(3 L of toluene, 16 g of Omnifluor, and 1 L of Triton X-100) and measured by liquid scintillation spectrometry (50% efficiency). Specific [^{3}H]-5-HT binding was defined as the difference between binding in the absence and presence of 1 μM metergoline.

Behavioral Assay. The drug discrimination training procedure for these animals has been reported previously.[16] Briefly, 30 male Sprague–Dawley rats were trained to discriminate racemic DOM (1.0 mg/kg) from saline in a two-lever operant task. In this procedure, the administration of saline or DOM 15 min prior to a variable-interval, 15-s (VI-15s) schedule of reinforcement served as the cue for the correct (reinforced) lever. Occasional periods (2.5 min) of nonreinforcement (extinction) were used to assess the degree of stimulus control exerted by saline and DOM over behavior and to evaluate the isoDMT derivatives. For those compounds where generalization (transfer, substitution) occurred, ED_{50} values were determined from the dose–response data by the method of Finney.[17] These ED_{50} values are the calculated doses at which the rats perform 50% appropriate drug-lever responding.

Time-course studies investigated the effects of increasing the time interval between the injection of doses of **7b** (10 mg/kg) and **10** (3 mg/kg) which produced stimulus generalization and the beginning of a test (extinction) session. Presession injection intervals were varied up to 1 h.

During antagonism tests, doses of **7b** (1 and 3 mg/kg), **7c** (3 and 12 mg/kg), or saline were injected just prior to the administration of the training dose of DOM (1.0 mg/kg). A subsequent 15-min time interval elapsed before the animals were exposed to the 2.5-min nonreinforced test session. Drugs were administered by intraperitoneal injection.

Acknowledgment. This work was supported in part by a grant from the A. D. Williams fund.

Registry No. 1, 61-50-7; 3, 6711-46-2; 4, 27692-91-7; 6 (free base), 87482-07-3; 6 oxalate, 87482-08-4; 7a (free base), 87482-09-5; 7a oxalate, 87482-10-8; 7b (free base), 87482-11-9; 7b oxalate, 87482-12-0; 7c (free base), 87482-13-1; 7c oxalate, 87482-14-2; 7d (free base), 87482-15-3; 7d oxalate, 87482-16-4; 7e (free base), 87482-17-5; 7e oxalate, 87482-18-6; 7f (free base), 87482-19-7; 7f oxalate, 87482-20-0; 7g (free base), 87482-21-1; 7g oxalate, 87482-22-2; 8 (free base), 87482-23-3; 8 oxalate, 87482-24-4; 9 (free base), 87482-25-5; 9 oxalate, 87482-26-6; 10, 1019-45-0; 2-(dimethylamino)ethyl chloride hydrochloride, 4584-46-7; indoline, 496-15-1; 5-methoxyindole, 1006-94-6; 2-(dimethylamino)ethyl chloride, 107-99-3; benzimidazole, 51-17-2; 4-methylindole, 16096-32-5; oxalyl chloride, 79-37-8; 4,*N*,*N*-trimethyl-α,β-dioxo-1*H*-indole-3-ethanamine, 87482-28-8; 4,*N*,*N*-trimethyltryptamine, 28289-23-8; 4,*N*,*N*-trimethyltryptamine hydrogen oxalate, 87482-27-7; serotonin, 50-67-9.

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8-Hydroxy-2-(alkylamino)tetralins and Related Compounds as Central 5-Hydroxytryptamine Receptor Agonists

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A series of 2-(alkylamino)tetralins related to 8-hydroxy-2-(di-*n*-propylamino)tetralin (**21**) were prepared and tested as dopamine (DA) and 5-hydroxytryptamine (5-HT) receptor agonists. Several of the compounds were potent 5-HT agonists devoid of DA-mimetic effects. *N*-Ethyl or N-propyl substitution of 8-hydroxy-2-aminotetralin gave the most potent agonists. It was shown that the most potent compound, (+)-**21**, has the 2*R* configuration. 5,8-Dimethoxy-2-(di-*n*-propylamino)tetralin (**31**) was found to be a weak DA agonist devoid of 5-HT activity. The corresponding indan derivative, 4,7-dimethoxy-2-(di-*n*-propylamino)indan (**39**), has been reported to be active on both DA and 5-HT receptors. The 5-HT-stimulating properties of compounds **21** and **39** as compared to the incapability of compound **31** to activate the 5-HT receptor is tentatively explained by the assumed mode of binding of the compounds to the 5-HT receptor.

The tricyclic antidepressants have become the most widely used drugs in the treatment of endogenous depressions. The therapeutic effects have previously been attributed to their capability of inhibiting the uptake of the monoamines noradrenaline (NA)[1] and 5-hydroxytryptamine (5-HT).[2] This mechanism of action is presently challenged,[3] but it is likely that 5-HT mechanisms are involved. A disadvantage with the use of the tricyclic antidepressants is that there is a latency period of 1–3 weeks before the appearance of clinical improvement. In order to surmount this problem, drugs that act by a different mechanism than the tricyclic antidepressants would be needed. One of the possibilities would be the use of selective 5-HT agonists.[4]

Presently known 5-HT agonists, like *d*-LSD, 5-methoxy-*N*,*N*-dimethyltryptamine, and 1-(2,5-dimethoxy-4-methylphenyl)-2-propylamine (**37**, DOM), have the dis-

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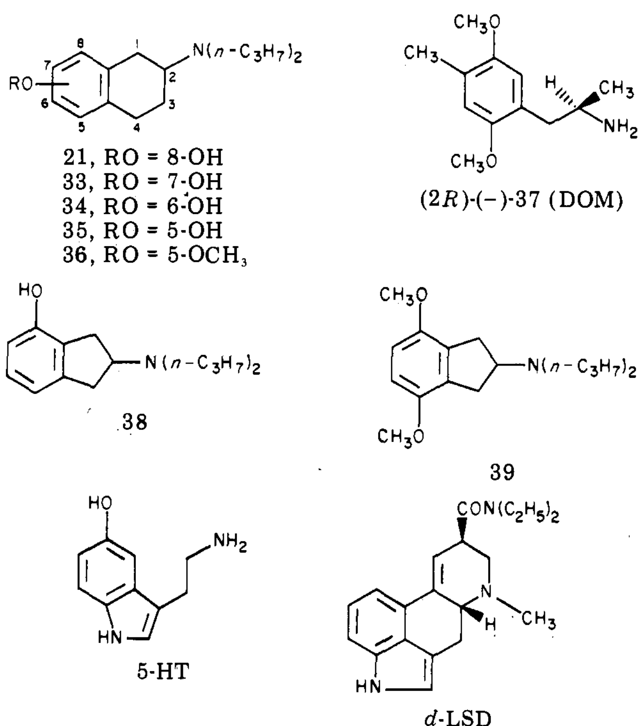
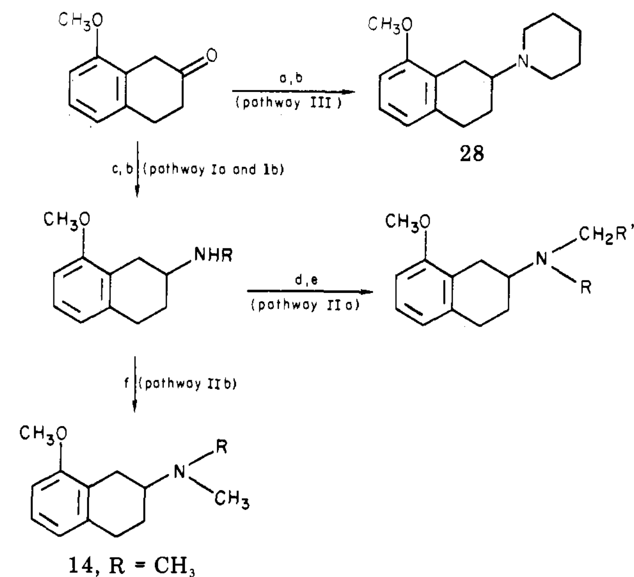


advantage of being potent hallucinogens.[4,5] In order to explain the mechanism behind drug-induced hallucinations, several hypotheses have been developed.[5-7] One of the most discussed ideas in recent years implies that hallucinogenic drugs are more potent on presynaptic than on postsynaptic 5-HT receptors.[6] However, this hypothesis has been questioned,[8] and the underlying mechanisms of hallucinations are still poorly understood. In the light of the existence of several types of 5-HT receptor sites in the CNS,[9] a 5-HT receptor agonist may not necessarily be hallucinogenic. Instead, it might be possible to find nonhallucinogenic 5-HT receptor agonists with selectivity for one or the other of the various 5-HT receptor sites in the CNS. This could lead to the development of selective 5-HT receptor agonists with antidepressive activity and devoid of hallucinogenic properties. Furthermore, such 5-HT agonists would be of interest in the evaluation of the role of 5-HT in sleep,[10] body temperature,[11] pain,[12] sexual behavior,[13] etc.

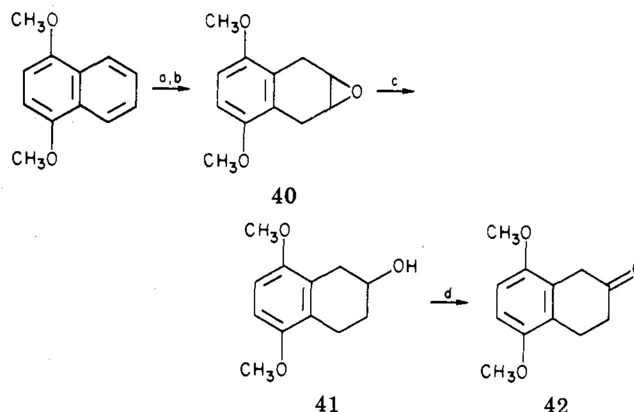
In a recent communication, we described a new centrally acting 5-HT receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (**21**).[14] This compound was found to be

Scheme I[a]



[a] Reagents: a = piperidine, TsOH; b = H_2, PtO_2; c = RNH_2, H^+; d = R'COCl, Et_3N; e = $LiAlH_4$; f = HCHO, $NaCNBH_3$.

Scheme II[a]



[a] Reagents: a = Na, EtOH; b = MCPBA; c = $LiAlH_4$; d = PCC.

devoid of dopamine (DA) and NA receptor stimulating properties in the CNS. The most active enantiomer was (+)-**21**, although (−)-**21** also was found to be a potent agonist. A more detailed pharmacological study of **21** has recently been published.[15]

We have now started a structure–activity study of 8-hydroxy-2-aminotetralins and related compounds. In this paper we describe N-alkylated derivatives of 8-hydroxy-2-aminotetralin and also give a detailed report of the work presented in our prior publication. Furthermore, we have included the 5,8-dimethoxy (**31**) and 5,8-dihydroxy (**32**) derivatives of 2-(di-*n*-propylamino)tetralin and also report the absolute configuration of (+)-**21**.

Chemistry. Resolution of (±)-8-methoxy-2-(benzylamino)tetralin (**11**) was performed as previously described.[14] The compounds (+)- and (−)-**5** were formed by acylation of (+)- and (−)-**11**, respectively, followed by reduction with $LiAlH_4$ and hydrogenolysis of the *N*-benzyl group over Pd on charcoal. All the racemic secondary

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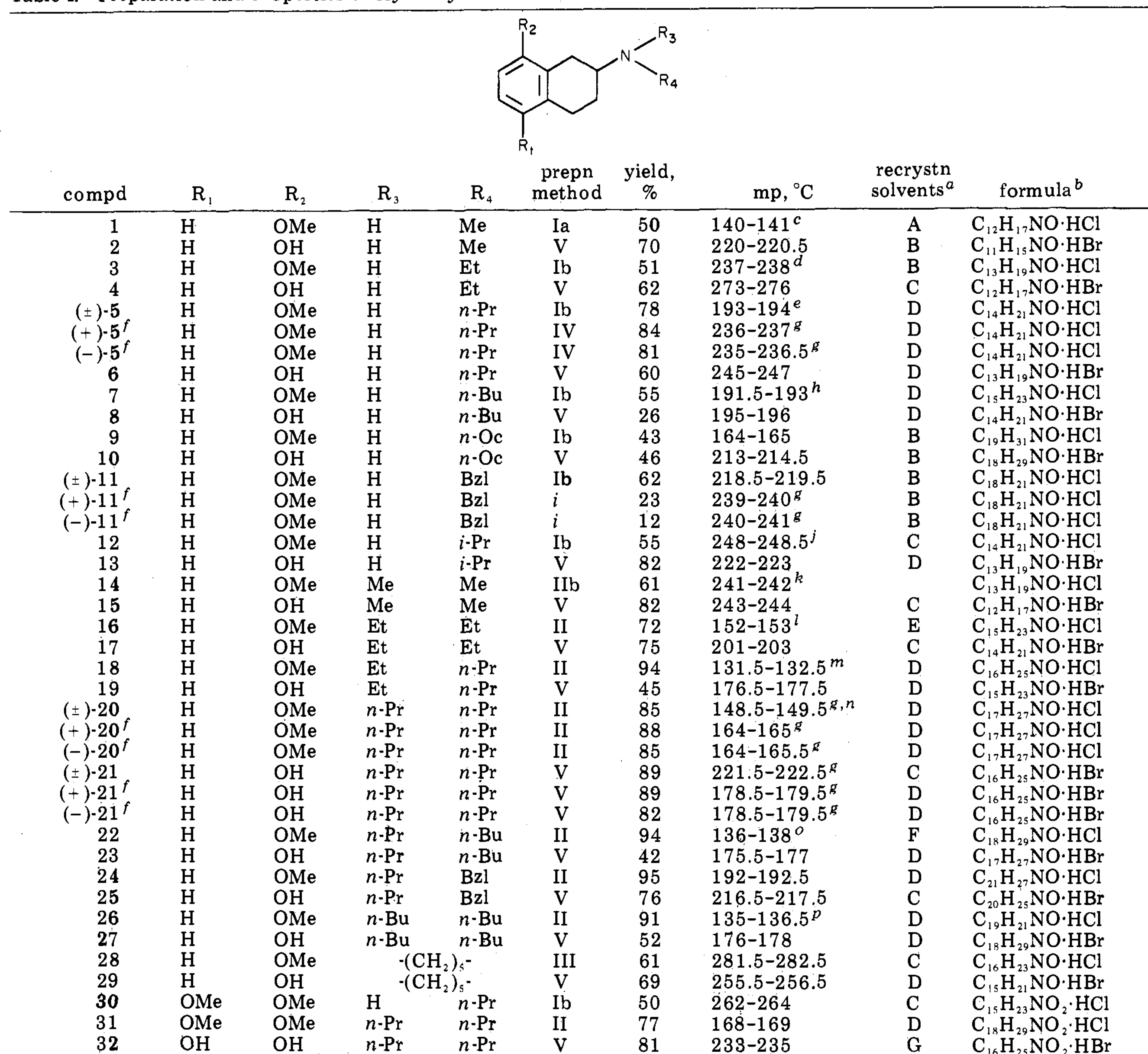
Table I. Preparation and Properties of Hydroxylated 2-Aminotetralins and Their Intermediates



compd	R_1	R_2	R_3	R_4	prepn method	yield, %	mp, °C	recrystn solvents[a]	formula[b]
1	H	OMe	H	Me	Ia	50	140-141[c]	A	$C_{12}H_{17}NO\cdot HCl$
2	H	OH	H	Me	V	70	220-220.5	B	$C_{11}H_{15}NO\cdot HBr$
3	H	OMe	H	Et	Ib	51	237-238[d]	B	$C_{13}H_{19}NO\cdot HCl$
4	H	OH	H	Et	V	62	273-276	C	$C_{12}H_{17}NO\cdot HBr$
(±)-5	H	OMe	H	n-Pr	Ib	78	193-194[e]	D	$C_{14}H_{21}NO\cdot HCl$
(+)-5[f]	H	OMe	H	n-Pr	IV	84	236-237[g]	D	$C_{14}H_{21}NO\cdot HCl$
(−)-5[f]	H	OMe	H	n-Pr	IV	81	235-236.5[g]	D	$C_{14}H_{21}NO\cdot HCl$
6	H	OH	H	n-Pr	V	60	245-247	D	$C_{13}H_{19}NO\cdot HBr$
7	H	OMe	H	n-Bu	Ib	55	191.5-193[h]	D	$C_{15}H_{23}NO\cdot HCl$
8	H	OH	H	n-Bu	V	26	195-196	D	$C_{14}H_{21}NO\cdot HBr$
9	H	OMe	H	n-Oc	Ib	43	164-165	B	$C_{19}H_{31}NO\cdot HCl$
10	H	OH	H	n-Oc	V	46	213-214.5	B	$C_{18}H_{29}NO\cdot HBr$
(±)-11	H	OMe	H	Bzl	Ib	62	218.5-219.5	B	$C_{18}H_{21}NO\cdot HCl$
(+)-11[f]	H	OMe	H	Bzl	*i*	23	239-240[g]	B	$C_{18}H_{21}NO\cdot HCl$
(−)-11[f]	H	OMe	H	Bzl	*i*	12	240-241[g]	B	$C_{18}H_{21}NO\cdot HCl$
12	H	OMe	H	i-Pr	Ib	55	248-248.5[j]	C	$C_{14}H_{21}NO\cdot HCl$
13	H	OH	H	i-Pr	V	82	222-223	D	$C_{13}H_{19}NO\cdot HBr$
14	H	OMe	Me	Me	IIb	61	241-242[k]		$C_{13}H_{19}NO\cdot HCl$
15	H	OH	Me	Me	V	82	243-244	C	$C_{12}H_{17}NO\cdot HBr$
16	H	OMe	Et	Et	II	72	152-153[l]	E	$C_{15}H_{23}NO\cdot HCl$
17	H	OH	Et	Et	V	75	201-203	C	$C_{14}H_{21}NO\cdot HBr$
18	H	OMe	Et	n-Pr	II	94	131.5-132.5[m]	D	$C_{16}H_{25}NO\cdot HCl$
19	H	OH	Et	n-Pr	V	45	176.5-177.5	D	$C_{15}H_{23}NO\cdot HBr$
(±)-20	H	OMe	n-Pr	n-Pr	II	85	148.5-149.5[g,n]	D	$C_{17}H_{27}NO\cdot HCl$
(+)-20[f]	H	OMe	n-Pr	n-Pr	II	88	164-165[g]	D	$C_{17}H_{27}NO\cdot HCl$
(−)-20[f]	H	OMe	n-Pr	n-Pr	II	85	164-165.5[g]	D	$C_{17}H_{27}NO\cdot HCl$
(±)-21	H	OH	n-Pr	n-Pr	V	89	221.5-222.5[g]	C	$C_{16}H_{25}NO\cdot HBr$
(+)-21[f]	H	OH	n-Pr	n-Pr	V	89	178.5-179.5[g]	D	$C_{16}H_{25}NO\cdot HBr$
(−)-21[f]	H	OH	n-Pr	n-Pr	V	82	178.5-179.5[g]	D	$C_{16}H_{25}NO\cdot HBr$
22	H	OMe	n-Pr	n-Bu	II	94	136-138[o]	F	$C_{18}H_{29}NO\cdot HCl$
23	H	OH	n-Pr	n-Bu	V	42	175.5-177	D	$C_{17}H_{27}NO\cdot HBr$
24	H	OMe	n-Pr	Bzl	II	95	192-192.5	D	$C_{21}H_{27}NO\cdot HCl$
25	H	OH	n-Pr	Bzl	V	76	216.5-217.5	C	$C_{20}H_{25}NO\cdot HBr$
26	H	OMe	n-Bu	n-Bu	II	91	135-136.5[p]	D	$C_{19}H_{21}NO\cdot HCl$
27	H	OH	n-Bu	n-Bu	V	52	176-178	D	$C_{18}H_{29}NO\cdot HBr$
28	H	OMe	-$(CH_2)_5$-		III	61	281.5-282.5	C	$C_{16}H_{23}NO\cdot HCl$
29	H	OH	-$(CH_2)_5$-		V	69	255.5-256.5	D	$C_{15}H_{21}NO\cdot HBr$
30	OMe	OMe	H	n-Pr	Ib	50	262-264	C	$C_{15}H_{23}NO_2\cdot HCl$
31	OMe	OMe	n-Pr	n-Pr	II	77	168-169	D	$C_{18}H_{29}NO_2\cdot HCl$
32	OH	OH	n-Pr	n-Pr	V	81	233-235	G	$C_{16}H_{25}NO_2\cdot HBr$

[a] Recrystallization solvents: A, *i*-PrOH-ether; B, MeOH-ether; C, EtOH; D, EtOH-ether; E, MeOH-EtOAc-ether; F, acetone-ether; G, MeOH. [b] The elemental analyses (C, H, and N) for all new compounds were within ±0.4% of the theoretical values. [c] Literature[18] mp 143-144 °C. [d] Literature[18] mp 232-233 °C. [e] Literature[18] mp 189-190 °C. [f] For Optical rotations, see Experimental Section. [g] Previously reported.[14] [h] Literature[18] mp 190-192 °C. [i] See Experimental Section. [j] Literature[18] mp 242-244 °C. [k] Literature[18] mp 242-243 °C. [l] Literature[18] bp 115-117 °C (0.6 mmHg). [m] Literature[18] bp 130-132 °C (0.5 mmHg). [n] Literature[18] bp 128-121 °C (0.3 mmHg). [o] Literature[18] bp 141-143 °C (0.6 mmHg). [p] Literature[18] bp 136-139 °C (0.2 mmHg).

amines were prepared by reductive amination[16] of 8-methoxy-2-tetralone according to pathways Ia or Ib in Scheme I. Condensation of 8-methoxy-2-tetralone with piperidine and catalytic hydrogenation of the resulting enamine afforded the piperidino derivative **28**. Reductive methylation[17] of the secondary amine **1** with formaldehyde and $NaCNBH_3$ gave the *N*,*N*-dimethyl derivative **14** (pathway IIb, Scheme I). The remaining N,N-dialkylated derivatives of 8-methoxy-2-aminotetralin were prepared by acylation of secondary amines with the appropriate acid chloride, followed by $LiAlH_4$ reduction of the crude amide[18] (pathway IIa, Scheme I). The phenols presented in Table I were all prepared from the corresponding methoxy compounds using 48% aqueous HBr.

Compound **31** was prepared, according to pathways Ib and IIa in Scheme I, from the ketone **42**, which was synthesized as outlined in Scheme II. Dissolving metal reduction of 1,4-dimethoxynaphthalene with sodium in ethanol gave crude 5,8-dimethoxy-1,4-dihydronaphthalene, which when treated with *m*-chloroperbenzoic acid gave the epoxide **40**. Reduction of **40** with $LiAlH_4$, followed by oxidation of the alcohol **41** with pyridinium chlorochromate,[19] afforded the ketone **42**.

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Table II. Effects of 2-Aminotetralins on Rat Brain 5-HTP and Dopa Formation

compd	R_1	R_2	R_3	R_4	Dopa accumulation:[a] ED_{50},[b,c] nmol/kg sc, ± SEM: limbic	Dopa accumulation: striatum	5-HTP accumulation:[a] ED_{50},[d] nmol/kg sc, ± SEM: limbic	5-HTP: striatum	5-HTP: hemispheres (cortex)
2	H	OH	H	Me	I[e]	I	1500	1600	1800
4	H	OH	H	Et	I	I	270 ± 34	200 ± 120	220 ± 100
6	H	OH	H	*n*-Pr	I	I	140 ± 45	150 ± 35	180 ± 20
8	H	OH	H	*n*-Bu	I	I	4300	4500	6300
10	H	OH	H	*n*-Oc	I	I	I	I	I
13	H	OH	H	*i*-Pr	I	I	2600	2900	4100
15	H	OH	Me	Me	I	I	380 ± 105	430 ± 145	360 ± 80
17	H	OH	Et	Et	I	I	54 ± 20	68 ± 34	70 ± 34
19	H	OH	Et	*n*-Pr	I	I	57 ± 27	59 ± 3	66 ± 15
20	H	OMe	*n*-Pr	*n*-Pr	I	I	340 ± 190	290 ± 125	230 ± 60
(±)-21	H	OH	*n*-Pr	*n*-Pr	I	I	52 ± 18	52 ± 9	63 ± 20
(+)-21	H	OH	*n*-Pr	*n*-Pr	I	I	36 ± 9	47 ± 6	50 ± 11
(−)-21	H	OH	*n*-Pr	*n*-Pr	I	I	61 ± 15	65 ± 9	77 ± 12
23	H	OH	*n*-Pr	*n*-Bu	I	I	270 ± 70	260 ± 60	340 ± 20
25	H	OH	*n*-Pr	Bzl	I	I	2700	2900	2300
27	H	OH	*n*-Bu	*n*-Bu	I	I	5000	6600	5700
29	H	OH	-$(CH_2)_5$-		I	I	1600	1100	1400
31	OMe	OMe	*n*-Pr	*n*-Pr	905	1240	I	I	I
32	OH	OH	*n*-Pr	*n*-Pr	5200	5400	I	I	I
d-LSD					390 ± 110[f]	395 ± 100	36 ± 7	35 ± 11	36 ± 4

[a] For experimental details, see ref 39. [b] Dose giving a half-maximal decrease of Dopa formation in the rat brain part, estimated from a dose-response curve comprising four to six dose levels (n = 3–5). The maximal reduction of the Dopa level was empirically found to be 65% from the control level (635 ng of Dopa/g of tissue) for the limbic and 80% from the control level (1670 ng of Dopa/g of tissue) for the striatal brain portions. For low active compounds, fewer animals were used, and statistical limits could therefore not be obtained. [c] No significant effect on Dopa accumulation was obtained in the hemispheral portions (cortex). [d] Dose giving a half-maximal decrease of 5-HTP formation in the rat brain part, estimated from a dose-response curve comprising four to six dose levels (n = 3–5). The maximal reduction of the 5-HTP level was empirically found to be 50% from the control levels (120 ng of 5-HTP/g of limbic tissue, 75 ng of 5-HTP/g of striatal tissue, and 75 ng of 5-HTP/g of hemispheral tissue). For low active compounds, fewer animals were used, and statistical limits could therefore not be obtained. [e] Inactive; compounds with an ED_{50} value > 45 μmol/kg have been considered inactive. [f] The dopa accumulation was not determined in the hemispheral portions (cortex).

The absolute configuration of (+)-**21** was determined by a known method for replacement of phenolic hydroxyl groups by hydrogen.[20] (+)-**21** was converted into the crude 8-(1-phenyl-1*H*-5-tetrazolyl) ether of (+)-**21**, which after catalytic hydrogenolysis afforded the known (2*R*)-(+)-2-(di-*n*-propylamino)tetralin.[21]

Pharmacology. The compounds were tested in reserpinized rats according to the biochemical test method previously described.[16] Behavioral observations were made throughout the biochemical test performance.

The in vivo biochemical test method utilizes the well-established phenomenon of receptor-mediated feedback inhibition of the presynaptic neuron.[22] Thus, the synthetic rate of the catecholamines DA and NA is inhibited by agonists activating dopaminergic and adrenergic receptors, respectively. Similarly the synthesis of 5-HT is inhibited by 5-HT-receptor agonists. The Dopa accumulation, following decarboxylase inhibition by means of 3-hydroxybenzylhydrazine (NSD 1015), was thus used as an indicator of the rate of DA synthesis in the DA-predominated parts (i.e., limbic system, corpus striatum) and the rate of NA synthesis in the NA-dominated remaining hemispheral portions (mainly cortex). The 5-HTP accumulation was taken as an indicator of the rate of 5-HT synthesis in the three brain parts.

Results and Discussion

The biochemical results for the compounds tested are given in Table II. All compounds that showed 5-HT activity in the biochemical test induced the 5-HT-like behavioral syndrome[23] in the rat. Although there are some variations in the ED_{50} values between the different rat brain parts, these values are of the same order of magnitude. In the following discussion, when comparing the potency of different compounds, we will use the ED_{50} values that were obtained from the tissue with the highest concentration of 5-HTP, i.e., the limbic part of the rat brain.

The subclassification of 5-HT receptors is still in its initial stage. We therefore consider it premature to determine if **21** is selective for any subtype of 5-HT receptor sites.[15] Therefore, the central 5-HT receptors will be discussed as one conception, although some precaution has to be considered.

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The N-alkylated or N,N-dialkylated derivatives of 8-hydroxy-2-aminotetralin, carrying at least one *N*-ethyl or *N*-*n*-propyl group, are all very potent agonists, comparable with the potency of *d*-LSD. The only exception is 8-hydroxy-2-(*N*-benzyl-*N*-propylamino)tetralin (**25**). The low activity of **25** can be a result of lowered basicity through the benzyl group and/or the steric bulk of the phenyl ring. Steric bulk in the vicinity of the nitrogen seems to lower the potency of this class of compounds, since compound **13** with an *N*-isopropyl group is about 16 times less potent than compound **6** carrying an *N*-*n*-propyl group. This suggestion is also strengthened by the marked loss in activity when the N-substitution is changed from *n*-propyl (**6**) and di-*n*-propyl (**21**) to *n*-butyl (**8**) and di-*n*-butyl (**27**), respectively. Furthermore, the secondary amine **10**, with an *N*-*n*-octyl group, is inactive. Based upon these observations and the low activity of the piperidino derivative **29**, it can be assumed that a part of the 5-HT receptor, e.g., a cavity, can well accomodate an *n*-alkyl group not larger than *n*-propyl. This is illustrated by the very potent *N*,*N*-diethyl (**17**) and *N*,*N*-di-*n*-propyl (**21**) compounds. The rather weak activities displayed by the *N*-methyl (**2**) and *N*,*N*-dimethyl (**15**) compounds can to some extent be a result of inferior binding to the receptor part and partly be due to a lower ability, at least for compound **2**, to penetrate the blood–brain barrier.

In the prior communication[14] we showed that the 5-, 6-, and 7-hydroxy isomers of 2-(di-*n*-propylamino)tetralin (**35**, **34**, and **33**, respectively) are DA receptor agonists without inherent 5-HT stimulating properties, while the isomeric 8-hydroxy-2-(di-*n*-propylamino)tetralin (**21**) is a centrally acting 5-HT receptor agonist lacking DA and NA receptor stimulating properties even at a dosage of 40 times the ED_{50} value. Similar observations have also been made for a series of monophenolic octahydrobenzo[*f*]quinolines.[24] A monohydroxyl group in the 8-position of the 2-aminotetralin therefore seems to be indispensable for selective 5-HT receptor stimulation. This is also supported by Feenstra et al.,[25] who found that **21** did not alter the dopamine metabolism (DOPA, HVA, and dopamine levels) in the rat striatum and by the fact that 7,8-dihydroxy-2-(di-*n*-propylamino)tetralin[26] is a DA receptor agonist. In addition, we have now tested 8-methoxy-2-(di-*n*-propylamino)tetralin (**20**), and this compound also showed to be a 5-HT receptor agonist, although about 7 times less potent than compound **21**. This result is in agreement with what has been reported from binding studies of the 5-HT agonists 5-methoxy- and 5-hydroxy-*N*,*N*-dimethyltryptamine, with rat brain homogenates, where the latter compound has the highest affinity.[27] Compound **20** probably is active per se, since it has an almost immediate onset of action (the appearance of the 5-HT syndrome in the rat). This can be compared to the DA agonist 5-methoxy-2-(di-*n*-propylamino)tetralin (**36**),[16] which induces stereotypies in the rat after a latency period of 15 min, a probable result of metabolic activation.

The topography of the 5-HT receptor(s) is virtually unknown. However, 5-HT itself may serve as a model or mirror image of the receptor, and in the following discussion, one specific conformation of 5-HT derived from the structure of LSD has been used. This structure may serve as a template for the receptor, and other compounds may be compared by superimposing them on this conformation of 5-HT.

We have earlier pointed out the structural similarities between compound **21**, *d*-LSD, and 5-HT.[24] When the the indole nucleus of 5-HT is superimposed on the indole moiety of *d*-LSD, the 5-OH group will correspond to the 12-position of *d*-LSD. Assuming that this is the correct way of comparing 5-HT and *d*-LSD, it implies that 5-HT has the above-mentioned conformation (see formula of 5-HT) when activating the same 5-HT receptor as *d*-LSD.

Compound **21** will fit both 5-HT in the above conformation and the aminotetralin moiety (the A–C rings) of *d*-LSD. The 8-hydroxy group of **21** will correspond to the 12-position of *d*-LSD. We therefore assume that the 8-hydroxy group binds to a site on the receptor, which is located in the vicinity of the 12-position of *d*-LSD, when compound **21** interacts with the receptor.

Previously, we have shown that (+)-**21** is significantly more potent than (−)-**21**, and we predicted that (+)-**21** should have the 2*R* configuration,[14] i.e., the same absolute configuration as at C-5 of *d*-LSD. This assumption has now been reconciled (see Chemistry section), and this further supports the hypothesis of Nichols et al.[7] and others[28] that the phenethylamine moiety or the aminotetralin fragment is of primary importance for the 5-HT activity of *d*-LSD.

Comparisons of methoxy- or hydroxy-substituted 2-aminotetralins or 2-aminoindans reveal interesting features. A methoxy or hydroxy substitution in position 5 in the tetralin series gives pure DA agonists[16] (**35** and **36**), whereas the corresponding 8-substitution gives pure 5-HT agonists (**20** and **21**). In the indan series, the 4-OH derivative (**38**)[29] is a pure DA agonist devoid of 5-HT effects in spite of the fact that this compound has a great structural similarity with both **35** and **21**. This contrasts to what has been found for 4,7-dimethoxy-2-(di-*n*-propylamino)indan (**39**), which Sindelar et al. described as a DA, as well as a 5-HT, agonist[30] with higher potency for the DA receptors.[31] On the other hand, we found that the corresponding dimethoxytetralin (**31**) and the dihydroxytetralin (**32**) are DA agonists with no 5-HT effects. This is in agreement with the findings of Arnerič et al.[31] for compound **31**.

In their report on compound **39**, Sindelar et al.[30] discussed the 5-HT activity of this substance and compared its structure with that of 5-HT in an unspecified conformation. They suggested that the effect of **39** could be understood if the two methoxy groups and the amino group were brought to coincide with the 5-OH group, the indole NH group, and the side-chain amino group of 5-HT, respectively. However, this overlap cannot be achieved with 5-HT in the conformation derived from *d*-LSD

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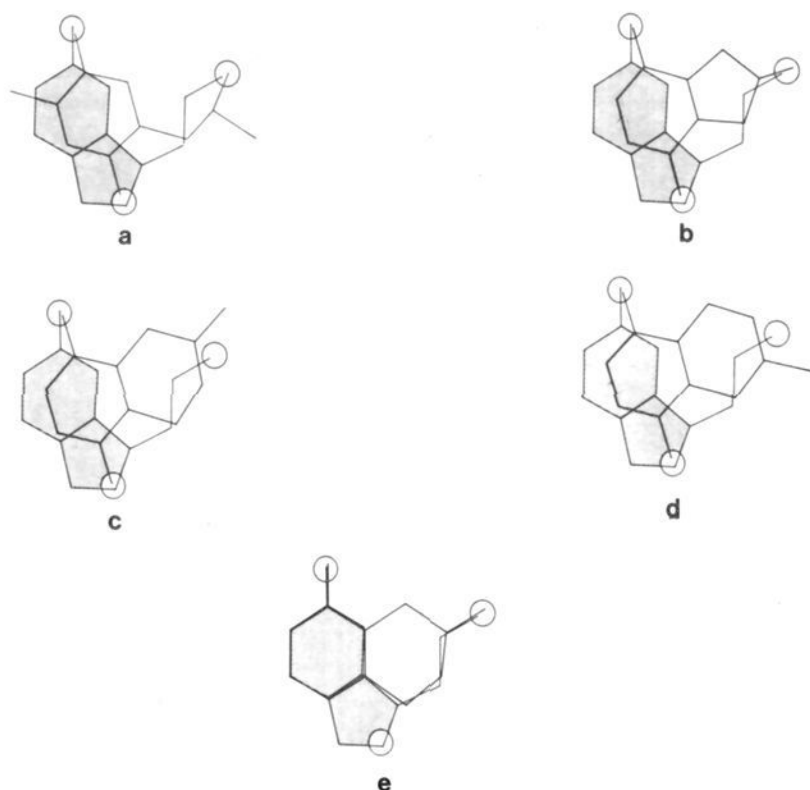

Figure 1. Frameworks, from Dreiding models, of different phenethylamines superimposed on the 5-hydroxytryptamine moiety (shaded areas) in a conformation derived from *d*-LSD. The unfilled circular areas represent potential binding regions on the receptor surface. The following phenethylamines have been superimposed: (a) (2*R*)-(−)-1-(2,5-dimethoxy-4-methylphenyl)-2-propylamine (**37**, DOM); (b) 4,7-dimethoxy-2-(di-*n*-propylamino)indan (**39**); (c and d) 5,8-dimethoxy-2-(di-*n*-propylamino)tetralin (**31**); (e) and 8-hydroxy-2-(di-*n*-propylamino)tetralin. The orientation of the molecules in a-d are in accordance with that proposed by Nichols et al.[32]

(above), and, in addition, the 5-HT-inactive compound **31** would fit in their comparison even better than **39**.

A more pertinent explanation can be derived from a hypothesis worked out by Nichols et al.[32] They related the structure of (2*R*)-(−)-1-(2,5-dimethoxy-4-methylphenyl)-2-propylamine (**37**, DOM) to the structure of 5-HT in the conformation derived from *d*-LSD, as illustrated in Figure 1a. The model suggests that the 2- and 5-methoxy groups of **37** correspond to the 2-position and the 5-hydroxy group of 5-HT, respectively. We have applied this receptor model for some of the compounds in Figure 1. Compound **39** fits the model well (Figure 1b). The distance between the side-chain nitrogen of 5-HT and the nitrogen of **39** is only approximately 0.5 Å (Dreiding models). The corresponding distance between the nitrogens of **31** and 5-HT is about 1.2 Å (Figure 1c,d); hence, the 2-amino group of **31** may be out of position for proper binding to the receptor. On the other hand, the potent agonists **21** and **20**, with one hydroxy and one methoxy group, respectively, in the 8-position, are best related to 5-HT, as depicted in Figure 1e.

The receptor model indicates that 5-HT receptor agonists of the type studied here may be differently oriented on the receptor depending on the aromatic substitution pattern of the agonist. This possibility has also been suggested by Glennon et al.[33] An 8-hydroxy- or 8-methoxy-2-aminotetralin would overlap with 5-HT, as shown in Figure 1e. With this overlap, a tetralin derivative of type **35** or **36** or a monosubstituted indan of type **38** would be inactive at the 5-HT receptor, since the nitrogens would be far apart. Nichols et al.[32] suggested that the 5-HT receptor has an electrophilic site corresponding to the 2-position of 5-HT and of *d*-LSD. The 7-OCH_3 group of **39** could bind to this site and force compound **39** to assume the orientation depicted in Figure 1b, i.e., a close overlap with 5-HT. However, a similar binding of the two methoxy groups of **31** would place the tetralin molecule in such a position that there is no overlap between the side-chain nitrogens of 5-HT and that of **31**, thus offering a tentative explanation for the inactivity of this aminotetralin.

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Experimental Section

Chemistry. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. ^{1}H NMR spectra recorded on a Perkin-Elmer R 12B spectrometer or on a JEOL FX 100 spectrometer, IR spectra recorded on a Perkin-Elmer 157G spectrophotometer, and mass spectra recorded at 70 eV on a LKB spectrometer were all in accordance with the assigned structures. Optical rotations were obtained with a Perkin-Elmer 241 polarimeter. The elemental analyses (C, H, and N) for the new substances (Microanalytical Laboratory, Agricultural College, Uppsala, Sweden) were within ±0.4% of the theoretical values. For purity tests, TLC was performed on fluorescent silica gel or alumina plates. For all compounds, only one spot (visualized by UV light and I_2 vapor) was obtained.

8-Methoxy-2-(methylamino)tetralin (1). Method Ia. This compound was prepared from 8-methoxy-2-tetralone[18] according to the procedure for the synthesis of 5-methoxy-2-(methylamino)tetralin from 5-methoxy-2-tetralone.[16]

8-Methoxy-2-(propylamino)tetralin (5). Method Ib. The reductive amination of 8-methoxy-2-tetralone[18] was accomplished as described for the preparation of 5-methoxy-2-(propylamino)-tetralin from 5-methoxy-2-tetralone.[16]

2-(Dipropylamino)-8-methoxytetralin (20). Method IIa. Acylation of **5** with propionyl chloride, followed by $LiAlH_4$ reduction of the resulting amide, was performed as described for the preparation of 2-(*N*-butyl-*N*-propylamino)-5-methoxytetralin from 2-(butylamino)-5-methoxytetralin.[16]

2-(Dimethylamino)-8-methoxytetralin (14). Method IIb. This compound was synthesized from **1** by using the method of Cannon et al.[17] for the preparation of 2-(dimethylamino)-5,7-dimethoxytetralin from 2-amino-5,7-dimethoxytetralin.

8-Methoxy-2-piperidinotetralin (28). Method III. 8-Methoxy-2-tetralone[18] (10.0 g, 0.057 mol) was heated under reflux with piperidine (14.5 g, 0.170 mol) and a catalytic amount of *p*-toluenesulfonic acid in 500 mL of toluene in a Dean–Stark apparatus. After 21 h, volatiles were evaporated, and the residue was dissolved in absolute ethanol and transferred to a Parr flask. The hydrogenation was performed over PtO_2 (0.2 g) at an initial pressure of 50 psig. After 24 h, the reduction mixture was filtered (Celite), and the solvent was removed from the filtrate under reduced pressure. The residue was purified on an alumina column with ether/light petroleum (1:1) as eluent, and then the free amine was converted to its HCl salt.

Resolution of (±)-2-(Benzylamino)-8-methoxytetralin (11). D-(−)-Tartaric acid (16.08 g, 0.107 mol) dissolved in hot ethanol (600 mL) was added to a hot solution of (±)-**11** (29.65 g, 0.107 mol) in ethanol (1700 mL). The solution was allowed to stand overnight at room temperature. The crystals thus formed were then recrystallized four times from ethanol. The crystals were stirred with ether and NaOH (1 M) solution to obtain the free base. The organic layer was dried (K_2CO_3), and the solvent was removed under reduced pressure, yielding 1.73 g (12 %) of (−)-2-(benzylamino)-8-methoxytetralin [(−)-**11**]. A small sample was converted to the HCl salt.

The mother liquors from the crystallization of the D-(−)-tartrate salt were evaporated, and then the salt was treated with NaOH (1 M) and extracted with ether to isolate the free base (25.9 g, 0.097 mol), which was treated with L-(+)-tartaric acid (14.54 g, 0.097 mol) in ethanol as described above. The precipitated L-(+)-tartrate was recrystallized four times from ethanol and converted as above to the free amine, (+)-2-(benzylamino)-8-methoxytetralin [(+)-**11**]: yield 3.31 g (23%). A small sample was converted to the HCl salt.

(+)-8-Methoxy-2-(propylamino)tetralin [(+)-5]. Method IV. (+)-2-(Benzylamino)-8-methoxytetralin [(+)-**11**; 3.65 g, 13.7

mmol] was acylated with propionyl chloride, and the resulting amide was reduced with $LiAlH_4$ (see method IIa) to give the hygroscopic HCl salt of the *N*-propyl derivative of (+)-**11**, which was dissolved in 100 mL of methanol. The hydrogenolysis was performed over Pd on charcoal at atmospheric pressure. Removal of catalyst (Celite) and solvent gave crude (*R*)-(+)-8-methoxy-2-(propylamino)tetralin hydrochloride [(+)-**5**], which was treated with 2 N NaOH. The free amine was extracted with ether and dried (K_2CO_3), and the ether was evaporated. The amine was then purified on an alumina column with ether as eluent to give 2.5 g (84 %) of (+)-**5**. A small sample was converted to its hydrochloride.

Demethylation of Methoxy Compounds. Method V. The phenols were obtained by heating the appropriate methoxy compound in freshly distilled aqueous 48% HBr for 2 h at 120 °C under N_2. The hydrobromic acid was evaporated in vacuo, and the residue was recrystallized at least twice.

2,3-Epoxy-5,8-dimethoxytetralin (40). To a stirred, refluxing solution of 1,4-dimethoxynaphthalene (26.7 g, 0.142 mol) in 250 mL of absolute ethanol was added sodium (25.0 g, 1.09 mol) in pieces under N_2. When all sodium was consumed, the heater was removed, and 15 min later, 100 mL of water was carefully added. The ethanol was distilled off, and the remaining aqueous phase was extracted with ether (2 × 100 mL). The combined ether layers were dried ($MgSO_4$) and filtered, and the filtrate was evaporated. The epoxidation of the residual crude 1,4-dihydro-5,8-dimethoxytetralin (28 g) with *m*-chloroperbenzoic acid was performed by using the reaction conditions described for the preparation of cholesterol α-epoxide from cholesterol.[34] The isolated crude 2,3-epoxy-5,8-dimethoxytetralin (**40**) was chromatographed on silica gel with ether as eluant to give 18.7 g (63 %) of **40**, mp 130–131 °C (lit.[35] mp 132–133 °C).

5,8-Dimethoxy-2-tetralol (41). 2,3-Epoxy-5,8-dimethoxytetralin (**40**; 7.7 g, 37.3 mmol) was continuously extracted with dry ether from a Soxhlet extraction apparatus into a refluxing suspension of $LiAlH_4$ (5.0 g, 131.7 mmol) in dry ether (500 mL). After the extraction was completed, the mixture was refluxed for 5 h, hydrolyzed, and filtered. The precipitated salts were washed with ether. The filtrate was then evaporated in vacuo, affording 7.1 g (91%) of **41**, mp 130–131 °C (lit.[36] mp 130.5–132 °C).

5,8-Dimethoxy-2-tetralone (42). A solution of **41** (6,4 g, 30.7 mmol) in dichloromethane was added to a solution of pyridinium chlorochromate[19] (9.94 g, 46.1 mmol) in dichloromethane. The reaction mixture was stirred at room temperature for 7 h and filtered through $MgSO_4$, and the solvent was evaporated in vacuo. The residual brown-red solid was purified on a silica column with chloroform as eluant to give 2.90 g (46%) of **42**, mp 98.5–99 °C (lit.[37] mp 99–100 °C).

Determination of Absolute Configuration of (+)-8-Hydroxy-2-(di-*n*-propylamino)tetralin [(+)-21]. A mixture of (+)-**21**·HBr (100 mg, 0.3 mmol), 5-chloro-1-phenyl-1*H*-tetrazol (110 mg, 0.6 mmol), and K_2CO_3 (170 mg, 1.2 mmol) in dry dimethylformamide was stirred under N_2 at 75 °C for 2 days. The volatiles were distilled in vacuo. The residue was treated with 5% NaOH (25 mL) and then extracted with ether (2 × 25 mL). Reextraction with 5% HCl (2 × 50 mL), alkalinization (1 M NaOH), extraction with ether (3 × 50 mL), and drying (K_2CO_3) yielded 150 mg of the crude 1-phenyltetrazolyl ether of (+)-**21**. This material was dissolved in a mixture of methanol (40 mL) and acetic acid (0.5 mL) and then hydrogenolyzed over 10% Pd on charcoal at atmospheric pressure. After 5 h, the reaction mixture was filtered (Celite), and and the filtrate was evaporated. The residue was acidified with 2 M HCl (50 mL), washed with ether, alkalinized (2 M NaOH), and extracted with ether (2 × 50 mL). The combined ether layers were dried (K_2CO_3) and evaporated, and the remaining oil was chromatographed on a silica gel column eluted with ether–petroleum ether (1:2). Precipitation with ethereal HCl gave 39 mg (48%) of (*R*)-(+)-2-(di-*n*-propylamino)tetralin hydrochloride:[21] mp 129–130 °C; $[\alpha]^{22}{}_D$ +76.4° (*c* 1.03, MeOH) [(lit.[38] mp 124-126 °C; $[\alpha]^{20}{}_D$ +78.1° (*c* 0.602, MeOH)].

Optical Rotations. The resolved compounds presented in Table I have the following optical rotations ($\alpha^{22}{}_D$, MeOH): (+)-**5**, +78.3° (*c* 1.05); (–)-**5**, –77.0° (*c* 1.03); (+)-**11**, +63.3° (*c* 1.01); (–)-**11**, –62.5° (*c* 1.01); (+)-**20**, +77.1° (*c* 1.04); (–)-**20**, –76.1° (*c* 1.00); (+)-**21**, +67.5° (*c* 1.03); (–)-**21**, –66.5° (*c* 1.01).

Pharmacology. Animals used in experiments were male rats of Sprague–Dawley strain (Anticimex, Stockholm) weighing 200–350 g. All substances to be tested were dissolved in saline immediately before use, occasionally with the addition of a few drops of glacial acetic acid and/or moderate heating in order to obtain complete dissolution. Reserpine was dissolved in a few drops of glacial acetic acid and made up to volume with 5.5% glucose. Injection volumes were 5 or 10 mL/kg, and injection solutions had neutral pH.

Biochemistry. The biochemical experiments and the spectrofluorometric determinations of 5-HTP and Dopa were performed as previously described.[39] Separate dose–response curves based on four to six dose levels for each substance (subcutaneous administration) and brain area were constructed (cf. ref 29). From these curves, the ED_{50} value (Table II), the dose yielding a half-maximal decrease of the 5-HTP and Dopa level, was estimated.

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Registry No. (±)-**1**, 87394-67-0; (±)-**1** (free base), 87394-99-8; (±)-**2**, 87394-68-1; (±)-**2** (free base), 87395-05-9; (±)-**3**, 87394-69-2; (±)-**4**, 87394-70-5; (±)-**4** (free base), 87395-06-0; (±)-**5**, 87395-00-4; (±)-**5** (free base), 87394-71-6; (*R*)-(+)-**5**, 78095-32-6; (*R*)-(+)-**5** (free base), 81185-23-1; (*S*)-(–)-**5**, 78095-35-9; (±)-**6**, 87394-72-7; (±)-**6** (free base), 87395-07-1; (–)-**7**, 87394-73-8; (±)-**8**, 87394-74-9; (±)-**8** (free base), 87395-08-2; (±)-**9**, 87394-75-0; (±)-**10**, 87394-76-1; (±)-**10** (free base), 87395-09-3; (±)-**11**, 87394-77-2; (*R*)-(+)-**11**, 78095-33-7; (*S*)-(+)-**11** (free base), 81185-18-4; (*S*)-(–)-**11**, 78095-36-0; (*S*)-(–)-**11** (free base), 87479-96-7; (±)-**12**, 87394-78-3; (±)-**13**, 87394-79-4; (±)-**13** (free base), 87395-10-6; (±)-**14**, 87394-80-7; (±)-**14** (free base), 87395-01-5; (±)-**15**, 87394-81-8; (±)-**15** (free base), 87395-11-7; (±)-**16**, 87394-82-9; (±)-**17**, 87394-83-0; (±)-**17** (free base), 87395-12-8; (±)-**18**, 87394-84-1; (±)-**19**, 87394-85-2; (±)-**19** (free base), 87412-11-1; (±)-**20** (free base), 87411-78-7; (±)-**20**, 87394-86-3; (+)-**20**, 78095-31-5; (–)-**20**, 78095-34-8; (±)-**21**, 87394-87-4; (±)-**21** (free base), 80300-08-9; (*R*)-(+)-**21**, 78095-19-9; (*R*)-(+)-**21** (free base), 80300-09-0; (*S*)-(–)-**21**, 78095-20-2; (*S*)-(–)-**21** (free base), 80300-10-3; (±)-**22**, 87394-88-5; (±)-**23**, 87394-89-6; (±)-**23** (free base), 87395-13-9; (±)-**24**, 87394-90-9; (±)-**25**, 87394-91-0; (±)-**25** (free base), 87395-14-0; (±)-**26**, 87394-92-1; (±)-**27**, 87394-93-2; (±)-**27** (free base), 87395-15-1; (±)-**28**, 87394-94-3; (±)-**28** (free base), 87395-02-6; (±)-**29**, 87394-95-4; (±)-**29** (free base), 87395-16-2; (±)-**30**, 87394-96-5; (±)-**31**, 87394-97-6; (±)-**31** (free base), 87395-17-3; (±)-**32**, 87394-98-7; (±)-**32** (free base), 87395-18-4; **40**, 58851-64-2; **41**, 69775-51-5; **42**, 37464-90-7; 8-methoxy-2-tetralone, 5309-19-3; piperidine, 110-89-4; 1,4-dimethoxynaphthalene, 10075-62-4; 1,4-dihydro-5,8-dimethoxynaphthalene, 55077-79-7; (*R*)-8-hydroxy-2-(dipropylamino)-tetralin 1-phenyltetrazolyl ether, 87395-03-7; (*R*)-(+)-2-(dipropylamino)tetralin hydrochloride, 87395-04-8.

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