**(2*S*,5*R*)-*trans*-2-Methyl-5-[(dimethylamino)methyl]-1,3-oxathiolane Methiodide [(-)-10].** An excess of MeI (1 mL) was added to a solution of (-)-**9** in anhydrous ether (0.5 g, 3 mmol, in 20 mL) and the mixture kept at room temperature overnight. The white solid obtained was crystallized from ethanol: yield 90%; mp 141-142 °C (lit.[5,16] mp 152-153 °C for the racemate); $[\alpha]^{20}_D$ -18.3° (EtOH); CD (EtOH) λ 245 nm, Δε -0.506; NMR ($Me_2SO$-$d_6$) δ 1.53 (d, 3, 2-$CH_3$), 2.4-4.0 (m, 4, 4-$H_2$ and 5-$CH_2$), 3.25 (s, 9, $N^+(CH_3)_3$), 4.95 (t, t, 1, 5 H), 5.48 (q, 1, 2 H).

In the same way, starting from (+)-**9**, **(2*R*,5*S*)-*trans*-2-methyl-5-[(dimethylamino)methyl]-1,3-oxathiolane methiodide [(+)-10]** was obtained: mp 140-142 °C; $[\alpha]^{20}_D$ +17.7° (EtOH); CD (EtOH) λ 245 nm, Δε +0.491. It shows the same IR and NMR spectra as the enantiomer.

**2-Methyl-1,3-oxathiolane-5-carboxylic Acid (11).** Racemic **5** (6 g, 40 mmol) was dissolved in 25 mL of 2 N NaOH and the resultant mixture refluxed for 2 h. Acidification of the cold solution with 2 N HCl and ether extraction gave 5 g of an oil that is suitable pure for the following reaction: IR (neat) ν 3500-2300 (OH), 1750 (CO) $cm^{-1}$; NMR ($CDCl_3$) δ 1.58 and 1.68 (d, 3, 2-$CH_3$, trans/cis isomers in 4:1 ratio), 3.36 (d, 2, 4-$H_2$), 4.56 and 4.94 (t, 1, 5 H, trans/cis isomers, $J_{trans}$ = 6 and $J_{cis}$ = 7 Hz), 5.46 (q, 1, 2 H). According to the NMR spectrum the pure *cis*-**5** had isomerized to 4:1 mixture of *trans*/*cis*-**11**.

**Pharmacology. Guinea Pig Ileum.** Male guinea pigs (200-300 g) were killed by cervical dislocation. Segments of ileum 1.5-2.0 cm long were carefully removed and suspended in a 10 mL of organ bath containing a solution of the following composition (mM): NaCl, 137; $NaHCO_3$, 12; KCl, 2.7; $MgSO_4$, 1; $NaHPO_4$, 0.4; $CaCl_2$, 1.8; glucose, 5 (which was kept at 37 °C and aerated with $O_2$ containing 5% $CO_2$). Contractions were recorded isotonically at a loading tension of 1 g on an electromechanical transducer connected to a Gemini II poligraph. After equilibration for 30 min, cumulative concentration responses were obtained, taking care not to reach supramaximal concentration in order to avoid desensitization. A full dose-response curve was then determined.

**Frog Rectus Abdominis.** The rectus abdominis muscle of frogs weighting 10-20 g was set up at room temperature in a 5-mL bath containing Clark frog Ringer solution of the following composition (mM): NaCl, 111; KCl, 1.88; $CaCl_2$, 1.08; $NaHPO_4$, 0.08; $NaHCO_3$, 2.38; glucose, 11.1 (which was aereated with oxygen as described by the Edimburgh Group).[22] Contractions were recorded on a Gemini II poligraph. Cumulative dose-response curves were established after a 1-h period at which the tissue was allowed to stabilize.

**Acknowledgment.** We thank Cristina Bellucci and Maria Scarlattini, who is on leave from the CNR Fisiologia Clinica, Pisa, for their excellent technical assistence.

**Registry No.** (+)-**1**, 102046-04-8; (-)-**1**, 103066-66-6; (±)-**2**, 103004-06-4; (±)-**2**·oxalate, 103004-07-5; (+)-**2**·(+)-di-*O*,*O*′-*p*-toluyltartaric acid, 103066-63-3; (-)-**2**·(-)-di-*O*,*O*′-*p*-toluyltartaric acid, 103066-65-5; (+)-**2**, 103066-62-2; (-)-**2**, 103066-64-4; (*S*)-**3** (S-benzyl)·brucine, 103004-08-6; (R)-**3** (S-benzyl)·brucine, 30134-78-2; (*S*)-**3** (S-benzyl), 30134-77-1; (*R*)-**3** (S-benzyl), 30134-76-0; (+)-(*S*)-**3**, 30163-03-2; (-)-(*R*)-**3**, 30163-02-1; (+)-(*S*)-**4**, 103004-09-7; (-)-(*R*)-**4**, 103004-10-0; (±)-**5**, 103066-74-6; (+)-**5**, 103066-69-9; (-)-**5**, 103004-11-1; (+)-**6**, 103066-68-8; (-)-**6**, 103066-67-7; (+)-**7**, 103004-12-2; (-)-**7**, 103066-71-3; (+)-**8**, 103066-72-4; (-)-**8**, 103066-70-2; (±)-**9**, 103004-13-3; (+)-**9**, 103129-06-2; (-)-**9**, 103066-73-5; (+)-**10**, 103066-76-8; (-)-**10**, 103066-75-7; (±)-*cis*-**11**, 103004-14-4; (±)-*trans*-**11**, 103004-15-5; $C_6H_5CH_2SCH_2CH(OH)CO_2H$, 30134-75-9.

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# Synthesis and Dopaminergic Activity of Some Halogenated Mono- and Dihydroxylated 2-Aminotetralins

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In a series of 7,8-dihydroxy-1-phenyltetrahydro-3-benzazepine dopamine receptor agonists introduction of a chloro or fluoro substituent into the 6-position increases dopaminergic potency. Also, in this series replacement of the 7-hydroxyl group with a halogen results in inversion of activity from dopamine receptor agonist to antagonist. The present study was aimed at exploring the possibility that the structure-activity observations in the 3-benzazepine series of dopaminergic agents might be extrapolated to another class of dopamine receptor agonists, the 2-aminotetralins. Thus, a series of chloro- and fluoro-substituted mono- and dihydroxylated 2-aminotetralins was prepared and evaluated for dopaminergic properties in D-1 and D-2 receptor-related tests. Introduction of a chloro substituent into the 8-position of the prototype of this series, i.e. 2-amino-6,7-dihydroxytetralin (ADTN), resulted in a compound with a high degree of selectivity for the D-1 subpopulation of dopamine receptors; it was equally or more potent than ADTN in the D-1 receptor-related tests with greatly decreased effectiveness in the tests involving D-2 receptors. A similar effect was observed with 8-fluoro-ADTN; however, the *N*-(4-hydroxyphenethyl)-*N*-propyl derivative **4g** of the 8-chloro-substituted ADTN showed marked D-2 binding affinity. Conversely, introduction of a chloro substituent into the 5-position of ADTN markedly decreased D-1 receptor affinity and efficacy. This effect was not seen with the related 5-fluoro derivative, suggesting D-1 receptors are more sensitive to bulk in the 5-position of ADTN than are the D-2 receptors. Replacement of either the 6- or 7-hydroxyl groups of ADTN with a chloro or fluoro substituent, in contrast, did not parallel the response seen in the benzazepine series (i.e., the compounds uniformly demonstrated less receptor affinity and did not have dopamine receptor antagonist activity); however, the decrease in agonist potency was less marked in the case of 2-amino-6-fluoro-7-hydroxytetralins than in the chlorinated monohydroxyaminotetralins. Thus, a parallelism in structure-activity relationships in the benzazepine and aminotetralin series of dopamine receptor agonists was not observed. The differences may reflect altered modes of receptor binding in the two series.

2-Amino-5,6-dihydroxytetralin (A-5,6-DTN, **1a**)[1-5] and its 6,7-dihydroxy isomer (ADTN, **1b**)[2-10] have significant dopamine-like activity in a number of pharmacological and biochemical test systems that measure responses resulting

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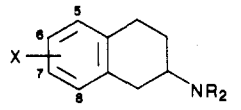
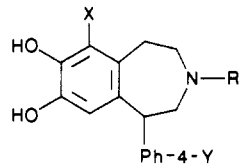
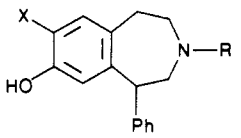
from activation of D-1, D-2[11] or $DA_1$, $DA_2$[12] receptor subpopulations. The monohydroxylated 2-aminotetralins have also been the subject of extensive investigation. In various binding studies dopamine receptor affinity is in the order 7-OH (**1c**) > 5-OH (**1d**) > 6-OH (**1e**).[13-16] The 8-monohydroxylated derivative **1f** has little activity on dopamine receptors;[13] however, its *N*,*N*-di-*n*-propyl derivative **1g** is a potent agonist of central serotonin receptors.[17,18]



**1a**: X = 5,6-$(OH)_2$; R = H
**b**: X = 6,7-$(OH)_2$; R = H
**c**: X = 7-OH; R = H
**d**: X = 5-OH; R = H
**e**: X = 6-OH; R = H
**f**: X = 8-OH; R = H
**g**: X = 8-OH; R = *n*-$C_3H_7$



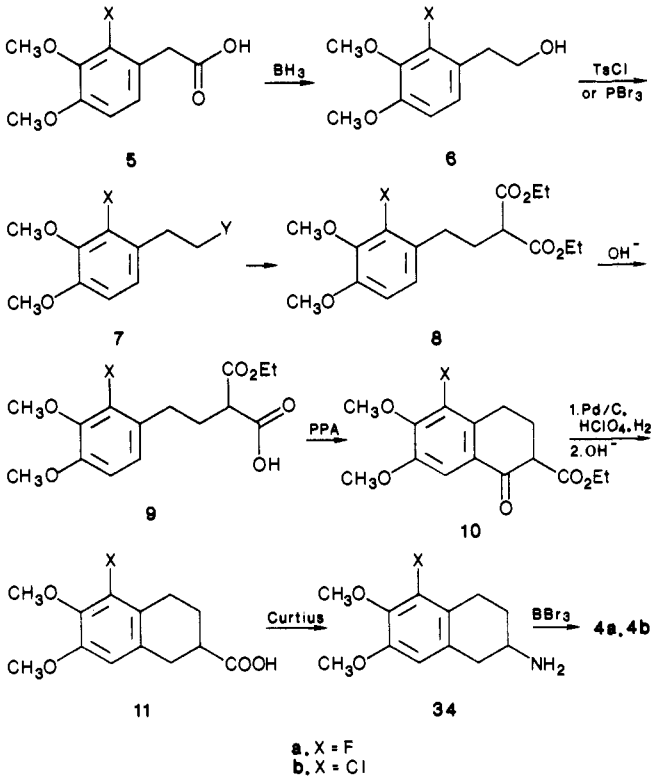
**2a**: R = X = Y = H
**b**: R = H; X = Cl; Y = OH
**c**: R = $CH_2CH{=}CH_2$; X = Cl; Y = OH
**d**: R = H; X = F; Y = OH



**3a**: R = $CH_3$; X = Cl
**b**: R = H; X = Cl
**c**: R = $CH_3$; X = Br

In another series of dopamine receptor agonists, the tetrahydro-3-benzazepines, e.g. **2a**,[19-25] introduction of a halogen, particularly a chloro, substituent into the catecholic system markedly affects dopaminergic potency. Thus, **2b** (fenoldopam, SK&F 82526)[26-29] and **2c**[24,30,31] are

**Scheme I**



**a**, X = F
**b**, X = Cl

**Scheme II**

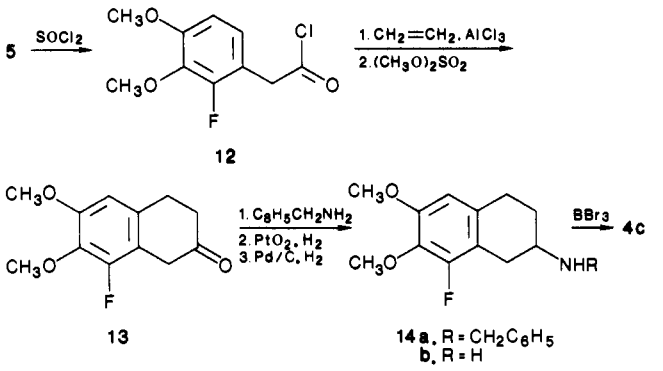



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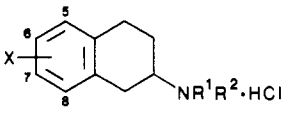
**Table I.** Halogenated Mono- and Dihydroxylated 2-Aminotetralins




4

| no. | X | $R^1$ | $R^2$ | starting[a] matl. | mp, °C | yield, % | recryst solvent | formula[b] |
|---|---|---|---|---|---|---|---|---|
| **4a** | 5-F, 6,7-$(OH)_2$ | H | H | **11a**[c] | 269–270 dec | 94 | MeOH–EtOAc | $C_{10}H_{12}FNO_2$·HBr |
| **4b** | 5-Cl, 6,7-$(OH)_2$ | H | H | **11b**[c] | 250 dec | 98 | MeOH–EtOAc | $C_{10}H_{12}ClNO_2$·HBr |
| **4c** | 8-F, 6,7-$(OH)_2$ | H | H | **14b**[c] | 225–229 | 75 | MeOH–EtOAc | $C_{10}H_{12}FNO_2$·HBr |
| **4d** | 8-Cl, 6,7-$(OH)_2$ | H | H | **18**[c] | 253–256 dec | 90 | MeOH–EtOAc | $C_{10}H_{12}ClNO_2$·HBr |
| **4e** | 8-Cl, 6,7-$(OH)_2$ | *n*-Pr | *n*-Pr | **19**[c] | 190–191 | 96 | MeOH–EtOAc | $C_{16}H_{24}ClNO_2$·HBr[d] |
| **4f** | 8-Cl, 6,7-$(OH)_2$ | $(CH_2)_2$Ph-4-OH | H | **20b**[c] | 240–241 dec | 100 | MeOH | $C_{18}H_{20}ClNO_3$·HBr |
| **4g** | 8-Cl, 6,7-$(OH)_2$ | $(CH_2)_2$Ph-4-OH | *n*-Pr | **21**[c] | 195–200 | 50 | EtOH | $C_{21}H_{26}ClNO_3$·HBr[e] |
| **4h** | 6-F, 7-OH | H | H | **26a** | 264–270 dec | 63 | MeOH–EtOAc | $C_{10}H_{12}FNO$·HBr |
| **4i** | 6-F, 7-OH | $CH_3$ | $CH_3$ | **27a** | 237–241 | 76 | MeOH–EtOH | $C_{12}H_{16}FNO$·HBr[f] |
| **4j** | 6-F, 7-OH | *n*-Pr | *n*-Pr | **27b** | 221–223 | 11 | MeOH–$Et_2O$[g] | $C_{16}H_{24}FNO$·HCl[h] |
| **4k** | 6-F, 7-OH | $NR^1R^2 = CH_2N(n\text{-}Pr)_2$ | | **29**[c] | 198–200 | 70 | 2-PrOH–MeOH–$Et_2O$ | $C_{17}H_{26}FNO$·HBr |
| **4l** | 6-Cl, 7-OH | H | H | **34c** | >265 | 56 | MeOH–$Et_2O$ | $C_{10}H_{12}ClNO$·HBr |
| **4m** | 6-Cl, 7-OH | $CH_3$ | $CH_3$ | **34d** | 246–247 | 73 | MeOH–$Et_2O$ | $C_{12}H_{16}ClNO$·HBr |
| **4n** | 6-Cl, 7-OH | *n*-Pr | *n*-Pr | **34e** | 227 | 83 | MeOH–$Et_2O$ | $C_{16}H_{24}ClNO$·HBr |
| **4o** | 6,8-$Cl_2$, 7-OH | H | H | **34f** | >250 | 85 | MeOH–MeCN | $C_{10}H_{11}Cl_2NO$·HBr[e] |
| **4p** | 6,8-$Cl_2$, 7-OH | $CH_3$ | $CH_3$ | **34g** | >265 | 91 | MeOH[i] | $C_{12}H_{15}Cl_2NO$·HBr[j] |
| **4q** | 6,8-$Cl_2$, 7-OH | *n*-Pr | *n*-Pr | **34h** | 246 | 77 | MeOH–$Et_2O$ | $C_{16}H_{23}Cl_2NO$·HBr |
| **4r**[k] | 5-Cl, 6-OH | H | H | **34i** | >275 | 34 | MeOH–MeCN | $C_{10}H_{12}ClNO$·HBr |
| **4s** | 5-Cl, 6-OH | $CH_3$ | $CH_3$ | **34j** | 257–258 | 69 | MeOH–$Et_2O$ | $C_{12}H_{16}ClNO$·HBr[h] |
| **4t**[k] | 5-Cl, 6-OH | *n*-Pr | *n*-Pr | **34k** | 230–232 | 85 | MeOH–$Et_2O$ | $C_{16}H_{24}ClNO$·HBr[j] |
| **4u** | 7-Cl, 6-OH | H | H | **34l** | >265 | 61 | MeOH–$Et_2O$ | $C_{10}H_{12}ClNO$·HBr |
| **4v** | 7-Cl, 6-OH | $CH_3$ | $CH_3$ | **34m** | 231–232 | 87 | MeOH–$Et_2O$ | $C_{12}H_{16}ClNO$·HBr[h] |
| **4w** | 7-Cl, 6-OH | *n*-Pr | *n*-Pr | **34n** | 190–192 | 81 | MeOH–$Et_2O$ | $C_{16}H_{24}ClNO$·HBr |
| dopamine | 2-(3,4-dihydroxyphenyl)ethylamine | | | | | | | |
| ADTN | 6,7-$(OH)_2$ | H | H | | | | | |

[a] Compounds were prepared by HBr cleavage of the indicated corresponding methoxy derivative by general method B (Experimental Section), unless indicated otherwise. [b] All compounds analyzed satisfactorily for C, H, N. [c] Prepared by general method 2, Experimental Section. [d] Anal. for 0.75 $H_2O$. [e] Anal. for 0.5 $H_2O$. [f] Anal. for 0.4 $H_2O$. [g] Crude HBr salt was purified by chromatography on $SiO_2$ with gradient of 0.5 to 4.5% MeOH in $CH_2Cl_2$ to give base that was converted to HCl salt. [h] Anal. for 0.25 $H_2O$. [i] Compound purified by trituration with MeOH. [j] Analyzed satisfactorily for Cl. [k] References 60–62.

more potent activators of dopamine receptors than is the prototype **2a**. Substitution of position 6 of **2a** with fluorine to give **2d** likewise results in a potent dopaminomimetic with unique pharmacological actions.[31] Equally of interest, replacement of the 7-hydroxyl group of **2a**, or even more strikingly its *N*-methyl derivative, with either a chloro or bromo substituent, i.e. to afford **3a** (SCH 23390),[32-39] **3b** (SK&F 83509),[34] or **3c** (SK&F 83566),[40] results in compounds that are the most potent and selective antagonists of the D-1, or $DA_1$, subpopulation of dopamine receptors presently known.

Consideration of the potent dopaminergic activity of the mono- and dihydroxylated 2-aminotetralins, coupled with the striking effect of halogen substitution in the benzazepine class of dopamine receptor agonists, led us to study the dopaminergic effects of chloro and fluoro substitution and hydroxyl replacement in the aminotetralins. The synthesis and results of pharmacological and biochemical studies of these halogenated mono- and dihydroxylated 2-aminotetralins (**4**, Table I) are the subject of this paper.

**Chemistry.** Synthesis of a series of halogenated mono- and dihydroxylated 2-aminotetralins (**4**, Table I) was accomplished as outlined in Schemes I–VI.

The preparation of 5-fluoro (**4a**) and 5-chloro (**4b**) derivatives of ADTN is illustrated in Scheme I. Accordingly, (2-fluoro-3,4-dimethoxyphenyl)acetic acid (**5a**), prepared by hydrolysis of the corresponding nitrile,[41] and (2-chloro-3,4-dimethoxyphenyl)acetic acid (**5b**)[42] were converted to the ethyl hydrogen malonates **9a** and **9b** by the general procedure of Eistetter and Wolf.[43] These malonates cyclized to 1-oxo-1,2,3,4-tetrahydronaphthoates **10a** and **10b** upon treatment with polyphosphate ester (PPE). Subsequent hydrogenolysis and hydrolysis gave tetrahydronaphthoic acids **11a** and **11b** that were converted to **4a** and **4b** via a modified Curtius reaction[44] and subsequent

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(43) Eistetter, K.; Wolf, H. P. O. *J. Med. Chem.* **1982**, *25*, 109.

**Scheme III**

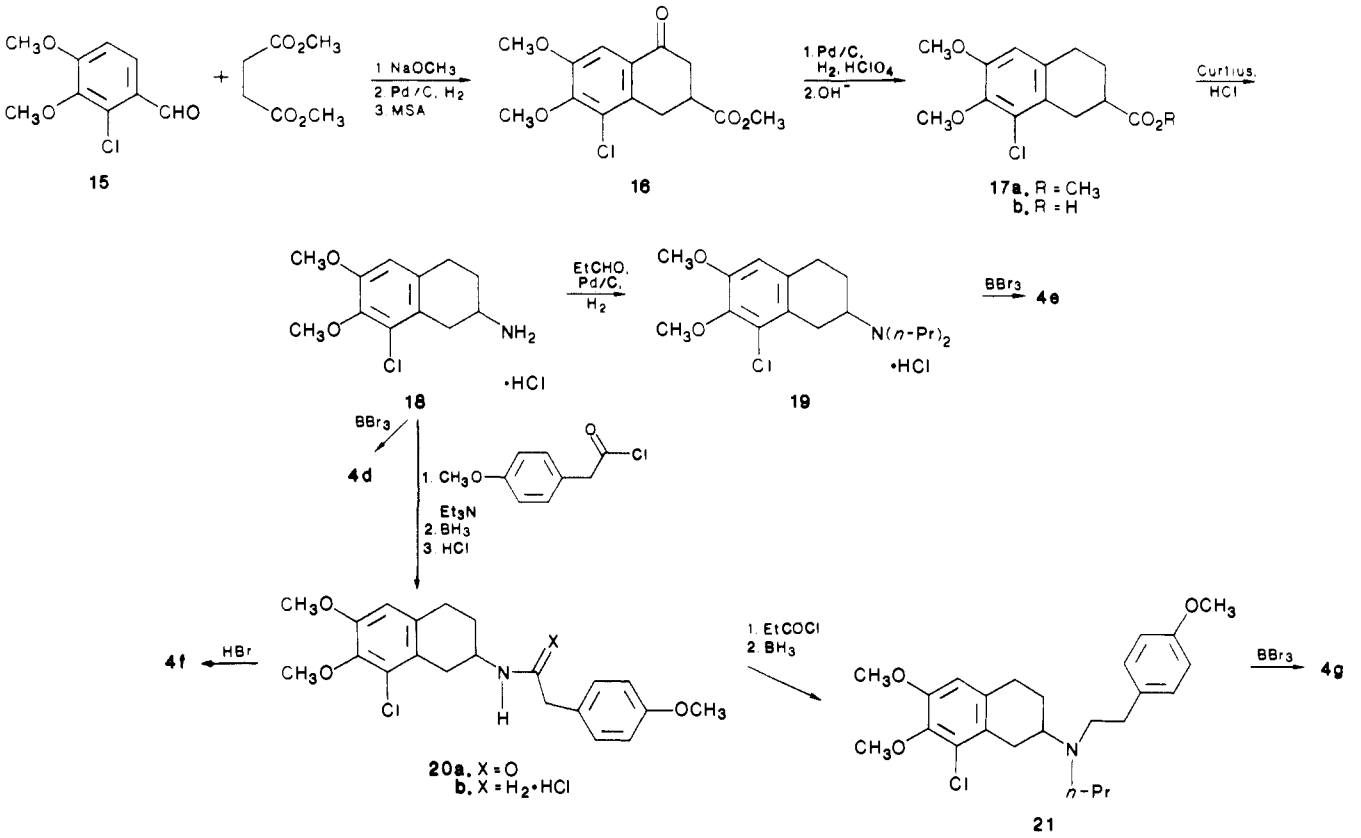
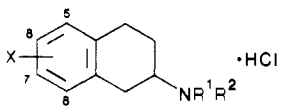



**Table II.** Halogenated Mono- and Dimethoxylated 2-Aminotetralin Hydrochlorides



34

| no. | X | $R^1$ | $R^2$ | starting compd | mp, °C | yield, % | recryst solvent | formula[a] |
|---|---|---|---|---|---|---|---|---|
| **34a** | 5-F, 6,7-$(CH_3O)_2$ | H | H | **11a** | 237–239 | 97 | MeOH–$Et_2O$ | $C_{12}H_{16}FNO_2$·HCl |
| **34b** | 5-Cl, 6,7-$(CH_3O)_2$ | H | H | **11b** | 242–244 | 48 | MeOH–EtOAc | $C_{12}H_{16}ClNO_2$·HCl |
| **34c** | 6-Cl, 7-$CH_3O$ | H | H | **33** | >255 | 47 | MeOH–MeCN | $C_{11}H_{14}ClNO$·HCl[b] |
| **34d** | 6-Cl, 7-$CH_3O$ | $CH_3$ | $CH_3$ | **33** | 224–225 | 44 | MeOH–$Et_2O$ | $C_{13}H_{18}ClNO$·HCl |
| **34e** | 6-Cl, 7-$CH_3O$ | *n*-Pr | *n*-Pr | **34c** | 240 | 29 | MeOH–$Et_2O$ | $C_{17}H_{26}ClNO$·HCl |
| **34f** | 6,8-$Cl_2$, 7-$CH_3O$ | H | H | **35b** | >250 | 53 | EtOH | $C_{11}H_{13}Cl_2NO$·HCl |
| **34g** | 6,8-$Cl_2$, 7-$CH_3O$ | $CH_3$ | $CH_3$ | **34f** | 197–199 | 65 | 2-PrOH | $C_{13}H_{17}Cl_2NO$·HCl |
| **34h** | 6,8-$Cl_2$, 7-$CH_3O$ | *n*-Pr | *n*-Pr | **34f** | 188–189 | 60 | 2-PrOH | $C_{17}H_{25}Cl_2NO$·HCl[b] |
| **34i** | 5-Cl, 6-$CH_3O$ | H | H | **38a** | >270 | 28 | MeOH | $C_{11}H_{14}ClNO$·HCl |
| **34j** | 5-Cl, 6-$CH_3O$ | $CH_3$ | $CH_3$ | **34i** | 259–260 | 45 | MeOH–$Et_2O$ | $C_{13}H_{18}ClNO$·HCl |
| **34k** | 5-Cl, 6-$CH_3O$ | *n*-Pr | *n*-Pr | **34i** | 194–197 | 53 | 2-PrOH | $C_{17}H_{26}ClNO$·HCl[c] |
| **34l** | 7-Cl, 6-$CH_3O$ | H | H | **38b** | >280 | 25 | MeOH–MeCN | $C_{11}H_{14}ClNO$·HCl |
| **34m** | 7-Cl, 6-$CH_3O$ | $CH_3$ | $CH_3$ | **38b** | >270 | 60 | MeOH–$Et_2O$ | $C_{13}H_{18}ClNO$·HCl |
| **34n** | 7-Cl, 6-$CH_3O$ | *n*-Pr | *n*-Pr | **34l** | 216–218 | 58 | MeOH–$Et_2O$ | $C_{17}H_{26}ClNO$·HCl |

[a] All compounds analyzed satisfactorily for C, H, N. [b] Analyzed satisfactorily for Cl. [c] Anal. for 0.25 $H_2O$.

$BBr_3$ cleavage[45] of the methyl ethers (see Table II).

2-Amino-8-fluoro-6,7-dihydroxytetralin (**4c**) was derived from **5a**, which was transformed to **13** via the Burckhalter–Campbell reaction,[46] followed by reductive amination and methoxyl scission as shown in Scheme II.

As indicated in Scheme III, Stobbe condensation of 2-chloroveratraldehyde (**15**)[47] with dimethyl succinate, followed by reduction and methanesulfonic acid (MSA) cyclization, gave **16**, which upon sequential reduction, ester hydrolysis, and Curtius[44] reaction gave **18**. Cleavage of the 6,7-dimethoxyl substituents of **18** afforded **4d**. Reductive dipropylation of **18** with excess propionaldehyde followed by ether cleavage produced the *N,N*-di-*n*-propyl derivative **4e**. The other N-substituted derivatives of **4d**, i.e. **4f** and **4g**, were obtained by conventional methods as outlined.

Preparation of the 2-amino-6-fluoro-7-hydroxytetralins **4h–4j**, as well as the (dipropylamino)methyl homologue

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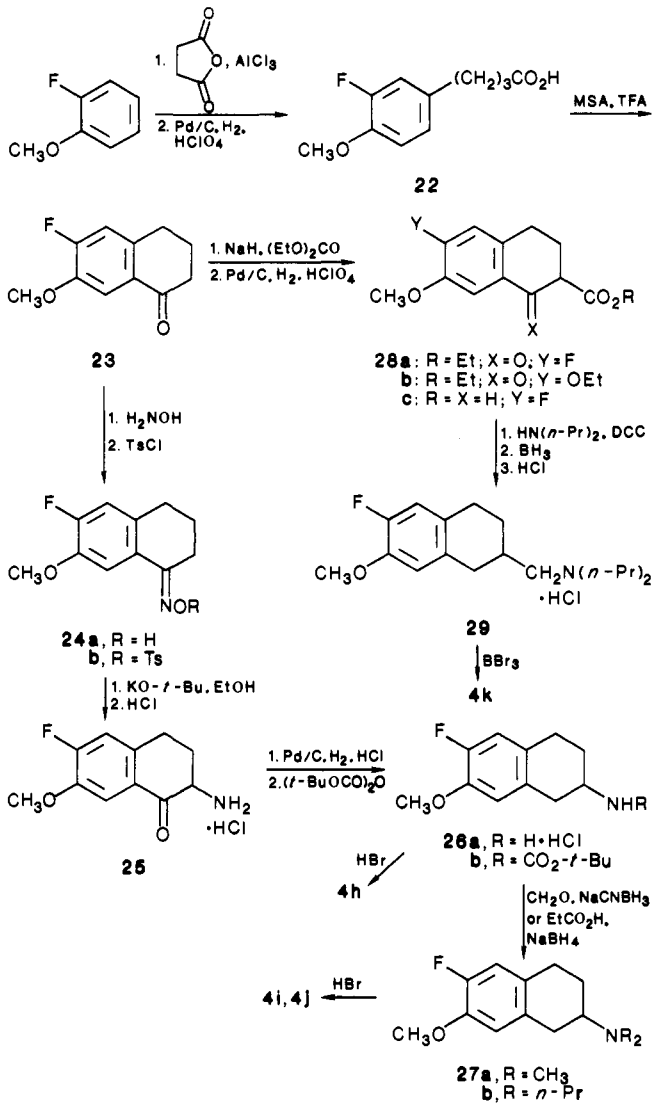
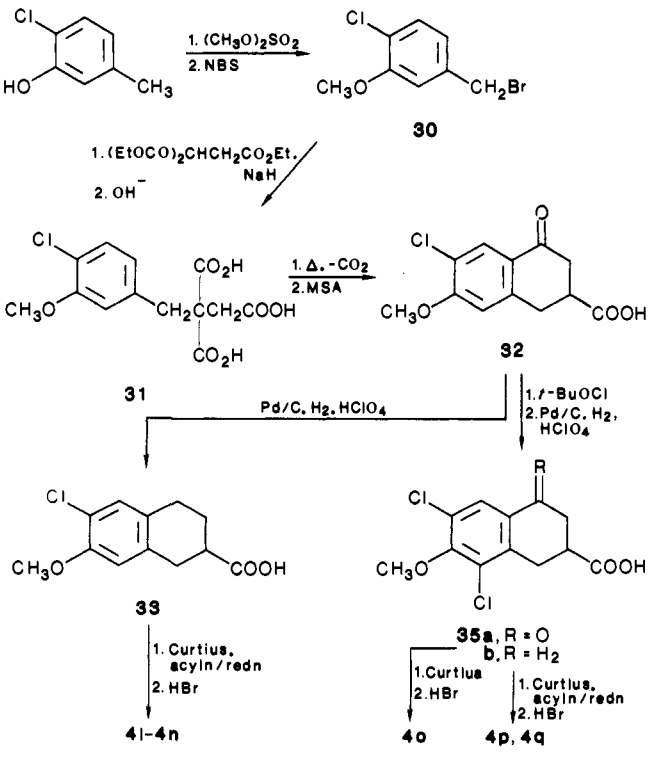
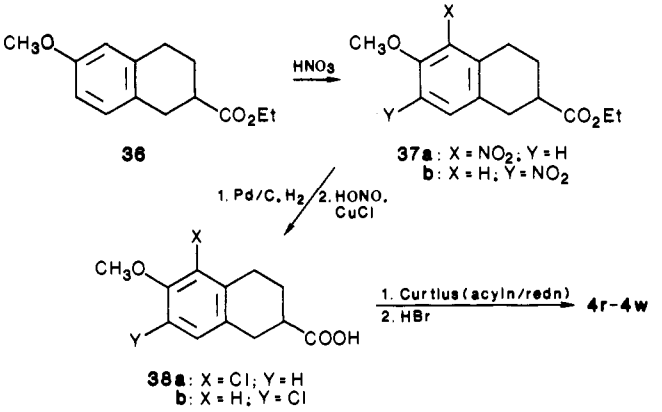
**Scheme IV**




**Scheme V**




**Scheme VI**




**4k**, was achieved as shown in Scheme IV. Thus, the butyric acid **22**, obtained by Friedel–Crafts acylation of 2-fluoroanisole with succinic anhydride followed by reduction of the resulting succinic acid, was cyclized[48,49] to a single product, the tetralone **23**, whose structure was established by $^1$H NMR (two doublets for ortho and meta H–F coupling with the expected coupling constants of 11.2 and 8.8 Hz, respectively). The tetralone **23** was converted to the aminotetralone **25** by Neber rearrangement[50,51] of the intermediate oximino tosylate **24b**. Hydrogenolysis of **25** to **26a** was best accomplished with palladium-on-carbon catalyst in an acetic acid–aqueous hydrochloric acid solution. Purification of **26a** was accomplished via the *tert*-butyl carbamate **26b**, which was reconverted to **26a** with concentrated hydrobromic acid. The *N*,*N*-dimethyl **27a** and *N*,*N*-dipropyl **27b** derivatives of **26a** were obtained by reductive alkylation.[48,52,53] Hydrobromic acid cleavage of **26a**, **27a**, and **27b** produced **4h–4j**, respectively. Carbethoxylation of **23** afforded **28a** (85%) along with 15% of **28b** that resulted from ethoxide displacement of the 6-fluoro substituent. Catalytic hydrogenation of the ester **28a** under conventional conditions was incomplete; however, the corresponding carboxylic acid was readily hydrogenolyzed to afford **28c**. Conversion of **28c** to its *N*,*N*-di-*n*-propyl carboxamide, followed by borane reduction[54] and $BBr_3$ cleavage of the 7-methoxy group gave the (2-aminomethyl)tetralin **4k**.

The synthetic route employed for derivation of **4l–4q** is outlined in Scheme V; it is patterned after the sequence described by Cannon et al.[48] In this fashion 2-chloro-5-methylphenol was converted via **30** and **31** to **32** and **33**, which by various modifications of the Curtius reaction[44,55–59] followed by several alkylation/reduction pro-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(57) Smith, P. A. S. *Org. React.* **1946**, *3*, 337.
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cesses[51-54] and HBr cleavage of the appropriate methoxylated derivatives **34** (see Table II) produced **4l**, **4m**, and **4n**. The intermediate oxonaphthoic acid **32** was chlorinated to afford an intermediate dichlorinated derivative **35a**, whose structure was confirmed by $^1$H NMR (singlet one proton signal at $\delta$ 7.95). Hydrogenolysis of **35a** gave **35b**, which was subjected to Curtius reaction, followed by appropriate alkylation/reduction and methoxy cleavage of the intermediate **34** to afford **4o**, **4p**, and **4q**.

2-Amino-5-chloro-6-hydroxytetralins **4r–4t**[60-62] and the isomeric 7-chloro-6-hydroxy derivatives **4u–4w** were synthesized as outlined in Scheme VI. Accordingly, nitration of ethyl 1,2,3,4-tetrahydro-6-methoxynaphthoate (**36**)[63] afforded a mixture of 5- (**37a**) and 7-nitro (**37b**) derivatives, whose identity was established by $^1$H NMR. The 5-nitro isomer had single proton doublets at $\delta$ 6.8 and 7.1, corresponding to the protons in positions 7 and 8, respectively. The 7-nitro isomer had one proton singlets at $\delta$ 6.8 and 7.7 attributable to the protons in positions 5 and 8, respectively. The individual isomers were catalytically hydrogenated, and the resulting amines were converted to the corresponding chloro derivatives **38a** and **38b** by diazotization followed by treatment with CuCl.[64] Curtius reaction and appropriate acylation/reduction gave methoxyl derivatives (Table II) that were cleaved with HBr to provide **4r–4w** (see Table I).

## Results and Discussion

The affinity of halogenated mono- and dihydroxy-2-aminotetralins **4a–4w** (Table III) for D-1 dopamine receptor binding sites was measured in a test involving displacement of [$^3$H]fenoldopam from homogenized rat striatum.[40] Affinity for D-2 receptors was evaluated from the ability of the compounds to displace [$^3$H]spiroperidol from homogenized bovine pituitary.[40] The efficacies of some of the compounds having greatest affinity in the D-1 and D-2 receptor binding studies were examined. A test that measures the ability of a compound to stimulate dopamine-sensitive rat caudate adenylate cyclase or to antagonize the stimulant effect of dopamine in this preparation was used as a measure of D-1 efficacy.[40] Similarly, for selected compounds D-2 efficacy was evaluated in a previously described[65,66] isolated, perfused rabbit ear artery test.

Results obtained with 5- and 8-fluoro and -chloro derivatives **4a–4g** of ADTN are consistent with the conceptual model of the dopamine receptor proposed by McDermed et al.[67] Thus, as has been observed with the 5- and 8-*n*-propyl derivatives[68] of ADTN in a [$^3$H]dopamine displacement test using rat striatal membrane, D-1 dopamine receptor affinity and efficacy comparable to that of ADTN are retained by 2-amino-8-chloro-6,7-dihydroxytetralin (**4d**), whereas the 5-chloro-substituted isomer **4b** had about 20-fold less affinity for the [$^3$H]fenoldopam binding sites and did not stimulate dopamine-sensitive adenylate cyclase to a significant degree. In contrast, **4d** was about one-tenth as effective as ADTN in displacing [$^3$H]spiroperidol from its binding sites and it was only about $^1/_{100}$ as effective in inhibiting the constrictor response of the isolated, perfused rabbit ear artery to nerve stimulation, whereas **4b** was one-half and one-tenth as potent as ADTN in these tests, respectively. These data suggest that 8-chloro, but not 5-chloro, substitution of ADTN results in a relatively selective agonist of the D-1 subpopulation of dopamine receptors. The relatively high degree of D-2 receptor potency produced by the 5-chloro derivative **4b** may suggest bulk tolerance in this subtype of dopamine receptors that is not seen in the D-1 subpopulation. This has not been addressed in previous models of the dopamine receptor(s). Both the 5- and 8-fluoro derivatives, **4a** and **4c**, respectively, were approximately equipotent with ADTN in tests for D-1 receptor affinity and activity. This is in conformity with the hypothetical model[67] of the dopamine receptor if one considers that the bulk of the fluorine substituent is about the same as that of a hydrogen; i.e., the fluoro group does not abut the postulated site of bulk intolerance to prevent access of the molecule to the hypothesized primary binding sites on the receptor. In tests involving D-2 receptors, **4a** and **4c** were similar. Both were less potent than ADTN in displacing [$^3$H]spiroperidol, but they were equally or slightly more potent than the parent in the rabbit ear artery paradigm.

The N-substituted derivatives **4e**, **4f**, and **4g** of 2-amino-8-chloro-6,7-dihydroxytetralin (**4d**), as noted for the N,N-dipropylated derivative of ADTN,[13] had decreased effectiveness in D-1 receptor-related tests whereas they were more potent than **4d** in the D-2 receptor-related tests. This was most strikingly observed with the *N*-propyl-*N*-(*p*-hydroxyphenethyl) derivative **4g**, which was the most potent member of the series as a displacer of [$^3$H]-spiroperidol binding (7-fold more effective than ADTN) but was less than one-tenth as potent as ADTN in the rabbit ear artery test.[69]

2-Amino-6-fluoro-7-hydroxytetralin (**4h**) was about one-fifth as potent as ADTN as a displacer of [$^3$H]fenoldopam binding and about one-third as effective as the prototype in the [$^3$H]spiroperidol displacement test. N,-N-Dimethylation of **4h**, i.e. to give **4i**, and N,N-dipropylation, i.e. to afford **4j**, decreased affinity in the D-1 receptor binding test, but slightly increased it in the D-2 receptor binding procedure. The latter compound was about one-third as potent as ADTN in the rabbit ear artery test. The homologue of **4j**, i.e., the aminomethylated tetralin **4k**, which lacks a dopaminergic phenethylamine pharmacophore,[70] as anticipated, had little or no activity

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(69) The difference in data obtained in the D-2 receptor-related tests, i.e. [$^3$H]spiroperidol displacement and the rabbit ear artery test, may be reflective of a measure of overall (high and low) affinity binding in the former procedure and predominantly high-affinity D-2 receptor binding in the latter. In addition, binding reflects both agonist and antagonist potential, whereas the rabbit ear artery test indicates only agonist activity. Although the rabbit ear artery test also shows a positive response to $\alpha_2$ agonists, aminotetralins described in this paper were demonstrated to have activity at D-2 receptors by their dissociation constants ($K_B$) for (*S*)-sulpiride. These $K_B$ values were consistently between 5 and 50 nM: Flaim, K. E.; Hieble, J. P., unpublished observations.

in either of the binding tests.

Compared to the 2-amino-6-fluoro-7-hydroxytetralins, **4h**, **4i**, and **4j**, the related 2-amino-6-chloro-7-hydroxytetralin (**4l**) was relatively weakly effective in both binding studies, and affinity was decreased further by N,N-dimethylation (**4m**) or N,N-dipropylation (**4n**), although the latter compound had weak activity in the isolated perfused rabbit ear artery preparation. None of the 2-amino-6-chloro-7-hydroxytetralins, i.e. **4l**, **4m**, or **4n**, were significantly effective in stimulating or antagonizing dopamine-sensitive adenylate cyclase. The reason for decreased dopamine receptor affinity of the chlorinated derivatives, **4l**, **4m**, and **4n**, as compared to their fluoro counterparts, **4h**, **4i**, and **4j**, is not certain. For example, it may be the consequence of unfavorable steric effects of the larger chloro substituent, the effects of the halogen substitution on the acidity of the *o*-hyroxyl group, or the result of the fluoro substituent's ability to form hydrogen bonds with appropriate sites on the receptor. The 2-amino-6,8-dichloro-7-hydroxytetralins, **4o**, **4p**, and **4q**, were even less effective than their monochlorinated counterparts as displacers of [$^3$H]fenoldopam and [$^3$H]spiroperidol binding. In addition, the *N,N*-dipropyl derivative **4q** neither stimulated adenylate cyclase nor affected the activation of the enzyme by dopamine.

The 5- (**4r**, **4s**, **4t**) and 7- (**4u**, **4v**, **4w**) chlorinated 6-hydroxy-2-aminotetralins, which lack the dopaminergic *m*-hydroxyphenethylamine pharmacophore[70] (the hydroxyl group is para to the embedded ethylamine chain) were generally weakly effective in the test for displacement of [$^3$H]fenoldopam. Further, the 7-chloro derivatives, **4u**, **4v**, and **4w**, did not stimulate or inhibit dopamine-sensitive adenylate cyclase. The N,N-dipropylated compounds **4t** and **4w** did show significant D-2 receptor related activity. They were about one-fourth as effective as ADTN in displacing [$^3$H]spiroperidol from bovine pituitary homogenate binding sites, and they were 10- to 15-fold less potent than the prototype in the rabbit ear artery test.

In summary, the results of our study of halogenated mono- and dihydroxylated 2-aminotetralins indicate that in contrast to the 3-benzazepine series of dopamine receptor agonists[26-31] introduction of a properly located halogen, i.e. in the 8-position of ADTN, results in a slight increase in affinity for dopaminergic receptors of the D-1 subtype. In addition, 8-chloro substitution of the parent, perhaps as a consequence of increasing the acidity of the *o*-hydroxyl group or by binding to a complementary lipophilic site on the receptor, greatly enhances selectivity for the D-1 vs. D-2 dopamine receptor subpopulation. These observations are in general agreement with hypothetical models suggested for the dopamine receptor(s).[13,67-70] In contrast to the 3-benzazepine series of dopaminergic agents,[32-40] however, replacement of either the 6- or 7-hydroxy group of ADTN or various N-substituted derivatives with a halogen does not change the activity of the compound from dopamine receptor agonist to antagonist. The reason for this difference in structure–activity properties in the two series of dopamine receptor modulators is not readily apparent. Possibly, this difference may result from the tightness with which the two classes bind to D-1 receptors. 1-Phenylbenzazepines bind more tightly to D-1 receptors than do the 2-aminotetralins perhaps as a consequence of the attraction of the properly oriented 1-phenyl group to an accessory site on this receptor subtype.[24] Thus, the $K_{Bind}$ in a test for displacement of [$^3$H]fenoldopam binding to rat caudate homogenate is 5.1 nM for **2a**, the prototype of benzazepine D-1 receptor agonists, whereas for ADTN it is 70 nM. Consequently, the halogenated benzazepine D-1 antagonists, which lack the catecholic system needed for efficacy, may bind tightly to the receptor to prevent the effector event from occurring. In contrast, binding of the halogenated monohydroxylated 2-aminotetralins to the receptors may be insufficiently tight to enable blockade of these receptors.

## Experimental Section

Melting points were determined in open capillary tubes on a Thomas-Hoover Uni-Melt apparatus; they are uncorrected. Elemental analyses were carried out by the Analytical, Physical and Structural Chemistry Department of Smith Kline & French Laboratories. Where analyses are reported by symbols of the elements, results were within 0.4% of the calculated value unless indicated otherwise. IR, NMR, and MS data were determined for all numbered compounds in this section and were evaluated as consistent with the indicated structures. These data are presented only where required for structural assignment. IR spectra were obtained using a Perkin-Elmer 727 IR spectrophotometer. NMR spectra were determined using an Hitachi Perkin-Elmer R-24 spectrometer with $Me_4Si$ as an internal standard. Mass spectra were obtained on an Hitachi Perkin-Elmer 6E spectrometer. TLCs were carried out on Analtech Uniplates, silica gel GF, 250 μm. The acronyms TFA and MSA are used for trifluoroacetic and methanesulfonic acids, respectively.

**Chemistry. General Methods. Methoxyl Cleavage. Method A (Boron Tribromide).**[45] A 0.2 M solution of $BBr_3$ in $CH_2Cl_2$ (100 mL) was added dropwise to a stirred mixture of 20 mmol of the methoxylated or dimethoxylated 2-aminotetralin in 100 mL of $CH_2Cl_2$ at −78 °C. The cooling bath was removed, and the reaction was stirred at ambient temperature for 24 h. After the mixture was cooled in an ice–$H_2O$ bath, 100 mL of MeOH was added dropwise. The resulting solution was again concentrated. The residue was dissolved in 100 mL of MeOH, and the solution was agan concentrated. This procedure was repeated three times, and then the solid residue was recrystallized to give the amine *hydrobromide* (see Table I).

**Method B (Hydrobromic Acid).** A stirred solution of 10 mmol of the appropriate methoxylated 2-aminotetralin derivative and 30 mL of freshly distilled concentrated HBr was heated at 110 °C for 2.5 h. After the solution was concentrated in vacuo to about 10–20 mL, it was cooled to 0–10 °C and the crystalline hydrobromide was filtered and recrystallized from the appropriate solvent (Table I). In some cases the hydrobromide was converted to the free base, chromatographed, and then treated with HCl to give a hydrochloride.

**(2-Fluoro-3,4-dimethoxyphenyl)acetic Acid (5a).** A mixture of 50.4 g (0.26 mol) of (2-fluoro-3,4-dimethoxyphenyl)acetonitrile,[41] KOH (254.7 g, 4.5 mol), 500 mL of EtOH, and 500 mL of $H_2O$ was stirred and refluxed for 20 h. The resulting solution was concentrated to a volume of about 700 mL. After being cooled at 25 °C, the solution was extracted twice with $Et_2O$. The aqueous phase was filtered, and the filtrate was poured slowly into a stirred solution of 450 mL of 12 N HCl in 600 mL of $H_2O$. The resulting suspension was stirred for 1 h at −10 to 0 °C, and then it was filtered. After the solid was washed with $H_2O$, it was dried to give 44.0 g (80%) of colorless crystals, mp 100–101 °C. Anal. ($C_{10}H_{11}FO_4$) C, H.

**(2-Fluoro-3,4-dimethoxyphenyl)ethanol (6a).** To a stirred solution of 52.4 g (0.25 mol) of (2-fluoro-3,4-dimethoxyphenyl)-acetic acid (**5a**) in 500 mL of THF, under Ar, was added dropwise during 1 h 300 mL (0.3 mol) of a 1 M solution of $BH_3$ in THF. After being stirred at 25 °C for 24 h, the reaction mixture was cooled to 0–5 °C and 160 mL of MeOH was added dropwise. The resulting solution was concentrated in vacuo to leave a liquid residue. A solution of this residue in 300 mL of $Et_2O$ was washed twice with a saturated solution of $NaHCO_3$. The ethereal solution was dried ($Na_2SO_4$) and concentrated, and the residue was distilled to give 46.6 g (98%) of a colorless liquid, bp 128–130 °C (0.15 torr). Anal. ($C_{10}H_{13}FO_3$) C, H.

**2-(2-Chloro-3,4-dimethoxyphenyl)ethanol (6b)** was prepared by $BH_3$ reduction of (2-chloro-3,4-dimethoxyphenyl)acetic acid

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(71) Gunter, M. J.; Mander, L. N. *Austr. J. Chem.* **1981**, *34*, 695.

(**5b**)[42] in the same manner as described for the fluoro analogue **5a**. The yield of colorless liquid, bp 128–132 °C (0.2 torr), was 94%. Anal. ($C_{10}H_{13}ClO_3$) C, H.

**2-(2-Fluoro-3,4-dimethoxyphenyl)ethyl Tosylate (7a).**[72] Tosyl chloride (8.1 g, 0.04 mol) was added in small portions to a stirred solution of **6a** (4.2 g, 0.02 mol) in 15 mL of dry pyridine. The resulting suspension was stirred at 5 °C for 16 h, and then 5 mL of $H_2O$ was added slowly. After the mixture was stirred at 5 °C for 1 h, it was diluted with 50 mL of cold $H_2O$. The mixture was extracted with $Et_2O$, and the ethereal extracts were washed with 0.1 N HCl, $H_2O$, and finally a saturated aqueous solution of $NaHCO_3$. The $Et_2O$ solution was dried ($Na_2SO_4$) and concentrated to leave a 6.6 g (89%) of a solid residue, mp 72–73 °C, after trituration with petroleum ether. Anal. ($C_{17}H_{19}FO_5S$) C, H.

**2-(2-Chloro-3,4-dimethoxyphenyl)ethyl Bromide (7b).** $PBr_3$ (3.8 g, 14 mmol) in 30 mL of $Et_2O$ was added to a stirred solution of 6.03 g (28 mmol) of **6b** in 30 mL of $Et_2O$. The solution was refluxed for 1 h, cooled to 5 °C, and *cautiously* poured onto 60 g of crushed ice. After the $Et_2O$ phase was separated and washed successively with a saturated aqueous solution of $NaHCO_3$, $H_2O$, and brine, it was dried ($Na_2SO_4$) and concentrated. The residual liquid was distilled, and the fraction (5.3 g, 68%), bp 112–115 °C (0.15 torr), was collected. Anal. ($C_{10}H_{12}BrClO_2$) C, H.

**Diethyl α-[2-(2-Fluoro-3,4-dimethoxyphenyl)ethyl]-malonate (8a).** Diethyl malonate (13.7 g, 86 mmol) was added dropwise at 20 °C to a stirred suspension of 1.4 g (56 mmol) of NaH in 55 mL of THF under an atmosphere of Ar. To the resulting reaction mixture was added dropwise a solution of 15.2 g (43 mmol) of **7a** in 50 mL of THF. The mixture, under Ar, was stirred and refluxed for 40 h, and then it was concentrated in vacuo. The residue was partitioned between 50 mL of $Et_2O$ and 50 mL of $H_2O$. The layers were separated, and the aqueous phase was extracted with $Et_2O$. After the combined $Et_2O$ extracts were washed with $H_2O$ and brine, they were dried ($Na_2SO_4$) and concentrated. The residue was fractionally distilled to give 9.8 g (67%) of a colorless liquid, bp 175 °C (0.13 torr). Anal. ($C_{17}H_{23}FO_6$) C, H.

**Diethyl α-[2-(2-chloro-3,4-dimethoxyphenyl)ethyl]-malonate (8b)** was prepared from **7b** and diethyl malonate by essentially the same procedure described for preparation **32a** (48 h reflux period). The product (83%) was obtained as a colorless liquid, bp 172 °C (0.15 torr). Anal. ($C_{17}H_{23}ClO_6$) C, H.

**Ethyl Hydrogen α-[2-(2-Fluoro-3,4-dimethoxyphenyl)-ethyl]malonate (9a).** A solution of 1.6 g (28 mmol) of KOH in EtOH was added dropwise, over a period of 1 h, to a stirred solution of 9.6 g (28 mmol) of **8a** in 25 mL of EtOH. After being stirred at ambient temperature for 60 h, the mixture was concentrated in vacuo. The residue was diluted with $H_2O$, and the resulting mixture was extracted with $Et_2O$. The aqueous phase was acidified with 2.5 N HCl, and the mixture was extracted with $Et_2O$. After being washed with $H_2O$ and brine, the $Et_2O$ extract was dried and concentrated in vacuo to give 7.3 g (83%) of a colorless syrup. Anal. ($C_{15}H_{19}FO_6$) C, H.

**Ethyl hydrogen α-[2-(2-chloro-3,4-dimethoxyphenyl)-ethyl]malonate (9b)** was prepared from **8b** by the same procedure described for synthesis of **9a** from **8a**. The product (81%) was obtained as a viscous, colorless liquid; TLC (silica gel GF, 95:5:0.2 $CHCl_3$–$CH_3OH$–HCOOH) gave a single spot, $R_f$ 0.9. It was employed for further reaction without additional purification.

**Ethyl 5-Fluoro-6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthoate (10a).** A solution of 6.7 g (21 mmol) of **9a** in 35 mL of approximately 3 M PPE in $CHCl_3$ was stirred under Ar at ambient temperature for 24 h. The reaction mixture was poured onto 50 g of crushed ice with vigorous stirring. After the layers were separated, the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed successively with $H_2O$, 5% aqueous $NaHCO_3$, $H_2O$, and brine. After being dried ($Na_2SO_4$), the organic extract was concentrated to give 3.1 g of a viscous liquid that solidified on standing at 25 °C. Unreacted **9a** (2.6 g) was recovered from the $NaHCO_3$ extracts. This was treated with PPE as described initially to give an additional 1.9 g of crude product. The combined crude product (4.9 g) was chromatographed by MPLC using a 2.5 × 50 cm column packed with 124 g of 230–400-mesh silica gel and a mobile phase of 3.3 mL of 97% formic acid/L of $CHCl_3$. A total of 54 fractions (15 mL) were collected at a flow rate of 5 mL/min. Fractions 6–34 were combined and concentrated to give 1.8 g of a viscous liquid that crystallized on standing at 25 °C; TLC (silica gel GF, 100:0.2 $CHCl_3$–HCOOH) showed one spot at $R_f$ 0.35. Recrystallization from EtOH gave 1.2 g (20%) of colorless needles, mp 77–79 °C. Anal. ($C_{15}H_{17}FO_5$) C, H.

**Ethyl 5-chloro-6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthoate (10b)** was prepared from **9b** in the same manner as described for the preparation of **10a** from **9a**. In this case, however, the crude product was purified by silica gel column chromatography using $CHCl_3$ for elution. All fractions that gave a single spot at $R_f$ 0.3 (silica gel GF, $CHCl_3$) were combined and concentrated. The residue was crystallized from aqueous EtOH to give colorless crystals (41% yield), mp 79–83 °C. Anal. ($C_{15}H_{17}ClO_5$) C, H.

**5-Fluoro-6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic Acid (11a).** A mixture of 1.9 g (6.3 mmol) of **10a**, 0.4 g of 10% Pd/C catalyst, 0.4 mL of 70% $HClO_4$, and 25 mL of HOAc was hydrogenated for 4 h on a Parr apparatus at 25 °C and an initial $H_2$ pressure of 45 psi. NaOAc (0.4 g) was added, and the mixture was stirred for 5 min. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was taken into $Et_2O$. After the ethereal solution was washed with a saturated aqueous solution of $NaHCO_3$, it was dried and concentrated to give 1.7 g (96%) of crude *ethyl 5-fluoro-6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate*. To this ester (1.5 g, 5.4 mmol) in 10 mL of MeOH was added a solution of 0.6 g (11 mmol) of KOH in 10 mL of $H_2O$. The resulting mixture was stirred and refluxed for 2 h. After the MeOH was distilled from the reaction mixture, the remaining solution was diluted with 50 mL of $H_2O$. The resulting solution was washed with $Et_2O$, and then it was acidified with 2.5 N HCl to give 1.3 g (93%) a crystalline product, mp 178–181 °C. Anal. ($C_{13}H_{15}FO_4$) C, H.

**5-Chloro-6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic acid (11b)** was prepared from **10b** in the same fashion as that described for conversion of **10a** to **11a**. Crude intermediate *ethyl 5-chloro-6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate* (96% yield) was obtained as colorless crystals, mp 56–57 °C. The acid **35b** (97% yield) was a colorless solid, mp 172–174 °C. Anal. $C_{13}H_{15}ClO_4$) C, H.

**2-Amino-5-fluoro-6,7-dimethoxytetralin Hydrochloride (34a).**[42] A suspension of 1.2 g (4.7 mmol) of **11a** in 2 mL of $SOCl_2$ was heated at 60 °C for 4 h. The resulting solution was concentrated and stripped twice with toluene. The resulting acid chloride was dissolved in 2 mL of acetone, and the solution was added dropwise to a stirred solution of 0.5 g (7.2 mmol) of $NaN_3$ in 2 mL of $H_2O$ at 0 °C. After the resulting suspension was stirred for 30 min at 0–20 °C, it was diluted with 50 mL of $H_2O$ and cooled to 0–5 °C. The solid acid azide was filtered, washed with $H_2O$, and dried in the air at 25 °C. A solution of the azide in 3 mL of toluene was heated at 100 °C for 1 h, and then it was concentrated. The resulting isocyanate was dissolved in 2.3 mL of benzyl alcohol, and the resulting solution was heated at 100 °C for 6 h. After standing at 25 °C, the mixture solidified. It was triturated with $n$-$C_6H_{14}$ to give 1.53 g (90%) of tan crystalline benzyl carbamate, mp 128–130 °C. Hydrogenolysis of a mixture of the carbamate, 0.7 mL of concentrated HCl, 300 mg of Pd/C and 100 mL of EtOH at an initial pressure of 50 psi of $H_2$ at 25 °C, following filtration, concentration and trituration of the residue with $Et_2O$ gave 1.06 g (97%) of colorless crystals, mp 237–239 °C dec (Table II).

**2-Amino-5-chloro-6,7-dimethoxytetralin Hydrochloride (34b).**[58] A solution of ethyl chloroformate (1.1 g, 10.1 mmol) in 2 mL of acetone was added slowly to a stirred solution of **11b** (2.5 g, 9.2 mmol) and $Et_3N$ (10.2 mmol) in 17 mL of acetone at −5 °C. The mixture was stirred at 0 °C, and a solution of $NaN_3$ (1.2 g, 18.3 mmol) in 34 mL of $H_2O$ was added *dropwise* during 30 min. After the mixture was stirred at 0 °C for 1 h, it was poured into 34 mL of ice–$H_2O$. The mixture was extracted with toluene. After the toluene extracts were dried ($MgSO_4$), they were added dropwise to 100 mL of stirred toluene at 100 °C. Heating at 100 °C was continued for 1 h, and then the solution was concentrated. To the residual liquid was added 18.6 mL of 8 N HCl, and the

(72) Furchgott, R. F. *Annu. Rev. Pharmacol.* **1964**, *4*, 21.

mixture was stirred at 100 °C for 1 h. The mixture was concentrated, and the residue was dissolved in $H_2O$. The aqueous solution was made alkaline with 2 N NaOH. After the mixture was extracted with $Et_2O$, the extracts were dried ($MgSO_4$) and concentrated. A solution of the residual liquid in $Et_2O$ was acidified with HCl. The crystalline solid was washed with $Et_2O$ to give 0.73 g (48%) of colorless crystals after recrystallization from MeOH–EtOAc (Table II).

**(2-Fluoro-3,4-dimethoxyphenyl)acetyl Chloride (12).** A stirred suspension of 43 g (0.2 mol) of **5** and 72 g (0.6 mol) of $SOCl_2$ in 460 mL of toluene was heated at 100 °C for 2.5 h. Stirring was continued at 25 °C for 16 h, and then the solution was concentrated under reduced pressure. Distillation of the residue afforded 45.7 (97%) of a pale pink liquid, bp 128–132 °C (0.26 torr). Anal. ($C_{10}H_{10}ClFO_3$) H; C: calcd, 51.63; found, 51.03.

**8-Fluoro-6,7-dimethoxy-2-tetralone (13)** was prepared according to the general method of Burckhalter and Campbell.[46] A solution of 45.5 g (0.2 mol) of **12** in 200 mL of $CH_2Cl_2$ was added dropwise during 1.5 h to a stirred suspension of $AlCl_3$ (52.2 g, 0.39 mol) in 800 mL of $CH_2Cl_2$ at −78 °C. Ethylene was bubbled rapidly through the mixture for 25 min. After removal of the cooling bath, stirring was continued for 3.5 h and 250 mL of $H_2O$ was added dropwise with *caution*. The organic layer was separated and washed with 2 N HCl, a saturated aqueous solution of $NaHCO_3$, and brine. After being dried ($Na_2SO_4$), the solution was concentrated in vacuo to give 44.1 g of a viscous liquid that was triturated with a small volume of cold $Et_2O$ to give 11.3 g of a crude monohydroxy monomethyl derivative. A mixture of 10.3 g (49 mmol) of this crude material, 7.4 g (59 mmol) of dimethyl sulfate and 31.3 g (0.23 mol) of $K_2CO_3$ in 80 mL of DMF was stirred at 100 °C for 1.5 h. The cooled mixture was diluted with $H_2O$ and extracted with $Et_2O$. The $Et_2O$ extracts were washed with $H_2O$, dried, and concentrated. The residue was chromatographed by MPLC (silica gel 60, 230–400 mesh; mobile phase 98:2 $CH_2Cl_2$–MeOH). Fractions giving a single spot at $R_f$ 0.3 (70:30 c-$C_6H_{12}$–$Et_2O$) were combined and concentrated, and the residual solid was recrystallized from c-$C_6H_{12}$–*n*-$C_6H_{14}$ to give 2.1 g (19%) of colorless crystals, mp 94–95 °C. Anal. ($C_{12}H_{13}FO_3$) C, H.

**2-(Benzylamino)-8-fluoro-6,7-dimethoxytetralin Hydrochloride (14a).** A solution of 2.0 g (9 mmol) of **13b**, *p*-toluenesulfonic acid (0.06 g), and benzylamine (1.2 g, 11 mmol) in 100 mL of toluene was refluxed azeotropically under Ar for 2 h. After $CO_2$ was bubbled through the solution, it was washed successively with $H_2O$, a saturated aqueous $NaHCO_3$ solution, and brine, dried, and concentrated. A mixture of the residual imine, 280 mg of $PtO_2$, and 100 mL of EtOH was hydrogenated at 25 °C and an initial pressure of 50 psi of $H_2$ for 1.5 h. After the mixture was filtered, the filtrate was made acidic with HCl and concentrated in vacuo. The residual solid was recrystallized from MeOH–EtOH to give 2.1 g (70%) of a white solid, mp 247–250 °C. Anal. ($C_{19}H_{22}FNO_2$·HCl) C, H, N.

**2-Amino-8-fluoro-6,7-dimethoxytetralin Hydrochloride (14b).** A suspension of 2.1 g (5.9 mmol) of **14a**, 0.5 mL of 12 N HCl, and 100 mL of EtOH was hydrogenated at 60 °C and an initial $H_2$ pressure of 45 psi for 5 h. The mixture was filtered and the filtrate concentrated. Recrystallization of the solid residue from MeOH–EtOAc gave 1.5 g (94%) of colorless crystals, mp 225–228 °C dec. Anal. ($C_{12}H_{16}FNO_2$·HCl) C, H, N.

**Methyl 8-Chloro-6,7-dimethoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (16).** A warm solution of 2-chloroveratraldehyde[44] (100.3 g, 0.5 mol) and dimethyl succinate (83 g, 0.57 mol) in 170 mL of MeOH was added to a refluxing solution of NaOMe in MeOH, prepared by the *cautious* portionwise addition of 13.8 g (0.6 mol) of Na to 500 mL of MeOH under $N_2$. After the mixture was refluxed for 2 h, 350 mL of solvent was distilled off. The remaining solution was cooled to 10 °C, made acidic with 2 N HCl, and diluted with 1.5 L of $H_2O$. Precipitated solid was filtered and partitioned between equal volumes of $Et_2O$ and a saturated aqueous solution of $NaHCO_3$. The aqueous $NaHCO_3$ solution was acidified with 12 N HCl. After the resulting mixture was extracted with EtOAc, the organic extract was washed ($H_2O$), dried ($MgSO_4$), and concentrated to give 52.8 g of a solid *benzylidene derivative*, mp 140–143 °C, after recrystallization from EtOAc–*n*-$C_6H_{14}$. This was dissolved in EtOAc and hydrogenated in the presence of 10% Pd/C catalyst at 25 °C and 65 psi of $H_2$ to give 52.1 g of a *benzyl derivative*, mp 118–121 °C. A mixture of this material and 375 mL of MSA was heated at 100 °C for 15 min. The resulting solution was poured onto 2 L of ice–$H_2O$. Precipitated solid was filtered, washed with $H_2O$, dried in vacuo at 80 °C, and recrystallized from aqueous MeOH to give 43.1 g (92%) of crystalline solid, mp 146–147 °C. Anal. ($C_{14}H_{15}ClO_5$) C, H.

**Methyl 8-Chloro-6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate (17a)** was prepared by reductive hydrogenolysis of **16** in the same manner as described for reduction of **34a** to **35a**. The crystals, mp 92–93 °C (99% yield), were recrystallized from MeOH; TLC (silica gel GF, $CHCl_3$) showed a single spot at $R_f$ 0.4. Anal. ($C_{14}H_{17}ClO_4$) C, H.

**8-Chloro-6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic Acid (17b).** A suspension of 29.6 g (97 mmol) of **17a** in a solution of 10.9 g (0.184 mol) of KOH in 200 mL of 50% aqueous MeOH was stirred and refluxed for 24 h. The solution was concentrated to 100 mL in vacuo, cooled, washed with $Et_2O$, and made acidic with 12 N HCl to give 25.26 g of colorless crystals, mp 212–214 °C, after recrystallization from EtOAc. Anal. ($C_{13}H_{15}ClO_4$) C, H.

**2-Amino-8-chloro-6,7-dimethoxytetralin hydrochloride (18)** was prepared from **17b** by the same procedure as that described for conversion of **11a** to **34a**. The intermediate benzyl carbamate (83%) melted at 119–121 °C after recrystallization from 2-PrOH. The yield of colorless crystals, mp 269–271 °C dec, after trituration with $Et_2O$ was 96%. Anal. ($C_{12}H_{16}ClNO_2$·HCl) C, H, N.

**8-Chloro-6,7-dimethoxy-2-(di-*n*-propylamino)tetralin Hydrochloride (19).** A mixture of **18** (5.6 g, 20 mmol), 5.81 g (0.1 mol) of propionaldehyde, 1.6 g (20 mmol) of NaOAc, and 2 g of 10% Pd/C catalyst was hydrogenated for 10 h at 25 °C and an initial $H_2$ pressure of 60 psi. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was suspended in $H_2O$, and the mixture was made alkaline with 10 N NaOH and extracted into $Et_2O$. After the ethereal solution was washed ($H_2O$) and dried ($MgSO_4$), it was concentrated. The residue was taken into $Et_2O$ and acidified with gaseous HCl. The resulting hydrochloride was recrystallized from MeCN–$Et_2O$ to give 3.8 g (52%) of crystals, mp 158–160 °C. Anal. ($C_{18}H_{28}ClNO_2$·HCl) C, H, N.

**8-Chloro-6,7-dimethoxy-2-[[(4-methoxyphenyl)acetyl]amino]tetralin (20a).** To a suspension of **18** (2.5 g, 9 mmol) in 50 mL of THF was added 2.17 g (21.4 mmol) of $Et_3N$. The mixture was stirred for 10 min at ambient temperature, and then it was cooled to 0 °C and 2.2 g (12 mmol) of 4-methoxyphenylacetyl chloride in 10 mL of THF was added dropwise. The mixture was stirred at 25 °C for 16 h, and then it was filtered. The filtrate was concentrated in vacuo. A solution of the residual solid in $CHCl_3$ was washed ($H_2O$, saturated aqueous $NaHCO_3$ solution, $H_2O$), dried ($MgSO_4$), and concentrated. The residue was triturated with a small volume of cold $Et_2O$ to give 2.4 g (67%) of colorless crystals, mp 144–147 °C. Anal. ($C_{21}H_{24}ClNO_4$) C, H, N.

**8-Chloro-6,7-dimethoxy-2-[[2-(4-methoxyphenyl)ethyl]amino]tetralin Hydrochloride (20b).**[54] A solution of 2.3 g (5.9 mmol) of **20a** in 20 mL of THF was added dropwise at 0 °C to a stirred solution of 14 mL of a 1 M solution of $BH_3$ in THF under Ar. After the reaction mixture was refluxed for 2 h, it was cooled, 4 mL of 3 N HCl was added, and the THF was removed by distillation. The resulting suspension was cooled to 10 °C, 30 mL of THF was added, and the crystals (2.1 g, 87%), mp 268–270 °C, were filtered. Anal. ($C_{12}H_{26}ClNO_3$·HCl) C, H, N.

**8-Chloro-6,7-dimethoxy-2-[*N*-[2-(4-methoxyphenyl)ethyl]-*N*-*n*-propylamino]tetralin (21).** To a stirred suspension of **20b** (1.7 g, 4.1 mmol) and $K_2CO_3$ (3 g, 22 mmol) in 10 mL of $H_2O$ and 10 mL of $CHCl_3$ was added 0.9 g (10 mmol) of propionyl chloride. After being stirred at 25 °C for 1 h, the mixture was filtered and the organic phase was separated. The $CHCl_3$ solution was washed (2 N HCl, $H_2O$), dried ($MgSO_4$), and concentrated to give 1.5 g of a viscous amide. This amide was reduced with $BH_3$ as described in the preceding example. An aqueous solution of the resulting crude hydrochloride was made alkaline with 2.5 N NaOH. After the mixture was extracted with $Et_2O$, the extracts were washed ($H_2O$), dried ($MgSO_4$), and concentrated to give 1.4 g (96%) of a crude product; TLC (silica gel GF, 98:2 $CHCl_3$–MeOH) $R_f$ 0.45. This material was used for conversion to **4g** without further purification.

**4-(3-Fluoro-4-methoxyphenyl)butyric Acid (22).** To a stirred mixture of 113 g (0.9 mol) of 2-fluoroanisole, 1 L of 1,2-dichloroethane, and 99 g (0.1 mol) of succinic anhydride at 0–10 °C was added, in portions, during 30 min, 293 g (2.2 mol) of $AlCl_3$. The mixture was gradually heated to 65 °C during 40 min. After 20 min at 65 °C, the mixture was allowed to return to ambient temperature during 3 h, and then it was poured into a mixture of 1 kg of ice and 500 mL of 12 N HCl. The solid was filtered and dried. Recrystallization from EtOH afforded 153 g (76%) of *3-(3-fluoro-4-methoxybenzoyl)propionic acid*, mp 168–170 °C. A mixture of 27 g (0.12 mol) of this acid, 200 mL of EtOH, 60 mL of HOAc, and 3 mL of 10% $HClO_4$ was warmed to effect solution. After being cooled slightly, the solution was added to 3 g of 10% Pd/C catalyst (wetted with a small volume of EtOAc), and the mixture was hydrogenated for 3.5 h at ambient temperature at an initial pressure of 60 psi of $H_2$. The mixture was filtered, and the filtrate was adjusted to pH 5.5 with NaOAc. After concentration of the solution in vacuo, the residue was dissolved in a mixture of equal volumes of EtOAc and $H_2O$. The organic phase was washed with brine, dried, and concentrated. The residual syrup was recrystallized from $Et_2O$–*n*-$C_6H_{14}$ to give 15.7 g (62%) of colorless crystals, mp 61–62 °C. Anal. ($C_{11}H_{13}FO_3$) C, H.

**6-Fluoro-7-methoxy-1-tetralone (23).** A solution of 20 g (0.094 mol) of **22**, 30 mL of MSA, and 100 mL of TFA was stirred at 100 °C for 45 min. It was then poured onto 500 mL of ice–$H_2O$, and the mixture was extracted with EtOAc. The extracts were washed ($H_2O$, saturated aqueous $NaHCO_3$, brine), dried ($MgSO_4$), and concentrated. The residue was crystallized from 50 mL of EtOH to afford 11.85 g (65%) of colorless crystals: mp 93.5–95 °C; TLC (silica gel, 50:50 EtOAc–c-$C_6H_{12}$) gave a single spot having $R_f$ 0.67; NMR (270 MHz) ($CDCl_3$) $\delta$ 6.91 [d, 1 H, $J$ = 11.2 Hz, Ar*H* (5)], 7.62 [d, 1 H, $J$ = 8.8 Hz, Ar*H* (8)]. Anal. ($C_{11}H_{11}FO_2$) C, H.

**6-Fluoro-7-methoxy-1-oximinotetralin (24a).** To a stirred solution of 1.2 g (6.2 mmol) of **23** in 15 mL of warm EtOH was added a solution of 0.64 g (9.3 mmol) of hydroxylamine hydrochloride and 0.43 g (3.1 mmol) of $K_2CO_3$ in 6 mL of $H_2O$. The mixture was stirred at reflux temperature for 2 h, and then it was concentrated. The residual solid was triturated with $H_2O$ and recrystallized from EtOH to give 1.2 g (94%) of colorless crystals, mp 166–168 °C. Anal. ($C_{11}H_{12}FNO_2$) C, H, N.

**6-Fluoro-7-methoxy-1-oximinotetralin Tosylate (24b).** Freshly crystallized tosyl chloride (1.7 g, 8.7 mmol) was added to a solution of 1.2 g (5.8 mmol) of **24a** in 10 mL of pyridine. The resulting suspension was stirred at 25 °C for 3 h and poured into ice–$H_2O$, and the white precipitate was filtered. Rapid recrystallization (the product decomposes rapidly) from EtOH gave 2 g (97%) of crystals, mp 147–149 °C. Anal. ($C_{18}H_{18}FNO_4S$) C, H, N.

**2-Amino-6-fluoro-7-methoxy-1-tetralone Hydrochloride (25).** At 0 °C, under $N_2$, a solution of 2 g (5.6 mmol) of **24b** in 40 mL of $CH_2Cl_2$ and 5 mL of EtOH was added to a stirred solution of 0.78 g (6.4 mmol) of *t*-BuOK in 15 mL of EtOH. After the mixture was stirred at 0 °C for 24 h, it was filtered. The filtrate was diluted with 50 mL of 6 N HCl. The acid layer was separated, washed with $CH_2Cl_2$, and then concentrated in vacuo at 40 °C. Azeotroping several times with EtOH gave 0.75 g of off-white crystals: mp 224–226 °C dec; MS ($CH_4$, CI) $m/e$ 210 (supports M + 1 structure of the base); TLC (silica gel, 5:95:1 $CH_3OH$–$CH_2Cl_2$–concentrated aqueous $NH_3$) gave a single spot having $R_f$ 0.38. Anal. ($C_{11}H_{12}FNO_2$·HCl·0.75$H_2O$) C, H; N: calcd, 5.40; found, 6.01.

**2-Amino-6-fluoro-7-methoxytetralin Hydrochloride (26a).** A mixture of 8.4 g (34 mmol) of **25**, 6.7 g of 10% Pd/C catalyst, 800 mL of 3 N HCl, and 150 mL of HOAc was hydrogenated at 60 °C and an initial $H_2$ pressure of 60 psi for 30 h. The mixture was filtered and filtrate concentrated. The residue was azeotroped several times with EtOH–toluene to give 7.5 g (94%) crude **26a** as an amorphous solid that was used for further reaction without additional purification.

***tert*-Butyl 6-fluoro-7-methoxytetralin-2-carbamate (26b)** was prepared to separate **26a** from minor impurities. Crude **26a** (2.5 g, 10.8 mmol) was dissolved in 50 mL of DMF and 3 mL of $Et_3N$, 4.7 g (21 mmol) of di-*tert*-butyl dicarbonate was added, and the mixture was stirred at 25 °C for 17 h. The mixture was concentrated in vacuo, and the residue was partitioned between EtOAc and $H_2O$. The organic layer was separated, washed with cold 1.5 N HCl, $H_2O$, 5% aqueous $NaHCO_3$, $H_2O$, and brine, dried, and concentrated. The residue was triturated with *n*-$C_6H_{14}$ to give 0.9 g (29%) of crystals: mp 116–118.5 °C; TLC (silica gel 66:33 c-$C_6H_{12}$–EtOAc) showed a single spot at $R_f$ 0.81; MS, $m/e$ 266 (M + 1). The material was used for conversion to **4h**.

**6-Fluoro-7-methoxy-2-(dimethylamino)tetralin (27a).** Crude **26a** (3.5 g, 15 mmol) was added (exotherm) to a mixture of 4.5 g (72 mmol) of $NaBH_3CN$, 5.1 mL of a 37% solution of formaldehyde, and 35 mL of MeOH. After the stirred mixture was maintained at 25 °C and pH 6.2–6.5 (by addition of HOAc) for 20 h, it was gradually acidified to pH 1 with 3 N HCl and volatiles were removed at 30 °C in vacuo. The residue was partitioned between $H_2O$ and EtOAc, and the aqueous phase was made basic with 2.5 N NaOH. The mixture was extracted with EtOAc. The extracts were washed ($H_2O$), dried ($MgSO_4$), and concentrated to give 1.2 g (35%) of an oily product that showed a single spot at $R_f$ 0.48 on TLC (silica gel, 15:85:1 $CH_3OH$–$CH_2Cl_2$–concentrated aqueous $NH_3$). This material was used for conversion to **4i**.

**6-Fluoro-7-methoxy-2-(di-*n*-propylamino)tetralin Hydrochloride (27b).** To a stirred solution of 43 mL (0.57 mol) of propionic acid in 300 mL of toluene under $N_2$ was added, in portions, 7.2 g (0.19 mol) of $NaBH_4$ with intermittent cooling to maintain the temperature at 15–20 °C. The mixture was stirred at 15–20 °C until $H_2$ evolution had ceased (about 1.5 h). Then, 4 g (17 mmol) of crude **26a** was added. After the stirred mixture, under $N_2$, was heated at 80–85 °C for 22 h, it was cooled, excess 2.5 N NaOH was added, and it was extracted with EtOAc. The extracts were washed (brine), dried ($MgSO_4$), and concentrated. The residual liquid in EtOAc was treated with HCl to give crude **27b** that was used for preparation of **4j**.

**2-Carboethoxy-6-fluoro-7-methoxy-1-tetralone (28a).** To a stirred suspension of 1 g (21 mmol) of NaH (50% dispersion in mineral oil) in 40 mL of THF under $N_2$ was added dropwise 2.36 g (20 mmol) of diethyl carbonate, followed by 1.9 g (10 mmol) of **23** in 10 mL of THF. After being refluxed for 17 h, the mixture was cooled and 5 mL of HOAc was added dropwise with *caution*. The mixture was extracted with $Et_2O$. The $Et_2O$ extracts were washed (saturated aqueous $NaHCO_3$ solution, brine), dried ($MgSO_4$), and concentrated. The residual liquid was chromatographed over silica gel, eluting with a gradient of $CH_2Cl_2$ to 0.5% MeOH in $CH_2Cl_2$. The first fraction gave 2.2 g (85%) of crystals, mp 70–72 °C, after crystallization from EtOH: NMR ($CDCl_3$) $\delta$ 1.29 (t, 3 H, $CH_2CH_3$), 2.41 (m, 2 H), 2.96 (t, 2 H), 3.54 (q, 1 H), 3.91 (s, 3 H, $OCH_3$), 4.24 (q, 2, H, $OCH_2CH_3$), 6.91 (d, 1 H, $J$ = 12 Hz, Ar*H*), 7.61 (d, 1 H, $J$ = 8 Hz, Ar*H*). Anal. ($C_{14}H_{15}FO_4$) C, H.

Further elution gave 0.44 g of a second solid, mp 92–94 °C, after recrystallization from EtOH. This was identified as *2-carboethoxy-6-ethoxy-7-methoxy-1-tetralone* (**28b**): MS ($CH_4$, CI) $m/e$ 293 (M + 1); NMR ($CDCl_3$) $\delta$ 1.29 (t, 3 H, $CO_2CH_2CH_3$), 1.48 (t, 3 H, $ArOCH_2CH_3$), 6.75 [s, 1 H, Ar*H* (5)], 7.54 [s, 1 H, Ar*H* (8)]. Anal. ($C_{16}H_{20}O_5$) C, H.

**6-Fluoro-7-methoxy-1,2,3,4-tetrahydronaphthoic Acid (28c).** A mixture of 1.6 g (6 mmol) of **28a**, 35 mL of EtOH, 15 mL of HOAc, 16 drops of 70% $HClO_4$, and 2 g of 10% Pd/C catalyst at 25 °C was hydrogenated for 6 h at an initial $H_2$ pressure of 60 psi. The mixture was filtered, and the filtrate was brought to pH 4.5 with NaOAc. The solution was concentrated in vacuo. A solution of the residue in 10 mL of 6 N HCl and 10 mL of HOAc was heated at 100 °C for 4 h, and 5 mL of $H_2O$ was added. Upon being cooled to −5 °C, 0.66 g (49%) of crystals, mp 165–169 °C, after recrystallization from EtOH, deposited from the solution. Anal. ($C_{12}H_{13}FO_3$) C, H.

**6-Fluoro-7-methoxy-2-(di-*n*-propylamino)tetralin Hydrochloride (29).** A solution of 0.6 g (2.7 mmol) of **28c**, 0.74 g (5.4 mmol) of 1-hydroxybenzotriazole, 0.28 g (2.7 mmol) of di-*n*-propylamine, and 0.56 g (2.7 mmol) of dicyclohexylcarbodiimide in 15 mL of THF was stirred at ambient temperature for 17 h. The resulting mixture was filtered, the filtrate was concentrated, and the residue was partitioned between EtOAc and $H_2O$. The organic layer was washed (1 N HCl, $H_2O$, 5% aqueous $NaHCO_3$ solution, brine), dried ($MgSO_4$), and concentrated to give 0.9 g of a semisolid. This material was chromatographed on a silica

gel column with a gradient of $CH_2Cl_2$ to 0.5% MeOH in $CH_2Cl_2$ to provide 0.8 g of the tertiary carboxamide as a colorless liquid; MS ($CH_4$, CI) gave $m/e$ 308 (M + 1). To a stirred solution of this material (0.8 g, 2.6 mmol) in 20 mL of THF under $N_2$ at 0–5 °C was added dropwise 20 mL of 1 M $BH_3$ in THF. After being stirred at 25 °C for 5 h, the mixture was again cooled to 0–5 °C, 20 mL of MeOH was added dropwise, and it was concentrated in vacuo. The residue was azeotroped several times with MeOH. Next, it was dissolved in MeOH, made acidic with HCl, and concentrated to give an amorphous solid: TLC (silica gel, 3:97 MeOH–$CH_2Cl_2$) gave a single spot having $R_f$ 0.11; MS, $m/e$ 294 (M + 1). This was employed for conversion to **4k** without additional purification.

**4-Chloro-3-methoxybenzyl Bromide (30).** A stirred mixture of 2-chloro-5-methylphenol (43 g, 0.3 mol), dimethyl sulfate (41.6 g, 0.33 mol), and powdered $K_2CO_3$ (103.5 g, 0.75 mol) in 500 mL of $Me_2CO$ was heated at reflux for 16 h. After the mixture was concentrated, 500 mL of $H_2O$ was added to the residue. The resulting mixture was extracted with $Et_2O$. The $Et_2O$ extracts were washed ($H_2O$, brine), dried, and concentrated. Distillation of the residue afforded 45 g (95%) of *2-chloro-5-methylanisole*, bp 75 °C (0.5 torr). A solution of 30 g (0.19 mol) of this anisole derivative and 37.3 g (0.21 mol) of NBS in 250 mL of $CCl_4$ was stirred and refluxed, while being irradiated with a 350-W IR flood lamp, for 3.5 h. After the mixture was cooled to 0 °C, it was filtered. The filtrate was concentrated and the residue distilled to give a colorless liquid: bp 115 °C (0.4 torr); NMR ($CDCl_3$) $\delta$ 3.73 (s, 3 H, $CH_3O$), 4.40 (s, 2 H, $CH_2$), 6.73–7.38 (m, 3 H, Ar*H*). This material was used for conversion to **31** without additional characterization.

**3-(4-Chloro-3-methoxyphenyl)-1,2,2-propanetricarboxylic Acid (31).**[48] A dispersion of 4.5 g (0.19 mol) of NaH in mineral oil was washed several times with $n$-$C_6H_{14}$ and dried in vacuo. Triethyl 1,1,2-ethanetricarboxylate (45 g, 0.183 mol) in 70 mL of $Me_2SO$ was added dropwise to a stirred suspension of the NaH in 20 mL of $Me_2SO$. After addition was completed, the mixture was stirred and heated at 60 °C for 1 h. After the stirred solution was cooled to 20 °C, a solution of 43 g (0.183 mol) of 4-chloro-3-methoxybenzyl bromide in 70 mL of $Me_2SO$ was added slowly. The mixture was stirred at 60 °C for 1.5 h, and then the resulting solution was poured into 2 L of ice–$H_2O$. The mixture was extracted with $Et_2O$. The combined extracts were washed ($H_2O$), dried ($MgSO_4$), and concentrated. Distillation of the residual liquid afforded 64.7 g of triester, bp 200 °C (0.3 torr). The triester (10.5 g, 26.2 mmol) and a solution of 3.5 g (87 mmol) of NaOH in 40 mL of $H_2O$ were stirred and refluxed for 4 days. The solution was diluted with 100 mL of ice–$H_2O$ and extracted with $Et_2O$. The aqueous phase was made acidic with 12 N HCl, and the resulting mixture was extracted with EtOAc. After being washed ($H_2O$, brine) and dried ($MgSO_4$), the extracts were concentrated. Trituration of the residue with $n$-$C_6H_{14}$ gave 5.0 g (60%) of colorless crystals, mp 161–163 °C, after recrystallization from MeCN. Anal. ($C_{13}H_{13}ClO_7$) C, H.

**6-Chloro-7-methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (32).** Decarboxylation of **31** (4.8 g, 15 mmol) to (4-chloro-3-methoxybenzyl)succinic acid, mp 157–160 °C (81% yield), was carried out at 180–185 °C by the general procedure of Cannon et al.[48] This succinic acid (20 g, 73 mmol) was added slowly to 140 mL of stirred MSA. After being stirred at 100 °C for 30 min, the solution was poured into 1 L of ice–$H_2O$. The solid was filtered and recrystallized from $Me_2CO$ to afford 16.7 g (90%) of colorless crystals: mp 233–235 °C; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 6.97 (s, 1 H, Ar*H* (8)), 7.88 (s, 1 H, Ar*H* (5)). Anal. ($C_{12}H_{11}ClO_4$) C, H.

**6-Chloro-7-methoxy-1,2,3,4-tetrahydronaphthoic Acid (33).** A mixture of 2 g (7.9 mmol) of **32**, 40 mL of HOAc, 0.5 mL of 70% $HClO_4$, and 0.5 g of 10% Pd/C catalyst was hydrogenated at 25 °C and an initial $H_2$ pressure of 60 psi for 2.5 h. The mixture was filtered, and 1 g of NaOAc was added to the filtrate. Most of the solvent was evaporated in vacuo. The residue was diluted with 100 mL of $H_2O$. The solid was filtered and recrystallized from EtOH to give 1.5 g (79%) of colorless crystals: mp 169–171 °C; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 6.65 (s, 1 H, Ar*H* (8)), 6.97 (s, 1 H, Ar*H* (5)). Anal. ($C_{12}H_{13}ClO_3$) C, H, Cl.

**2-Amino-6-chloro-7-methoxytetralin hydrochloride (34c)** was prepared from **33** by the same procedure described for conversion of **11b** to **34b**[53,56,57] (see Table II).

**6-Chloro-7-methoxy-2-(dimethylamino)tetralin Hydrochloride (34d).** A solution of 2.37 g, 10 mmol of the isocyanate derived from **33** (by the procedure described for conversion of **11b** to its isocyanate) in 30 mL of $Et_2O$ was added dropwise to a stirred suspension of $LiAlH_4$ (0.76 g, 20 mmol) in 50 mL of $Et_2O$. After the mixture was stirred and refluxed for 2 h, excess $LiAlH_4$ was decomposed by *cautious* addition of 1 mL of $H_2O$, followed by 1 mL of 2.5 N NaOH and 3 mL of $H_2O$. The mixture was filtered and the filtrate concentrated to give the *N*-monomethyl derivative. To a stirred solution of this secondary amine (2.25 g, 10 mmol) in 20 mL of $CHCl_3$ was added a solution of $K_2CO_3$ (1.4 g, 10 mmol) in 20 mL of $H_2O$. To the stirred mixture was added methyl chloroformate (1.56 g, 12 mmol) in 5 mL of $CHCl_3$. After being stirred for 15 min, the $CHCl_3$ layer was separated, washed with $H_2O$, dried ($MgSO_4$), and concentrated to give the corresponding *N*-methyl methyl carbamate, which was reduced with $LiAlH_4$ as described previously to afford the *N,N*-dimethylamine which was converted to the hydrochloride in the solvent indicated in Table II.

**6-Chloro-7-methoxy-2-(di-*n*-propylamino)tetralin Hydrochloride (34e).** The base derived from **34c** (4.96 g, 20 mmol) by treatment with 2 N NaOH followed by $Et_2O$ extraction, drying ($MgSO_4$), and concentration was heated with 20 mL of propionic anhydride at 100 °C for 2 h. The solution was poured into $H_2O$, and the mixture was extracted with $CH_2Cl_2$. The organic extract was washed (5% aqueous $NaHCO_3$, $H_2O$, brine), dried ($MgSO_4$), and concentrated. To a stirred solution of the residual *N*-propionamide in 2 mL of THF, under $N_2$, was added 30 mL of 1 M $BH_3$ in THF. The stirred mixture was refluxed for 4 h and cooled, and 2.5 N HCl was added until the evaporation of gas stopped. The mixture was heated at 100 °C, allowing the THF to evaporate. The resulting solid was collected. This hydrochloride was converted to its base, which was again propionylated and reduced in the same manner to give the *N,N*-dipropyl derivative. The resulting aqueous solution of hydrochloride was converted to the base by addition of 2 N NaOH. The base was extracted with EtOAc. The extracts were washed with $H_2O$, dried ($MgSO_4$), and concentrated to afford the tertiary amine, which was converted into a hydrochloride in the solvent indicated in Table II.

**6,8-Dichloro-7-methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (35a).** *tert*-Butyl hypochlorite (5.4 g, 50 mmol) was added to a suspension of 11.5 g (45 mmol) of **32** in 110 mL of HOAc. After being stirred at 60 °C for 20 h, the mixture was poured into 250 mL of ice–$H_2O$. The resulting solid was filtered and recrystallized from EtOH to give 10 g (77%) of colorless crystals: mp 184–185 °C; $^1$H NMR ($Me_2SO$-$d_6$ + $CDCl_3$) $\delta$ 7.95 (s, 1 H, Ar*H* (5)). Anal. ($C_{12}H_{10}Cl_2O_4$) C, H.

**6,8-Dichloro-7-methoxy-1,2,3,4-tetrahydronaphthoic acid (35b)** was prepared by hydrogenolysis of **35a** in the same manner as described for the preparation of **28c**. In this experiment it was necessary to extract the filtered catalyst with warm HOAc. The combined filtrates and HOAc extracts were diluted with ice–$H_2O$. The precipitated solid was filtered and recrystallized from MeOH to give 9.5 g (90%) of colorless crystals, mp 175 °C. Anal. ($C_{12}H_{12}Cl_2O_3$) C, H; Cl: calcd, 25.77; found, 25.15.

**2-Amino-6,8-dichloro-7-methoxytetralin Hydrochloride (34f).**[59] To a suspension of 2.2 g (8 mmol) of **35b** and 0.9 mL of $SOCl_2$ in 60 mL of $CH_2Cl_2$ was added 2 drops of DMF. After being stirred at 25 °C for 4 h, the resulting solution was concentrated and the residue was stripped twice with toluene. The resulting acid chloride was dissolved in 12 mL of $CH_2Cl_2$ containing 8 mg of tetrabutylammonium bromide (TBAB). The solution was stirred at 0 °C as a solution of $NaN_3$ (0.65 g, 10 mmol) in $H_2O$ (2 mL) was added dropwise. After the mixture was stirred at 0 °C for 1 h, additional $CH_2Cl_2$ was added. The $CH_2Cl_2$ solution was washed with $H_2O$ and brine, and then it was concentrated in vacuo at 20 °C. A solution of the resulting carboxylic acid azide in 50 mL of toluene was refluxed for 1 h, and then it was concentrated in vacuo. The resulting isocyanate was dissolved in $CH_2Cl_2$ (30 mL) and TFA (0.84 mL) was added. After the solution was refluxed for 16 h, it was cooled to 25 °C and washed successively with a saturated solution of $NaHCO_3$, $H_2O$, and brine. The solution was dried ($MgSO_4$) and concentrated. The residual trifluoroacetamide was dissolved in a solution of 1.5 g of $K_2CO_3$ in 20 mL of MeOH. After the solution was refluxed for 1 h, it

**Table III.** Pharmacological Properties of Halogenated Mono- and Dihydroxy-2-aminotetralins (4a–4w)

| no. | [$^3$H]fenoldopam rat striatum: $K_{Bind}$ ± SE,[a] μM (N) | dopamine-sens adenylate cyclase stim: $ED_{50}$,[a] μM | [$^3$H]spiroperidol, bovine pituitary: $K_{Bind}$, μM (N)[a] | rabbit ear artery test: $ED_{50}$ ± SE,[a] nM ($K_B$) |
|---|---|---|---|---|
| **4a** | 0.074 (2) | 1.6 | 0.52 ± 0.23 (3) | 2.6 ± 0.8 (13) |
| **4b** | 0.84 ± 0.15 (3) | *b* | 0.47 ± 0.19 (3) | 76.5 ± 32 (10) |
| 4c | 0.062 (2) | 2.2 | 1.27 ± 0.30 (3) | 4.5 ± 1.4 (6) |
| **4d** | 0.043 ± 0.003 (3) | 1.4 | 3.16 ± 0.82 (3) | 536 ± 131 (43) |
| 4e | 0.62 ± 0.17 (3) | | 0.24 ± 0.06 (3) | 17 ± 2.3 |
| 4f | 0.145 (2) | | 0.41 (2) | |
| **4g** | 0.27 ± 0.06 (3) | | 0.033 (2) | 62 ± 44 |
| 4h | 0.37 (2) | | 0.66 ± 0.13 (3) | |
| 4i | 0.76 ± 0.12 (4) | | 0.47 (2) | |
| 4j | 1.74 ± 0.50 (3) | | 0.43 (2) | 13 ± 1.1 |
| 4k | >50 (2) | | 14.11 ± 1.96 (3) | |
| 4l | 1.44 (2) | *b* | 1.05 (2) | *c* |
| 4m | 2.63 (2) | *b* | 1.55 (2) | |
| 4n | 4.71 (2) | *b* | 1.63 ± 0.40 (3) | 126 ± 48 |
| 4o | 2.97 (2) | | 30 ± 5% @ 10 μM (4) | |
| 4p | >20 (2) | | 29 ± 3% @ 10 μM (4) | |
| 4q | >10 (2) | *b* | 10.4 ± 1.5 (3) | |
| 4r | >10 (2) | | 11.61 ± 4.12 (3) | |
| 4s | 5.95 (2) | | 3.5 (2) | |
| 4t | 2.25 (2) | | 0.85 ± 0.06 (3) | 53 ± 11 |
| 4u | 1.97 ± 0.59 (3) | *b* | 4.47 ± 0.91 (4) | |
| 4v | 2.30 (2) | *b* | 0.09 ± 0.45 (3) | |
| 4w | 8.23 (2) | *b* | 0.90 (2) | 58 ± 17 (5) |
| dopamine | 0.15 | 3.5 | 2.35 | 37 ± 6 (35) |
| ADTN | 0.07 | 2.7 | 0.21 | 4.6 ± 0.8 (10.5) |

[a] See the Experimental Section for description of test and calculation of $K_{Bind}$, $K_i$, $ED_{50}$, and $K_B$ values ± standard error (SE). Although $K_B$ values are presented for only selected compounds, all those for which an $ED_{50}$ is presented had values consistent with a D-2 action, i.e. between 5 and 50 nM vs. (*S*)-sulpiride. [b] Stimulation and inhibition of adenylate cyclase was determined at two to six compound concentrations each done in triplicate in a single experiment. This compound did not stimulate dopamine-sensitive adenylate cyclase or inhibit stimulation in the presence of 50 μM dopamine by >20%; therefore, it was considered inactive. [c] No response at 1 μM.

was filtered and the filtrate was concentrated. The residue was suspended in 20 mL of $H_2O$, and the mixture was extracted with $Et_2O$. After the $Et_2O$ extracts were washed with $H_2O$ and brine, they were concentrated. The residue was dissolved in MeOH–$Et_2O$ and treated with HCl to give **34f** (Table II).

**6,8-Dichloro-7-methoxy-2-(dimethylamino)tetralin Hydrochloride (34g).**[48,52,53] The hydrochloride **34f** (1.2 g, 4.2 mmol) was converted to base in the usual fashion ($NH_4OH$, $CH_2Cl_2$). A solution of the base in 5 mL of MeOH was added slowly to a solution of 0.8 g (12.3 mmol) of $NaCNBH_3$ and 2.2 mL (0.021 mol) of 37% aqueous formaldehyde in 10 mL of MeOH. After the mixture was stirred at 25 °C for 2 h (following an initial slight exotherm), it was adjusted to pH 6 with AcOH and stirred for an additional 16 h. The solution was concentrated, and the residue was made alkaline with 2.5 N NaOH. The aqueous mixture was extracted with $Et_2O$. After being washed with $H_2O$ and brine, the $Et_2O$ extracts were dried ($MgSO_4$) and concentrated. The residual liquid in MeOH–$Et_2O$ was treated with HCl to afford **34g** (Table II).

**6,8-Dichloro-7-methoxy-2-(di-*n*-propylamino)tetralin hydrochloride (34h)** was prepared from the base derived from **34f** in the same manner as described for conversion of **34c** to **34e**. The hydrochloride was prepared in the solvent indicated in Table II.

**Ethyl 6-Methoxy-5-nitro-1,2,3,4-tetrahydronaphthoate (37a) and Ethyl 6-Methoxy-7-nitro-1,2,3,4-tetrahydronaphthoate (37b).** To a stirred solution of 100 g (0.427 mol) of ethyl 1,2,3,4-tetrahydro-6-methoxynaphthoate (**36**)[63] in 220 mL of $Ac_2O$ at −5 °C was added dropwise 27 mL of 70% $HNO_3$. After being stirred at −5 to 0 °C for 1 h, the mixture was held at −10 °C for 20 h. The crystalline 7-nitro isomer **37b** was filtered and washed with EtOH to give 32.0 g (27%) of pale yellow crystals: mp 119–121 °C; $^1$H NMR δ 6.8 (s, 1 H, Ar*H* (5)), 7.7 (s, 1 H, Ar*H* (8)). Anal. ($C_{14}H_{17}NO_5$) C, H, N. The $Ac_2O$ filtrate was poured into 500 mL of ice–$H_2O$. The liquid phase was decanted from the resulting viscous residue that was triturated with EtOH to give 17.5 g (15%) of yellow crystals of the 5-nitro isomer **37a**, mp 92–95 °C, after recrystallization from EtOH: $^1$H NMR δ 6.8 (d, 1 H, Ar*H* (7)), 7.1 (d, 1 H, Ar*H* (8)). Anal. ($C_{14}H_{17}NO_5$) C, H, N.

**5-Chloro-6-methoxy-1,2,3,4-tetrahydronaphthoic Acid (38a).** A mixture of 24.4 g (87.5 mmol) of **37a** in 200 mL of HOAc and 0.9 g of 10% Pd/C catalyst was hydrogenated for 1 h at 25 °C and an initial pressure of 60 psi of $H_2$. After the mixture was filtered, the filtrate was concentrated to afford crude 5-amino derivative (16.9 g, 78%), mp 75–76 °C, after recrystallization from EtOH. This crude amino ester (10 g, 40 mmol) was suspended in 15 mL of $H_2O$ and 60 mL of 12 N HCl. The mixture was heated until solution occurred. After the resulting solution was cooled to 0 °C, 4.1 g (60 mmol) of $NaNO_2$ in 30 mL of $H_2O$ was added dropwise into the bottom of the reaction vessel while the temperature was maintained at 0 °C. After the reaction was stirred at 30 °C for 30 min, it was added slowly to a solution of 7.92 g (80 mmol) of freshly prepared CuCl[64] in 30 mL of 12 N HCl. The reaction mixture was stirred at 25 °C for 10 min and then at 100 °C for 1 h. The resulting mixture was diluted with 200 mL of $H_2O$ and extracted with EtOAc. The extracts were washed ($H_2O$, brine), dried ($MgSO_4$), and concentrated to give 4.6 g (48%) of crystals, mp 195–197 °C. Anal. ($C_{12}H_{13}ClO_3$) C, H.

**2-Amino-5-chloro-6-methoxytetralin hydrochloride (34i)** was prepared from **38a** in the same manner as that described for conversion of **35b** to **34f** (see Table II).

**5-Chloro-6-methoxy-2-(dimethylamino)tetralin hydrochloride (34j)** was obtained from **34i** in the same fashion as that detailed for conversion of **34f** to **34g** (see Table II).

**5-Chloro-6-methoxy-2-(di-*n*-propylamino)tetralin hydrochloride (34k)** was derived from **34i** by the same procedure as that described for conversion of **34c** to **34e** (see Table II).

**7-Chloro-6-methoxy-1,2,3,4-tetrahydronaphthoic acid (38b)** was prepared from **37b** in the same manner as described for conversion of **37a** to **38a**. The intermediate 7-amino derivative (77% crude yield), mp 78–81 °C, gave 73% of crystals, mp 163–165 °C. Anal. ($C_{12}H_{13}ClO_3$) C, H, Cl.

**2-Amino-7-chloro-6-methoxytetralin hydrochloride (34l)** was prepared from **38b** by a procedure identical with that described for conversion of **35b** to **34f** (see Table II).

**7-Chloro-6-methoxy-2-(dimethylamino)tetralin hydrochloride (34m)** was obtained from **34l** by a procedure identical with that detailed for conversion of the isocyanate derived from **33** to **34d** (see Table II).

**7-Chloro-6-methoxy-2-(di-*n*-propylamino)tetralin hydrochloride (34n)** was prepared from **34l** by a procedure identical with that employed for the conversion of **34c** to **34e** (see Table II).

**Pharmacology. Competition for [$^3$H]Fenoldopam in Rat Striatum.**[40] This assay performed with homogenized and washed membrane preparations from rat caudate nuclei was carried out as described previously.[40] In each experiment the amount of [$^3$H]fenoldopam bound was determined in the absence (total) and presence (nonspecific) of $10^{-6}$ M (+)-butaclamol, the difference yielding specific [$^3$H]fenoldopam binding. The ability of each compound to compete with [$^3$H]fenoldopam (approximately 2.0 nM) was tested at concentrations of $10^{-7}$ and $10^{-6}$ M. If a compound displaced fenoldopam by 50% at a concentration of $10^{-6}$ M, it was considered to have significant activity and was further tested to obtain an $IC_{50}$ for competition against fenoldopam. The $K_{Bind}$ of a compound was calculated from the equation $K_{Bind} = IC_{50}/(1 + L/K_D)$ where $L$ is the concentration of [$^3$H]fenoldopam and $K_D$ is the equilibrium dissociation constant for fenoldopam (2.3 ± 0.1 nM).

**Stimulation or inhibition of dopamine-sensitive adenylate cyclase** was carried out as described previously.[40] $EC_{50}$ values refer to the concentration of compound required to produce 50% of the maximum stimulation attainable with the test compound.

**Competition for [$^3$H]spiroperidol in bovine anterior pituitary** was performed as described previously.[40] The ability of each compound to compete with [$^3$H]spiroperidol (approximately 0.25 nM) was tested at concentrations of $10^{-5}$ and $10^{-7}$ M. Compounds displacing [$^3$H]spiroperidol by 50% or more were tested further to obtain an $IC_{50}$. The $K_{Bind}$ of a compound equals $IC_{50}/(1 + L/K_D)$ where $L$ is the concentration of [$^3$H]spiroperidol and $K_D$ is the dissociation constant for spiroperidol (0.3 nM).

**Isolated Perfused Rabbit Ear Artery Test.**[65,66] This test was conducted as described perviously.[65,66] The concentration-dependent inhibition of the constrictor response of the rabbit ear artery to brief intermittent periods of nerve stimulation was measured. The $EC_{50}$ is the concentration of drug required to produce 50% inhibition of the neuroeffector response (constriction) to nerve stimulation. Dissociation constants ($K_B$) for (*S*)-sulpiride, a selective $DA_2$ receptor antagonist, are expressed in nM concentrations and were determined according to the method of Furchgott.[72]

**Registry No.** **4a**, 103347-58-6; **4a**·HBr, 103347-79-1; **4b**, 103347-59-7; **4b**·HBr, 103347-38-2; **4c**, 103347-60-0; **4c**·HBr, 103347-39-3; **4d**, 103347-61-1; **4d**·HBr, 103347-40-6; **4e**, 103347-62-2; **4e**·HBr, 103347-41-7; **4f**, 103347-63-3; **4f**·HBr, 103347-42-8; **4g**, 103366-72-9; **4g**·HBr, 103347-43-9; **4h**, 103347-64-4; **4h**·HBr, 103347-44-0; **4i**, 103347-65-5; **4i**·HBr, 103347-45-1; **4j**, 103366-73-0; **4j**·HBr, 103347-46-2; **4k**, 103347-66-6; **4k**·HBr, 103347-47-3; **4l**, 103347-67-7; **4l**·HBr, 103347-48-4; **4m**, 103347-68-8; **4m**·HBr, 103366-71-8; **4n**, 103347-69-9; **4n**·HBr, 103347-49-5; **4o**, 103347-70-2; **4o**·HBr, 103347-50-8; **4p**, 103347-71-3; **4p**·HBr, 103347-51-9; **4q**, 103347-72-4; **4q**·HBr, 103347-52-0; **4r**, 103347-73-5; **4r**·HBr, 67544-45-0; **4s**, 103347-74-6; **4s**·HBr, 103347-53-1; **4t**, 103347-75-7; **4t**·HBr, 103347-54-2; **4u**, 103347-76-8; **4u**·HBr, 103347-55-3; **4v**, 103347-77-9; **4v**·HBr, 103347-56-4; **4w**, 103347-78-0; **4w**·HBr, 103347-57-5; **5a**, 78495-65-5; **5b**, 6834-51-1; **6a**, 103346-70-9; **6b**, 103346-71-0; **7a** (Y = OTs), 103346-72-1; **7b** (Y = Br), 103346-73-2; **8a**, 103346-74-3; **8b**, 103346-75-4; **9a**, 103346-76-5; **9b**, 103346-77-6; **10a**, 103346-78-7; **10b**, 103346-79-8; **11a**, 103346-80-1; **11a** ethyl ester, 103346-81-2; **11a** acid chloride, 103346-85-6; **11a** acid azide, 103346-86-7; **11b**, 103346-82-3; **11b** ethyl ester, 103346-83-4; **12**, 103346-89-0; **13**, 103346-90-3; **14a**·HCl, 103346-91-4; **14b**·HCl, 103346-92-5; **15**, 5417-17-4; **16**, 103346-95-8; **17a**, 103346-96-9; **17b**, 103346-97-0; **18**·HCl, 103346-98-1; **19**·HCl, 103346-99-2; **20a**, 103347-00-8; **20b**·HCl, 103347-01-9; **21**, 103347-02-0; **22**, 331-42-0; **23**, 345-08-4; **24a**, 103347-03-1; **24b**, 103347-04-2; **25**·HCl, 103347-05-3; **26a**·HCl, 103347-06-4; **26b**, 103347-07-5; **27a**, 103347-08-6; **27b**, 103347-09-7; **28a**, 103347-10-0; **28b**, 103347-11-1; **28c**, 103347-12-2; **29**·HCl, 103347-13-3; **30**, 103347-14-4; **31**, 103347-15-5; **31** (triethyl ester), 103347-16-6; **32**, 103347-17-7; **33**, 103347-18-8; **33** (isocyanate), 103347-21-3; **34** (X = 5-F; 6,7-$(MeO)_2$; $R^1$ = H; $R^2$ = Cbz), 103346-87-8; **34** (X = 6,7-$(MeO)_2$; 8-Cl; $R^1$ = H; $R^2$ = Cbz), 103347-80-4; **34a**·HCl, 103346-84-5; **34b**·HCl, 103346-88-9; **34c**·HCl, 103347-19-9; **34d**·HCl, 103347-20-2; **34e**·HCl, 103347-22-4; **34f**·HCl, 103347-25-7; **34g**·HCl, 103347-26-8; **34h**·HCl, 103347-27-9; **34i**·HCl, 103347-31-5; **34j**·HCl, 103347-32-6; **34k**·HCl, 103347-33-7; **34l**·HCl, 103347-34-8; **34m**·HCl, 103347-35-9; **34n**·HCl, 103347-36-0; **35a**, 103347-23-5; **35b**, 103347-24-6; **36**, 88285-43-2; **37a**, 103347-28-0; **37a** (5-amino deriv.), 103347-81-5; **37b**, 103347-29-1; **38a**, 103347-30-4; **38b**, 103347-37-1; CH $(CO_2Et)_2$, 105-53-3; $CO_2MeCH_2CH_2CO_2Me$, 106-65-0; $CH_3CH_2CHO$, 123-38-6; 4-$MeOC_6H_4CH_2COCl$, 4693-91-8; 2-$MeOC_6H_4F$, 321-28-8; 4-MeO-3-F-$C_6H_3$-$CO(CH_2)_2CO_2H$, 347-63-7; $NH(Pr)_2$, 142-84-7; 3,4-dimethoxy-2-fluorobenzeneacetonitrile, 7537-08-8; 2-(2-chloro-3,4-dimethoxybenzylidene)succinic acid dimethyl ester, 103346-93-6; 2-(2-chloro-3,4-dimethoxybenzyl)succinic acid dimethyl ester, 103346-94-7; succinic anhydride, 108-30-5; 2-chloro-5-methylanisole, 73909-16-7; 2-chloro-5-methylphenol, 615-74-7; triethyl 1,1,2-ethanetricarboxylate, 7459-46-3; 6(or 7)-methoxy-8-fluoro-2-tetralone, 103347-83-7.