Compound 13 was obtained as a colorless amorphous powder: yield 230 mg (89%). For homogenicity criteria and characterization, see Tables III and IV.

Adip[(Lys(H·CH_3CO_2H))$_{10}$-OSuco]$_2$ (11a). Compound 11 (360 mg, 66.78 μmol) was deprotected and worked up as described for **10b**: yield 300 mg (98%).

Adip[(Lys(BPO))$_{10}$-OSuco]$_2$ (14). Compound **11a** (115 mg, 25.1 μmol) and potassium benzylpenicillinate (186 mg, 0.501 mmol) were dissolved in H_2O (1.5 mL), and the pH was brought to 11 by adding 3 M K_2CO_3. After 12 and 24 h again potassium benzylpenicillinate (186 mg, 0.501 mmol) was added and the pH adjusted to 11. After 36 h the reaction mixture was worked up as described for **13**. After demineralization and lyophilization, **14** was obtained as a colorless, amorphous powder: yield 306 mg (90%). For homogenicity criteria and characterization, see Tables III and IV.

Immunological Methods. Immunizations. Six to eight weeks old BALB/c mice of either sex were obtained from Blomholtgård, Ry, Denmark, and assembled in groups of four, mice were immunized by intraperitoneal injections of 6 or 10 μg BPO_9-Asc absorbed on 2 mg $Al(OH)_3$. BPO_9-Asc was prepared as described elsewhere.[49] Each mouse was bled from the retical orbital sinus as indicated in Figures 1 and 2, and pooled sera were assayed for anti-BPO and anti-Asc IgE titers.

Determination of IgE Titers. IgE titers were evaluated using rat passive cutaneous anaphylaxis (PCA) as described by Watanabe and Ovary.[50] In brief, Wistar rats of either sex, weighing 200–280 g, were obtained from the Institute's own animal facilities and were intradermally injected (100 μL) with the diluted mouse sera (1/5, 1/10, ..., 1/1280). After 24 h, 2 μmol of $(BPO)_{20}$-polylysine or 4 mg of Asc, dissolved in 1 mL 0.5% Evans blue, was injected intravenously. After 20 min the BPO or Asc specific anaphylactic reaction was read. All reactions were set up in duplicate, and the titer was expressed as the reciprocal of the antiserum dilution yielding a reaction of 5-mm diameter (endpoint). The maximal variation is one doubling dilution step.

Acknowledgment. This work was supported by the Swiss National Foundation for Scientific Research (Grant 3.725-0.80). I thank Prof. C. H. Schneider for taking interest in this work and Dr. H. P. Rolli for many helpful discussions.

Registry No. **1**, 91177-68-3; **2**, 47551-11-1; **2a**, 91110-85-9; **2b**, 91110-86-0; **3a**, 91110-88-2; **4**, 91110-83-7; **5**, 91110-84-8; **6**, 91129-62-3; **7**, 91129-63-4; **8**, 90522-20-6; **9**, 91129-64-5; **10**, 91239-82-6; **10a**, 91110-89-3; **10b**, 91110-91-7; **11**, 91239-83-7; **11a**, 91110-93-9; **12**, 91239-84-8; **12**·Na, 87713-97-1; **13**, 91239-86-0; **14**, 91239-85-9; Nps-(Lys(Boc))-OSuco, 91110-87-1; Nps-Lys(Boc)-OH, 47551-11-1; H-(Lys(Boc))$_7$-OSuco, 91110-94-0; Nps-Lys(Boc)-ONSu, 60654-30-0; Boc-Lys(Boc)-ONSu, 30189-36-7; mono-3β-cholestanyl succinate, 91177-69-4; 1,4-bis(hydroxymethyl)benzene, 589-29-7; adipinic acid, 124-04-9; potassium benzylpenicillinate, 113-98-4.

(49) K. Blaser, T. Nakagawa, and A. L. de Weck, *J. Immunol.*, **125**, 24 (1980).

(50) N. Watanabe and Z. Ovary, *J. Immunol. Methods*, **14**, 381 (1977).

Nontricyclic Antidepressant Agents Derived from *cis*- and *trans*-1-Amino-4-aryltetralins

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The need for drugs that lack the obtrusive and limiting side effects of the tricyclic antidepressants has prompted the search for agents with greatly enhanced selectivity for specific mechanisms believed to be essential for antidepressant efficacy. The potential role of derangements of 5-HT pathways in the etiology of depression has long been suspected and has given impetus to the development of newer compounds that accentuate inhibition of serotonin reuptake. This paper presents structure–activity relationships for a series of *cis*-1-amino-4-(substituted-aryl)tetralins, which are surprisingly potent and selective inhibitors of serotonin uptake in in vitro models. These compounds are pharmacologically distinct from corresponding members of the trans series, which also potently block uptake of dopamine and norepinephrine. The activity in both cis and trans series is stereospecific, being restricted to the cis-(1*S*,4*S*) and the trans-(1*R*,4*S*) enantiomers.

Research directed toward establishing an etiology of endogenous depression on a molecular basis has continued over two decades. The early "catecholamine hypothesis" of Schildkraut,[1] suggesting a deficiency of monoamine neurotransmitters at their postsynaptic receptors, led to the discovery of maprotiline, desmethylimipramine, and nortriptyline, compounds that are relatively specific inhibitors of norepinephrine (NE) uptake.[2,3] The slow onset of clinical improvement with these antidepressants has led to recent proposals that desensitization of norepinephrine transmission (down regulation of β-adrenoreceptors) is involved in the therapeutic activity of antidepressants.[4] Other investigators have suggested a role for serotonin in depression.[5,6] Supporting the latter view are observations that certain subgroups of depressed patients responded better to an antidepressant with more serotonin uptake blocking activity[7,8] and other reports suggesting that the serotonin synthesis inhibitor *p*-chlorophenylalanine caused rapid, reversible relapse of depressed patients stabilized with imipramine[9] or tranylcypromine.[10] The search for more selective serotonin uptake blockers with reduced anticholinergic and cardiovascular liabilities of the tricyclic antidepressants has resulted in newer agents like zimelidine, fluvoxamine, and fluoxetine, which are reported to exert antidepressant activity in man.[11]

(1) Schildkraut, J. J. *Am. J. Psychiat.* **1965**, *122*, 509.
(2) Pinder, R. M.; Brogden, R. N.; Speight, T. M.; Avery, G. S. *Drugs* **1977**, *13*, 321.
(3) Salama, A. I.; Insalaco, J. R.; Maxwell, R. A. *J. Pharmacol. Exp. Ther.* **1971**, *178*, 474.
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(9) Shopsin, B.; Gershon, S.; Goldstein, M.; Friedman, E.; Wilk, S. *Psychopharmacol. Commun.* **1975**, *1*, 239.
(10) Shopsin, B.; Friedman, E.; Gershon, S. *Arch. Gen. Psychiatry* **1976**, *33*, 811.

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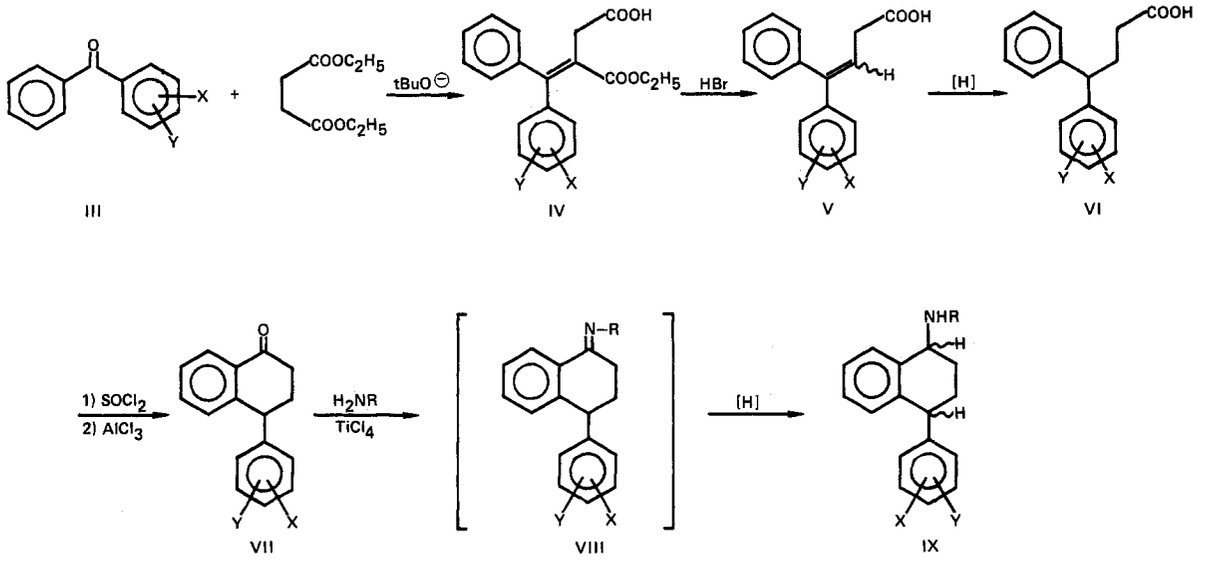
Scheme I



Earlier studies from these laboratories revealed that compounds from a series of *trans*-1-amino-4-phenyltetralins (I) possessed potent norepinephrine (NE) uptake blocking activity. Thus, *trans*-(1*R*,4*S*)-4-phenyl-1-(methylamino)tetralin (I, R_1 = H, R_2 = CH_3) is a potent in-

I II

hibitor of NE uptake in rat brain synaptosomes,[12] reverses reserpine-induced hypothermia in mice, and blocks uptake of [^{3}H]NE into rat heart,[13] all effects characteristic of antidepressant agents of the NE uptake blocking type. This activity was highly specific for the 1*R*,4*S* enantiomer and was confined solely to the trans derivatives. The corresponding 1*S*,4*R* isomer was much less active, and the diastereoisomeric cis racemates II were virtually inactive as monoamine uptake blockers.

Although effects of substitution on nitrogen in I had previously been explored,[13] no systematic study of aromatic substitution had been undertaken. Comparison of molecular geometries and substituent effects of a number of inhibitors of monoamine uptake[12] suggested to us the possibility that this type of substitution, particularly in the 4-aryl ring, might enhance activity. As will be discussed below, this hypothesis was confirmed by the discovery of potent new compounds in the trans series. In addition, we have found that many compounds from the 4-(substituted-aryl) diastereoisomeric cis series are unexpectedly potent and selective inhibitors of serotonin (5-HT) uptake and are thus pharmacologically distinct from compounds of the trans series.

Chemistry. The compounds of the present series were prepared by two routes (Schemes I and II) that have been previously described[14] for the preparation of 4-aryl-1-aminotetralins. The route outlined in Scheme I was utilized for those compounds bearing electron-withdrawing substituents in the pendant aryl ring. As expected, Friedel–Crafts cyclization of the diarylbutyric acid derivatives VI to the most reactive ring was observed with little or none of the alternate isomer being detected. To prepare compounds with electron-donating substituents in the 4-ring, the procedure in Scheme II was used. The $KMnO_4$ oxidation of the 1-phenyltetralins XII was observed to give 4-hydroxy-4-aryltetralones XIII instead of the expected tetralone VII as previously reported.[14] As a result of this finding, direct oxidation of Grignard adduct X was attempted and was found to be a more efficient route to XIII. Subsequent conversion of keto alcohol XIII to imine XIV and reduction with sodium borohydride gave a mixture of amino alcohols XV. This mixture could be smoothly dehydrated to dihydronaphthalene XVI and then catalytically reduced to yield the desired diastereoisomeric mixture IX.

Racemic cis and trans diastereoisomers of each IX pair were separated by column chromatography. In several instances, these compounds were further resolved into optically active enantiomers by fractional crystallization of diastereoisomeric salts.

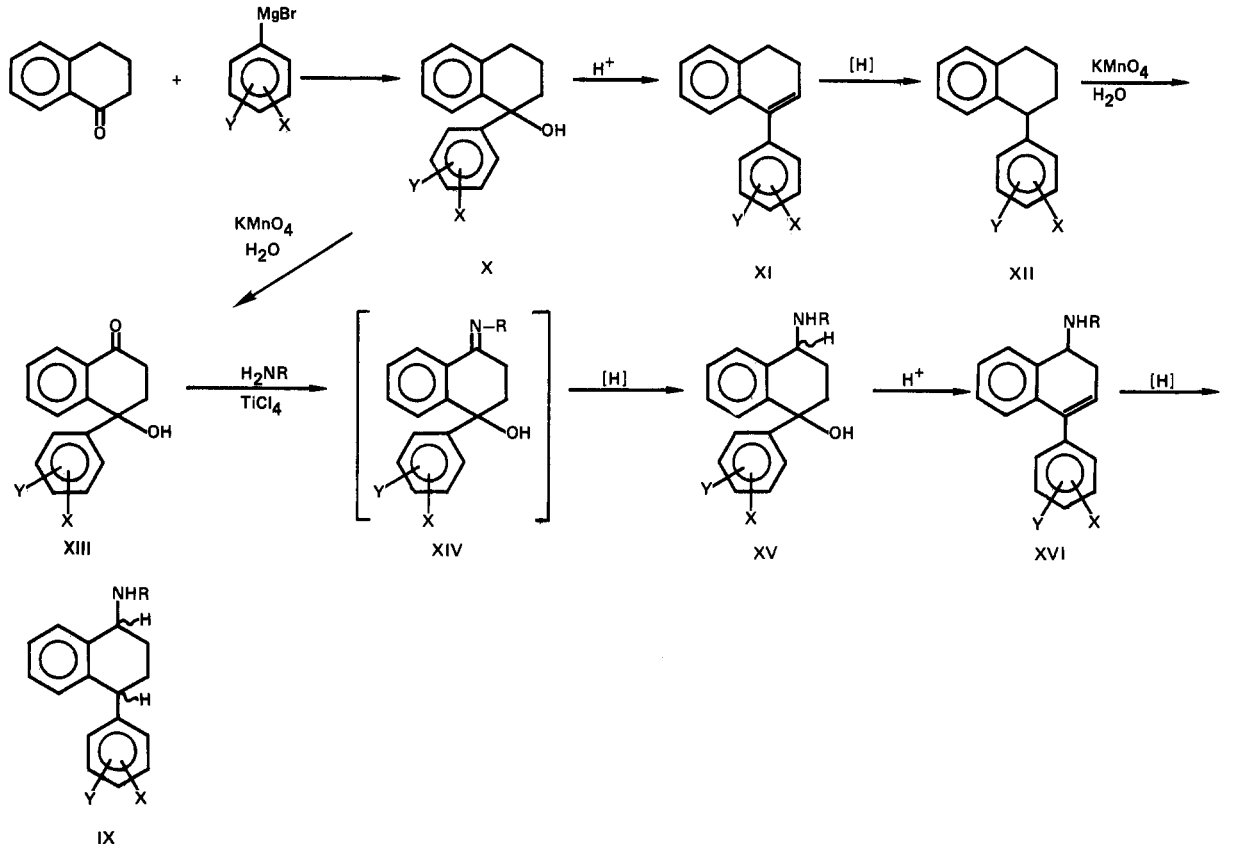
Earlier attempts[14] to resolve *cis*-1-(methylamino)-4-phenyl-1,2,3,4-tetrahydronaphthalene (II, R_1 = H, R_2 = CH_3) were unsuccessful, even though a number of attempts involving a variety of resolving agents had been tried. This problem was solved in the present instance by oxidation and hydrolysis of the resolved trans enantiomers **44** and **45** to the corresponding 4*S* and 4*R* ketones XVII and XVIII. Each ketone was then reductively aminated, and

XVII XVIII

the resulting optically active diastereoisomers were separated chromatographically to give compounds **50** and **51**. Since the absolute configurations of **44** and **45** are known,[13]

(11) Shopsin, B.; Cassano, G. B.; Conti, L. In "Antidepressants: Neurochemical, Behavioral and Clinical Perspectives"; Enna, S. J., Malick, J. B., Richelson, E., Ed.; Raven Press: New York, 1981; pp 219–251.
(12) Koe, B. K. *J. Pharmacol. Exp. Ther.* **1976**, *199*, 649.
(13) Sarges, R.; Koe, B. K.; Weissman, A.; Schaefer, J. P. *J. Pharmacol. Exp. Ther.* **1974**, *191*, 393.
(14) Sarges, R. *J. Org. Chem.* **1975**, *40*, 1216.

Scheme II



compound **50** is of the 1*S*,4*S* geometry while the configuration of **51** is 1*R*,4*R*.

Discussion

Cis and trans racemic diastereoisomers obtained from the synthetic procedures outlined above were initially tested in vitro for their ability to inhibit the uptake of [^{3}H]DA and [^{3}H]-5-HT in corpus striatum and of [^{3}H]NE in hypothalamus of rats. The concentration of drug blocking uptake by 50% (IC_{50}) was estimated on log probit paper[15] from data obtained at several concentrations and is presented as means of from two to eight runs. The procedure is described fully under Biological Methods in the Experimental Section.

The monoamine uptake blocking activities of the variously substituted trans aminotetralins synthesized in this study are summarized in Table I. The unsubstituted analogue **1** is an effective inhibitor of NE uptake,[12] approximating imipramine and nomifensine in this respect and displays modest DA uptake and weak 5-HT uptake blocking activity. Substitution of electron-withdrawing halogen moieties in the 4-position of the 4-aryl ring left NE uptake blocking activity relatively unchanged but enhanced DA activity somewhat and 5-HT uptake blocking activity dramatically, especially in the chloro and bromo compounds **3** and **4**, which display potent activity vs. all three neurotransmitters in this test. Trifluoromethyl substitution in either the 4- or 3-positions (compounds **5** and **6**) caused a marked and somewhat surprising decrease in activity compared to the 4-halogen derivatives. Additional chlorine substitution in the 3-position of **3**, giving the 3,4-dichloro species **7**, led to the most potent trans derivative, a compound highly active vs. all three neurotransmitters, but insertion of the second halogen into the 2-position (compound **8**) causes a loss of activity. Substitution of a methoxy group in the 3- or 4-position (compounds **11** and **12**) enhanced 5-HT uptake blockade relative to **1**, but methoxy substitution in the 2-position (compound **13**) decreased activity against all three neurotransmitters. These findings suggest that specific steric as well as electronic requirements exist for potent activity in the trans series.

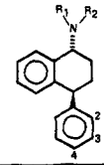
Methylation of compounds **1**, **3**, **5**, **6**, and **7** gave the *N*,*N*-dimethyl analogues **16–20**. The primary result of this substitution appears to be a decrease in NE uptake blocking activity without much effect on 5-HT activity. Compounds **18** and **19** now become selective for 5-HT but are not exceedingly potent in comparison with compounds from the cis series (vide infra). Since metabolism is unlikely in this in vitro assay, the results reflect the intrinsic activity of the compounds regarding uptake blocking activity. In vivo, however, demethylation to the secondary amines would be an anticipated process,[16] and prediction of the in vivo activity of **16–20** would probably be more accurately derived from consideration of the relative activities of their monosubstituted analogues.

Monoamine uptake blocking properties of variously substituted *cis*-4-aryl-1-aminotetralins are summarized in Table II. It had earlier been determined that the unsubstituted analogue **21** and a number of its analogues variously substituted on nitrogen lacked significant monoamine uptake blocking activity.[12,13] However, substitution in the 4-aryl group provided some surprising results, the most significant of which involved several compound displaying selective enhancement of 5-HT activity. For example, substitution with electron-withdrawing groups such as Cl, Br, or CF_3 in the 4-position of this ring strongly

(15) Horn, A. S.; Coyle, J. T.; Snyder, S. H. *Mol. Pharmacol.* **1971**, *7*, 66.

(16) Testa, B.; Jenner, P. "Drug Metabolism: Chemical and Biochemical Aspects"; Marcel Dekker: New York, 1976; p 82.

Table I. Inhibition of Monoamine Uptake by Trans Aminotetralin Derivatives



compd	R_1	R_2	2-	3-	4-	mp, °C	formula[a]	inhibn of monoamine uptake in synaptosomal preparations of rat brain: IC_{50},[b] μM: corpus striatum DA	corpus striatum 5-HT	hypothalamus NE
1	H	CH_3	H	H	H	222–224	$C_{17}H_{19}N\cdot HCl$	0.21	1.48	0.04
2	H	CH_3	H	H	F	210–211	$C_{17}H_{18}NF\cdot HCl$	0.22	0.58	0.03
3	H	CH_3	H	H	Cl	247–250	$C_{17}H_{18}NCl\cdot HCl$	0.10	0.12	0.03
4	H	CH_3	H	H	Br	288–289	$C_{17}H_{18}NBr\cdot HCl$	0.08	0.09	0.03
5	H	CH_3	H	H	CF_3	260–261	$C_{18}H_{18}NF_3\cdot HCl$	4.40	0.43	0.69
6	H	CH_3	H	CF_3	H	143–145	$C_{18}H_{18}NF_3\cdot C_4H_4O_4$	2.60	0.39	0.26
7	H	CH_3	H	Cl	Cl	214–216	$C_{17}H_{17}NCl_2\cdot HCl$	0.06	0.05	0.02
8	H	CH_3	Cl	H	Cl	195–196	$C_{17}H_{17}NCl_2\cdot HCl\cdot {}^1/_8H_2O$	6.10	1.05	0.97
9	H	CH_3	H	CF_3	Cl	218–219	$C_{18}H_{17}NClF_3\cdot HCl$	7.30	1.40	0.89
10	H	CH_3	H	OCH_3	F	168–170	$C_{18}H_{20}NOF\cdot C_4H_4O_4\cdot H_2O$	1.20	0.60	0.34
11	H	CH_3	H	H	OCH_3	230–233	$C_{18}H_{21}NO\cdot HCl\cdot {}^1/_8H_2O$	0.40	0.38	0.15
12	H	CH_3	H	OCH_3	H	166–169	$C_{18}H_{21}NO\cdot HCl$	0.53	0.34	0.06
13	H	CH_3	OCH_3	H	H	201–203	$C_{18}H_{21}NO\cdot HCl\cdot {}^1/_3H_2O$	5.70	4.50	0.48
14	H	CH_3	H	H	OC_4H_9	181–182	$C_{21}H_{27}NO\cdot HCl\cdot {}^1/_4H_2O$	6.80	7.00	1.15
15	H	CH_3	H	H	OC_6H_5	183–184	$C_{23}H_{23}NO\cdot HCl\cdot {}^1/_8H_2O$	8.40	12.00	2.30
16	CH_3	CH_3	H	H	H	228–230	$C_{18}H_{21}N\cdot HCl$	0.84	0.46	0.14
17	CH_3	CH_3	H	H	Cl	140–141	$C_{18}H_{20}NCl\cdot HCl\cdot {}^1/_2H_2O$	0.38	0.12	0.13
18	CH_3	CH_3	H	H	CF_3	120–122	$C_{19}H_{20}NF_3\cdot C_4H_4O_4\cdot {}^1/_4H_2O$	9.80	0.49	4.70
19	CH_3	CH_3	H	CF_3	H	99–101	$C_{19}H_{20}NF_3\cdot C_4H_4O_4\cdot {}^1/_2H_2O$	6.10	0.22	1.40
20	CH_3	CH_3	H	Cl	Cl	229–231	$C_{18}H_{19}NCl_2\cdot HCl\cdot {}^1/_4H_2O$	0.17	0.04	0.04
imipramine								20.00	0.81	0.06
nomifensine								0.41	5.40	0.02

[a] Analyses for C, H, and N were within ±0.4% of the theoretical values. [b] The concentration of test compound inhibiting uptake of each neurotransmitter by 50% as described in the Experimental Section. IC_{50} values are means of two to eight determinations.

enhanced 5-HT uptake blocking activity while DA and NE values remained relatively unchanged (compounds **23–25**). Incorporation of an additional chlorine substituent in the 3-position of **23** further enhanced both 5-HT uptake blocking potency and selectivity, leading to the highly potent and selective 3,4-dichloro derivative **27**. Substitution with a CF_3 group in the 3-position of **23** yielded **26**, a selective 5-HT uptake inhibitor with good potency. In the cis series, substitution in the 2-position was not as deleterious to potency (compounds **28** and **33**) as it was in the trans series (cf. compounds **8** and **13**), but both the 2,4-dichloro derivative **28** and the 2-methoxy derivative **33** lacked 5-HT selectivity. These results suggest that electronic and geometric requirements for blockade of 5-HT uptake mechanisms are quite stringent but that spatial requirements for substituents on the aromatic ring are somewhat more lenient than for NE uptake blockade, the cis-3-CF_3,4-Cl derivative **29** being quite active with regard to 5-HT in this test. These compounds are also relatively inactive toward blockade of DA uptake in tissues of the corpus striatum. This property can be perceived as a potential advantage in that enhanced synaptosomal DA levels may be equated with undesirable stimulant properties of certain compounds of the trans series.[17]

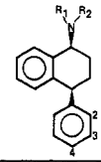
Cis compounds **36–40** disubstituted on nitrogen were generally very selective 5-HT uptake blockers, although most were less potent than **27** in this respect. In relative terms, several of the disubstituted analogues were superior to **27** with regard to selectivity, the DA/5-HT and NE/5-HT ratios (for, e.g., **38**) being exceptionally high. With regard to intrinsic activity, arguments presented above for disubstituted trans compounds must certainly pertain here, and potential in vivo activity should be predicted on the basis of the activities of monosubstituted derivatives.

Since *N*-methyl analogues such as **23**, **25**, and **27** might also be subject to rapid demethylation metabolically,[16] it was of interest to determine how the activity of such compounds would change after metabolism. The primary amines **41–43** were prepared for evaluation, and the results of testing (Table II) demonstrate the demethylated derivatives are substantially less active than the parents. It would therefore appear that in vivo activity would derive primarily from N-alkylated analogues.

As was previously mentioned,[13] resolution of compounds **1** demonstrated that the activity of this compound derived

(17) Spyraki, C.; Fibiger, H. C. *Science* **1981**, *212*, 1167.

Table II. Inhibition of Monoamine Uptake by Cis Aminotetraline Derivatives



compd	R_1	R_2	2-	3-	4-	mp, °C	formula[a]	inhibn of monoamine uptake in synaptosomal preparations of rat brain: IC_{50},[b] μM: corpus striatum DA	corpus striatum 5-HT	hypothalamus NE
21	H	CH_3	H	H	H	238–239	$C_{17}H_{19}N\cdot HCl$	5.10	3.50	1.86
22	H	CH_3	H	H	F	281–282	$C_{17}H_{18}NF\cdot HCl$	4.70	1.70	2.30
23	H	CH_3	H	H	Cl	267–269	$C_{17}H_{18}NCl\cdot HCl$	1.38	0.26	1.41
24	H	CH_3	H	H	Br	274–275	$C_{17}H_{18}NBr\cdot HCl$	1.60	0.19	1.40
25	H	CH_3	H	H	CF_3	274–275	$C_{18}H_{18}NF_3\cdot HCl$	7.80	0.82	9.80
26	H	CH_3	H	CF_3	H	260–261	$C_{18}H_{18}NF_3\cdot HCl$	2.54	0.25	2.55
27	H	CH_3	H	Cl	Cl	275–277	$C_{17}H_{17}NCl_2\cdot HCl$	0.52	0.07	0.72
28	H	CH_3	Cl	H	Cl	288–289	$C_{17}H_{17}NCl_2\cdot HCl$	1.70	0.50	0.31
29	H	CH_3	H	CF_3	Cl	253–254	$C_{18}H_{17}NClF_3\cdot HCl\cdot {}^1/_2H_2O$	1.50	0.22	4.30
30	H	CH_3	H	OCH_3	F	240–242	$C_{18}H_{20}ONF\cdot HCl$	0.85	0.38	3.30
31	H	CH_3	H	H	OCH_3	224–226	$C_{18}H_{21}NO\cdot HCl\cdot {}^1/_8H_2O$	4.20	0.70	3.00
32	H	CH_3	H	OCH_3	H	226–227	$C_{18}H_{21}NO\cdot HCl\cdot {}^1/_4H_2O$	5.00	0.76	1.40
33	H	CH_3	OCH_3	H	H	247–248	$C_{18}H_{21}NO\cdot HCl\cdot {}^1/_3H_2O$	11.20	4.20	2.30
34	H	CH_3	H	H	OC_4H_9	147–150	$C_{21}H_{27}NO\cdot HCl\cdot {}^1/_2H_2O$	12.50	5.80	0.94
35	H	CH_3	H	H	OC_6H_5	256–257	$C_{23}H_{23}NO\cdot HCl\cdot {}^1/_2H_2O$	6.80	9.40	3.90
36	CH_3	CH_3	H	H	H	192–194	$C_{18}H_{21}N\cdot HCl$	10.00	1.60	0.31
37	CH_3	CH_3	H	H	Cl	125–126	$C_{18}H_{20}NCl\cdot HCl\cdot {}^3/_4H_2O$	5.60	0.24	1.16
38	CH_3	CH_3	H	H	CF_3	144–146	$C_{19}H_{20}NF_3\cdot C_4H_4O_4$	12.20	0.35	14.20
39	CH_3	CH_3	H	CF_3	H	120–121	$C_{19}H_{20}NF_3\cdot C_4H_4O_4\cdot {}^1/_4H_2O$	7.00	0.19	0.89
40	CH_3	CH_3	H	Cl	Cl	199–202	$C_{18}H_{19}NCl_2\cdot CH_3SO_3H$	2.00	0.07	0.40
41	H	H	H	Cl	Cl	>295	$C_{16}H_{15}NCl_2\cdot HCl$	1.25	0.40	0.25
42	H	H	H	CF_3	H	270–271	$C_{17}H_{16}NF_3\cdot HCl$	4.70	4.10	3.50
43	H	H	H	H	CF_3	273–274	$C_{17}H_{16}NF_3\cdot HCl\cdot {}^3/_4H_2O$	10.00	5.60	7.50
zimelidine								43.00	4.50	12.00
fluvoxamine								45.00	0.54	1.90

[a] Analyses for C, H, and N were within ±0.4% of the theoretical values. [b] The concentration of test compound inhibiting uptake of each neurotransmitter by 50% as described in the Experimental Section. IC_{50} values are means of two to eight determinations.

primarily from the dextrorotatory 1*R*,4*S* isomer **44** (Table III). The 4-chloro and 3,4-dichloro trans compounds **3** and **7** from the present series were resolved during this study, and a similar pattern emerged. The dextro enantiomers **46** and **48** retained substantially all of the uptake blocking activity, and the levo enantiomers **47** and **49** were substantially less active. Among cis compounds, however, a different result was obtained in that a separation of activities was seen. This separation fortuitously enhanced the already surprising selectivity of these compounds in that the dextro enantiomers in all cases retained essentially all of the 5-HT uptake blocking activity, whereas the levo enantiomers were more potent in blocking DA activity than were the racemates. This is illustrated most graphically by the resolution of compound **27**. The dextro isomer **58** is several times as selective for 5-HT uptake blocking activity as the levo isomer **59**, which is a relatively potent and selective DA uptake blocker. Compound **58**[18] exhibits the full range of in vitro biochemical and in vivo behavioral effects expected of a potent and selective 5-HT uptake blocker. The results of the complete pharmacological evaluation of compound **58** have been reported in greater detail elsewhere.[19]

Single-crystal X-ray analysis of compound **58** demonstrates that the absolute configuration of the molecule is 1*S*,4*S*.[20]

Experimental Section

Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on Varian A-60, T-60, and XL-100 spectrometers with Me_4Si as an internal standard. IR spectra were determined with a Perkin-Elmer Model 21 spectrometer. UV spectra were recorded on a Cary Model 14 spectrometer. Mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department.

3-(Ethoxycarbonyl)-4-(3,4-dichlorophenyl)-4-phenylbut-3-enoic Acid (IV, X = Y = 3,4-Cl_2). A solution of 3,4-di-

(18) Compound **58** (CP-51,974-1) has been assigned the United State Adopted Name sertraline hydrochloride by the USAN Council.

(19) Koe, B. K.; Weissman, A.; Welch, W. M.; Browne, R. G. *J. Pharmacol. Exp. Ther.* **1983**, *226*, 686.

(20) Bordner, J.; Welch, W. M., unpublished results.

Table III. Monoamine Uptake Blocking Properties of Resolved Trans and Cis Aminotetraline Derivatives

				inhibn of monoamine uptake in synaptosomal preparations of rat brain: IC_{50}, μM		
				corpus striatum		hypothalamus
compd	conformation	$[\alpha]_D$	substituent(s)	DA	5-HT	NE
1	trans		H	0.21	1.48	0.037
44		+41.2		0.15	0.84	0.018
45		−41.4		1.40	14.00	0.37
3	trans		4-Cl	0.10	0.12	0.03
46		+48.2		0.052	0.084	0.019
47		−50.6		1.40	3.50	0.46
7	trans		3,4-Cl_2	0.06	0.05	0.022
48		+41.0		0.044	0.039	0.01
49		−39.2		0.27	0.47	0.044
21	cis		H	5.10	3.50	1.86
50		+39.5		5.50	3.50	1.80
51		−38.7		10.20	11.60	4.20
23	cis		4-Cl	1.38	0.26	1.41
52		+38.9		3.40	0.50	4.25
53		−41.0		1.40	2.30	1.05
25	cis		4-CF_3	7.80	0.82	9.80
54		+32.8		6.40	1.10	9.40
55		−33.0		5.60	2.20	12.00
26	cis		3-CF_3	2.54	0.25	2.55
56		+11.4		9.70	0.20	2.70
57		−11.6		2.50	3.10	7.80
27	cis		3,4-Cl_2	0.52	0.074	0.72
58		+37.9		1.30	0.06	1.20
59		−37.2		0.32	0.46	0.30
29	cis		4-Cl, 3-CF_3	1.50	0.22	4.30
60		+27.8		6.20	0.37	4.90
61		−28.5		0.49	1.22	2.30

chlorobenzophenone[21] (398 g, 1.58 mmol) in *tert*-butyl alcohol (1500 mL) was treated sequentially with potassium *tert*-butoxide (169 g, 1.5 mol) and diethyl succinate (402 mL, 2.4 mol). A mildly exothermic reaction ensued and the initially clear solution set up as a solid mass. The reaction mixture was slowly heated to reflux, at which time it became a stirrable white suspension, which was then stirred at reflux under nitrogen for about 16 h. The reaction mixture was then cooled and poured into 2 L of ice/water. The resulting mixture was acidified with 10% HCl and extracted with ethyl acetate (3 × 1 L). The combined ethyl acetate extract was extracted with 1 N NH_4OH (3 × 1 L), and the combined aqueous basic extract was washed with ethyl acetate (2 L), cooled to 0–5 °C, acidified slowly to a pH below 1.0 with concentrated HCl, and extracted with ethyl acetate (4 × 2 L). The combined ethyl acetate extract was dried ($MgSO_4$) and evaporated under vacuum to a light yellow oil slightly contaminated with diethyl succinate (477 g, 80% yield). An analytical sample was crystallized from petroleum ether, mp 128–130 °C. Anal. ($C_{19}H_{16}Cl_4O_2$) C, H, Cl.

4-(3,4-Dichlorophenyl)-4-phenylbut-3-enoic Acid (V, X = Y = 3,4-Cl_2). A suspension of 3-(ethoxycarbonyl)-4-(3,4-dichlorophenyl)-4-phenylbut-3-enoic acid (227 g, 0.60 mol) in 48% aqueous HBr–glacial acetic acid (1:1, 1.80 L) was stirred at reflux for 36 h and was then cooled to room temperature. A gum separated from the reaction mixture, which was isolated by decantation of the aqueous layer and then dissolved in ethyl acetate (2 L). The resulting organic solution was extracted with 10% aqueous NH_4OH (2 × 2 L). The combined extract was cooled to 0–5 °C, acidified slowly to a pH below 1.0 with concentrated HCl, and extracted with ethyl acetate (3 × 1 L). The combined ethyl acetate extract was washed with water, dried ($MgSO_4$), and evaporated under vacuum to a light brown oil (120 g), which was crystallized from hexane (91.4 g, 50% yield, mp 115–120 °C). An analytical sample was recrystallized from hot ethyl acetate–hexane, mp 147–148 °C. Anal. ($C_{16}H_{12}Cl_2O_2$) C, H, Cl.

4-(3,4-Dichlorophenyl)-4-phenylbutanoic Acid (VI, X = Y = 3,4-Cl_2). A solution of 4-(3,4-dichlorophenyl)-4-phenylbut-3-enoic acid (223 g, 0.73 mol) in ethyl acetate (2 L) was hydrogenated over 8 g of 5% Pd/C catalyst at atmospheric pressure and room temperature until hydrogen uptake ceased (about 24 h). The catalyst was separated by filtration, and the filtrate was evaporated under vacuum to a light brown oil containing traces of solvent (ca. 100% yield). An analytical sample was crystallized from hexane, mp 118–120 °C. Anal. ($C_{16}H_{14}Cl_2O_2$) C, H, Cl.

4-(3,4-Dichlorophenyl)-4-dihydro-1(2*H*)-naphthalenone (VII, X = Y = 3,4-Cl_2). A solution of 4-(3,4-dichlorophenyl)-4-phenylbutanoic acid (228 g, 0.74 mol) in toluene (1.2 L) was treated with thionyl chloride (66 mL, 0.90 mol), and the resulting solution was heated at reflux for 75 min, with provision made for trapping HCl gas given off from the refluxing reaction solution. The reaction mixture was then cooled, and the solvent was evaporated under vacuum to about 230 g of light brown oil. The oil was dissolved in carbon disulfide (360 mL), and the resulting solution was added to a well-stirred suspension of $AlCl_3$ (1.5 kg, 12.5 mol) in carbon disulfide (1.20 L), with the mixture held below 8 °C during the addition period. After the addition was completed, the reaction mixture was stirred for about 16 h at room temperature and then slowly poured over ice (vigorous reaction). The resulting suspension was extracted with ethyl acetate (2 × 4 L). The combined extract was washed with water and with saturated aqueous sodium bicarbonate solution and was then dried and evaporated under vacuum to a residue, which was crystallized from hexane (500 mL) to yield the named product (104.1 g, 48% yield, mp 99–101 °C). Anal. ($C_{16}H_{12}Cl_2O$) C, H.

***cis*- and *trans*-*N*-Methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine Hydrochloride (27 and 7).** A solution of 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2*H*)-naphthalenone (13.5 g, 46.3 mmol) in toluene (190 mL) was cooled to 0–5 °C and treated with 13 mL (316 mmol) of methylamine (condensed at 0 °C). Titanium tetrachloride (4.46 g, 23.5 mmol) was added dropwise to the resulting solution (vigorous reaction), with stirring and cooling to maintain the internal temperature below 10 °C during the addition period. After the addition was completed, the reaction mixture was stirred for 17 h at room temperature under nitrogen and was then filtered. The solids were washed thoroughly with toluene, and the combined filtrates were then concentrated under vacuum to a reddish tan solid, which

(21) Newton, H. P.; Groggins, P. H. *Ind. Eng. Chem.* **1935**, *27*, 1397.

was generally used in the next reaction without further purification.

A suspension of the above Schiff base in methanol (75 mL) was cooled to 14 °C and then treated with sodium borohydride (1.70 g, 45 mmol, added in portions). The temperature rose to about 28 °C during the addition period. The resulting mixture was stirred for about 90 min at room temperature and was then evaporated under vacuum to a gum, which was diluted with water and ether and then filtered to remove insolubles. The aqueous layer of the filtrate was extracted twice with ether. The combined organic extracts were then dried with $MgSO_4$ and evaporated under vacuum to an oil, which was chromatographed on silica gel, with use of an ethyl acetate–hexane–triethylamine (30:20:1) solvent mixture for elution to separate the racemic cis and trans diastereoisomers. The racemic cis diastereoisomer **27**, which eluted first, was dissolved in ether and converted to its HCl salt with HCl gas dissolved in ether to give 4.68 g of product, mp 275–277 °C. The racemic trans diastereoisomer **7** was similarly converted to its HCl salt to give 4.67 g of product, mp 214–216 °C.

***cis*-(1*S*,4*S*)-*N*-Methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine Hydrochloride (58).** Racemic *cis*-*N*-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride (67.1 g) was partitioned between 20% aqueous NaOH and ethyl acetate, followed by drying of the organic layer and evaporation to yield the cis-racemate free base (60.2 g, 0.197 mol). This oil was dissolved in absolute ethanol (600 mL) and treated with D-(−)-mandelic acid (29.94 g, 0.197 mol). The resulting mixture was warmed on a steam bath to effect solution and then held overnight at room temperature to afford a white crystalline solid. This solid was separated by filtration, washed with ether, and air-dried (38.7 g, mp 188–189 °C) and was then recrystallized from hot absolute ethanol to give 32.6 g of solid, mp 190–191 °C. An additional crop (4.4 g, mp 190–191 °C) was obtained by evaporation of the mother liquors under vacuum followed by crystallization of the residues from boiling ethanol (150 mL).

The combined crops of mandelate salt were suspended in ethyl acetate (about 2 L). The ethyl acetate suspension was treated with 10% aqueous NaOH solution, thereby converting the amine to the free base. The resulting ethyl acetate solution was then dried, diluted with ether (2 L), and treated with excess gaseous HCl to give a gelatinous suspension, which crystallized overnight. The crystalline HCl salt was separated by filtration, washed with ether, and air-dried to give 25.96 g of the 1*S*,4*S* enantiomer (39% yield), mp 243–245 °C, $[\alpha]^{23}_D$ +37.9° (CH_3OH, *c* 2).

In like manner to that described above, the 1*R*,4*R* enantiomer **59** was prepared by using L-(+)-mandelic acid in place of D-(−)-mandelic acid as the selective precipitant (mp 243–245 °C, $[\alpha]^{23}_D$ −37.2° (CH_3OH, *c* 2)).

***trans*-(1*S*,4*R*)- and (1*R*,4*S*)-*N*-Methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine Hydrochlorides (48 and 49).** A 171-mg (0.50 mmol) sample of racemic *trans*-*N*-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride was partitioned between aqueous sodium carbonate solution and ethyl acetate to yield an ethyl acetate solution of the trans-racemate free base, which was washed with water, dried ($MgSO_4$), evaporated under vacuum, and treated with a solution of L-(+)-mandelic acid (76 mg, 0.50 mmol) in ethanol. The resulting mixture was evaporated under vacuum to afford a crude material, which was redissolved in ethanol (5 mL). This ethanol solution was treated with ether (about 15 mL) to afford a crystalline product (92 mg, mp 128–130 °C), which was recrystallized from a mixture of ethanol, ether, and hexane to give 51 mg of product (mp 133–135 °C). This recrystallized product was partitioned between aqueous sodium carbonate solution and ethyl acetate to yield an ethyl acetate solution of the free base, which was washed with water, dried ($MgSO_4$), and evaporated under vacuum to a residue. The residue was dissolved in ether and treated with gaseous hydrogen chloride to yield the HCl salt, which was recrystallized from a mixture of methanol and ether to give 25.7 mg of the product **49** (15% yield), mp 257–258 °C, $[\alpha]^{22}_D$ −39.2° (CH_3OH, *c* 2).

In like manner to that described above, the 1*R*,4*S* enantiomer **48** was prepared by using D-(−)-mandelic acid in place of L-(+)-mandelic acid as the selective precipitant (mp 255–257 °C, $[\alpha]^{22}_D$ +41.0° (CH_3OH, *c* 2)).

1-Hydroxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydronaphthalene (X, X = 4-OCH_3, Y = H). A solution of 4-bromoanisole (25 g, 0.134 mol) in tetrahydrofuran (100 mL) was prepared. Magnesium (3.24 g, 0.123 mol) was treated with a small portion of this solution and heated until a reaction started (55 °C). The remainder of the solution was added dropwise, and after the addition was complete, the mixture was stirred for 2 h at 55 °C. The reaction mixture was then cooled to room temperature, and a solution of 1-tetralone (17.92 g, 0.123 mol) in tetrahydrofuran (100 mL) was slowly added. Stirring was continued at room temperature for 16 h after the addition was complete. Ether (200 mL) and water (200 mL) were then added to the reaction mixture, followed by 10% aqueous ammonium chloride solution (100 mL). The ether layer was separated, dried ($MgSO_4$), filtered, and evaporated under vacuum to provide 18 g (58%) of the product as an oil, which was used without further purification in the next step.

1-(4-Methoxyphenyl)-3,4-dihydronaphthalene (XI, X = 4-OCH_3, Y = H). A solution of 1-hydroxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydronaphthalene (18 g, 0.071 mol) in toluene (250 mL) was treated with toluenesulfonic acid (5 mg), and the resulting solution was stirred at reflux for 16 h, with complete water removal accomplished by means of a Dean–Stark trap. The reaction mixture was then cooled to room temperature, washed sequentially with 10% aqueous sodium bicarbonate solution (100 mL), water (100 mL), and saturated aqueous sodium chloride solution (100 mL), dried ($MgSO_4$), and evaporated under vacuum to an oil, which was purified by silica gel chromatography (elution with a hexane–toluene gradient) to give 12 g (67%) of the desired compound, mp 60.5–62.0 °C (hexane; lit.[22] mp 61.5 °C).

1-(4-Methoxyphenyl)-1,2,3,4-tetrahydronaphthalene (XII, X = 4-OCH_3, Y = H). 1-(4-Methoxyphenyl)-3,4-dihydronaphthalene (12 g, 0.051 mol) was added to a mixture of 10% Pd-on-carbon catalyst (1.0 g) and ethanol (250 mL) and hydrogenated for 4 h at room temperature and 50 psi of H_2. The reaction mixture was then filtered and evaporated under vacuum to an oil, which was used in the next step without further purification (11.2 g, 92.5% yield).

4-Hydroxy-4-(4-methoxyphenyl)-1-tetralone (XIII, X = 4-OCH_3, Y = H). 1-(4-Methoxyphenyl)-1,2,3,4-tetrahydronaphthalene (11.2 g, 0.047 mol) was dissolved in a solution of potassium permanganate (36.7 g) in acetone (1.6 L) and water (33 mL), and the resulting solution was stirred at reflux for 16 h. The reaction mixture was then filtered, treated again with potassium permanganate (36.7 g), and stirred at reflux for another 16 h. This process was continued through three reaction period cycles. The reaction mixture was then filtered, treated with activated charcoal, filtered, and evaporated under vacuum to a residue. The residue was taken up in ethyl acetate (200 mL), and the ethyl acetate solution was washed twice with saturated aqueous sodium chloride solution (200 mL), dried ($MgSO_4$), and evaporated under vacuum to yield a solid, which was recrystallized from a mixture of ethyl acetate and hexane to give 3.9 g (23% yield) of the desired product, mp 118.0–119.5 °C. Anal. ($C_{17}H_{16}O_3$) C, H.

***N*-Methyl-4-hydroxy-4-(4-methoxyphenyl)-1,2,3,4-tetrahydro-1-naphthalenamine (XV, X = 4-OCH_3, Y = H, R = CH_3).** A solution of 4-hydroxy-4-(4-methoxyphenyl)-1-tetralone (3.9 g, 0.0138 mol) in tetrahydrofuran (40 mL) was cooled to 0 °C and treated with methylamine (5 mL), followed by dropwise addition of titanium tetrachloride (1 mL). The resulting mixture was stirred for 16 h at room temperature, filtered, and evaporated under vacuum to an oil, which was dissolved in absolute ethanol (20 mL). The ethanol solution was treated with sodium borohydride (1.0 g, 0.0264 mol) and stirred for 1 h at room temperature. The reaction mixture was then evaporated under vacuum to a residue, which was taken up in ethyl acetate (125 mL). The ethyl acetate solution was washed with water (125 mL) and with saturated aqueous sodium chloride solution (125 mL), dried ($MgSO_4$), filtered, and evaporated under vacuum to an oil, which was used in the next step without further purification (3.4 g, 83% yield, mixture of cis and trans isomers).

***N*-Methyl-4-(4-methoxyphenyl)-1,2-dihydro-1-naphthalenamine Hydrochloride (XVI, X = 4-OCH_3, Y = H,**

(22) Dubois, J. E.; Hegarty, A. F. *J. Chem. Soc. B* **1969**, 638.

R = CH_3). A solution of *N*-methyl-4-hydroxy-4-(4-methoxyphenyl)-1,2,3,4-tetrahydro-1-naphthalenamine (1.9 g, 0.0069 mol, mixture of cis and trans isomers) in ether (50 mL) was treated with gaseous hydrogen chloride. The solution was then evaporated under vacuum to yield a white solid, which was recrystallized from ethyl acetate to give 1.5 g of product (72% yield), mp 221–222 °C. Anal. ($C_{18}H_{19}ONCl\cdot HCl\cdot {}^1/_2H_2O$) C, H, N.

***cis*- and *trans*-*N*-Methyl-4-(methoxyphenyl)-1,2,3,4-tetrahydro-1-naphthalenamine Hydrochloride (31 and 11).** *N*-Methyl-4-(4-methoxyphenyl)-1,2-dihydro-1-naphthalenamine hydrochloride (1.5 g, 4.9 mmol) was mixed with ethanol (30 mL) and 10% palladium-on-carbon catalyst (250 mg) and hydrogenated for 4 h at room temperature and 45 psi of H_2. The reaction mixture was then filtered and evaporated under vacuum. The residue was chromatographed on silica gel (elution with ethyl acetate containing 1% ammonium hydroxide) to separate the cis and trans isomers. The cis isomer **31** was converted to the hydrochloride salt, which was recrystallized from a mixture of chloroform and ether (221 mg, 15% yield, mp 224–226 °C). The trans isomer **11** was converted to the hydrochloride salt, which was recrystallized from a mixture of chloroform and ether (461 mg, 34% yield, mp 230–233 °C).

(4*S*)- and (4*R*)-3,4-Dihydro-4-phenyl-1(2*H*)-naphthalenone (XVII and XVIII). A solution of 4.34 g (18.3 mmol) of **44** was dissolved in 150 mL of acetone. A solution of 4.7 g (30 mmol) of $KMnO_4$ in 150 mL of H_2O was added dropwise to this solution over 20 min. A mildly exothermic reaction occurred. After stirring at room temperature for 1 h, the solids were filtered off and washed thoroughly with acetone and EtOAc. Evaporation of the organic solvents in vacuo gave an oily suspension, which was brought to pH 1 with concentrated HCl and then warmed on a steam bath for 1 h. The cooled suspension was extracted with $CHCl_3$, and the organic solution was then dried and evaporated to give the 4*S* ketone XVII as a red oil, which was essentially pure by TLC and which was used without further purification in the next step.

A 210-mg (0.95 mmol) sample of this oil was dissolved in 2 mL of EtOH and 0.5 mL of HOAc, and 113 mg (1.05 mmol) of phenylhydrazine was added. The resulting solution was heated on a steambath for 1 h. Crystals formed upon cooling, which were collected and recrystallized from absolute EtOH to give the analytically pure phenylhydrazone, mp 118–120 °C, $[\alpha]^{25}_D$ +95.6° (CH_3OH, *c* 1). Anal. ($C_{22}H_{20}N_2$) C, H, N.

In like manner, the 4*R* ketone XVIII was prepared together with its phenylhydrazone, mp 118–120 °C, $[\alpha]^{25}_D$ −95.4° (CH_3OH, *c* 1). Anal. ($C_{22}H_{20}N_2$) C, H, N.

Blockade of Synaptosomal Uptake of Serotonin (5-HT), Dopamine (DA), and Norepinephrine (NE) in Vitro.[15] Sprague–Dawley CD male rats weighing 180–220 g (Charles River Laboratories, Inc.; Wilmington, MA) were used in this procedure. A crude synaptosomal fraction of rat corpus striatum (for 5-HT and DA uptake) or hypothalamus (for NE uptake) tissue was prepared by homogenizing tissue (25 mL/g, wet) in ice-cold 0.32 M sucrose containing 1 mg/mL glucose, 0.0001 M EDTA, and tris(hydroxymethyl)aminomethane to pH 7.4. The homogenate was centrifuged at 1000*g* for 10 min at 0.4 °C, the pellet discarded, and the supernatant centrifuged at 17000*g* for 20 min at 0–4 °C. The resulting pellet was resuspended in the ice-cold 0.32 M sucrose pH 7.4 solution at 10 mL/g original tissue (wet) for corpus striatum and 5 mL/g original tissue (wet) for hypothalamus. An incubation buffer was prepared: 26 mM tris(hydroxymethyl)-aminomethane, adjusted to pH 7.4 with HCl, containing 124 mM NaCl, 4.5 mM KCl, 1.2 mM KH_2PO_4, 13 mM $MgCl_2\cdot 6H_2O$, 0.001 mM ascorbic acid, 0.0125 mM nialamide hydrochloride, and 2.8 mM $CaCl_2$. Duplicate 0.1-mL aliquots of the tissue suspension were incubated for 10 min at 37 °C with 0.02 mL of a solution containing a known quantity of the named test compound and 1.0 mL of the incubation buffer containing additionally 1 mg/mL glucose and 0.001 mM labeled monoamine ([^{14}C]-5-HT, [^{14}C]DA, or [^{3}H]NE). After incubation, the mixtures were filtered through 0.45-μm filters and the filters washed with the incubation buffer. The filtered materials were dissolved in 1.0 mL of 2-methoxyethanol and analyzed for radioactivity by liquid scintillation counting (uptake at 0 °C taken as radiation blank). Uptake was calculated as picomoles of 5-HT, DA, or NE per milligram of protein (protein was determined by measurement with Folin phenol reagent). The IC_{50}, the concentration of named test compound (expressed as micromoles per liter in ca. 1 mL of incubation mixture) inhibiting uptake by 50% from that calculated for test compound-free control aliquots, was estimated from plots of percent uptake inhibition vs. concentration on semilog paper.

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Registry No. **1**, 52758-04-0; **1**·HCl, 52758-06-2; **2**, 91742-82-4; **2**·HCl, 79836-49-0; **3**, 91742-83-5; **3**·HCl, 79896-33-6; **4**, 91742-84-6; **4**·HCl, 79836-56-9; **5**, 91742-85-7; **5**·HCl, 79896-36-9; **6**, 79836-51-4; **7**, 79836-45-6; **7**·HCl, 79617-99-5; **8**, 91742-86-8; **8**·HCl, 79836-66-1; **9**, 91742-87-9; **9**·HCl, 79896-37-0; **10**, 91742-89-1; **11**, 91742-90-4; **11**·HCl, 79836-63-8; **12**, 91742-91-5; **12**·HCl, 79836-65-0; **13**, 91742-92-6; **13**·HCl, 79836-64-9; **14**, 91742-94-8; **14**·HCl, 91742-93-7; **15**, 91742-96-0; **15**·HCl, 91742-95-9; **16**, 91742-97-1; **16**·HCl, 52789-20-5; **17**, 91742-98-2; **17**·HCl, 79836-75-2; **18**, 79836-74-1; **19**, 79836-70-7; **20**, 91742-99-3; **20**·HCl, 79836-76-3; **21**, 52758-03-9; **21**·HCl, 52758-05-1; **22**, 79836-48-9; **22**·HCl, 79559-99-2; **23**, 91743-00-9; **23**·HCl, 79559-98-1; **24**, 91743-01-0; **24**·HCl, 79560-04-6; **25**, 91743-02-1; **25**·HCl, 79560-00-2; **26**, 79836-53-6; **26**·HCl, 79560-01-3; **27**, 79617-95-1; **27**·HCl, 79617-89-3; **28**, 91743-03-2; **28**·HCl, 79560-08-0; **29**, 91743-04-3; **29**·HCl, 79560-02-4; **30**, 91743-06-5; **30**·HCl, 91743-05-4; **31**, 79836-62-7; **31**·HCl, 79560-05-7; **32**, 91743-07-6; **32**·HCl, 79560-07-9; **33**, 91743-08-7; **33**·HCl, 79560-06-8; **34**, 91743-10-1; **34**·HCl, 91743-09-8; **35**, 91743-12-3; **35**·HCl, 91743-11-2; **36**, 91798-45-7; **36**·HCl, 52789-21-6; **37**, 91743-13-4; **37**·HCl, 79560-13-7; **38**, 79560-12-6; **39**, 79560-10-4; **40**, 79560-15-9; **41**, 91797-58-9; **41**·HCl, 91797-57-8; **42**, 91743-15-6; **42**·HCl, 91743-14-5; **43**, 91743-17-8; **43**·HCl, 91743-16-7; **44**, 52795-04-7; **44**·HCl, 52760-48-2; **45**, 52795-02-5; **45**·HCl, 52760-47-1; **46**, 91797-76-1; **46**·HCl, 79896-34-7; **47**, 91797-59-0; **47**·HCl, 79896-35-8; **48**, 91797-60-3; **48**·HCl, 79896-31-4; **48**·D-(−)-mandelate, 91797-74-9; **49**, 79951-46-5; **49**·HCl, 79896-32-5; **49**·L-(+)-mandelate, 91797-73-8; **50**, 91797-61-4; **50**·HCl, 55056-87-6; **51**, 91797-62-5; **51**·HCl, 55056-88-7; **52**, 91797-63-6; **52**·HCl, 79646-00-7; **53**, 91797-64-7; **53**·HCl, 79617-90-6; **54**, 91797-65-8; **54**·HCl, 79617-91-7; **55**, 91797-75-0; **55**·HCl, 79617-92-8; **56**, 91797-66-9; **56**·HCl, 91839-80-4; **57**, 91797-67-0; **57**·HCl, 91839-81-5; **58**, 79617-96-2; **58**·HCl, 79559-97-0; **58**·D-(−)-mandelate, 79617-97-3; **59**, 79617-98-4; **59**·HCl, 79645-15-1; **59**·L-(+)-mandelate, 91797-72-7; **60**, 91797-68-1; **60**·HCl, 79617-93-9; **61**, 91797-69-2; **61**·HCl, 79617-94-0; IV, 79560-16-0; V, 79560-17-1; VI, 79560-18-2; VII, 79560-19-3; X, 79560-27-3; XI, 21855-80-1; XII, 19353-89-0; XIII, 79560-28-4; *cis*-XIII, 91743-18-9; *trans*-XIII, 91743-19-0; XVI, 79560-31-9; XVII, 91797-70-5; XVII phenylhydrazone, 91743-20-3; XVIII, 91797-71-6; XVIII phenylhydrazone, 91743-21-4; 3,4-dichlorobenzophenone, 6284-79-3; diethyl succinate, 123-25-1; 4-bromoanisole, 104-92-7; 1-tetralone, 529-34-0; dopamine, 51-61-6; serotonin, 50-67-9; norepinephrine, 51-41-2.