C1- and C3-Methyl-Substituted Derivatives of 7-Hydroxy-2-(di-*n*-propylamino)tetralin: Activities at Central Dopamine Receptors

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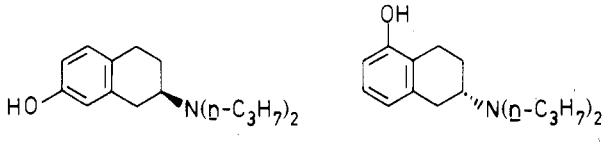
C1- and C3-methyl-substituted derivatives of the potent dopamine (DA) receptor agonist 7-hydroxy-2-(di-*n*-propylamino)tetralin (7-OH-DPAT) have been synthesized, and their conformational preferences have been studied by use of NMR spectroscopy, X-ray crystallography, and molecular mechanics (MMP2) calculations. The compounds were tested for activity at central DA receptors, by use of biochemical and behavioral tests in rats. (1*S*,2*R*)-7-Hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin [(+)-**10**] was demonstrated to be sevenfold less potent than (2*R*)-7-OH-DPAT as a DA receptor agonist. The other new compounds were of lower potency or inactive.

Racemic 7-hydroxy-2-(di-*n*-propylamino)tetralin (7-OH-DPAT)[1,2] is a potent centrally acting dopamine (DA) receptor agonist that acts at both pre- and postsynaptic receptors. Resolution of (±)-7-OH-DPAT and pharmacological evaluation of the enantiomers revealed that the more active enantiomer has the 2*R* configuration.[1e-g,3]

(2*S*)-5-Hydroxy-2-(di-*n*-propylamino)tetralin [(2*S*)-5-OH-DPAT][1a,b,e-g,3] has been shown to be the most potent DA receptor agonist of the monohydroxylated 2-(dipropylamino)tetralins. It has been suggested by McDermed et al.[1e] that the dopaminergic activity of (2*S*)-5-OH-DPAT and (2*R*)-7-OH-DPAT can be rationalized by fitting the compounds as shown in Figure 1.



(2R)-7-OH-DPAT (2S)-5-OH-DPAT

Compounds with a methyl group in the C1-,[4] C2-,[5] or C3-position[6] of 5-OH-DPAT have different effects at central monoaminergic neurons. However, in that series the DA receptor agonists have the same sense of chirality at C2 and they are able to assume a "DA D_2 receptor agonist conformation" with Φ values around 0° and τ_N values around 60°.[4c,6,7,9]

To further elucidate the stereochemical requirements for DA D_2 receptor agonism[11] and antagonism, we have synthesized and evaluated pharmacologically some C1- and C3-methylated derivatives of 7-OH-DPAT. In addition, we have analyzed their conformational preferences. In the present series, all compounds seem to be less potent as DA receptor agonists[12] than (2*R*)-7-OH-DPAT.

Chemistry

Syntheses. The 2-aminotetralin derivatives presented in Table I were prepared from 7-methoxy-1-methyl-2-tetralone (**1**)[13] or from 7-methoxy-3-methyl-2-tetralone (**2**),[14] which was synthesized from *p*-methoxybenzyl alcohol (**3**). The syntheses of the 2-aminotetralin derivatives, which are based on literature procedures,[4a,b,d,6,15] are outlined in Scheme I.

trans-2-Amino-7-methoxy-1-methyltetralin (**4**) was prepared from the oxime of **1** by reduction with sodium

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(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) Feenstra, M. G. P.; Rollema, H.; Dijkstra, D.; Grol, C. J.; Horn, A. S.; Westerink, B. H. C. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1980**, *313*, 213. (d) Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H. *J. Med. Chem.* **1981**, *24*, 921. (e) 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. (f) Seiler, M. P.; Markstein, R. *Mol. Pharmacol.* **1982**, *22*, 281. (g) Seiler, M. P.; Markstein, R. *Mol. Pharmacol.* **1984**, *26*, 452.

(2) The numbering system used in the running text, Experimental Section, and most of the tables is defined in the structure in Table I. The X-ray numbering system, which is different, is defined in Figure 2 and is used in Tables III and IV and in the supplementary material.

(3) 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.

(4) (a) 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. (b) 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. (c) Johansson, A. M.; Karlén, A.; Grol, C. J.; Sundell, S.; Kenne, L.; Hacksell, U. *Mol. Pharmacol.* **1986**, *30*, 258. (d) Johansson, A. M.; Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G.; Svensson, K.; Carlsson, A. *J. Med. Chem.* **1987**, *30*, 602. (e) 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. (f) Svensson, K.; Carlsson, A.; Johansson, A. M.; Arvidsson, L.-E.; Nilsson, J. L. G. *J. Neural Transm.* **1986**, *65*, 29. (g) Svensson, K.; Johansson, A. M.; Magnusson, T.; Carlsson, A. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1986**, *334*, 234. (h) Svensson, K.; Carlsson, M.; Carlsson, A.; Hjorth, S.; Johansson, A. M.; Eriksson, E. *Eur. J. Pharmacol.* **1986**, *130*, 237. (i) Svensson, K.; Alföldi, P.; Hajos, M.; Rubicsek, G.; Johansson, A. M.; Carlsson, A.; Obal, F., Jr. *Pharmacol., Biochem. Behav.* **1987**, *26*, 123. (j) Svensson, K. thesis, ISBN 91-7900-078-9, Department of Pharmacology, University of Göteborg, Göteborg, Sweden, 1986.

(5) (a) Andersson, B.; Sanchez, D.; Lindberg, P.; Wikström, H.; Svensson, K.; Hjorth, S.; Carlsson, A.; Arvidsson, L.-E.; Johansson, A. M.; Hacksell, U.; Nilsson, J. L. G. *Acta Pharm. Suec. Suppl. 2*, **1985**, 139. (b) 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.

(6) Johansson, A. M.; Nilsson, J. L. G.; Karlén, A.; Hacksell, U.; Svensson, K.; Carlsson, A.; Kenne, L.; Sundell, S. *J. Med. Chem.* **1987**, *30*, 1135.

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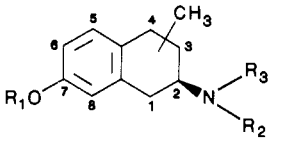
Table I. Physical Data of the Compounds Studied



compd	CH_3 pos	R_1	R_2	R_3	prepn meth	yield, %	mp, °C	recrystn[a] solvents	formula
(±)-4	C1-trans	Me	H	H	I	41	231–232.5[b]	A	$C_{12}H_{17}NO{\cdot}HCl{\cdot}^1/_4H_2O$
(+)-4	C1-trans	Me	H	H	*c*	62	247–249[b]	A	$C_{12}H_{17}NO{\cdot}HCl$
(−)-4	C1-trans	Me	H	H	*c*	60	256–257[b]	A	$C_{12}H_{17}NO{\cdot}HCl$
(+)-5	C1-trans	Me	*n*-Pr	*n*-Pr	III	84	157.5–158.5	A	$C_{18}H_{29}NO{\cdot}HCl$
(−)-5	C1-trans	Me	*n*-Pr	*n*-Pr	III	81	157.5–158.5	A	$C_{18}H_{29}NO{\cdot}HCl$
(+)-6	C1-trans	H	*n*-Pr	*n*-Pr	IV	82	206–207.5	B	$C_{17}H_{27}NO{\cdot}HCl$
(−)-6	C1-trans	H	*n*-Pr	*n*-Pr	IV	85	207–209	B	$C_{17}H_{27}NO{\cdot}HCl$
(±)-7	C1-cis	Me	*n*-Pr	H	II	40	177.5–179	A	$C_{15}H_{23}NO{\cdot}HCl$
(+)-7	C1-cis	Me	*n*-Pr	H	*c*	43	230–231	B	$C_{15}H_{23}NO{\cdot}HCl$
(−)-7	C1-cis	Me	*n*-Pr	H	*c*	56	229–231	B	$C_{15}H_{23}NO{\cdot}HCl$
(+)-8	C1-cis	H	*n*-Pr	H	IV	93	255–256.5	B	$C_{14}H_{21}NO{\cdot}HCl$
(−)-8	C1-cis	H	*n*-Pr	H	IV	90	253–255	A	$C_{14}H_{21}NO{\cdot}HCl{\cdot}^1/_5H_2O$
(+)-9	C1-cis	Me	*n*-Pr	*n*-Pr	III	73	195–196	B	$C_{18}H_{29}NO{\cdot}HCl$
(−)-9	C1-cis	Me	*n*-Pr	*n*-Pr	III	89	195–196	B	$C_{18}H_{29}NO{\cdot}HCl$
(+)-10	C1-cis	H	*n*-Pr	*n*-Pr	IV	89	188.5–190	A	$C_{17}H_{27}NO{\cdot}HCl$
(−)-10	C1-cis	H	*n*-Pr	*n*-Pr	IV	79	159–161	B	$C_{17}H_{27}NO{\cdot}HCl$[d]
11	C3-trans	Me	H	H	I	42	272–274[b,e]	B	$C_{12}H_{17}NO{\cdot}HCl{\cdot}1H_2O$
12	C3-trans	Me	*n*-Pr	*n*-Pr	III	81	162–162.5	B	$C_{18}H_{29}NO{\cdot}HCl$
13	C3-trans	H	*n*-Pr	*n*-Pr	IV	92	185–187	A	$C_{17}H_{27}NO{\cdot}HCl{\cdot}^1/_5H_2O$
14	C3-cis	Me	*n*-Pr	H	II	31	245.5–247	B	$C_{15}H_{23}NO{\cdot}HCl$
15	C3-cis	Me	*n*-Pr	*n*-Pr	III	76	197–197.5	A	$C_{18}H_{29}NO{\cdot}HCl$
16	C3-cis	H	*n*-Pr	*n*-Pr	IV	90	224.5–226	A	$C_{17}H_{27}NO{\cdot}HCl$

[a] Recrystallization solvents: A, methanol–ether; B, ethanol–ether. [b] Decomposition. [c] See Experimental Section. [d] Anal. Calcd for $C_{17}H_{27}NO{\cdot}HCl$: C, 68.6. Found: C, 68.1. [e] Sublimation occurred.

in 2-propanol (method I). This reaction produced a mixture of cis and trans isomers, from which the pure trans isomer was obtained by crystallization of the hydrochlorides. Racemic **4** was resolved into the (+)- and (−)-enantiomers by crystallization of the diastereomeric dibenzoyltartrates. N-Alkylation of (−)-**4** and (+)-**4** by use of 1-iodopropane (method III) gave (+)-**5** and (−)-**5**, respectively.

cis-7-Methoxy-1-methyl-2-(*n*-propylamino)tetralin (**7**)

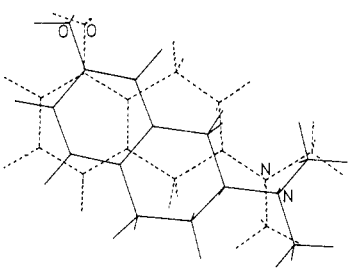


Figure 1. Computer-generated fit of "DA D_2 receptor agonist conformations" of (2*R*)-7-OH-DPAT (Φ = 164°; τ_N = −57°; solid lines) and (2*S*)-5-OH-DPAT (Φ = 344°; τ_N = 57°; dashed lines). Mean distance between fitted atoms [O, O–*H*, C7, C8a, N, N-*electron pair* in (2*S*)-5-OH-DPAT and O, O–*H*, C6, C4a, N, N-*electron pair* in (2*R*)-7-OH-DPAT] is 0.59 Å. For clarity, only the dimethylamino moieties are shown.

(7) To characterize different conformations of the 2-aminotetralins, 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

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

maximal value (64.73°) of the torsion angle τ(C1,C2,C3,C4).[8] 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 pseudoaxially oriented amino group corresponds to Φ = 180°. In contrast, a half-chair conformation of (2*R*)-2-aminotetralin with a pseudoequatorial amino group corresponds to Φ = 180° while a half-chair conformation with a pseudoaxial amino group corresponds to Φ = 0°. Φ values of 90° and 270° correspond to boat conformations. 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 definitions of additional geometrical parameters, see footnotes *e* and *f* in Table V. For further details, see ref 4c and 10.

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

(9) Recently, others have also discussed stereochemical requirements for DA receptor agonists and antagonists with corroborating conclusions. (a) Froimowitz, M.; Neumeyer, J. L.; Baldessarini, R. J. *J. Med. Chem.* **1986**, *29*, 1517. (b) Liljefors, T.; Wikström, H. *J. Med. Chem.* **1986**, *29*, 1896.

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

(11) For recent reviews discussing the 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.

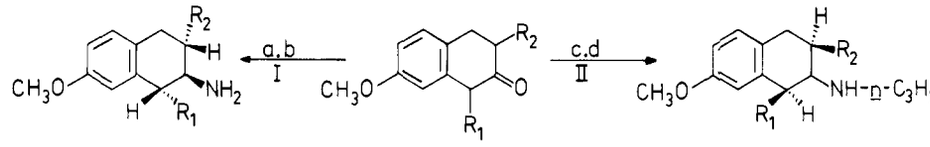
(12) Due to structural and pharmacological similarities between (2*R*)-7-OH-DPAT and (+)-**10**, it is reasonable to assume that they bind to DA D_2 receptors. See also discussion in the pharmacology section and in ref 4c and 6.

(13) Kuehne, M. E. *J. Am. Chem. Soc.* **1961**, *83*, 1492.

(14) Johansson, A. M.; Mellin, C.; Hacksell, U. *J. Org. Chem.* **1986**, *51*, 5252.

(15) Hacksell, U.; Svensson, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Wikström, H.; Lindberg, P.; Sanchez, D. *J. Med. Chem.* **1979**, *22*, 1469.

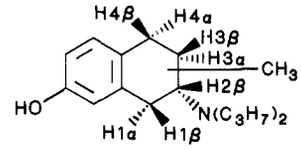
Scheme I[a]



4: R_1=CH_3, R_2=H; 1: R_1=CH_3, R_2=H; 7: R_1=CH_3, R_2=H
11: R_1=H, R_2=CH_3; 2: R_1=H, R_2=CH_3; 14: R_1=H, R_2=CH_3

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

Table II. ^{1}H NMR Spectral Data of Five 2-Aminotetralin Derivatives in CD_3OD



		chemical shifts, δ						
compd	CH_3 pos	H1α	H1β	H2β	H3α	H3β	H4α	H4β
6·HCl	1β	3.16		3.66	1.8[a]	2.33	2.7[a]	2.7[a]
10·HCl	1α		3.36	3.67	2.08	2.23	2.96	2.86
13·HCl	3β	3.00	3.06	3.49	2.27		2.90	2.54
16·HCl	3α	2.95	3.2[a]	3.68		2.7[a]	2.7[a]	3.03
7-OH-DPAT·HCl		3.04	3.10	3.72	1.91	2.29	2.91	2.84

	coupling constants (J, Hz)										
compd	$J_{1\alpha,1\beta}$	$J_{1\alpha,2\beta}$	$J_{1\beta,2\beta}$	$J_{2\beta,3\alpha}$	$J_{2\beta,3\beta}$	$J_{3\alpha,3\beta}$	$J_{3\alpha,4\beta}$	$J_{3\alpha,4\alpha}$	$J_{3\beta,4\beta}$	$J_{3\beta,4\alpha}$	$J_{4\beta,4\alpha}$
6·HCl	b	3.6		b	5.5	−13.6	b	b	5.6	5.5	b
10·HCl	b		4.4	12.4	3.2	−12.2	11.8	6.5	6.4	2.0	−17.4
13·HCl	−15.6	9.2	6.0	≈8.0[c]			9.1	5.1			−15.7
16·HCl	−15.9	11.8	5.8		2.8				5.0	b	−17.0
7-OH-DPAT·HCl	−15.6	11.2	5.6	11.6	3.0	−12.0	11.8	5.8	5.0	2.9	−16.5

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

was obtained by reductive amination of **1** (method II); the catalytic hydrogenation of the intermediate imine afforded a mixture of cis and trans stereoisomers. Pure (±)-**7** was obtained by crystallization of the hydrochlorides. Racemic **7** was resolved into the (+)- and (−)-enantiomers by crystallization of the diastereomeric di-*p*-toluoyltartrates. Compounds (+)-**7** and (−)-**7** were N-alkylated with 1-iodopropane (method III) to afford (+)-**9** and (−)-**9**, respectively.

The racemic 2-amino-7-methoxy-3-methyltetralin derivatives **11** and **14** were prepared from **2**, by use of methods I and II. N-Alkylation (method III) of **11** and **14** gave **12** and **15**, respectively.

The phenols presented in Table I were prepared from the corresponding methoxy-substituted derivatives by use of aqueous 48% hydrogen bromide, followed by halogen interchange.

NMR Spectroscopy. High-resolution ^{1}H NMR spectral data of **6**·HCl, **10**·HCl, **13**·HCl, **16**·HCl, and 7-OH-DPAT·HCl in CD_3OD are shown in Table II.[16]

Use of 400-MHz spectroscopy allowed analysis of several resonances by first-order approximations, but some spectra were complicated to interpret due to overlapping resonances. Thus, although COSY spectroscopy allowed unambiguous assignments of all proton resonances, several coupling constants remain undetermined. Nevertheless, on the basis of the observed coupling constants, the following conclusions can be drawn. The large dipseudoaxial coupling constants $J_{1\alpha,2\beta}$ in **13**·HCl, **16**·HCl, and 7-OH-DPAT·HCl and $J_{2\beta,3\alpha}$ in **10**·HCl, **13**·HCl, and 7-OH-DPAT·HCl indicate that these four compounds prefer to assume half-chair conformations with pseudoequatorial dipropylammonium substituents in CD_3OD.[4c,6,9,16] This is supported by the large value of $J_{3\alpha,4\beta}$ in **10**·HCl, **13**·HCl, and 7-OH-DPAT·HCl and by the small value of $J_{3\beta,4\alpha}$ in **10**·HCl and 7-OH-DPAT·HCl. The COSY spectra (in which detection of long-range couplings was optimized) of **16**·HCl and 7-OH-DPAT·HCl revealed small couplings (*W* couplings[17]) between H1β and H3β and, for **16**·HCl, also between the C3-methyl hydrogens and H4β, which provide additional support for the suggested predominating solution conformations of **16**·HCl and 7-OH-DPAT·HCl.

In the ^{1}H NMR spectrum of **6**·HCl, no large vicinal coupling constants are present. Thus, this spectrum differs considerably from spectra of the other compounds investigated. Also the ^{1}H NMR spectra of *trans*-5-hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin hydrochloride (**17**; AJ-116·HCl; in CD_3OD)[4c] and 2-amino-6,7-dimethoxy-2-methyltetralin (**18**; in $CDCl_3$)[16a] have been observed to lack large (diaxial) coupling constants. This may be due to the existence of two approximately equally populated tetralin ring conformations (with the dipropylammonium group in pseudoaxial or pseudoequatorial positions; Φ values being around 0° and 180°, respectively) in solution.[4c,16a] Thus, the spectrum of **6**·HCl may also reflect a time average of equilibrating tetralin ring conformations. The rather small (3.6 Hz) coupling constant $J_{1\alpha,2\beta}$ might, for example, be the weighted average of a small dipseudoe-

(16) For other NMR spectral studies of 2-aminotetralins, see ref 4c, 6, 10, 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.

(17) See, for example: Jackman, L. M.; Sternhell, S. *Applications of NMR Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon: Oxford, 1969.

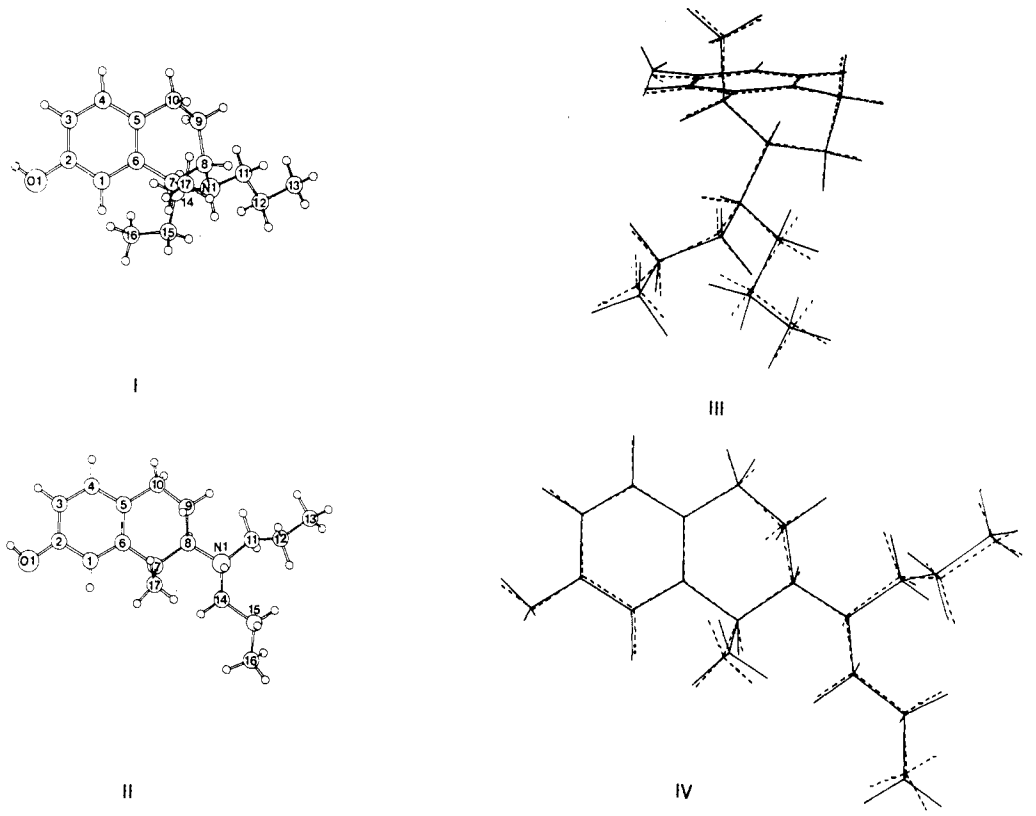


Figure 2. Molecular conformations and atomic labeling schemes for (+)-**6**·HCl (I; $\Phi = 293°$; $\tau_N = -54°$) and (+)-**10**·HCl (II; $\Phi = 165°$; $\tau_N = -69°$). The best fit (III and IV) between the carbon, oxygen, and nitrogen atoms of the MMP2 minimized conformations and the X-ray conformations (I and II, respectively) gave average distances of 0.09 Å (III) and 0.14 Å (IV).

Table III. Atomic Coordinates for the Non-Hydrogen Atoms of (+)-**6**·HCl[a]

atom	*x*	*y*	*z*
Cl	1.0912 (1)	0.2425 (1)	0.8052 (1)
O	0.8196 (4)	0.2675 (3)	0.3369 (2)
N	0.7634 (5)	0.2093 (3)	0.7378 (2)
C1	0.8535 (6)	0.2009 (4)	0.4719 (3)
C2	0.7799 (6)	0.1931 (5)	0.3963 (3)
C3	0.6710 (6)	0.1127 (5)	0.3828 (3)
C4	0.6332 (6)	0.0415 (5)	0.4456 (4)
C5	0.7053 (6)	0.0472 (4)	0.5225 (3)
C6	0.8166 (6)	0.1272 (4)	0.5352 (3)
C7	0.9016 (6)	0.1283 (4)	0.6167 (3)
C8	0.7967 (6)	0.1040 (4)	0.6917 (3)
C9	0.6479 (7)	0.0428 (5)	0.6714 (3)
C10	0.6621 (7)	−0.0251 (5)	0.5929 (4)
C11	0.6779 (7)	0.1847 (5)	0.8162 (3)
C12	0.6894 (9)	0.2695 (7)	0.8807 (4)
C13	0.6049 (11)	0.2356 (6)	0.9581 (4)
C14	0.6849 (6)	0.2951 (4)	0.6860 (3)
C15	0.7460 (8)	0.4078 (5)	0.6957 (4)
C16	0.6772 (9)	0.4865 (5)	0.6341 (5)
C17	1.0346 (6)	0.0443 (6)	0.6142 (3)

[a] Estimated standard deviations are given in parentheses.

Table IV. Atomic Coordinates for the Non-Hydrogen Atoms of (+)-**10**·HCl[a]

atom	*x*	*y*	*z*
Cl	0.4724 (1)	0.4111 (1)	0.7097 (2)
N	0.4767 (3)	0.6163 (3)	0.8220 (4)
O	0.6087 (3)	0.8724 (4)	0.1093 (5)
C1	0.5635 (3)	0.7936 (4)	0.3387 (6)
C2	0.5368 (4)	0.8435 (3)	0.2069 (6)
C3	0.4425 (4)	0.8634 (4)	0.1812 (6)
C4	0.3749 (4)	0.8276 (4)	0.2831 (8)
C5	0.3985 (4)	0.7754 (3)	0.4135 (7)
C6	0.4954 (3)	0.7573 (3)	0.4401 (5)
C7	0.5293 (3)	0.6951 (3)	0.5719 (5)
C8	0.4510 (3)	0.6836 (3)	0.6936 (5)
C9	0.3560 (3)	0.6574 (3)	0.6156 (6)
C10	0.3232 (4)	0.7373 (4)	0.5183 (8)
C11	0.3996 (6)	0.6234 (8)	0.9488 (10)
C12	0.3708 (9)	0.5481 (6)	1.0190 (18)
C13	0.3058 (5)	0.5728 (8)	1.1636 (8)
C14	0.5730 (4)	0.6384 (4)	0.8922 (7)
C15	0.6071 (6)	0.5691 (5)	1.0135 (9)
C16	0.7083 (5)	0.5896 (7)	1.0672 (9)
C17	0.5670 (4)	0.6033 (4)	0.5019 (6)

[a] Estimated standard deviations are given in parentheses.

quatorial and a large dipseudoaxial coupling constant. ^{13}C NMR spectroscopy revealed that rotation around the C2–N bond is slow on the NMR time scale in compounds **6**·HCl, **10**·HCl, **13**·HCl, and **16**·HCl; this was evident from the magnetic nonequivalence of Cα and Cα' (**6**·HCl, **13**·HCl, and **16**·HCl) and of Cβ and Cβ' (**10**·HCl and **13**·HCl).[18]

X-ray Crystallography.[19] X-ray crystallography of (+)-**6**·HCl and (+)-**10**·HCl established the absolute configurations as 1*S*,2*S* and 1*S*,2*R*, respectively (see Figure 2 and the Experimental Section; atomic coordinates for the non-hydrogen atoms of (+)-**6**·HCl and (+)-**10**·HCl are given in Tables III and IV, respectively). This also establishes the absolute configuration of (−)-**6**, (−)-**10**, and the enantiomers of **4**, **5**, and **7**–**9**. In the crystal structure of (+)-**10**·HCl, the C11–C12 bond length appears to be short (1.298 Å). As indicated by the high temperature factors of C11 and C12 (supplementary material), this is most likely due to disorder in the crystal.

It should also be noted that *the sign of the optical rotation at the* D *line is not strictly correlated with the*

(18) For definitions of Cα, Cα', Cβ, and Cβ', see ref 4c and 10.
(19) For X-ray crystallographic studies of other 2-aminotetralin derivatives, see ref 4c, 6, and: (a) Giesecke, J. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1980**, *B36*, 110. (b) Horn, A.; Rodgers, J. R. *J. Pharm. Pharmacol.* **1980**, *32*, 521.

Table V. Geometrical Parameters for Low-Energy MMP2 Conformations[a] of (2*R*)-7-OH-DPAT, (1*R*,2*R*)-**6**, (1*S*,2*R*)-**10**, (2*S*,3*S*)-**13**, and (2*S*,3*R*)-**16**

conformation	Φ,[b] deg	τ_1,[c] deg	τ_N,[d] deg	τ_A,[e] deg	τ_B,[e] deg	$\tau_{A'}$,[f] deg	$\tau_{B'}$,[f] deg	rel steric energy, kcal/mol
				(2*R*)-7-OH-DPAT				
A	195[g]	−66	55	−49	−170	175	−170	0.5
B	195[g]	−66	54	−50	−170	173	−55	0.8
C	195[g]	−66	53	−53	−56	174	−170	1.0
D	195[g]	−66	52	−55	−55	171	−53	1.0
E	180[g]	−66	31	66	174	172	−170	2.5
F	180[g]	−66	176	−173	170	52	171	0.0[h]
G	180[g]	−66	177	−172	169	55	56	0.4
H	180[g]	−66	177	−171	54	54	171	0.2
I	180[g]	−66	177	−170	53	56	56	0.4
J	164	−62	−57	178	170	−61	−178	0.6
K	164	−62	−57	−179	56	−60	−178	1.0
L	163	−62	−64	63	178	−177	−171	0.6
M	164	−62	−64	63	179	180	−57	1.2
N	25[g]	68	−61	177	171	−64	−177	0.9
O	25[g]	68	−61	−179	57	−64	−178	1.2
P	25[g]	68	−66	62	180	180	−170	0.6
Q	25[g]	69	−66	62	180	176	−56	0.8
				(1*R*,2*R*)-**6**				
A	180[g]	−66	52	−50	−169	171	−55	0.1
B	180[g]	−66	53	−49	−170	174	−170	0.0[i]
C	180[g]	−66	51	−53	−56	173	−170	0.2
D	180[g]	−66	51	−55	−55	169	−53	0.0[i]
E	160[g]	−66	29	65	175	168	−55	2.3
F	160[g]	−66	29	66	174	171	−171	2.2
G	120[g]	−50	−56	−179	170	−64	179	2.5
H	25[g]	56	60	−52	−172	169	−169	2.5
I	25[g]	66	−61	176	171	−63	−176	1.0
J	25[g]	66	−61	180	57	−63	−177	1.3
K	25[g]	67	−66	60	180	176	−56	0.8
L	25[g]	67	−66	61	179	−179	−170	0.7
				(1*S*,2*R*)-**10**				
A	195	−62	−54	180	170	−61	180	0.0[j]
B	195	−62	−54	−177	56	−61	180	0.2
C	196	−62	−59	64	177	−179	−58	0.8
D	196	−62	−59	64	177	−179	−171	0.3
				(2*S*,3*S*)-**13**				
A	180[g]	−64	180	−167	170	53	170	0.0[k]
B	180[g]	−64	−179	−166	170	56	55	0.1
C	180[g]	−63	180	−168	54	53	170	0.1
D	180[g]	−63	−179	−168	53	57	55	0.0[k]
				(2*S*,3*R*)-**16**				
A	160	−61	−60	178	170	−62	−178	0.0[l]
B	160	−61	−60	−179	57	−61	−179	0.4
C	159	−60	−65	64	178	−178	−171	0.0[l]
D	159	−60	−65	64	179	179	−57	0.4

[a] Only conformations with τ(C6, C7, O, H) ≈ 0° are included, and conformations with energies larger than 2.5 kcal/mol above the respective global minimum have been omitted. [b] Tetralin inversion angle (Φ) that defines the conformation of the nonaromatic ring of any tetraline derivative. For definition, see footnote 7. [c] Value of the torsion angle τ(C1, C2, C3, C4). [d] $\tau_N = \tau$(C1, C2, N, electron pair). [e] The torsion angles $\tau_A = \tau$(C2, N, C_α, C_β) and $\tau_B = \tau$(N, C_α, C_β, C_γ) define the conformation of that *N*-propyl group which, in a clockwise sense, it next to the N–H bond (or the electron pair) when viewed along the C2–N bond. For further details, see ref 10. [f] The conformation of the second *N*-propyl group is defined by the torsion angles $\tau_{A'} = \tau$(C2, N, $C_{\alpha'}$, $C_{\beta'}$) and $\tau_{B'} = \tau$(N, $C_{\alpha'}$, $C_{B'}$, $C_{\gamma'}$). For further details, see ref 10. [g] Approximate Φ value estimated by comparison with relevant conformations of C2-unsubstituted tetralin. See tetralin geometries in the tetralin inversion wheel in ref 10. [h] Steric energy = 14.6 kcal/mol. [i] Steric energy = 17.7 kcal/mol. [j] Steric energy = 18.0 kcal/mol. [k] Steric energy = 15.5 kcal/mol. [l] Steric energy = 17.0 kcal/mol.

absolute configuration. For example, (1*S*,2*S*)-**4**·HCl is levorotatory and (1*S*,2*S*)-**5**·HCl is dextrorotatory when dissolved in methanol (compare ref 4d).

Molecular Mechanics Calculations. Slight modifications[6] of a previously described strategy[10] were used to identify low-energy conformations of 7-OH-DPAT and its C1- and C3-methyl-substituted derivatives. The starting geometry of the hydroxyl group was always set at τ(C6,C7,O,H) = 0° (test calculations have shown that conformations with τ(C6,C7,O,H) around 180° consistently have energies equal to those of the corresponding conformations with τ(C6,C7,O,H) around 0°).

Four conformations[7] of (1*S*,2*R*)-**10**, (2*S*,3*S*)-**13**, and (2*S*,3*R*)-**16**, respectively, 12 conformations of (1*R*,2*R*)-**6**, and 17 conformations of (2*R*)-7-OH-DPAT were identified within 2.5 kcal/mol of the respective global minimum (geometries and steric energies of low-energy conformations are given in Table V; the lowest energy conformation of each compound is depicted in Figure 3). Thus, the conformational mobility of **10**, **13**, and **16** appears to be considerably lower than that of **6** and (2*R*)-7-OH-DPAT. Figure 4 shows that (1*R*,2*R*)-**6**, (1*S*,2*R*)-**10**, (2*S*,3*S*)-**13**, (2*S*,3*R*)-**16**, and (2*R*)-7-OH-DPAT preferentially assume Φ values around 180° and that they except for (1*R*,2*R*)-**6**

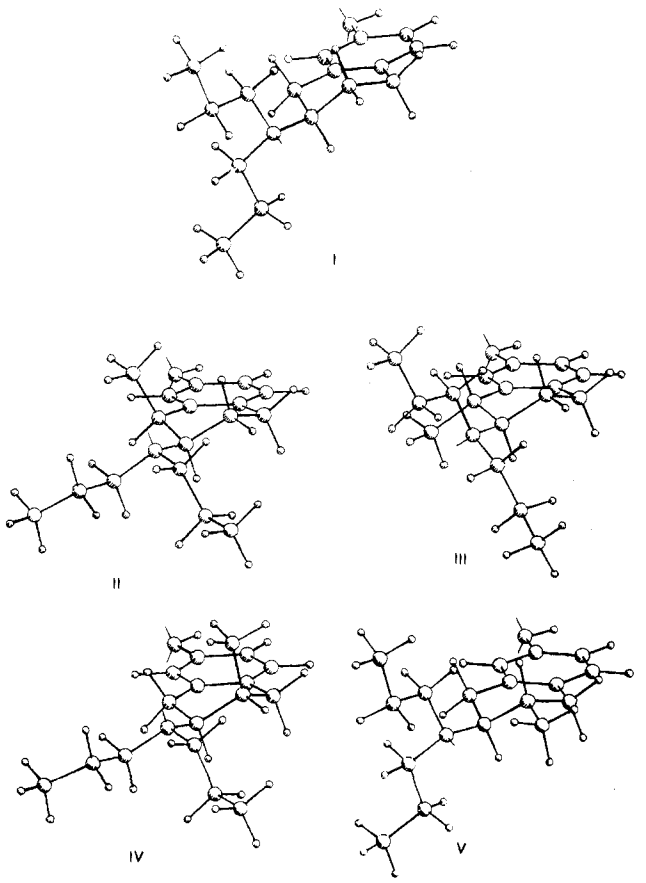


Figure 3. Calculated minimum energy MMP2 conformations of (2*R*)-7-OH-DPAT (I), (1*S*,2*R*)-**10** (II), (1*R*,2*R*)-**6** (III), (2*S*,3*R*)-**16** (IV), and (2*S*,3*S*)-**13** (V).

and (2*R*)-7-OH-DPAT, prefer to assume only one of the three possible dipropylamino group rotamers in tetralin conformations with Φ values around 180°. The driver option in the MIMIC[20] program was used to estimate if rotation around the C2–N bond is restricted in the *N*,*N*-dimethyl derivatives of (2*R*)-7-OH-DPAT, (1*R*,2*R*)-**6**, (1*S*,2*R*)-**10**, (2*S*,3*S*)-**13**, and (2*S*,3*R*)-**16** in conformations with Φ values around 180° (see Figure 5). The same preferred τ_N values were identified by the driver procedure and the nonrestricted minimization procedure (see Figures 4 and 5). The results demonstrate that there is a considerable barrier to rotation in the model compounds of the C1- and C3-methyl-substituted compounds. The restricted rotation around the C2–N bond in the C1- and C3-methylated derivatives and their preference for half-chair conformations with pseudoequatorial nitrogen substituents [except for (1*R*,2*R*)-**6**] were also demonstrated in the ^1H and ^{13}C NMR studies (vide supra). Thus, as in previous investigations,[4c,6,10] there is a good agreement between the experimentally determined (by NMR) and theoretically calculated (by MMP2) conformational preferences of the present series of 2-aminotetralins.

It is noteworthy that the solid-state conformations of (+)-**6**·HCl and (+)-**10**·HCl correspond to MMP2 conformations of fairly high energy; the molecular conformations of (+)-**6**·HCl and (+)-**10**·HCl were not similar to any of the low-energy MMP2 conformations. However, when the X-ray conformations of (+)-**6**·HCl and (+)-**10**·HCl were minimized, local minima with E_s = 4.2 kcal/mol (Φ = 306°, τ_N = −52°) and E_s = 3.2 kcal/mol (Φ = 200°, τ_N = −67°), respectively, were identified (Figure 2). We are presently attempting to rationalize these and several similar results (see, for example, ref 6).

(20) Liljefors, T. *Mol. Graphics* **1983**, *1*, 111.

Table VI. Effects on in Vivo DOPA Accumulation and on Locomotor Activity in Reserpine-Pretreated Rats

compd	DOPA accumulation:[a] ED_{50}, μmol/kg sc		locomotor act.:[b] accum counts/30 min, mean ± SEM (μmol/kg sc)
	limbic	striatal	
(+)-**5**	I[c]	I	4 ± 2 (52.0)
(−)-**5**	I	I	4 ± 2 (52.0)
(+)-**6**	I	I	17 ± 3 (52.0)*
(−)-**6**	I	I	14 ± 4 (52.0)
(+)-**8**	1.4 (35%)[d]	1.2 (20%)[d]	59 ± 29 (16.0)***
(−)-**8**	I	I	8 ± 5 (52.0)
(+)-**9**	0.9 (35%)[d]	1.3 (20%)[d]	28 ± 3 (16.0)***
(−)-**9**	I	I	8 ± 4 (52.0)
(+)-**10**	0.07 (35%)[e]	0.06 (20%)[e]	50 ± 4 (4.0)***
(−)-**10**	3.5 (35%)	3.0 (20%)	20 ± 13 (16.0)
13	I	I	35 ± 24 (52.0)*
16	I	I	331 ± 103 (52.0)***
(2*R*)-7-OH-DPAT	0.01 (35%)[f]	0.01 (20%)[f]	46 ± 18 (0.31)*[f,g]
(2*S*)-7-OH-DPAT	1.9 (35%)[f]	2.4 (20%)[f]	33 ± 6 (39.0)*[f]
(*R*)-apomorphine	0.04 (35%)[h]	0.04 (20%)[h]	366 ± 36 (3.2)***[i]
haloperidol	I[j]	I[j]	NT[k]

[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 regions, estimated from dose–response curves comprising four to seven dose levels (n = 3–5). Minimal levels obtained are shown in parentheses; controls = 100%. [b] Animals were injected with reserpine (5 mg/kg sc) 18 h before 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 Student's t test: (***) $p < 0.001$, (*) $p < 0.05$ vs. saline controls. [c] Inactive; no significant decrease at 52 μmol/kg sc. [d] A 40–50% decrease in limbic and striatal 5-HTP formation was noted at 16.0 μmol/kg sc. [e] A 30% decrease in limbic and striatal 5-HTP formation was noted at 4.0 μmol/kg sc. [f] From ref 2. [g] This effect was blocked by haloperidol (0.5 μmol/kg ip 30 min before drug administration). [h] From ref 23. [i] From ref 4d. [j] Inactive; no significant effect at 1.4 μmol/kg ip. From ref 19b. [k] Not tested.

Pharmacology

The compounds were tested for central DA and 5-HT receptor activity by use of in vivo biochemical and behavioral methods in reserpinized and nonpretreated rats as previously described.[4e,21] In the in vivo biochemical screening method, we utilize the ability of DA (D_2) receptor agonists and antagonists to decrease and increase, respectively, via regulatory feedback mechanisms, the synthesis rate of DA in the presynaptic neurons in reserpinized and/or in nonpretreated rats. Analogous conditions likely prevail also for central 5-HT neurons. The DOPA and 5-HTP formation [as determined after in vivo inhibition of the aromatic L-amino acid decarboxylase by (3-hydroxybenzyl)hydrazine hydrochloride (NSD 1015, 100 mg/kg)] in the limbic and striatal brain regions are taken as indirect measures of DA and 5-HT synthesis rates.

(21) 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.

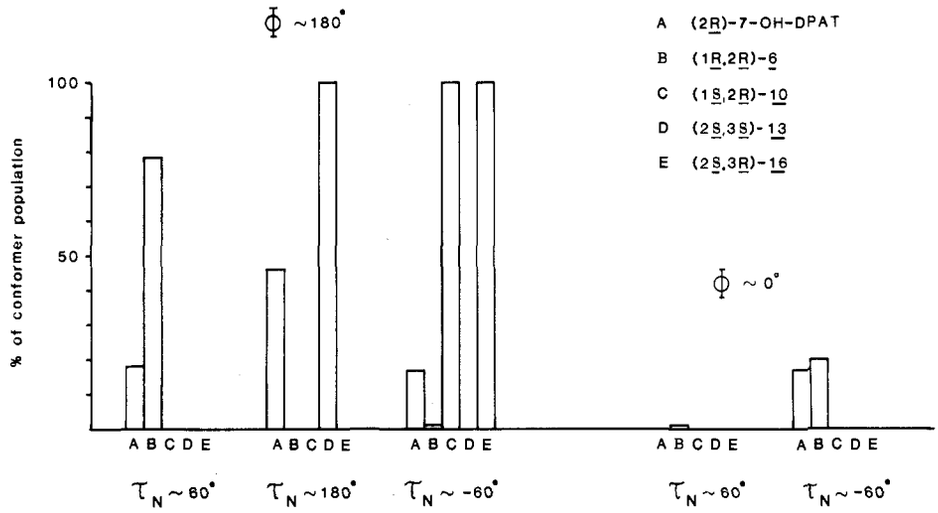


Figure 4. Conformational distribution of (2*R*)-7-OH-DPAT (A), (1*R*,2*R*)-**6** (B), (1*S*,2*R*)-**10** (C), (2*S*,3*S*)-**13** (D), and (2*S*,3*R*)-**16** (E). The probability of existence of each conformation (at 37 °C) was estimated from a Boltzmann distribution based on calculated (MMP2) steric energies. The bars represent the three staggered rotamers of the dipropylammonium group (having τ_N values around 60°, 180°, and -60°, respectively). Only conformations with Φ values around 0° and 180° seem to be populated.

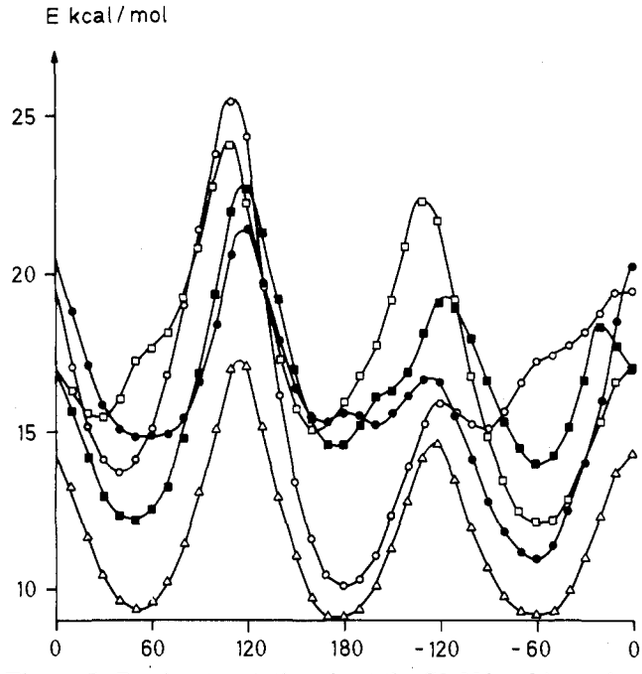


Figure 5. Barriers to rotation about the C2–N bond in conformations having Φ values around 180° of *N*,*N*-dimethyl analogues of (2*R*)-7-OH-DPAT (△), (1*R*,2*R*)-**6** (■), (1*S*,2*R*)-**10** (□), (2*S*,3*S*)-**13** (○), and (2*S*,3*R*)-**16** (●). The steric energies were obtained by use of the driver option in the MIMIC program.[20] The τ_N values were varied in 10° increments. In this mode, the program operates by minimizing all atoms, except those defining the torsion angle, with respect to all internal coordinates. Variations in Φ values were as follows: (2*R*)-7-OH-DPAT, 156–200°; (1*R*,2*R*)-**6**, 136–170°; (1*S*,2*R*)-**10**, 195–220°; (2*S*,3*S*)-**13**, 150–205°; (2*S*,3*R*)-**16**, 155–190°.

Motor activity recordings were carried out with motility meters as previously described.[21] The results obtained in the biochemical and motor activity tests are presented in Tables VI and VII.

On the basis of the experimental data (cf. Tables VI and VII), seven of the compounds [(+)-**5**, (−)-**5**, (−)-**6**, (−)-**8**, (−)-**9**, **14**, and **15**] were considered inactive.

Compounds (+)-**8**, (+)-**9**, (+)-**10**, and (−)-**10** decreased the limbic and striatal DOPA levels in reserpinized rats (ED_{50} = 0.06–3.5 μmol/kg, Table VI) to about the same extent as, for example, (*R*)-apomorphine. Central DA autoreceptors (presynaptic receptors) are considered to belong to the D_2 receptor category.[22] The ED_{50} values for reducing the DOPA accumulation in DA-dominated brain regions of reserpinized rats are taken as measures of DA presynaptic receptor and, thus, D_2 receptor stimulating abilities for the compounds under evaluation (cf. ref 15 and 23). The 5-HTP levels were partially reduced by (+)-**8**, (+)-**9**, and (+)-**10** (extrapolated limbic $ED_{50} \approx 4$ μmol/kg for these compounds). Thus, these compounds may possess weak (partial) 5-HT receptor agonist properties.

The reserpine-induced akinesia was counteracted by (+)-**6**, (+)-**8**, (+)-**10**, **13**, and **16**. The increased locomotion following (+)-**8**, (+)-**9**, and (+)-**10** was accompanied by typical DA receptor agonist induced stereotyped behavior (such as sniffing) but also by flat body posture and forepaw treading, which is characteristic for 5-HT agonists. The weak locomotor stimulation induced by (+)-**6** and **13** consisted mainly of occasional jerks (Table VI). Compounds (+)-**6** and **13** were inactive in all other tests. Thus, these compounds seem to be of very low potency or even inactive as DA receptor agonists. The pronounced locomotor stimulation produced by **16** (Table VI) was not characteristic for either DA or 5-HT receptor agonism; it consisted of tremor and irregular movements.

In reserpinized rats, (+)-**10** was the most potent DA agonist in this series. However, it was about 7 times less potent than (2*R*)-7-OH-DPAT (see Table VI). Compound (−)-**10** was considerably less potent than (+)-**10**. It should be noted that the dopaminergic effects of (−)-**10** (Table VI) may be due to contamination with the more potent (+)-**10**. HPLC analysis of derivatized (−)-**7** [a synthetic precursor to (−)-**10**] indicated that (−)-**7** was contaminated with ≤2% of (+)-**7** (see Experimental Section).

Only (+)-**10** and **16** produced effects in nonpretreated rats (Table VII). Compound (+)-**10** decreased the DOPA accumulation in the striatal and limbic brain parts. In addition, it induced hypomotility at doses up to 200 μmol/kg (data not shown). This action is characteristic for compounds acting on presynaptic DA receptors. At doses ≥4 μmol/kg, (+)-**10** also decreased the 5-HTP levels

(22) See, for example: (a) Grigoriadis, D.; Seeman, P. *Can. J. Neurol. Sci.* 1984, *11*, 10. (b) Seeman, P.; Grigoriadis, D. E.; Niznik, H. B. *Drug Dev. Res.* 1986, *9*, 63.

(23) 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.

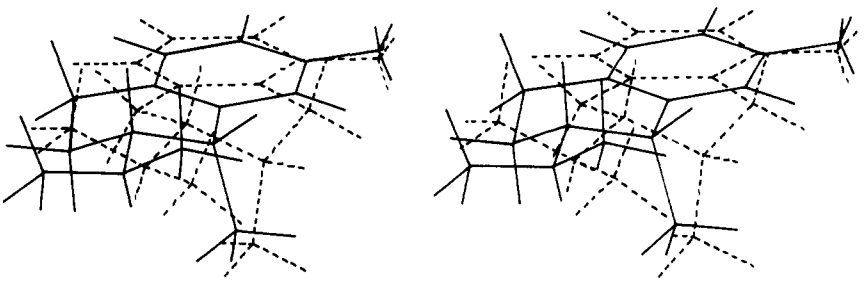


Figure 6. Computer-generated stereopair of the best fit of (1*S*,2*R*)-**10** (solid lines) and (2*R*,3*S*)-**20** (dashed lines) in their minimum energy conformations. Mean distance between fitted atoms [O, O-*H*, C6, C4a, N, N-*electron pair* in (1*S*,2*R*)-**10** and O, O-*H*, C7, C8a, N, N-*electron pair* in (2*R*,3*S*)-**20**] is 0.60 Å. For clarity, only the dimethylamino moieties are shown.

Table VII. Effects on in Vivo DOPA Accumulation and on Locomotor Activity in Nonpretreated Rats

compd	DOPA accumulation:[a] ED_{50}, μmol/kg sc		locomotor act.:[b] % of saline controls, mean ± SEM (μmol/kg sc)
	limbic	striatal	
(+)-**5**	I[c]	I	109 ± 16 (52.0)
(−)-**5**	I	I	92 ± 6 (52.0)
(+)-**6**	I	I	136 ± 49 (52.0)
(−)-**6**	I	I	126 ± 30 (52.0)
(+)-**9**	I[d]	I[d]	38 ± 4 (52.0)**
(−)-**9**	I	I	126 ± 13 (52.0)
(+)-**10**	0.70 (50%)[e]	1.0 (40%)[e]	59 ± 6 (1.0)*
			26 ± 3 (52.0)***
(−)-**10**	I[f]	I[f]	84 ± 14 (52.0)
13	I	I[g]	89 ± 7 (52.0)
14	I	I	128 ± 4 (52.0)
15	I	I	96 ± 22 (52.0)
16	11.0 (160%)[h]	7.5 (230%)[h]	119 ± 8 (25.0)
(*R*)-apomorphine	*i*	*i*	52 ± 6 (0.32)**[j]
			227 ± 4 (3.2)***[j]
haloperidol	0.19 (210%)[k]	0.19 (310%)[k]	3 ± 1 (2.7)***[l]

[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 or increase of DOPA formation in rat limbic and striatal regions, estimated from dose–response curves comprising four to five dose levels (n = 3–5). Minimal and maximal levels obtained are shown in parentheses; controls = 100%. Control levels: limbic region, 447 ± 23 ng/g; striatum, 1045 ± 47 ng/g, n = 16. [b] Animals were injected with test drug 5 min before the activity session, and the accumulated counts over a 30-min period were recorded. Shown is the locomotor activity expressed in percent of saline controls (100%; 232 ± 14 counts/30 min, n = 25), mean ± SEM, n = 3–5. Statistical differences were calculated by using Student's t test: (***) $p < 0.001$, (**) $p < 0.01$, (*) $p < 0.05$ vs. saline controls. [c] Inactive; no significant effects at 52.0 μmol/kg sc. [d] Inactive; a 20–30% decrease in limbic and striatal DOPA formation was noted at 52.0 μmol/kg sc. [e] A 30% decrease in limbic and striatal 5-HTP formation was noted at 16.0 μmol/kg sc. [f] Inactive; a 30% decrease in limbic and striatial DOPA formation was noted at 16.0 μmol/kg sc. [g] Inactive; a 35% increase in striatal DOPA formation was noted at 52.0 μmol/kg sc. [h] The ED_{50} in cortical brain parts is ≈12 μmol/kg (205%). A 35% increase in limbic 5-HTP formation was noted at 52 μmol/kg sc. [i] (*R*)-Apomorphine elicited a biphasic dose–response curve with two ED_{50}'s. From ref 38. [j] From ref 4b. [k] From ref 24. [l] The dose tested was administered ip 30 min before the activity session. This dose produced catalepsy, observed 30–60 min after injection.

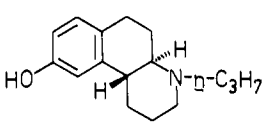
in striatal and limbic brain parts of nonpretreated rats. Compound **16** increased the DOPA accumulation to 160–230% of controls in nonpretreated rats. This action is similar to that of classical DA receptor antagonists, such as haloperidol.[24] However, in contrast to haloperidol, compound **16** did not produce hypomotility. It should be noted that **16** is a racemic mixture, and thus, the final classification of its effects has to be done by use of the enantiomers.

Structure–Activity Relationships

Previous studies using the enantiomers of 7-OH-DPAT have demonstrated that (2*R*)-7-OH-DPAT is a potent DA D_2 receptor agonist, whereas (2*S*)-7-OH-DPAT is of low potency.

Recently, we suggested that the "DA D_2 receptor agonist conformation" of 5-hydroxylated 2-aminotetralins corresponds to a half-chair conformation with a pseudoequatorial amino group ($\Phi \approx 0°$) and a τ_N value around 60°.[4c]

A comparison of the "agonist conformation" of (2*S*)-5-OH-DPAT with the low-energy conformations of (2*R*)-7-OH-DPAT using the concept of McDermed et al.[1e] shows that the "agonist conformations" of 7-oxygenated 2-aminotetralins should have Φ values around 180° and τ_N values around −60° (see Figure 1). In fact, such conformations correspond to a low-energy conformation of the more rigid and a potent DA receptor agonist (4a*R*,10b*R*)-9-hydroxy-*N*-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline [(4a*R*,10b*R*)-**19**].[9b,25]



(4a*R*,10b*R*)-**19**

The novel DA receptor agonist (+)-**10** easily adopts "agonist conformations" (Figures 4 and 5). In contrast, the DA inactive/weakly active (−)-**6**, (+)-**6**, and (±)-**13** are unable to assume energetically accessible "DA D_2 receptor agonist conformations". Similar results were recently obtained with the weakly potent 5-hydroxylated isomers (1*S*,2*S*)-**17**[4c] and (2*R*,3*R*)-5-hydroxy-3-methyl-2-(di-*n*-propylamino)tetralin [(−)-AJ-164].[6] These compounds provide evidence for the importance of conformational energetics in relation to DA receptor activation.

The 2*S* configuration of (−)-**10** and (+)-**6** makes these compounds unable to assume "DA D_2 receptor agonistic lone pair (N–H) orientations" (cf. ref 4c and 6).

The most potent DA D_2 receptor agonist in this series is the cis-C1-methylated (+)-**10**; as has been observed previously in a series of C5-oxygenated 2-aminotetralins,[4d,15] both the *N*-*n*-propyl analogues and the methyl ethers are of lower potency than the *N*,*N*-di-*n*-propyl-substituted phenols. The cis-C3-methyl-substituted (2*R*,3*S*)-5-hydroxy-3-methyl-2-(di-*n*-propylamino)tetralin

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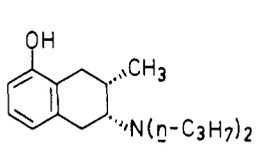
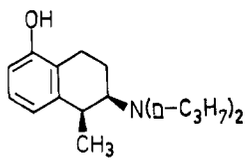
[(2*R*,3*S*)-**20**; (−)-AJ-166][6] is the most potent member of the C1-, C2-, and C3-methyl-substituted 2-amino-5-hydroxytetralins. Both (+)-**10** and (2*R*,3*S*)-**20** are able to assume



(2R,3S)-20



(1S,2R)-21

energetically favorable "DA D_2 agonist conformations", in which the methyl groups are pseudoaxially located. Interestingly, when such conformations of (+)-**10** and (2*R*,3*S*)-**20** are compared according to the concept of McDermed et al.[1e] (see Figure 6), the pseudoaxial methyl groups become located close to each other and (+)-**10** should fit well into the previously defined partial "DA D_2 receptor excluded volume".[6]

The considerable *decrease* in locomotor activity after a high dose of (+)-**10** (see above) indicates a preferential stimulation of presynaptic DA receptors. Interestingly, also 7-OH-DPAT has been reported[26] to have a greater preference for presynaptic DA receptors than apomorphine and 5-OH-DPAT.

Compound **16** increases the DOPA accumulation in nonpretreated rats. This may indicate an antagonistic action of **16** at DA receptors. On the basis of structural comparisons (according to the concept of McDermed et al.) of **16** with the DA antagonist (1*S*,2*R*)-5-hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin [(1*S*,2*R*)-**21**; (+)-UH-242], it may be speculated that the DA antagonist properties reside in the 2*R*,3*S* enantiomer.

Experimental Section

Chemistry. General Comments. Routine ^1H and ^{13}C NMR spectra were recorded at 90 MHz and 22.5 MHz, respectively, on a JEOL FX 90Q spectrometer and were referenced to internal tetramethylsilane. For the conformational analysis, 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. In order to optimize detection of long-range couplings, a delay time was introduced in the COSY pulse sequence. Pulse sequences used for the different COSY experiments were obtained from the GX-400 software. Mass spectra[27] 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 with hexane–ethyl acetate–ethanol (91:7.5:1.5) as the mobile phase, in the pressure range 1000–3000 psi and with a flow rate of 2 mL/min. Detection was made by a Waters Model 440 UV monitor. 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. 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).

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

***trans*-2-Amino-7-methoxy-3-methyltetralin (11). Method I.** A mixture of 7-methoxy-3-methyl-2-tetralone[14] (**2**; 2.25 g, 11.8 mmol), hydroxylamine hydrochloride (1.66 g, 23.9 mmol), and sodium acetate (3.17 g, 38.6 mmol) in ethanol (20 mL) was heated under reflux for 2 h. The ethanol was evaporated in vacuo, and the residue was partitioned between dichloromethane and water. The dried (magnesium sulfate) organic layer was filtered and concentrated in vacuo, affording yellowish crystals, which were rinsed with ether. The crude 7-methoxy-3-methyl-2-tetralone oxime (1.45 g, 60%) was used in the next step without further purification.

Granulated sodium (4.82 g, 0.209 mol) was added during 1 h to a solution of the above oxime (1.20 g, 5.85 mmol) in dry 2-propanol (72 mL) kept at gentle reflux under nitrogen. The heating was continued for 1 h, and water (20 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 60% de (diastereomeric excess; as indicated by ^1H 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 pure **11**·HCl in 21% yield as calculated from **3**: ^1H NMR (methanol-d_4) δ 7.06–6.97 (m, 1 H), 6.79–6.67 (m, 2 H), 3.74 (s, OMe), 3.34–2.37 (m, 5 H), 2.27–1.85 (m, 1 H), 1.18 (d, C3-Me); mass spectrum, m/z 191 (29, M^+), 174 (100, $M^+ - NH_3$), 159 (87), 134 (97).

***cis*-7-Methoxy-1-methyl-2-(*n*-propylamino)tetralin (7). Method II.** A mixture of 7-methoxy-1-methyl-2-tetralone[13] (1; 14.2 g, 74.6 mmol), *n*-propylamine (9.32 g, 158 mmol), and *p*-toluenesulfonic acid monohydrate (5 mg) in dry benzene (300 mL) was refluxed under nitrogen in a Dean–Stark apparatus. More *n*-propylamine (3.6 g, 60.6 mmol) was added after 24 h. The heating was interrupted after 48 h, 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 hydrogen chloride. The aqueous phase was alkalinized with 5 M sodium hydroxide and extracted with ether. The combined ether layers were dried (potassium carbonate), filtered, and concentrated. The oily residue was purified on an alumina column with ether as eluant, affording a product of 60% de (as indicated by GC). The diastereomeric mixture of amines was converted to the hydrochlorides and recrystallized repeatedly from methanol–ether to give 8.14 g (40%) of pure **7**·HCl: ^1H NMR (methanol-d_4) δ 7.07–6.96 (m, 1 H), 6.80–6.69 (m, 2 H), 3.75 (s, OMe), 3.63–2.81 (m, 6 H), 2.20–1.60 (m, 4 H), 1.27 (d, C3-Me), 1.06 (t, 3 H); mass spectrum, m/z 233 (49, M^+), 204 (29, $M^+ - C_2H_5$), 175 (35, $M^+ - NHC_3H_7$), 148 (100).

***cis*-7-Methoxy-3-methyl-2-(di-*n*-propylamino)tetralin (15). Method III.** 1-Iodopropane (0.174 g, 1.04 mmol) was added to a mixture of **14**·HCl (0.250 g, 0.927 mmol), potassium carbonate (0.70 g, 5.06 mmol), and acetonitrile (10 mL). The mixture was stirred at 50 °C under nitrogen. Two portions of potassium carbonate (0.70 g, 2.53 mmol) and 1-iodopropane (0.176 g, 1.04 mmol) were added during the next 3 days. After 4 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 (1:9) as eluant. The amine was converted into the hydrochloride and recrystallized from methanol–ether, yielding 0.221 g (76%) of pure **15**·HCl: ^1H NMR (methanol-d_4) δ 7.07–6.97 (m, 1 H), 6.80–6.65 (m, 2 H), 3.83–3.70 (m, 1 H), 3.75 (s, OMe), 3.45–3.17 (m, 7 H), 3.03–2.93 (m, 1 H), 2.80–2.57 (m, 2 H), 2.02–1.58 (m, 4 H), 1.06 (t, 6 H), 1.02 (d, C3-Me); mass spectrum, m/z 275 (42, M^+), 246 (100, $M^+ - C_2H_5$), 175 (78, $M^+ - NC_6H_{14}$).

(+)-*cis*-7-Hydroxy-1-methyl-2-(*n*-propylamino)tetralin [(+)-8]. Method IV. A solution of (+)-**7**·HCl (0.350 g, 1.30 mmol) in freshly distilled aqueous 48% hydrogen bromide (20 mL) was stirred for 2 h at 120 °C under nitrogen. The volatiles were evaporated in vacuo, and the solid residue was partitioned between

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ether and a saturated sodium bicarbonate solution. 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 ethanol–ether to afford 0.307 g (93%) of pure (+)-**8**·HCl: ^{1}H NMR (methanol-d_4) δ 6.97–6.87 (m, 1 H), 6.66–6.56 (m, 2 H), 3.61–2.77 (m, 6 H), 2.16–1.58 (m, 4 H), 1.25 (d, C3-Me), 1.06 (t, 3 H); mass spectrum, m/z 219 (81, M^+), 190 (63, $M^+ - C_2H_5$), 161 (69, $M^+ - NHC_3H_7$).

Resolution of (±)-*trans*-2-Amino-7-methoxy-1-methyltetralin [(±)-4]. (–)-Dibenzoyl-L-tartaric acid monohydrate (10.55 g, 28.0 mmol) was added to a hot solution of (±)-**4** (5.36 g, 28.0 mmol) in ethanol (320 mL) and water (320 mL). The solution was allowed to stand overnight at room temperature. The salt thus formed was recrystallized three 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 1.92 g (60%) of (–)-**4**·HCl. The free amine (3.55 g, 18.6 mmol) isolated from the mother liquors in the preparation of (–)-**4** was treated with (+)-dibenzoyl-D-tartaric acid monohydrate (6.98 g, 18.6 mmol) as described above. After two recrystallizations from ethanol–water, the hydrochloride was prepared and recrystallized to give 1.97 g (62%) of (+)-**4**·HCl.

Resolution of (±)-*cis*-7-Methoxy-1-methyl-2-(*n*-propylamino)tetralin [(±)-7]. (–)-Di-*p*-toluoyl-L-tartaric acid monohydrate (12.2 g, 30.2 mmol) was added to a hot solution of (±)-**7** (7.04 g, 30.2 mmol) in ethanol (140 mL). The solution was allowed to stand overnight at room temperature. The salt thus formed was recrystallized three times from ethanol. 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 ethanol–ether afforded 1.74 g (43%) of (+)-**7**·HCl. The free amine (4.50 g, 19.3 mmol) isolated from the mother liquors in the preparation of (+)-**7** was treated with (+)-di-*p*-toluoyl-D-tartaric acid monohydrate (7.80 g, 19.3 mmol) as described above. After three recrystallizations from ethanol, the hydrochloride was prepared and recrystallized to give 2.29 g (56%) of (–)-**7**·HCl.

Determination of Enantiomeric Excess. The enantiomeric excess of the primary amines (+)- and (–)-**4** was determined as follows. The sample to be tested [(+)- or (–)-**4**·HCl; 20 mg, 87.8 mmol] was mixed with water (0.26 mL) and 1 M sodium hydroxide (0.12 mL) and kept in a flask equipped with a magnetic stirrer under nitrogen. A solution of (*R*)-(–)-2-methoxy-2-phenylacetyl chloride (114 μmol) [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 with stirring at room temperature. After 1 h, the organic layer was separated, washed with 1 M hydrogen chloride and 1 M sodium hydroxide, dried (magnesium sulfate), filtered, and concentrated. The enantiomeric excess of the primary amines (+)- and (–)-**4**·HCl was determined by capillary GC to be ≈92% and ≈100%, respectively. HPLC analysis of (+)- and (–)-**6**, by use of an optically active counterion in the eluant,[28] showed no impurity of the (–)-enantiomer in the (+)-enantiomer and vice versa. The enantiomeric excess of the secondary amines (+)- and (–)-**7** was determined by HPLC analysis of the corresponding diastereomeric (*R*)-*O*-methylmandelic amides (prepared as above for (+)- and (–)-**4**·HCl) to be ≈96%.

Optical Rotations. To resolved compounds presented in Table I have the following optical rotations ($[\alpha]^{22}_D$, methanol): (+)-**4**, +3.8° (*c* 1.0); (–)-**4**, –4.0° (*c* 1.0); (+)-**5**, +18.8° (*c* 1.0); (–)-**5**, –18.5° (*c* 1.1); (+)-**6**, +21.7° (*c* 1.0); (–)-**6**, –21.1° (*c* 1.0); (+)-**7**, +64.0° (*c* 1.1); (–)-**7**, –64.0° (*c* 1.0); (+)-**8**, +68.7° (*c* 1.0); (–)-**8**, –69.0° (*c* 1.0); (+)-**9**, +69.0° (*c* 1.0); (–)-**9**, –68.2° (*c* 1.0); (+)-**10**, +68.6° (*c* 1.0); (–)-**10**, –69.1° (*c* 1.0).

Absolute Configuration Determination by Single-Crystal X-ray Analysis for (+)-6·HCl and (+)-10·HCl. Crystals of (+)-**6**·HCl and (+)-**10**·HCl were grown from methanol–ether solutions. Crystals with the dimensions 0.48 × 0.13 × 0.07 mm of (+)-**6**·HCl and 0.46 × 0.24 × 0.08 mm of (+)-**10**·HCl were used for data collections with an Enraf-Nonius CAD4F-11 diffractometer. Angular settings of 25 reflections were measured to calculate the lattice parameters (cf. Table VIII for crystal data). Intensity data for reflections within one-quarter of the sphere of reflection and with $\theta < 60°$ were collected by the $\theta/2\theta$ scan method using monochromated Cu Kα radiation. Three intensity control reflections, which were measured every 2 h, indicated slight decays (5% for (+)-**6**·HCl and 4% for (+)-**10**·HCl) of the crystals. The measured intensities were rescaled to account for these decays. A total of 2857 and 2871 reflections were measured for (+)-**6**·HCl and (+)-**10**·HCl, respectively. Of these, 1786 for (+)-**6**·HCl and 2112 for (+)-**10**·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 VIII. Crystal Data for (+)-6·HCl and (+)-10·HCl

	(+)-6·HCl	(+)-10·HCl
formula	$C_{17}H_{27}NO$·HCl	$C_{17}H_{27}NO$·HCl
space group	$P2_12_12_1$	$P2_12_12_1$
a, Å	8.690 (3)	13.910 (1)
b, Å	12.212 (3)	14.285 (1)
c, Å	16.205 (6)	8.623 (2)
d_{calcd}, g cm^{-3}	1.150	1.155
μ, cm^{-1}	19.2	19.3

The structures were solved by a combination of the Patterson heavy atom method and direct methods using the program DIRDIF,[29] which provided the non-hydrogen atom positions. Methyl and hydroxyl hydrogen positions were determined from Fourier difference synthesis maps, and the 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. For the determination of the absolute configurations of (+)-**6**·HCl and (+)-**10**·HCl, anomalous dispersion factors[30] 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 (+)-**6**·HCl was finished, the residuals for the 1*S*,2*S* and 1*R*,2*R* enantiomers were calculated to be R = 0.040 (R_w = 0.057) and R = 0.050 (R_w = 0.071), respectively. Corresponding residuals for the 1*S*,2*R* and 1*R*,2*S* enantiomers of (+)-**10**·HCl were R = 0.066 (R_w = 0.099) and R = 0.074 (R_w = 0.113), respectively. When Hamilton's test[31] was used, the ratios $R_w(1R,2R)/R_w(1S,2S)$ for (+)-**6**·HCl and $R_w(1R,2S)/R_w(1S,2R)$ for (+)-**10**·HCl were sufficiently great to reject the 1*R*,2*R* and 1*R*,2*S* enantiomers, respectively, at the 0.005 significance level. Furthermore, among the 15 Bijvoet pairs for the 1*S*,2*S* enantiomer of (+)-**6**·HCl and the 34 Bijvoet pairs for the 1*S*,2*R* enantiomer of (+)-**10**·HCl for which $|F_c(h,k,l) - F_c(h,k,-l)| > 1.5$, all of the F_c differences had the same sign as the corresponding F_o differences. The weighting scheme used in the later part of the refinements was $w = 1/[1 + [(|F_o| - A)/B]^2]$,[32] where A = 8 and B = 10 for (+)-**6**·HCl and A = 4 and B = 6 for (+)-**10**·HCl. The form factors used were those given by Cromer and Mann.[33] All the calculations were performed on a DEC-

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system-10 computer using mainly the X-ray 72 program system.[34]

The molecular conformations and the atom labeling schemes are shown in Figure 2.

Molecular Mechanics Calculations. The structural modelling was performed by use of the interactive computer graphics program MIMIC (methods for interactive modelling in chemistry).[20] Calculations were performed on a VAX 11/780 computer using Allingers MMP2 force field[35] to which had been added parameters for the phenol[36] and amino groups.[37] Computational times ranged from 1 to 30 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, occasionally with a few drops of glacial acetic acid and/or moderate heating to obtain complete dissolution. 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.[4j] For biochemical results and experimental details, see Tables VI and VII and footnotes *a* in Tables VI and VII.

Locomotor Activity. The motor activity was measured by means of photocell recordings (M/P 40 Fc electronic motility meter, Motron Products, Stockholm) as previously described.[21] For experimental details, see footnotes *b* in Tables VI and VII. 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 VI and VII.

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Supplementary Material Available: Lists of X-ray data of (+)-**6**·HCl and (+)-**10**·HCl, including thermal parameters for all atoms, positional parameters for the hydrogen atoms, and bond lengths and bond angles for the non-hydrogen atoms (5 pages). Ordering information is given on any current masthead page.

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α,α-Difluoro-β-aminodeoxystatine-Containing Renin Inhibitory Peptides

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The preparations of sodium 4(*S*)-[(*tert*-butyloxycarbonyl)amino]-2,2-difluoro-3(*S*)- and -3(*R*)-[(4-methoxyphenyl)amino]-6-methylheptanoates (**7a** and **7b**) from sodium 4(*S*)-[(*tert*-butyloxycarbonyl)amino]-2,2-difluoro-3(*R*)- and -3(*S*)-hydroxy-6-methylheptanoates (**1a** and **1b**) are described. The key step involves the stereospecific intramolecular displacement via a Mitsunobu reaction for the conversion of a β-hydroxy hydroxamate to a β-lactam ring. Compounds **7a** and **7b** are useful as synthetic intermediates for the preparation of enzyme inhibitors that contain 3(*S*),4(*S*)- and 3(*R*),4(*S*)-diamino-2,2-difluoro-6-methylheptanoic acid inserts. Angiotensinogen analogues VII and VIII that contain these novel amino analogues of difluorostatine were shown to be inhibitors of the enzyme renin. The α,α-difluoro-β-aminodeoxystatine-containing compounds were shown to be weaker inhibitors than the corresponding difluorostatine-containing congeners.

Pepstatin, Iva-Val-Val-Sta-Ala-Sta, is a naturally occurring pentapeptide that is a general aspartyl protease inhibitor.[1] It has been proposed that the central statine residue (Sta), 4(*S*)-amino-3(*S*)-hydroxy-6-methylheptanoic acid (A), acts as a structural analogue of the tetrahedral species formed during enzymatic hydrolysis of a peptidic bond.[2] Utilization of the concept of transition-state analogue[3] has generated numerous pepstatin-derived inhibitors of aspartyl proteinases.[4]

We have continuing interest in the design of enzyme inhibitors of the aspartyl protease renin. It is a highly specific proteolytic enzyme produced mainly in the juxtaglomerular apparatus of the kidney[5] and cleaves the circulating α-globulin angiotensinogen to form the decapeptide angiotensin I.[6] The N-terminal sequence of human angiotensinogen is shown in Figure 1. The cleaved angiotensin I is further converted to the octapeptide angiotensin II by the converting enzyme by removal of the C-terminal histidylleucine. Angiotensin II is a very potent vasoconstrictor and also stimulates the release of aldosterone from the adrenal gland to induce salt and water retention. The renin–angiotensin system has thus been implicated in several forms of hypertension.[7] Interest in

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