.0	25
49	0.0021 (0.0015-0.0030)[e]	9×10^{-2}	2.4
50	0.0047 (0.0041-0.0054)[e]	4×10^{-6}	1.0
apomorphine	0.022 (0.02-0.03)[e]	7×10^{-4}	1.1

[a] Inactive at 4 μmol/kg ($n = 3$). [b] Produced 10-25% inhibition at 4 μmol/kg (highest dose tested; $n = 3$). [c] Increased heart rate at 4 μmol/kg. [d] Increased heart rate at 0.4 μmol/kg. Thus, higher doses could not be tested for neuronal inhibition. [e] $n = 5$. [f] Experiments performed in triplicate, average shown.

Reduction of the enamine system **21** (Scheme III) gave the saturated system **22** as a 2:1 mixture of the cis/trans-fused isomers. The geometry of the products **23** and **24** was established on the basis of Bohlmann band intensity in the infrared and the magnitude of the chemical-shift differences of the proton NMR signals for the magnetically nonequivalent *N*-benzyl methylene protons in the cis (**23**) and trans (**24**) isomers, as utilized previously[11] for methoxy group positional isomers of the octahydrobenzo[*f*]quinoline system **5**.

The cis and trans isomers **23** and **24** were catalytically N-debenzylated, and the resulting secondary amines were appropriately N-alkylated by literature procedures. The ether linkages were cleaved with hydrobromic acid–acetic acid. See Table I. Spectral (IR and NMR) data on all intermediates and final compounds were consistent with the proposed structures.

Pharmacological Results and Discussion

The only octahydrobenzo[*g*]quinoline derivative demonstrating inhibition of the cardioaccelerator nerve of the cat was the *N*-*n*-propyl homologue **44** (Table II). In the octahydrobenzo[*f*]quinoline series, the cis-fused compounds **45**–**47** demonstrated only very weak effects on the cat cardioaccelerator nerve. In the trans-fused series, the secondary amine homologue **48** produced an increase in heart rate and a decrease in arterial pressure. These responses were blocked by propranolol. However, the *N*-ethyl (**49**) and *N*-*n*-propyl (**50**) homologues were very active agents in the cat cardioaccelerator nerve, and onset of action occurred within 1 min of administration. The active compounds **44**, **49**, and **50** produced a decrease in blood pressure in the cat that, like the effects of many dopamine receptor agonists, rarely exceeded 20 mmHg. Also, the negative chronotropic response produced by these compounds in the cat was of much longer duration than was the inhibition of neuronal transmission (cardioaccelerator nerve). The neuronal transmission produced by **44**, **49**, and **50** was prevented by intravenous injection of haloperidol (100 μg/kg).

The *N*-*n*-propyl homologue of the *trans*-octahydrobenzo[*f*]quinoline system, **50**, was approximately 100 times more active than apomorphine in displacing [^{3}H]dopamine from specific binding sites in rat caudate tissue. The *N*-ethyl homologue **49** was much less active. A similar rank order of potency was found for these compounds and for apomorphine when [^{3}H]spiroperidol was used as the ligand. In both the [^{3}H]dopamine and [^{3}H]spiroperidol assays, the remaining resorcinol derivatives were much less active. See Table II.

Comparison of analogous compounds in the linearly and the angularly annulated ring systems (**43** and **44** vs. **49** and **50**) illustrates the marked enhancement of activity exhibited by the angularly annulated compounds.

As previously reported,[12] octahydrobenzo[*g*]quinolines are very active dopaminergic agents if they bear phenolic groups in a catechol pattern at positions 6 and 7 (structure **4**), but activity is low with the catechol OH groups at

(12) Cannon, J. G.; Beres, J. A.; Lee, T.; Long, J. P. *Med. Chem. Adv.* **1981**, 369.

positions 7 and 8. It may be that in this ring system, hydroxy-group substitution at the 8-position interferes with interaction with dopamine receptor(s).

Experimental Section

Pharmacology. Methods. Cat Cardioaccelerator Nerve Assay. Cats were anesthetized by injecting pentobarbital sodium (30 mg/kg) into the thoracic cavity. The right cardioaccelerator nerve was isolated and then stimulated with bipolar platinum electrodes. A frequency of 2 Hz, a pulse of 2-ms duration, and supramaximal voltage were used. The duration of stimulation was usually 30 s. The arterial pressure was recorded from the right femoral artery with a Statham P-23AA transducer, and heart rate was recorded with a Beckman 7813 cardiotachometer.

Dopamine Receptor Binding Studies. Antagonist Binding. A method of Seeman et al.[13] was employed, using [^{3}H]-spiroperidol and rat striatal tissue. Details of application of this assay have been published.[2]

Agonist Binding Studies. A method of Bacopoulos[14] was employed, using [^{3}H]dopamine and rat striatal tissue. Details of application of this assay have been published.[2]

Chemistry. Melting points were determined in open glass capillaries with a Laboratory Devices Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Where analyses are indicated by the symbols of the elements, analytical results were within ±0.4% of the theoretical values. IR spectra were recorded on a Beckman IR 4240 instrument. NMR spectra were recorded on a Varian Associates EM-360 spectrometer with tetramethylsilane as the internal standard. Mass spectra were obtained on Finnigan 3200 and Ribermag 10/10 mass spectrometers. Gas chromatography was performed with a Hewlett-Packard 5750B instrument with 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. Flow rates were as follows: carrier gas (He), 70 mL/min (50 psig); H_2, 40 mL/min (13 psig); air, 405 mL/min (24 psig). The relative percentages of each isomer in isomeric mixtures were determined by relative peak areas in the gas chromatograms.

Diethyl (2-Cyanoethyl)[(3,5-dimethoxyphenyl)acetyl]-malonate (8). A method of Michne and Albertson[3] was used. A mineral oil dispersion containing 4.52 g (0.113 mol) of NaH was washed with three 100-mL portions of pentane, then 200 mL of Na-dried toluene was added, followed by a solution of 22.0 g (0.113 mol) of diethyl (2-cyanoethyl)malonate (7) in 50 mL of dry toluene. The slurry was heated under reflux for 8 h. The resulting solution was cooled in an ice bath, (3,5-dimethoxyphenyl)acetyl chloride (6)[15] in 80 mL of dry toluene was added over 3 min, and the reaction mixture was stirred at room temperature for 16 h. The mixture was filtered through a *Celite* pad, and the filtrate was evaporated under reduced pressure to give 40 g of crude keto nitrile 8 as a pale yellow oil. This was used in the next step without purification.

Diethyl 2-(3,5-Dimethoxybenzyl)piperidine-3,3-dicarboxylate Hydrobromide (9). Compound 8 (40 g, 0.10 mol) in 450 mL of glacial AcOH was hydrogenated over 1.2 g of PtO_2 at an initial pressure of 45 psig until 3 equiv of H_2 was absorbed. The reduction mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was treated with 25 mL of concentrated HCl in 150 mL of H_2O, and then the solution was washed with 100 mL of Et_2O. Evaporation of this ethereal extract gave 6.0 g of recovered (3,5-dimethoxyphenyl)acetic acid. The pH of the aqueous layer was adjusted to 8–9 with 40% NaOH, and then it was extracted with four 100-mL portions of Et_2O. The pooled extracts were dried ($MgSO_4$) and evaporated to leave a clear oil. This was taken up in 200 mL of benzene, and this solution was treated with 15 mL of 48% HBr in 50 mL of *n*-PrOH. The resulting solution was evaporated under reduced pressure to leave a white crystalline mass. This was triturated with cold Et_2O and collected on a filter to provide 23.8 g [80%, based upon the amount of recovered (3,5-dimethoxyphenyl)acetic acid] of white needles: mp 127–130 °C; MS, *m/e* 379 (M^+ – HBr). Anal. ($C_{20}H_{30}BrNO_6$) C, H, N.

Diethyl 1-(Benzyloxycarbonyl)-2-(3,5-dimethoxybenzyl)piperidine-3,3-dicarboxylate (10). To a solution of 18.5 g (0.04 mol) of 9 and 8.41 g (0.049 mol) of benzyl chloroformate in 100 mL of $CHCl_3$ at 0 °C under N_2 was added, over 3 min, 9.9 g (0.1 mol) of Et_3N in 10 mL of $CHCl_3$. The resulting solution was warmed to room temperature and stirred for 3 h. Washing of the reaction mixture with H_2O, dilute HCl, and saturated $NaHCO_3$ gave a clear solution, which was dried (Na_2SO_4) and filtered, and the filtrate was evaporated under reduced pressure to give 20.6 g (100%) of a colorless oil. An analytical sample was crystallized from Et_2O–pentane to give white needles: mp 63–65 °C; MS, *m/e* 513 (M^+). Anal. ($C_{28}H_{35}NO_8$) C, H, N.

***cis*- and *trans*-1-(Benzyoxycarbonyl)-2-(3,5-dimethoxybenzyl)piperidine-3-carboxylic Acid (13).** Compound 10 (10.8 g, 0.021 mol) and 4.2 g (0.021 mol) of KOH in 120 mL of 95% EtOH were heated under reflux for 5 h. Evaporation of the volatiles under reduced pressure left a white paste, which was partitioned between 75 mL of Et_2O and 75 mL of H_2O. The aqueous layer was adjusted to pH 2–3 with concentrated HCl and extracted with four 75-mL portions of Et_2O. The combined organic extracts were dried (Na_2SO_4) and filtered, and the filtrate was evaporated to give 10.0 g (97%) of the half acid ester 11 as a white powder.

This material (14.6 g) was heated in an oil bath at 175–180 °C for 30 min. CO_2 was rapidly evolved. The resulting oil was dissolved in 100 mL of 95% EtOH containing 4.2 g (0.021 mol) of KOH, and this mixture was heated under reflux for 4 h; then it was stirred at room temperature overnight. The volatiles were removed under reduced pressure, the residue was taken up in 100 mL of H_2O, and this solution was washed with 100 mL of Et_2O. Evaporation of the ether extract yielded 4.5 g of unhydrolyzed ester 12. Acidification of the aqueous layer yielded 7.1 g (90%, based upon the amount of recovered unhydrolyzed ester 12) of a white powder: mp 186–188 °C; MS, *m/e* 413 (M^+). Anal. ($C_{23}H_{27}NO_6$) C, H, N.

***cis*- and *trans*-2-(3,5-Dimethoxybenzyl)piperidine-3-carboxylic Acid (14).** Product 13 (4.0 g, 0.00967 mol) in 200 mL of glacial AcOH was hydrogenated over 0.5 g of 5% Pd/C at an initial pressure of 45 psig for 12 h. Filtration of the reaction mixture and evaporation of the filtrate under reduced pressure left an oil, which slowly crystallized from MeOH–Et_2O to give 2.5 g (92%) of a finely divided white powder: mp 208–211 °C; MS, *m/e* 279 (M^+). Anal. ($C_{15}H_{21}NO_4$) C, H, N.

***trans*-6,8-Dimethoxy-5-keto-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydrobromide (15).** Compound 14 (2.4 g, 0.00859 mol) was added over 5 min, with efficient manual stirring, to 60 g of polyphosphoric acid at 95 °C. After stirring for 1 h, the reaction mixture was cooled, quenched with 100 mL of crushed ice, and then brought to pH 10–12 with 40% NaOH. The resulting solution was extracted with four 100-mL portions of Et_2O, then the pooled extracts were dried (Na_2SO_4) and filtered, and the filtrate was evaporated under reduced pressure to leave a white solid. This was dissolved in 150 mL of benzene, and the solution was treated with 1 mL of 48% HBr in 15 mL of *n*-PrOH. The resulting mixture was taken to dryness under reduced pressure to afford a white solid, which was recrystallized from MeOH–Et_2O to yield 2.79 g (95%) of fine white needles: mp 190–193 °C; MS, *m/e* 261 (M^+ – HBr). Anal. ($C_{15}H_{20}BrNO_3$) C, H, N.

***trans*-6,8-Dimethoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo-[*g*]quinoline Hydrobromide (16).** Following a procedure of Nystrom and Berger,[5] 5.1 g (0.038 mol) of $AlCl_3$ was added in small portions over 10 min to a stirred slurry of 1.5 g (0.038 mol) of $LiAlH_4$ in 70 mL of freshly distilled tetrahydrofuran. After an addditional 5 min, 2.5 g (0.00956 mol) of the free base of 15 in 50 mL of tetrahydrofuran was added dropwise, and the reaction mixture was stirred at 60 °C for 3.5 h. The excess hydride was destroyed with H_2O, and sufficient 10% NaOH was added to dissolve the Al salts. Five extractions of this solution with 30-mL portions of CH_2Cl_2, drying of the pooled extracts (Na_2SO_4), and evaporation afforded a colorless oil, which was taken up in benzene and treated with 48% HBr in 10 mL of *n*-PrOH. Evaporation of this solution under reduced pressure gave a white powder, which was recrystallized from MeOH to yield 2.2 g (70%) of a white

(13) Seeman, P.; Chau-Wong, M.; Tedesco, J.; Wong, K. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 4376.
(14) Bacopoulos, N. G. *Biochem. Pharmacol.* **1982**, *31*, 3085.
(15) Bullimore, B. K.; McOmie, J. F.; Turner, A. B.; Galbraith, M. N.; Whalley, W. B. *J. Chem. Soc.* **1967**, 1289.

powder: mp 280 °C dec; MS, m/e 247 (M^+ - HBr). Anal. ($C_{15}H_{22}BrNO_2$) C, H, N.

***trans*-6,8-Dimethoxy-1-benzyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydrobromide (33).** Benzoyl chloride (0.5 g, 0.0035 mol) was added to a solution of 0.7 g (0.0028 mol) of the free base of **16** in 15 mL of CH_2Cl_2 and 10 mL of 5% NaOH with vigorous stirring at room temperature. After 2 h, the aqueous layer was extracted with three 25-mL portions of CH_2Cl_2. The pooled extracts were washed with 5% NaOH, H_2O, and 1% HCl, and then they were dried (Na_2SO_4) and evaporated under reduced pressure. The crude *N*-benzoyl derivative in 30 mL of tetrahydrofuran was added to a stirred slurry of 0.5 g (0.0132 mol) of $LiAlH_4$ in 50 mL of tetrahydrofuran. After heating under reflux for 5 h, the reaction mixture was cooled and quenched with 50 mL of 10% NaOH. Five extractions of this solution with 25 mL portions of CH_2Cl_2, followed by drying of the pooled extracts (Na_2SO_4) and evaporation under reduced pressure, yielded an orange oil, which was shown by gas chromatography to be homogeneous. This oil was taken up in 100 mL of benzene, and this solution was treated with 1 mL of 48% HBr in 10 mL of *n*-PrOH and evaporated under reduced pressure. The residue was recrystallized from MeOH to give 0.6 g (64%) of white crystals: mp 261 °C; IR (free base, film) 2790, 2840 cm^{-1} (strong; Bohlmann bands); NMR (free base in $CDCl_3$) δ 3.69 (AB system, J = 14 Hz, $\Delta\nu$ = 65 Hz, 2 H, Ar CH_2). Anal. ($C_{22}H_{28}BrNO_2$) C, H, N.

***trans*-6,8-Dimethoxy-1-*n*-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydrobromide (34).** Following a procedure of Marchini et al.,[16] 0.3 g (0.0079 mol) of $NaBH_4$ was added in small portions to 2.03 g (0.0275 mol) of propionic acid in 30 mL of benzene, maintaining the temperature below 25 °C. The reaction was stirred at room temperature for 5 h. To this mixture was added 0.35 g (0.00141 mol) of the free base of **16** in 15 mL of benzene, and the reaction mixture was heated overnight under reflux. The cooled solution was quenched with 30 mL of 2 N NaOH, and then it was extracted with 100 mL of CH_2Cl_2. The organic layer was washed with 30 mL of 2 N NaOH, dried (Na_2SO_4), and evaporated under reduced pressure to give a yellow oil. This was taken up in 100 mL of benzene, treated with 1 mL of 48% HBr in 10 mL of *n*-PrOH, and evaporated to dryness. The residue was recrystallized from MeOH to give 0.35 g (67%) of a white powder, mp 268–270 °C. Anal. ($C_{18}H_{28}BrNO_2$) C, H, N.

***trans*-6,8-Dimethoxy-1-ethyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydrobromide (35).** The method described for **34** was followed, using 0.37 g (0.010 mol) of $NaBH_4$, 2.52 g (0.034 mol) of glacial AcOH, 30 mL of benzene, and 0.37 g (0.00152 mol) of the free base of **16** in 10 mL of benzene. The reaction mixture was treated as described for **34**, giving 0.364 g (67%) of white needles, mp 225–228 °C (from MeOH). Anal. ($C_{17}H_{26}BrNO_2$) C, H, N.

Ethyl (3,5-Dimethoxyphenyl)acetate (25). (3,5-Dimethoxyphenyl)acetic acid (19.6 g, 0.099 mol), 2 mL of concentrated H_2SO_4, 30 mL of 99% EtOH, and 130 mL of benzene were heated under reflux in a Dean–Stark apparatus. When no more H_2O azeotroped, the volatiles were removed from the benzene solution under reduced pressure. The residue was taken up in 200 mL of benzene, washed with dilute NaOH, dried (Na_2SO_4), and evaporated to give a pale yellow oil, which was distilled at 148 °C (2 mm) to give 20.9 g (93%) of a clear liquid: MS, m/e 224 (M^+). Anal. ($C_{12}H_{16}O_4$) C, H.

Ethyl (2-Formyl-3,5-dimethoxyphenyl)acetate (27). Freshly distilled *N*-methylformanilide (63.17 g, 0.467 mol) was added to 71.68 g (0.467 mol) of freshly distilled $POCl_3$ under N_2 with vigorous stirring. After the solution was stirred for 45 min, 52.4 g (0.234 mol) of **25** was added in a slow stream while maintaining the reaction mixture at 25 °C. Stirring was continued for 17 h, and then the resulting red syrup was diluted to 900 mL with crushed ice. The yellow crystals that separated were collected on a filter, washed with H_2O, and recrystallized from Me_2CO to give 52.7 g (90%) of white needles: mp 102–103 °C; MS, m/e 252 (M^+). Anal. ($C_{13}H_{16}O_5$) C, H.

Ethyl 3-[2,4-Dimethoxy-6-(carbethoxymethyl)phenyl]propenoate (28). Compound **27** (44.9 g, 0.178 mol) and 64.4 g (0.185 mol) of (carboxymethylene)triphenylphosphorane in 350 mL of dry toluene under N_2 were stirred under reflux for 18 h. The volatiles were removed under reduced pressure to give a pale yellow solid, which was treated with 300 mL of boiling Et_2O. The resulting mixture was cooled and filtered to remove 40 g of triphenylphosphine oxide. The filtrate was evaporated, and an ethereal solution of the residue was passed through a column containing 600 g of neutral Al_2O_3. Evaporation of the eluate gave 48.8 g (85%) of large white needles, mp 67–69 °C. Anal. ($C_{17}H_{22}O_6$) C, H.

Ethyl 3-[2,4-Dimethoxy-6-(carbethoxymethyl)phenyl]propanoate (29). Compound **28** (48.8 g, 0.151 mol) in 550 mL of MeOH was hydrogenated over 3 g of 5% Pd/C at an initial pressure of 45 psig until 1 equiv of H_2 was taken up. The reduction mixture was filtered, and volatiles were removed from the filtrate to leave a clear oil, which solidifed upon cooling. Recrystallization from Et_2O gave 47.8 g (98%) of short white needles: mp 43–45 °C; MS, m/e 324 (M^+). Anal. ($C_{17}H_{24}O_6$) C, H.

5,7-Dimethoxy-3,4-dihydro-2(1*H*)-naphthalenone (17). Compound **29** (17.6 g, 0.054 mol) in 150 mL of dimethoxyethane was added dropwise over 1.5 h to a refluxing mixture of 4.8 g (0.12 mol) of NaH (washed with three 100-mL portions of pentane) and 500 mL of dimethoxyethane. The reaction mixture was heated under reflux for an additional 30 min, and then it was cooled and quenched with 15 mL of EtOH. It was then poured into a mixture of 25 mL of concentrated HCl and 200 mL of crushed ice. The resulting mixture was extracted with four 100-mL portions of CH_2Cl_2, and the volatiles were evaporated from the pooled extracts to give the crude Dieckmann condensation product **30** as a pale orange oil: NMR ($CDCl_3$) δ 1.40 (t, 3 H, CH_3), 2.53 (center) (br m, 4 H, aliphatic H), 3.70 (s, 6 H, OCH_3), 4.30 (q, 2 H, OCH_2), 6.23 (s, 1 H, Ar H), 7.0 (s, 1 H, Ar H), 13.6 (s, 1 H, C=COH). This material was used in the next step without purification.

The crude Dieckmann product in 50 mL of 95% EtOH and 60 mL of 20% HCl was heated under reflux for 18 h. The cooled reaction mixture was extracted with four 75-mL portions of EtOAc. The pooled extracts were evaporated, and the residue was treated with 125 mL of saturated $NaHSO_3$. The resulting solid was collected on a filter, washed with 300 mL of Et_2O, and air-dried. The ketone was liberated by treatment with excess saturated Na_2CO_3. The resulting mixture was extracted with three 100-mL portions of EtOAc. The pooled extracts were evaporated under reduced pressure, and the residue was distilled in a *Kugelrohr*, bp 130 °C (0.1 mm), to give 8.6 g (77%) of a white solid: mp 80–81 °C; MS, m/e 206 (M^+). Anal. ($C_{12}H_{14}O_3$) C, H.

7,9-Dimethoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (19). To a refluxing solution of 17.7 g (0.0763 mol) of **17** and 0.1 g of *p*-toluenesulfonic acid in 100 mL of benzene was added, over 5 min, 6.6 g (0.0926 mol) of pyrrolidine in 10 mL of benzene. The mixture was heated under reflux in a Dean–Stark apparatus. When no more H_2O azeotroped, volatiles were removed to leave the enamine **18** as a yellow oil. Acrylamide (20.3 g, 0.285 mol) was added in one portion to the stirred oil, and the resulting mixture was heated at 80 °C for 3 h and then at 130 °C for 30 min. The reaction mixture was then diluted to 150 mL with hot H_2O and brought to pH 3–4 with concentrated HCl. The resulting precipitate was collected on a filter and triturated with 300 mL of Et_2O, to leave a white powder, which was recrystallized from Me_2CO to give 14.9 g (81%) of a finely divided white powder: mp 208–210 °C; MS, m/e 259 (M^+). Anal. ($C_{15}H_{17}NO_3$) C, H, N.

7,9-Dimethoxy-4-benzyl-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (20). A mixture of 25.3 g (0.0957 mol) of **19** and 5.0 g (0.125 mol) of pentane-washed NaH in 500 mL of 1,2-dimethoxyethane was heated under reflux for 3 h. The mixture was cooled to room temperature, 18.8 g (0.110 mol) of benzyl bromide in 50 mL of 1,2-dimethoxyethane was added, and the mixture was heated under reflux for 3 h and then stirred at room temperature for 3 h. The reaction was quenched with 15 mL of EtOH and evaporated under reduced pressure. The residue was taken up in 200 mL of $CHCl_3$; this solution was washed with 100 mL of H_2O, dried ($MgSO_4$), and filtered through a *Florisil* pad, and the filtrate was evaporated to leave a pale yellow solid. Trituration of this with 200 mL of Et_2O gave 29.5 g (86%) of white crystals: mp 156–158 °C; MS, m/e 349 (M^+). Anal. ($C_{22}H_{23}NO_3$) C, H, N.

(16) Marchini, P.; Liso, G.; Reho, A.; Liberatore, F.; Moracci, R. M. *J. Org. Chem.* **1975**, *40*, 3453.

7,9-Dimethoxy-4-benzyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline (21). To a stirred solution of 3.79 g (0.1 mol) of $LiAlH_4$ in 200 mL of tetrahydrofuran was added 33.5 g (0.096 mol) of **20** in 300 mL of tetrahydrofuran over 1 h. The resulting mixture was heated under reflux for 6 h, and then it was cooled and quenched with 16 mL of H_2O and 4 mL of 20% NaOH. The precipitated Al salts were dissolved in 200 mL of 20% NaOH, and the resulting mixture was extracted with 200 mL of Et_2O. The extract was dried (Na_2SO_4) and evaporated to leave 32.1 g of a yellow oil, which was used in the next step without purification.

***cis*- and *trans*-7,9-Dimethoxy-4-benzyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (22).** To a solution of 32.1 g (0.096 mol) of **21** in 400 mL of MeCN was added 13.8 (0.220 mol) of $NaCNBH_3$ in six portions over 5 min with stirring. Glacial AcOH was added from time to time to maintain the pH at 6–7 (pH paper), and the solution was stirred at room temperature for 18 h. The reaction was quenched with 40 mL of concentrated HCl, and the resulting mixture was evaporated under reduced pressure to give a white paste. This was dissolved in 80 mL of 10% NaOH, and the resulting solution was extracted with four 100-mL portions of CH_2Cl_2. The pooled extracts were dried ($MgSO_4$) and evaporated to give a white foam, which was distilled at 160 °C (0.5 mm) to give 24.5 g (75%) of a colorless liquid.

Separation of *cis*- and *trans*-7,9-Dimethoxy-4-benzyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrobromides (23 and 24). Gas Chromatographic Analysis. Operating conditions were as follows: column temperature, 250 °C; injection port temperature, 300 °C; detector temperature, 300 °C. Retention times of 6.2 and 7.2 min were recorded for the cis and trans isomers, respectively. GC analysis of distilled **22** revealed a cis/trans ratio of 2:1. This mixture (24.2 g) in 200 mL of benzene was treated with 25 mL of 48% HBr in 50 mL of *n*-PrOH, and the resulting mixture was evaporated to dryness under reduced pressure. The white residue was dissolved in 250 mL of MeOH, and Et_2O was added to the cloud point. On cooling, a crop of crystalline material was formed. Three similar additional dilutions of mother liquor with Et_2O provided three more crops of crystalline material. GC of the first three crops (7.8 g total) showed a predominance of the cis isomer **23**, and GC analysis of the fourth crop showed a predominance of the trans isomer **24**. Recrystallization of the combined first three crops from MeOH-Et_2O gave 4.8 g of cis isomer **23** (homogeneous by GC analysis) as small colorless cubes: mp 225–228 °C; MS, *m/e* 337 (M^+ – HBr); NMR (free base in $CDCl_3$) δ 1.40–3.19 (m, 12 H, aliphatic H), 3.73 (s, 8 H, OCH_3 and Ar CH_2), 6.23 (s, 2 H, Ar H), 7.28 (s, 5 H, Ar H). Anal. ($C_{22}H_{28}BrNO_2$) C, H, N.

Recrystallization of the fourth fraction from MeOH–Et_2O gave 2.8 g of trans isomer **24** (homogeneous by GC analysis) as fluffy white needles: mp 230–232 °C; MS, *m/e* 337 (M^+ – HBr); IR (free base in CH_2Cl_2) 2860 cm^{-1} (Bohlmann band); NMR (free base in $CDCl_3$) δ 1.01–3.03 (m, 12 H, aliphatic H), 3.78 (AB system, J = 14 Hz, $\Delta\nu_{AB}$ = 52 Hz, 2 H, Ar CH_2), 3.80 (s, 6 H, OCH_3), 6.43 (m, 2 H, Ar H), 7.26 (s, 5 H, Ar H). Anal. ($C_{22}H_{28}BrNO_2$) C, H, N.

***trans*-7,9-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrobromide (36).** Compound **24** (1.5 g, 0.00358 mol) in 100 mL of MeOH was hydrogenated over 0.6 g of 5% Pd/C at an initial pressure of 45 psig. After 22 h, the reduction mixture was filtered, and the filtrate was evaporated under reduced pressure to give 0.96 g (82%) of white crystals, mp 255–257 °C. Anal. ($C_{15}H_{22}BrNO_2$) C, H, N.

***trans*-7,9-Dimethoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrobromide (37).** The method described for **34** was followed, using 0.3 g (0.0079 mol) of $NaBH_4$, 2.0 g (0.027 mol) of propionic acid, 20 mL of benzene, and 0.34 g (0.00137 mol) of the free base of **36** in 10 mL of benzene. The reaction mixture was treated as described for **34**, giving 0.46 g (92%) of a white powder, mp 253–255 °C (from MeOH–Et_2O). Anal. ($C_{18}H_{28}BrNO_2$) C, H, N.

***trans*-7,9-Dimethoxy-4-ethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrobromide (38).** The method described for **34** was followed, using 0.39 g (0.0103 mol) of $NaBH_4$, 2.6 g (0.043 mol) of glacial AcOH, 25 mL of benzene, and 0.35 g (0.0014 mol) of the free base of **36** in 10 mL of benzene. The reaction mixture was treated as described for **34**, giving 0.36 g (73%) of an off-white powder, mp 277–279 °C. Anal. ($C_{17}H_{26}BrNO_2$) C, H, N.

***cis*-7,9-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrobromide (39).** Compound **23** (2.3 g, 0.00549 mol) in 150 mL of MeOH was hydrogenated over 1.4 g of 5% Pd/C at an initial pressure of 45 psig. After 16 h, the reaction mixture was filtered, and the filtrate was evaporated to give 1.65 g (92%) of colorless cubes, mp 273–275 °C. Anal. ($C_{15}H_{22}BrNO_2$) C, H, N.

***cis*-7,9-Dimethoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrobromide (40).** The method described for **34** was followed, using 0.31 g (0.0082 mol) of $NaBH_4$, 2.1 g (0.028 mol) of propionic acid, 25 mL of benzene, and 0.37 g (0.00152 mol) of the free base of **39** in 10 mL of benzene. The reaction mixture was treated as described for **34**, giving 0.44 g (78%) of white needles, mp 186–188 °C (from MeOH-Et_2O). Anal. ($C_{18}H_{28}BrNO_2$) C, H, N.

***cis*-7,9-Dimethoxy-4-ethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrobromide (41).** The method described for **34** was followed, using 0.37 g (0.010 mol) of $NaBH_4$, 2.5 g (0.034 mol) of glacial AcOH, 50 mL of benzene, and 0.37 g (0.00152 mol) of the free base of **39** in 10 mL of benzene. The reaction mixture was treated as described for **34**, giving 0.41 g (77%) of a white powder, mp 256–257 °C (from MeOH–Et_2O). Anal. ($C_{17}H_{26}BrNO_2$) C, H, N.

Ether Cleavage Reactions. The amine hydrohalide (0.001 mol) in 10 mL of 48% HBr and 1 mL of glacial AcOH was heated under reflux under N_2 for 2 h. The cooled reaction mixture deposited a solid, which was recrystallized from MeOH–Et_2O. See Table I.

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Registry No. **6**, 15601-07-7; **7**, 17216-62-5; **8**, 87656-73-3; **9**, 87656-74-4; **9**·HBr, 87656-75-5; **10**, 87656-76-6; **11**, 87656-77-7; *cis*-**12**, 87656-78-8; *trans*-**12**, 87656-79-9; *cis*-**13**, 87656-80-2; *trans*-**13**, 87656-81-3; *cis*-**14**, 87656-82-4; *trans*-**14**, 87656-83-5; **15**, 87656-84-6; **15**·HBr, 87656-85-7; **16**, 87656-86-8; **16**·HBr, 87656-87-9; **16** (*N*-benzoyl derivative), 87656-88-0; **17**, 87656-89-1; **18**, 87656-90-4; **19**, 87656-91-5; **20**, 87656-92-6; **21**, 87656-93-7; **23**, 87656-94-8; **23**·HBr, 87656-95-9; **24**, 87656-96-0; **24**·HBr, 87656-97-1; **25**, 65976-77-4; **26**, 93-61-8; **27**, 66761-54-4; **28**, 87656-98-2; **29**, 87656-99-3; **30**, 87657-00-9; **33**, 87657-01-0; **33**·HBr, 87657-02-1; **34**, 87657-03-2; **34**·HBr, 87657-04-3; **35**·HBr, 87657-05-4; **36**, 87657-06-5; **36**·HBr, 87657-07-6; **37**·HBr, 87657-08-7; **38**·HBr, 87657-09-8; **39**, 87657-10-1; **39**·HBr, 87657-11-2; **40**·HBr, 87657-12-3; **41**·HBr, 87657-13-4; **42**, 87657-14-5; **42**·HBr, 87657-15-6; **43**, 87657-16-7; **43**·HBr, 87657-17-8; **44**, 87657-18-9; **44**·HBr, 87657-19-0; **45**, 87657-20-3; **45**·HBr, 87657-21-4; **46**, 87657-22-5; **46**·HBr, 87657-23-6; **47**, 87657-24-7; **47**·HBr, 87657-25-8; **48**, 87657-26-9; **48**·HBr, 87657-27-0; **49**, 87657-28-1; **49**·HBr, 87657-29-2; **50**, 87657-30-5; **50**·HBr, 87657-31-6; $(C_6H_5)_3P{=}CHCOOEt$, 1099-45-2; $H_2C{=}CHCONH_2$, 79-06-1; (3,5-dimethoxyphenyl)acetic acid, 4670-10-4.