George A. Olah for helpful suggestions during the preparation of this manuscript.

Registry No. 1, 4730-83-0; 2, 106471-30-1; 2a, 106471-37-8; 3, 50630-24-5; 3a, 62-53-3; 3b, 2179-79-5; 3c, 1666-13-3; 4, 50630-23-4; 5, 57878-08-7; 5a, 104-94-9; 5b, 32111-94-7; 5c, 38762-70-8; 6, 52178-49-1; 6a, 106-49-0; 6b, 21856-93-9; 6c, 21856-94-0; 7, 106471-31-2; 7a, 63-74-1; 7b, 106471-33-4; 7c, 106471-34-5; 8, 106471-32-3; 9, 57878-11-2; 9a, 100-01-6; 9b, 19188-18-2; 9c, 36297-89-9; KSeCN, 3425-46-5; $CH_2{=}CH_2$, 74-85-1; p-$NH_2SO_2C_6H_4SeBr$, 106471-35-6; $(ClCH_2CH_2)_2SeCl_2$, 106471-36-7; $Cl(CH_2)_2Br$, 107-04-0.

Resolved *cis*- and *trans*-2-Amino-5-methoxy-1-methyltetralins: Central Dopamine Receptor Agonists and Antagonists

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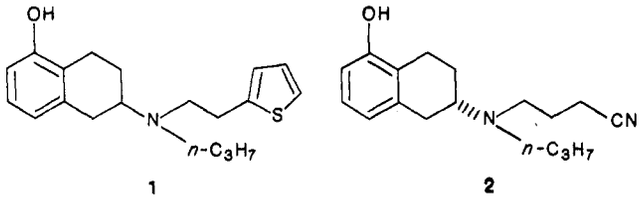
A series of 35 stereochemically well-defined C_1-methyl-substituted derivatives of the potent dopamine (DA) receptor agonist 5-hydroxy-2-(di-*n*-propylamino)tetralin (5-OH-DPAT) have been synthesized. The compounds were tested for central DA receptor agonistic and antagonistic activity, by use of biochemical and behavioral tests in rats. In addition, the compounds were tested for in vivo interactions with 5,6-dihydroxy-2-(di-*n*-propylamino)tetralin (DiPr-5,6-ADTN). On the basis of pharmacological activity profiles, the active compounds have been classified into four groups: (a) classical pre- and postsynaptic DA receptor agonists, (b) DA receptor agonists with preferential action at presynaptic receptors, (c) pre- and postsynaptic DA receptor antagonists, and (d) DA receptor antagonists with preferential action at presynaptic receptors. Results obtained indicate that both 2*R* and 2*S* enantiomers of C_5-oxygenated 2-aminotetralins may be able to bind to DA receptors but that only 2*S* antipodes are able to activate the receptors. O-Methylation of the C_5-oxygenated (1*S*,2*R*)-2-amino-1-methyltetralin derivatives tends to increase their DA receptor antagonistic activity, whereas decrease of the size of the N-substituent(s) from *n*-propyl to ethyl or methyl appears to increase their activity at postsynaptic DA receptors.

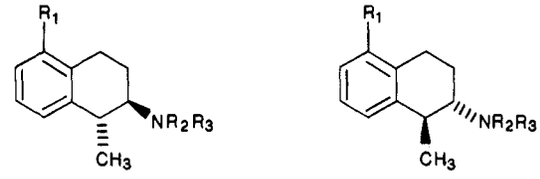
Fifteen years after the report of the dopaminergic activity of 5,6-dihydroxy-2-(dimethylamino)tetralin ("M7"),[1] 2-aminotetralin derivatives still continue to attract intense interest.[2] Recently, several laboratories have reported interesting pharmacological properties of novel 2-aminotetralin derivatives, for example, 2-[*N*-*n*-propyl-*N*-(2-thienylethyl)amino]-5-hydroxytetralin[3] (**1**) and (2*S*)-2-(*N*-*n*-propyl-*N*-(3-cyanopropyl)amino]-5-hydroxytetralin[4] (**2**), have been reported to be potent dopamine (DA) agonists while (1*S*,2*R*)-5-methoxy-1-methyl-2-(di-*n*-propylamino)-tetralin[5] ((1*S*,2*R*)-**18**; (+)-UH-232) appears to be a DA antagonist with preferential action on presynaptic DA receptors (DA autoreceptors).



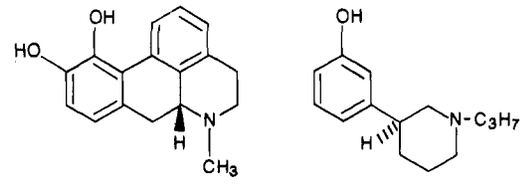
1 **2**

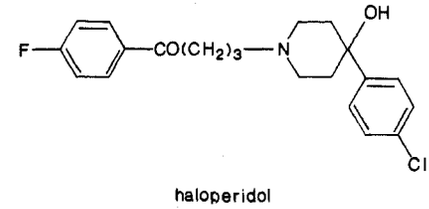
In the present investigation we have synthesized 35 stereochemically well-defined C_1-methyl-substituted 2-aminotetralin derivatives (Schemes I and II). The compounds have been tested for central monoaminergic activity by use of several biochemical and behavioral test methods and can be classified into four groups according to their pharmacological profile: (a) classical pre- and postsynaptic DA receptor agonists (having profiles similar to that of (*R*)-apomorphine),[6] (b) DA receptor agonists with preferential action at presynaptic receptors (having profiles similar to that of (*S*)-3-PPP),[7] (c) pre- and postsynaptic DA receptor antagonists (having profiles similar to that of haloperidol),[8] (d) DA receptor antagonists with preferential action at presynaptic receptors.

Scheme I



	R_1	R_2	R_3
3	OMe	*n*-Pr	H
4	OMe	*n*-Pr	*n*-Pr
5	OH	*n*-Pr	*n*-Pr



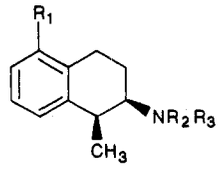


† University of Uppsala.
‡ University of Göteborg.

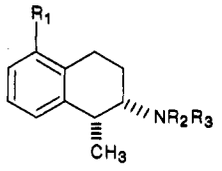
(1) Cannon, J. G.; Kim, J.-C.; Aleem, M. A.; Long, J. P. *J. Med. Chem.* **1972**, *15*, 348.

0022-2623/87/1830-0602$01.50/0

Scheme II



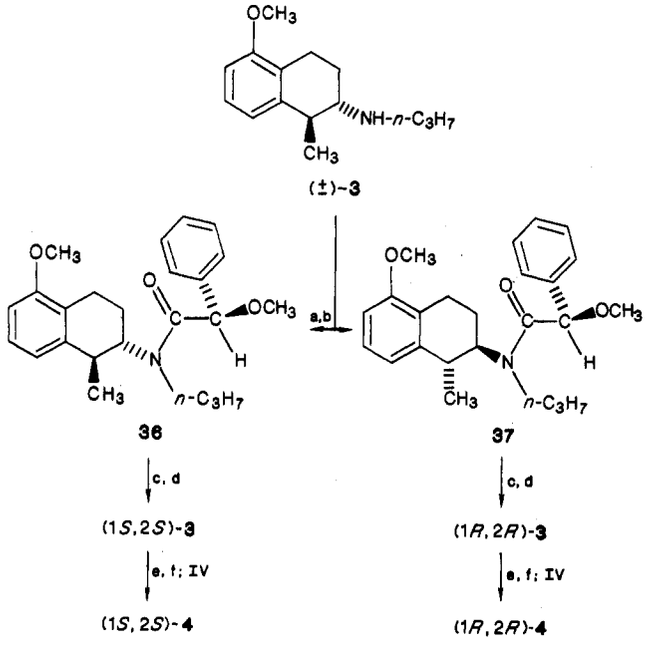
cis-(1*S*,2*R*)



cis-(1*R*,2*S*)

	R_1	R_2	R_3
6	OMe	H	H
7	OH	H	H
8	OMe	Me	H
9	OH	Me	H
10	OMe	Me	Me
11	OH	Me	Me
12	OMe	Et	H
13	OH	Et	H
14	OMe	Et	Et
15	OH	Et	Et
16	OMe	*n*-Pr	H
17	OH	*n*-Pr	H
18	OMe	*n*-Pr	*n*-Pr
19	OH	*n*-Pr	*n*-Pr
20	OMe	*n*-Bu	H
21	OH	*n*-Bu	H
22	OMe	*n*-Bu	*n*-Bu
23	OH	*n*-Bu	*n*-Bu

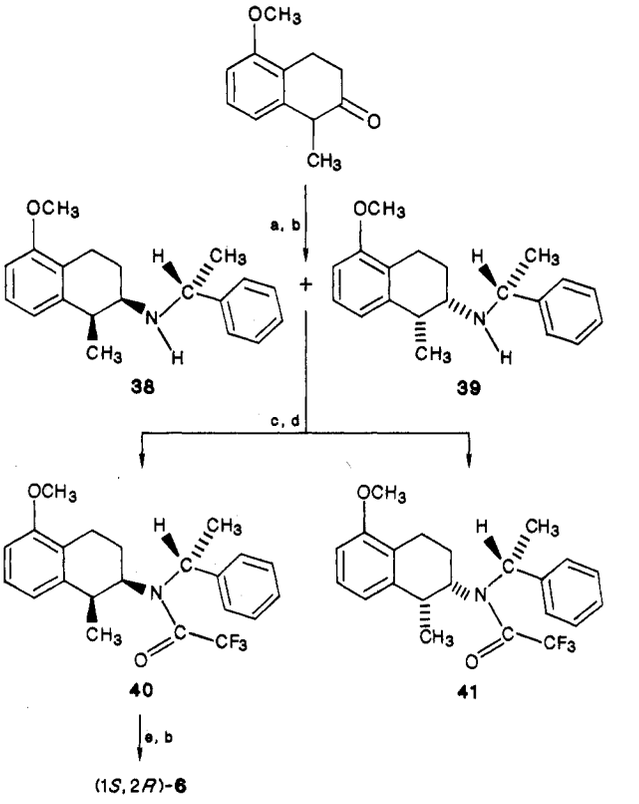
Scheme III. Resolution of *trans*-5-Methoxy-1-methyl-2-(*n*-propylamino)tetralin[a]



[a] Reagents: a = (*R*)-2-methoxy-2-phenylacetyl chloride; b = separation of the diastereomeric amides; c = *t*-C_4H_9OK; *d* = CH_3-Li; e = C_2H_5COCl, $(C_2H_5)_3N$; f = $LiAlH_4$.

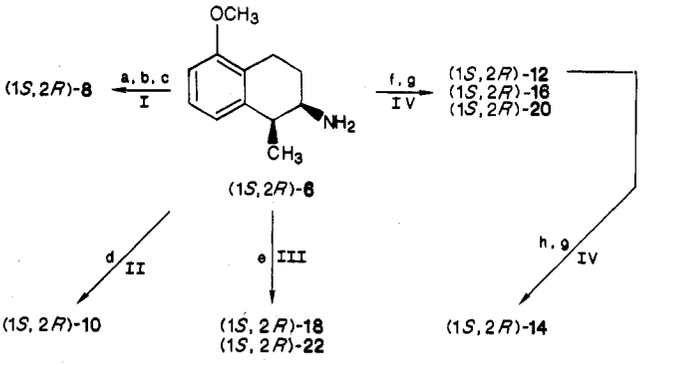
Chemistry. The compounds presented in Table I were synthesized from the resolved key intermediates (1*S*,2*S*)-**3**,[9] (1*R*,2*R*)-**3**,[9] (1*S*,2*R*)-**6**,[5a] and (1*R*,2*S*)-**6**[5a] as outlined in Schemes III–V.

Scheme IV[a]



[a] Reagents: a = (*R*)-(+)-α-phenylethylamine; b = Pd/C, H_2; c = $(CF_3CO)_2O$, $(C_2H_5)_3N$; d = separation of the diastereomeric amides; e = $NaBH_4$.

Scheme V. Synthesis of (1*S*,2*R*)-2-Amino-5-methoxy-1-methyltetralin Derivatives[a]



[a] Reagents: a = $(CF_3CO)_2O$, $(C_2H_5)_3N$; b = KH, CH_3I; c = KOH, CH_3OH, H_2O; d = HCHO, $NaCNBH_3$; e = RX, K_2CO_3; f = RCOCl, $(C_2H_5)_3N$; g = $LiAlH_4$; h = CH_3COCl, $(C_2H_5)_3N$.

(2) For recent reviews, see: (a) Kaiser, C.; Jain, T. *Med. Res. Rev.* **1985**, *5*, 145. (b) Cannon, J. G. *Prog. Drug Res.* **1985**, *29*, 303.

(3) (a) van Oene, J. C.; de Vries, J. B.; Dijkstra, D.; Renkema, R. J. W.; Tepper, P. G.; Horn, A. S. *Eur. J. Pharmacol.* **1984**, *102*, 101. (b) Beaulieu, M.; Itho, Y.; Tepper, P.; Horn, A.; Kebabian, J. W. *Eur. J. Pharmacol.* **1984**, *105*, 15. (c) Horn, A. S.; Tepper, P.; van der Weide, J.; Watanabe, M.; Grigoriadis, D.; Seeman, P. *Pharm. Weekbl. Sci. Ed.* **1985**, *7*, 208. (d) van der Weide, J.; de Vries, J. B.; Tepper, P. G.; Horn, A. S. *Eur. J. Pharmacol.* **1986**, *125*, 273.

(4) Seiler, M. P.; Stoll, A. P.; Closse, A.; Frick, W.; Jaton, A.; Vigouret, J. *J. Med. Chem.* **1986**, *29*, 912.

(5) (a) Johansson, A. M.; Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Clark, D.; Carlsson, A.; Sanchez, D.; Andersson, B.; Wikström, H. *J. Med. Chem.* **1985**, *28*, 1049. (b) Svensson, K.; Hjorth, S.; Clark, D.; Carlsson, A.; Wikström, H.; Andersson, B.; Sanchez, D.; Johansson, A. M.; Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G. *J. Neural Transm.* **1986**, *65*, 1. (c) Svensson, K.; Carlsson, A.; Johansson, A. M.; Arvidsson, L.-E.; Nilsson, J. L. G. *J. Neural Transm.* **1986**, *65*, 29. (d) Svensson, K.; Johansson, A. M.; Magnusson, T.; Carlsson, A. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1986**, *334*, 234. (e) Svensson, K.; Carlsson, M.; Carlsson, A.; Hjorth, S.; Johansson, A. M.; Eriksson, E. *Eur. J. Pharmacol.* **1986**, *130*, 237. (f) Svensson, K. Thesis, Department of Pharmacology, University of Göteborg, Göteborg, Sweden, 1986.

Table I. Physical Data of the Compounds Studied

compd	prepn method	yield, %	mp, °C	recrystn solvent[a]	$[\alpha]^{22}_D$ (c, CH_3OH)	formula[b]
(1*R*,2*R*)-**3**	*c*	37	195.5–196	A	−9.3 (1.0)	$C_{15}H_{23}NO\cdot HCl$
(1*R*,2*R*)-**4**	IV	63	188.5–189.5	A	+7.8 (1.0)	$C_{18}H_{29}NO\cdot HCl$
(1*R*,2*R*)-**5**	V	90	223.5–225	A	+11.8 (1.0)	$C_{17}H_{27}NO\cdot HCl$
(1*S*,2*S*)-**3**	*c*	39	196.5–198	A	+9.8 (1.0)	$C_{15}H_{23}NO\cdot HCl$
(1*S*,2*S*)-**4**	IV	77	188–190	A	−8.0 (1.0)	$C_{18}H_{29}NO\cdot HCl$
(1*S*,2*S*)-**5**	V	79	224.5–225.5	A	−11.5 (1.0)	$C_{17}H_{27}NO\cdot HCl$
(1*S*,2*R*)-**6**	*d*	71	238[d,e]	B	+47.3 (1.0)	$C_{12}H_{17}NO\cdot HCl$
(1*S*,2*R*)-**7**	V	72	298–300[e]	C	+46.9 (1.0)	$C_{11}H_{15}NO\cdot HCl$
(1*S*,2*R*)-**8**	I	48	220.5–221.5	D	+54.7 (1.0)	$C_{13}H_{19}NO\cdot HCl$
(1*S*,2*R*)-**9**	V	82	289–290	C	+56.9 (0.9)	$C_{12}H_{17}NO\cdot HCl$
(1*S*,2*R*)-**10**	II	83	230.1–231[e]	A	+67.2 (1.0)	$C_{14}H_{21}NO\cdot HCl$
(1*S*,2*R*)-**11**	V	94	265.5–266[e]	A	+70.0 (1.0)	$C_{13}H_{19}NO\cdot HCl\cdot {}^1/_3H_2O$
(1*S*,2*R*)-**12**	IV	36	235[f]	D	+54.6 (0.9)	$C_{14}H_{21}NO\cdot HCl$
(1*S*,2*R*)-**13**	V	90	273–274	C	+55.6 (1.0)	$C_{13}H_{19}NO\cdot HCl$
(1*S*,2*R*)-**14**	IV	53[g]	150–151	A	+51.5 (1.0)	$C_{16}H_{25}NO\cdot HCl$
(1*S*,2*R*)-**15**	V	92	262–262.5	E	+53.1 (1.0)	$C_{15}H_{23}NO\cdot HCl$
(1*S*,2*R*)-**16**	IV, *c*	73	282–283[g]	F	+54.9 (0.9)	$C_{15}H_{23}NO\cdot HCl$
(1*S*,2*R*)-**17**	V	86	294–295[e]	A	+54.9 (1.0)	$C_{14}H_{21}NO\cdot HCl$
(1*S*,2*R*)-**18**	III	63	160.5–161.5[d]	C	+49.4 (1.0)	$C_{18}H_{29}NO\cdot HCl$
(1*S*,2*R*)-**19**	V	75	228.5–229.5[d]	C	+49.0 (1.0)	$C_{17}H_{27}NO\cdot HCl$
(1*S*,2*R*)-**20**	IV	52	219–219.5	D	+52.1 (1.0)	$C_{16}H_{25}NO\cdot HCl$
(1*S*,2*R*)-**21**	V	95	258.5–260[e]	C	+50.8 (1.0)	$C_{15}H_{23}NO\cdot HCl$
(1*S*,2*R*)-**22**	III	76	185.5–187	A	+42.7 (1.0)	$C_{20}H_{33}NO\cdot HCl$
(1*S*,2*R*)-**23**	V	96	175–175.5	A	+45.3 (1.0)	$C_{19}H_{31}NO\cdot HCl$
(1*R*,2*S*)-**6**	*d*	71	238[d,e]	B	−45.3 (1.0)	$C_{12}H_{17}NO\cdot HCl$
(1*R*,2*S*)-**10**	II	72	230–231	A	−66.8 (1.0)	$C_{14}H_{21}NO\cdot HCl$
(1*R*,2*S*)-**11**	V	95	266–266.5[e]	A	−71.0 (1.0)	$C_{13}H_{19}NO\cdot HCl\cdot {}^1/_3H_2O$
(1*R*,2*S*)-**14**	IV	53[h]	150.5–151	A	−52.0 (1.0)	$C_{16}H_{25}NO\cdot HCl$
(1*R*,2*S*)-**15**	V	92	262–262.5[e]	E	−54.1 (1.0)	$C_{15}H_{23}NO\cdot HCl$
(1*R*,2*S*)-**16**	IV, *c*	69	269–270	A	−53.4 (1.0)	$C_{15}H_{23}NO\cdot HCl$
(1*R*,2*S*)-**17**	V	95	293–294[e]	A	−55.7 (1.0)	$C_{14}H_{21}NO\cdot HCl$
(1*R*,2*S*)-**18**	III	83	160.5–161[d]	C	−48.6 (1.0)	$C_{18}H_{29}NO\cdot HCl$
(1*R*,2*S*)-**19**	V	88	227–227.5[d]	C	−50.1 (1.0)	$C_{17}H_{27}NO\cdot HCl$
(1*R*,2*S*)-**22**	III	67	185.5–187	A	−43.0 (1.0)	$C_{20}H_{33}NO\cdot HCl$
(1*R*,2*S*)-**23**	V	96	174.5–175.5	A	−44.2 (1.0)	$C_{19}H_{31}NO\cdot HCl$

[a] Recrystallization solvents: A, acetonitrile–ether; B, acetonitrile–ethanol; C, ethanol–ether; D, methanol–ether; E, acetonitrile–methanol–ether; F, methanol. [b] The elemental analyses (C, H, and N) for all new compounds were within ±0.4% of the theoretical values. [c] See Experimental Section. [d] Previously reported; see ref 5a. [e] Decomposition. [f] Sublimation occurred. [g] As calculated from (1*S*,2*R*)-**6**. [h] As calculated from (1*R*,2*R*)-**6**.

The resolution of the trans compound (±)-**3** into the enantiomers was accomplished as depicted in Scheme III. Attempts to separate the diastereomeric (*R*)-*O*-methylmandelic amides of racemic *trans*-2-amino-5-methoxy-1-methyltetralin[9,10] were unsuccessful. However, the diastereomeric (*R*)-*O*-methylmandelic amides of racemic *trans*-5-methoxy-1-methyl-2-(*n*-propylamino)tetralin[9,10] **36** and **37** could be separated by flash chromatography (compare ref 11). The diastereomeric excess (% de) of **36** and **37** was determined by HPLC analysis to be 98% and 96%, respectively. The separated amides were treated with potassium *tert*-butoxide in tetrahydrofuran,[11a,12] to afford a mixture of the secondary amine ((1*S*,2*S*)-**3** or (1*R*,2*R*)-**3**) and the corresponding *N*-formyl derivatives.[11a,13] The latter were converted to (1*S*,2*S*)-**3** or (1*R*,2*R*)-**3** by treatment with methyllithium in ether. The tertiary amines (1*S*,2*S*)-**4** and (1*R*,2*R*)-**4** were prepared from (1*S*,2*S*)-**3** and (1*R*,2*R*)-**3**, respectively, by N-acylation followed by reduction of the resulting amides (Scheme III).

We have previously reported[5a] that the synthesis of the cis key intermediates (1*S*,2*R*)-**6** and (1*R*,2*S*)-**6** from 5-methoxy-1-methyl-2-tetralone, via the diastereomeric amines **38** and **39**, respectively (Scheme IV), proceeded under a remarkably stereoselective control.[5a] However, when the reductive amination of 5-methoxy-1-methyl-2-tetralone was repeated by use of a new batch of Pd(C), a mixture of diastereoisomers **38** and **39**, in a 9:1 ratio, was formed (as indicated by ^1H and ^{13}C NMR spectroscopy). The diastereomeric amines could not be separated by fractional crystallization or column chromatography. Instead, the separation was accomplished by column chromatography of the corresponding trifluoroacetamides (**40** and **41**, Scheme IV). The diastereomeric excess of the separated trifluoroacetamide **40** was determined by ca-

(6) (a) Colpaert, F. C.; van Bever, W. F. M.; Leysen, J. E. M. F. *Int. Rev. Neurobiol.* **1976**, *19*, 225. (b) Neumeyer, J. L.; Lal, S.; Baldessarini, R. J. Proceedings of Symposium on Clinical Pharmacology of Apomorphine and Other Dopaminomimetics; Vilassimius, Sardinia, Sept 1980. (c) DiChiara, G; Gessa, G. L. *Adv. Pharmacol. Chemother.* **1978**, *15*, 88.

(7) (a) Clark, D.; Hjorth, S.; Carlsson, A. *J. Neural Transm.* **1985**, *62*, 1. (b) Clark, D.; Hjorth, S.; Carlsson, A. *J. Neural Transm.* **1985**, *62*, 171.

(8) Carlsson, A. In *Psychopharmacology: A Generation of Progress*; Lipton, M. A., DiMascio, A., Killam, K. F., Eds.; Raven: New York, 1978; pp 1057–1070.

(9) Johansson, A. M.; Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G.; Svensson, K.; Carlsson, A.; Sanchez, D.; Andersson, B.; Wikström, H. *Acta Pharm. Suec. Suppl.* **1985**, *1*, 447.

(10) Hacksell, U.; Johansson, A. M.; Arvidsson, L.-E.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Wikström, H.; Sanchez, D.; Lindberg, P. *J. Med. Chem.* **1984**, *27*, 1003.

(11) (a) Wikström, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L.-E.; Johansson, A. M.; Thorberg, S.-O.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Clark, D.; Carlsson, A. *J. Med. Chem.* **1984**, *27*, 1030. (b) Helmchen, G.; Strubert, W. *Chromatographia* **1974**, *7*, 713.

(12) Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275.

(13) Wikström, H.; Andersson, B.; Sanchez, D.; Lindberg, P.; Arvidsson, L.-E.; Johansson, A. M.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1985**, *28*, 215.

pillary GC to be 96%. The trifluoroacetamide function was cleaved by use of sodium borohydride[14] (see Experimental Section). Alternatively, the resolution was accomplished by chromatographic separation of the (*R*)-*O*-methylmandelic amides of racemic **16**, in analogy with the resolution of the racemic trans diastereomer **3**. The cleavage of the "cis amides" was performed at −8 to −10 °C to minimize elimination of the C_2 functional group and a vicinal hydrogen.

The *N*-alkyl derivatives of (1*S*,2*R*)-2-amino-5-methoxy-1-methyltetralin ((1*S*,2*R*)-**6**) were prepared as outlined in Scheme V; the *N*-methyl derivative (1*S*,2*R*)-**8** was prepared by methylation of the trifluoroacetamide of (1*S*,2*R*)-**6**, followed by hydrolysis of the amide[15] (pathway I, Scheme V). The other secondary amines ((1*S*,2*R*)-**12**, (1*S*,2*R*)-**16**, and (1*S*,2*R*)-**20**) were prepared by acylation of (1*S*,2*R*)-**6** with the appropriate acyl chloride, followed by reduction of the crude amides (pathway IV, Scheme V). Reductive methylation of (1*S*,2*R*)-**6** with formaldehyde and sodium cyanoborohydride[16] gave the *N*,*N*-dimethyl derivative (1*S*,2*R*)-**10** (pathway II, Scheme V). The *N*,*N*-dialkyl derivatives (1*S*,2*R*)-**18** and (1*S*,2*R*)-**22** were prepared by alkylation of the primary amine (1*S*,2*R*)-**6** with 1-iodopropane and 1-bromobutane, respectively (pathway III, Scheme V). Acylation of the *N*-ethyl derivative ((1*S*,2*R*)-**12**) followed by reduction of the resulting amide gave (1*S*,2*R*)-**14** (pathway IV, Scheme V).

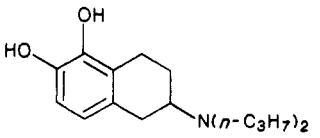
The N-alkylated (1*R*,2*S*)-2-amino-5-methoxy-1-methyltetralin derivatives were prepared from (1*R*,2*S*)-**6** in the same manner as the 1*S*,2*R* enantiomers (Scheme V).

Throughout, demethylation of the methoxy compounds was accomplished by use of 48% aqueous hydrogen bromide. The desired phenolic amine hydrochlorides were prepared from the initially formed hydrobromides by halogen interchange.

The absolute configuration of (+)-**19**·HBr and (−)-**5**·HCl have been established[17] by X-ray crystallography to be 1*S*,2*R* and 1*S*,2*S*, respectively. This also establishes the absolute configuration of the other resolved cis and trans compounds. It should be noted that the sign of the optical rotation, at the D line, is not strictly correlated with the absolute configuration. For example, (1*S*,2*S*)-**3**·HCl is dextrorotatory and (1*S*,2*S*)-**4**·HCl is levorotatory when recorded in methanol.

The enantiomeric excess exceeds 90% ee in all compounds reported herein.

Pharmacology. The compounds were tested for central DA receptor activity by use of in vivo biochemical and behavioral methods in reserpinized and nonpretreated (nonreserpinized) rats (Table II). In addition, the compounds were tested for their ability to displace the DA receptor agonist 5,6-dihydroxy-2-(di-*n*-propylamino)tetralin[18] (DiPr-5,6-ADTN) from rat striatal binding sites in vivo[19] and to antagonize the locomotor hyperactivity and hypothermia induced by DiPr-5,6-ADTN (Table III).



DiPr-5,6-ADTN

Biochemical Test Method. The biochemical screening method has been described previously.[20] The concept of this method is that a DA receptor agonist will stimulate the DA receptors and through regulatory feedback systems induce a decline in tyrosine hydroxylase activity and, thus, reduce the synthesis rate of DA in the presynaptic neuron. The DOPA formation (as determined after in vivo inhibition of the aromatic L-amino acid decarboxylase by NSD 1015 ((3-hydroxybenzyl)hydrazine hydrochloride)) in the limbic and striatal brain regions is taken as an indirect measure of DA-synthesis rate. DA receptor agonists decrease DOPA formation in reserpinized as well as in nonpretreated rats. DOPA levels in reserpinized rats are not expected to be affected by DA receptor antagonists. However, in nonpretreated rats, DA receptor antagonists increase the DA synthesis rate.[8,21]

Locomotor Activity. The behavioral observations and motor activity recordings were carried out with reserpinized and nonpretreated rats in motility meters as previously described.[20]

Postsynaptic DA receptor agonists induce locomotor activity and stereotyped behavior such as sniffing, rearing, and licking in reserpinized rats. In contrast, DA receptor antagonists or selective presynaptic DA receptor agonists are not expected to antagonize reserpine-induced akinesia. Thus, antagonism of reserpine-induced akinesia is taken as an indication of postsynaptic DA receptor stimulation.

In nonpretreated rats, classical DA receptor agonists (such as (*R*)-apomorphine) induce hypomotility after low doses and locomotor stimulation and stereotypies after high doses. This has been suggested to reflect a stimulation of presynaptic DA receptors at low doses and a stimulation of postsynaptic DA receptors at high doses.[22] Classical DA receptor antagonists (such as haloperidol) produce hypomotility and induce catalepsy at high doses.[8] This latter effect is probably related to antagonism of postsynaptic DA receptors. It has also been shown that

(14) Weygand, F.; Frauendorfer, E. *Chem. Ber.* **1970**, *103*, 2437.
(15) Nordlander, J. E.; Catalane, D. B.; Eberlein, T. H.; Farkas, L. V.; Howe, R. S.; Stevens, R. M.; Tripoulas, N. A. *Tetrahedron Lett.* **1978**, *50*, 4987.
(16) Cannon, J. G.; Brubaker, A. N.; Long, J. P.; Flynn, J. R.; Verimer, T.; Harnirattisai, P.; Costall, B.; Naylor, R. J.; Nohria, V. *J. Med. Chem.* **1981**, *24*, 149.
(17) Johansson, A. M.; Karlén, A.; Grol, C. J.; Sundell, S.; Kenne, L.; Hacksell, U. *Mol. Pharmacol.* **1986**, *30*, 258.
(18) (a) McDermed, J. D.; McKenzie, G. M.; Philips, A. P. *J. Med. Chem.* **1975**, *18*, 362. (b) Feenstra, M. G. P.; Rollema, H.; Horn, A. S.; Dijkstra, D.; Grol, C. J.; Westerink, B. H. C.; Westerbrink, A. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1980**, *310*, 219. (c) Hacksell, U.; Svensson, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Wikström, H.; Lindberg, P.; Sanchez, D. *J. Med. Chem.* **1979**, *22*, 1469.
(19) (a) Feenstra, M. G. P.; Rollema, H.; Mulder, T. B. A.; Westerink, B. H. C.; Horn, A. S. *Life Sci.* **1983**, *32*, 1313. (b) Feenstra, M. G. P.; Rollema, H.; Mulder, T. B. A.; de Vries, J. B.; Horn, A. S. *Eur. J. Pharmacol.* **1983**, *90*, 433. (c) Feenstra, M. G. P. Thesis, Department of Pharmaceutical and Analytical Chemistry, State University at Groningen, Groningen, The Netherlands, 1984. (d) Rollema, H.; Feenstra, M. G. P.; Grol, C. J.; Lewis, M. H.; Staples, L.; Mailman, R. B. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1986**, *332*, 338. (e) Carlsson, A.; Löfberg, L. *J. Neural Transm.* **1985**, *64*, 173.
(20) For discussions of the experimental design and the underlying concepts, see for example: (a) Wikström, H.; Lindberg, P.; Martinsson, P.; Hjorth, S.; Carlsson, A.; Hacksell, U.; Svensson, U.; Nilsson, J. L. G. *J. Med. Chem.* **1978**, *21*, 864. (b) Hjorth, S.; Carlsson, A.; Clark, D.; Svensson, K.; Wikström, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L.-E. Johansson, A.; Nilsson, J. L. G. *Psychopharmacology* **1983**, *81*, 89. (c) Andén, N.-E.; Carlsson, A.; Häggendahl, J. *Ann. Rev. Pharmacol.* **1969**, *9*, 119.
(21) (a) Carlsson, A. *Am. J. Psychiatry* **1978**, *135*, 164. (b) Kehr, W.; Carlsson, A.; Lindqvist, M.; Magnusson, T.; Atack, C. V. *J. Pharm. Pharmacol.* **1972**, *24*, 744.
(22) Strömbom, U. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1976**, *292*, 167.

Table II. Effects on in Vivo DOPA Accumulation in the Rat Brain and on Locomotor Activity in the Rat

	no pretreatment				reserpine pretreatment		
	DOPA accumulation:[a] ED_{50}, μmol/kg sc		locomotor activity:[b] percent of saline controls, mean ± SEM		DOPA accumulation:[c] ED_{50} μmol/kg sc		locomotor activity:[d] accumulated counts/30 min, mean ± SEM
compd	limbic	striatum	3.2 μmol/kg sc	52 μmol/kg sc	limbic	striatum	(μmol/kg sc)
(1*R*,2*R*)-4	I[e]	I	NT[f]	88 ± 13	I	I	NT[g]
(1*R*,2*R*)-5	I	I	NT	97 ± 15	I	I	NT[g]
(1*S*,2*S*)-4	I	I	NT	82 ± 7	I	I	NT[g]
(1*S*,2*S*)-5	*h*	*h*	79 ± 8	74 ± 17	7.3 (50%)	7.9 (40%)	19 ± 11 (52)
(1*S*,2*R*)-6	4.4 (190%)	4.2 (230%)	136 ± 18*	62 ± 11*(*)	NT	NT	NT
(1*S*,2*R*)-7	I	I	94 ± 24	97 ± 6	NT	NT	NT
(1*S*,2*R*)-8	4.7 (300%)	1.8 (420%)	86 ± 12	29 ± 10***	NT	NT	NT
(1*S*,2*R*)-9	5.5 (210%)	7.5 (340%)	143 ± 28	47 ± 7**	NT	NT	NT
(1*S*,2*R*)-10	2.2 (330%)	2.9 (410%)	100 ± 10	9 ± 3***[i]	NT	NT	NT
(1*S*,2*R*)-11	5.5 (220%)	3.4 (300%)	76 ± 8	1 ± 0.8***[i]	NT	NT	NT
(1*S*,2*R*)-12	5.3 (310%)	4.8 (440%)	108 ± 13	60 ± 8**	NT	NT	NT
(1*S*,2*R*)-13	15.0 (200%)	6.0 (300%)	83 ± 8	62 ± 2*(*)	NT	NT	NT
(1*S*,2*R*)-14	5.5 (300%)	2.9 (410%)	100 ± 9	46 ± 16*	NT	NT	NT
(1*S*,2*R*)-15	13.0 (260%)	6.5 (420%)	113 ± 16	19 ± 3**	NT	NT	NT
(1*S*,2*R*)-16	4.6 (240%)	4.4 (320%)	132 ± 15	159 ± 23*(*)	NT	NT	NT
(1*S*,2*R*)-17	9.0 (200%)	16.0 (280%)	114 ± 15	125 ± 19	NT	NT	NT
(1*S*,2*R*)-18	12.8 (285%)[j]	9.6 (380%)[j]	152 ± 19**	70 ± 13**	I[j]	I[j]	4 ± 2 (52)[j]
(1*S*,2*R*)-19	10.0 (240%)[j]	9.4 (340%)[j]	110 ± 4	102 ± 8	I[j]	I[j]	6 ± 2 (52)[j]
(1*S*,2*R*)-20	18.0 (190%)	20.0 (280%)	113 ± 20	135 ± 15*	NT	NT	NT
(1*S*,2*R*)-21	*k*	*k*	89 ± 17	76 ± 9	NT	NT	NT
(1*S*,2*R*)-22	I	I	NT	96 ± 14	NT	NT	NT
(1*S*,2*R*)-23	*l*	*l*	NT	82 ± 16	NT	NT	NT
(1*R*,2*S*)-11	8.5 (200%)	8.5 (300%)	NT	15 ± 4***	28.0 (64%)	25.0 (58%)	7 ± 2 (204)
(1*R*,2*S*)-15	*k*	*k*	NT	40 ± 8***	1.4 (40%)	1.6 (30%)	5 ± 2 (52)
(1*R*,2*S*)-16	I	I	113 ± 21	119 ± 14	I	I	12 ± 6 (52)
(1*R*,2*S*)-17	NT	NT	NT	NT	4.0 (40%)	5.0 (20%)	26 ± 6 (125)***
(1*R*,2*S*)-18	I[j]	I[j]	I[j]	I[j]	5.5 (60%)[j]	5.8 (50%)[j]	8 ± 4 (204)[j]
(1*R*,2*S*)-19	0.84 (51%)[j]	0.84 (47%)[j]	65 ± 9**[j,m]	171 ± 28*[j,n]	0.30 (35%)[j]	0.34 (20%)[j]	121 ± 14 (3.2)***
(1*R*,2*S*)-23	NT	NT	NT	NT	I	I	6 ± 1 (52)
(*R*)-apomorphine	*o*	*o*	52 ± 6**[j,p]	277 ± 14***[j,q]	0.041 (35%)[r]	0.044 (20%)[r]	366 ± 36 (3.2)***
haloperidol	0.19 (210%)[s]	0.19 (310%)[s]	3 ± 1***[i,t]		I[u]	I[u]	NT

[a] Animals were injected with test drug 65 min and NSD 1015 (100 mg/kg ip) 30 min before death. Controls received corresponding saline injections. Shown are the doses giving a half-maximal increase or decrease of DOPA formation in rat limbic or striatal region, estimated from dose–response curves comprising four to five dose levels (n = 3–5). Maximal or minimal levels obtained are shown in brackets; controls = 100%. Control levels: limbic region, 447 ± 23 ng/g; striatum, 1045 ± 47 ng/g, n = 16. [b] Animals were injected with test drug 5 min before the activity session and the accumulated counts over a 30-min period were recorded. Shown is the locomotor activity expressed in percent of saline controls (100%; 232 ± 14 counts/30 min, n = 25), means ± SEM, n = 3–5. Statistical differences were calculated by using the Student's t test: (***) $p < 0.001$, (**) $p < 0.01$, (*(*)) $p < 0.025$, and (*) $p < 0.05$ vs. saline controls. [c] Animals were injected with reserpine (5 mg/kg sc) 18 h, test drug 60 min, and NSD 1015 (100 mg/kg ip) 30 min before death. Controls received corresponding saline injections. Shown are the doses giving a half-maximal decrease of DOPA formation in rat limbic and striatal regions, estimated from dose–response curves comprising four to seven dose levels (n = 3–5). Minimal levels obtained are shown in brackets; controls = 100%. [d] Animals were injected with reserpine (5 mg/kg sc) 18 h and test drug immediately before the activity session. Shown are the accumulated counts/30 min (mean ± SEM, n = 3–4). Reserpine controls: 3 ± 1 counts/30 min, n = 13. [e] I = inactive: no significant effect on limbic or striatal DOPA formation at 52 μmol/kg sc. [f] NT = not tested. [g] There were no signs of behavioral stimulation when observing the animals' gross behavior. [h] A 20–25% *decrease* in limbic and striatal DOPA formation was noted after 52 μmol/kg sc. [i] This dose produced catalepsy, observed 30–60 min after injection. [j] From ref 5a. [k] A 40–50% increase in limbic and striatal DOPA formation was noted after 52 μmol/kg sc. [l] A 40–80% increase in limbic and striatal DOPA formation was noted after 52 μmol/kg sc. [m] The dose tested was 0.84 μmol/kg sc. [n] The dose tested was 13.4 μmol/kg sc. [o] (*R*)-Apomorphine elicited a biphasic dose–response curve with two ED_{50}'s. From ref 33. [p] The dose tested was 0.32 μmol/kg sc. [q] The dose tested was 3.2 μmol/kg sc. [r] From ref 27. [s] From ref 8. [t] The dose tested was 2.7 μmol/kg ip, 30 min before the activity session. [u] Inactive; no significant effect at 1.4 μmol/kg ip. From ref 20b.

low doses of DA receptor antagonists such as haloperidol,[23] spiperone,[24] (–)-sulpiride,[23c] and pimozide[25] induce behavioral stimulation in nonpretreated rats. Most likely this effect reflects antagonism at presynaptic DA receptors. Low doses of molindone[26] has also been shown to selectively antagonize presynaptic DA receptors, thereby resulting in an activation of postsynaptic DA receptors.

Interactions with DiPr-5,6-ADTN. A modification[19e] of the recently described[19a–d] in vivo binding assay for displacement of DiPr-5,6-ADTN from DA receptor binding sites in the rat striatum has been used. The binding of DiPr-5,6-ADTN appears to occur predominantly to postsynaptic DA receptors.[19a] However, this does not exclude that DiPr-5,6-ADTN has some affinity also for presynaptic DA receptors. It is noteworthy that DA receptor agonists appear to be less potent than antagonists in displacing this ligand.[19c,e]

The locomotor hyperactivity and the hypothermia induced by DiPr-5,6-ADTN are antagonized by classical DA receptor antagonists. Therefore, behavioral observations were made during the in vivo binding assay. It should be noted that in a previous (as well as in the present) in-

(23) (a) Monti, J. M.; Hance, A. J. *Psychopharmacologia (Berlin)* **1967**, *12*, 34. (b) Ahlenius, S.; Engel, J. *J. Pharm. Pharmacol.* **1971**, *23*, 301. (c) Costall, B.; Domene, A. M.; Naylor, R. B. *Eur. J. Pharmacol.* **1983**, *90*, 307.
(24) Maj, J.; Przewlocka, B.; Kukulka, L. *Pol. J. Pharmacol. Pharm.* **1977**, *29*, 11.
(25) Wauquier, A.; Clincke, G. H. C.; van der Broeck, W. A. E.; de Prins, E. In *Sleep: Neurotransmitters and Neuromodulators*; Wauquier, A., Gaillard, J. M., Monti, J. M., Radulovacki, M., Eds.; Raven: New York, 1985; pp 107–120.
(26) Ålander, T.; Grabowska-Andén, M.; Andén, N.-E. *J. Pharm. Pharmacol.* **1980**, *32*, 780.

Table III. Interactions with DiPr-5,6-ADTN in Vivo

compd	dose, μmol/kg sc	DiPr-5,6-ADTN binding[a]	locomotor activity[b]	body temp changes[c]
(1*S*,2*S*)-**5**	13.0	91 ± 6	92 ± 12	−0.83 ± 0.35
(1*S*,2*R*)-**6**	13.0	83 ± 16	88 ± 9	−1.33 ± 0.10*
(1*S*,2*R*)-**7**	13.0	98 ± 4	86 ± 17	−0.70 ± 0.19
(1*S*,2*R*)-**8**	13.0	51 ± 6**(*)	35 ± 8**(*)	−0.25 ± 0.17
	52.0	20 ± 18**(*)	9 ± 1***	0.93 ± 0.22***
(1*S*,2*R*)-**9**	13.0	54 ± 7**(*)	73 ± 7	0.15 ± 0.19**
(1*S*,2*R*)-**10**	3.2	60 ± 7**	62 ± 15*	−0.15 ± 0.47
	13.0	40 ± 8***[d]	15 ± 4***[d]	1.60 ± 0.19**[d]
	52.0	14 ± 5***	8 ± 6***	0.28 ± 0.27*
(1*S*,2*R*)-**11**	13.0	39 ± 4***	11 ± 2***	1.48 ± 0.32**
(1*S*,2*R*)-**12**	13.0	36 ± 1***	69 ± 3*	1.33 ± 0.10***
(1*S*,2*R*)-**13**	13.0	64 ± 3**	95 ± 8	−0.50 ± 0.25
(1*S*,2*R*)-**14**	13.0	44 ± 6***[d]	40 ± 9***[d]	1.20 ± 0.26*(*)[d]
	52.0	28 ± 4***	14 ± 3**(*)	1.40 ± 0.13***
(1*S*,2*R*)-**15**	13.0	49 ± 6**(*)	63 ± 17*(*)	0.20 ± 0.16*(*)
(1*S*,2*R*)-**16**	13.0	85 ± 6[d]	95 ± 6[d]	1.30 ± 0.21*(*)[d]
	52.0	41 ± 3***	54 ± 6*(*)	1.05 ± 0.16**
	204.0	35 ± 6***	29 ± 10**(*)	0.47 ± 0.25**(*)
(1*S*,2*R*)-**17**	13.0	66 ± 4*	107 ± 11	0.10 ± 0.21
(1*S*,2*R*)-**18**	3.2	83 ± 6	105 ± 9	−0.03 ± 0.57
	13.0	61 ± 4**[d]	78 ± 17[d]	1.40 ± 0.85*(*)[d]
	52.0	34 ± 5***	24 ± 7**(*)	0.45 ± 0.25*
	204.0	31 ± 4***	22 ± 13**	0.45 ± 0.23**
(1*S*,2*R*)-**19**	10.0	61 ± 7*(*)	NT[e]	1.70 ± 0.06***
	40.0	21 ± 4***	NT	1.70 ± 0.10***
(1*S*,2*R*)-**20**	13.0	76 ± 4*(*)	82 ± 11	−0.25 ± 0.30
(1*S*,2*R*)-**21**	13.0	46 ± 6**(*)	80 ± 11	−0.93 ± 0.12
(1*S*,2*R*)-**22**	13.0	115 ± 9[d]	96 ± 13[d]	−0.27 ± 0.49[d]
(1*S*,2*R*)-**23**	13.0	96 ± 5	89 ± 13	−0.43 ± 0.33
(1*R*,2*S*)-**11**	13.0	63 ± 12*	34 ± 8**	0.88 ± 0.23**(*)
	52.0	22 ± 6***	4 ± 1***	1.82 ± 0.16***
(1*R*,2*S*)-**15**	13.0	70 ± 7*	100 ± 13	0.22 ± 0.28*
(1*R*,2*S*)-**17**	52.0	66 ± 6**	80 ± 21	−0.45 ± 0.26
(1*R*,2*S*)-**18**	22.0	106 ± 9	NT	0.12 ± 0.10[f]
	45.0	94 ± 8	NT	0.50 ± 0.15[f]
(1*R*,2*S*)-**19**	10.0	90 ± 25	NT	0.10 ± 0.18[f]
	40.0	37 ± 6***	NT	−0.20 ± 0.10*[f]
(1*R*,2*S*)-**23**	13.0	124 ± 10	87 ± 17	−0.70 ± 0.20
DiPr-5,6-ADTN	0.25	100 ± 8	100 ± 5	−0.70 ± 0.10
haloperidol	2.7	26 ± 5***	10 ± 2***	1.34 ± 0.12***

[a] The animals were injected with DiPr-5,6-ADTN (0.25 μmol/kg sc) 100 min and the test compounds (2.7–204 μmol/kg sc) 40 min before death. Shown is the striatal level of DiPr-5,6-ADTN (after subtraction of cerebellum "blank") expressed as percent of DiPr-5,6-ADTN controls (48 ± 1.9 pmol/g, n = 36). Student's test: (***) $p < 0.001$, (**(*)) $p < 0.0025$, (**) $p < 0.01$, (*(*)) $p < 0.025$, and (*) $p < 0.05$ vs. DiPr-5,6-ADTN only. [b] The locomotor activity was recorded 5–35 min after injection of the test compounds and is expressed as percent of DiPr-5,6-ADTN controls (saline, 203 ± 15 (11); DiPr-5,6-ADTN, 565 ± 23 (36), counts/30 min, (n), $p < 0.001$ vs. saline). Statistics, see footnote *a*. [c] DiPr-5,6-ADTN decreased the rectal temperature (−2.3 ± 0.14 °C, n = 36; saline controls, 38.0 ± 0.06 °C, n = 36) measured at 60 min after injection. Shown is the temperature changes (in °C) induced by the test compounds between 60 and 100 min after DiPr-5,6-ADTN. All values represent the mean ± SEM, n = 4. Statistics: see footnote *a*. [d] From ref 5c. [e] NT = not tested. [f] In these experiments the temperature changes for the DiPr-5,6-ADTN controls (measured between 60 and 100 min after DiPr-5,6-ADTN) differed and was found to be 0.46 ± 0.10 °C (mean ± SEM), n = 8.

vestigation[19c] classical DA receptor agonists did not induce behavioural effects superimposed on the effects of DiPr-5,6-ADTN.

Results and Discussion

The screening procedure used in the present investigation should reveal activity at DA, noradrenaline (NA), and 5-hydroxytryptamine (5-HT) receptors. All the activities observed could be attributed to effects at DA receptors: none of the compounds tested did affect 5-HTP formation in any brain region, indicating that these compounds are inactive on central 5-HT receptors. Only compound (1*S*,2*R*)-**18** (52–205 μmol/kg) increased cortical DOPA formation, suggesting that higher doses of (1*S*,2*R*)-**18** may influence central noradrenergic systems.[5a,b,d] Nine of the compounds, (1*S*,2*S*)-**4** ((−)-AJ-115), (1*R*,2*R*)-**4** ((+)-AJ-115), (1*R*,2*R*)-**5** ((+)-AJ-116), (1*S*,2*R*)-**7**, (1*S*,2*R*)-**21–23**, (1*R*,2*S*)-**16** ((−)-AJ-76), and (1*R*,2*S*)-**23**, were considered inactive. The others were active in at least two of the assays used. The most striking observation of this study is that stereochemical variations (cis vs. trans, *R* vs. *S* configuration, etc.) may change the activity of the compounds from agonists to antagonists or to give selectivity for presynaptic receptors. On the basis of the test results obtained in the present and other studies,[5] the active analogues have been classified into the following four groups according to their pharmacological profile.

Classical Pre- and Postsynaptic DA Receptor Agonists: (1*S*,2*S*)-5, (1*R*,2*S*)-17–19. These compounds reduced the limbic and striatal DOPA levels in reserpinized rats (Table II). Although (1*R*,2*S*)-**19** ((−)-UH-242) is the most potent of the four analogues, it is 10 times less potent than (*R*)-apomorphine[27] ($ED_{50} \approx 40$ nmol/kg) and 100 times less potent than (*S*)-5-hydroxy-2-(di-*n*-propylamino)tetralin[13] ((*S*)-5-OH-DPAT; ED_{50} = 3.7 nmol/kg), in this respect. None of the compounds antagonized the hypothermia induced by DiPr-5,6-ADTN, and (1*R*,2*S*)-**17** and (1*S*,2*S*)-**5** ((−)-AJ-116) did not antagonize the hyperactivity induced by DiPr-5,6-ADTN.

(27) Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, J. L. G.; Wikström, H.; Lindberg, P.; Sanchez, D.; Hjorth, S.; Carlsson, A.; Paalzow, L. *J. Med. Chem.* 1981, *24*, 429.

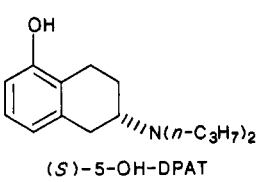
Compounds (1*R*,2*S*)-**17** and (1*R*,2*S*)-**19** were able to reverse the reserpine-induced akinesia and to displace DiPr-5,6-ADTN in the in vivo binding assay.

In nonpretreated rats, (1*R*,2*S*)-**19** decreased DOPA formation and produced a biphasic action on the locomotor activity, whereas (1*R*,2*S*)-**18** ((−)-UH-232) and (1*S*,2*S*)-**5** were considered inactive (Table II). Thus the pharmacological classification of (1*S*,2*S*)-**5** and (1*R*,2*S*)-**18** into this group of compounds should be regarded as tentative.

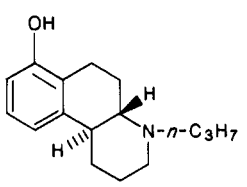
In agreement with previous studies[18c] on other C_5-oxygenated 2-aminotetralins, the methyl ether (1*R*,2*S*)-**18** was found to be less potent than the phenol (1*R*,2*S*)-**19**. Also in accordance with previous findings, the *N*-*n*-propyl derivative (1*R*,2*S*)-**17** was less potent than the *N*,*N*-di-*n*-propyl analogue.[18c]

The DA receptor agonists (1*S*,2*S*)-**5** and (1*R*,2*S*)-**17**–**19** have the 2*S* configuration, i.e., the same configuration at C_2 as the more potent enantiomer of the DA receptor agonist 5-OH-DPAT.[13,28] Also (*R*)-apomorphine has the same sense of chirality at C_{6a} (see Schemes I and II). Compounds (1*S*,2*S*)-**5** and (1*R*,2*S*)-**19** are, however, considerably less potent than (*S*)-5-OH-DPAT.

The low potency of the trans compound (1*S*,2*S*)-**5** is noteworthy, since it has the same absolute configuration as (4a*S*,10b*S*)-7-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline[13] ((4a*S*,10b*S*)-OHBQ), a potent DA receptor agonist.



(*S*)-5-OH-DPAT



(4a*S*,10b*S*)-OHBQ

A conformational study,[17] involving use of X-ray crystallography, NMR spectroscopy, and molecular mechanics (MMP2) calculations, demonstrated that (1*R*,2*S*)-**19** and (*S*)-5-OH-DPAT have similar conformations of the nonaromatic ring and prefer the same direction of the N-electron pair[29,30] (or N–H). This indicates that it is the steric bulk of the pseudoaxial C_1-methyl group in (1*R*,2*S*)-**17**, (1*R*,2*S*)-**18** and (1*R*,2*S*)-**19** that prevents an optimal DA receptor interaction. The same study indicated that the low potency of (1*S*,2*S*)-**5** is related to conformational factors, i.e., (a) its inability to assume the same direction of the N-electron pair (N–H) as (*S*)-5-OH-DPAT and (4a*S*,10b*S*)-OHBQ in "DA receptor agonist 2-aminotetralin conformations" or (b) to unfavorable receptor interactions by the C_1-methyl group or the nonaromatic ring in conformations with the proper orientation of the N-electron pair (N–H) or c) to unfavorable energies of such conformations.[17]

DA Receptor Agonists with Preferential Action at Presynaptic Receptors: (1*R*,2*S*)-11, (1*R*,2*S*)-15. These two compounds decreased DOPA formation in reserpinized rats. Compound (1*R*,2*S*)-**15** induced an almost maximal reduction in DOPA levels, with an ED_{50} value comparable to that of (*S*)-3-PPP[11a] ($ED_{50} \approx 1.3$ μmol/kg), while (1*R*,2*S*)-**11** only induced a 35–40% decrease in DOPA levels. Both compounds failed to antagonize the hypomotility induced by reserpine (Table II). In nonpretreated rats, (1*R*,2*S*)-**11** increased the DOPA levels one- to twofold, while (1*R*,2*S*)-**15** (52 μmol/kg) was considered inactive (Table II). Both compounds induced hypomotility in nonpretreated rats, displaced DiPr-5,6-ADTN, and reversed the DiPr-5,6-ADTN-induced hypothermia. In addition, (1*R*,2*S*)-**11** antagonized the hypermotility induced by DiPr-5,6-ADTN.

The observations that (1*R*,2*S*)-**11** and (1*R*,2*S*)-**15** (a) induced a decrease in DOPA accumulation in reserpinized rats, (b) were unable to antagonize the reserpine induced akinesia, and (c) induced hypomotility in nonpretreated rats over a wide dose range indicate that these compounds are agonists with preferential actions at presynaptic DA receptors. Administration of (1*R*,2*S*)-**11** to nonpretreated rats produced an increase in DOPA accumulation. This is an action expected from a DA antagonist. Thus, (1*R*,2*S*)-**11** (and possible also (1*R*,2*S*)-**15**) seems to have a profile similar to that of (*S*)-3-PPP.[7a]

Pre- and Postsynaptic DA Receptor Antagonists: (1*S*,2*R*)-8–15. In nonpretreated rats, the DOPA levels in both the striatal and limbic brain regions were markedly increased by the 1*S*,2*R* enantiomers of **8**–**15** (Table II). All these compounds induced an increase in DOPA levels to 200–440% of control values. This can be compared with the maximal increase obtained (210% and 310% in the limbic and striatal brain parts, respectively) after administration of the classical DA receptor antagonist haloperidol.[8] Hypomotility with catalepsy was noted after the highest dose of (1*S*,2*R*)-**10** and (1*S*,2*R*)-**11**. DiPr-5,6-ADTN was displaced from striatal binding sites by all the compounds, and, except for (1*S*,2*R*)-**13**, they also antagonized the hypothermia induced by the ligand (Table III). All compounds except (1*S*,2*R*)-**9** and (1*S*,2*R*)-**13** antagonized the locomotor hyperactivity produced by DiPr-5,6-ADTN.

In this group of compounds the tertiary amines appear to be more potent than the corresponding secondary amines, and in general methyl substitution at the nitrogen appears to give higher potency than *N*-ethyl substitution. Although there are no large potency differences among the compounds, the *N*,*N*-dimethyl-substituted derivatives (1*S*,2*R*)-**10** and (1*S*,2*R*)-**11** seem to be the most potent analogues.

The pharmacological results indicate that (1*S*,2*R*)-**10** and (1*S*,2*R*)-**11** are DA receptor antagonists, similar in profile to classical neuroleptics such as haloperidol.[8] However, the classification of the other compounds into this group should presently be considered as tentative. It should be noted that (*S*)-apomorphine[31] and (6a*S*)-*N*-*n*-propylnor-

(28) (a) McDermed, J. D.; McKenzie, G. M.; Freeman, H. S. *J. Med. Chem.* **1976**, *19*, 547. (b) Tedesco, J. L.; Seeman, P.; McDermed, J. D. *Mol. Pharmacol.* **1979**, *16*, 369. (c) Seiler, M. P.; Markstein, R. *Mol. Pharmacol.* **1982**, *22*, 281. (d) Seiler, M. P.; Markstein, R. *Mol. Pharmacol.* **1984**, *26*, 452.

(29) The torsion angle $\tau_N = \tau(C_1, C_2, N, H \text{ or electron pair})$ defines the relative direction of the N–H bond or the electron pair. See ref 30.

(30) We have not excluded the possibility that DA agonists and antagonists interact with DA receptors in their protonated forms. Compare: (a) Karlén, A.; Johansson, A. M.; Kenne, L.; Arvidsson, L.-E.; Hacksell, U. *J. Med. Chem.* **1986**, *29*, 917. (b) The dimethylsulfonium analogue of DA possesses DA agonistic properties: Andersson, K.; Kuruvilla, A.; Uretsky, N.; Miller, D. D. *J. Med. Chem.* **1981**, *24*, 683.

(31) (a) Riffee, W. H.; Wilcox, R. E.; Smith, R. V.; Davis, P. J.; Brubaker, A. *Adv. Biosci.* **1982**, *37*, 357. (b) Lehman, J.; Smith, R. V.; Langer, S. Z. *Eur. J. Pharmacol.* **1983**, *88*, 81. (c) Goldman, M. E.; Kebabian, J. W. *Mol. Pharmacol.* **1984**, *25*, 18. (d) Neumeyer, J. L.; Baldessarini, R. J.; Arana, G. W.; Campbell, A. In *New Methods in Drug Design*; Makriyannis, A., Ed.; Prous Science Publishers: Barcelona, 1985; pp 153–166. (e) Campbell, A.; Baldessarini, R. J.; Teicher, M. H.; Neumeyer, J. L. *Neuropharmacology* **1985**, *24*, 391. (f) Saller, C. F.; Salama, A. I. *Eur. J. Pharmacol.* **1986**, *121*, 181. (g) Campbell, A.; Baldessarini, R. J.; Teicher, M. H.; Neumeyer, J. L. *Psychopharmacology* **1986**, *88*, 158.

apomorphine[31d,e,g] ((S)-NPA) also exhibit central DA antagonistic properties.

DA Receptor Antagonists with Preferential Action at Presynaptic Receptors: (1*S*,2*R*)-6, (1*S*,2*R*)-16–20. In nonpretreated rats, all the compounds induced an increase in striatal and limbic DOPA levels (Table II). At a low dose (3.2 μmol/kg), (1*S*,2*R*)-**6** and (1*S*,2*R*)-**18** ((+)-UH-232) induced locomotor stimulation in nonpretreated rats. On the other hand, a high dose (52 μmol/kg) of (1*S*,2*R*)-**6** and (1*S*,2*R*)-**18** produced hypomotility, whereas (1*S*,2*R*)-**16** ((+)-AJ-76) and (1*S*,2*R*)-**20** induced hypermotility at this dose. Compounds (1*S*,2*R*)-**17** and (1*S*,2*R*)-**19** ((+)-UH-242) did not affect locomotor activity in the doses tested.

Compounds (1*S*,2*R*)-**16**, (1*S*,2*R*)-**18**, and (1*S*,2*R*)-**19** have also been tested in reserpine-pretreated rats, and they affected neither DOPA formation in limbic or striatal brain regions nor the reserpine-induced akinesia (Table II).[5a–d,f]

All compounds, except (1*S*,2*R*)-**6**, displaced DiPr-5,6-ADTN in the in vivo binding assay (Table III). Hypothermia (induced by DiPr-5,6-ADTN) was antagonized by all the compounds except (1*S*,2*R*)-**20**, and the DiPr-5,6-ADTN-induced hypermotility was antagonized by (1*S*,2*R*)-**16** and (1*S*,2*R*)-**18**.

The ability of the compounds to increase DOPA accumulation in nonpretreated rats, without inducing hypomotility, suggests that they are more potent antagonists at presynaptic than at postsynaptic DA receptors. Compounds (1*S*,2*R*)-**16** and (1*S*,2*R*)-**18** seem to be the most potent analogues. Further evidence for the preferential presynaptic DA receptor antagonistic properties in vivo of (1*S*,2*R*)-**16**, (1*S*,2*R*)-**18**, and (1*S*,2*R*)-**19** have been published by Svensson et al.[5b–f] These studies indicated that (1*S*,2*R*)-**16** has the "highest" selectivity for presynaptic DA receptors.

Conclusions

Compound (1*R*,2*S*)-**19** is the most potent classical DA receptor agonist of the 1*R*,2*S* enantiomers. It is, however, 100-fold less potent than (*S*)-5-OH-DPAT. The methyl ether (1*R*,2*S*)-**18**, the *N*-*n*-propyl-substituted analogues ((1*R*,2*S*)-**16** and (1*R*,2*S*)-**17**), and the *N*,*N*-di-*n*-butyl-substituted analogue (1*R*,2*S*)-**23** are of lower potency or inactive as DA receptor agonists. This is in agreement with earlier findings with C_5-oxygenated 2-aminotetralin derivatives; dipropylamino substituents and free phenolic functions give the most potent DA receptor agonists.[18c]

Compounds (1*R*,2*S*)-**11** and (1*R*,2*S*)-**15** appear to have a profile similar to that of (*S*)-3-PPP.

Of the 1*S*,2*R* enantiomers, compounds with *n*-propyl substituent(s) on the nitrogen ((1*S*,2*R*)-**16–19**) and also (1*S*,2*R*)-**6** and (1*S*,2*R*)-**20** appear to be antagonists with preferential action at presynaptic DA receptors. A profile more similar to classical DA receptor antagonists is achieved when the size of the nitrogen substituent(s) is decreased to ethyl or methyl (as in (1*S*,2*R*)-**8–15**).

In agreement with previous studies,[5,17] the present results indicate that both 2*R* and 2*S* enantiomers of C_5-oxygenated 2-aminotetralins may be able to bind to DA receptors but that only 2*S* antipodes are able to activate the receptors. In general, a decrease in the size of the *N*-alkyl group(s) in the C_5-oxygenated (1*R*,2*S*)-2-amino-1-methyltetralins, from *n*-propyl to ethyl or methyl, appears to increase the selectivity for presynaptic receptors. In contrast, a decreased size of the N-substituent(s) in the enantiomeric 1*S*,2*R* series seems to increase the relative activity at postsynaptic DA receptors. Interestingly, O-methylation tends to increase DA receptor antagonistic activity (compare, for example, (1*S*,2*R*)-**17** and (1*S*,2*R*)-**16**; (1*S*,2*R*)-**11** and (1*S*,2*R*)-**10**), whereas O-methylation in phenolic DA receptor agonists considerably decreases activity (compare, for example, (1*R*,2*S*)-**19** and (1*R*,2*S*)-**18**).

Experimental Section

Chemistry. General Comments. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. ^1H and ^{13}C NMR spectra (recorded on a JEOL FX 90Q spectrometer and referenced to internal tetramethylsilane) and mass spectra[32] (recorded at 70 eV on a LKB 9000 spectrometer using a direct insertion probe) were all in accordance with the assigned structures. GC was performed on a Varian 2700 instrument with a flame ionization detector. A glass column (3 m) with 3% OV-17 on 80/100 mesh Varaport was used. Capillary GC was performed on a Carlo Erba 4200, by use of a SE 54 column (10 m). HPLC was performed on a Waters 5 Si 10 column using hexane/ethyl acetate/ethanol (different compositions) as the mobile phase, working in the pressure range 1000–3000 psi and with the flow rate of 2 mL/min. A Waters Model 440 UV monitor was used. Optical rotations were obtained with a Perkin-Elmer 241 polarimeter. The elemental analyses (C, H, and N) were performed by the Microanalytical Laboratory, Agricultural College, Uppsala, Sweden, and Mikro Kemi AB, Uppsala, Sweden. For purity tests, TLC was performed on fluorescent silica gel or alumina plates.

Synthesis. Below are given representative examples of the reactions presented in Table I.

(1*S*,2*R*)-*cis*-5-Methoxy-1-methyl-2-(methylamino)tetralin ((1*S*,2*R*)-8). Method I. A solution of trifluoroacetic anhydride (0.74 g, 3.5 mmol) in dry ether (5 mL) was added dropwise to a solution of (1*S*,2*R*)-2-amino-5-methoxy-1-methyltetralin ((1*S*,2*R*)-**6**;[5a] 0.32 g, 1.7 mmol) and triethylamine (0.36 g, 3.5 mmol) in dry ether (25 mL) kept under nitrogen at 0–5 °C. After 30 min, more triethylamine and trifluoroacetic anhydride (0.32 g, 3.5 mmol and 0.74 g, 3.5 mmol, respectively) were added. After 1 h at room temperature, saturated aqueous ammonium chloride was added. The ether layer was dried (magnesium sulfate), filtered, and concentrated. The residue was chromatographed on an alumina column with ether–light petroleum (1:1) as eluant and then recrystallized from ether–*n*-hexane, yielding 0.44 g (91%; mp 141–141.5 °C) of the trifluoroacetamide of (1*S*,2*R*)-**6**: ^1H NMR (chloroform-d_3) δ 1.14 (d, 3 H), 1.75–1.96 (m, 2 H), 2.64–2.78 (m, 2 H), 3.1–3.4 (m, 1 H), 3.73 (s, 3 H), 4.1–4.4 (m, 1 H), 6.2–6.4 (m, 1 H), 6.57–6.73 (m, 2 H), 6.99–7.17 (m, 1 H).

The methylation of the monosubstituted trifluoroacetamide was performed according to the method described by Nordlander et al;[15] a solution of the trifluoroacetamide (0.41 g, 1.4 mmol) in anhydrous tetrahydrofuran (10 mL) was added to a suspension of 20% potassium hydride (0.068 g, 1.7 mmol, freed from mineral oil by three *n*-hexane washings) in anhydrous tetrahydrofuran under nitrogen at 0–5 °C. After 5 min dibenzo-18-crown-6 (a few grains) and methyl iodide (0.28 g, 2.0 mmol) were added. The reaction mixture was stirred at room temperature for 2 h and then heated to reflux overnight. The reaction mixture was diluted with ether and 30 mL of 0.1 M hydrogen chloride was cautiously added. The organic layer was separated and the aqueous layer was extracted three times with ether. The combined organic layers were washed with 0.6 M sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated. The residue was chromatographed on an alumina column with ether–light petroleum (1:2) as eluant and then recrystallized from *n*-hexane, affording 0.34 g (77%; mp 97.5–99 °C) of the N-methylated trifluoroacetamide: ^1H NMR (chloroform-d_3) δ 1.14 (d, 3 H), 1.8–3.5 (m, 5 H), 3.04 (q, 3 H), 3.74 (s, 3 H), 4.5–4.7 (m, 1 H), 6.56–6.68 (m, 2 H), 6.70–7.18 (m, 1 H).

The N-methylated trifluoroacetamide (0.32 g, 1.1 mmol) was deacylated by treatment with 1 M methanolic potassium hydroxide (60 mL) and water (10 mL) under nitrogen at room temperature overnight. The methanol was evaporated and ether

(32) Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, J. L. G.; Wikström, H.; Lindberg, P.; Sanchez, D. *Biomed. Mass Spectrom.* **1981**, *8*, 90.

(33) Carlsson, A.; Kehr, W.; Lindqvist, M. *J. Neural Transm.* **1977**, *40*, 99.

was added to the residue. The ether solution was extracted with 1 M hydrogen chloride and with 1 M sodium hydroxide. The ether layer was dried (potassium carbonate), filtered, and concentrated. The crude amine was converted into the hydrochloride and recrystallized from methanol–ether to give 0.19 g (48%) of (1*S*,2*R*)-**8**·HCl: ^{1}H NMR (methanol-d_4) δ 1.26 (d, 3 H), 1.6–3.6 (m, 6 H), 2.81 (s, 3 H), 3.80 (s, 3 H), 6.72–7.25 (m, 3 H); MS (70 eV), *m/z* 205 (49), 174 (28), 148 (100).

(1*S*,2*R*)-*cis*-5-Methoxy-1-methyl-2-(dimethylamino)tetralin ((1*S*,2*R*)-10). Method II. Compound (1*S*,2*R*)-**10** was prepared from (1*S*,2*R*)-2-amino-5-methoxy-1-methyltetralin hydrochloride ((1*S*,2*R*)-**6**·HCl) by use of a method described by Cannon et al.[16] for reductive methylation of primary amines. (1*S*,2*R*)-**6**·HCl (0.93 g, 4.1 mmol) was added to a stirred suspension of 37% aqueous formaldehyde (0.61 g, 20 mmol), 95% sodium cyanoborohydride (0.77 g, 12 mmol), and methanol (10 mL) kept under nitrogen. The pH of the mixture was adjusted to 6 by addition of glacial acetic acid, and then the mixture was stirred at room temperature overnight. The methanol was evaporated and the residue was treated with 2 M sodium hydroxide solution. The aqueous solution was extracted with dichloromethane and the organic layer was dried (potassium carbonate), filtered, and concentrated. The residue was passed through an alumina column with ether–light petroleum (1:1) as eluant. The crude amine was converted into the hydrochloride and recrystallized from acetonitrile–ether, yielding 0.87 g (83%) of (1*S*,2*R*)-**10**·HCl: ^{1}H NMR (methanol-d_4) δ 1.28 (d, 3 H), 1.7–3.6 (m, 6 H), 3.02 (s, 6 H), 3.80 (s, 3 H), 6.72–7.25 (m, 3 H); MS (70 eV), *m/z* 219 (50), 174 (16), 148 (100).

(1*S*,2*R*)-*cis*-2-(Di-*n*-butylamino)-5-methoxy-1-methyltetralin ((1*S*,2*R*)-22). Method III. 1-Bromobutane (0.93 g, 6.8 mmol) was added to a stirred mixture of (1*S*,2*R*)-2-amino-5-methoxy-1-methyltetralin hydrochloride ((1*S*,2*R*)-**6**·HCl) (0.70 g, 3.1 mmol), potassium carbonate (2.1 g, 15.3 mmol), and acetonitrile (12 mL) kept under nitrogen. The mixture was stirred at room temperature for 6 h and then at 85 °C for 3 days. Additional 1-bromobutane (0.46 g, 3.4 mmol) and potassium carbonate (1.1 g, 7.7 mmol) were added, and after 6 more days the heating was interrupted and ether was added. The reaction mixture was filtered, and the volatiles were evaporated. The residue was treated with etheral hydrogen chloride and then recrystallized from acetonitrile–ether, yielding 0.79 g (76%) of pure (1*S*,2*R*)-**22**·HCl: ^{1}H NMR (methanol-d_4) δ 1.02 (t, 3 H), 1.33 (d, 3 H), 1.4–3.7 (m, 18 H), 3.80 (s, 3 H), 6.72–7.26 (m, 3 H); MS (70 eV), *m/z* 303 (20), 260 (100), 175 (85).

(1*S*,2*R*)-*cis*-5-Methoxy-1-methyl-2-(*n*-propylamino)tetralin ((1*S*,2*R*)-16). Method IV. Propionyl chloride (0.73 g, 7.9 mmol) in dry ether was added to a stirred solution of (1*S*,2*R*)-2-amino-5-methoxy-1-methyltetralin ((1*S*,2*R*)-**6**; 0.76 g, 4.0 mmol) and triethylamine (0.80 g, 7.9 mmol) in dry ether under nitrogen at 0–5 °C. The reaction mixture was stirred for 2 h at room temperature. Ether was added and the mixture was extracted first with 1 M hydrogen chloride and then with 1 M sodium hydroxide. The organic layer was dried (magnesium sulfate), filtered, and concentrated. The resulting amide was dissolved in dry tetrahydrofuran and added to a stirred suspension of lithium tetrahydridoaluminate (4.5 g, 119 mmol) in dry tetrahydrofuran under nitrogen. The reaction mixture was heated under reflux for 7 h and then quenched by cautious addition of water and 4 M sodium hydroxide. The mixture was stirred at room temperature for 1 h and then filtered. The filtrate was dried (potassium carbonate), filtered, and concentrated. The crude amine was converted into the hydrochloride and recrystallized from methanol to afford 0.78 g (73%) of pure (1*S*,2*R*)-**16**·HCl: ^{1}H NMR (methanol-d_4) δ 1.08 (t, 3 H), 1.25 (d, 3 H), 1.6–3.6 (m, 10 H), 3.80 (s, 3 H), 6.71–7.24 (m, 3 H); MS (70 eV), *m/z* 233 (54), 204 (51), 148 (100).

Demethylation of Methoxy Compounds. Method V. The phenols were obtained by heating the appropriate methoxy compound in freshly distilled 48% aqueous hydrogen bromide for 2 h at 120 °C under nitrogen, followed by evaporation of the volatiles in vacuo. The conversion of the resulting hydrobromides into the corresponding hydrochlorides is illustrated in the following example: **(1*S*,2*R*)-*cis*-5-Hydroxy-1-methyl-2-(*n*-propylamino)tetralin ((1*S*,2*R*)-17).** The crude (1*S*,2*R*)-**17**·HBr resulting from demethylation of (1*S*,2*R*)-**16**·HCl (0.25 g, 0.93 mmol) was partitioned between ether and saturated aqueous sodium bicarbonate. The ether layer was dried (sodium sulfate), filtered, and concentrated. Etheral hydrogen chloride was added to an etheral solution of the residue and the precipitate was recrystallized from acetonitrile–ether, yielding 0.20 g (86%) of pure (1*S*,2*R*)-**17**·HCl: ^{1}H NMR (methanol-d_4) δ 1.06 (t, 3 H), 1.25 (d, 3 H), 1.6–3.6 (m, 10 H), 6.56–7.08 (m, 3 H); MS (70 eV), *m/z* 219 (89), 190 (77), 161 (100), 134 (82).

Resolution of (±)-*trans*-5-Methoxy-1-methyl-2-(*n*-propylamino)tetralin ((±)-3). (See Scheme III.) (*R*)-2-Methoxy-2-phenylacetyl chloride (2.8 g, 15 mmol) was added to a stirred mixture of (±)-*trans*-5-methoxy-1-methyl-2-(*n*-propylamino)-tetralin ((±)-**3**; 2.8 g, 12 mmol), dichloromethane (18 mL), water (18 mL), and 1 M sodium hydroxide (8.9 mL) under nitrogen. After 1 h at room temperature, the layers were separated. The organic layer was washed with saturated aqueous sodium carbonate and with 0.5 M hydrogen chloride, dried (magnesium sulfate), filtered, and concentrated. The resulting diastereomeric amides (**36** and **37**) were separated on silica gel columns with ether–light petroleum–ethyl acetate (7:7:2) as eluant. Each of the separated amides contained less than 3% of the corresponding diastereomeric amide (HPLC). To a solution of the first eluted amide (**36**) (2.1 g, 5.5 mmol) in dry tetrahydrofuran at 0 °C were added water (0.2 mL) and potassium *tert*-butoxide (4.0 g, 36 mmol). The mixture was stirred at 0 °C and the temperature was slowly increased to room temperature. Additional portions of potassium *tert*-butoxide (10 g) and water (0.2 mL) were added. Ice and water were added when GC analyses indicated that the reaction was completed. Ether was added and the organic layer was extracted with 1 M hydrogen chloride and saved. The water layer was alkanilized (5 M sodium hydroxide) and extracted with ether. The ether layer was dried (potassium carbonate), filtered, and concentrated. The resulting crude amine was converted into the hydrochloride and recrystallized from ethanol–ether to afford 0.18 g (11%) of pure (1*S*,2*S*)-**3**·HCl.

The organic layer that was saved from the above extraction with 1 M hydrogen chloride was first extracted with saturated aqueous sodium carbonate and water and then was dried (magnesium sulfate), filtered, and evaporated. The residue was purified on a silica gel column with ether–light petroleum (1:1) as eluant. The resulting *N*-formyl derivative[11a,13] (0.56 g, 2.1 mmol) was dissolved in dry ether and a 1.5 M solution of methyllithium in ether (0.05 g, 2.3 mmol) was added at −8 °C under nitrogen. After 30 min, saturated aqueous ammonium chloride was added. The ether layer was extracted with 2 M hydrogen chloride. The aqueous layer was alkalinized with 2 M sodium hydroxide and extracted with ether. The combined ether layers were dried (potassium carbonate), filtered, and concentrated. The resulting crude amine was converted into the hydrochloride and recrystallized from ethanol–ether to yield 0.45 g (28%) of pure (1*S*,2*S*)-**3**·HCl: ^{1}H NMR (methanol-d_4) δ 1.01 (t, 3 H), 1.37 (d, 3 H), 1.51–3.52 (m, 10 H), 3.82 (s, 3 H), 6.75–7.28 (m, 3 H); MS (70 eV), *m/z* 233 (91), 204 (52), 175 (65), 148 (100).

The last eluted amide (**37**) was processed in the same way as the first eluted amide (**36**), to give 0.18 g (11%) of pure (1*R*,2*R*)-**3**·HCl (acetonitrile) from the amide cleavage and 0.42 g (26%) of pure (1*R*,2*R*)-**3**·HCl (acetonitrile) from the hydrolysis of the *N*-formyl derivative. Spectral data of (1*R*,2*R*)-**3**·HCl were identical with those of (1*S*,2*S*)-**3**·HCl.

The cis compounds (1*S*,2*R*)-**16**·HCl and (1*R*,2*S*)-**16**·HCl were also resolved by this procedure, but during the amide cleavage reaction with potassium *tert*-butoxide, the temperature of the reaction mixture was kept at −8 to −10 °C. Higher temperatures resulted in an elimination reaction and lower temperatures gave no reaction.

Separation of (1*S*,2*R*,α*R*)- and (1*R*,2*S*,α*R*)-*cis*-5-Methoxy-2-[(α-phenylethyl)amino]tetralin (38 and 39, See Scheme IV). Trifluoroacetic anhydride (18.5 g, 88 mmol) in dry ether was added to a solution of triethylamine (8.9 g, 88 mmol) and a 9:1 mixture of **38**[5a] and **39**[5a] (13 g, 44 mmol) in dry ether at 0 °C under nitrogen. After 1 h at room temperature saturated aqueous ammonium chloride was added. The ether layer was dried (magnesium sulfate), filtered, and concentrated. The amides were separated by use of flash chromatography with ether–light petroleum (1:19) as eluant, to afford 13.7 g of crude **40** (the last eluted amide). The diastereomeric excess was determined by capillary

GC to be 96% de. The following deacylation of amide **40** was performed by a slightly modified literature procedure.[14]

Sodium borohydride (5.2 g, 138 mmol) was added to a stirred solution of compound **40** (13.6 g, 35 mmol) in dry ethanol under nitrogen at room temperature. An additional portion of sodium borohydride (2.6 g, 69 mmol) was added after 2 days. After 2 more days, the solution was acidified by addition of 5 M hydrogen chloride. The ethanol was evaporated and the residue was extracted with ether. The water layer was alkalinized (5 M sodium hydroxide) and extracted with ether. The combined ether layers were dried (potassium carbonate), filtered, and concentrated. The residue was passed through a silica gel column first with ether–light petroleum (1:4) and then with ether as eluant. The resulting crude amine was converted into the hydrochloride, yielding 10.8 g (82%) of **38**·HCl; ^{1}H NMR and MS (70 eV), see ref 5a. The conversion of **38** into (1*S*,2*R*)-**6** has been described previously.[5a]

Pharmacology. Materials and Methods. Male Sprague-Dawley rats weighing 200–300 g (ALAB, Stockholm, Sweden) were used. Reserpine and haloperidol were dissolved in a few drops of glacial acetic acid and made up to volume with 5.5% glucose solution. The other substances were dissolved in saline immediately before use, occasionally with a few drops of glacial acetic acid and/or moderate heating to obtain complete dissolution. Injection volumes were 5 mL/kg.

Biochemistry. Brain levels of DOPA and 5-HTP were analyzed by HPLC with electrochemical detection.[5f] For biochemical results and experimental details, see Table II and footnotes *a* and *c* in Table II.

Locomotor Activity. The motor activity was measured by means of photocell recordings ("M/P40Fc Electronic Motility Meter", Motron Products, Stockholm, Sweden) as previously described.[18c] For experimental details, see footnotes *b* and *d* in Table II and footnote *b* in Table III. Each box was equipped with a semitransparent mirror that allowed gross behavior observations of the animals during the experiments. The motor activity results are shown in Tables II and III.

DiPr-5,6-ADTN in Vivo Binding. Levels of DiPr-5,6-ADTN in rat striatum and cerebellum were measured by use of HPLC with electrochemical detection.[19e] For results and experimental details, see Table III and footnote *a* in Table III.

Body Temperature. Body temperatures were measured by use of a rectal thermometer (Yellow Springs Instrumental Co., Inc.). For results and experimental details, see Table III and footnote *c* in Table III.

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Registry No. (±)-**3**, 106499-55-2; (1*R*,2*R*)-**3**·HCl, 106499-58-5; (1*S*,2*S*)-**3**, 106499-56-3; (1*S*,2*S*)-**3**·HCl, 106499-57-4; (1*R*,2*R*)-**4**, 106499-59-6; (1*R*,2*R*)-**4**·HCl, 106499-60-9; (1*S*,2*S*)-**4**, 106499-61-0; (1*S*,2*S*)-**4**·HCl, 106499-62-1; (1*R*,2*R*)-**5**, 105927-73-9; (1*R*,2*R*)-**5**·HCl, 106456-44-4; (1*S*,2*S*)-**5**, 105927-72-8; (1*S*,2*S*)-**5**·HCl, 105927-74-0; (1*S*,2*R*)-**6**, 102607-13-6; (1*S*,2*R*)-**6**·HCl, 96092-90-9; (1*R*,2*S*)-**6**·HCl, 96092-89-6; (1*S*,2*R*)-**6** (R_1 = OMe, R_2 = H, R_3 = $COCF_3$), 106456-34-2; (1*S*,2*R*)-**6** (R_1 = OMe, R_2 = Me, R_3 = $COCF_3$), 106456-35-3; (1*S*,2*R*)-**6** (R_1 = OMe, R_2 = H, R_3 = COEt), 106499-54-1; (1*S*,2*R*)-**7**, 106456-45-5; (1*S*,2*R*)-**7**·HCl, 106456-46-6; (1*S*,2*R*)-**8**, 106456-33-1; (1*S*,2*R*)-**8**·HCl, 106456-36-4; (1*S*,2*R*)-**9**, 106456-47-7; (1*S*,2*R*)-**9**·HCl, 106456-48-8; (1*S*,2*R*)-**10**, 102607-14-7; (1*S*,2*R*)-**10**·HCl, 106456-37-5; (1*R*,2*S*)-**10**·HCl, 106456-64-8; (1*S*,2*R*)-**11**, 106456-49-9; (1*S*,2*R*)-**11**·HCl, 106456-50-2; (1*R*,2*S*)-**11**, 106456-65-9; (1*R*,2*S*)-**11**·HCl, 106456-66-0; (1*S*,2*R*)-**12**, 106456-51-3; (1*S*,2*R*)-**12**·HCl, 106456-52-4; (1*S*,2*R*)-**13**, 106456-53-5; (1*S*,2*R*)-**13**·HCl, 106456-54-6; (1*S*,2*R*)-**14**, 102607-15-8; (1*S*,2*R*)-**14**·HCl, 106456-55-7; (1*R*,2*S*)-**14**·HCl, 106456-67-1; (1*S*,2*R*)-**15**, 106456-56-8; (1*S*,2*R*)-**15**·HCl, 106456-57-9; (1*R*,2*S*)-**15**, 106456-68-2; (1*R*,2*S*)-**15**·HCl, 106456-69-3; (1*S*,2*R*)-**16**, 85379-09-5; (1*S*,2*R*)-**16**·HCl, 85378-82-1; (1*R*,2*S*)-**16**, 85378-78-5; (1*R*,2*S*)-**16**·HCl, 85378-79-6; (1*S*,2*R*)-**17**, 106469-07-2; (1*S*,2*R*)-**17**·HCl, 106456-39-7; (1*R*,2*S*)-**17**, 106456-70-6; (1*R*,2*S*)-**17**·HCl, 106456-71-7; (1*S*,2*R*)-**18**, 95999-12-5; (1*S*,2*R*)-**18**·HCl, 85378-81-0; (1*R*,2*S*)-**18**, 95999-11-4; (1*R*,2*S*)-**18**·HCl, 85548-44-3; (1*S*,2*R*)-**19**, 96148-67-3; (1*S*,2*R*)-**19**·HCl, 85379-04-0; (1*R*,2*S*)-**19**, 96148-66-2; (1*R*,2*S*)-**19**·HCl, 85379-05-1; (1*S*,2*R*)-**20**, 106456-58-0; (1*S*,2*R*)-**20**·HCl, 106456-59-1; (1*S*,2*R*)-**21**, 106456-60-4; (1*S*,2*R*)-**21**·HCl, 106456-61-5; (1*S*,2*R*)-**22**, 102607-16-9; (1*S*,2*R*)-**22**·HCl, 106456-38-6; (1*R*,2*S*)-**22**, 106456-72-8; (1*S*,2*R*)-**23**, 106456-62-6; (1*S*,2*R*)-**23**·HCl, 106456-63-7; (1*R*,2*S*)-**23**, 106456-73-9; (1*R*,2*S*)-**23**·HCl, 106456-74-0; **36**, 106456-40-0; **37**, 106456-41-1; **38**, 95999-17-0; **38**·HCl, 95999-18-1; **39**, 106456-42-2; **40**, 106456-43-3; DA, 51-61-6; $F_3CCO_2COCF_3$, 407-25-0; HCHO, 50-00-0; $Br(CH_2)_3Me$, 109-65-9; $MeCH_2COCl$, 79-03-8; (*R*)-C_6H_5CH(OMe)COCl, 34713-98-9.