sions that give predictions significantly better than chance are retained in the model.

Finally, we have shown in two of the four examples that the predicted activities for new sets of compounds that were not involved in the model development were close to the actually observed values, much closer than would be expected by chance (Figures 2 and 4).

With the current view on peptides, one would expect the variation in conformation of the peptides to have a great influence on the biological activity. The present description does not explicitly take the conformation into account. Hence, the success of the modelling of three out of four peptide families may be interpreted in either of three ways: (1) Conformation is not important in these families. (2) Conformation is important, but in some way implicitly described by the z scales. (3) Conformation is important but all peptides in each set can adopt the bioactive conformation with low energy.

We refrain from taking a strong position for one of these three possibilities and just note that in these examples the prediction of the biological activities of small flexible peptides seems to be considerably simpler than can be expected from their conformation flexibilities.

For the future development of peptide QSAR, we have proposed the estimation of improved descriptors for the amino acids and also an extension to noncoded amino acids and other fragments of interest.

Another area for improvement is the often overlooked problem of how to construct a series of peptide analogues suited for structure–activity studies. Here we propose fractional factorial designs as a possibility for constructing informative training sets. This design problem has also been discussed in a separate paper.[33d]

A designed test series can be used in different peptide families. Thus a set of designed peptide fragments (as those 16 proposed in Table VI) can be introduced as tetrapeptide units in different peptide families. Such predesigned sets of peptide fragments simplify the synthesis of multipositionally varied peptides. Furthermore, for a design with only coded amino acids, a set of codon sequences can be constructed that corresponds to a set of designed peptide fragments. The rapid development of protein engineering[43] may then make it possible to produce designed sets of mature proteins and enzymes for QSAR studies.

Acknowledgment. Grants from the Swedish Natural Science Council (NFR), the Swedish Council for Planning and Coordination of Research (FRN), and the National Swedish Board for Technical Development (STU) are gratefully acknowledged.

Registry No. A, 56-41-7; V, 72-18-4; L, 61-90-5; I, 73-32-5; P, 147-85-3; F, 63-91-2; W, 73-22-3; M, 63-68-3; K, 56-87-1; R, 74-79-3; H, 71-00-1; G, 56-40-6; S, 56-45-1; T, 72-19-5; C, 52-90-4; Y, 60-18-4; N, 70-47-3; Q, 56-85-9; D, 56-84-8; E, 56-86-0; Bradykinin, 58-82-2.

Supplementary Material Available: Tables containing the property matrix for the amino acids, PLS model parameters, and biological activities for the oxytocins, pepstatins, and pseudopeptides (8 pages). Ordering information is given on any current masthead page.

(43) Fox, J. L. *ASM News* **1985**, *51*, 566.

C3-Methylated 5-Hydroxy-2-(dipropylamino)tetralins: Conformational and Steric Parameters of Importance for Central Dopamine Receptor Activation

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C3-Methyl-substituted derivatives of the potent dopamine (DA) receptor agonist 5-hydroxy-2-(di-*n*-propylamino)tetralin (5-OH-DPAT) have been synthesized and their conformational preferences have been studied by use of NMR spectroscopy, X-ray crystallography, and molecular mechanics calculations (MMP2). The compounds were tested for activity at central DA receptors, by use of biochemical and behavioral tests in rats. (2*R*,3*S*)-5-Hydroxy-3-methyl-2-(di-*n*-propylamino)tetralin [(−)-8] was demonstrated to be a highly potent DA receptor agonist, while the other new compounds were of low potency or inactive. Results obtained confirmed the hypothesis that the tetralin inversion angle Φ and the direction of the N-electron pair (*N*-H) τ_N are conformational parameters of critical importance for DA D_2 receptor activation in the 2-aminotetralin series. The high potency of (−)-8 allowed an extension of a previously defined "partial DA D_2 receptor excluded volume".

Previous studies of the pharmacology, stereochemistry, and conformational dynamics of the enantiomers of the potent dopamine (DA) receptor agonist 5-hydroxy-2-(di-*n*-propylamino)tetralin (5-OH-DPAT)[1] and their C1-methyl-substituted derivatives[2,3] have demonstrated that DA agonistic C5-oxygenated 2-aminotetralins have the same sense of chirality at the nitrogen-bearing carbon (C2). In addition, results obtained[2b] suggested that, in this series, only compounds that easily assume τ_N values[4] around 60° in tetralin conformations with Φ values[4] around 0° are

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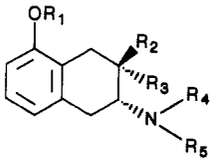
‖ Department of Structural Chemistry, University of Göteborg.

(1) (a) McDermed, J. D.; McKenzie, G. M.; Freeman, H. S. *J. Med. Chem.* **1976**, *19*, 547. (b) Tedesco, J. L.; Seeman, P.; McDermed, J. D. *Mol. Pharmacol.* **1979**, *16*, 369. (c) Freeman, H. S.; McDermed, J. D. In *The Chemical Regulation of Biological Mechanisms*; Creighton, A. M., Turner, S., Eds.; Royal Society of Chemistry: London, 1982; p 154. (d) Seiler, M. P.; Markstein, R. *Mol. Pharmacol.* **1982**, *22*, 281. (e) Seiler, M. P.; Markstein, R. *Mol. Pharmacol.* **1984**, *26*, 452. (f) Wikström, H.; Andersson, B.; Sanchez, D.; Lindberg, P.; Arvidsson, L.-E.; Johansson, A. M.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1985**, *28*, 215.

0022-2623/87/1830-1135$01.50/0

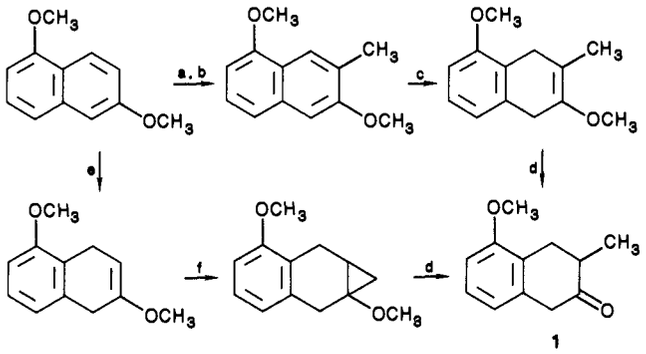
Table I. Physical Data of the Compounds Studied



compd	R_1	R_2	R_3	R_4	R_5	prepn method	yield, %	mp, °C	recrystn solvents[a]	formula
(±)-2	Me	Me	H	H	H	I	39	268–270[b,c]	A	$C_{12}H_{17}NO{\cdot}HCl{\cdot}^1/_5H_2O$
(±)-3	Me	Me	H	*n*-Pr	H	II	72	199.5–201.5	B	$C_{15}H_{23}NO{\cdot}HCl$
(+)-3	Me	Me	H	*n*-Pr	H	*d*	46	208–209	B	$C_{15}H_{23}NO{\cdot}HCl$[e]
(−)-3	Me	Me	H	*n*-Pr	H	*d*	38	207.5–208.5	B	$C_{15}H_{23}NO{\cdot}HCl$
(±)-4	Me	Me	H	*n*-Pr	*n*-Pr	III	89	158–160	A	$C_{18}H_{29}NO{\cdot}HCl$
(+)-4	Me	Me	H	*n*-Pr	*n*-Pr	III	70	146–147	B	$C_{18}H_{29}NO{\cdot}HCl$
(−)-4	Me	Me	H	*n*-Pr	*n*-Pr	III	82	146–147	B	$C_{18}H_{29}NO{\cdot}HCl$
(±)-5	H	Me	H	*n*-Pr	*n*-Pr	V	83	149–151	A	$C_{17}H_{27}NO{\cdot}HCl{\cdot}^1/_2H_2O$
(+)-5	H	Me	H	*n*-Pr	*n*-Pr	V	94	162.5–164	B	$C_{17}H_{27}NO{\cdot}HCl$
(−)-5	H	Me	H	*n*-Pr	*n*-Pr	V	86	162.5–163.5	B	$C_{17}H_{27}NO{\cdot}HCl$
(±)-6	Me	H	Me	*n*-Pr	H	IV	41	225–227	A	$C_{15}H_{23}NO{\cdot}HCl$
(+)-6	Me	H	Me	*n*-Pr	H	*d*	72	254–255	B	$C_{15}H_{23}NO{\cdot}HCl$
(−)-6	Me	H	Me	*n*-Pr	H	*d*	68	254–255	B	$C_{15}H_{23}NO{\cdot}HCl$
(±)-7	Me	H	Me	*n*-Pr	*n*-Pr	III	62	186.5–187.5	A	$C_{18}H_{29}NO{\cdot}HCl{\cdot}^1/_4H_2O$
(+)-7	Me	H	Me	*n*-Pr	*n*-Pr	III	82	164–165	B	$C_{18}H_{29}NO{\cdot}HCl{\cdot}^1/_3H_2O$
(−)-7	Me	H	Me	*n*-Pr	*n*-Pr	III	86	164–165	B	$C_{18}H_{29}NO{\cdot}HCl{\cdot}^1/_5H_2O$
(±)-8	H	H	Me	*n*-Pr	*n*-Pr	V	90	211–213[b]	A	$C_{17}H_{27}NO{\cdot}HCl{\cdot}^3/_4H_2O$
(+)-8	H	H	Me	*n*-Pr	*n*-Pr	V	91	223.5–225	B	$C_{17}H_{27}NO{\cdot}HCl$
(−)-8	H	H	Me	*n*-Pr	*n*-Pr	V	84	222.5–224	A	$C_{17}H_{27}NO{\cdot}HCl$

[a] Recrystallization solvents: A, ethanol/ether; B, methanol/ether. [b] Decomposition. [c] Sublimation occurred. [d] See Experimental Section. [e] Anal. Calcd for $C_{15}H_{23}NO{\cdot}HCl$: C, 66.8. Found: C, 66.3.

Scheme I[a]



[a] Reagents: (a) *n*-BuLi; (b) CH_3I; (c) Na, C_2H_5OH; (d) HCl, CH_3OH; (e) Na, 2-C_3H_7OH; (f) $(C_2H_5)_2Zn$, CH_2I_2.

potent DA-receptor[7] agonists.

In a further elucidation of the structural and conformational requirements for DA-receptor agonism,[8] we now present the synthesis, the conformational analysis, and the pharmacological evaluation of the C3-methyl-substituted derivatives of the 5-OH-DPAT enantiomers.

(2) (a) Johansson, A. M.; Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Clark, D.; Carlsson, A.; Sanchez, D.; Andersson, B.; Wikström, H. *J. Med. Chem.* **1985**, *28*, 1049. (b) Johansson, A. M.; Karlèn, A.; Grol, C. J.; Sundell, S.; Kenne, L.; Hacksell, U. *Mol. Pharmacol.* **1986**, *30*, 258. (c) Johansson, A. M.; Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G.; Svensson, K.; Carlsson, A. *J. Med. Chem.* **1987**, *30*, 602. (d) Svensson, K.; Hjorth, S.; Clark, D.; Carlsson, A.; Wikström, H.; Andersson, B.; Sanchez, D.; Johansson, A. M.; Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G. *J. Neural Transm.* **1986**, *65*, 1. (e) Svensson, K.; Carlsson, A.; Johansson, A. M.; Arvidsson, L.-E.; Nilsson, J. L. G. *J. Neural Transm.* **1986**, *65*, 29. (f) Svensson, K.; Johansson, A. M.; Magnusson, T.; Carlsson, A. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1986**, *334*, 234. (g) Svensson, K.; Carlsson, M.; Carlsson, A.; Hjorth, S.; Johansson, A. M.; Eriksson, E. *Eur. J. Pharmacol.* **1986**, *130*, 237. (h) Svensson, K.; Alföldi, P.; Hajos, M.; Rubicsek, G.; Johansson, A. M.; Carlsson, A.; Obal, F., Jr. *Pharmacol. Biochem. Behav.*, in press. (i) Svensson, K. Thesis, ISBN 91-7900-078-9, Department of Pharmacology, University of Göteborg, Göteborg, Sweden, 1986.

(3) The numbering system used in the running text, in the Experimental Section, and in most of the tables is defined in the structure in Table II. The X-ray numbering system, which is different, is defined in Figure 1 and is used in the supplementary material.

(4) To characterize the different conformations, two conformational parameters, the tetralin inversion angle Φ, and the dihedral angle τ(C1, C2, N, *N*-H or electron pair) (τ_N), are of particular utility. The tetralin inversion angle Φ defines the conformation of the nonaromatic ring of any tetralin derivative. Ideally, this parameter is simply calculated from eq 1 where τ_{obsd} is the observed value and τ_{max} is the maximal value

$$\Phi = \text{arc cos } (\tau_{obsd}/\tau_{max}) \quad (1)$$

(64.73°) of the torsion angle τ(C1,C2,C3,C4).[5] However, in some conformations bond lengths and/or angles are slightly distorted, and therefore, eq 1 is no longer strictly applicable. In such cases, an approximate tetralin inversion angle is estimated by comparison with relevant conformations of C2-unsubstituted tetralin. Φ is configurationally dependent, and enantiomeric conformations differ in Φ values with ±180°. In, e.g., (2*S*)-2-aminotetralin a half-chair conformation with a pseudoequatorial amino group corresponds to Φ = 0° while a half-chair conformation with a pseudoaxial oriented amino group corresponds to Φ = 180°. The dihedral angle τ_N defines the relative direction of the N–H bond (or the electron pair) and indirectly the preferred arrangement around the C2–N bond. For further details, see ref 2b and 6.

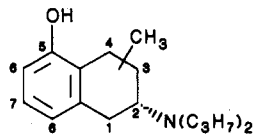
(5) Compare: Vanhee, P.; Tavernier, D.; Baas, J. M. A.; van de Graaf, B. *Bull. Soc. Chim. Belg.* **1981**, *90*, 697.

(6) Karlèn, A.; Johansson, A. M.; Kenne, L.; Arvidsson, L.-E.; Hacksell, U. *J. Med. Chem.* **1986**, *29*, 917.

(7) Due to structural and pharmacological similarities between (2*S*)-5-OH-DPAT, (*R*)-apomorphine, (−)-**5**, and (−)-8, it is reasonable to assume that they all bind to DA D_2 receptors. See also discussion in the Pharmacology section and in ref 2b.

(8) For recent reviews discussing structure–activity relationships of DA-receptor agonists, see, for example: (a) Kaiser, C.; Jain, T. *Med. Res. Rev.* **1985**, *5*, 145. (b) Cannon, J. G. *Prog. Drug Res.* **1985**, *29*, 303.

Table II. ^{1}H NMR Spectral Data of Three 2-Aminotetralin Derivatives That Assume Mainly Half-Chair Conformations in CD_3OD

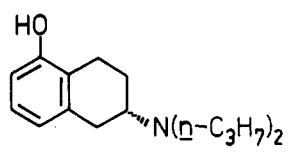


compd	CH_3 pos	chemical shifts, δ						
		H1ax	H1eq	H2ax	H3ax	H3eq	H4ax	H4eq
5·HCl	C3-*trans*	3.04	3.11	3.50	2.30		2.42	3.05
8·HCl	C3-*cis*	3.04	3.26	3.66		≈2.7[a]	2.75	2.92
5-OH-DPAT·HCl		≈3.0[a]	≈3.0[a]	3.69	1.89	2.33	2.64	≈3.0[a]

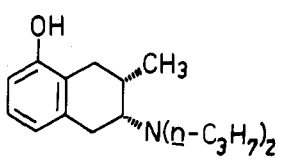
compd	coupling constants (*J*, Hz)										
	$J_{1ax,1eq}$	$J_{1ax,2ax}$	$J_{1eq,2ax}$	$J_{2ax,3ax}$	$J_{2ax,3eq}$	$J_{3ax,3eq}$	$J_{3ax,4ax}$	$J_{3ax,4eq}$	$J_{3eq,4ax}$	$J_{3eq,4eq}$	$J_{4ax,4eq}$
5·HCl	−15.8	9.0	5.4	≈8.0[b]			9.3	5.0			−16.8
8·HCl	−15.8	12.0	5.6		2.7				4.9	1.7	−16.8
5-OH-DPAT·HCl	*c*	9.3	4.5	10.5	2.5	−10.5	10.5	5.6	5.8	3.0	−16.0

[a] Obscured. [b] Estimated from spin–spin simulations. [c] Not determined.

The present paper provides additional support for the idea that Φ and τ_N are conformational parameters of critical importance for dopaminergic activity. Interestingly, (2*R*,3*S*)-5-hydroxy-3-methyl-2-(di-*n*-propylamino)-tetralin [(−)-8; (−)-AJ-166] is demonstrated to be a highly potent DA-receptor agonist—this allows extension of a previously defined[2b] "partial DA D_2 receptor excluded volume".[9]



(2S)-5-OH-DPAT



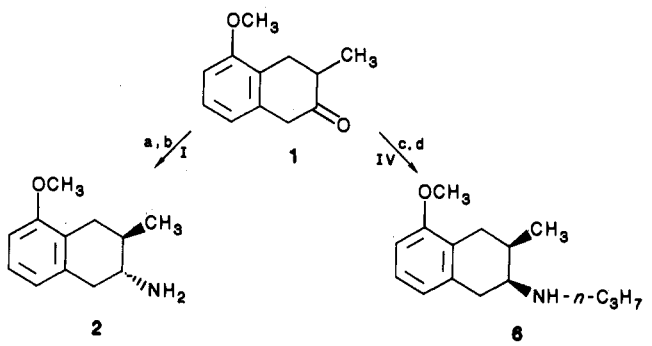
(-)-8

Chemistry

Syntheses. The 2-aminotetralin derivatives presented in Table I were prepared from 5-methoxy-3-methyl-2-tetralone[10] (**1**), which is available from 1,6-dimethoxynaphthalene by two synthetic routes[10] (Scheme I). The syntheses of 2-aminotetralin derivatives, which follow known procedures,[2a,c,11] are outlined in Scheme II.

trans-2-Amino-5-methoxy-3-methyltetralin (**2**) was prepared from the oxime of **1** by reduction with sodium in 2-propanol (method I). This reaction produced a mixture of cis and trans isomers from which the pure trans isomer was obtained by fractional crystallization of the hydrochlorides. Compound **2** was N-propylated by acylation followed by reduction (method II) or N,N-dipropylated by alkylation with 1-iodopropane (method III) to afford **3** or **4**, respectively. Attempts to resolve **2** were unsuccessful. However, **3** could be resolved into the (+) and (−) enantiomers by fractional crystallization of the diastereomeric dibenzoyltartrates. N-Alkylation of (+)-**3** and (−)-**3** by use of method III gave (+)-**4** and (−)-**4**, respectively.

Scheme II[a]



[a] Reagents: (a) H_2NOH·HCl, NaOAc; (b) Na, 2-C_3H_7OH; (c) *n*-$C_3H_7NH_2$; (d) H_2, Pd(C).

cis-5-Methoxy-3-methyl-2-(*n*-propylamino)tetralin (**6**) was obtained by reductive amination of **1** (method IV). The catalytic hydrogenation of the intermediate imine afforded a mixture of the cis and trans stereoisomers **6** and **3**, respectively. Pure **6** was obtained by fractional crystallization of the hydrochlorides. Compound **6** was resolved into the (+) and (−) enantiomers by fractional crystallization of the diastereomeric di-*p*-toluoyltartrates. N-Alkylation of (±)-**6**, (+)-**6**, and (−)-**6** by use of method III gave (±)-**7**, (+)-**7**, and (−)-**7**, respectively.

The phenols presented in Table I were prepared from the corresponding methoxy-substituted derivatives by use of 48% aqueous hydrogen bromide. The desired phenolic amino hydrochlorides were prepared from the initially formed hydrobromides by halogen interchange.

NMR Spectroscopy. High-resolution ^{1}H NMR spectral data for 5-HCl and 8-HCl in CD_3OD are shown in Table II.[12] Previously reported[2b,6] ^{1}H NMR data for 5-OH-DPAT-HCl, which preferentially assumes a half-chair conformation with a pseudoequatorial dipropylammonium group in CD_3OD, are also included in Table II.

Use of 400-MHz spectroscopy allowed analysis of several resonances by first-order approximations. Some spectra were complicated to interpret due to overlapping resonances. However, COSY spectroscopy allowed unambig-

(9) For definitions of receptor-excluded and receptor-essential volumes and related concepts, see: Surfin, J. R.; Dunn, D. A.; Marshall, G. R. *Mol. Pharmacol.* **1980**, *19*, 307, Klunk, W. E.; Kalman, B. L.; Ferrendelli, J. A.; Covey, D. F. *Mol. Pharmacol.* **1981**, *23*, 511.

(10) (a) Lundkvist, J. R. M.; Johansson, A. M.; Arvidsson, L.-E.; Hacksell, U. *Acta Chem. Scand., Ser. B* **1986**, *40*, 508. (b) Johansson, A. M.; Mellin, C.; Hacksell, U. *J. Org. Chem.* **1986**, *51*, 5252.

(11) (a) Hacksell, U.; Svensson, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson A.; Wikström, H.; Lindberg, P.; Sanchez, D. *J. Med. Chem.* **1979**, *22*, 1469. (b) Hacksell, U.; Johansson, A. M.; Arvidsson, L.-E.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Wikström, H.; Sanchez, D.; Lindberg, P. *J. Med. Chem.* **1984**, *27*, 1003.

(12) For other NMR spectral studies of 2-aminotetralins, see ref 2b, 6, and (a) Nichols, D. E.; Jacob, J. N.; Hoffman, A. J.; Kohli, J. D.; Glock, D. J. *J. Med. Chem.* **1984**, *27*, 1701. (b) de Jong, A. P.; Fesik, S. W.; Makriyannis, A. *J. Med. Chem.* **1982**, *25*, 1438.

uous assignments of all proton resonances. Based on the deduced coupling constants, the following conclusions can be drawn: The large dipseudoaxial coupling constants $J_{1ax,2ax}$ in 5·HCl, 8-HCl, and 5-OH-DPAT-HCl and $J_{2ax,3ax}$ in 5-HCl and 5-OH-DPAT-HCl indicate that these three compounds prefer to assume half-chair conformations with pseudoequatorial dipropylammonium substituents in solution.[2b,6,12] This is further supported by the large value of $J_{3ax,4ax}$ in 5-HCl and 5-OH-DPAT-HCl and by the small value of $J_{3eq,4eq}$ in 8-HCl and 5-OH-DPAT·HCl. The COSY spectrum of 8-HCl indicated small couplings between H1eq and H3eq and between the C3-methyl hydrogens and H4ax. Such long-distance couplings occur when the interacting nuclei are arranged in a *W* conformation.[13] The presence of these *W* couplings support the suggested predominating solution conformation of 8-HCl.

^{13}C NMR spectroscopy revealed that rotation around the C_2–N bond is slow on the NMR time scale in 5-HCl and 8-HCl; this was evident from the magnetic nonequivalence of C_α and $C_{\alpha'}$ (5-HCl and 8-HCl).[14]

X-ray Crystallography.[15] X-ray crystallography established the absolute configuration of (–)-5-HBr and (–)-7·HCl to be 2*R*,3*R* and 2*R*,3*S*, respectively (see Figure 1, Experimental Section, and supplementary material). This also establishes the absolute configuration of the other resolved compounds. It is noteworthy that neither of the two crystallographically independent molecules of (–)-7·HCl nor the X-ray conformation of (–)-5-HBr correspond to the lowest energy conformations obtained from the MMP2 calculations (compare Figure 1). We are presently attempting to rationalize these and several similar results.

Molecular Mechanics Calculations. The C3-methyl-substituted derivatives of 5-OH-DPAT are flexible molecules that can exist in several conformations. To identify conformations of low energy we have applied a strategy that has been described in detail elsewhere.[6] In the present study, this strategy was modified to a minor extent; only 2-(dimethylamino)- and 2-(diethylamino)-tetralin conformations with energies less than or equal to 2.9 and 2.7 kcal/mol above the respective global minimum were considered, and in the final minimization of the 2-(di-*n*-propylamino)tetralin geometries, all staggered di-*n*-propylamino rotamers were minimized (not only those indicated from study of conformational maps).

Four low-energy conformations[4] of (2*R*,3*R*)-5 and (2*R*,3*S*)-8 respectively were identified within 2.5 kcal/mol of the respective global minimum (geometries and steric energies of low-energy conformations are given in the supplementary material). Thus, the conformational mobility of 5 and 8 appears to be considerably lower than that of 5-OH-DPAT.[2b,6] Preferred tetralin ring conformations and τ_N values (at 37 °C) were obtained by calculations of Boltzmann distributions based on the steric energies of the identified low-energy conformations of the compounds. Figure 2 shows that (2*R*,3*R*)-5 and (2*R*,3*S*)-8 as well as (2*S*)-5-OH-DPAT preferentially assume Φ values around 0° and that they, unlike (2*S*)-5-OH-DPAT, prefer to assume only one of the three possible dipropylamino group rotamers in tetralin conformations with Φ values around 0°.

Table III. Effects on in Vivo Dopa Accumulation and on Locomotor Activity in Reserpine-Pretreated Rats

compd	DOPA accumulation:[a] ED_{50}, μmol/kg sc		locomotor activity:[b] accumulated counts/30 min, mean ± SEM (μmol/kg sc)
	limbic	striatum	
(+)-5	25.0 (35%)	25.0 (20%)	55 ± 25 (52.0)***
(–)-5	3.5 (35%)	3.1 (20%)	53 ± 26 (52.0)***
(+)-8	I[c]	I[c]	12 ± 9 (10.0)
(–)-8	0.005 (35%)	0.005 (20%)	110 ± 28 (0.32)***[d]
(2*S*)-5-OH-DPAT	0.004 (35%)[e]	0.004 (20%)[e]	155 ± 27 (0.31)*[e]
(2*R*)-5-OH-DPAT	0.41 (35%)[e]	0.65 (20%)[e]	43 ± 9 (39.0)*[e]
(*R*)-apomorphine	0.041 (35%)[f]	0.044 (20%)[f]	366 ± 36 (3.2)***[g]

[a] Animals were injected with reserpine (5 mg/kg sc) 18 h, test drug 60 min, and NSD 1015 (100 mg/kg ip) 30 min before death. Controls received corresponding saline injections. Shown are the doses giving a half-maximal decrease of DOPA formation in rat limbic and striatal brain regions, estimated from dose–response curves comprising four to seven dose levels (n = 3–5). Minimal levels obtained are shown in brackets; controls = 100%. [b] Animals were injected with reserpine (5 mg/kg sc) 18 h and test drug immediately before the activity session. Shown are the accumulated counts/30 min (mean ± SEM, n = 3–4). Reserpine controls: 3 ± 1 counts/30 min, n = 13. Statistical differences were calculated by using the Student's t test: (***) $p < 0.001$, (*) $p < 0.05$ vs. saline controls. [c] I = inactive: no significant effect on limbic or striatal DOPA formation at 10 μmol/kg sc. [d] This dose was significantly antagonized [(**) $p < 0.025$] by haloperidol pretreatment (0.5 mg/kg ip 30 min before, n = 4). [e] From ref 1f. [f] From ref 19. [g] From ref 2c.

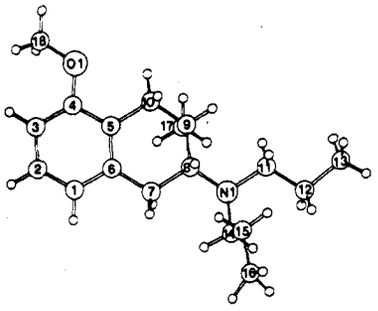
The driver option in the MIMIC program[16] was used to estimate if rotation around the C2–N bond is restricted in the *N*,*N*-dimethyl derivatives of (2*S*)-5-OH-DPAT, (–)-5, and (–)-8. The results (Figure 3) demonstrate that there is a considerable barrier to rotation in the model compounds of (–)-5 and (–)-8 in conformations with Φ values around 0°. The same preferred τ_N values were identified by the driver procedure and by the nonrestricted minimization procedure (compare Figures 2 and 3). The restricted mobility around the C2–N bond in these C3-methylated derivatives and their preference for half-chair conformations with pseudoequatorial nitrogen substituents were also demonstrated in the ^1H and ^{13}C NMR studies (vide supra).

Pharmacology

The compounds were tested for central DA receptor activity by use of in vivo biochemical and behavioral methods in reserpinized and nonpretreated rats as previously described.[2d,17]

In the in vivo biochemical screening method we utilize the ability of DA-receptor agonists to stimulate the DA receptors and through regulatory feedback systems induce a decline in tyrosine hydroxylase activity and, thus, reduce the synthesis rate of DA in the presynaptic neuron. The DOPA formation [as determined after in vivo inhibition of the aromatic L-amino acid decarboxylase by NSD 1015

(13) See, for example: Jackman, L. Y.; Sternhell, S. *Applications of NMR Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon: Oxford, 1969.
(14) For definitions of Cα, Cα′, Cβ, and Cβ′, see ref 2b and 6.
(15) For X-ray crystallographic studies of other 2-aminotetralin derivatives, see ref 2b and (a) Giesecke, J. *Acta Crystallogr., Sect. B* **1980**, *B36*, 110. (b) Horn, A.; Rodgers, J. R. *J. Pharm. Pharmacol.* **1980**, *32*, 521.
(16) Liljefors, T. *Mol. Graphics* **1983**, *1*, 111.
(17) For discussions of the experimental design and the underlying concepts, see, for example: (a) Wikström, H.; Lindberg, P.; Martinsson, P.; Hjorth, S.; Carlsson, A.; Hacksell, U.; Svensson, U.; Nilsson, J. L. G. *J. Med. Chem.* **1978**, *21*, 864. (b) Hjorth, S.; Carlsson, A.; Clark, D.; Svensson, K.; Wikström, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L.-E.; Johansson, A.; Nilsson, J. L. G. *Psychopharmacology* **1983**, *81*, 89. (c) Andén, N.-E.; Carlsson, A.; Häggendahl, J. *Annu. Rev. Pharmacol.* **1969**, *9*, 119.



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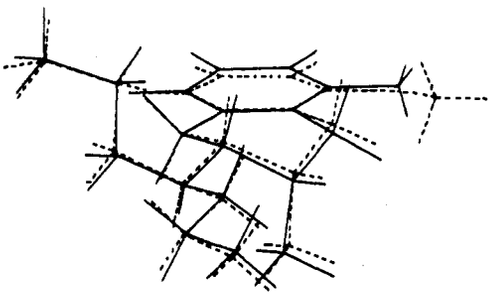

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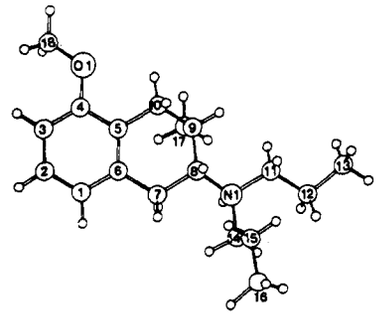

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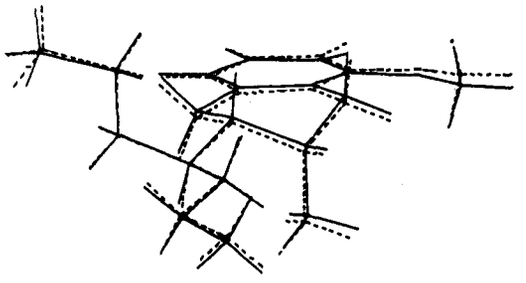

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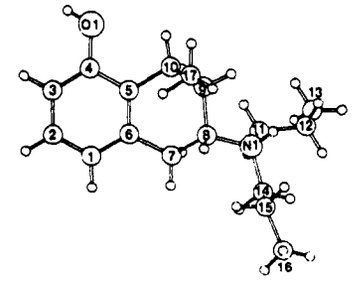

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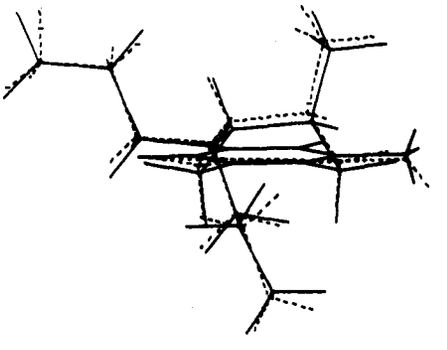


VI

Figure 1. Molecular conformation and atomic numbering scheme of (−)-**5**·HBr (III) and of the two independent molecules A and B of (−)-**7**·HCl (I and II, respectively). Conformations A and B of (−)-**7**·HCl are similar: A, $\Phi = 335°$, $\tau_N = 61.8°$; B, $\Phi = 325°$, $\tau_N = 52.6°$. A computer-generated best fit of the carbon, oxygen, and nitrogen atoms of A and B (V) gave an average distance between fitted atoms of 0.09 Å. Both the A and B conformations are similar to one of the low-energy conformations (C; $\Phi = 339°$, $\tau_N = 64°$; $\Delta E_s = 0.1$ kcal/mol) that was identified in the molecular mechanics calculations. The best fit (IV) of conformation A and the MMP2-generated conformation C gave an average distance of 0.13 Å. When conformation B was fitted similarly (not shown), the average distance between fitted atoms of B and C was 0.17 Å. The molecular conformation of (−)-**5**·HBr (III; $\Phi = 101°$, $\tau_N = 179°$) was not similar to any of the low-energy MMP2 conformations. However, when the X-ray conformation of (−)-**5**·HBr was MMP2 minimized, a local minimum ($\Phi = 100°$, $\tau_N = 180°$) with $\Delta E_s = 3.7$ kcal/mol was identified. The best fit (VI) between this MMP2-generated conformation and the X-ray conformation (III) gave an average distance of 0.19 Å.

(3-hydroxybenzylhydrazine hydrochloride)] in the limbic and striatal brain regions is taken as an indirect measure of DA synthesis.

Motor activity recordings were carried out with motility meters as previously described.[17] The results obtained in the biochemical and motor activity tests are presented in Tables III and IV.

Observed activities could be attributed to effects at central DA receptors; none of the compounds tested appeared to affect 5-hydroxytryptamine (5-HT) or noradrenaline (NA) formation, indicating that the compounds are inactive on central 5-HT and NA receptors.

Compound (+)-**8** was shown to be inactive, whereas (+)-**5**, (−)-**5**, and (−)-**8** were able to maximally reduce the

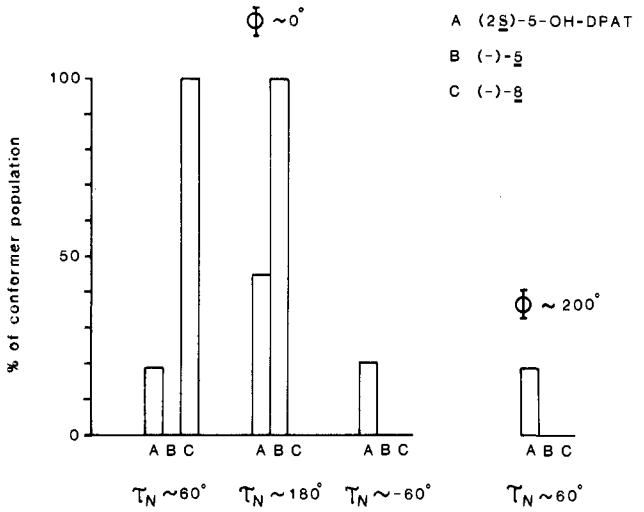


Figure 2. Conformational distribution of (2*S*)-5-OH-DPAT (A), (−)-**5** (B), and (−)-**8** (C). The probability of existence of each conformation (at 37 °C) was estimated from a Boltzmann distribution based on calculated (MMP2) steric energies. The bars represent the three staggered rotamers of the dipropylamino group (having τ_N values around 60°, 180°, and −60°, respectively). Only conformations with Φ values around 0° and 200° seem to be populated.

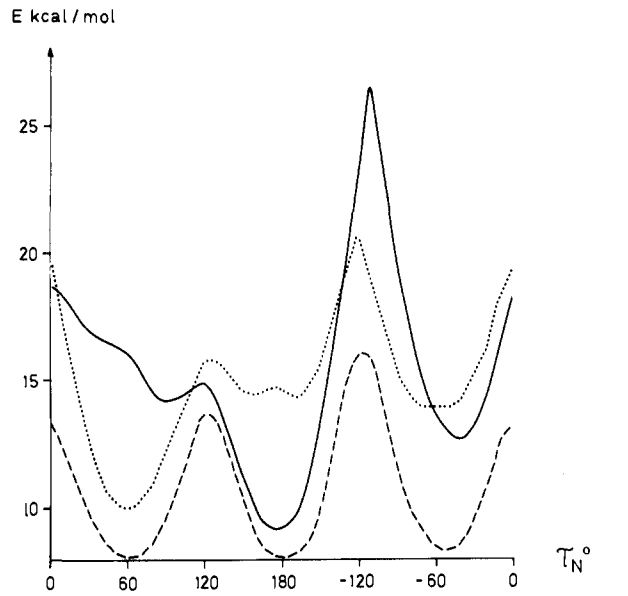


Figure 3. Barriers to rotation about the C2-N bond in conformations having Φ values around 0° in *N,N*-dimethyl analogues of (2*S*)-5-OH-DPAT (dashed line), (−)-**5** (solid line), and (−)-**8** (dotted line). The steric energies were obtained by use of the driver option in the MIMIC program.[16] The τ_N values were varied in 10° increments. Variations in Φ values were as follows: A, 335°–25°; B, 328°–25°; C, 339°–20°.

limbic and striatal DOPA levels in reserpinized rats. Similarly, (+)-**5**, (−)-**5**, and (−)-**8**, but not (+)-**8**, were able to reverse the reserpine-induced akinesia and produced stereotyped behavior including sniffing and licking in rats (Table III). Compounds (+)- and (−)-**5** were considerably less active than (−)-**8** in this respect. The hyperactivity and stereotypies induced by (−)-**8** in reserpinized rats was significantly antagonized by the DA receptor antagonist haloperidol[18] (see footnote *d* in Table III), indicating a direct postsynaptic DA-receptor agonism of (−)-**8**.

Table IV. Effects on in Vivo Dopa Accumulation and on Locomotor Activity in Nonpretreated Rats

compd	DOPA accumulation:[a] ED_{50}, μmol/kg sc, limbic	DOPA accumulation:[a] ED_{50}, μmol/kg sc, striatum	locomotor activity:[b] percent of saline controls, means ± SEM (μmol/kg sc)
(+)-**5**	I[c]	I	84 ± 22 (52.0)
(+)-**8**	I	I	70 ± 24 (52.0)
(*R*)-apomorphine	*d*	*d*	52 ± 6 (0.32)**[e]
			277 ± 14 (3.2)***[e]

[a] Animals were injected with test drug 65 min and NSD 1015 (100 mg/kg ip) 30 min before death. Controls received corresponding saline injections. Shown are the doses giving a half-maximal decrease of DOPA formation in rat limbic or strital brain regions, estimated from dose–response curves comprising four to five dose levels (n = 3–5). Maximal levels obtained are shown in brackets, controls = 100%. Control levels: limbic region, 447 ± 23 ng/g; striatum, 1045 ± 47 ng/g; n = 16. [b] Animals were injected with test drug 5 min before the activity session, and the accumulated counts over a 30-min period were recorded. Shown is the locomotor activity expressed as percentage relative to control values (232 ± 14 counts/30 min, n = 25) means ± SEM, n = 3–5. Statistical differences were calculated by using the Student's t test: (***) $p < 0.001$, (**) $p < 0.01$ vs. saline controls. [c] I = inactive: no significant effect on limbic or striatal DOPA formation at 52 μmol/kg sc. [d] (*R*)-Apomorphine elicited a biphasic dose–response curve from which two ED_{50} values can be obtained. Compare ref 36. [e] From ref 2c.

Compound (−)-**8** is the most potent compound of the substances tested. It has an ED_{50} value (5 nmol/kg sc) in the same range as that of the potent DA receptor agonist (2*S*)-5-OH-DPAT[1] (ED_{50} = 4 nmol/kg sc).[1f] Compound (+)-**5** and (−)-**5** seem to be several hundred times less potent than (2*S*)-5-OH-DPAT. It should be noted that the dopaminergic effects of (+)-**5** (Table III) may partially be due to contamination with the more potent levorotatory antipode. In fact, GC analysis of derivatized (+)-**3** [a synthetic precursor to (+)-**5**] indicated that (+)-**3** was contaminated with ≤3% of (−)-**3** (see Experimental Section).

The potencies (ED_{50} values; Table III) of the compounds to lower the synthesis rate of DA in reserpinized rats can be taken as a measure of DA-autoreceptor potency (compare ref 11a and 19). Recent findings indicate the the DA autoreceptor is a functional correlate for the D_2^{high} binding site.[20] Thus, we consider compounds with DA autoreceptor stimulatory properties as putative DA D_2 receptor agonists.

In nonpretreated rats, neither the DOPA levels in the striatal and limbic brain parts nor the locomotor activity were affected by (+)-**5** or (+)-**8**. This establishes that these compounds lack DA receptor agonistic or antagonistic effects at the doses tested.

Structure–Activity Relationships

On the basis of a computer-generated fit of the DA receptor agonists (2*S*)-5-OH-DPAT, (4a*S*,10b*S*)-7-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]-quinoline[2f,21] [**9**, (4a*S*,10b*S*)-7-OHBQ], and (*R*)-apomorphine[22] [(*R*)-APO] we previously suggested[2b] that a

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

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

(20) See, for example: Grigoriadis, D.; Seeman, P. *Can. J. Neurol. Sci.* **1984**, *11*, 108.

(21) Wikström, H.; Sundell, S.; Lundmark, M. *Acta Pharm. Suec.* **1985**, *22*, 75.

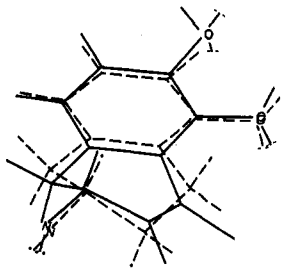


Figure 4. Computer-generated best fit of the 2-aminotetralin fragments of the minimum-energy (MMP2) conformations of (*R*)-apomorphine (solid lines) and **9** (dashed lines) which indicates that the "DA D_2 receptor agonistic 2-aminotetralin conformation" has a Φ value around 0° and a τ_N value around 60°. Mean distance between fitted atoms (C4a, C5, C6, C7, C8, C5, O, N, and N-electron pair) is 0.15 Å. See ref 2b for further details.

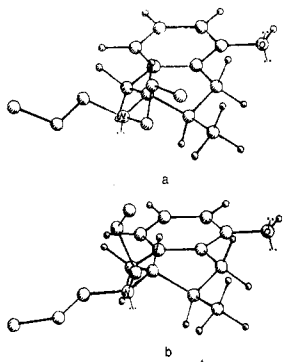
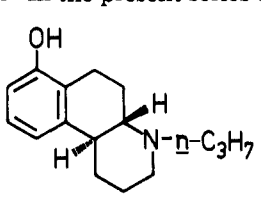


Figure 5. Starting geometry (a; Φ = 10° and τ_N = 60°) and MMP2 minimized conformation (b; Φ = 10° and τ_N = 98°; relative steric energy = 6.1 kcal/mol) of (−)-**5**. For clarity, the hydrogens have been omitted from the *N*-propyl groups.

2-amino-5-hydroxytetralin moiety in a half-chair conformation with a pseudoequatorial dipropylamino substituent ($\Phi \approx 0°$) and a τ_N value around 60° should correspond to a "DA D_2-receptor agonist conformation" (compare Figure 4). In the present series of compounds, this conformation



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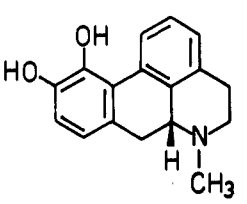
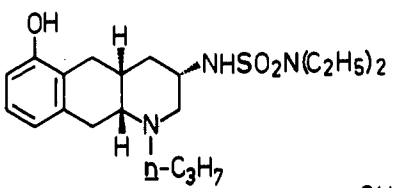


(R)-Apomorphine

is easily adopted only by the potent DA receptor agonist (−)-**8** [(2*R*,3*S*)-**8**]. In (−)-**5** [(2*R*,3*R*)-**5**], "agonist conformations" are energetically disfavored and attempts to minimize geometries of (−)-**5** with Φ values around 0° and τ_N values around 60° were unsuccessful; the minimization consistently changed the τ_N value into 98° (Figure 5). Furthermore, the energy of this conformation is 6.1 kcal/mol above the global energy minimum of (−)-**5**. This is in agreement with the results from the sequential rotation around the C2–N bond (Figure 3), which show that low-energy conformations of (−)-**5** with Φ values around 0° have T_N values around 180°. The reluctance of (−)-**5** to assume "agonist conformations" provides an attractive rationale for the low in vivo biochemical potency of (−)-**5** as compared to that of (−)-**8** and (2*S*)-5-OH-DPAT. The high dopaminergic potency of (−)-*N*,*N*-diethyl-*N*'-[(3*S*,4a*R*,10b*R*)-1,2,3,4,4a,5,10,10b-octahydro-6-hydroxy-1-propyl-3-benzo[*g*]quinolinyl]sulfamide (**10**, 206-962),[23] which contains the same structural elements as (−)-**5**, indicates that the C3-methyl substituent of (−)-**5** should not prevent a proper receptor interaction by sterical means. Thus, the low potency of (−)-**5** supports the suggestion[2b] that in the 2-amino-5-hydroxytetralin series a Φ value around 0° and a τ_N value around 60° correspond to a "DA D_2 receptor agonistic conformation" (vide supra). In addition, the configuration at C2 of the inactive and homochiral[24] (+)-**8** [(2*S*,3*R*)-**8**] and (2*R*)-5-OH-DPAT makes these compounds unable to assume "DA D_2 receptor agonistic nitrogen lone pair (*N*-H) orientations".[2b]



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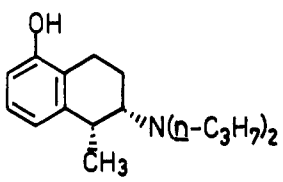

11

It is interesting to compare the *cis*-C1-methyl-substituted analogue (1*R*,2*S*)-5-hydroxy-2-(di-*n*-propylamino)-tetralin [**11**, (1*R*,2*S*)-UH-242],[2a-d,i] which is a DA agonist of relatively low potency ($ED_{50} \approx 320$ nmol/kg), with (−)-**8** (ED_{50} = 5 nmol/kg): Both compounds are able to assume "DA D_2 receptor agonist conformations" (Φ values around 0° and τ_N values around 60°) of low energy. In these conformations, both the C1- and the C3-methyl groups are pseudoaxially located, but only the C1-methyl group seems to have a negative influence on the receptor interaction. The pseudoaxial C3-methyl substituent does not seem to provide any sterical hindrance for the interaction with DA receptors since (−)-**8** is equipotent to (2*S*)-5-OH-DPAT.

Recently we obtained[2b] a partial "DA D_2 receptor excluded volume" by combining the van der Waals volumes of the 2-aminotetralin moieties of (2*S*)-5-OH-DPAT, **9**, and (*R*)-APO. We now add the van der Waals volume of (−)-**8** to this volume, to get an *extended*, partial "Da D_2 receptor excluded volume" (Figure 6).

To summarize, methyl substitution close to or at the N-bearing carbon of 5-OH-DPAT has given interesting results. First, compounds with novel pharmacological profiles of potential clinical value have been discovered. Second, the low potencies of some derivatives that do not appear to present a "DA D_2 receptor essential volume"[9] have allowed us to test and verify a hypothesis about the "DA D_2 receptor active conformations" of 2-amino-5-hydroxytetralins. Third, the high dopaminergic potency of (−)-**8** makes possible an extension of a previously defined "DA D_2 receptor excluded volume".

Experimental Section

Chemistry. General Comments. Routine ^1H and ^{13}C NMR spectra were recorded at 90 and 22.5 MHz, respectively, on a JEOL FX 90Q spectrometer and were referenced to internal tetra-

(22) (a) Colpaert, F. C.; van Bever, W. F. M.; Leysen, J. E. M. F. *Int. Rev. Neurobiol.* **1976**, *19*, 225. (b) DiChiara, G.; Gessa, G. L. *Adv. Pharmacol. Chemother.* **1978**, *15*, 88. (c) Neumeyer, J. L.; Lal, S.; Baldesarini, R. J. In *Apomorphine and Other Dopaminomimetics, Vol. 1, Basic Pharmacology*; Gessa, G. L., Corsini, G. U., Eds.; Raven: New York, 1981; pp 1–17.

(23) Nordmann, R.; Widmer, A. *J. Med. Chem* **1985**, *28*, 1540.

(24) Homochiral compounds have the same sense of chirality but not necessarily the same absolute configuration.

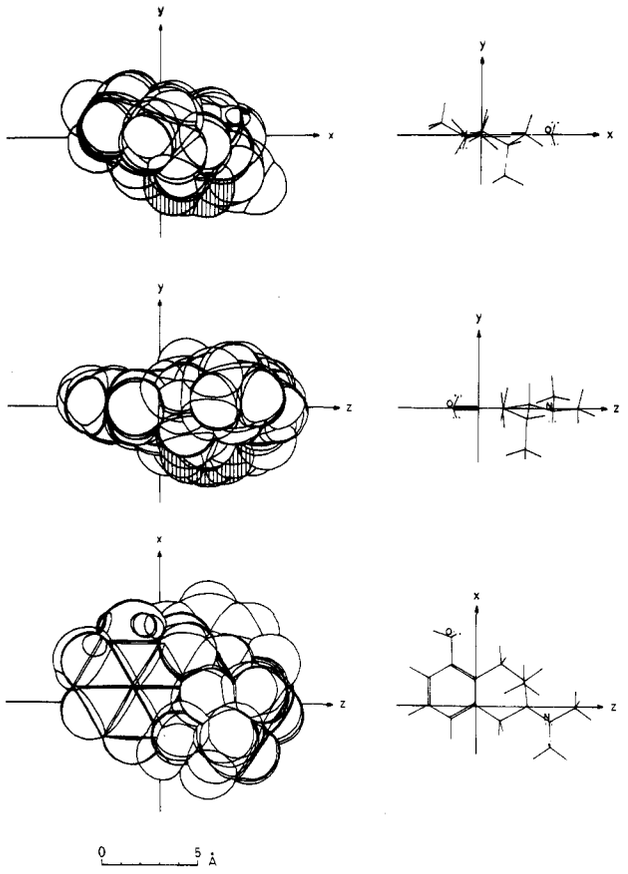

Figure 6. Partial DA D_2 receptor excluded volume[9] (left) obtained by combination of the van der Waals volumes of (*R*)-APO, the *N*-methyl derivative of (4a*S*,10b*S*)-7-OHBQ, and the *N*,*N*-dimethyl derivatives of (2*S*)-5-OH-DPAT and (−)-8 in their DA receptor agonistic conformations. Three perspectives of this volume are shown. For clarity, each perspective of the coordinate system is defined to the right by insertion of line projections of (−)-8. Dashed areas represent projections of the van der Waals volume of (−)-8 that exceeds the volume formed by combination of the other three compounds. Volumes were combined by fitting the hydroxyl groups, C7, C8a, N, and the N-electron pair of the 2-aminotetralin moieties of the compounds to the *N*,*N*-dimethyl derivative of (2*S*)-5-OH-DPAT.

methylsilane. For the conformational analysis, ^{1}H NMR spectra were recorded on a JEOL GX-400 spectrometer using 0.1 M CD_3OD solutions of the hydrochlorides at 25 °C. Apparent proton–proton coupling constants were measured from expanded (1–2 Hz/cm) spectra and refined by use of the JEOL FASNO 5 NMR spectrum simulation program. Pulse sequences used for COSY spectroscopy were obtained from the GX-400 software. Mass spectra[25] were recorded at 70 eV on a LKB 9000 spectrometer using a direct insertion probe. All spectra were in accordance with the assigned structures. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter. HPLC was performed on a Waters 5 Si 10 column by use of hexane/ethyl acetate/ethanol (91:7.5:1.5) as the mobile phase, working in the pressure range 1000–3000 psi and with the flow rate of 2 mL/min. Detection was made by a Waters Model 440 UV monitor. GC was performed on a Varian 2700 instrument equipped with a flame-ionization detector. A glass column (3 m) with 3% OV-17 on 80/100 mesh Varaport was used throughout. Capillary GC was performed on a Carlo Erba 4200, by use of an SE 54 column (10 m). The elemental analyses (C, H, and N), which were within ±0.4% of the theoretical values, were performed by Mikro Kemi AB, Uppsala, Sweden. For purity tests, TLC was performed on fluorescent silica gel or alumina plates.

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

***trans*-2-Amino-5-methoxy-3-methyltetralin (2). Method I.** A mixture of 5-methoxy-3-methyl-2-tetralone[10] (1) (15.0 g, 78.8 mmol), hydroxylamine hydrochloride (11.0 g, 158 mmol), and sodium acetate (21.0 g, 256 mmol) in ethanol (150 mL) was heated under reflux for 3 h. The ethanol was evaporated in vacuo, and the residue was partitioned between dichloromethane and water. The dried (magnesium sulfate) organic layer was concentrated in vacuo, affording yellowish crystals. The 5-methoxy-3-methyl-2-tetralone oxime (15.2 g, 94%) thus obtained was used in the next step without further purification.

Thin slices of sodium (64.3 g, 2.80 mol) were added during 7 h to a solution of the above oxime (15 g, 73.1 mmol) in dry 2-propanol (1000 mL) kept at gentle reflux under nitrogen. The heating was interrupted and water (150 mL) was added. The 2-propanol was evaporated in vacuo and the residue was extracted with ether. The ether layer was dried (potassium carbonate), filtered, and concentrated, affording a product of 70% de (diastereomeric excess) (as indicated by ^{1}H NMR). Ethereal hydrogen chloride was added to an ethereal solution of the oily residue and the precipitate was recrystallized repeatedly from ethanol/ether to give 7.09 g (39%) of pure **2**·HCl: ^{1}H NMR (methanol-d_4) δ 7.21–7.04 (m, 1 H), 6.79–6.67 (m, 2 H), 3.80 (s, 3 H, OMe), 3.22–2.55 (m, 4 H), 2.45–1.75 (m, 2 H), 1.80 (d, 3 H, C3-Me); mass spectrum, *m*/*z* 191 (50, M^+), 174 (100, $M^+ - NH_3$), 159 (85).

***trans*-5-Methoxy-3-methyl-2-(*n*-propylamino)tetralin (3). Method II.** To a cold solution of **2** (1.0 g, 5.23 mmol) and triethylamine (1.06 g, 10.5 mmol) in dry ether (50 mL) kept under nitrogen was added a solution of propionyl chloride (0.96 g, 10.4 mmol) in dry ether (10 mL). After the mixture was stirred overnight, dichloromethane was added and the mixture was extracted with 1 M hydrogen chloride and saturated aqueous sodium carbonate. The organic layer was dried (magnesium sulfate), filtered, and concentrated. The oily residue was passed through a silica gel column with ether as eluant. The resulting amide was dissolved in dry tetrahydrofuran (25 mL) and added to a suspension of lithium tetrahydridoaluminate (1.39 g, 36.6 mmol) in dry tetrahydrofuran under nitrogen. The reaction mixture was heated under reflux for 2 h and was then quenched by addition of water and sodium hydroxide. The resulting precipitate was filtered off and the filtrate was dried (potassium carbonate), filtered, and concentrated. The amine was converted into the hydrochloride and recrystallized from methanol/ether to afford 1.02 g (72%) of pure **3**·HCl: ^{1}H NMR (methanol-d_4) δ 7.30–7.06 (m, 1 H), 6.81–6.72 (m, 2 H), 3.81 (s, 3 H, OMe), 3.50–2.80 (m, 6 H), 2.65–1.60 (m, 4 H), 1.79 (d, 3 H, C3-Me), 1.04 (t, 3 H); mass spectrum,[26] *m*/*z* 233 (100, M^+), 204 (50, $M^+ - C_2H_5$), 175 (28, $M^+ - NHC_3H_7$).

(−)-*cis*-5-Methoxy-3-methyl-2-(di-*n*-propylamino)tetralin [(−)-7]. Method III. 1-Iodopropane (0.35 g, 2.08 mmol) was added to a mixture of (−)-**6**·HCl (0.50 g, 1.85 mmol), potassium carbonate (1.41 g, 10.2 mmol), and acetonitrile (5 mL). The mixture was stirred at 50 °C under nitrogen. Two portions of potassium carbonate (1.41 g, 10.2 mmol) and of 1-iodopropane (0.35 g, 2.08 mmol) were added during the next 2 days. After 5 days the heating was interrupted and ether was added. The reaction mixture was filtered, and the volatiles were evaporated in vacuo. The oily residue was purified on an alumina column with ether/petroleum ether (1:19) as eluant. The amine was converted into the hydrochloride and recrystallized from methanol/ether, yielding 0.50 g (86%) of pure (−)-**7**·HCl: ^{1}H NMR (methanol-d_4) δ 7.25–7.06 (m, 1 H), 6.81–6.73 (m, 2 H), 3.80 (s, 3 H, OMe), 3.80–3.55 (m, 1 H), 3.45–2.60 (m, 9 H), 2.00–1.55 (m, 4 H), 1.05 (t, 6 H), 1.01 (d, 3 H, C3-Me); mass spectrum,[26] *m*/*z* 275 (51, M^+), 246 (100, $M^+ - C_2H_5$), 175 (34, $M^+ - NC_6H_{14}$).

***cis*-5-Methoxy-3-methyl-2-(*n*-propylamino)tetralin (6). Method IV.** A mixture of 5-methoxy-3-methyl-2-tetralone[10] (1) (12.6 g, 66.2 mmol), *n*-propylamine (7.83 g, 133 mmol), and *p*-toluenesulfonic acid monohydrate (5 mg) in dry benzene (350 mL) was heated to reflux under nitrogen in a Dean–Stark apparatus.

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The heating was interrupted after 1 week, and the volatiles were evaporated in vacuo. The residue was dissolved in dry methanol (125 mL) and hydrogenated at atmospheric pressure with palladium (10%) on activated carbon as catalyst. When the hydrogen uptake had ceased, the catalyst was filtered off (Celite), and the volatiles were evaporated in vacuo. The residue was dissolved in ether and extracted with 1 M aqueous hydrogen chloride. The aqueous phase was alkalinized with 2 M sodium hydroxide and extracted with ether. The combined ether layers were dried (potassium carbonate), filtered, and concentrated, affording a product of 54% de (as indicated by capillary GC). The diastereomeric mixture of amines was converted to the hydrochlorides and recrystallized repeatedly from ethanol/ether to give 6.53 g (41%) of pure **6**-HCl: ^{1}H NMR (methanol-d_4) δ 7.23–7.05 (m, 1 H), 6.81–6.71 (m, 2 H), 3.80 (s, 3 H, OMe), 3.70–3.57 (m, 1 H), 3.17–2.45 (m, 7 H), 2.00–1.60 (m, 2 H), 1.05 (t, 3 H), 1.01 (d, 3 H, C3-Me); mass spectrum, m/z 233 (100, M^+), 204 (87, $M^+ - C_2H_5$), 175 (79, $M^+ - NHC_3H_7$).

(+)-*cis*-5-Hydroxy-3-methyl-2-(di-*n*-propylamino)tetralin [(+)-8]. Method V. A solution of (+)-**7**-HCl (0.20 g, 0.64 mmol) in freshly distilled aqueous 48% hydrogen bromide (10 mL) was stirred for 2 h at 120 °C under nitrogen. The volatiles were evaporated in vacuo, and the solid residue was partitioned between ether and saturated aqueous sodium bicarbonate. The ether layer was dried (sodium sulfate), filtered, and concentrated. Ethereal hydrogen chloride was added to an ethereal solution of the residue and the precipitate was recrystallized from methanol/ether to afford 0.173 g (91%) of pure (+)-**8**·HCl: ^{1}H NMR (methanol-d_4) δ 7.07–6.90 (m, 1 H), 6.69–6.58 (m, 2 H), 3.80–3.55 (m, 1 H), 3.40–2.60 (m, 9 H), 2.00–1.55 (m, 4 H), 1.06 (t, 6 H), 1.02 (d, 3 H, C3-Me); mass spectrum, m/z 261 (32, M^+), 232 (100, $M^+ - C_2H_5$), 161 (64, $M^+ - NC_6H_{14}$).

Resolution of (±)-*trans*-5-Methoxy-3-methyl-2-(*n*-propylamino)tetralin [(±)-3]. (−)-Dibenzoyl-L-tartaric acid monohydrate (1.82 g, 4.84 mmol) was added to a hot solution of (±)-**3** (1.13 g, 4.84 mmol) in ethanol (15.2 mL) and water (7.4 mL). The solution was allowed to stand for 2 days at room temperature. The salt thus formed was recrystallized five times from ethanol/water. The crystals were treated with 1 M sodium hydroxide and the free amine was extracted with ether. The organic layer was dried (potassium carbonate), filtered, and concentrated. The resulting base was converted into the hydrochloride. Recrystallization from methanol/ether afforded 0.248 g (38%) of (−)-**3**·HCl. The free amine (0.81 g, 3.47 mmol) that was isolated from the mother liquors in the resolution of (−)-**3** was treated with (+)-dibenzoyl-D-tartaric acid monohydrate (1.31 g, 3.48 mmol) as described above. After four recrystallizations from ethanol and water, the hydrochloride was prepared and recrystallized to give 0.298 g (46%) of (+)-**3**·HCl.

Resolution of (±)-*cis*-5-Methoxy-3-methyl-2-(*n*-propylamino)tetralin [(±)-6]. (−)-Di-*p*-toluoyl-L-tartaric acid monohydrate (9.60 g, 23.7 mmol) was added to a hot solution of (±)-**6** (5.54 g, 23.7 mmol) in ethanol (140 mL) and water (39 mL). The solution was allowed to stand for 1 week at room temperature. The salt thus formed was recrystallized twice from ethanol/water. The crystals were treated with 1 M sodium hydroxide and the free amine was extracted with ether. The organic layer was dried (potassium carbonate), filtered, and concentrated. The resulting base was coverted to the hydrochloride. Recrystallization from methanol/ether afforded 2.19 g (68%) of (−)-**6**·HCl. The free amine (3.46 g, 14.8 mmol) isolated from the mother liquors in the preparation of (−)-**6** was treated with (+)-di-*p*-toluoyl-D-tartaric acid monohydrate (6.00 g, 14.8 mmol) as described above. After two recrystallizations from ethanol/water the hydrochloride was prepared and recrystallized to give 2.32 g (72%) of (+)-**6**·HCl.

Determination of Enantiomeric Excess. The enantiomeric excess (% ee) of the secondary amines (+)-**3** and (−)-**3** was determined as follows: The sample to be tested [(+)- or (−)-**3**·HCl; 20 mg, 74.1 μmol] was mixed with water (0.26 mL) and 1 M sodium hydroxide (0.12 mL) under nitrogen, in a flask equipped with a magnetic stirrer. A solution of (*R*)-(−)-2-methoxy-2-phenylacetyl chloride (114 mmol) [prepared from (*R*)-*O*-methylmandelic acid and thionyl chloride, by stirring at room temperature for 2 h followed by evaporation of volatiles] in dichloromethane (0.5 mL) was added under stirring at room temperature. After 1 h the organic layer was separated, dried (magnesium sulfate), filtered, and concentrated. The enantiomeric excess was determined by capillary GC to be ≈94% for (+)- and (−)-**3**, respectively. The enantiomeric excess of the secondary amines (+)- and (−)-**6** was determined by HPLC analysis of the corresponding diastereomeric (*R*)-*O*-methylmandelic amides (prepared as above for (+)- and (−)-**3**·HCl), to be ≈96%, respectively.

Optical Rotations. The resolved compounds presented in Table I have the following optical rotations ($[\alpha]^{22}_D$, methanol): (+)-**3**, +67.0° (*c* 0.9); (−)-**3**, −67.3° (*c* 1.0); (+)-**4**, +90.9° (*c* 1.0); (−)-**4**, −90.6° (*c* 0.9); (+)-**5**, +95.7° (*c* 0.9); (−)-**5**, −91.7° (*c* 0.8); (+)-**6**, +36.3° (*c* 0.9); (−)-**6**, −36.8° (*c* 1.0); (+)-**7**, +45.4° (*c* 1.0); (−)-**7**, −45.5° (*c* 1.0); (+)-**8**, +45.3° (*c* 1.0); (−)-**8**, −47.6° (*c* 1.0).

Absolute Configuration Determination by Single-Crystal X-ray Analysis for (−)-5·HBr and (−)-7·HCl. Crystals of (−)-**5**·HBr and (−)-**7**·HCl were grown from methanol/ether solutions. Crystals with the dimensions 0.67 × 0.05 × 0.03 mm of (−)-**5**·HBr and 0.35 × 0.30 × 0.20 mm of (−)-**7**·HCl were used for data collections with an Enraf-Nonius CAD4F-11 diffractometer. The angular settings of 25 reflections were measured to calculate the lattice parameters (cf. Table V for crystal data). Intensity data for reflections within one hemisphere and with $\theta < 60°$ were collected by the $\theta/2\theta$ scan method with monochromated Cu Kα radiation. Three intensity control reflections, which were measured every 2 h, indicated a slight decay (2% for (−)-**5**·HBr and 3% for (−)-**7**·HCl) of the crystals. The measured intensities were rescaled to account for these decays. A total of 2738 and 5804 reflections were recorded for (−)-**5**·HBr and (−)-**7**·HCl, respectively. Of these 2207 for (−)-**5**·HBr and 5312 for (−)-**7**·HCl having $I > 3\sigma(I)$ were considered observed. All intensities were corrected for Lorentz and polarization effects but not for absorption or extinction.

Table V. Crystal Data for (−)-**5**·HBr and (−)-**7**·HCl

	(−)-**5**·HBr	(−)-**7**·HCl
formula	$C_{17}H_{27}NO$·HBr	$C_{18}H_{29}NO$·HCl
space group	$P2_1$	$P2_1$
a, Å	8.786 (2)	7.684 (1)
b, Å	7.549 (5)	15.015 (3)
c, Å	13.618 (2)	15.633 (2)
β, deg	105.69 (2)	93.35 (1)
d_{calcd}, g cm^{-3}	1.310	1.150
μ, cm^{-1}	35.2	18.6

The structures were solved by a combination of the Patterson heavy-atom method and direct methods with the program DIRDIF[27] which provided the non-hydrogen atom positions. Methyl and hydroxyl hydrogen positions were determined from Fourier difference synthesis maps and remaining hydrogen atoms were included at expected positions. Refinements were carried out by the full-matrix least-squares method using anisotropic temperature factors for the non-hydrogen atoms. The hydrogen atoms were assigned a common temperature factor (B = 5 Å^2). The hydrogen atom parameters were not refined. In order to determine the absolute configurations of (−)-**5**·HBr and (−)-**7**·HCl, anomalous dispersion factors[28] were introduced for the non-hydrogen atoms. The atomic parameters of the non-hydrogen atoms for both enantiomers were then refined. 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 for (−)-**5**·HBr was finished, the residuals for the 2*R*,3*R* and 2*S*,3*S* enantiomers were calculated to be R = 0.034 (R_w = 0.047) and R = 0.043 (R_w = 0.062), respectively. Corresponding residuals for the 2*R*,3*S* and 2*S*,3*R* enantiomers of (−)-**7**·HCl were R = 0.040 (R_w = 0.051) and R = 0.060 (R_w = 0.082), respectively. With Hamilton's test,[29] the ratios R_w (2*S*,3*S*)/R_w (2*R*,3*R*) for (−)-**5**·HBr and R_w (2*S*,3*R*)/R_w (2*R*,3*S*) for (−)-**7**·HCl were sufficiently great to reject the 2*S*,3*S* and 2*S*,3*R* enantiomers, respectively, at the 0.005 significance level. Furthermore, among

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the 35 Bijvoet pairs for the 2*R*,3*R* enantiomer of (–)-**5**-HBr and the 2*R*,3*S* enantiomer of (–)-**7**-HCl, for which $|F_c(h,k,l) - F_c(h,-k,l)| > 1.1$ for (–)-**5**·HBr and 1.8 for (–)-**7**-HCl, 68 and 33 of the *Fc* differences, respectively, had the same sign as the corresponding F_o differences. The weighting scheme used in the later part of the refinement was $w = 1/[1 + ((|F_o| - A)/B)^2]$,[30] where $A = 10$ and $B = 9$ for (–)-**5**-HBr and $A = 8$ and $B = 4$ for (–)-**7**-HCl. The form factors used were those given by Cromer and Mann.[31] All calculations have been performed on a DEC-system-10 computer using mainly the X-ray 72 program system.[32]

The molecular conformations and atomic labeling schemes are shown in Figure 1.

Molecular Mechanics Calculations. The structural modelling was performed by use of the interactive computer graphics program MIMIC (methods for interactive modelling in chemistry).[16] Calculations were performed on a VAX 11/780 computer using Allingers MMP2 force field,[33] to which had been added parameters for the phenol[34] and amino groups.[35] Computational times ranged from 1 to 25 min/minimization.

Pharmacology. Materials and Methods. Male Sprague–Dawley rats weighing 200–300 g (ALAB, Stockholm, Sweden) were used. Reserpine and haloperidol were dissolved in a few drops of glacial acetic acid and made up to volume with 5.5% glucose solution. The other test compounds were dissolved in saline immediately before use. Injection volumes were 5 mL/kg, and injection solutions had approximately neutral pH.

Biochemistry. Brain levels of DOPA and 5-HTP were analyzed by HPLC with electrochemical detection.[21] For biochemical results and experimental details, see Tables III and IV and footnotes *a* in Tables III and IV.

Locomotor Activity. The motor activity was measured by means of photocell recordings ("M/P 40 Fc Electronic Motility Meter", Motron Products, Stockholm, Sweden) as previously described.[17] For experimental details, see footnotes *b* in Tables III and IV. Each box was equipped with a semitransparent mirror that allowed gross behavior observations of the animals during the experiments. The motor activity results are shown in Tables III and IV.

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Supplementary Material Available: Complete lists of identified low-energy conformations and steric energies and X-ray data of (–)-**5**·HBr and (–)-**7**-HCl, including positional and thermal parameters, bond lengths, and bond angles (6 pages); tables of observed and calculated structure factors (61 pages). Ordering information is given on any current masthead page.

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N,N-Dialkylated Leucine Enkephalins as Potential δ Opioid Receptor Antagonists[1]

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A series of N,N-dialkylated leucine enkephalins were prepared in order to study the effect of substitution on antagonist activity at the δ opioid receptor. The target peptides **1–7** were evaluated in the mouse vas deferens (MVD) and guinea pig ileum (GPI) at 1 μM. All of the compounds except [*N*,*N*-di-2-phenethyl,Leu^5]enkephalin (**7**) showed antagonist activity in the MVD against the δ receptor agonist [D-Ala^2,D-Leu^5]enkephalin. The most potent congener, [*N*,*N*-dibenzyl,Leu^5]enkephalin (**3**), was 2.5-fold more potent than [*N*,*N*-diallyl,Leu^5]enkephalin (**1**). None of the compounds at 1 μM showed any antagonist activity against agonists for other receptor types. The *N*,*N*-di-2-phenethyl (**7**) and *N*,*N*-dioctyl (**6**) analogues showed significant agonist activity at 1 μM in the MVD.

Since Martin and co-workers[3,4] reported evidence for multiple opioid receptors, a considerable amount of research has focused on the development of ligands specific for each of the receptor types. Such specific ligands, especially antagonists, can be very useful biochemical tools, both for determining differences between receptor types and for studying their roles in various biological processes.

The discovery of the enkephalins[5] introduced a new class of ligands for the opioid receptor and another receptor type, the δ receptor.[6] Because the classical alkaloid opiate antagonists, such as naloxone and naltrexone, interact preferentially with the μ receptor,[7,8] attention was turned

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