uation of results was performed by the multiple regression method, utilizing "dummy variables" to identify the conditions of validity of the bioassay (parallelism, regression, curvature).

Acknowledgment. We are grateful to M. Mondoni for NMR studies and to L. Frigerio for HPLC determinations. We are also indebted to G. Navarra for skilled assistance in preparing the compounds.

Registry No. 1, 56337-96-3; **2b**, 118714-30-0; **2c**, 118714-31-1; **2d**, 118714-32-2; **3a**, 83184-40-1; **3b**, 118714-33-3; **3b**·xH_2SO_4, 118714-36-6; **3c**, 118714-34-4; **3d**, 118714-35-5; **3e**, 83184-32-1; $FCH_2CH_2NH_2$·HCl, 460-08-2; $F_2CHCH_2NH_2$·HCl, 79667-91-7; $F_3CCH_2NH_2$·HCl, 373-88-6; 2,2-difluoroacetamide, 359-38-6; 4-(5)-(4-aminophenyl)-1*H*-imidazole, 29528-28-7; ethyl 4-imidazol-4-ylphenyldithiocarbamate, 118714-29-7; mifentidine, 83184-43-4.

Synthesis and Dopaminergic Activity of 2-Substituted Octahydrobenzo[*f*]quinolines

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A series of 2-substituted octahydrobenzo[*f*]quinolines has been synthesized and assayed for dopamine agonist activity. Only the compounds corresponding to the β-rotameric conformation of dopamine showed biphasic activity in competition binding studies with the radioligand [^{3}H]spiroperidol. These findings suggest that the congeners possessing the β-rotamer conformation show receptor-binding characteristics that resemble those of the ergolines more closely than do those of the corresponding α-rotamer congeners.

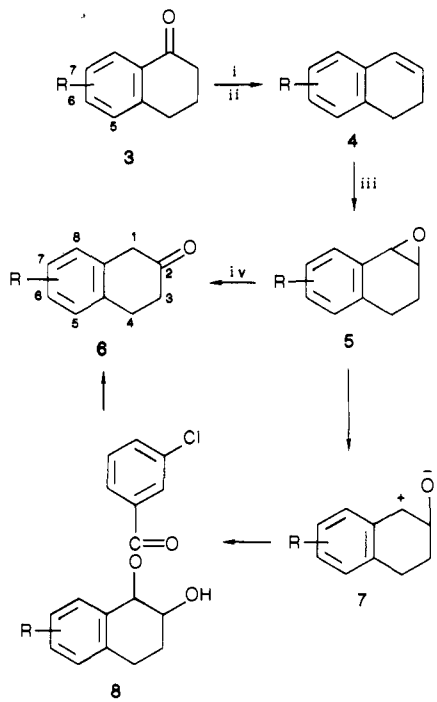
Dopamine agonist drugs have seen a remarkable growth in therapeutic utility during the last few years, following the successful use[1-5] of compounds derived from ergot alkaloids, such as bromocriptine, pergolide (1, Chart I), and lisuride, for the treatment of hyperprolactinemia, acromegaly, and Parkinsonism. Increasing efforts have been directed toward the synthesis of new derivatives and partial structures with the aim of isolating the dopaminergic pharmacophore from the multitude of pharmacological effects inherent in the ergo-agonists.[7]

Cannon et al. have reported[6,8] that the octahydrobenzo[*f*]quinolines **2e** were potent dopaminergics. Since the C ring of these compounds, although unsubstituted, is structurally analogous to the D ring of the dihydro ergot alkaloids, it seemed reasonable to propose that the addition of appropriate substituents at the 2-carbon position (corresponding to the 8-position in the ergot alkaloids) would produce more specific dopamine agonists that, while retaining or exceeding the potent dopaminergic activity of the ergot alkaloids, might be free of their undesirable side effects.[9] This was of importance because it is known[10] that the nature of the 8-position in an ergoline profoundly affects its biological properties. For instance, while relatively simple amides of lysergic acid are potent oxytocic drugs, more complex peptide-like amides are vasoconstrictors, the simple diethyl amide (LSD) is a potent hallucinogen, and many variously 8-substituted ergolines exhibit dopaminergic properties.[10] Ten 2-substituted octahydrobenzo[*f*]quinolines related to compounds **2a-d** have been prepared and are reported here to be dopamine receptor agonists. The choice of the 2-substituents was conceptually derived from pergolide ((methylthio)methyl) and lergotrile (cyanomethyl)[6,7] while hydroxymethyl and methyl were chosen for their enhanced and reduced hydrophilicity, respectively.

Chemistry

Preparation of 2-substituted octahydrobenzo[*f*]-quinolines utilized the appropriate 2-tetralones **6** as the starting materials (Scheme I). Reduction and dehydration of 5-methoxy-1-tetralone (**3a**) gave 8-methoxy-1,2-di-

Scheme I[a]



a, R = 5-OMe; **b**, R = 7-OMe; **c**, R = 5,6-$(OMe)_2$; **d**, R = 6,7-$(OMe)_2$

[a] Reagents: (i) $NaBH_4$, (ii) C_6H_6, *p*-toluenesulfonic acid, (iii) *m*-chloroperoxybenzoic acid, (iv) ZnI_2 in C_6H_6.

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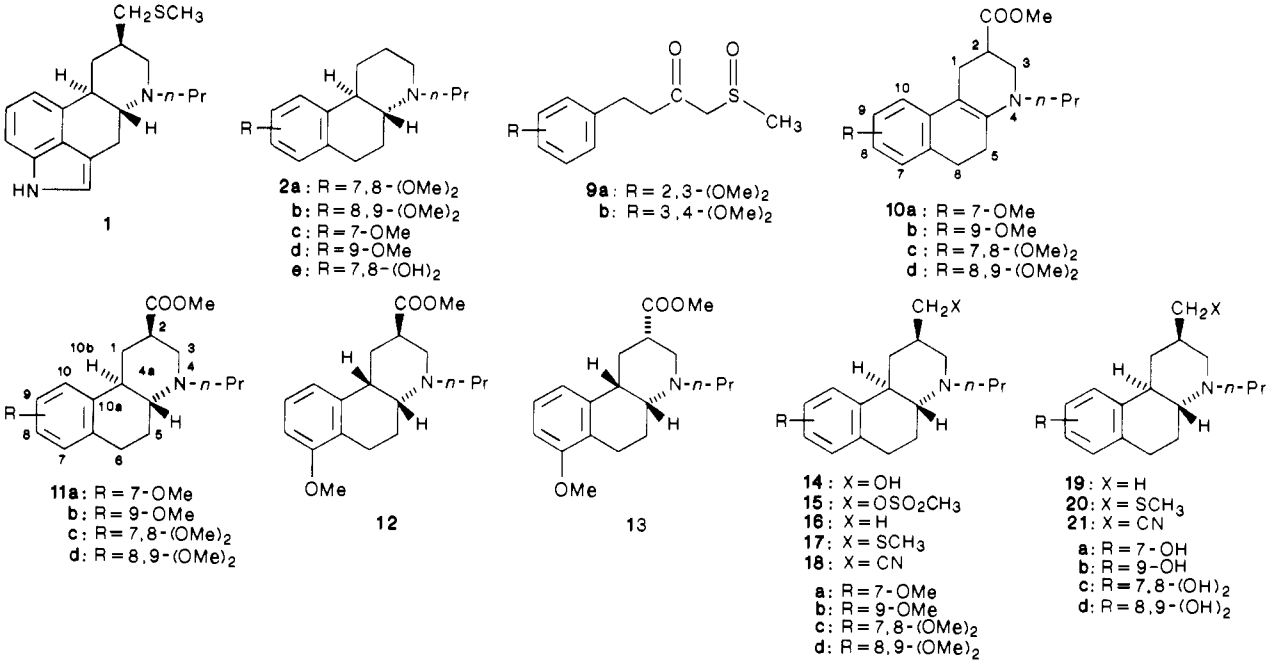
Chart I



hydronaphthalene[11] (**4a**), which was oxidized with *m*-chloroperoxybenzoic acid to afford the epoxide **5a** in quantitative yield. Isomerization of the epoxide to the 2-tetralone **6a** was carried out with zinc iodide as Lewis acid catalyst.[12,13] Commercial zinc iodide failed to react, but a very fine, dry suspension of zinc iodide in benzene prepared as described (Experimental Section) converted the epoxide cleanly into the desired 2-tetralone **6a** in excellent yield, and was an improvement over the published procedure[11] employing osmium tetraoxide oxidation of the olefin to the *cis*-diol and subsequent dehydration to **6a**. The isomerization of 7-methoxy-1-tetralone (**3b**) to the corresponding 7-methoxy-2-tetralone (**6b**) similarly proceeded in quantitative yield via the epoxide **5b**.

Table I. 500-MHz Chemical Shifts (δ, ppm) and Coupling Constants (Hertz) of Protons in the Piperidine Ring of Compound 11a[a]

proton	δ	J
$HC(1)_{ax}$	a	
$HC(1)_{eq}$	2.12	t
HC(2)	2.82	tt, 10/3
$HC(3)_{ax}$	2.67	q, 10
$HC(3)_{eq}$	3.17	t, 5
HC(4a)	2.46	ddd, 10/10/5
HC(10b)	2.76	m

[a] a = not visible. t = triplet, q = quartet, d = doublet, m = multiplet.

Cyclization of 4-(3′,4′-dimethoxyphenyl)butanoic acid by the published procedure[14] gave 6,7-dimethoxy-1-tetralone (**3d**) in high yield. Borohydride reduction of this compound followed by *p*-toluenesulfonic acid catalyzed dehydration was reported[15a] to yield only 10–15% of the required olefin **4d**, the rest of the product being a dimer. However, conversion of the 1-tetralone into the desired olefin could be effected in excellent yield (free from dimer) by utilizing anhydrous benzene for the dehydration step. Treatment of the olefin **4d** with *m*-chloroperoxybenzoic acid[15b] gave a product whose molecular weight (m/z 362) corresponded to a monoester of a *trans*-1,2-diol **8d**, formed by ring opening of the intermediate epoxide **5d** by *m*-chlorobenzoate ion. The greatly enhanced susceptibility of this epoxide to ring opening is consonant with the high degree of resonance stabilization of the benzylic transition state **7d**. The corresponding *trans*-diol was easily formed by reacting **5d** with aqueous ethanolic hydrochloric acid, resulting in an immediate conversion to the desired 2-tetralone **6d** by in situ acid-catalyzed dehydration of the benzylic hydroxyl group.[15b]

5,6-Dimethoxy-1-tetralone (**3c**) was obtained from 2,3-dimethoxybenzaldehyde in a six-step procedure[16-20] via

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3-(2',3'-dimethoxyphenyl)propionic acid and was converted in excellent yield into the required 2-tetralone **6c** by the method developed for the 6,7-dimethoxy isomer (above), via the monoester of the *trans*-1,2-diol **8c**.[15b]

An alternative pathway to the 2-tetralone **6c** from the above acid[21,22] was substantially improved by the use of dimsyllithium[23,24] (instead of the reported dimsylsodium)[22,25] for the preparation of the intermediate β-keto sulfoxide **9a**. The same modification was successfully applied to the conversion of 3-(3',4-dimethoxyphenyl)-propionic acid[21,22] into 6,7-dimethoxy-2-tetralone (**6d**).

Condensation of the 2-tetralones **6** with *n*-propylamine and methyl 2-(bromomethyl)acrylate[13] gave the hexahydrobenzo[*f*]quinoline esters **10**.

Reduction of the enamine ester **10a** with sodium borohydride in ethanol proceeded rapidly and gave a product mixture consisting of a 2:1:1 ratio of three isomers: the trans-anti isomer **11a**, the cis-anti isomer **12** and the cis-syn isomer **13**. Similar results, with the trans-anti isomer as the main product, had been reported by Horii[26] in the simplified ergoline series. An attempt to increase the proportion of **11a** by using the perchlorate salt of **10a** as the substrate for borohydride reduction[26] resulted only in a minor improvement of the product ratio to 3:1:1; sodium cyanoborohydride gave the identical result (3:1:1).

When the enamine **10a** was subjected to catalytic hydrogenation,[26] only the cis isomers **12** and **13** were formed, establishing the main product of the cyanoborohydride reaction as the trans-anti isomer **11a**, isolated as the crystalline perchlorate. Although Horii's[26] and Cassady's[27,28] related studies in the ergoline series suggested that the stereochemistry of the main product of the cyanoborohydride reduction was **11**, it was desirable to establish the trans-anti configuration of our main product by independent means. A study of the 500-MHz ^{1}H NMR spectrum of the main product confirmed the stereochemical assignments shown in **11**, and is summarized in Table I.

The ring-junction protons 4a and 10b were used to assign the trans ring junction. H_{10b} appears as a multiplet because of its association with three other protons. However, it occupies trans diaxial relationships with the 1 axial and 4a axial protons. H_{4a} appears as a doublet of doublets of doublets (ddd), of which two of the couplings are large (10 Hz) and one medium (5 Hz). This pattern can arise only from two diaxial and one axial/equatorial orientation. In addition, it has been shown that H_2 is axial. The spectra also show long-range coupling from H_1 equatorial to H_3 equatorial. Collectively, this information places the piperidine ring in the normal chair conformation, and supports the trans ring junction.

The catalytic hydrogenation product of enamine **10a** consisted of the isomers **12** and **13** in a 1:3 ratio (NMR), with the major product (cis-syn) displaying its methyl ester (OCH_3) singlet at 4.64 ppm while that of the minor product (cis-anti) was found at 3.71 ppm. These assignments agree closely with the corresponding values obtained for analogous products in the ergoline series by Horii[26] and Cassidy.[27,28]

The NMR spectrum of the main product of the cyanoborohydride reduction of enamine **10a** showed the methyl ester singlet at 3.73 ppm, in excellent agreement with the value of 3.74 ppm reported for the corresponding trans-anti compound in the ergolines.[28]

The influence of temperature on the stereochemical outcome of the cyanoborohydride reduction of **10a** was further examined in order to increase the proportion of the desired trans-anti isomer **11a**. While at 25 °C the product ratio (3:1:1) was not changed over that at 10 °C, a reduction in temperature to −20 °C gave an improved ratio of 4:1:1, and an optimum ratio of 10:3:1 of **11a**, **12**, and **13** was obtained when the reaction was run at −25 to −30 °C. The stereoselectivity was not further improved at lower temperatures. The three isomers could be separated by column chromatography, and the pure trans-anti isomer **11a** was isolated as its perchlorate salt.

The cyanoborohydride reduction of the 9-methoxy enamine isomer **10b** was similar to that of **10a**, and the trans-isomer **11b** was obtained in the same favorable ratio and isolated as the perchlorate salt. The reduction of the dimethoxy enamines **10c** and **10d** proceeded similarly; however, the ratio of the corresponding trans-anti isomers was not as favorable as with the monomethoxy analogues, yielding a 3:1:1 ratio with an isomer mixture containing 60% of the desired trans-anti compound **11c** and **11d**, respectively. Isomers **11c** and **11d** were also isolated by column chromatography and purified as their perchlorate salts.

The corresponding primary alcohols **14** were obtained in quantitative yield from the ester **11** by lithium aluminum hydride reduction and were converted to the mesylate esters **15**. The NMR spectrum of the 7-methoxy mesylate **15a** showed the oxymethylene protons as a doublet at 4.33 ppm, while the corresponding 9-methoxy mesylate **15b** displayed the same doublet at 4.41 ppm. The isomeric cis-anti and cis-syn mesylate esters obtained in a similar manner from the catalytic hydrogenation products **12** and **13** of the enamine **10a** in a 1:3 ratio had the oxymethylene protons as a multiplet centered at 4.05 ppm, markedly upfield from those of the trans-anti isomers. The 8,9-dimethoxy mesylate **15d** showed the oxymethylene protons as a doublet at 4.42 ppm in agreement with the trans-anti isomers **15a** and **15b**.

The mesylate derivatives served as a common intermediate for three different substitutions. The reduction of mesylates **15** with lithium triethylborohydride[29] produced the 2-methyl compounds **16**. The mesylate moieties were also displaced by an 18-crown-6 complex of potassium cyanide[30] to give the corresponding nitriles **18** in nearly quantitative yield. Substitution of the mesylate ester could also be carried out with lithium thiomethoxide[31] to yield the sulfides **17**. Lithium thiomethoxide in HMPT proved

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Table II. Biological Potency of Dopamine Agonists

compd	competition for [^{3}H]spiperone[a]				
	$K_{i\,high}$, nM	% high[b]	$K_{i\,low}$, nM	% low[b]	f value[a]
19a			620	100	
20a			250	100	
21a			5390	100	
20c			1730	100	
21c			1460	100	
19b	8	13	1940	87	13.4
20b	14	21	1210	79	17.0
21b	4	30	280	70	18.0
20d	2	33	110	67	5.9
21d	6	44	360	56	37.6
dopamine	34	31	3380	69	49.9

[a] See Experimental Section for description of test and calculation of K_i values and f values. [b] Obtained from computer analysis of competition curves for the affinity of the compound for the different states of the receptor and the proportion of these states. See Experimental Section for description.

to be markedly superior to sodium thiomethoxide in DMF for this reaction.

A variety of methods were investigated for effecting a high-yield cleavage of the aromatic ether functions to the corresponding phenols. The demethylation of the sulfides **17** presented a problem since the compound possessed a thioether linkage in addition to the aromatic methyl ether moiety. With a nucleophilic demethylating reagent, sodium thioethoxide in DMF gave the phenol **20** in moderate yield, while lithium thioethoxide in HMPT (based on the reported[32] use of lithium thio-*n*-propoxide in HMPT) afforded an excellent yield of the desired phenol. The same reagent was successful for the conversion of the 2-methyl compounds **16** to the phenols **19**. The demethylation of **16a** with hot 48% hydrobromic acid afforded the same product **19a** but in lower yield.

As expected, the demethylation of the dimethoxy analogues **16** and **17** by the lithium thioethoxide/HMPT procedure was slower probably because, subsequent to the cleavage of one ether linkage, they would resist further demethylation. However, by extending the reaction time to 24 h, products free of the starting ethers were obtained.

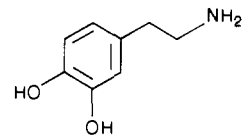
For the demethylation of the cyanides **18**, neither hot 48% hydrobromic acid nor lithium thioethoxide could be used because of the instability of the cyano group to these reagents.[33] Attempted demethylation with trimethylsilyl iodide[34] proceeded only in very low yield. The use of sodium cyanide[33] in DMSO at 180 °C gave the desired products **21** in moderate yield; no reaction occurred when potassium cyanide was substituted for the sodium salt, and the success of the reaction was markedly dependent on the concentration of sodium cyanide in the DMSO solution. While boron tribromide in dichloromethane[35] was fairly successful, application of the boron tribromide–dimethyl sulfide complex[36] gave excellent yields of the phenols **21**.

Pharmacology

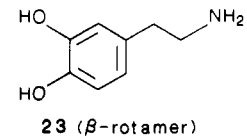
The 10 new 2-substituted octahydrobenzo[*f*]quinolines were evaluated for their binding interactions with D-2 dopamine receptors on bovine anterior pituitary membranes. Competition binding studies were performed with the specific dopamine radioligand [^{3}H]spiroperidol (spiperone) according to methods previously described by Cronin and Weiner.[37] The competition curves were evaluated for a one- or two-site interaction by computer-assisted data analysis.

The following observations may be made on the basis of the results summarized in Table II.

(a) The 2-substituted compounds **19a**, **20a**, **21a**, **20c**, and **21c** were relatively weak dopaminergics, and exhibited monophasic low affinity binding. These five substances, like Cannon's series[6c] of octahydrobenzo[*f*]quinolines, all correspond to the α-rotamer **22** conformation of dopamine. In this group, the presence of the catechol moiety did not increase activity.



22 (α-rotamer)



23 (β-rotamer)

The 2-substituted compounds **19b**, **20b**, **21b**, **20d**, and **21d** were substantially more active, and exhibited a biphasic competition curve as observed for dopamine, showing both high- and low-affinity binding. This group of five substances all correspond to the β-rotamer conformation **23** of dopamine, and in this group the possession of a catechol ring significantly enhanced the percentage of binding to the high-affinity sites compared to that found for the monohydroxylic phenols.

Taking into account the observation that ergolines exhibit a high percentage of high affinity site binding of the D-2 receptor,[38] the results suggest that the congeners possessing the β-rotamer conformation **23** show binding characteristics that more closely resemble those of the ergolines than do those of the corresponding α-rotamer congeners. This conclusion is also consonant with the fact that the active β-rotamer aminotetralin congeners have the same absolute configuration as the dopaminergic active *d*-ergolines,[39] and suggests that by manipulating the substituent in the 2-position in this type of compound it may be possible to synthesize octahydrobenzo[*f*]quinoline analogues that approach or exceed the specific dopaminergic activity of the ergolines while remaining free of their undesirable side effects. Further work along these lines is currently in progress. Additional studies on the biological evaluation of the series will be published elsewhere.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The 80-MHz NMR spectra were recorded on a Varian FT-80 instrument operating in the Fourier transform mode with tetramethylsilane as internal standard. The 500-MHz NMR spectra were recorded on a General Electric GN-500 instrument. The electron-impact mass spectra were obtained on an AEI MS-12 instrument at 70 eV. GLC analyses were performed on a Varian Aerograph Model 2100 gas chromatograph with a 6-ft U-tube Pyrex column packed with 3% SE-30 on Chromosorb W. Elemental analyses were performed by the Microanalytical Laboratory, University of California, Berkeley. As a drying agent, Na_2SO_4 was employed when the desired compound was an amine while $MgSO_4$ was used in the preparation of non-amino compounds. All reagents were purified before use.

7,8-Dimethoxy-1,2-dihydronaphthalene (4c). Sodium borohydride (2.01 g, 0.053 mol) was added in small portions to a magnetically stirred solution of the ketone **3c**[18] (21.6 g, 0.105 mol)

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in 250 mL of 95% EtOH. When the addition was complete, the reaction was heated under reflux for 15 min and then cooled. Water (250 mL) was added and the EtOH was removed under reduced pressure. The product was extracted into CH_2Cl_2 and dried, and the solvent was evaporated. Benzene (500 mL) was distilled from CaH_2 directly into the flask containing the alcohol and *p*-toluenesulfonic acid (0.1 g) was added. The solution was refluxed overnight under a Dean–Stark trap and then washed with $NaHCO_3$, dried, and evaporated. The residue was distilled in vacuo to yield 17.6 g (88%) of the olefin **4c**: bp 106–108 °C (0.15 mm); NMR (80 MHz) ($CDCl_3$) δ 6.7–6.5 (m, 2, aromatic *H*), 6.39 (2, br t, 1, C-4 *H*), 5.89 (2t, 1, C-3 *H*), 3.84 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 2.84 (t, 2, C-1 *H*), 2.4–2.0 (m, 2, C-2 *H*). Anal. ($C_{12}H_{14}O_2$) C, H.

6,7-Dimethoxy-1,2-dihydronaphthalene (4d). The procedure for the preparation of the title compound was identical with that used for the isomer **4c**. Starting with 61.8 g (0.30 mol) of the tetralone **3d**[14] and adjusting all solvents and reagents proportionally, 52.37 g (35%) of olefin **4d** was obtained: bp 119–121 °C (0.3 mm); mp 33–35 °C (lit.[15a] mp 35.3–36 °C); NMR (80 MHz) ($CDCl_3$) δ 6.62 (s, 1, aromatic *H*), 6.55 (s, 1, aromatic *H*), 6.33 (d of br t, 1, C-4 H), 5.84 (d of t, 1, C-3 *H*), 3.84 (s, 6, OCH_3), 2.69 (t, 2, C-1 *H*), 2.5–2.0 (m, 2, C-2 *H*). Anal. ($C_{12}H_{14}O_2$) C, H.

2-(2′,3′-Dimethoxyphenyl)ethyl (Methylsulfinyl)methyl Ketone (9a). Lithium methylsulfinyl carbanion was prepared by adding 0.32 mol of *n*-butyllithium (200 mL of 1.6 M) to an ice-cooled stirred solution of DMSO (27.5 mL) in 240 mL of THF at a rate so the temperature was kept below 10 °C. The mixture was stirred in an ice bath for 30 min. A solution of ethyl 3-(2′,3′-dimethoxyphenyl)propionate[16,17] (38.1 g, 0.16 mol) in 210 mL of THF was added dropwise with stirring over 30 min while the temperature was maintained below 10 °C. The mixture was then stirred at room temperature for 2 h, poured over 1300 mL of ice, and brought to pH 3–4 with HCl. The produt was thoroughly extracted with CH_2Cl_2, dried, and evaporated. The residue was dissolved in ethyl acetate; diisopropyl ether was added to just below clouding, and the mixture was placed in the freezer overnight. The precipitate was collected and washed with the minimum of diisopropyl ether (at −10 °C) and dried to yield 40.85 g (95%) of **9a**: mp 55–56 °C (lit.[22] mp 55.5–56.5 °C); NMR (80 MHz) ($CDCl_3$) δ 7.1–6.6 (m, 3, aromatic *H*), 3.83 (s, 3, OCH_3), 3.81 (s, 3 OCH_3), 3.72 (2, $CH_2S{=}O$), 3.4–2.1 (m, 4, C-1 and C-2 *H*), 2.77 (d, 3, $CH_3S{=}O$). Anal. ($C_{13}H_{18}O_4S$) C, H, S.

2-(3′,4′-Dimethoxyphenyl)ethyl (Methylsulfinyl)methyl Ketone (9b). From 0.20 mol of lithium methylsulfinyl carbanion and 23.8 g (0.10 mol) of ethyl 3-(3′,4′-dimethoxyphenyl)propionate, 25.8 g (96%) of **9b** was afforded (following the procedure for the preparation of the isomer **9a**): mp 83–85 °C (lit.[21] mp 85–87 °C); NMR (80 MHz) ($CDCl_3$) δ 6.73 (s, 3, aromatic *H*), 3.84 (s, 6, OCH_3), 3.71 (d, 2, $CH_2S{=}O$), 3.2–2.5 (m, 4, C-1 and C-2 *H*), 2.75 (d, 3, $CH_3S{=}O$). Anal. ($C_{13}H_{18}O_4S$) C, H, S.

5-Methoxy-3,4-dihydro-2(1*H*)-naphthalenone (6a). The olefin 8-methoxy-1,2-dihydronaphthalene[11] (35.3 g, 0.22 mol) was dissolved in 1 L of CH_2Cl_2 and the solution was cooled to 0 °C. *m*-Chloroperoxybenzoic acid (42.0 g, 0.242 mol) was added in portions with stirring and the mixture was kept at 0–5 °C overnight. The solution was filtered, washed with saturated Na_2SO_3, saturated $NaHSO_3$, dried, and evaporated to leave the crude epoxide in quantitative yield. Dry ZnI_2 (26.0 g, 80 mmol) was dissolved in a minimum amount of ether. About 1300 mL of dry benzene was added and the ether was distilled over with stirring until a very fine ZnI_2 suspension resulted. The crude epoxide in 300 mL of dry benzene was added to the hot suspension and the mixture was refluxed with stirring for 3 h under N_2. It was cooled, washed with H_2O, and dried. The solvent was evaporated and the residue distilled to yield 33.3 g (86%) of **6a**: bp 118–120 °C (0.4 mm): mp 35–37 °C (lit.[11] mp 35–37 °C); NMR (80 MHz) ($CDCl_3$) δ 7.2–6.6 (m, 3, aromatic *H*), 3.82 (s, 3, OCH_3), 3.52 (s, 2, C-1 *H*), 3.06 (t, 2, C-4 *H*), 2.47 (t, 2, C-3 *H*).

7-Methoxy-3,4-dihydro-2(1*H*)-naphthalenone (6b). The title compound was prepared from 6-methoxy-1,2-dihydronaphthalene[11] (24.7 g, 0.14 mol) by the procedure outlined above for **6a** to afford 23.03 g (93%) of **6b**: bp 110–112 °C (0.10 mm) (lit.[11] bp 123–126 °C (1.5 mm)); NMR (80 MHz) ($CDCl_3$) δ 7.2–6.4 (m, 3, aromatic *H*), 3.77 (s, 3, OCH_3), 3.54 (s, 2, C-1 *H*), 2.99 (t, 2, C-4 *J*), 2.52 (t, 2, C-3 *H*).

General Procedure for the Preparation of Methoxy-Substituted Methyl 4-*n*-Propyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylates (10). To a cooled solution consisting of a 19.65 g of *n*-propylamine in 70 mL of benzene was added dropwise a chilled solution of 21.2 g of methyl 2-(bromomethyl)acrylate[13] in 55 mL of benzene with stirring. The mixture was stirred for 15 min to give a clear solution. A chilled solution of 0.10 mol of the various methoxy-2-tetralones (**6**) in 70 mol of benzene was added all at once. The mixture was heated under reflux with a Dean–Stark separator overnight under N_2. The cooled solution was extracted with 5% HCl (250 mL). The combined extracts were washed twice with ether, basified with Na_2CO_3, and extracted with CH_2Cl_2. The organic layer was dried and evaporated to yield the crude enamine. The purification details for each compound are given below.

Methyl 4-*n*-Propyl-7-methoxy-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate (10a). The crude enamine was distilled to give a 69% yield of the pure compound, bp 207–209 °C (0.15 mm). The perchlorate salt was crystallized from EtOH–Et_2O: mp 168–170 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.7–6.5 (m, 3, aromatic *H*), 3.80 (s, 3, OCH_3), 3.73 (s, 3, $COOCH_3$), 3.7–2.2 (m, 11, C-2, C-3, C-5, C-6 *H*, and NCH_2), 1.51 (quar, 2, NCH_2CH_2), 0.88 (t, 3, CH_3). Anal. ($C_{19}H_{26}ClNO_7$) C, H, N.

Methyl 4-*n*-Propyl-9-methoxy-1,2,3,4,5,6-hexadrobenzo[*f*]quinoline-2-carboxylate (10b). The enamine was distilled to give a 71% yield of **10b**, bp 204–208 °C (0.2 mm). The perchlorate salt was crystallized from EtOH–Et_2O: mp 157–159 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.0–6.2 (m, 3, aromatic *H*), 3.77 (s, 3, OCH_3), 3.73 (s, 3, $COOCH_3$), 3.6–2.0 (m, 11, C-1, C-2, C-3, C-5, C-6 *H* and NCH_2), 1.47 (quin, 2, NCH_2CH_2), 0.88 (t, 3, CH_3). Anal. ($C_{19}H_{26}ClNO_7$) C, H, N.

Methyl 4-*n*-Propyl-7,8-dimethoxy-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate (10c). The enamine was distilled to give a 55% yield of **10c**, bp 220–222 °C (0.2 mm). The perchlorate salt crystallized from EtOH–Et_2O: mp 167–169.5 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 6.72 (s, 2, aromatic *H*), 3.82 (s, 3, OCH_3), 3.73 (s, 3, $COOCH_3$), 3.5–2.0 (m, 11, C-1, C-2, C-3, C-5, C-6 *H* and NCH_2), 1.52 (quar, 2, NCH_2CH_2), 0.88 (t, 3, CH_3). Anal. ($C_{20}H_{28}ClNO_8$) C, H, N.

Methyl 4-*n*-Propyl-8,9-dimethoxy-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate (10d). The pure enamine was obtained in a 74% yield by utilizing the procedure for compound **10c**, bp 196–198 °C (0.1 mm). The perchlorate salt was crystallized from EtOH–Et_2O: mp 211–213 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 6.63 (br s, 2, aromatic *H*), 3.88 (s, 6, 2 OCH_3), 3.78 (s, 3, $COOCH_3$), 3.5–1.9 (m, 11, C-1, C-2, C-3, C-5, C-6 *H* and NCH_2), 1.46 (sex., 2, NCH_2CH_2), 0.92 (t, 3, CH_3). Anal. ($C_{20}H_{28}ClNO_8$) C, H, N.

General Procedure for the Preparation of Methyl 4-*n*-Propyl(di)methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylate (11). The corresponding methyl 4-*n*-propyl(di)methoxy-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate (**10**) (0.050 mol) was dissolved in 750 mL of anhydrous ether and HCl–Et_2O was added until precipitation was complete. The mixture was put in the freezer for 10–15 min and the ether was decanted. The residue was dissolved quickly in 225 mL of MeOH and 675 mL of THF was added. The solution was then cooled to −25 to −30 °C and 15.0 g of $NaCNBH_3$ was added gradually with stirring so that the temperature of the reaction mixture did not rise above −25 °C. Stirring and cooling was continued for 1.5 h when the reaction mixture was allowed to warm to room temperature, poured into water, and basified with Na_2CO_3. It was extracted with CH_2Cl_2, dried, and evaporated to leave an oil which was distilled under high vacuum. The distillate (consisting of the trans-anti and cis isomers) was chromatographed over neutral alumina with benzene as an eluant. The trans-anti isomer **10** eluted first as the major product. The addition of CH_2Cl_2 to the benzene eluted the cis-syn isomer **13** next followed by the cis-anti isomer **12**. Pure samples of the trans-anti isomers **11** were obtained as their perchlorate salts. The details for each compound are given under their appropriate headings below.

Methyl 4-*n*-Propyl-7-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylate (11a). The trans-anti compound obtained from chromatography was vacuum distilled, resulting in a 55% yield of **11a**, bp 208–210 °C (0.05 mm). The perchlorate salt crystallized from EtOH–Et_2O: mp 212–214 °C;

NMR (80 MHz) ($CDCl_3$) (free base) δ 7.4–6.5 (m, 3, aromatic *H*), 3.80 (s, 3, OCH_3), 3.73 (s, 3, $COOCH_3$), 3.4–2.6 (m, 13, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H* and NCH_2), 1.43 (quin, 2, NCH_2CH_2), 0.86 (t, 3, CH_3). Anal. ($C_{19}H_{28}ClNO_7$) C, H, N.

Methyl 4-*n*-Propyl-9-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylate (11b). The title compound was obtained in 62% yield, bp 168–170 °C (0.007 mm). The perchlorate salt crystallized from EtOH–Et_2O: mp 152–153 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.0–6.4 (m, 3, aromatic *H*), 3.72 (s, 3, OCH_3), 3.67 (s, 3, $COOCH_3$), 3.3–1.4 (m, 13, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H* and NCH_2), 1.42 (sex., 2, NCH_2CH_2), 0.82 (t, 3, CH_3). Anal. ($C_{19}H_{28}ClNO_7$) C, H, N.

Methyl 4-*n*-Propyl-7,8-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylate (11c). This compound was prepared in 57% yield, bp 220–223 °C (0.02 mm). The perchlorate salt crystallized from EtOH–Et_2O: mp 170–172 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.1–6.6 (m, 2, aromatic *H*), 3.83 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 3.71 (s, 3, $COOCH_3$), 3.4–1.0 (m, 15, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b, *H*, NHH_2, and NCH_2CH_2), 0.88 (t, 3, CH_3). Anal. ($C_{20}H_{30}ClNO_8$) C, H, N.

Methyl 4-*n*-Propyl-8,9-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylate (11d). This compound had bp 222–224 °C (0.02 mm) (50% yield). The perchlorate salt crystallized from EtOH–Et_2O: mp 174–176 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 6.8–6.4 (2d, 2, aromatic *H*), 383 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 3.69 (s, 3, $COOCH_3$), 3.4–1.2 (m, 15, C-1, C-2, C-3, C-4a, C-5, C-6, C-1]0b *H*, NCH_2, and NCH_2CH_2), 0.86 (t, 3, CH_3). Anal. ($C_{20}H_{30}ClNO_8$) C, H, N.

General Procedure for the Preparation of 2-(Hydroxymethyl)-4-*n*-propyl(di)methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines (14). The ester 11 (0.025 mol) was dissolved in 400 mL of THF and then treated with portions of 8.0 g of lithium aluminum hydride with stirring. Stirring was continued for 18 h and the solution was then cooled with ice water and decomposed with 5% sodium potassium tartrate. The solids were filtered off, water was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried and evaporated to yield an oil which was used in the following reaction without further purification. The crude alcohol 14 was obtained in quantitative yield from the ester 11 in all the cases below.

2-(Hydroxymethyl)-4-*n*-propyl-7-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (14a). The picrate (from the base and excess picric acid in ethanol) was recrystallized from EtOH to give yellow crystals: mp 170–172 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.4–6.5 (m, 3, aromatic *H*), 3.97 (t, 2, CH_2O), 3.86 (s, 3, OCH_3), 3.3–1.5 (m, 14, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, NCH_2, and O*H*), 1.41 (quin, 2, NCH_2CH_2), 0.84 (t, 3, CH_3). Anal. ($C_{24}H_{30}N_4O_9$) C, H, N.

2-(Hydroxymethyl)-4-*n*-propyl-9-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (14b). The picrate formed an amorphous solid: mp 68–78 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.1–6.4 (m, 3, aromatic *H*), 3.93 (br t, 2, CH_2O), 3.76 (s, 3, OCH_3), 3.7–2.7 (m, 14, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, NCH_2, and O*H*), 1.59 (sept, 2, NCH_2CH_2), 0.90 (t, 3, CH_3). Anal. ($C_{24}H_{30}N_4O_9$) C, H, N.

2-(Hydroxymethyl)-4-*n*-propyl-7,8-dimethoxy-1,2,3,4,4a,5,6,10b-octrahydrobenzo[*f*]quinoline (14c). The picrate precipitated as fluffy yellow needles and crystallized from EtOH: mp 188–190 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.1–6.6 (m, 2, aromatic *H*), 3.90 (m, 2, CH_2O), 3.82 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 3.3–1.5 (m, 14, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, NCH_2OH), 1.54 (quar, 2, NCH_2CH_2), 0.89 (t, 3, CH_3). Anal. ($C_{25}H_{32}N_4O_{10}$) C, H, N.

2-(Hydroxymethyl)-4-*n*-propyl-8,9-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (14d). The picrate recrystallized from EtOH: mp 170–172 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 6.8–6.4 (t, 2, aromatic *H*), 3.93 (m, 2, CH_2O), 3.84 (s, 6, 2 OCH_3), 3.8–1.6 (m, 14, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, NCH_2, O*H*), 1.59 (sept, 2, NCH_2CH_2), 0.90 (t, 3, CH_3). Anal. ($C_{25}H_{32}N_4O_{10}$) C, H, N.

General Procedure for the Preparation of 2-[[(Methylsulfonyl)oxy]methyl]-4-*n*-propyl(di)methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines (15). The corresponding crude 2-(hydroxymethyl)-4-*n*-propyl(di)methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline 14 (35.0 mmol) was dissolved in 500 mL of dry pyridine and was treated while being stirred with dropwise addition of a solution of 14 mL of methanesulfonyl chloride in 200 mL of dry pyridine. The solution was stirred at room temperature under N_2 for 1 day. It was then diluted with excess H_2O, basified with Na_2CO_3, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried, evaporated, and left in vacuo overnight to remove the last traces of pyridine. The crude mesylate 15 was suitable for the next step. A portion was chromatographed on silica gel ($CHCl_3$–3% MeOH) to obtain analytical samples.

2-[[(Methylsulfonyl)oxy]methyl]-4-*n*-propyl-7-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (15a). The picrate was recrystallized from EtOH to give orange-yellow crystals: mp 141–144 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.3–6.5 (m, 3, aromatic *H*), 4.33 (d, 2, CH_2O), 3.75 (s, 3, OCH_3), 3.01 (s, 3, O_2SCH_3), 3.1–1.5 (m, 13, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H* and NCH_2), 1.48 (quin, 2, NCH_2CH_2), 0.85 (t, 3, CH_3). Anal. ($C_{25}H_{32}N_4O_{11}S$) C, N, S.

2-[[(Methylsulfonyl)oxy]methyl]-4-*n*-propyl-9-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (15b). No crystalline salts could be prepared but the free base formed tan crystals from Et_2O–hexane: mp 89–92 °C; NMR (80 MHz) ($CDCl_3$) δ 7.1–6.4 (m, 3, aromatic *H*), 4.41 (d, 2, CH_2O), 3.76 (s, 3, OCH_3), 3.02 (s, 3, O_2SCH_3), 3.1–1.6 (m, 13, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H* and NCH_2), 1.50 (sept, 2, NCH_2CH_2), 0.87 (t, 3, CH_3). Anal. ($C_{19}H_{29}NO_4S$) C, H, N, S.

2-[[(Methylsulfonyl)oxy]methyl]-4-*n*-propyl-7,8-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (15c). The picrate was recrystallized from EtOH: mp 179–182 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.0–6.5 (m, 2, aromatic *H*), 4.39 (d, 2, CH_2O), 3.83 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 3.3–1.3 (m, 15, C-1, C-2, C-4a, C-5, C-6, C-10b *H*, NCH_2, and NCH_2CH_2), 3.03 (s, 3, O_2SCH_3), 0.88 (t, 3, CH_3). Anal. ($C_{26}H_{34}N_4O_{12}S$) C, H, N, S.

2-[[(Methylsulfonyl)oxy]methyl]-4-*n*-propyl-8,9-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (15d). The free base crystallized from acetone–hexane: mp 142–144 °C; NMR (80 MHz) ($CDCl_3$) δ 6.8–6.4 (m, 2, aromatic *H*), 4.42 (d, 2, CH_2O), 3.82 (s, 3, 2 OCH_3), 3.02 (s, 3, O_2SCH_3), 3.1–1.4 (m, 15, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, NCH_2, and NCH_2CH_2), 0.88 (t, 3, CH_3). Anal. ($C_{20}H_{31}NO_5S$) C, H, N, S.

2-Methyl-4-*n*-propyl-7-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (16a). To a solution of the mesylate **15a** (1.5 g, 4.1 mmol) in 10 mL of THF was added 9 mL of 1 M lithium triethylborohydride (in THF) in one portion with a syringe. The mixture was refluxed for 4 h and cooled. The mixture was poured into 1 M HCl and then washed twice with ether. The aqueous layer was basified (Na_2CO_3) and extracted with CH_2Cl_2, and the extract was dried and evaporated to leave an oil which was distilled to yield 0.89 g (78%) of **16a**, bp 140–142 °C (0.10 mm). The perchlorate salt was recrystallized (EtOH): mp 193–195 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.3–6.5 (m, 3, aromatic *H*), 3.79 (s, 3, OCH_3), 3.2–1.1 (m, 15, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, NCH_2, and NCH_2CH_2), 0.96 (d, 3, C-2 CH_3), 0.83 (t, 3, *n*-propyl CH_3). Anal. ($C_{18}H_{28}ClNO_5$) C, H, N.

2-Methyl-4-*n*-propyl-9-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (16b). The mesylate **15b** (1.5 g, 4.1 mmol) by the above procedure yielded 0.83 g (74%) of **16b**, bp 138–140 °C (0.10 mm). The perchlorate recrystallized from EtOH: mp 208–209 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.2–6.4 (m, 3, aromatic *H*), 3.76 (s, 3, OCH_3), 3.2–1.7 (m, 13, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H* and NCH_2), 1.44 (quin, 2, NCH_2CH_2), 0.97 (d, 3, C-2 CH_3), 0.86 (t, 3, *n*-propyl CH_3). Anal. ($C_{18}H_{28}ClNO_5$) C, H, N.

General Procedure for the Preparation of 2-[(Methylthio)methyl]-4-*n*-propyl(di)methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (17). The corresponding 2-[[(methylsulfonyl)oxy]methyl]-4-*n*-propyl(di)methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (20 mmol) was dissolved in 130 mL of HMPT and 8.0 g of lithium thiomethoxide was added. After dissolving, the mixture was stirred for 2 h at room temperature. Water was added and the solution extracted three times with ethyl acetate. The combined extracts were dried and evaporated; the last of the HMPT was removed by distillation and the remaining oil was treated as described under the following headings.

2-[(Methylthio)methyl]-7-methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (17a). The oil

was distilled to give 81% of **17a**, bp 182–184 °C (0.10 mm). The perchlorate was recrystallized from EtOH: mp 160–161 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.4–6.4 (m, 3, aromatic *H*), 3.78 (s, 3, OCH_3), 3.3–1.1 (m, 17, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, CH_2S, NCH_2, and NCH_2CH_2), 2.06 (s, 3, SCH_3), 0.87 (t, 3, CH_3). Anal. ($C_{19}H_{30}ClNO_5S$) C, H, N, S.

2-[(Methylthio)methyl]-9-methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (17b). Distillation of the oil gave 71% of **17b**, bp 180–182 °C (0.15 mm). Crystallization from EtOH–Et_2O gave the oxalate: mp 152–153 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.2–6.4 (m, 3, aromatic *H*), 3.76 (s, 3, OCH_3), 3.2–1.2 (m, 17, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, NCH_2, NCH_2CH_2, and CH_2S), 2.05 (s, 3, SCH_3), 0.87 (t, 3, CH_3). Anal. ($C_{21}H_{31}NO_5S$) C, H, N, S.

2-[(Methylthio)methyl]-7,8-dimethoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (17c). The oil distilled to give 80% of **17c**, bp 196–198 °C (0.17 mm). The picrate crystallized from EtOH as yellow plates: mp 180–183 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.1–6.5 (m, 2, aromatic *H*), 3.82 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), 3.3–1.0 (m, 17, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, CH_2, NCH_2, and NCH_2CH_2), 2.06 (s, 1.5, SCH_3), 0.88 (t, 3, CH_3). Anal. ($C_{26}H_{34}N_4O_9S$) C, H, N, S.

2-[(Methylthio)methyl]-8,9-dimethoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (17d). Distillation of the oil gave 74% of **17d**, bp 196–200 °C (0.25 mm). The oxalate recrystallized from EtOH: mp 162–164 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 6.69 (s, 1, aromatic *H*), 6.55 (s, 1, aromatic *H*), 3.83 (s, 3, OCH_3), 3.82 (s, 3, OCH_3), 3.1–1.1 (m, 17, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, CH_2S, NCH_2, and NCH_2CH_2), 2.06 (s, 3, SCH_3), 0.87 (t, 3, CH_3). Anal. ($C_{22}H_{33}NO_6S$) C, H, N, S. The picrate crystallized from EtOH, mp 131–134 °C. Anal. ($C_{26}H_{34}N_4O_9S$) C, H, N, S.

General Procedure for the Preparation of 2-(Cyanomethyl)-4-*n*-propyl(di)methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (18). A mixture consisting of 1.0 mmol of mesylate **15**, 0.25 g of KCN, and 0.025 g of 18-crown-6 in 5 mL of acetonitrile was refluxed with vigorous stirring for 2 days. After cooling, the mixture was poured into 1 M HCl and washed twice with ether. The aqueous solution was basified to pH >10 and extracted with CH_2Cl_2. The extract was dried, evaporated, and distilled in vacuo.

2-(Cyanomethyl)-4-*n*-propyl-7-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (18a). The above procedure gave 80% of **18a**, bp 208–210 °C (0.10 mm). The picrate recrystallized from EtOH: mp 187–188 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.3–6.3 (m, 3, aromatic *H*), 3.78 (s, 3, OCH_3), 3.2–1.1 (m, 15, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, NCH_2, and NCH_2CH_2), 2.61 (d, 2, CH_2CN), 0.88 (t, 3, CH_3). Anal. ($C_{24}H_{27}N_5O_8$) C, H, N.

2-(Cyanomethyl)-4-*n*-propyl-9-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (18b). Starting from the mesylate **15b**, an 81% yield of **18b** was obtained, bp 206–208 °C (0.15 mm). The picrate had the following: mp 146–148 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.2–6.5 (m, 3, aromatic *H*), 3.77 (s, 3, OCH_3), 3.2–1.2 (m, 17, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, CH_2CN, NCH_2, and NCH_2CH_2), 0.91 (t, 3, CH_3). Anal. ($C_{24}H_{27}N_5O_8$) C, H, N.

2-(Cyanomethyl)-4-*n*-propyl-7,8-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (18c). The mesylate **15c** gave 78% of **18c**, bp 220–222 °C (0.1 mm). The picrate had the following: mp 191–193 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 6.77 (2d, 2, aromatic *H*), 3.83 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 3.3–1.2 (m, 17, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, CH_2CN, NCH_2, and NCH_2CH_2), 0.89 (t, 3, CH_3). Anal. ($C_{25}H_{29}N_5O_9$) C, H, N.

2-(Cyanomethyl)-4-*n*-propyl-8,9-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (18b). The mesylate **15d** gave an 81% yield of **18d**, bp 206–208 °C (0.05 mm). The picrate (from EtOH) had the following: mp 230–231 °C; NMR δ 6.56 (s, 1, aromatic *H*), 6.53 (s, 1, aromatic *H*), 3.84 (s, 3, OCH_3), 3.83 (s, 3, OCH_3), 3.2–1.2 (m, 17, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, CH_2CN, NCH_2, and NHC_2CH_2), 0.89 (t, 3, CH_3). Anal. ($C_{25}H_{29}N_5O_9$) C, H, N.

General Procedure for the Demethylation of Compounds 16 and 17 Using Lithium Thioethoxide. The ether **16** or **17** (15 mmol) was mixed with 7.0 g of lithium thioethoxide and 8.0 mL of HMPT and the mixture was stirred and heated at 120 °C under N_2 for 3 h (24 h for the dimethoxy compounds). It was then cooled and poured into 5% HCl and washed three times with ether. The aqueous layer was brought to pH 9 and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried and evaporated to leave an oil from which the traces of HMPT were distilled off under high vacuum. The residue was dissolved in ether and treated with oxalic acid to yield the oxalates described below.

2-Methyl-4-*n*-propyl-7-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (19a). The oxalate crystallized from EtOH–Et_2O to give a 77% yield of the title compound: mp 220–221 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.2–6.3 (m, 3, aromatic *H*), 4.77 (br s, 1, O*H*), 3.2–1.0 (m, 15, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, NCH_2, NCH_2CH_2), 0.95 (d, 3, C-2, CH_3), 0.86 (t, 3, *n*-propyl CH_3). Anal. ($C_{19}H_{27}NO_5$), C, H, N.

2-Methyl-4-*n*-propyl-9-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (19b). A 75% yield of the oxalate salt was obtained: mp 207–209 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.1–6.4 (m, 3, aromatic *H*), 3.87 (m, 1, O*H*), 3.2–1.0 (m, 15, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, NCH_2, NCH_2CH_2), 0.96 (d, 3, C-2 CH_3), 0.86 (t, 3, *n*-propyl CH_3). Anal. ($C_{19}H_{27}NO_5$) C, H, N.

2-[(Methylthio)methyl]-7-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (20a). The oxalate crystallized from EtOH to give an 86% yield of **20a**: mp 204–205 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.2–6.2 (m, 3, aromatic *H*), 3.4–1.2 (m, 16, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*), O*H*, NCH_2, and NCH_2CH_2), 2.17 (d, 2, CH_2S), 2.09 (s, 3, SCH_3), 0.81 (t, 3, CH_3). Anal. ($C_{20}H_{29}NO_5S$) C, H, N, S.

2-[(Methylthio)methyl]-9-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (20b). A 70% yield was obtained as the oxalate salt (from EtOH–Et_2O): mp 218–218.5 °C; NMR (80 MHz) (DMSO-d_6) (free base) δ 7.0–6.3 (m, 3, aromatic *H*), 3.5–1.2 (m, 18, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, CH_2S, O*H*, NCH_2, and NCH_2CH_2), 2.08 (s, 3, SCH_3), 0.87 (t, 3, CH_3). Anal. ($C_{20}H_{29}NO_5S$) C, H, N, S.

2-[(Methylthio)methyl]-4-*n*-propyl-7,8-dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (20c). By following the procedure as amended for dimethoxy compounds (heated at 120 °C for 24 h), a 90% yield of the oxalate of **20c** was obtained: mp 228–230 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 6.9–6.4 (br s, 2, aromatic *H*), 5.9–4.7 (m, 2, 2 O*H*), 3.3–1.0 (m, 17, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, CH_2S, NCH_2, NCH_2CH_2), 2.05 (s, 3, SCH_3), 0.85 (t, 3, CH_3). Anal. ($C_{20}H_{29}NO_6S$), C, H, N, S.

2-[(Methylthio)methyl]-4-*n*-propyl-8,9-dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (20d). Starting with ether **17d**, an 84% yield of the oxalate of **20d** was obtained: mp 224–226 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 6.62 (s, 1, aromatic *H*), 4.18 (br s, 2, 2 O*H*), 3.3–1.1 (m, 17, C-1, C-2, C-3, C-4a, C-5, C-6, C-10a *H*, CH_2S, NCH_2, and NCH_2CH_2), 2.05 (s, 3, SCH_3), 0.87 (t, 3, CH_3). Anal. ($C_{20}H_{29}NO_6S$) C, H, N, S.

General Procedure for the Dimethylation of Compounds 18 Using BBr_3–Me_2S. A mixture consisting of 4.0 mmol of **18**, 7.5 g of BBr_3–Me_2S, and 80 mL of 1,2-dichloroethane was refluxed for 18 h. The mixture was then cooled and hydrolyzed with 5% oxalic acid. The aqueous layer was washed with ether, basified to pH 9, and extracted with CH_2Cl_2, and the extract was dried. The solvent was evaporated and the solid phenol **21** was dissolved in EtOH–Et_2O and treated with oxalic acid to obtain the oxalates described below.

2-(Cyanomethyl)-4-*n*-propyl-7-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (21a). Starting from ether **18a**, a 79% yield of the oxalate of **21a** was obtained. It was recrystallized from EtOH: mp 247–248 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.2–6.3 (m, 3, aromatic *H*), 3.4–1.2 (m, 18, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, O*H*, CH_2CN, and NCH_2CH_2), 0.88 (t, 3, CH_3). Anal. ($C_{20}H_{26}N_2O_5$) C, H, N.

2-(Cyanomethyl)-4-*n*-propyl-9-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (21b). According to the above procedure, a 79% yield of the title compound (as the oxalate salt) recrystallized from EtOH: mp 177–179 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.1–6.3 (m, 3, aromatic *H*), 6.45 (m, 1, O*H*), 3.2–1.0 (m, 17, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, CH_2CN, NCH_2CH_2), 0.90 (t, 3, CH_3). Anal. ($C_{20}H_{26}N_2O_5$), C, H, N.

2-(Cyanomethyl)-4-*n*-propyl-7,8-dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (21c). From ether **18c**, the above procedure gave a 76% yield of the title compound (as the

oxalate), recrystallized from EtOH: mp 188–190 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 6.57 (s, 2, aromatic *H*), 4.83 (br s, 2, O*H*), 3.3–1.0 (m, 17, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, CH_2CN, NCH_2CH_2), 0.89 (t, 3, CH_2). Anal. ($C_{21}H_{28}N_2O_6$) C, H, N.

2-(Cyanomethyl)-4-*n*-propyl-8,9-dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (21d). A 73% yield of **21d** (as the oxalate) was obtained, recrystallized from EtOH: mp 212–214 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.16 (s, 2, aromatic *H*), 6.75–6.25 (m, 2, 2 O*H*), 4.1–1.0 (m, 17, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, CH_2CN, NCH_2CH_2), 0.88 (t, 3, CH_3). Anal. ($C_{21}H_{28}N_2O_6$) C, H, N.

Dopamine Radioligand Binding Assay. Competition radioligand binding assays were performed by incubating bovine anterior pituitary membranes with the specific dopamine radioligand [^{3}H]spiroperidol (spiperone) (1.0–1.5 nM; sp act. 26.4 Ci/mmol; New England Nuclear) in the presence of increasing amounts of the indicated dopamine congeners (100 μM–0.1 nM, 19 concentrations). Membranes were prepared as previously described,[37] and the incubation was carried out at 23 °C for 60 min. The assay buffer employed consisted of 50 mM Tris, 120 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 2 mM $CaCl_2$, 0.1% ascorbic acid, and 12.5 μM nialamide (final pH 7.4). Membrane-bound [^{3}H]spiroperidol was separated from free by vacuum filtration through a Whitman GF/C glass fiber filter. Nonspecifically bound [^{3}H]spiroperidol was determined by performing parallel incubations in the presence of 1000-fold-excess of *d*-butaclamol (Ayerst), a potent dopamine agonist.

Competition curves were analyzed by an iterative, nonlinear least-squares curve-fitting procedure according to a one- or two-affinity-state model for ligand–receptor systems. This computer-assisted analysis provides estimates for the affinity of the congener for the different states of the receptor ($K_{i\,high}$ and $K_{i\,low}$) and the proportion of these states. The inhibition constant (K_i) was determined by the relationship: $K_i = IC_{50}/[1 + (L/K_D)]$,[42] where IC_{50} = competitor concentration which inhibited [^{3}H]-spiroperidol binding by 50%, L = concentration of [^{3}H]-spiroperidol used in the assay (1.0–1.5 nM) and K_D = the dissociation constant of [^{3}H]spiroperidol for its binding sites (0.16 nM). Statistical analysis comparing "goodness of fit" between the one- and two-affinity-state models was also performed and used to determine the appropriate model for the congener being examined.[43] An f value greater than 3.7 indicates statistical significance at the $p < 0.05$ confidence level.

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Registry No. **3a**, 33892-75-0; **3b**, 6836-19-7; **3c**, 24039-89-2; **3d**, 13575-75-2; **4a**, 60573-59-3; **4b**, 60573-58-2; **4c**, 52644-00-5; **4d**, 35491-96-4; **5a**, 95838-85-0; **6a**, 32940-15-1; **6b**, 4133-34-0; **6c**, 52644-01-6; **6d**, 2472-13-1; **9a**, 63307-15-3; **9b**, 33212-96-3; **10a**, 119530-27-7; **10a**·perchlorate, 119530-30-2; **10b**, 119530-28-8; **10b**·perchlorate, 119530-31-3; **10c**, 119530-29-9; **10c**·perchlorate, 119530-32-4; **10d**, 119567-30-5; **10d**·perchlorate, 119567-31-6; **11a**, 119530-33-5; **11a**·perchlorate, 119616-65-8; **11b**, 119530-34-6; **11b**·perchlorate, 119616-66-9; **11c**, 119530-35-7; **11c**·perchlorate, 119616-67-0; **11d**, 119530-36-8; **11d**·perchlorate, 119616-68-1; **12**, 119616-63-6; **13**, 119616-64-7; **14a**, 119530-37-9; **14a**·picrate, 119616-69-2; **14b**, 119530-38-0; **14b**·picrate, 119616-70-5; **14c**, 119530-39-1; **14c**·picrate, 119616-71-6; **14d**, 119530-40-4; **14d**·picrate, 119616-72-7; **15a**, 119530-41-5; **15a**·picrate, 119616-73-8; **15b**, 119567-32-7; **15c**, 119530-42-6; **15c**·picrate, 119616-74-9; **15d**, 119530-43-7; **16a**, 119530-44-8; **16a**·perchlorate, 119616-75-0; **16b**, 119530-45-9; **16b**·perchlorate, 119616-76-1; **17a**, 119530-46-0; **17a**·perchlorate, 119616-77-2; **17b**, 119530-47-1; **17b**·oxalate, 119616-78-3; **17c**, 119530-48-2; **17c**·picrate, 119616-79-4; **17d**, 119530-49-3; **17d**·oxalate, 119616-80-7; **18a**, 119530-50-6; **18a**·picrate, 119616-81-8; **18b**, 119530-51-7; **18b**·picrate, 119617-88-8; **18c**, 119530-52-8; **18c**·picrate, 119617-89-9; **18d**, 119530-53-9; **18d**·picrate, 119616-82-9; **19a**, 119530-54-0; **19a**·oxalate, 119616-83-0; **19b**, 119530-55-1; **19b**·oxalate, 119616-84-1; **20a**, 113528-14-6; **20a**·oxalate, 119616-85-2; **20b**, 113528-15-7; **20b**·oxalate, 119616-86-3; **20c**, 113528-18-0; **20c**·oxalate, 119616-87-4; **20d**, 113528-19-1; **20d**·oxalate, 119616-88-5; **21a**, 113528-16-8; **21a**·oxalate, 119616-89-6; **21b**, 113528-17-9; **21b**·oxalate, 119616-90-9; **21c**, 113540-43-5; **21c**·oxalate, 119617-90-2; **21d**, 113528-20-4; **21d**·oxalate, 119616-91-0; ethyl 3-(2′,3′-dimethoxyphenyl)propionate, 63307-08-4; ethyl 3-(3′,4′-dimethoxyphenyl)propionate, 5462-13-5; methyl 2-(bromomethyl)acrylate, 4224-69-5; propylamine, 107-10-8.

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Synthesis and Pharmacological Evaluation of 4,4-Disubstituted Piperidines

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A new class of piperidine derivatives is added to the increasing family of compounds related to fentanyl and carfentanil. Herein, we describe the synthesis and pharmacology of a number of 1-(arylethyl)-4-(acylamino)-4-[(acyloxy)-methyl]piperidines such as **9**, **15**, and **23**. As expected, many of these congeners of fentanyl are extremely potent narcotic agonists. The aim of the study was to identify short-acting analgesic agents (i.e. less than 6 min in the mouse hot-plate assay) for possible use in the surgical theater. Many of the drugs proved to be of intermediate and long duration (i.e. 6–15 min and >15 min, respectively). In addition to analgesic activity, many of the compounds exhibited anesthetic properties as well. The structure–activity relationship for these entities is presented and discussed.

The accentuated interest in the piperidine class of opiate agonists continues to be expressed in the pharmaceutical community; the synthesis and biological properties of these agents have been the subject of ongoing investigations in these laboratories as well. Our focus has been directed toward the preparation of more complex molecular derivatives related to fentanyl, sufentanil, and carfentanil that would exhibit fewer deleterious side effects. The prototype fentanyl[1] was discovered some 25 years ago in the laboratories of Janssen et al.[2] and has been the major

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