N,N-Dialkylated Monophenolic *trans*-2-Phenylcyclopropylamines: Novel Central 5-Hydroxytryptamine Receptor Agonists

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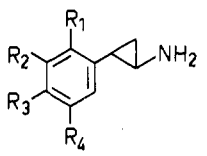
N,N-Dialkylated monophenolic derivatives of *trans*-2-phenylcyclopropylamine were synthesized and tested for central 5-hydroxytryptamine (5-HT) and dopamine (DA) receptor stimulating activity by use of a biochemical test method in rats. A hydroxy substituent in the 2- or 3-position of the phenyl ring was required for 5-HT-receptor stimulation. *N,N*-Diethyl or *N,N*-di-*n*-propyl substitution gave the most potent 5-HT-receptor agonists. The 4-hydroxy and 3,4-dihydroxy derivatives of *trans*-2-phenyl-*N,N*-di-*n*-propylcyclopropylamine were inactive at central DA and 5-HT receptors. In contrast, the corresponding 3-hydroxy derivative **18** and some of its derivatives weakly affected both DA and NE synthesis. Two of the most potent 5-HT-receptor agonists, *trans*-2-(2-hydroxyphenyl)-*N,N*-di-*n*-propylcyclopropylamine (**8**) and the 3-hydroxy isomer **18** were resolved into the enantiomers. The 1*R*,2*S* enantiomers of **8** and **18** displayed 5-HT activity, while the 1*S*,2*R* enantiomers were inactive. Compound (1*R*,2*S*)-**18**, but not (1*R*,2*S*)-**8**, weakly affected rat brain DA and NE synthesis.

In 1948 Burger and Yost[1] reported the synthesis of *trans*-2-phenylcyclopropylamine (**29**; tranylcypromine). Compound **29** was found to be an effective inhibitor of monoamine oxidase (MAO), and Burger and co-workers performed extensive structure–activity relationship (SAR) studies of 2-phenylcyclopropylamines.[2] Later studies suggested that the semirigid dopamine (DA) analogue **30** exhibits adrenoceptor-stimulating properties but seems to lack DA activity.[3,4] Compounds **31**[5,6] and **32**[7] are cyclopropyl analogues of the hallucinogens[8] 1-(2,5-dimethoxy-4-methylphenyl)-2-propylamine (DOM) and mescaline, respectively. The pharmacological actions of **31** and **32** have been described as LSD- or mescaline-like.[5a,b,7b]



29: $R_1 = R_2 = R_3 = R_4 = H$

30: $R_1 = R_2 = H$; $R_3 = R_4 = OH$

31: $R_1 = R_4 = OCH_3$; $R_2 = H$; $R_3 = CH_3$

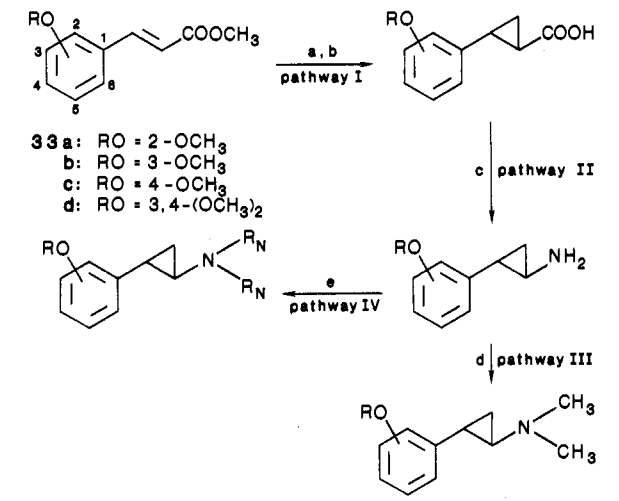
32: $R_1 = H$; $R_2 = R_3 = R_4 = OCH_3$

To our knowledge, no monophenolic derivatives of **29** have been previously reported. In the present paper, we describe the synthesis and the central pharmacological effects of some monophenolic N,N-dialkylated derivatives of **29** and of the *N,N*-di-*n*-propyl derivative of the DA analogue **30**. The novel compounds were tested for central monoaminergic activity in rats by use of a previously described biochemical screening method.[9] Several of the compounds were found to be centrally active 5-hydroxytryptamine (5-HT) receptor agonists. Two of the most potent 5-HT-receptor agonists, **8** and **18**, were resolved into the enantiomers, and their absolute configurations were determined.

Chemistry

Cyclopropanes are usually synthesized by using olefins as starting materials.[10] This is reflected in previous syntheses of *trans*-2-phenylcyclopropylamines, where the

Scheme I[a]



[a] Reagents: a = CH_2N_2, cat. $Pd(OAc)_2$; b = 50% NaOH, MeOH; c = diphenylphosphoryl azide, *tert*-BuOH; d = aqueous HCHO, $NaCNBH_3$; e = R_NX, K_2CO_3.

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∥ Department of Structural Chemistry, University of Göteborg.

(1) Burger, A.; Yost, W. L. *J. Am. Chem. Soc.* **1948**, *70*, 2198.
(2) For a review on SAR and pharmacology of MAO inhibitors, see: Kaiser, C.; Setler, P. E. In *Burger's Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; Wiley: New York, 1981; Part III, p 997. The enantiomers of *trans*-2-phenylcyclopropylamine have been reviewed with reference to their pharmacological actions. Smith, D. F. *Pharmakopsychiatr./Neuro-Psychopharmakol.* **1980**, *13*, 130.
(3) (a) Borgman, R. J.; Erhardt, P. W.; Gorczynski, R. J.; Anderson, W. G. *J. Pharm. Pharmacol.* **1978**, *30*, 193. (b) Erhardt, P. W.; Gorczynski, R. J.; Anderson, W. G. *J. Med. Chem.* **1979**, *22*, 907. (c) Gorczynski, R. J.; Anderson, W. G.; Erhardt, P. W.; Stout, D. M. *J. Pharmacol. Exp. Ther.* **1979**, *210*, 252.
(4) (a) Additional DA-inactive derivatives of *trans*-2-phenylcyclopropylamine have been reported: Rehse, K.; Behncke, S.; Siemann, U.; Kehr, W. *Arch. Pharm. (Weinheim, Ger.)* **1980**, *313*, 221. (b) *trans*-2-(3,4-Methylenedioxyphenyl)cyclopropylamine has been reported to exhibit central DA stimulating activity after intracerebral administration, but conclusive evidence for a direct DA-receptor stimulation was not given; see: Costall, B.; Naylor, R. J.; Pinder, R. M. *J. Pharm. Pharmacol.* **1974**, *26*, 753.

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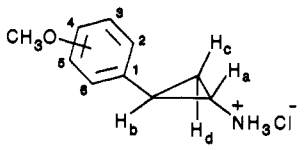
Table I. ^{1}H NMR Spectroscopic Data[a] of *trans*-2-Phenylcyclopropylamine Derivatives



no.	OCH_3 position	chemical shifts, ppm				coupling constants, Hz					
		δ_a	δ_b	δ_c	δ_d	J_{ab}	J_{ac}	J_{ad}	J_{bc}	J_{bd}	J_{cd}
2	2-OCH_3	2.52	2.75	1.35	1.31	3.5	10.1	6.8	4.4	7.8	−6.6
12	3-OCH_3	2.35	2.82	1.40	1.30	3.6	10.1	6.7	4.4	7.8	−6.7
22	4-OCH_3	2.27	2.71	1.32	1.21	3.7	10.0	6.6	4.3	7.8	−6.6
26	3,4-$(OCH_3)_2$	2.33	2.78	1.36	1.28	3.5	10.0	6.8	4.4	7.9	−6.7

[a] The spectra of the hydrochlorides in CD_3OD were recorded at 200 MHz (**12**, **22**, and **26**) or at 400 MHz (**2**) with tetramethylsilane as internal reference. Assignments were made in analogy with a previously reported analysis of the 270-MHz ^{1}H NMR spectrum of *trans*-*N*,*N*-dimethyl-2-phenylcyclopropylamine (ref 5b). Coupling constants and chemical shift values were refined by spin–spin simulation using a JEOL FASNO 5 NMR spectrum simulation program.

intermediate *trans*-2-phenylcyclopropanecarboxylic acids[11] have been formed by the following methods: (A) cyclopropanation of styrene derivatives with ethyl diazoacetate,[3b,12] (B) Simmons–Smith reaction of *trans*-cinnamic esters,[10e] and (C) reaction of *tert*-butyl cinnamate derivatives with dimethylsulfoxonium methylide.[13] Method A has been reported to give mixtures of *cis*- and *trans*-2-phenylcyclopropanecarboxylic acids,[3b,12,14] and the use of method B has resulted in widely varying yields.[10e] Therefore, preliminary experiments were performed by means of method C. The preparation of the *tert*-butyl cinnamates, a step that is necessary for controlling the stereochemistry of the cyclopropanation reaction,[5c] proceeded poorly (yields of the esters were 35–42%). Moderate yields (42–56%) were also obtained in the subsequent cyclopropanation with dimethylsulfoxonium methylide.

A method for palladium(II)-catalyzed cyclopropanation of olefins with diazomethane[15] did, however, work well. Thus, the N,N-dialkylated *trans*-2-phenylcyclopropyl-

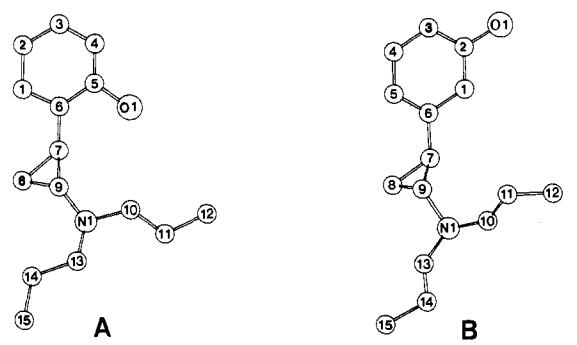


Figure 1. Atom numbering scheme and solid state (X-ray) conformation of (1*R*,2*S*)-(−)-**8**·HBr (A) and (1*R*,2*S*)-(−)-**18**·HBr (B).

(5) (a) (±)-**31** and analogues: Aldous, F. A. B.; Barrass, B. C.; Brewster, K.; Buxton, D. A.; Green, D. M.; Pinder, R. M.; Rich, P.; Skeels, M.; Tutt, K. J. *J. Med. Chem.* **1974**, *17*, 1100. (b) Pharmacology and SAR of (+)- and (−)-**31**: Nichols, D. E.; Pfister, W. R.; Yim, G. K. W. *Life Sci.* **1978**, *22*, 2165. (c) Synthesis, absolute configuration, and pharmacology of (+)- and (−)-**31**: Nichols, D. E.; Woodard, R.; Hathaway, B. A.; Lowy, M. T.; Yim, G. K. W. *J. Med. Chem.* **1979**, *22*, 458. (d) Conformational analysis of **31**: Weintraub, H. J. R.; Nichols, D. E. *Int. J. Quantum Chem., Quantum Biol. Symp.* **1978**, *No. 5*, 321.

(6) Recently, two cyclopropyl ring methylated homologues of **31** have been reported; see: Jacob, J. N.; Nichols, D. E. *J. Med. Chem.* **1982**, *25*, 526.

(7) (a) Synthesis: Cooper, P. D. *Can. J. Chem.* **1970**, *48*, 3882. (b) Pharmacology: Walters, G. C.; Cooper, P. D. *Nature (London)* **1968**, *218*, 298. Copper, P. D.; Walters, G. C. *Nature (London)* **1972**, *238*, 96.

(8) SAR of hallucinogens have recently been reviewed; see: (a) Nichols, D. E. *J. Pharm. Sci.* **1981**, *70*, 839. (b) Gupta, S. P.; Singh, P.; Bindal, M. C. *Chem. Rev.* **1983**, *83*, 633. (c) Nichols, D. E.; Glennon, R. A. In *Hallucinogens: Neurochemical, Behavioral and Clinical Perspectives*; Jacobs, B. L., Ed.; Raven: New York, 1984; p 95.

(9) For discussions of the experimental design and the underlying concept, 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) Andén, N.-E.; Carlsson, A.; Häggendal, J. *Annu. Rev. Pharmacol.* **1969**, *9*, 119. (c) Neff, N. H.; Neckers, L. M. *Adv. Exp. Med. Biol.* **1981**, *133*, 445.

(10) For reviews on the reactions and the synthesis of cyclopropanes, see: (a) Wendisch, D. In *Methoden der Organischen Chemie (Houben-Weyl)*, 4th ed.; Müller, E., Ed.; Georg Thieme: Stuttgart, 1971; Vol. IV, Part 3, p 15. (b) Boyle, P. H. In *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Ansell, M. F., Ed.; Elsevier: Amsterdam, 1974; Vol. IIA, Suppl., p 9 and also Vol. IIA of this series. (c) Halton, B. *Alicyclic Chem.* **1978**, *6*, 1 and the earlier volumes of this series. (d) Cooper, K. *Gen. Synth. Methods* **1980**, *3*, 227 and the earlier volumes of this series. (e) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React. (N.Y.)* **1973**, *20*, 1. (f) Bestmann, H. J.; Schmid, G.; Kisielowski, L. *Isr. J. Chem.* **1982**, *22*, 45.

(11) Derivatives of *trans*-2-phenylcyclopropylamine have also been synthesized by other methods than through *trans*-2-phenylcyclopropanecarboxylic acids: (a) By palladium(II) acetate catalyzed cyclopropanation of appropriate enamines with a large excess of diazomethane. The reported yields were low (10%); see ref 4a. (b) By an addition–elimination reaction of cinnamyl phenyl ether with lithium dialkylamides; see: Larcheveque, M.; Guillaumet, G.; Cuvigny, T.; Caubère, P. *Bull. Soc. Chim. Fr.* **1975**, 2275.

(12) See, for example, ref 1 and: (a) Burger, A.; Fitchett, G. T. *J. Am. Chem. Soc.* **1952**, *74*, 3415. (b) Kaiser, C.; Lester, B. M.; Zirkle, C. L.; Burger, A.; Davis, C. S.; Delia, T. J.; Zirngibl, L. *J. Med. Pharm. Chem.* **1962**, *5*, 1243. (c) Borne, R. F.; Forrester, M. L.; Waters, I. W. *J. Med. Chem.* **1977**, *20*, 771.

(13) See, for example: (a) Kaiser, C.; Trost, B. M.; Beeson, J.; Weinstock, J. *J. Org. Chem.* **1965**, *30*, 3972 and ref 5c and 7a.

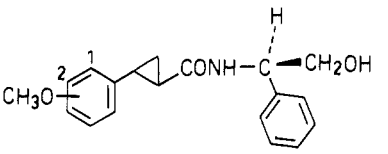
(14) The use of various metal catalysts, in the cyclopropanation of styrene with ethyl diazoacetate, gave improved yields of ethyl 2-phenylcyclopropanecarboxylate, but had only minor effects on the stereoselectivity (trans:cis ratios 0.9–2.3); see: Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssié, P. *J. Org. Chem.* **1980**, *45*, 695. Doyle, M. P.; Tamblyn, W. H.; Buhro, W. E.; Dorow, R. L. *Tetrahedron Lett.* **1981**, *22*, 1783. See also ref 15a.

(15) (a) Paulissen, R.; Hubert, A. J.; Teyssié, P. *Tetrahedron Lett.* **1972**, 1465. (b) This reaction has also been used for stereospecific cyclopropanation of methyl *trans*-cinnamates; see: Evans, D. A.; Tanis, S. P.; Hart, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 5813 and ref 3b.

amines were prepared as outlined in Scheme I. The required starting materials, the methyl *trans*-cinnamates **33a–d**, were prepared by a Knoevenagel condensation of malonic acid and the appropriate substituted benzaldehydes followed by esterification of the acids.[16] The cyclopropanation (pathway I, Scheme I) proceeded smoothly and gave, after alkaline hydrolysis, good yields (75–92%) of the substituted *trans*-2-phenylcyclopropanecarboxylic acids. The subsequent Curtius rearrangement (pathway II, Scheme I) was accomplished by use of diphenylphosphoryl azide[22] in *tert*-butyl alcohol. The *tert*-butyl carbamates thus formed were hydrolyzed in dilute hydrochloric acid to give the *trans*-2-phenylcyclopropylamines in moderate yields (48–72%). The trans stereochemistry of the amines was confirmed by analysis of the ^{1}H NMR spectra (Table I).

Reductive methylation[23] of the primary amines **2** and **12** with formaldehyde and $NaCNBH_3$ afforded the *N,N*-dimethyl derivatives **3** and **13** (pathway III, Scheme I). All other N,N-dialkylations[24] were performed by treating the primary amines with the appropriate alkyl halide (pathway IV, Scheme I). The resulting N,N-dialkylated methoxy compounds were demethylated in 47% aqueous HBr to furnish the desired phenols.

In order to prepare the enantiomers of compounds **8** and **18**, we resolved the carboxylic acids **1** and **11** via the diastereomeric amides **34/35** and **36/37**; the racemic carboxylic acids **1** and **11** were converted to the corresponding acyl chlorides, which were allowed to react with (*R*)-phenylglycinol.[25] The diastereomeric pairs of amides thus



34/35: 2-OCH_3
36/37: 3-OCH_3

formed, **34/36** and **36/37**, were separated by use of flash chromatography.[26] The choice of (*R*)-phenylglycinol as the alcohol component was based on its successful use in resolutions of other racemic carboxylic acids and the ease of cleavage of obtained diastereomeric amides under acidic conditions (*N,O*-acyl transfer occurs).[25b] Acid-catalyzed hydrolysis of **34–37** afforded, in high yields, the enantiomers of carboxylic acids **1** and **11**, which were converted to the enantiomers of compounds **8** and **18** according to the reaction sequence outlined in Scheme I. The preparation methods and physical data of the synthesized compounds are summarized in Table II.

The absolute configurations of (–)-**8** and (–)-**18** were established by means of single-crystal X-ray analysis. Both compounds were found to have the 1*R*,2*S* configuration (Figure 1). An indication of the absolute configuration was obtained from the elution order of the diastereomeric amides **34/35** and **36/37** according to the guidelines postulated by Helmchen and co-workers.[27]

Pharmacology

The compounds were tested in reserpinized rats by use of a previously described biochemical test method.[9a] Behavioral observations were made throughout the experiments.

The in vivo biochemical test method utilizes the well-established phenomenon of receptor-mediated feedback inhibition of the presynaptic neuronal activity.[9b,c,28] Thus, the synthesis rate of 5-HT is inhibited by 5-HT agonists. Similarly, the synthesis of DA and norepinephrine (NE) is inhibited by agonists activating DA and NE receptors, respectively. The 5-HTP accumulation, following decarboxylase inhibition by means of (3-hydroxybenzyl)-hydrazine (NSD 1015), was used as an index of the rate of 5-HT synthesis in the three brain parts (limbic, striatum, and hemispheres). The DOPA accumulation was taken as an indicator of the rate of DA synthesis in DA-predominated parts (i.e., limbic system, corpus striatum) and rate of NE synthesis in the NE-dominated remaining hemispheral portions (mainly cortex).

Results and Discussion

5-HT-Receptor-Mediated Effects. The biochemical results for the compounds tested are given in Table III. Compounds that decreased the brain 5-HTP levels also produced the 5-HT-like motor syndrome[29] in the rat. The 5-HT-like behavior effects induced by 10 μmol/kg, sc, of **8** and **18** persisted after combined treatment with the monoamine depletor reserpine (5 mg/kg, ip) and the 5-HT synthesis inhibitor α-propyldopacetamide (H 22/54, 500

(16) Compounds **33a–d** were prepared according to the procedure for the synthesis of methyl *trans*-3,4,5-trimethoxycinnamate[7a] with the following results (compound, yield from the corresponding benzaldehyde, bp/mp, reported bp/mp): **33a**, 91%, 87–89 °C (0.05 mmHg), 161–163 °C (13 mmHg);[17] **33b**, 88%, 120–126 °C (0.05–0.8 mmHg), 305–307 °C (748 mmHg);[18] **33c**, 79%, 88–89 °C, 88 °C,[19] 89–90 °C;[20] **33d**, 70%, 67–69 °C, 68–69 °C.[21]

(17) Von Anwers, K. *Justus Liebigs Ann. Chem.* **1916**, *413*, 253.

(18) Posner, T. *J. Prakt. Chem.* **1910**, *82*, 425.

(19) Grob, C. A.; Csapilla, J.; Cseh, G. *Helv. Chim. Acta* **1964**, *47*, 1590.

(20) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518.

(21) Adler, E.; Björkqvist, K. *J. Acta Chem. Scand.* **1951**, *5*, 241.

(22) (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203. (b) Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1974**, *22*, 849. (c) Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1974**, *22*, 855. (d) Ninomiya, K.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1974**, *22*, 1398. (e) Saikachi, H.; Kitagawa, T. *Chem. Pharm. Bull.* **1977**, *25*, 1651. (f) This reagent did not cause any epimerization in the Curtius reaction of *cis*-2-[3,4-bis(benzyloxy)phenyl]cyclopropanecarboxylic acid; see ref 3b.

(23) 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.

(24) It should be noted that use of lithium aluminum hydride for reduction of an *N*-acyl derivative of *trans*-2-phenylcyclopropylamine led to opening of the cyclopropane ring; see: Kaiser, C.; Burger, A.; Zirngibl, L.; Davis, C. S.; Zirkle, C. L. *J. Org. Chem.* **1962**, *27*, 768. Ring opening has also been reported when the same reagent was used for reduction of Schiff bases of *trans*-2-phenylcyclopropylamine. However, alkali metal borohydrides were compatible in the reduction of *N*-cyclopropyl imines; see: Bumgardner, C. L.; Lawton, E. L.; Carver, J. G. *J. Org. Chem.* **1972**, *37*, 407. Bolesov, I. G.; Surmina, L. S.; Yuzhakov, O. N.; Levina, R. Ya. *Zh. Org. Khim.* **1974**, *10*, 1661; *Chem. Abstr.* **1974**, *81*, 135582*j*.

(25) (a) (*R*)-Phenylglycinol was prepared by reduction of D-(–)-α-phenylglycine with $LiAlH_4$ although it is commercially available (Sigma, Fluka, Aldrich, etc.). (b) The compound has been used for resolution of several carboxylic acids; see: Helmchen, G.; Nill, G.; Flockerzi, D.; Youssef, M. S. K. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 63.

(26) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(27) Helmchen, G.; Nill, G.; Flockerzi, D.; Schühle, W.; Youssef, M. S. K. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 62.

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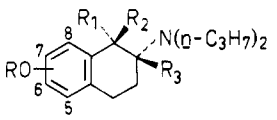
(29) Jacobs, B. L. *Life Sci.* **1976**, *19*, 777. Gerson, S. C.; Baldessarini, R. J. *Life Sci.* **1980**, *27*, 1435.

mg/kg, ip). This latter experiment rules out the possibility that indirect effects, such as, e.g., MAO inhibition, would be responsible for the behavioral effects. Consequently, 8 and 18 appear to be direct-acting 5-HT-receptor agonists.[30] Similar results were obtained with the 5-HT-receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (**38**, 8-OH-DPAT).[31] A wealth of experimental data has con-



	RO	R_1	R_2	R_3
38	8-OH	H	H	H
39	8-OCH_3	H	H	H
40	7-OH	H	H	H
41	6-OH	H	H	H
42	5-OH	H	H	H
43	5-OH	H	H	CH_3
44	5-OH	CH_3	H	H
45	5-OH	H	CH_3	H

firmed further the 5-HT-receptor activity of **38**.[31,32] The similarities in pharmacological profiles of **8**, **18**, and **38** are also supported by studies showing that these agents facilitate male rat sexual behavior, tentatively by interacting with 5-HT receptors (compare ref 33 and 34).

A hydroxy or methoxy group in the 2- or 3-position of the phenyl ring appears to be required for 5-HT-receptor-stimulating activity; the 4-hydroxy isomer **24** and the 3,4-dihydroxy isomer **28** did not decrease rat brain 5-HT synthesis (5-HTP formation) and failed to elicit clear-cut 5-HT-like behavioral effects even at high doses. The 2- and 3-methoxy derivatives **7** and **17** were about 3–4 times less potent than their phenolic analogues **8** and **18**, respectively. A similar potency ratio has been observed between the phenol **38** and its *O*-methyl derivative **39**.[35]

The DA-receptor agonists[36] 7-hydroxy- (**40**), 6-hydroxy- (**41**), and 5-hydroxy-2-(di-*n*-propylamino)tetraline (**42**) do not seem to stimulate central 5-HT receptors even at relatively high doses.[31a] However, the 8-hydroxy isomer **38** is a highly potent 5-HT-receptor agonist (see above).[31a] The hydroxy group, the benzene ring, and the nitrogen atom of **8** can be superimposed on the corresponding structural elements of the 5-HT-receptor-active 8-hydroxy-2-aminotetralin derivative **38**, thus resulting in a possible SAR rationalization of the similarities in the activity spectra displayed by these compounds. An equally good structural fit between the 5-HT-receptor agonists **18** and **38** is, however, not attainable. Instead, the 3-hydroxyphenethylamine moiety of the 5-HT agonist **18** is superimposable on the corresponding structural element of the DA-receptor agonists **40** and **42**, which do *not* seem to possess potent 5-HT-receptor-stimulating properties.[31a] The 5-HT-receptor-stimulating ability of **18** appears to be best rationalized by assuming that different conformations of **8** and **18** activate 5-HT receptors.[37]

Variations of the *N*-alkyl groups of the 2-hydroxy and 3-hydroxy isomers of *trans*-2-phenylcyclopropylamine revealed that the *N*,*N*-diethyl (**6**, **16**) and the *N*,*N*-di-*n*-propyl (**8**, **18**) derivatives were the most potent compounds in both series. The *N*,*N*-dimethyl derivatives **4** and **14** were about 15–18 times less potent than their *N*,*N*-di-*n*-propyl homologues **8** and **18**. The *N*,*N*-di-*n*-butyl derivatives **10** and **20** did not show any 5-HT stimulating properties. Similar structural requirements for the N-substituents have been observed previously in the 8-hydroxy-2-aminotetralin series.[35]

The stereoselectivity of the potent 5-HT-receptor agonist **38** is very low; (2*R*)-**38** is only twice as potent as its antipode in the 5-HTP accumulation test.[31a,35] In contrast, virtually all 5-HT-receptor activity of **8** and **18** resides in the 1*R*,2*S* enantiomers. The difference in stereoselectivity between the 2-aminotetralin **38** and the *trans*-2-phenylcyclopropylamine derivatives **8** and **18** might be due to the steric bulk of the cyclopropyl methylene group of the 1*S*,2*R* enantiomers of **8** and **18**, which may prevent proper alignments with 5-HT receptors (for a more detailed discussion, see ref 37).

Effects on DOPA Accumulation. The 5-HT-receptor-stimulating 2-hydroxy isomers, the 3,4-dihydroxy analogues, and the 4-hydroxy-substituted compounds lacked significant dopaminergic or nonadrenergic properties even at the highest doses tested. Thus, the *trans*-2-(2-hydroxyphenyl)cyclopropylamine derivatives are more selective than the 3-hydroxy isomers, which, in addition to 5-HT activity, weakly affected DA and NE systems; **14**, **16**, (±)-**18**, and (−)-**18** (0.8–1.5 μmol/kg, sc) reduced the DOPA levels in the DA-predominated brain parts (limbic system and corpus striatum) from 30% to 80% of control values and in the NE-dominated hemispheral portions from 53% to 78% of the control values. Larger doses of **16**, (±)-**18**, or (−)-**18** did not further reduce the DOPA levels. A high dose of **14** (50 μmol/kg, sc) did decrease

(30) We have not ruled out the possibility that part of the biochemical effects of **8** and **18** may be interpreted as being due to a modest inhibition of MAO. However, this possibility seems less likely since *N*,*N*-di-*n*-propyl substitution abolishes such activities in a related series of oxygenated 2-aminotetralins. Compare: Hacksell, U.; Arvidsson, L.-E.; Johansson, A. M.; Nilsson, J. L. G.; Sanchez, D.; Lindberg, P.; Wikström, H.; Svensson, K.; Hjorth, S.; Carlsson, A.; Ask, A.-L.; Ögren, S.-O. *Acta Pharm. Suec.* **1986**, *23*, 77 and ref 31.

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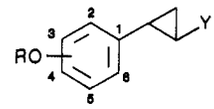
Table II. Preparation and Physical Properties of N,N-Dialkylated Phenolic *trans*-2-Phenylcyclopropylamines and Their Intermediates



no.	RO	Y	prepn meth	yield, %	mp, °C	recrystn solvents[b]	formula[c]
1	2-OCH_3	COOH	I	92	136–138[d]		$C_{11}H_{12}O_3$
(+)-1[e]	2-OCH_3	COOH	VII	97	73.5–75.5		$C_{11}H_{12}O_3$
(−)-1[e]	2-OCH_3	COOH	VII	97	74.5–75.5[d]		$C_{11}H_{12}O_3$
2	2-OCH_3	NH_2	II	63	193–194.5	A	$C_{10}H_{13}NO$·HCl
(+)-2[e]	2-OCH_3	NH_2	II	76	215–217.5	A	$C_{10}H_{13}NO$·HCl
(−)-2[e]	2-OCH_3	NH_2	II	78	215–217.5	A	$C_{10}H_{13}NO$·HCl
3	2-OCH_3	$N(CH_3)_2$	III	70	168–170	A	$C_{12}H_{17}NO$·HCl
4	2-OH	$N(CH_3)_2$	V[f]	62	191–192	B	$C_{11}H_{15}NO$·HCl
5	2-OCH_3	$N(C_2H_5)_2$	IV	56	155–156.5	B	$C_{14}H_{21}NO$·HBr
6	2-OH	$N(C_2H_5)_2$	V	48	134–134.5	B	$C_{13}H_{19}NO$·HCl
7	2-OCH_3	$N(n\text{-}C_3H_7)_2$	IV	67	158–159	B	$C_{16}H_{25}NO$·HBr
(+)-7[e]	2-OCH_3	$N(n\text{-}C_3H_7)_2$	IV	90	174–175	C	$C_{16}H_{25}NO$·HCl
(−)-7[e]	2-OCH_3	$N(n\text{-}C_3H_7)_2$	IV	88	174–175.5	C	$C_{16}H_{25}NO$·HCl
8	2-OH	$N(n\text{-}C_3H_7)_2$	V	79	190–191.5	B	$C_{15}H_{23}NO$·HBr
(+)-8[e]	2-OH	$N(n\text{-}C_3H_7)_2$	V	78	197.5–198.5	A	$C_{15}H_{23}NO$·HBr
(−)-8[e]	2-OH	$N(n\text{-}C_3H_7)_2$	V	75	197–198	A	$C_{15}H_{23}NO$·HBr
9	2-OCH_3	$N(n\text{-}C_4H_9)_2$	IV	80	95–97	B	$C_{18}H_{29}NO$·HCl
10	2-OH	$N(n\text{-}C_4H_9)_2$	V	78	156.5–157.5	B	$C_{17}H_{27}NO$·HBr
11	3-OCH_3	COOH	I	89	94–95[g]		$C_{11}H_{12}O_3$
(+)-11[e]	3-OCH_3	COOH	VII	94	oil		$C_{11}H_{12}O_3$
(−)-11[e]	3-OCH_3	COOH	VII	97	oil		$C_{11}H_{12}O_3$
12	3-OCH_3	NH_2	II	72	155–156	A	$C_{10}H_{13}NO$·HCl
(+)-12[e]	3-OCH_3	NH_2	II	68	161–162	D	$C_{10}H_{13}NO$·HCl
(−)-12[e]	3-OCH_3	NH_2	II	71	161–162	D	$C_{10}H_{13}NO$·HCl
13	3-OCH_3	$N(CH_3)_2$	III	75	169.5–171	D	$C_{12}H_{17}NO$·HCl
14	3-OH	$N(CH_3)_2$	V[f]	52	158–159	B	$C_{11}H_{15}NO$·HBr
15	3-OCH_3	$N(C_2H_5)_2$	IV	86	143–144	B	$C_{14}H_{21}NO$·HCl
16	3-OH	$N(C_2H_5)_2$	V	82	168.5–170	E	$C_{13}H_{19}NO$·HBr
17	3-OCH_3	$N(n\text{-}C_3H_7)_2$	IV	73	125.5–127	B	$C_{16}H_{25}NO$·HCl
(+)-17[e]	3-OCH_3	$N(n\text{-}C_3H_7)_2$	IV	82	143.5–145.5	B	$C_{16}H_{25}NO$·HCl
(−)-17[e]	3-OCH_3	$N(n\text{-}C_3H_7)_2$	IV	86	143.5–145.5	B	$C_{16}H_{25}NO$·HCl
18	3-OH	$N(n\text{-}C_3H_7)_2$	V	79	190.5–192	F	$C_{15}H_{23}NO$·HBr
(+)-18[e]	3-OH	$N(n\text{-}C_3H_7)_2$	V	77	203.5–204	A	$C_{15}H_{23}NO$·HBr
(−)-18[e]	3-OH	$N(n\text{-}C_3H_7)_2$	V	64	203–204	A	$C_{15}H_{23}NO$·HBr
19	3-OCH_3	$N(n\text{-}C_4H_9)_2$	IV	73	62.5–64	B	$C_{18}H_{29}NO$·HCl
20	3-OH	$N(n\text{-}C_4H_9)_2$	V	74	161.5–163	F	$C_{17}H_{27}NO$·HBr
21	4-OCH_3	COOH	I	84	113–114.5[h]		$C_{11}H_{12}O_3$
22	4-OCH_3	NH_2	II	58	180–182[i]	A	
23	4-OCH_3	$N(n\text{-}C_3H_7)_2$	IV	72	131–132.5	B	$C_{16}H_{25}NO$·HCl
24	4-OH	$N(n\text{-}C_3H_7)_2$	V	65	185–187	C	$C_{15}H_{23}NO$·HBr
25	3,4-$(OCH_3)_2$	COOH	I	75	107.5–108.5[j]		
26	3,4-$(OCH_3)_2$	NH_2	II	48	178–180[k]	D	$C_{11}H_{15}NO_2$·HCl
27	3,4-$(OCH_3)_2$	$N(n\text{-}C_3H_7)_2$	IV	76	108–110	B	$C_{17}H_{27}NO_2$·HCl
28	3,4-$(OH)_2$	$N(n\text{-}C_3H_7)_2$	V	52	146.5–147	B	$C_{15}H_{23}NO_2$·HBr

[a] Racemate unless otherwise denoted. [b] Recrystallization solvents: A, CH_3CN–C_2H_5OH; B, CH_3CN–ether; C, CH_3CN; D, CH_3CN–C_2H_5OH–ether; E, 2-C_3H_7OH–ether; F, C_2H_5OH–ether. [c] The elemental analyses (C, H, and N) for all new compounds were within ±0.4% of the theoretical values. [d] Reported as partially resolved (ref 53; $[\alpha]_D$ −13.7°; mp 136–136.5 °C). [e] For optical rotation, see Experimental Section. [f] Demethylation performed at 100 °C (bath temperature) for 2.5 h. [g] Reported without physical data (ref 54, 55). [h] Literature mp 112–113 °C (ref 56); literature mp 114–114.5 °C (ref 57). [i] Literature mp 178.5–180.5 °C (ref 12b). [j] Literature mp 105–105.5 °C (ref 12a). [k] Literature mp of base 68–70 °C (ref 12a).

DOPA levels in the limbic system to about 55% of control values and the DOPA levels in the striatal brain parts to around 30% of controls. The effects after **14**, **16**, and **18** may or may not be due to direct DA-receptor stimulation. It should, however, be noted that classical full DA-receptor agonists[36] like apomorphine decrease DOPA levels to around 20–30% of controls in the limbic and striatal brain parts and do not affect the DOPA levels in the hemispheral brain portions.[38]

Erhardt has suggested[39] that the inactivity of **30** at DA receptors is due to the steric bulk of the cyclopropyl group. The results obtained in the present investigation with compounds like **18** and **28** tend to support this idea, since **18**, **28**, and **30** probably can adopt "DA-receptor-active" phenethylamine conformations.[40,41] It is noteworthy that **43** appears to lack central DA-stimulating properties[42] and that the C1-methylated 2-aminotetralins **44** and **45** are

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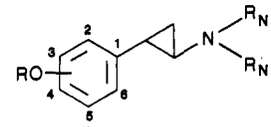
(39) Erhardt, P. W. *J. Pharm. Sci.* **1980**, *69*, 1059. Erhardt, P. W. *Acta Pharm. Suec. Suppl. n2*, **1983**, 56.

(40) It has been suggested that near coplanarity of the phenyl ring and the ethylamine side chain of DA analogues is required for DA agonism; see ref 36c,d.

(41) The barrier for internal rotation about the phenyl and the cyclopropyl ring of *trans*-2-phenylcyclopropylamines is small (see ref 37).

(42) Hacksell, U.; Arvidsson, L.-E.; Johansson, A. M.; Nilsson, J. L. G.; Sanchez, D.; Andersson, B.; Lindberg, P.; Wikström, H.; Hjorth, S.; Svensson, K.; Carlsson, A. *Acta Pharm. Suec.* **1985**, *22*, 65.

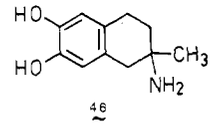
Table III. Effects of N,N-Dialkylated Phenolic *trans*-2-Phenylcyclopropylamines on Rat Brain 5-HTP Formation



			5-HTP accumulation:[b] ED_{50},[c,d] μmol/kg, sc		
no.[a]	RO	R_N	limbic	striatum	hemispheres (cortex)
4	2-OH	CH_3	6.20 (2.15–17.9)	3.45 (0.78–15.3)	9.31 (0.78–15.3)
6	2-OH	C_2H_5	0.82 (0.40–1.68)	1.20 (0.32–4.54)	0.80 (0.31–2.08)
7	2-OCH_3	n-C_3H_7	0.93 (0.12–6.99)	*e*	0.72 (0.06–9.29)
8	2-OH	n-C_3H_7	0.41 (0.10–1.61)	0.36 (0.10–1.25)	0.36 (0.11–1.17)
(+)-8	2-OH	n-C_3H_7	>50.0	14.5 (4.72–44.3)	>50.0
(−)-8	2-OH	n-C_3H_7	0.28 (0.07–1.13)	0.26 (0.05–1.20)	0.38 (0.09–1.61)
10	2-OH	n-C_4H_9	>50.0	>50.0	>50.0
14	3-OH	CH_3	10.8 (3.40–34.4)	8.59 (2.38–31.0)	25.1 (4.45–140)
16	3-OH	C_2H_5	0.34 (0.12–0.96)	0.32 (0.10–0.94)	0.40 (0.15–1.08)
17	3-OCH_3	n-C_3H_7	2.06 (0.55–7.75)	1.17 (0.33–4.14)	1.43 (0.31–6.64)
18	3-OH	n-C_3H_7	0.66 (0.31–1.41)	0.47 (0.19–1.13)	0.58 (0.10–1.65)
(+)-18	3-OH	n-C_3H_7	>50.0	>50.0	>50.0
(−)-18	3-OH	n-C_3H_7	0.34 (0.10–1.23)	0.28 (0.12–0.69)	0.35 (0.16–0.76)
20	3-OH	n-C_4H_9	>50.0	>50.0	>50.0
24	4-OH	n-C_3H_7	>50.0	>50.0	>50.0
28	3,4-$(OH)_2$	n-C_3H_7	>50.0	>50.0	>50.0
38			0.061[f]	0.065[f]	0.077[f]

[a] Racemate unless otherwise denoted. [b] For experimental details, see ref 9. [c] Dose giving a half-maximal decrease of 5-HTP formation in the rat brain part, estimated from a dose-response curve comprising four to six dose levels (n = 3–4). The maximal reduction of the 5-HTP level was empirically found to be 50% from the control levels (240 ± 9 ng of 5-HTP/g of limbic tissue, 155 ± 6 ng of 5-HTP/g of striatal tissue, and 136 ± 6 ng of 5-HTP/g of hemispheral tissue, n = 26–30). [d] Shown in parentheses are the 95% confidence limits of the ED_{50} values. [e] Available data do not allow proper evaluation of ED_{50} with confidence limits. [f] Values are from ref 35.

DA-receptor agonists of rather low potencies.[43] In addition, **46**, the C2-methylated analogue of 2-amino-6,7-



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dihydroxytetralin (6,7-ADTN), seems to be inactive as a DA_1-receptor agonist.[44] Thus, introduction of steric bulk in the vicinity of the nitrogen frequently decreases or abolishes DA-receptor activity in phenethylamine-based DA-receptor agonists.

Conclusions. In the present series of *trans*-2-phenylcyclopropylamines, aromatic C2- or C3-oxygen substituents and *N,N*-diethyl or *N,N*-di-*n*-propyl substituents gave potent 5-HT-receptor agonists. The 1*R*,2*S* enantiomers of *trans*-2-(2-hydroxyphenyl)-*N,N*-di-*n*-propylcyclopropylamine (**8**) and the 3-hydroxy isomer **18** displayed 5-HT-receptor-stimulating activity, while the enantiomers were found to be inactive. In contrast, the potent 5-HT-receptor agonist **38** is only weakly stereoselective. The high stereoselectivity of **8** and **18** may be due to the steric bulk of the methylene group of the cyclopropyl ring, which might prevent a proper alignment with 5-HT receptors.

The 2-hydroxy-substituted derivatives appear to be more selective pharmacologically than the other 5-HT-receptor agonists presented here; the latter compounds also seem to affect central DA and NE systems.

Experimental Section

Chemistry. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. ^1H NMR spectra recorded on JEOL FX 90Q, JEOL JNM-FX 200, or JEOL GX-400 spectrometers and mass spectra recorded at 70 eV on a LKB 9000 spectrometer were in accordance with the assigned structures. Optical rotations were obtained by use of a Perkin-Elmer 241 polarimeter. The elemental analyses (C, H, N) for the new substances (Mikro Kemi AB, S-750 19 Uppsala, Sweden) were all within ±0.4% of the theoretical values. For purity tests, TLC was performed on fluorescent silica gel or alumina plates. For all compounds, only one spot (visualized by UV light and I_2 vapor) was obtained.

***trans*-2-(2-Methoxyphenyl)cyclopropanecarboxylic Acid (1). Method I.** Diazomethane (**CAUTION**[45]) was prepared as previously described;[45] a solution of 22.3 g (104 mmol) of *N*-nitroso-*N*-methyl-4-toluenesulfonamide in ether (125 mL) was slowly added to a heated mixture of potassium hydroxide (6 g, 107 mmol), ether (10 mL), water (10 mL), and 2-(2-ethoxyethoxy)ethane (35 mL). The formed ether solution of diazomethane was continuously distilled into a stirred cooled (ice–salt bath) solution of 6.00 g (31.2 mmol) of methyl 2-methoxycinnamate (**33a**)[16] in ether (125 mL) and dichloromethane (50 mL), containing 50 mg of palladium(II) acetate. The reaction mixture was kept at −10 to −5 °C (bath temperature) until all diazomethane had been distilled (45 min). The cooling was discontinued after 1 h, and the reaction mixture was filtered (Celite) and concentrated in vacuo. The remaining oil was purified on a short alumina column eluted with ether. After evaporation of volatiles, the residual methyl *trans*-2-(2-methoxyphenyl)cyclopropanecarboxylate (6.4 g, ≈100%) was hydrolyzed by use of 10 mL of a 50% sodium hydroxide solution in methanol (125 mL) (room temperature, 4 h). The reaction mixture was poured into a stirred mixture of 1 L of water, 40 mL of concentrated HCl, and ice. The precipitated carboxylic acid was collected by filtration and washed with water until the filtrate had approximately neutral pH. The white solid was dried to afford 5.5 g (93%) of **1**.

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***trans*-2-(2-Methoxyphenyl)cyclopropylamine (2). Method II.** A stirred solution of 5.00 g (26.0 mmol) of carboxylic acid 1, 6.19 mL (28.6 mmol) of diphenylphosphoryl azide, and 4.00 mL (28.7 mmol) of triethylamine in 50 mL of dry *tert*-butyl alcohol was heated at 90 °C (bath temperature) for 27 h. The volatiles were evaporated, and a 10% sodium carbonate solution was added. The alkaline solution was extracted with ether (4 × 80 mL), and the combined ether layers were dried (sodium sulfate), filtered, and concentrated in vacuo to afford the crude *tert*-butyl carbamate. It was purified by use of flash chromatography[26] on a silica gel column eluted with ether–petroleum ether (1:1) to give 5.07 g of the intermediate *tert*-butyl carbamate, which was treated with 125 mL of 1 N hydrochloric acid at 100 °C (bath temperature) for 5 h. The acidic solution was washed with ether (2 × 100 mL) and then alkalinized with saturated aqueous potassium carbonate. The amine was extracted with ethyl acetate (3 × 175 mL), and the combined organic layers were dried (sodium sulfate and then potassium carbonate), filtered, and concentrated in vacuo. The residue was dissolved in ether and treated with ethereal HCl. The precipitate was collected by filtration to afford 2.85 g (55%) of **2**·HCl as an off-white powder. Recrystallization from acetonitrile–ethanol–ether gave an analytical sample.

***trans*-2-(2-Methoxyphenyl)-*N*,*N*-dimethylcyclopropylamine (3). Method III.** Compound **2**·HCl (0.40 g, 2.0 mmol) was dissolved in 12 mL of methanol, and 0.76 mL (10 mmol) of 37% aqueous formaldehyde and 0.42 g (6.0 mmol) of 90% sodium cyanoborohydride were added. The pH was adjusted to 6 by addition of acetic acid. The mixture was stirred at room temperature for 24 h, and the volatiles were evaporated. Addition of 20 mL of a 10% aqueous sodium carbonate solution, extraction with ether (3 × 20 mL), drying (potassium carbonate), filtration, and evaporation of volatiles gave an oil. The crude product was purified on a silica gel column eluted with ether by use of flash chromatography. The product was treated with ethereal HCl to afford 0.29 g (63%) of **3**·HCl as a white solid.

***trans*-2-(2-Methoxyphenyl)-*N*,*N*-di-*n*-propylcyclopropylamine (7). Method IV.** A mixture of 0.36 g (2.2 mmol) of **2**, 0.76 mL (7.9 mmol) of 1-iodopropane, and 1.50 g (10.9 mmol) of finely ground potassium carbonate in 10 mL of acetonitrile was stirred at room temperature for 4 days. Ether (15 mL) was added, and insoluble material was removed by filtration. The filtrate was concentrated in vacuo, and the residue was chromatographed on an alumina column eluted with ether–petroleum ether (1:2). Precipitation of the base with ethereal HCl afforded 0.41 g (66%) of **7**·HCl as a white solid. An analytical sample was obtained by recrystallization from acetonitrile–ether.

***trans*-2-(2-Hydroxyphenyl)-*N*,*N*-di-*n*-propylcyclopropylamine (8). Method V.** A stirred solution of 0.45 g (1.6 mmol) of **7**·HCl in 15 mL of freshly distilled 47% aqueous HBr was heated for 2 h at 110 °C (bath temperature) under nitrogen. The solution was concentrated in vacuo, and 20 mL of ethanol–toluene (1:1) was added. Volatiles were evaporated, and the resulting solid was recrystallized from acetonitrile–ether to afford 0.40 g (80%) of **8**·HBr as white crystals.

(1*R*,2*S*)-*N*-[(*R*)-2-Hydroxy-1-phenylethyl]-2-(2-methoxyphenyl)cyclopropanecarboxamide (34) and (1*S*,2*R*)-*N*-[(*R*)-2-Hydroxy-1-phenylethyl]-2-(2-methoxyphenyl)cyclopropanecarboxamide (35). Method VIa. Carboxylic acid **1** (8.00 g, 41.6 mmol) was converted to the corresponding acyl chloride by slow addition of thionyl chloride (8.00 mL, 110 mmol) at room temperature. The reaction mixture was stirred at 55 °C for 45 min and then concentrated in vacuo. Dichloromethane (25 mL) was added, and volatiles were evaporated. The residual acyl chloride of **1** in 75 mL of dichloromethane was slowly added (30 min) to a stirred ice-cooled solution of 6.30 g (45.9 mmol) of (*R*)-2-amino-2-phenylethanol[25] and 8.70 mL (62.4 mmol) of triethylamine in 250 mL of dichloromethane. After 30 min at 0 °C, the reaction mixture was left overnight at room temperature and then washed with 250 mL of 1 N hydrochloric acid, 250 mL of saturated aqueous sodium carbonate, and 150 mL of saturated aqueous sodium chloride. The organic layer was dried (magnesium sulfate) and concentrated in vacuo. The residual brown-yellow solid was passed through a short silica gel column with ethyl acetate as eluant to afford 12.2 g of a mixture of **34** and **35** as a light yellow solid. The mixture was divided into three portions, and the diastereomers were separated on a silica gel (220 g) column (88-mm o.d., 20-mL fractions) by use of flash chromatography. The samples were applied as solutions in chloroform, and the columns were eluted with ether–ethyl acetate (2:1). The three runs gave 4.91 g of the first-eluted compound (**34**) and 4.17 g of **35**. Additional portions of **34** (0.83 g) and **35** (1.42 g) were recovered from the impure fractions (2.52 g). This procedure gave 5.74 g (44%) of **34** mp 147–148 °C; $[\alpha]^{22}_D$ −122.5° (*c* 1.33, $CHCl_3$)] and 5.59 g (43%) of **35** [mp 123.5–124.5 °C; $[\alpha]^{22}_D$ +93.5° (*c* 1.31, $CHCl_3$)].

Table IV. Crystal Data for (−)-8·HBr and (−)-18·HBr

	(−)-8·HBr	(−)-18·HBr
formula	$C_{15}H_{23}NO$·HBr	$C_{15}H_{23}NO$·HBr
space group	$P2_12_12_1$	$P2_1$
a, Å	10.052 (1)	10.259 (1)
b, Å	7.653 (1)	7.845 (5)
c, Å	21.247 (5)	10.265 (10)
β, deg		102.46 (1)
d_{calcd}, g cm^{-3}	1.28	1.29
μ, cm^{-1}	36.9	37.4

(1*R*,2*S*)-*N*-[(*R*)-2-Hydroxy-1-phenylethyl]-2-(3-methoxyphenyl)cyclopropanecarboxamide (36) and (1*S*,2*R*)-*N*-[(*R*)-2-Hydroxy-1-phenylethyl]-2-(3-methoxyphenyl)cyclopropanecarboxamide (37). Method VIb. Carboxylic acid **11** (8.00 g, 41.6 mmol) was converted to a mixture of the diastereomeric amides **36** and **37** by use of the same procedure as described for the preparation of **34**/**35**. Prepurification on a short silica gel column gave 11.5 g of a yellowish solid. The mixture of **36** and **37** was divided into three portions and separated on a silica gel (220 g) column (88-mm o.d., 20-mL fractions) by use of flash chromatography. The samples were applied as solutions in warm ethyl acetate, and the columns were eluted with ethyl acetate. Fractions containing a mixture of **36** and **37** were pooled and chromatographed further. This procedure afforded 4.63 g (36%) of the first-eluted compound (**36**) [mp 147.5–149.0 °C; $[\alpha]^{22}_D$ −210.5° (*c* 1.14, $CHCl_3$)] and 4.56 g (35%) of **37** [mp 155.0–156.5 °C; $[\alpha]^{22}_D$ +176.5° (*c* 1.24, $CHCl_3$).

Estimation of Diastereomeric Purities of Amides 34–37. HPLC analyses of the compounds were performed by use of a Waters 5 Si 10 column (**34** and **35**) or a Waters 8 Si 5 column (**36** and **37**) with hexane–ethyl acetate–ethanol (80:15:5) as the mobile phase, working in the pressure range 1000–3000 psi and with a flow rate of 2 mL/min. Detections were made by a Waters Model 440 UV monitor. The diastereomeric excess (de), which was estimated by comparing peak areas (height × width at half-height), was found to be >98% de for **34** (t_R = 2.2 min), **35** (t_R = 3.0 min), **36** (t_R = 5.2 min), and **37** (t_R = 6.8 min).

(1*R*,2*S*)-2-(2-Methoxyphenyl)cyclopropanecarboxylic Acid [(−)-1]. Method VII. A solution of 5.50 g (17.7 mmol) of **34** in 100 mL of dioxane and 100 mL of 3 N sulfuric acid was stirred at 100 °C (bath temperature) for 24 h. The reaction mixture was concentrated in vacuo to half the volume and then extracted with ether (3 × 75 mL). The combined ether layers were dried (magnesium sulfate) and filtered. The volatiles were evaporated, and the remaining solid was chromatographed on a silica gel column eluted with ether to provide 3.30 g (97%) of (−)-**1** as a white solid.

Absolute Configuration Determination of (−)-8·HBr and (−)-18·HBr by Single-Crystal X-ray Analysis. Crystals of (−)-**8**·HBr and (−)-**18**·HBr were grown from acetonitrile–ethanol solutions. Crystals with the dimensions 0.30 × 0.10 × 0.02 mm [(−)-**8**·HBr] and 0.34 × 0.05 × 0.05 mm [(−)-**18**·HBr] were used for data collection with an Enraf-Nonius CAD4F-11 diffractometer. The angular settings of 25 [(−)-**8**·HBr] and 12 [(−)-**18**·HBr] reflections ($6° < \theta < 38°$) were measured to calculate the lattice parameters (cf. Table IV for crystal data). For each compound, two sets of independent reflections with $\theta < 60°$ were measured by the $\theta/2\theta$ scan method using monochromated Cu Kα radiation. Three intensity control reflections, which were measured every 2 h, indicated no crystal decay of (−)-**8**·HBr but a slight decay (3%) of the crystal of (−)-**18**·HBr. For (−)-**8**·HBr, a total of 2569 reflections were recorded and, of these, 1001 reflections with $I > 3\sigma(I)$ were considered observed. For (−)-**18**·HBr, a total of 2528 reflections were recorded and, of these, 1860 with $I > 3\sigma(I)$ were considered observed. All intensities were corrected for Lorentz

and polarization effects but not for absorption or extinction.

The structure was solved by a combination of the Patterson heavy atom method and direct methods using the program DIRDIF,[46] which provided the non-hydrogen atom positions. All hydrogen atom positions except those for hydrogen atoms connected to methyl groups were obtained from Fourier difference synthesis maps. Refinement was carried out by the full-matrix least-squares method using anisotropic temperature factors for the non-hydrogen atoms. The hydrogen atoms were assigned a temperature factor equal to the corresponding parent atom U_{eq} value. The hydrogen atom parameters were not refined. In order to determine the absolute configurations of (-)-8·HBr and (-)-18·HBr, we introduced anomalous dispersion factors[47] for the non-hydrogen atoms. The atomic parameters of the non-hydrogen atoms for both enantiomers were then refined. C14 of (-)-18·HBr did not respond correctly to the refinement, and its parameters were therefore kept fixed during the final cycles of the refinement. Two sets of unique reflections (h,k,l, $h-k,l$) were used in the refinement, and nonobserved reflections were allowed to contribute when $F_c > F_o$. When the refinement of (-)-8·HBr was finished, the residuals for the 1*R*,2*S* and 1*S*,2*R* enantiomers were calculated to be $R = 0.045$ and $R = 0.049$ ($R_w = 0.058$ and $R_w = 0.062$), respectively. Corresponding residuals for the 1*R*,2*S* and 1*S*,2*R* enantiomers of (-)-18-HBr were $R = 0.053$ ($R_w = 0.064$) and $R = 0.058$ ($R_w = 0.071$), respectively. When Hamilton's test is used,[48] the ratio $R_w(1S,2R)/R_w(1R,2S)$, which is 1.089 for (-)-8·HBr and 1.109 for (-)-18·HBr, is sufficiently great to reject the 1*S*,2*R* enantiomers at the 0.005 significance level. Furthermore, among the 41 Bijvoet pairs for the 1*R*,2*S* enantiomer of (-)-8·HBr and among the 52 Bijvoet pairs for the 1*R*,2*S* enantiomer of (-)-18·HBr for which $F_c(h,k,l) - F_c(h-k,l) > 1.0$, 38 and 48 of the respective F_c differences had the same sign as the corresponding F_o differences. The weighting scheme used in the later part of the refinement was $w = 1/(1 + ((|F_o| - 26)/28)^2)$.[49] The form factors used were those given by Cromer and Mann.[50] All calculations have been performed on a DEC-system-10 computer using mainly the X-ray 72 program system.[51] The molecular conformation and atomic labeling scheme for the two compounds are shown in Figure 1.

Optical Rotations. The resolved compounds presented in Table II have the following optical rotations ($[\alpha]^{22}_D$, concentration, solvent): (+)-1, +194.7° (*c* 0.5, $CHCl_3$); (-)-1, -196.5° (*c* 0.5, $CHCl_3$); (+)-2·HCl, +44.3° (*c* 1.7, CH_3OH); (-)-2·HCl, -43.7° (*c* 1.6, CH_3OH); (+)-7·HCl, +10.4° (*c* 1.1, CH_3OH); (-)-7·HCl, -10.0° (*c* 1.3, CH_3OH); (+)-8·HBr, +7.5° (*c* 1.1, CH_3OH); (-)-8·HBr, -7.1° (*c* 1.1, CH_3OH); (+)-11, +295.9° (*c* 1.2, $CHCl_3$); (-)-11, -304.1° (*c* 1.1, $CHCl_3$); (+)-12·HCl, +72.4° (c 1.8, CH_3OH); (-)-12·HCl, -69.8° (*c* 1.8, CH_3OH); (+)-17·HCl, +75.2° (*c* 1.3, CH_3OH); (-)-17·HCl, -75.5° (*c* 1.3, CH_3OH); (+)-18·HBr, +67.0° (*c* 1.1, CH_3OH); (-)-18·HBr, -67.3° (*c* 1.1, CH_3OH).

Pharmacology. Animals used in the experiments were male rats of Sprague–Dawley strain (ALAB, Stockholm) weighing 200–300 g. The 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. Compound 28·HBr was dissolved under nitrogen in saline containing ascorbic acid. Reserpine was dissolved in a few drops of glacial acetic acid and made up to the volume with 5.5% glucose. Injection volumes were 5 or 10 mL/kg, and injection solutions had approximately neutral pH.

The biochemical experiments were performed as previously described[9a] with one exception; the brain levels of 5-HTP and DOPA were analyzed by use of HPLC with electrochemical detection.[52] For biochemical results and experimental details, see Table III.

Acknowledgment. We thank Torgny Fornstedt for skillful synthetic assistance and Ingrid Bergh, Boel Göransson, and Lucia Gaete for skillful assistance in the pharmacological testing. We are indebted to Sven-Olof Larsson (Pharmacia) for 200-MHz ^1H NMR spectra and to Prof. Lennart Kenne for a 400-MHz ^1H NMR spectrum. The financial support from Bengt Lundkvists Minne, Astra Läkemedel AB, The Swedish Board of Technical Development, The Swedish Medical Research Council (Grants No. 155 and 7486), Knut and Alice Allenberg's Stiftelse, Anna Ahrenbergs Stiftelse, Magnus Bergvalls Stiftelse, Stiftelsen Lars Hiertas Minne, T. och R. Söderbergs Stiftelser, Gyllenstiernska Krapperups Stiftelsen, Helge Ax:son Johnsons Stiftelse, The Swedish Academy of Pharmaceutical Sciences, and the Medical Faculty, University of Göteborg, is gratefully acknowledged.

Registry No. 1, 110826-01-2; 1-(+), 110901-85-4; 1-(-), 5034-03-7; 1 (methyl ester), 110826-41-0; 1 (*tert*-butyl carbamate), 110826-42-1; 1 (acyl chloride), 110826-43-2; **2**, 110826-02-3; **2**-(+), 110901-86-5; **2**-(-), 110901-87-6; **3**, 110826-03-4; **4**, 110826-04-5; 4 (freebase), 110826-27-2; **5**, 110826-05-6; **6**, 110826-06-7; **6** (free base), 110826-28-3; **7**, 110826-07-8; **7**-(+), 110902-70-0; **7**-(-), 110901-88-7; **7** (free base), 110826-29-4; **8**, 110826-08-9; **8**-(+), 111001-14-0; **8**-(-), 111001-15-1; **8** (free base), 110826-30-7; **8**-(+) (free base), 110901-81-0; **8**-(-) (free base), 110901-82-1; **9**, 110826-09-0; **10**, 110826-10-3; **10** (free base), 110826-33-0; **11**, 96728-38-0; **11**-(+), 110901-89-8; **11**-(-), 110901-90-1; **12**, 110826-11-4; **12**-(+), 110901-91-2; **12**-(-), 110901-92-3; **13**, 110826-12-5; **14**, 110826-13-6; **14** (free base), 110826-34-1; **15**, 110826-14-7; **16**, 110826-15-8; **16** (free base), 110826-35-2; **17**, 110826-16-9; **17**-(+), 110901-93-4; **17**-(-), 110901-94-5; **17** (free base), 110826-36-3; **18**, 110826-17-0; **18**-(+), 111001-16-2; **18**-(-), 111001-17-3; **18** (free base), 110826-37-4; **18**-≤(+) (free base), 110901-83-2; **18**-(-) (free base), 110901-84-3; **19**, 110826-18-1; **20**, 110826-19-2; **20** (free base), 110826-38-5; **21**, 110826-20-5; **22**, 110826-21-6; **23**, 110850-48-1; **24**, 110826-22-7; **24** (free base), 110826-39-6; **25**, 110826-23-8; **26**, 110826-24-9; **27**, 110826-25-0; **28**, 110826-26-1; **28** (free base), 110826-40-9; **33a**, 98288-15-4;)**33b**, 38693-90-2; **33c**, 3901-07-3; **33d**, 30461-77-9; **34**, 110826-31-8; **35**, 110901-79-6; **36**, 110826-32-9; **37**, 110901-80-9; (*R*)-2-amino-2-phenylethanol, 56613-80-0.

Supplementary Material Available: Positional and thermal parameters, bond lengths, bond angles, and details about the determination of absolute configuration (8 pages); observed and calculated structure factors (38 pages). Ordering information is given on any current masthead page.

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