96327-09-2; **33**, 96327-10-5; **34**, 96327-11-6; **35**, 96327-12-7; **36**, 96327-13-8; **37**, 96327-14-9; **38**, 96327-15-0; **39**, 96348-37-7; **40**, 96327-16-1; **41**, 96327-17-2; **42**, 96327-18-3; **43**, 96327-19-4; **44**, 96327-20-7; **45**, 96327-21-8; **46**, 96327-22-9; **47**, 96327-23-0; **48**, 96327-24-1; **49**, 96327-25-2; **50**, 96327-26-3; **51**, 88777-62-2; **52**, 96327-27-4; **53**, 88777-68-8; **54**, 96327-28-5; **55**, 96327-29-6; **56**, 96348-38-8; **57**, 88777-70-2; **58**, 88777-71-3; **59**, 88777-64-4; **60**, 96327-30-9; **61**, 96327-31-0; **62**, 66635-83-4; **63**, 66635-84-5; **64**, 96327-32-1; **65**, 66635-73-2; **66**, 96327-33-2; **67**, 66635-90-3; **68**, 66635-87-8; **69**, 66635-88-9; **70**, 66635-89-0; **71**, 96327-34-3; **72**, 96327-35-4; **73**, 96327-36-5; **74**, 66635-85-6; **75**, 96327-37-6; **76**, 66635-86-7; **77**, 96327-38-7; **78**, 96327-39-8; **79**, 96327-40-1; **80**, 96327-41-2; **81**, 96327-42-3; **82**, 96327-43-4; **83**, 76786-67-9; **84**, 76786-74-8; **85**, 96327-44-5; **86**, 96327-45-6; **87**, 96327-46-7; **88**, 96327-47-8; **89**, 96327-48-9; **90**, 96327-49-0; **91**, 96327-50-3; **92**, 96327-51-4; **93**, 96327-52-5; **94**, 96327-53-6; **95**, 96327-54-7; **96**, 96327-55-8; **97**, 96327-56-9; **98**, 96327-57-0; **99**, 96327-58-1; **100**, 96327-59-2; **101**, 96327-60-5; **102**, 96327-61-6; **103**, 96327-62-7; **104**, 96327-63-8; **105**, 96327-64-9; **106**, 96327-65-0; **107**, 96327-66-1; **108**, 96327-67-2; **109**, 88777-63-3; **110**, 88777-65-5; **111**, 88777-59-7; **112**, 96327-68-3; **113**, 88777-67-7; **114**, 88777-66-6; **115**, 88777-73-5; **116**, 88777-74-6; **117**, 88777-72-4; **118**, 88777-69-9; **119**, 96327-69-4; **120**, 96327-70-7; **121**, 96327-71-8; **123**, 61338-78-1; **124**, 20929-02-6; **125**, 96327-72-9; **126**, 63486-71-5; **127**, 96327-73-0; **128**, 96327-74-1; **129**, 90526-03-7; **130**, 96327-75-2; V (R = *i*-Pr; *n* = 1), 66635-71-0; V (R = Me; *n* = 1), 76786-65-7; V (R = Me; *n* = 2), 83820-86-4; V (R = Me; *n* = 3), 83820-99-9; VII (*n* = 1), 76786-72-6; VII (*n* = 2), 83820-96-6; $PhCONMe_2$, 611-74-5; $2\text{-}CH_3C_6H_4CONMe_2$, 6639-19-6; $3\text{-}CH_3C_6H_4CONMe_2$, 6935-65-5; $4\text{-}CH_3C_6H_4CONMe_2$, 14062-78-3; $3\text{-}FC_6H_4CONMe_2$, 33322-64-4; $4\text{-}FC_6H_4CONMe_2$, 24167-56-4; $2\text{-}ClC_6H_4CONMe_2$, 6526-67-6; $3\text{-}ClC_6H_4CONMe_2$, 24167-52-0; $4\text{-}ClC_6H_4CONMe_2$, 14062-80-7; $3\text{-}CH_3OC_6H_4CONMe_2$, 7290-99-5; $4\text{-}CH_3OC_6H_4CONMe_2$, 7291-00-1; $3\text{-}EtOC_6H_4CONMe_2$, 96327-76-3; $4\text{-}PcC_6H_4CONMe_2$, 33322-67-7; $4\text{-}CH_3SC_6H_4CONMe_2$, 25771-25-9; $4\text{-}BrC_6H_4COCl$, 586-75-4; $2\text{-}IC_6H_4COCl$, 609-67-6; $4\text{-}CH_2{=}CHCH_2OC_6H_4COCl$, 36844-51-6; $4\text{-}CH{\equiv}CCH_2OC_6H_4COCl$, 96327-77-4; $4\text{-}CF_3C_6H_4COCl$, 329-15-7; $4\text{-}CH_3COC_6H_4COCl$, 31076-84-3; $4\text{-}CH_2{=}CHC_6H_4COCl$, 1565-41-9; $4\text{-}CH{\equiv}CC_6H_4COCl$, 62480-31-3; $3,4\text{-}OCH_2OC_6H_3COCl$, 25054-53-9; C_6F_5COCl, 2251-50-5; $3\text{-}CH_3CO_2C_6H_4COCl$, 16446-73-4; $4\text{-}CH_3CO_2C_6H_4COCl$, 27914-73-4; $4\text{-}CH_3SC_6H_4COCl$, 1442-06-4; $3\text{-}NO_2C_6H_4COCl$, 121-90-4; $4\text{-}NO_2C_6H_4COCl$, 122-04-3; $3\text{-}CNC_6H_4COCl$, 1711-11-1; $4\text{-}CNC_6H_4COCl$, 6068-72-0; $3\text{-}CF_3C_6H_4COCl$, 2251-65-2; $2,6\text{-}F_2C_6H_3COCl$, 18063-02-0; $2,4\text{-}F_2C_6H_3COCl$, 72482-64-5; $2,4\text{-}Cl_2C_6H_3COCl$, 89-75-8; $4\text{-}FC_6H_4COCl$, 403-43-0; PhCOCl, 98-88-4; $2\text{-}CH_3CO_2C_6H_4COCl$, 5538-51-2; $4\text{-}CH_3C_6H_4COCl$, 874-60-2; $3\text{-}ClC_6H_4COCl$, 618-46-2; $4\text{-}ClC_6H_4COCl$, 122-01-0; $4\text{-}CH_3OC_6H_4COCl$, 100-07-2; $RCONMe_2$ (R = β-napthyl), 13577-85-0; $RCONMe_2$ (R = cyclobutyl), 57056-80-1; $RCONMe_2$ (R = *tert*-butyl), 24331-71-3; $PhCH_2CONMe_2$, 18925-69-4; **63**·$(c\text{-}C_6H_{11})_2NH$, 96632-90-5; **68**·$(c\text{-}C_6H_{11})NH$, 96632-91-6.

Novel Dopamine Receptor Agonists and Antagonists with Preferential Action on Autoreceptors

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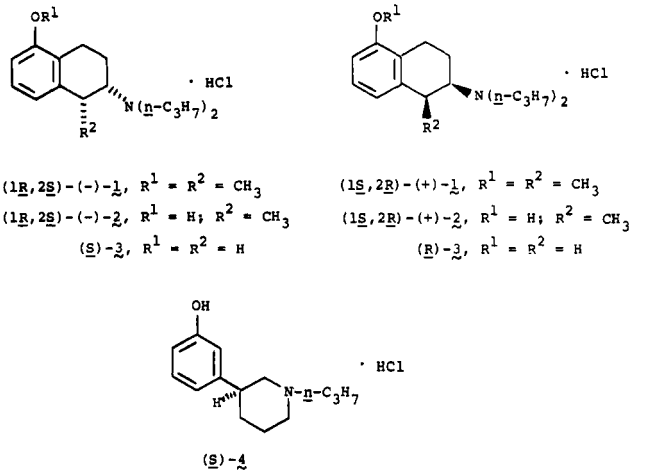
The enantiomers of *cis*-5-hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin (**2**) and its methyl ether (**1**) have been synthesized. The compounds were tested for central dopamine (DA) receptor activity, by using biochemical and behavioral tests in rats. The (1*R*,2*S*)-(−) enantiomers of **1** and **2** are characterized as centrally acting DA-receptor agonists while the corresponding (1*S*,2*R*)-(+) enantiomers are characterized as centrally acting DA-receptor antagonists. Compounds (+)-**1** and (+)-**2** differ from classical neuroleptics in being able to increase DA synthesis rate in a wide dose range without reducing locomotor activity, suggesting a pronounced selectivity for DA autoreceptors. Also the (−) enantiomers seem to act preferentially on DA autoreceptors.

Recently, racemic *cis*-5-hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin ((±)-**2**)[1] was classified as a centrally acting dopamine (DA) autoreceptor agonist without apparent postsynaptic DA stimulatory effects. This profile is similar to that of racemic 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (3-PPP, (±)-**4**).[2] We now report that the (1*R*,2*S*)-(−) enantiomers of **2** and its methyl ether (**1**) appear to be centrally acting DA-receptor agonists while the corresponding (1*S*,2*R*)-(+) enantiomers are characterized as DA-receptor antagonists. The four enantiomers investigated seem to exhibit a pronounced selectivity for DA autoreceptors, which makes them interesting as pharmacological tools and as potentially useful therapeutic agents.[3]

Chemistry. The preparation of the enantiomers of **1** and **2** is outlined in Scheme I. The enantiomers of **6** were synthesized from 5-methoxy-1-methyl-2-tetralone (**5**)[1] by use of a slightly modified literature procedure.[4] Thus, compound **5** was reacted with (*R*)-1-phenylethylamine and the resulting imine was hydrogenated (Pd/C) to afford



(+)-**6**. The use of (*S*)-1-phenylethylamine in the above reaction sequence gave (−)-**6**. This asymmetric reaction

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(1) 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.

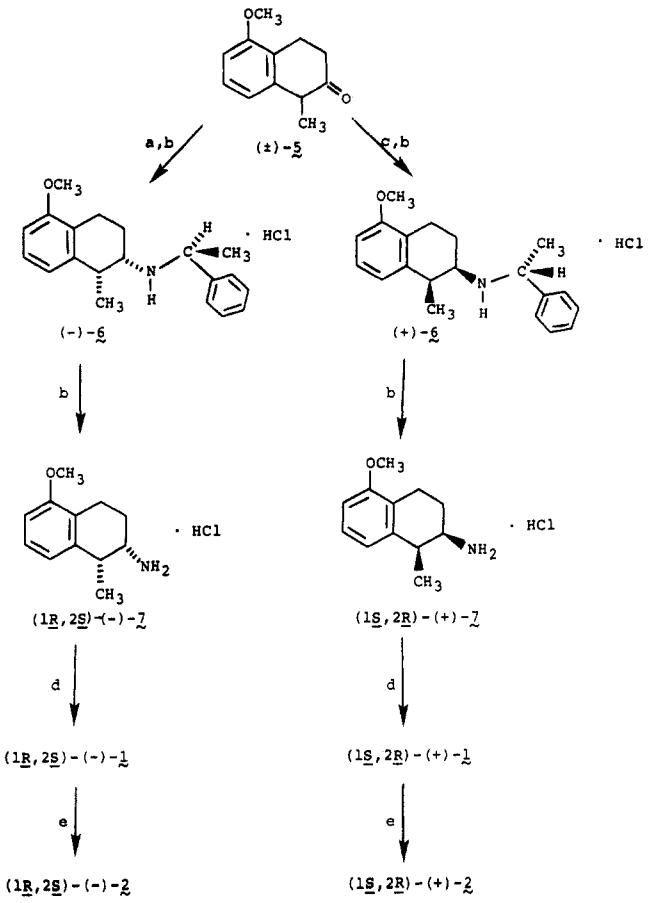
0022-2623/85/1828-1049$01.50/0

Table I. Effects of the Enantiomers of 1 and 2 on in Vivo DOPA Accumulation in the Rat Brain

compd	DOPA accumulation after reserpine pretreatment:[a] ED_{50}, mg/kg sc		DOPA accumulation after no pretreatment:[b] ED_{50}, mg/kg sc	
	limbic	striatum	limbic	striatum
(+)-1	I[c]	I[c]	4.0 (285%)	3.0 (380%)
(−)-1	1.7 (60%)	1.8 (50%)	I[c]	I[c]
(+)-2	I[c]	I[c]	3.0 (240%)	2.8 (340%)
(−)-2	0.09 (35%)	0.10 (20%)	0.25 (51%)	0.25 (47%)
(*R*)-apomorphine	0.06 (35%)[d]	0.07 (20%)[d]	*e*	*e*
haloperidol	I[f]	I[f]	0.07 (214%)[g]	0.07 (306%)[g]

[a] Animals were injected with reserpine (5 mg/kg ip) 18 hours, test drug 60 min, and NSD 1015 (100 mg/kg ip) 30 min before death. Controls received corresponding saline injections. Brain levels of DOPA and 5-HTP were analyzed by HPLC with electrochemical detection.[20] Shown are the doses giving a half maximal decrease of DOPA formation in rat limbic and striatal regions, estimated from a dose–response curve comprising four to seven dose levels (n = 3). Minimal levels obtained are shown in brackets; controls = 100%. [b] 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 (compound (−)-2) in rat limbic and striatal regions, estimated from a dose–response curve comprising four to five dose levels (n = 3–10); compare Figure 2. Maximal or minimal (compound (−)-2) levels obtained are shown in brackets; controls = 100%. [c] Inactive; no significant effect of 16 mg/kg sc. [d] From ref 9. These values are 0.01 and 0.01, respectively, if (*R*)-apomorphine is given 15 min before the administration of NSD 1015 (ref 7). [e] (*R*)-Apomorphine elicited a biphasic dose–response curve with two ED_{50}'s. From ref 21. [f] Inactive; no significant effect at 0.5 mg/kg ip. From ref 6b. [g] Haloperidol was injected ip 90 min before death. From ref 22.

Scheme I[a]



[a] Reagents: a = *S*-(−)-1-phenylethylamine; b = H_2, Pd/C; c = (*R*)-(+)-1-phenylethylamine; d = n-C_3H_7I; e = 48% HBr.

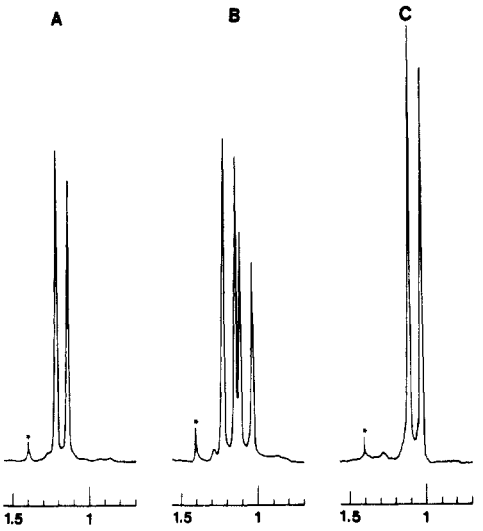


Figure 1. Partial 90-MHz ^1H NMR spectra (recorded in acetone-d_6) of the (R)-*O*-methylmandelamide of (+)-7 (A), a mixture of (*R*)-*O*-methylmandelamides of (+)-7 and (−)-7 in a 1:1.3 ratio (B), and the (R)-*O*-methylmandelamide of (−)-7 (C), which demonstrate that the enantiomeric purity of (+)-7 and (−)-7 is >95%, respectively. The small downfield peak (*) is due to an impurity.

seems to proceed under a remarkably stereoselective control since ^1H and ^{13}C NMR spectroscopy of the crude reaction products indicate the presence of only one diastereomer. Hydrogenolysis (H_2, Pd/C) of the benzylic C–N bond of (+)-6 and (−)-6 gave (+)-7 and (−)-7, respectively. In order to confirm the enantiomeric purities, (+)-7 and (−)-7 were converted to the corresponding *O*-methylmandelamides by reaction with an excess of (*R*)-2-methoxy-2-phenylacetyl chloride and NaOH (1 M) in dichloromethane. In the 90-MHz ^1H NMR spectra of the diastereomeric (*R*)-*O*-methylmandelamides, the doublets from the C_1-methyl protons were differently shifted (see

(2) (a) Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, J. L. G.; Sanchez, D.; Wikström, H.; Lindberg, P.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1981**, *24*, 1475. (b) Hjorth, S.; Carlsson, A.; Wikström, H.; Lindberg, P.; Sanchez, D.; Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, J. L. G. *Life Sci.* **1981**, *18*, 1225.

(3) (a) Goldstein, M.; Lieberman, A.; Battista, A. F. *TIPS* **1984**, 277. (b) Calne, D. B.; Larssen, T. A. In "Dopamine Receptors"; Kaiser, C., Kebabian, J. W., Eds.; American Chemical Society: Washington, DC, **1983**; pp 147–153. (c) Bianchine, J. R.; Shaw, G. M.; Greenwald, J. E.; Dandalides, S. M. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1978**, *37*, 2434.

(4) Frahm, A. W.; Knupp, G. *Tetrahedron Lett.* **1981**, *22*, 2633–2636. For experimental detail, see: Frahm, A. W. In "Methoden der Organischen Chemie (Houben-Weyl)", 4th ed.; Kropf, H., Ed.; George Thieme: Stuttgart, 1980; Vol. 4, Part 1c, p 440.

Table II. Effects of the Enantiomers of 1 and 2 on Rat Locomotor Activity

compd	locomotor activity after reserpine pretreatment:[a] accumulated counts/30 min ± SEM (mg/kg, sc)	locomotor activity after no pretreatment:[b] percent of saline controls ± SEM (mg/kg, sc)	
		low-dose region	high-dose region
(+)-1	4 ± 2 (16.0)	144 ± 10 (4.0)**	49 ± 9 (64.0)***
(−)-1	8 ± 4 (64.0)	I[c]	I[c]
(+)-2	6 ± 2 (16.0)	128 ± 7 (4.0)*	69 ± 11 (64.0)*
(−)-2	79 ± 17 (4.0)***,[d]	65 ± 9 (0.25)**	171 ± 28 (4.0)*
(*R*)-apomorphine	361 ± 42 (0.7)***,[d]	52 ± 6 (0.1)**	277 ± 14 (1.0)***
haloperidol	NT[e]	75 ± 4 (0.0625)*,[f]	3 ± 1 (1.0)***,[f]

[a] Animals were injected with reserpine (10 mg/kg ip) 6 h DL-α-methyl-*p*-tyrosine methyl ester hydrochloride (250 mg/kg ip) 1 h and test drug immediately before the activity session. Shown are the accumulated counts per 30 min (mean ± SEM, n = 4–9). Reserpine-α-MT controls: 5 ± 1, n = 8. Dose of test drug in mg/kg sc in brackets. Statistical difference depicted in the text: (***) $p < 0.001$, (**) $p < 0.01$, (*) $p < 0.05$ vs. saline controls (t test). [b] All active compounds (except haloperidol) elicited a biphasic dose–response curve. Representative doses for the low- and high-dose regions are presented. 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 as a percentage (mean ± SEM, n = 4–10) relative to control values 187 ± 7 counts/30 min, mean ± SEM, n = 34). They represent either the maximal (values > 100%) or minimal (values < 100%) activity level obtained after each drug. For statistical differences, see footnote *a*. [c] Inactive, no significant effect at 16.0 mg/kg sc. [d] Effect blocked by haloperidol (0.3 mg/kg ip) injected 30 min before test drug. [e] NT = not tested. [f] Haloperidol was injected ip 30 min before the activity session.

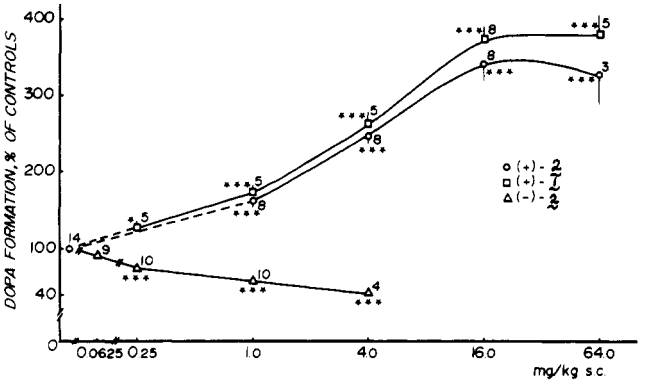


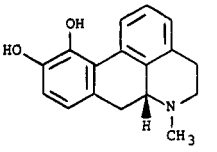
Figure 2. DOPA formation in nonpretreated rat striatal region. For experimental details, see Table I, footnote *b*. For statistical differences, see Table II, footnote *a*.

Figure 1). Since in each spectrum only one diastereomer was detected, the enantiomeric purity was determined to be >95% for both (+)-7 and (−)-7. The primary amine (+)-7 was alkylated with 1-iodopropane to afford (+)-1. Treatment of (+)-1 with 48% aqueous HBr followed by halogen interchange gave (+)-2. Similarly, compound (−)-7 was converted via (−)-1 to (−)-2. The absolute configuration of (+)-2 was determined by X-ray crystallography to be 1*S*,2*R*.[5] By analogy, this also establishes the absolute configuration of (−)-2 as well as of the enantiomers of 1, 6, and 7.

Pharmacological Results and Discussion

The enantiomers of 1 and 2 were tested in reserpinized as well as in nonpretreated rats by using biochemical and behavioral assays previously described[6] (Tables I and II and Figure 2). Test results obtained with the DA-receptor agonist (*R*)-apomorphine and the DA-receptor antagonist haloperidol are included for comparative purposes.

The (−) enantiomers of 1 and 2 exhibit a central DA receptor agonist profile (Tables I and II and Figure 2). Compound (−)-2 reduced DOPA formation in both reserpinized and nonpretreated animals (Table I). Furthermore, (−)-2 produced a biphasic action in the locomotor activity experiments in nonpretreated animals, that is, decreased and increased activity at low and high doses, respectively (Table II). Compound (−)-2 was also able to reverse the reserpine plus α-methyl-*p*-tyrosine-induced akinesia, an effect that was blocked by haloperidol pretreatment, thereby indicating a direct postsynaptic DA-receptor action. Compound (−)-2 was only slightly less potent than (*R*)-apomorphine in the biochemical assay (reserpinized animals) and in producing hypomotility in nonpretreated animals (supposedly reflecting a preferential DA autoreceptor agonist action). However, (−)-2 was considerably weaker than (*R*)-apmorphine in producing locomotor stimulation (Table II). Since these latter activity experiments are supposed to reflect a postsynaptic DA-receptor stimulation, (−)-2 appears to be more selective for autoreceptors than (*R*)-apomorphine.



(R)-Apomorphine

It has been shown that the potent (±)-3 has a DA agonist profile similar to that of (*R*)-apomorphine.[7] Thus, the relatively low potency of (−)-2 and its selectivity for autoreceptors seem to be caused by the presence of the C_1-methyl group. No significant difference in preferred conformation of the nonaromatic ring of 2 and 3 has been observed in solution or in the solid state.[5] Accordingly, the key intramolecular distances[8] in compounds 2 and 3 should be approximately the same. Taken together, the

(5) Johansson, A.; Karlén, A.; Sundell, S.; Kenne, L.; Hacksell, U., manuscript in preparation.

(6) 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.; Nilssson, J. L. G. *Psychopharmacology* **1983**, *81*, 89. (c) Andén, N.-E.; Carlsson, A.; Häggendal, J. *Ann. Rev. Pharmacol.* **1969**, *9*, 119.

(7) 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.

(8) For discussions on important intramolecular distances in DA-receptor agonists, see for example: ref 7 and (a) Seeman, P. *J. Pharmacol. Rev.* **1980**, *32*, 229. (b) Horn, A. S.; Rodgers, J. R. *J. Pharm. Pharmacol.* **1980**, *32*, 521. (c) Feenstra, M. G. P. Thesis, Department for Pharmaceutical and Analytical Chemistry of the State University at Groningen, Groningen, 1984. (d) Kaiser, C. In "Dopamine Receptors"; Kaiser, C., Kebabian, J. W., Eds.; American Chemical Society: Washington, DC, 1983; pp 223–246.

present observations indicate that the C_1-methyl substituent of (−)-2 prevents an optimal interaction with postsynaptic DA receptors by sterical means and that the interaction of (−)-2 with DA autoreceptors is less affected.

In analogy with results obtained with other C_5-oxygenated 2-aminotetralins,[9] methyl ether (−)-1 was found to be of lower potency than phenol (−)-2 in the biochemical assay in reserpinized rats. In the biochemical experiments in nonpretreated rats and in the activity experiments, (−)-1 was inactive in doses up to 16 mg/kg.

The (+) enantiomers of 1 and 2 appeared to be centrally acting DA-receptor antagonists. In nonpretreated animals, (+)-2, and (+)-1 increased DOPA formation in both striatal and limbic brain regions, with a maximal effect of 340–380% of control values in the striatum (Table I and Figure 2). As a comparison, the classical DA-receptor antagonist haloperidol maximally increased the DOPA formation in striatum to 306% of control values. Neither (+)-1, (+)-2 nor haloperidol influenced the DOPA formation in reserpinized rats (Table I and ref 6b). In the low-dose region in nonpretreated rats, (+)-1 and (+)-2 produced a significant increase in locomotor activity (Table II). Behavioral stimulation after low doses of haloperidol has earlier been described in mice[10] and rats,[11] although in the present work only sedation was noted after this drug. Presumably, the motor stimulatory effect obtained with (+)-2 and (+)-1 is mediated via DA autoreceptor antagonism leading to enhancement of DA release, which, in turn, results in an increased postsynaptic receptor stimulation.[12] Only (+)-1 was able to produce a significant sedation in the high-dose region. Furthermore, no sign of catalepsy was noted, which is in contrast to the findings with classical DA antagonists such as haloperidol.

The ability of (+)-2 and (+)-1 in a wide dose range to increase the DOPA formation in nonpretreated rats without producing any reduction in locomotor activity suggests that these compounds are more potent antagonists at DA autoreceptors than at postsynaptic DA receptors. The data also suggest that the compounds are approximately equipotent. Further evidence for the DA antagonistic properties of (+)-2 and (+)-1 is their ability to reverse the (*R*)-apomorphine-induced inhibition of DOPA formation in the γ-butyrolactone (GBL) model and to antagonize the locomotor stimulation produced by (*R*)-apomorphine and *d*-amphetamine.[13] Compound (+)-1 (16–64 mg/kg), but not the other compounds investigated, increased cortical DOPA formation, suggesting that higher doses of (+)-1 may influence central noradrenergic systems. The enantiomers of 1 and 2 did not affect 5-HTP formation in any brain region, indicating that these compounds are inactive on central 5-HT receptors.

The racemic mixture of 2 was recently reported to be very weak in producing locomotor stimulation in reserpinized rats.[1] This might be rationalized by taking into account the antagonistic action of the (+) enantiomer on the postsynaptic DA receptors. The present findings stress the importance of using optically pure compounds when exploring pharmacological mechanisms.

Compound (2*S*)-3 and (*R*)-apomorphine are potent DA-receptor agonists.[14] On the other hand, the 1*S*,2*R* enantiomers of 1 and 2 are DA-receptor antagonists, and also (*S*)-apomorphine behaves like a DA-receptor antagonist in several test systems.[15] Furthermore, (*S*)-(−)-4 has been reported to exhibit central DA receptor antagonistic properties.[6b,16] The pharmacological profiles of the enantiomers of apomorphine and compounds 1–4 indicate a structural relationship between DA-receptor agonists and antagonists, which has previously not been obvious.[17] This may provide new impulses in the design of DA-receptor antagonists from classical DA receptor agonists.

In conclusion, the (−) enantiomers of 1 and 2 are characterized as centrally acting DA-receptor agonists while the corresponding (+) enantiomers are characterized as centrally acting DA-receptor antagonists.[18] Compounds (+)-1 and (+)-2 differ from classical neuroleptics in being able to increase DA synthesis rate in a wide dose range without reducing locomotor activity, suggesting a pronounced selectivity for DA autoreceptors. Compounds with this profile may prove useful as experimental tools and as potential therapeutic agents.

Experimental Section

Chemistry. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX 90 Q spectrometer (referenced to Me_4Si). Mass spectra recorded at 70 eV on a 9000 LKB spectrometer were all in accordance with the assigned structures.[19] Optical rotations were obtained with a Perkin-Elmer 241 polarimeter. The elemental analyses (C, H, and N) were performed by Microanalytical Laboratory, Agricultural College, Uppsala, Sweden, and Mikro Kemi, Uppsala, Sweden. For purity tests, TLC was performed on fluorescent silica gel or alumina plates. For all the compounds, only one spot (visualized by UV light and I_2 vapor) was obtained. 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 30 was used.

(+)-*cis*-5-Methoxy-1-methyl-2-[(1-phenylethyl)amino]-tetralin ((+)-6). A solution of 5-methoxy-1-methyl-2-tetralone (5;[1] 25.0 g, 131.4 mmol) and (*R*)-1-phenylethylamine (23.9 g, 197.1 mmol) in 250 mL of dry benzene was refluxed under nitrogen in a Dean–Stark apparatus. After 60 h the volatiles were evaporated in vacuo. The residue was quickly dissolved in 250 mL of dry ethanol and hydrogenated at atmospheric pressure and room temperature with palladium (10%) on activated carbon as catalyst.

(9) Hacksell, U.; Svensson, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Wikström, H.; Lindberg, P.; Sanchez, D.; *J. Med. Chem.* **1979**, *22*, 1469.
(10) Strömbom, U. *J. Neural Transm.* **1977**, *40*, 191.
(11) Ahlenius, S.; Engel, J. *J. Pharm. Pharmacol.* **1971**, *23*, 175.
(12) Kehr, W.; Carlsson, A.; Lindqvist, M.; Magnusson, T.; Atack, C. V. *J. Pharm. Pharmacol.* **1972**, *24*, 744.
(13) Svensson, K., unpublished findings.
(14) (a) 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. (b) McDermed, J. D.; McKenzie, G. M.; Freeman, H. S. *J. Med. Chem.* **1976**, *19*, 547. (c) Sailer, M. P.; Markstein, R. *Mol. Pharmacol.* **1982**, *22*, 281.
(15) (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.
(16) 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.
(17) For recent reviews discussing structure–activity relationships of DA-receptor agonists and antagonists, see for example: ref 8d and 14a and (a) Freeman, H. S.; McDermed, J. D. In "The Chemical Regulation of Biological Mechanisms"; Chreighton, A. M., Turner, S., Eds.; Royal Society of Chemistry: London, 1982; pp 154–166. (b) Cannon, J. G. *Ann. Rev. Pharmacol. Toxicol.* **1983**, *23*, 103. (c) de Paulis, T. *Ann. Rep. Med. Chem.* **1983**, *18*, 21.
(18) We have not ruled out the possibility (suggested by one reviewer) that the methoxy compounds (+)-1 and (−)-1 are metabolically converted into phenols (+)-2 and (−)-2, respectively.
(19) Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, J. L. G.; Wikström, H.; Lindberg, P.; Sanchez, D. *Biol. Mass Spectrom.* **1981**, *8*, 90.

The catalyst was filtered off (Celite), and the volatiles were evaporated in vacuo. The residue was chromoatographed through a short alumina column eluted with ether–light petroleum (1:4). The amine was converted to the hydrochloride and recrystallized from acetonitrile–EtOH–ether, yielding 15.0 g (34%) of (+)-6·HCl: mp 257–259 °C; $[\alpha]^{22}_D$ +132.2° (*c* 1.00, MeOH); ^{1}H NMR (MeOH-d_4) δ 1.30 (d, 3 H), 1.76 (d, 3 H), 1.9–3.5 (m, 6 H), 3.75 (s, 3 H), 4.66 (q, 1 H), 6.67–7.65 (m, 8 H); MS (70 eV), *m/z* 295 (61), 280 (59), 148 (66), 105 (100). Anal. ($C_{20}H_{26}ClNO$) C, H, N.

(1*S*,2*R*)-*cis*-2-Amino-5-methoxy-1-methyltetralin ((+)-7). (+)-*cis*-5-Methoxy-1-methyl-2-[(1-phenylethyl)amino]tetralin ((+)-6) hydrochloride (14.3 g, 43.1 mmol) was dissolved in 150 mL of methanol, and the hydrogenolysis was performed over palladium (10%) on charcoal at atmospheric pressure and room temperature. Removal of catalyst (Celite) and solvent gave a crystalline residue, which was recrystallized from acetonitrile–EtOH to give 6.9 g (71%) of (+)-7·HCl: mp 238 °C dec; $[\alpha]^{22}_D$ +47.3° (*c* 1.00, MeOH); ^{1}H NMR (MeOH-d_4) δ 1.27 (d, 3 H), 1.9–3.7 (m, 6 H), 3.80 (s, 3 H), 6.71–7.25 (m, 3 H); MS (70 eV), *m/z* 191 (33), 174 (50), 148 (100). Anal. Calcd for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97; N, 6.15. Found: C, 62.2; H, 7.5; N, 5.85.

(1*S*,2*R*)-*cis*-5-Methoxy-1-methyl-2-(di-*n*-propylamino)tetralin ((+)-1). 1-Iodopropane (2.9 g, 17.1 mmol) was added to a stirred mixture of (+)-7 (1.5 g, 7.8 mmol), K_2CO_3 (3.8 g, 27.5 mmol), and acetonitrile (25 mL) kept under nitrogen. After 3 days at room temperature additional portions of 1-iodopropane (2.9 g, 17.1 mmol) and K_2CO_3 (3.8 g, 27.5 mmol) were added. After 7 more days, ether (25 mL) was added, the reaction mixture was filtered, and the volatiles were evaporated. The oily residue was purified on an alumina column with ether–light petroleum (1:4) as eluant. The amine was converted into the hydrochloride and recrystallized from EtOH–ether, yielding 1.5 g (63%) of pure (+)-1·HCl: mp 160.5–161 °C; $[\alpha]^{22}_D$ +48.1° (*c* 1.00, MeOH); ^{1}H NMR (MeOH-d_4) δ 1.05 (t, 6 H), 1.33 (d, 3 H), 1.5–3.7 (m, 14 H), 3.80 (s, 3 H), 6.72–7.25 (m, 3 H); MS (70 eV), *m/z* 275 (26), 246 (100), 175 (86). Anal. ($C_{18}H_{30}ClNO$) C, H, N.

(−)-*cis*-5-Methoxy-1-methyl-2-[(1-phenylethyl)amino]tetralin ((−)-6). This compound was prepared from **5** (35.0 g, 131.4 mmol) and (*S*)-1-phenylethylamine (23.9 g, 197.1 mmol) by use of the procedure described above for the preparation of (+)-6. The amine was converted into the hydrochloride, yielding 12.6 g (29%) of (−)-6·HCl: mp 257.5–260 °C (from acetonitrile–EtOH–ether); $[\alpha]^{22}_D$ −132.5° (*c* 1.03, MeOH); ^{1}H NMR (MeOH-d_4) δ 1.30 (d, 3 H), 1.76 (d, 3 H), 1.9–3.5 (m, 6 H), 3.75 (s, 3 H), 4.65 (q, 1 H), 6.67–7.70 (m, 8 H); MS (70 eV), *m/z* 295 (70), 280 (67), 148 (68), 105 (100). Anal. ($C_{20}H_{26}ClNO$) C, H, N.

(1*R*,2*S*)-*cis*-2-Amino-5-methoxy-1-methyltetralin ((−)-7). Hydrogenolysis of compound (−)-6·HCl (12.0 g, 36.2 mmol) was accomplished as described above for the preparation of (+)-7·HCl. The resulting hydrochloride was recrystallized from acetonitrile–EtOH to give 5.8 g (71%) of (−)-7: mp 238 °C dec; $[\alpha]^{22}_D$ −45.3° (*c* 1.02, MeOH); ^{1}H NMR (MeOH-d_4) δ 1.27 (d, 3 H), 1.9–3.7 (m, 6 H), 3.80 (s, 3 H), 6.72–7.25 (m, 3 H); MS (70 eV), *m/z* 191 (32), 174 (54), 148 (100). Anal. Calcd for $C_{12}H_{18}ClNO$: C, 63.29. Found: C, 62.65.

(1*R*,2*S*)-*cis*-5-Methoxy-1-methyl-2-(di-*n*-propylamino)tetralin ((−)-1). This compound was prepared from (−)-7 (1.8 g, 7.9 mmol) according to the procedure for the synthesis of compound (+)-1. The pure base was converted into the hydrochloride and recrystallized from EtOH–ether: yield 2.4 g (83%); mp 160.5–161 °C; $[\alpha]^{22}_D$ −48.6° (*c* 1.04, MeOH); ^{1}H NMR (MeOH-d_4) δ 1.05 (t, 6 H), 1.33 (d, 3 H), 1.6–3.7 (m, 14 H), 3.80 (s, 3 H), 6.72–7.25 (m, 3 H); MS (70 eV), *m/z* 275 (25), 246 (100), 175 (84). Anal. ($C_{18}H_{30}ClNO$) C, H, N.

Demethylation of Methoxy Compounds. The phenols were obtained by heating the appropriate methoxy compound in freshly distilled 48% aqueous HBr for 2 h at 120 °C under nitrogen, followed by evaporation of the volatiles in vacuo.

(1*S*,2*R*)-*cis*-5-Hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin ((+)-2). The crude (+)-2·HBr resulting from demethylation of (+)-1·HCl (1.3 g, 4.2 mmol) was converted to the corresponding hydrochloride and recrystallized from EtOH–ether, yielding 0.9 g (75%) of pure (+)-2·HCl: mp 228.5–229.5 °C; $[\alpha]^{22}_D$ +49.0° (*c* 1.00, MeOH); ^{1}H NMR (MeOH-d_4) δ 1.05 (t, 6 H), 1.32 (d, 3 H), 1.6–3.8 (m, 14 H), 6.56–7.09 (m, 3 H); MS (70 eV), *m/z* 261 (38), 232 (100), 161 (78). Anal. ($C_{17}H_{28}ClNO$) C, H, N.

(1*R*,2*S*)-*cis*-5-Hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin ((−)-2). The crude (−)-2·HBr resulting from demethylation of (−)-1·HCl (2.0 g, 6.4 mmol) was converted to the corresponding hydrochloride (−)-2·HCl: yield 1.7 g (88%); mp 227–227.5 °C; $[\alpha]^{22}_D$ −50.1° (*c* 1.01, MeOH); ^{1}H NMR (MeOH-d_4) δ 1.05 (t, 6 H), 1.32 (d, 3 H), 1.6–3.8 (m, 14 H), 6.56–7.09 (m, 3 H); MS (70 eV), *m/z* 261 (36), 232 (100), 161 (93). Anal. ($C_{17}H_{28}ClNO$) C, H, N.

Estimation of the Enantiomeric Purity of the Primary Amines (+)-7 and (−)-7 by ^{1}H NMR. Compound (+)-7·HCl (20 mg, 0.09 mmol) was mixed with H_2O (0.5 mL), CH_2Cl_2 (0.5 mL), and 1 M NaOH (0.3 mL) and (*R*)-2-methoxy-2-phenylacetyl chloride (21 mg, 0.11 mmol) (prepared from (*R*)-*O*-methylmandelic acid and $SOCl_2$) in CH_2Cl_2 (0.3 mL) was added with stirring. After 2 h the organic layer was washed with acid (1 M HCl) and base (1 M NaOH) and then dried ($MgSO_4$) and evaporated to afford the (*R*)-*O*-methylmandelamide of (+)-7. The (*R*)-*O*-methylmandelamide of (−)-7 was prepared by using the same procedure. ^{1}H NMR spectra (acetone-d_6) of the above amides showed no diastereomeric impurities (see Figure 1). Thus, the enantiomeric purity of (+)-7 and (−)-7 is >95%, respectively.

Pharmacology. Biochemistry. Animals used in the biochemical and motor activity experiments were male rats of the Sprague–Dawley strain (Anticimex, Stockholm), weighing 200–300 g. All test compounds were dissolved in saline immediately before use, occasionally with a few drops of glacial acetic acid and/or moderate heating in order to obtain complete dissolution. Reserpine (Ciba-Geigy) and haloperidol (LEO) were dissolved in a few drops of glacial acetic acid and made up to volume with 5.5% glucose solution. Injection volumes were 5 or 10 mL/kg, and injection solutions had approximately neutral pH.

Brain levels of DOPA and 5-HTP were analyzed by HPLC with electrochemical detection.[20] For biochemical results and experimental details, see Table I and footnotes *a* and *b* in Table I, respectively.

Motor Activity. The motor activity was measured by means of photocell recordings ("M/P 40 Fc Electronic Motility Meter", Motron Products, Stockholm) as previously described.[9] For experimental details, see footnotes *a* and *b* in Table II. 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 Table II.

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Registry No. (−)-1, 95999-11-4; (−)-1·HCl, 85548-44-3; (+)-1, 95999-12-5; (+)-1·HCl, 85378-81-0; (−)-2, 96148-66-2; (−)-2·HBr, 96148-68-4; (−)-2·HCl, 85379-05-1; (+)-2, 96148-67-3; (+)-2·HBr, 96148-69-5; (+)-2·HCl, 85379-04-0; (±)-5, 40266-67-9; 5 (imine, isomer 1), 95999-13-6; 5 (imine, isomer 2), 95999-14-7; (−)-6, 95999-15-8; (−)-6·HCl, 95999-16-9; (+)-6, 95999-17-0; (+)-6·HCl, 95999-18-1; (−)-7·HCl, 96092-89-6; (+)-7·HCl, 96092-90-9; (−)-$NH_2(Ph)CHCH_3$, 2627-86-3; (+)-$NH_2(Ph)CHCH_3$, 3886-69-9.

(20) Svensson, K.; Lindberg, M., manuscript in preparation.
(21) Carlsson, A.; Kehr, W.; Lindqvist, M. *J. Neural Transm.* **1977**, *40*, 99.
(22) Carlsson, A. In "Psychopharmacology: A Generation of Progress"; Lipton, M. A., DiMascio, A., Killam, K. F., Eds.; Raven, Press: New York, 1978; pp 1057–1070.