phate-buffered saline, fixed with 10% Formalin, and stained with crystal violet. Cell colonies, as representatives of single viable original cells, were counted under a dissecting microscope. Relative plating efficiency, as percent survival, was calculated as the average number of colonies grown from drug-treated cells divided by the average number of control (untreated) cells grown under similar growth conditions.

Antitumor Evaluation. L1210 leukemia and P388 lymphoid neoplasm were maintained in RPMI-1640 medium supplemented with 10% heat inactivated fetal calf serum. For determination of cell growth inhibition, L1210 and P388 cells were seeded in 13 × 100 tubes at 5 × 10^4 cells/mL (2 mL/tubes). Cells were grown in the presence of the compound of interest, at 4–5 log doses, for 48 h at 37 °C. Cell growth was assessed by cell count, using a Coulter cell counter. Cell growth at each dose level was expressed as a percentage of growth in control tubes and dose resulting in 50% inhibition of growth was determined.

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Resolved 3-(3-Hydroxyphenyl)-*N*-*n*-propylpiperidine and Its Analogues: Central Dopamine Receptor Activity

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Seven enantiomeric pairs of *N*-alkyl analogues of 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (3-PPP, **12**) have been synthesized and evaluated pharmacologically (biochemistry and behavior) in order to examine their ability to interact with central dopamine (DA) receptors, particularly DA autoreceptors. In the *R* series it seems as if all compounds behave as classical DA receptor agonists with affinity and intrinsic activity for both pre- and postsynaptic receptors. The same bifunctional profile seems to be valid for the *S* enantiomers with N-substituents larger or bulkier than *n*-propyl. Likewise, the *S* enantiomers with ethyl or *n*-propyl N-substituents seem to have affinity for both pre- and postsynaptic receptors but intrinsic activity at presynaptic receptors only, thus appearing as antagonists at postsynaptic receptors. In the total series, (*S*)-(−)-3-PPP [(*S*)-**12**] seems to be the most interesting compound both from the theoretical and the therapeutical point of view, possibly attenuating DA function in two different ways by stimulating the presynaptic receptors and blocking the postsynaptic receptors. This compound has been selected for extended pharmacological studies as a potential antipsychotic drug.

The introduction of the modern antipsychotic agents in the 1950's has revolutionized the treatment of schizophrenia and other psychotic conditions. However, these agents are far from ideal. They are not always effective, and, moreover, they may cause serious side effects. Tardive dyskinesia, which can develop during long-term treatment with such drugs, may persist after cessation of treatment, suggesting an irreversible brain lesion within the extrapyramidal system. It is thus obvious that there is a need for more efficacious and less toxic agents in the treatment of schizophrenia. The antipsychotic drugs used today are all centrally acting dopamine (DA) postsynaptic receptor-blocking agents (for a review, see ref 1). In recent years an alternative way of inhibiting central dopaminergic function has attracted considerable interest, i.e., selective stimulation of presynaptic dopaminergic receptors, the so-called DA autoreceptors.[2] Interestingly, low doses of the DA-receptor agonist apomorphine has been found to preferentially activate presynaptic DA receptors,[3] an effect associated with gross behavioral sedation.[2,4] Some clinical studies have reported an antipsychotic action of low doses of apomorphine[5,6] with a concomitant reduction of serum homovanillic acid (HVA) concentrations,[7] which likewise may be explained in terms of preferential activation of dopaminergic autoreceptors. It would appear that the development of selective dopaminergic autoreceptor agonists might offer some promise in the treatment of psychotic conditions.

In two recent papers,[8,9] we have reported on the discovery and properties of the central DA autoreceptor agonist 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (3-PPP, **12**). A structure–activity (SAR) study of analogues of this compound showed that the 3-(3-hydroxyphenyl)piperidine moiety was necessary for high and selective DA-autoreceptor stimulating activity.[9] The optimal N-substituent has been less well defined, although we found that *N*-

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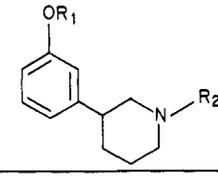
Table I. Physical Data



no. (abs confign)	R_1	R_2	prepn method	yield, %	mp, °C	$[\alpha]^{22}_D$, deg (MeOH)	formula
1 (*R*)	CH_3	CH_2Ph	A	45	164–165	+42.6 (*c* 2.1)	$C_{19}H_{23}NO\cdot HCl$
1 (*S*)	CH_3	CH_2Ph	A	32	164–165	−43.1 (*c* 2.1)	
2 (*R*)	CH_3	H	B (C)	40 (93)	175.5–177	−10.4 (*c* 2.2)	$C_{12}H_{17}NO\cdot HCl$
2 (*S*)	CH_3	H	B (C)	30 (93)	175.5–177	+10.1 (*c* 2.1)	
3 (*R*)	CH_3	CH_3	D	52	172–174	−5.5 (*c* 1.0)	$C_{13}H_{19}NO\cdot HCl$
3 (*S*)	CH_3	CH_3	D	57	174–176	+7.3 (*c* 1.0)	
4 (*R*)	CH_3	C_2H_5	D	82	170–172	+6.4 (*c* 1.0)	$C_{14}H_{21}NO\cdot HCl$
4 (*S*)	CH_3	C_2H_5	D	91	170–172	−6.3 (*c* 1.0)	
5 (*R*)	CH_3	n-C_3H_7	G	83	200.5–202	+6.4 (*c* 2.1)	$C_{15}H_{23}NO\cdot HCl$
5 (*S*)	CH_3	n-C_3H_7	E	73	200.5–202	−6.7 (*c* 2.1)	
6 (*R*)	CH_3	i-C_3H_7	F	91	190.5–192	+9.7 (*c* 2.2)	$C_{15}H_{23}NO\cdot HCl$
6 (*S*)	CH_3	i-C_3H_7	F	92	190.5–192	−9.7 (*c* 2.1)	
7 (*R*)	CH_3	n-C_4H_9	G	93	163–163.5	+10.3 (*c* 2.1)	$C_{16}H_{25}NO\cdot HCl$
7 (*S*)	CH_3	n-C_4H_9	G	91	163–164	−10.4 (*c* 2.1)	
8 (*R*)	CH_3	i-C_5H_{11}	F	84	130–131	+10.9 (*c* 2.1)	$C_{17}H_{27}NO\cdot HCl$
8 (*S*)	CH_3	i-C_5H_{11}	F	84	130–131	−10.8 (*c* 2.2)	
9 (*R*)	H	H	H	57	230–232	−9.3 (*c* 2.0)	$C_{11}H_{15}NO\cdot HCl$[a]
9 (*S*)	H	H	H	57	220–221	+9.8 (*c* 2.0)	
10 (*R*)	H	CH_3	I	55	202–205	−6.3 (*c* 1.0)	$C_{12}H_{17}NO\cdot HCl$
10 (*S*)	H	CH_3	I	64	200–205	+5.2 (*c* 2.0)	
11 (*R*)	H	C_2H_5	I	39	168–169	+7.8 (*c* 1.0)	$C_{13}H_{19}NO\cdot HCl$
11 (*S*)	H	C_2H_5	I	39	164–169	−7.6 (*c* 1.0)	
12 (*R*)	H	n-C_3H_7	H	77	187–188	+7.1 (*c* 2.1)	$C_{14}H_{21}NO\cdot HCl$
12 (*S*)	H	n-C_3H_7	H	74	187–188	−7.1 (*c* 2.2)	
13 (*R*)	H	i-C_3H_7	H	85	195–196	+9.2 (*c* 0.7)	$C_{14}H_{21}NO\cdot HCl$
13 (*S*)	H	i-C_3H_7	H	85	189–192	−9.2 (*c* 0.9)	
14 (*R*)	H	n-C_4H_9	H	86	127.5–129	+10.7 (*c* 2.2)	$C_{15}H_{23}NO\cdot HCl$
14 (*S*)	H	n-C_4H_9	H	75	127.5–129	−10.8 (*c* 2.1)	
15 (*R*)	H	i-C_5H_{11}	H	67	oil[b]	+8.0 (*c* 1.1)	$C_{16}H_{25}NO\cdot HCl$[b]
15 (*S*)	H	i-C_5H_{11}	H	67	oil[b]	−10.7 (*c* 1.1)	
16 (*R*)	H	CH_2CH_2Ph	I	50	202–202.5	−5.9 (*c* 2.2)	$C_{19}H_{23}NO\cdot HCl$
16 (*S*)	H	CH_2CH_2Ph	H	42	201.5–202.5	+6.4 (*c* 2.2)	

[a] Anal. [(*R*)-9] C: calcd., 61.8; found, 60.2. Anal. [(*S*)-9] C: calcd., 61.8; found, 60.9; H: calcd., 6.6; found, 5.9. [b] Elemental analysis was not performed due to oil formation. TLC and GLC show no impurities, and GC/MS shows M^+ at *m/e* 177 and the base peak at *m/e* 44.

isopropyl, *N*-*n*-butyl, *N*-*n*-pentyl, and *N*-phenethyl were more potent than the *N*-*n*-propyl compound. More recently, we have noted that some of the racemic compounds with *N*-alkyl substituents larger than *n*-Pr can also be postsynaptic DA agonists at higher doses (unpublished results). It thus seems that the selectivity for the DA autoreceptor is determined by a delicate balance among several structural moieties of the agonists.

To elucidate further the structural requirements for the autoreceptor selectivity of 3-(3-hydroxyphenyl)piperidines related to **12**, we here report the preparation and the central DA-receptor stimulating activity of a series of N-substituted enantiomers of 3-(3-hydroxyphenyl)-piperidine (**9**). The compounds were tested in rats by biochemical and behavioral methods previously described.[10] The compounds synthesized and the biological data obtained are presented in Tables I–IV.

Chemistry. We have previously presented the synthesis of racemic **12**.[9] The secondary amines 3(*R*)- and 3(*S*)-(3-methoxyphenyl)piperidine [(*R*)- and (*S*)-**2**] were found to be suitable intermediates for the preparation of the present series of compounds. The resolution of these compounds was achieved in the following two different ways: (a) by a classical recrystallization procedure of diastereomeric salts[11] and (b) by a chromatographic method based on the findings of Helmchen et al.[12] for resolution of primary amines and developed further by our group. The method utilizes optically pure (+)- or (−)-*O*-methylmandelic acid, both of which are converted to their corresponding acid chlorides and reacted separately with the racemic secondary amine (**2**) to form two diastereomeric amides, which can easily be separated. This method has been used previously only analytically.[13] The separated mandelic amides were cleaved in a THF solution of potassium *tert*-butoxide, a method reported previously for the cleavage of tertiary amides.[14] The two methods of resolution are depicted in Scheme I.

During amide cleavage two interesting observations were made when following the reaction on GLC. Firstly, racemization occurred (in the acid part of the molecule), and secondly, the secondary amine product is formed (at least partly) via the corresponding *N*-formyl derivative (NMR and GC/MS).

The optical purity of the resolved amines was determined by HPLC (see Experimental Section). The sec-

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Table II. Biochemical Data

no. (abs confign)	Dopa accumulation[a] reserpine pretreatment: ED_{50}, μmol/kg[b-d] limbic	striatum	no pretreatment limbic dose, μmol/kg	limbic % contr[e]	striatum dose, μmol/kg	striatum % contr
9 (*R*)	17	14	NT		NT	
9 (*S*)	*f*	*f*	227	50*	227	44*
10 (*R*)	2.2	2.9	NT		NT	
10 (*S*)	6.8	10	227	48	227	51
11 (*R*)	2.4	2.6	NT		NT	
11 (*S*)	6.4	6.5	176	82	176	120
12 (*R*)	1.0	1.3	0.8	86*	0.8	81*
12 (*S*)	0.8	1.7	213	95 (ns)	27	147*
13 (*R*)	6.7	13	3.9	77*	0.98	85*
13 (*S*)	0.37	0.45	0.98	74*	0.24	76*
14 (*R*)	2.3	2.2	3.7	72*	3.7	76*
14 (*S*)	0.86	0.77	0.83	84*	3.7	86*
15 (*R*)	1.9	1.8	0.84	92*	3.5	70*
15 (*S*)	0.35	0.25	0.84	77*	3.5	80*
16 (*R*)	9.2	6.9	NT[g]		NT	
16 (*S*)	0.17	0.13	NT[g]		NT	
apomorphine	0.19[h]	0.22[h]	NT		NT	

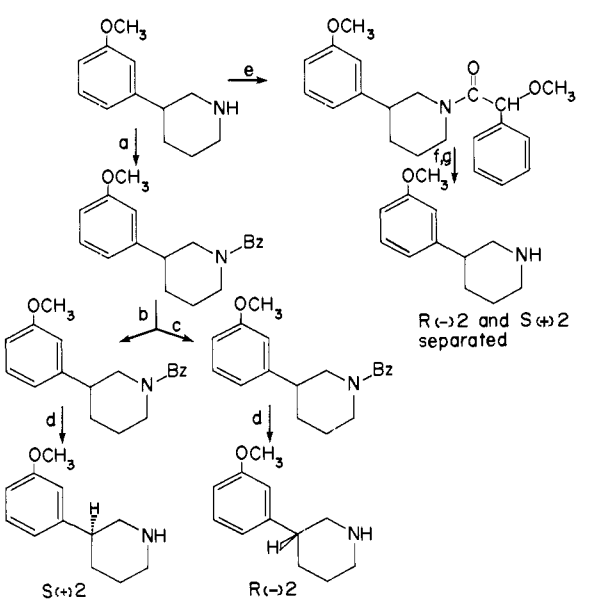
[a] For experimental details, see Experimental Section. [b] Dose giving a half-maximal decrease of Dopa formation in the rat brain, estimated from a dose–response curve comprising four to six dose levels (n = 3–5) of the compound tested. [c] Significant effects of Dopa accumulation was only obtained in the hemispheral portions (cortex) of reserpinized animals treated with (*S*)-**9** and (*R*)-**10** (100 μmol/kg) and (*R*)-**11** (32 μmol/kg). [d] No effects were seen on 5-HTP accumulation of any of the compounds tested at any dose tested. [e] Statistics according to Student's t test. An asterisk indicates $p < 0.05$ or less. [f] Maximal reduction of the Dopa levels could not be obtained. For the limbic brain portions a 19% reduction (at 100 μmol/kg), and for the striatal brain portions a 26% reduction (at 100 μmol/kg) from the control levels were reached. When the dose was raised (200 μmol/kg), no further decrease occurred. Both the limbic and the striatal brain portions show control values (104 and 114% of controls, respectively). [g] Not tested due to toxic effects in reserpinized animals at low doses (see footnote *i*) in Table III. [h] From ref 10.

ondary amines (*R*)- and (*S*)-**2**, produced after (a) hydrogenolysis of the corresponding *N*-benzyl enantiomers or (b) amide cleavage, were also tested for optical purity by the same method. This showed that no racemization in the amine part of the molecule took place during either hydrogenolysis or amide cleavage.

The absolute configuration of (−)-3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine [(−)-**12**] was determined by X-ray crystallography to be *S*.[15] During the preparation of this paper, Arnold et al. published the resolution and the absolute configuration of (+)-3-(3-methoxyphenyl)-*N*-*n*-propylpiperidine [(+)-**5**], which was assigned the *R* configuration.[16]

Pharmacology. The in vivo biochemical test method utilizes the well-established phenomenon of receptor-mediated feedback inhibition of the presynaptic neuron.[17] Thus, the synthesis rate of the catecholamines DA and norepinephrine (NE) is inhibited by agonists activating dopaminergic and α-adrenergic receptors, respectively. Similarly, the synthesis rate of 5-HT is inhibited by 5-HT-receptor agonists.[18,19] The dopa accumulation, following decarboxylase inhibition by means of (3-hydroxybenzyl)hydrazine (NSD 1015), was thus used as an indicator of the DA-synthesis rate in the DA-predominant parts (i.e., limbic system and corpus striatum) and the NE-synthesis rate in the remaining NE-dominant hemispheral portions (mainly cortex). The 5-HTP accumulation was taken as an indicator of the 5-HT-synthesis rate in the three brain parts (for details, see Experimental Section). Motor-activity recordings were carried out as previously described[10] with motility meters. The data are presented in Tables II–IV.

Scheme I. Resolution of 3-(3-Methoxyphenyl)piperidine by Two Different Methods[a]



[a] a = benzyl chloride; b = (+)-dibenzoyl-D-tartaric acid and recrystallization from MeOH; c = the filtrate was alkalized and treated with (−)-dibenzoyl-L-tartaric acid and recrystallized from MeOH; d = Pd/C (10%), H_2 (g); e = (*R*)-(−)-*O*-methylmandeloyl chloride; f = chromatographic separation; g = *t*-BuOK in THF.

Results and Discussion

In reserpinized animals, all compounds tested, except compound (*S*)-**9** markedly reduced brain Dopa formation (for ED_{50} values, see Table II). At these comparatively low

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Table III. Motor Activity

no. (abs confign)	motor activity[a] reserpine pretreatment[b] dose, μmol/kg	acc counts	no pretreatment[c] low dose, μmol/kg	high dose, μmol/kg
9 (*R*)	265	47 ± 7*[d]	NT	NT
9 (*S*)	200	I[e]	NT	227 (55)*
10 (*R*)	133	88 ± 22*	NT	NT
10 (*S*)	100	36 ± 8*[f]	NT	227 (40) (ns)
11 (*R*)	133	141 ± 28*	NT	NT
11 (*S*)	100	I[e]	NT	176 (54) (ns)
12 (*R*)	13	78 ± 14*	1.6 (75)*	213 (230)*
12 (*S*)	213	12 ± 2*[g]	0.8 (74)*	213 (40)
13 (*R*)	53	49 ± 29*[h]	0.2 (53)*	13 (168)*
13 (*S*)	3.3	38 ± 8*	0.2 (41)*	13 (137)
14 (*R*)	53	180 ± 23*	3.7 (58)*	53 (92)
14 (*S*)	53	63 ± 4*	3.7 (32)*	53 (49)
15 (*R*)	13	77 ± 11*	3.3 (57)*	53 (182)*
15 (*S*)	13	122 ± 20*	0.8 (39)*	53 (60)
16 (*R*)	14	26 ± 8*[i]	NT[j]	NT
16 (*S*)	7.0	71 ± 12*[i]	NT[j]	NT
16 (*RS*)	13	41 ± 26[i]	NT[j]	NT

[a] For experimental details, see Experimental Section. [b] The lowest dose giving accumulated counts (0–30 min) significantly higher than controls (4 ± 2). [c] Lowest dose giving significant reduction and increase, respectively, of motor activity (5–35 min). Percent of controls (184 ± 11; n = 39) is shown in parentheses. [d] Statistics according to footnote *e* of Table II. [e] Inactive at this dose, i.e., control values. [f] This effect was blocked by haloperidol (0.5 mg/kg 30 min before drug administration). [g] A small, but significant, degree of stimulation was noted after this dose. However, this effect was not classically dopaminergic but was due to occasional jerks. [h] Statistics according to Mann–Whitney U test: * = p <0.01. [i] Convulsive doses: (*RS*)-**16**, 16 μmol/kg; (*R*)-**16**, 13 μmol/kg; (*S*)-**16**, 6.5 μmol/kg. [j] Not tested due to toxic effects in reserpinized animals.

Table IV. Effects of the Enantiomers of **12–15** on DOPAC and HVA Levels in Rat Brain Regions[a]

no. (abs confign)	limbic DOPAC	limbic HVA	striatum DOPAC	striatum HVA	n
12 (*R*)	59 ± 6.0*	52 ± 4.2*	63 ± 4.6*	45 ± 0.7*	4
12 (*S*)	114 ± 5.0	100 ± 6.6	145 ± 9.3*	162 ± 11*	4
13 (*R*)	70 ± 9.0*	80 ± 26	74 ± 4.2*	89 ± 33	4
13 (*S*)	60 ± 8.0*	51 ± 26*	81 ± 7.3*	68 ± 21	4
14 (*R*)	55 ± 5.5*	52 ± 11*	58 ± 8.6*	52 ± 5.6*	4
14 (*S*)	91 ± 9.1*	103 ± 7.9	118 ± 15	142 ± 9.9*	4
15 (*R*)	55 ± 10*	55 ± 11*	60 ± 4.2*	54 ± 4.5*	4
15 (*S*)	75 ± 9.3*	70 ± 12*	80 ± 7.6*	83 ± 6.5*	4

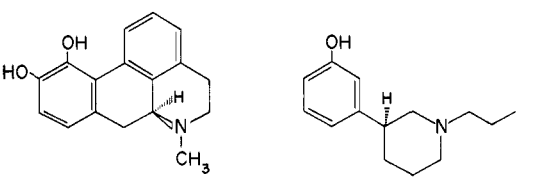
[a] The compounds were given in a dose of 27 μmol/kg sc 60 min before death. DOPAC and HVA levels were determined by HPLC techniques. The values are expressed as percent of control means plus or minus standard error of the mean (ranges of mean control values: limbic DOPAC, 310–375; HVA, 167–201; striatum DOPAC, 874–903; HVA, 609–702 ng/g (n = 4)]. For statistics, see footnote *e* of Table II.

doses, no significant postsynaptic DA receptor activation was monitored (gross behavior observation and also cf. Table III). For compounds with N-alkyls smaller than n-Pr (**9–11**), the R isomer is more potent than its corresponding S isomer. For N-n-Pr (**12**), R and S are equipotent, while compounds with N-alkyls larger or bulkier than n-Pr (**13–16**) are more potent in their S than in their R form.

The ability of the compounds tested to antagonize reserpine-induced akinesia was taken to indicate the presence of postsynaptic DA receptor stimulation. As seen from Table III, the only compounds failing to elicit postsynaptic stimulation in this model are the S isomers of **9**, **11**, and **12**. All the other compounds exhibit accumulated counts (0–30 min) between 30 and 180 at the doses tested.

Interestingly, high doses of compounds (*S*)-**11** and (*S*)-**12** tended to stimulate Dopa formation in striatum in nonreserpinized rats (Table II). This might suggest DA receptor-blocking properties of these compounds in this model.[20] This is further substantiated for compound (*S*)-**12** by its ability to stimulate the formation of the DA metabolites DOPAC and HVA in the striatal parts of rats recieving this drug (see Table IV) and also by its apomorphine antagonism in otherwise nonpretreated rats.[21]

Chart I. Absolute Configurations of (6a*S*)-Apomorphine and (*S*)-3-PPP



A thorough study of the two enantiomers of compound **12** has recently been presented.[22] Thus, in racemic **12**, the postsynaptic stimulation of the R enantiomer is negated by the blocking properties of the S enantiomer, thereby resulting in a selective autoreceptor profile of the racemate.[8] The possibility that one of the two enantiomers of racemic **12** might act as an antagonist at the DA receptor has previously been speculated upon by Seeman as one of several conceivable explanations for the fact that racemic **12** fits a putative model of the D2 receptor without showing

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any behavioral syndrome connected to stimulation of this receptor.[23] A finding parallelling our results on the enantiomers of **12** is that (+)-apomorphine antagonizes the effects of (−)-apomorphine.[24] This comparison, however, is relevant only from a pharmacological and not from a structural point of view, since the chiral carbon of (*S*)-**12** does not overlap with that of (*S*)-(+)-apomorphine as seen from Chart I.

In order to further investigate both DA autoreceptor and postsynaptic receptor stimulating activity in a behavioral model, we performed motor activity measurements on nonpretreated rats. The results are presented in Table III. The only compounds giving a monophasic decrease in spontaneous locomotor activity are compounds (*S*)-**9**–(*S*)-**12**. All the other compounds tested showed at least a tendency toward a biphasic action, i.e., inhibitory at low (presynaptic) doses and stimulatory at high (postsynaptic) doses. The reason for also including the toxic compound **16** in this study was to see if both enantiomers are toxic or if, by chance, the toxic and the dopaminergic properties could be separated into different enantiomers. Obviously (Tables II and III and footnotes), the dopaminergic as well as the toxic properties (convulsions) of racemic **16** reside in both enantiomers, even though compound (*S*)-**16** has a more favorable ratio between these two activities than has compound (*R*)-**16**.

Recently, Carlsson[25] proposed that the very complex pharmacology of compound (*S*)-**12** that has been presented[22] might be explained in terms of differences in the responsiveness of the receptors involved in the pharmacological models used. It is proposed that the intrinsic activity of a receptor agonist depends, in part, on the responsiveness of the receptor, which in turn is determined by the degree of previous agonist occupancy on the receptor. A change in agonist occupancy on the receptor will induce a slow conformational change influencing the responsiveness of the receptor. In this way, one and the same receptor agonist will show a varying intrinsic activity, depending on the state of the receptor.

The different DA receptor states involved in the models used in this study could be rated in order of increasing apparent sensitivity as follows: normal postsynaptic receptor < reserpine pretreated postsynaptic receptor[26] < normal autoreceptor < reserpine pretreated autoreceptor.[27]

In the present series of resolved phenylpiperidines, it seems as if most compounds have the profile of a classical DA receptor agonist (e.g., apomorphine), having affinity and intrinsic activity for both pre- and postsynaptic DA receptors. Likewise, compounds (*S*)-**11** and (*S*)-**12** seem to have affinity and intrinsic activity for presynaptic receptors, while these compounds have affinity but very low intinsic activity for postsynaptic receptors. This would explain the dual action of these compounds as agonists at presynaptic and antagonists at postsynaptic DA receptors. It might be speculated that this dual attenuation of dopaminergic function would be important for the putative antipsychotic action of these compounds. Furthermore, we have demonstrated that although compound (*S*)-**12** possesses strong antidopaminergic effects in some behavioral tests, it does not produce the serious motor disturbances (e.g., catalepsy) associated with classical postsynaptic DA receptor antagonists.[21,22,28] Interestingly, Gunne et al. have demonstrated that compound (*S*)-**12** is effective in alleviating involuntary movements, similar to human tardive dyskinesia, in Cebus monkeys subjected to long-term treatment with a classical neuroleptic drug.[29]

Compound (*S*)-**12** may be a prototype for a second generation of antipsychotic drugs, likely to be free of tardive dyskinetic effects and could conceivably be used to relieve these symptoms in patients treated with conventional neuroleptics.

Experimental Section

Chemistry. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. ^{1}H NMR spectra were recorded with a Varian EM-360 instrument (Me_4Si). GC/MS spectra were recorded on a Finnegan MAT 44S instrument at 70 eV. All spectra analyzed were in accordance with assigned structures. GLC was performed with a Hewlett Packard 5830A instrument with a flame-ionization detector. A glass column (2 m × 5 mm i.d.) packed with 3 % OV-17 or 3 % OV-11 on Gas chrom. Q (Supelco, Inc.) was used throughout. HPLC was performed on a Waters 5 Si 10 column with hexane/EtOAc/EtOH (85:12:3) as the mobile phase, working in the pressure range 1000–3000 psi and with a flow rate of 2 mL/min. Detection was made by a Waters Model 440 UV monitor. Optical purity was estimated by comparing peak areas (height times width at half height). Optical rotation was measured with a Perkin-Elmer 141 polarimeter equipped with a thermostat (22 °C). The elemental analyses (C, H, and N) for the new substances were within ±0.4% of the theoretical values. For purity tests, TLC was performed on fluorescent silica gel plates developed in at least two different systems. For all the compounds, only one spot (visualized by UV light and I_2 vapor) was obtained.

***N*-Benzyl-3(*S*)-(3-methoxyphenyl)piperidine [(*S*)-1]. Method A.** (+)-Dibenzoyl-D-tartaric acid (28.2 g, 0.075 mol) in hot methanol (350 mL) was added to *N*-benzyl-3-(3-methoxyphenyl)piperidine[9] (**1**; 21.1 g, 0.075 mol) in hot methanol (100 mL). After 2 days, the salt that separated was recrystallized three times from methanol. The collected salt (8.3 g) was treated with 1 M NaOH (250 mL), and the free amine was extracted with ether (3 × 150 mL). The combined ether layers were dried (K_2CO_3), and the solvent was evaporated. The residual amine was then passed through a short alumina column with ether as eluant and then converted to the hydrochloride. One recrystallization from methanol–ether gave 3.8 g (32%) of (*S*)-**1**·HCl.

***N*-Benzyl-3(*R*)-(3-methoxyphenyl)piperidine [(*R*)-1]. Method A.** The free amine isolated from the first two of the (+)-dibenzoyl-D-tartaric salt mother liquors in the resolution of (*S*)-**1** above was treated with (−)-dibenzoyl-L-tartaric acid as described above. After two recrystallizations (MeOH), the hydrochloride was prepared and recrystallized once to give 5.4 g (45%) of (*R*)-**1**·HCl.

3(*S*)-(3-Methoxylphenyl)piperidine [(*S*)-2]. Method C. *N*-Benzyl-3(*S*)-(3-methoxyphenyl)piperidine [(*S*)-**1**] hydrochloride (3.8 g, 0.0120 mol) was dissolved in ethanol (80 mL), 10% Pd/C was added, and the mixture was hydrogenated at room temperature and atmospheric pressure (28 h). The catalyst was removed (Celite) by filtration, the solvent was evaporated, and the crystalline residue was recrystallized from methanol–ether to give the desired 3(*S*)-(3-methoxyphenyl)piperidine [(S)-**2**] hydrochloride (2.54 g, 93%). The optical purity was determined by HPLC to be 100%.

3(*R*)-(3-Methoxyphenyl)piperidine [(*R*)-2]. Method C. *N*-Benzyl-3(*R*)-(3-methoxyphenyl)piperidine [(*R*)-**1**] hydrochloride (7.6 g, 0.024 mol) was hydrogenolyzed as described for the preparation of compound (*S*)-**2**, giving the desired 3(*R*)-(3-

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methoxyphenyl)piperidine [(*R*)-**2**] hydrochloride (5.05 g, 93%). The optical purity was determined by HPLC to be 100%.

3(*S*)-(3-Methoxyphenyl)piperidine [(*S*)-2]. Method B. (*R*)-(−)-α-Methoxyphenylacetic acid (11.0 g, 0.066 mol) was dissolved in CH_2Cl_2 (250 mL), $SOCl_2$ (85 mL) was added, and the mixture was refluxed for 30 min. Excess $SOCl_2$ was evaporated, and the residual acid chloride oil was dissolved in CH_2Cl_2 (280 mL). The solution was added at 20 °C to a vigorously stirred mixture of 3-(3-methoxyphenyl)piperidine (**2**) hydrochloride (15.1 g, 0.066 mol), CH_2Cl_2 (280 mL) and 5% aqueous NaOH (560 mL). After the mixture was stirred for 15 min, the phases were separated, and the organic phase was washed once with water and dried (Na_2SO_4). Filtration and evaporation of the solvent gave 1-[(*R*)-methoxyphenylacetyl]-3-(3-methoxyphenyl)piperidine as a crude oil (21.8 g), which was chromatographed on a SiO_2 column (600 g SiO_2) with light petroleum–ether (starting with 50:50 mixture and successively increasing the ether content to 100%) as eluant. The fractions containing the diastereomer that eluated first, in nearly pure form, were combined, and the solvent was evaporated to give the desired diastereomeric amide as an oil (8.7 g, 0.026 mmol) (containing 0.5% of the other diastereomer according to HPLC). This was dissolved in dry THF (400 mL), and potassium *tert*-butoxide (16.1 g, 0.144 mol) and water (1.30 g, 0.072 mol) were added under stirring at room temperature. The mixture was stirred at this temperature overnight and was then partitioned between ether and water. After the organic phase was dried (Na_2SO_4), excess HCl-saturated ethanol was added, and the solvent was evaporated. The residue was redissolved twice in absolute ethanol, and the solvent was evaporated, giving a crystalline residue. Recrystallization from ethanol–ether gave 4.52 g (30% total yield and 76% in the amide cleavage step) of the desired (*S*)**2**·HCl. The optical purity was determined by HPLC to be 99.9%.

3(*R*)-(3-Methoxyphenyl)piperidine [(*R*)-2]. Method B. The other diastereomer, which is eluted last (from the preparation of (*S*)-**2** above), was collected in two different fractions, one yielding 2.0 g of an oil (containing 5% of the first eluted diastereomer) and the other yielding 3.6 g (containing 2% of the first eluted diastereomer). The first fraction (2.0 g, 0.0059 mol) was dissolved in dry THF (100 mL) and potassium *tert*-butoxide (4.2 g, 0.037 mol), and water (0.34 g, 0.079 mol) was added under stirring at room temperature. The mixture was stirred at this temperature overnight and was then partitioned between ether and water. After the organic phase was dried (Na_2SO_4), excess HCl-saturated ethanol was added, and the solvent was evaporated, giving a crystalline residue. Recrystallization from ethanol–ether gave 1.07 g (40% total yield and 80% in the amide cleavage step) of (*R*)-**2**·HCl. The optical purity was determined by HPLC to be 97.2%. Two consecutive recrystallizations from ethanol–ether gave 0.72 g (67% in the recrystallization) of crystals with the optical purity 99.4%, while the mother liquor from the last of the two recrystallizations showed the optical purity was 97.5%.

3(*S*)-(3-Methoxyphenyl)-*N*-methylpiperidine [(*S*)-3]. Method D. To compound (*S*)-**2**·HCl (0.65 g, 2.9 mmol) of 100% optical purity were added 37% CH_2O (1.5 mL, 15 mmol), MeOH (20 mL), molecular sieves (3Å, 2 g), and $NaBH_3CN$ (0.60 g, 9.5 mmol). The mixture was stirred under nitrogen for 30 min and then filtered. MeOH was evaporated off, and the residue was stirred with 10% HCl (10 mL) for 15 min before alkalizing with 10% Na_2CO_3 and extracting with ether. The organic layer was separated and dried (Na_2SO_4), and the solvent was evaporated to give an oil, which was converted to the hydrochloride. Recrystallization from EtOH–ether gave 0.40 g (57%) of (*S*)-**3**·HCl.

3(*S*)-(3-Methoxyphenyl)-*N*-*n*-propylpiperidine [(*S*)-5]. Method E. $NaBH_4$ (0.61 g, 0.016 mol) was added portionwise under stirring to a solution of propionic acid (3.8 g, 0.051 mol) in dry benzene (15 mL). The temperature was kept below 15 °C for 2 h and then 3(*S*)-(3-methoxyphenyl)piperidine (*S*)-**2** (0.61 g, 0.0032 mol), dissolved in dry benzene (10 mL), was added, and the mixture was refluxed for 3 h. The reaction mixture was allowed to reach room temperature, and excess 2 N NaOH was added. After stirring for 30 min, the reaction mixture was extracted with ether, all the organic phases were mixed and dried (Na_2SO_4), and the solvent was evaporated, giving an oily residue. The product precipitated as the hydrochloride and was recrystallized from MeOH–ether, yielding 0.60 g (73%) of (*S*)-**5**·HCl.

3(*R*)-(3-Methoxyphenyl)-*N*-isopropylpiperidine [(*R*)-6]. Method F. To compound (*R*)-**2**·HCl (1.1 g, 4.9 mmol) was added CH_3CN (50 mL), ground K_2CO_3 (4 g) and isopropyl bromide (0.89 g, 7.3 mmol). This mixture was refluxed for 18 h, the salts were filtered off, and the solvent was evaporated. The residue was partitioned between ether and 10% Na_2CO_3. The ether layer was separated, dried (Na_2SO_4), and treated with ethereal HCl, and the solvent was evaporated off. The residual oil was crystallized from MeOH–ether, yielding 1.2 g (91%) of the desired compound (*R*)-**6**·HCl.

***N*-*n*-Butyl-3(*R*)-(3-methoxyphenyl)piperidine [(*R*)-7]. Method G.** Compound (*R*)-**2**·HCl (1.2 g, 5.3 mmol) was acylated with butanoic acid chloride (0.82 mL, 7.9 mmol) in the presence of triethylamine (1.1 mL, 7.9 mmol) at 0 °C, yielding 1.32 g of crude amide; this was reduced in THF with $LiAlH_4$ (0.60 g, 16 mmol) and worked up in the usual way, yielding an oil (1.26 g), which was converted to its hydrochloride salt and recrystallized (MeOH–ether) to give 1.4 g (93%) of (*R*)-**7**·HCl.

Demethylation of Methoxy Compounds. Method H. The phenols were obtained by heating the appropriate methoxy compounds in 48% aqueous HBr for 2 h at 125 °C under nitrogen. The hydrobromic acid was evaporated, and the residue was recrystallized. Alternatively, the residue was alkalinized (10% Na_2CO_3) to pH 10 and extracted with ether or EtOAc. The organic layer was separated and dried (Na_2SO_4). After filtration, the solvent was evaporated, leaving an oil, which was converted to its hydrochloride with ethereal HCl. Evaporation of the solvent and recrystallization gave the product.

Method I. The base of the appropriate methoxy compound was dissolved in CH_2Cl_2, and the solute was chilled to −70 °C. At this temperature, 2 equiv of BBr_3 was added, and the temperature was allowed to reach room temperature (overnight). The reaction mixture was quenched with water. The mixture was alkalized (10% Na_2CO_3) to pH 10, and the organic layer was worked up as described under Method H.

Estimation of the Optical Purity of the Secondary Amines (+)- and (−)-2 by HPLC.[30] The sample to be tested, (*R*)-**2**·HCl or (*S*)-**2**·HCl (2.0 mg, 8.6 μmol), was mixed with H_2O (2 mL), CH_2Cl_2 (2 mL), and 1 M NaOH (0.5 mL) in a 10-mL flask equipped with a magnetic stirrer. Under vigorous stirring, 10 μL of (+)- or (−)-*O*-methylmandeloyl chloride [prepared from (+)- or (−)-*O*-methylmandelic acid and $SOCl_2$ under 30 min stirring at room temperature and then evaporation] was added at room temperature. The stirring was stopped after 20 min, and the organic layer was separated and passed through a Pasteur pipet containing Na_2SO_4. Twenty microliters of the dried sample was injected into the HPLC apparatus. Peak areas (height times width at half height) were compared. No racemization was observed in this derivatization procedure.[30] However, if triethylamine is used as the base and the mandeloyl chloride is left with this base in CH_2Cl_2 for a while (1 min), total racemization occurs at room temperature.[31] The separation factor α was determined to be 1.50 for the system used.

Pharmacology. Animals used in the biochemical and motor activity experiments were male rats of the Sprague–Dawley strain (Anticimex, Stockholm) weighing 200–300 g. All substances to be tested were dissolved in saline immediately before use, occasionally with the addition of a few drops of glacial acetic acid and/or moderate heating in order to obtain complete dissolution. Reserpine was dissolved in a few drops of glacial acetic acid and made up to volume with 5.5% glucose. Injection volumes were 5 or 10 mL/kg.

Biochemistry. Reserpine Pretreatment. Eighteen hours prior to administration of the "test" compounds, the rats were pretreated with reserpine (Ciba) in a dose of 5 mg/kg ip. Substances to be tested were injected in various doses subcutaneously (sc) in the neck region at the beginning of the experiments. Changes in motility, stereotypies, and other aspects of behavior were either monitored by means of motor activity cages (see below), or just noted. Thirty minutes after the administration of the "test" compounds, the animals received 100 mg/kg of

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(3-hydroxybenzyl)hydrazine hydrochloride[32] (NSD 1015), an inhibitor of L-aromatic amino acid decarboxylase. After an additional 30 min, the rats were killed by decapitation, and their brains were rapidly taken out, put on an ice-chilled glass plate, and dissected into limbic forebrain (containing, e.g., the nucleus accumbens and the olfactory tubercles), corpus striatum, and the remaining hemispheral (cortical) parts. Immediately after dissection, the brain parts were frozen on dry ice and later analyzed for their contents of Dopa and 5-HTP (and in some cases DOPAC and HVA) by HPLC techniques with electrochemical detection.[33] Separate dose–response curves based on four to six dose levels for each substance and brain area were constructed. From these curves, the dose of the drug yielding a half-maximal decrease of the Dopa level (ED_{50}) was estimated (Table II).

No Pretreatment. The only differences from above were that no reserpine was administered and that the time interval between the injections of the test drug and NSD 1015 was 35 min instead of 30 min.

Motor Activity. The motor activity was measured in motility meters ("M/P 40 Fc Electronic Motility Meter", Motron Products, Stockholm) as previously described.[10,34] Each box was equipped with a semitransparent mirror that allowed gross behavior observations of the animals during the experiments.

Reserpine Pretreatment. Eighteen hours prior to the motility testing (carried out between 9 a.m. and 1 p.m.), the rats were injected intraperitoneally with reserpine (5 mg/kg). The test compounds were administered subcutaneously in the neck region ($n = 4$). Immediately after drug administration, the rats were placed in the test cages (one rat per cage) and put into the motility meters. Motor activity was then followed and recorded for the subsequent 30 min.

No Pretreatment. The different compounds under investigation were administered subcutaneously in the neck region ($n = 4$). Immediately after drug administration, the rats were placed in the test cages (one rat per cage) and put into the motility meters 5 min later. Motor activity was then followed and recorded for the subsequent 30 min. The motor activity results are shown in Table III.

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Registry No. 1, 88784-36-5; (*S*)-1, 89874-44-2; (*R*)-1, 89920-95-6; (*S*)-1·HCl, 88851-66-5; (*R*)-1·HCl, 89920-96-7; 2·HCl, 88824-83-3; (*S*)-2, 88784-37-6; (*S*)-2·HCl, 88768-66-5; (*R*)-2·HCl, 89920-97-8; (*R*)-3, 89874-65-7; (*S*)-3, 89874-49-7; (*R*)-3·HCl, 89874-57-7; (*S*)-3·HCl, 89874-50-0; (*R*)-4, 89874-66-8; (*S*)-4, 89874-67-9; (*R*)-4·HCl, 89874-58-8; (*S*)-4·HCl, 89874-59-9; (*S*)-5, 89874-51-1; (*R*)-5·HCl, 89874-60-2; (*S*)-5·HCl, 86533-96-2; (*R*)-6, 89874-52-2; (*R*)-6·HCl, 89874-53-3; (*S*)-6·HCl, 89874-61-3; (*R*)-7, 89874-55-5; (*R*)-7·HCl, 89874-56-6; (*S*)-7·HCl, 89874-62-4; (*R*)-8·HCl, 89874-63-5; (*S*)-8·HCl, 89874-64-6; (*R*)-9, 89874-68-0; (*S*)-9, 89874-69-1; (*R*)-9·HCl, 89874-74-8; (*S*)-9·HCl, 89874-75-9; (*R*)-10, 89874-70-4; (*S*)-10, 89874-71-5; (*R*)-10·HCl, 89874-76-0; (*S*)-10·HCl, 89874-77-1; (*R*)-11, 89874-72-6; (*S*)-11, 89874-73-7; (*R*)-11·HCl, 89874-78-2; (*S*)-11·HCl, 89874-79-3; (*R*)-12, 85976-54-1; (*S*)-12, 85966-89-8; (*R*)-12·HCl, 89874-80-6; (*S*)-12·HCl, 88768-67-6; (*R*)-13, 89874-89-5; (*S*)-13, 89874-90-8; (*R*)-13·HCl, 89874-81-7; (*S*)-13·HCl, 89874-82-8; (*R*)-14, 89874-91-9; (*S*)-14, 89874-92-0; (*R*)-14·HCl, 89874-83-9; (*S*)-14·HCl, 89874-84-0; (*R*)-15, 89874-93-1; (*S*)-15, 89874-94-2; (*R*)-15·HCl, 89874-85-1; (*S*)-15·HCl, 89874-86-2; (R)-16, 89874-95-3; (S)-16, 89874-96-4; (R)-16·HCl, 89874-87-3; (S)-16·HCl, 89874-88-4; (+)-dibenzoyl-D-tartaric acid compd with *N*-benzyl-3-(3-methoxyphenyl)piperidine, 89874-46-4; (*R*)-(−)-α-methoxyphenylacetic acid, 3966-32-3; (*R*)-(−)-α-methoxyphenylacetyl chloride, 34713-98-9; [*R*-(*R**,*R**)]-1-(methoxyphenylacetyl)-3-(3-methoxyphenyl)piperidine, 89874-47-5; [*R*-(*R**,*S**)]-1-(methoxyphenylacetyl)-3-(3-methoxyphenyl)piperidine, 89874-48-6; (*R*)-1-butanoyl-3-(3-methoxyphenyl)piperidine, 89874-54-4; (+)-*O*-methylmandelic acid, 26164-26-1; (+)-*O*-methylmandeloyl chloride, 55137-68-3; [*S*-(*R**,*S**)]-1-(methoxyphenylacetyl)-3-(3-methoxyphenyl)piperidine, 89874-97-5; [*S*-(*R**,*R**)]-1-(methoxyphenylacetyl)-3-(3-methoxyphenyl)piperiidne, 89874-98-6; isopropyl bromide, 75-26-3; butanoic acid chloride, 141-75-3.

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