Tris·HCl, pH 7.5.[52] After incubation for 4 h at 25 °C, the generation of *p*-nitroaniline was measured by absorbance at 405 nm. The average absorbencies from triplicate experiments were plotted (semilog plots) versus concentration (molarity). The ED_{50} values were determined by finding the midpoint between the maximal and minimal absorbance values.

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Registry No. **3**, 3917-41-7; **4**, 6802-75-1; **6**, 113089-08-0; **7**, 113158-87-5; **8**, 20013-34-7; **9**, 113089-09-1; **10**, 113089-10-4; **11**, 113089-11-5; **12**, 113089-12-6; **13**, 113158-88-6; **14**, 113214-81-6.

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Central Dopaminergic and 5-Hydroxytryptaminergic Effects of C3-Methylated Derivatives of 8-Hydroxy-2-(di-*n*-propylamino)tetralin

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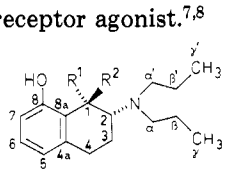
A number of stereochemically well defined C3-methylated derivatives of the potent 5-hydroxytryptamine (5-HT) receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) have been synthesized, and their stereochemical characteristics have been studied by use of NMR spectroscopy, X-ray crystallography, and molecular mechanics calculations. The compounds were tested for activity at central 5-HT and dopamine (DA) receptors, by use of biochemical and behavioral tests in rats. In addition, the ability of the *cis*- and *trans*-8-hydroxy-3-methyl-2-(di-*n*-propylamino)tetralins (**15** and **11**) to displace [^{3}H]-8-OH-DPAT from 5-HT_{1A} binding sites was evaluated. The stereoselectivity of the interaction of **11** and **15** with 5-HT receptors was much greater than that of 8-OH-DPAT. Observed rank order of potencies in the 5-HT_{1A} binding assay corresponds to that in the in vivo biochemical assay.

8-Hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT, **1**)[1] is a potent and highly interesting, centrally active, 5-hydroxytryptamine (serotonin; 5-HT) receptor agonist.[2] Compound **1** appears to lack prominent effects on dopamine (DA)[3] and norepinephrine (NE) receptors[3] and has a pronounced selectivity for 5-HT_{1A} sites.[4,5] Most likely, **1** will prove very useful as a pharmacological tool in the elucidation of central 5-hydroxytryptaminergic mechanisms and as a lead compound in structure–activity relationship studies. In fact, tritiated **1** has already turned out to be useful as a ligand for 5-HT_{1A} sites.[6]

Compound **1** is weakly stereoselective in its interaction with 5-HT receptors.[1] In contrast, *cis*-8-hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin (**2**), a Cl-methylated derivative of **1**, exhibits a pronounced stereoselectivity; the 1*S*,2*R* enantiomer is equipotent to **1** as a 5-HT-receptor agonist while (1*R*,2*S*)-**2** appears to be inactive.[7,8] The racemic trans diastereomer **3** has been reported to be inactive as a 5-HT-receptor agonist.[7,8]



(2*R*)-**1**: $R^1 = R^2 = H$
(1*S*,2*R*)-**2**: $R^1 = CH_3$; $R^2 = H$
(1*R*,2*R*)-**3**: $R^1 = H$; $R^2 = CH_3$

In the present study, which is part of a current effort to develop novel and selective 5-HT-receptor agonists and antagonists, we have synthesized a number of stereo-

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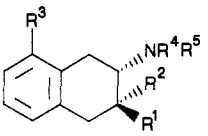
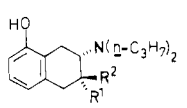
Table I. Physical Data of the Compounds Studied



compd	R^1	R^2	R^3	R^4	R^5	prepn method	yield, %	mp, °C	recrystn[a] solvents	formula
(±)-7	Me	H	OMe	H	H	I	39	264.5–265.5	A	$C_{12}H_{17}NO\cdot HCl$
(+)-7	Me	H	OMe	H	H	*b*	29	266–269	B	$C_{12}H_{17}NO\cdot HCl$
(−)-7	Me	H	OMe	H	H	*b*	34	268–271	B	$C_{12}H_{17}NO\cdot HCl$
(±)-8	Me	H	OMe	*n*-Pr	H	III	68	170–171.5	B	$C_{15}H_{23}NO\cdot HCl$
(+)-8	Me	H	OMe	*n*-Pr	H	III	66	203–205	B	$C_{15}H_{23}NO\cdot HCl$
(−)-8	Me	H	OMe	*n*-Pr	H	III	67	203–205.5	B	$C_{15}H_{23}NO\cdot HCl$
(±)-9	Me	H	OH	*n*-Pr	H	V	81	255.5–256	B	$C_{14}H_{21}NO\cdot HCl$
(+)-9	Me	H	OH	*n*-Pr	H	V	70	264.5–267	B	$C_{14}H_{21}NO\cdot HCl\cdot{}^1/_4H_2O$
(−)-9	Me	H	OH	*n*-Pr	H	V	67	264.5–267	B	$C_{14}H_{21}NO\cdot HCl\cdot{}^1/_4H_2O$
(±)-10	Me	H	OMe	*n*-Pr	*n*-Pr	IV	58	*c*	C	$C_{18}H_{29}NO\cdot HCl\cdot{}^1/_2H_2O$
(+)-10	Me	H	OMe	*n*-Pr	*n*-Pr	IV	95	*c*	*d*	$C_{18}H_{29}NO\cdot HCl\cdot{}^3/_4H_2O$
(−)-10	Me	H	OMe	*n*-Pr	*n*-Pr	IV	95	*c*	*d*	$C_{18}H_{29}NO\cdot HCl\cdot{}^3/_4H_2O$
(±)-11	Me	H	OH	*n*-Pr	*n*-Pr	V	84	192–193	B	$C_{17}H_{27}NO\cdot HCl\cdot{}^1/_4H_2O$
(+)-11	Me	H	OH	*n*-Pr	*n*-Pr	V	90	188–190	*d*	$C_{17}H_{27}NO\cdot HBr$
(−)-11	Me	H	OH	*n*-Pr	*n*-Pr	V	81	187–190	*d*	$C_{17}H_{27}NO\cdot HBr\cdot{}^1/_2H_2O$
(±)-12	H	Me	OMe	*n*-Pr	H	II	47	256–258	A	$C_{15}H_{23}NO\cdot HCl$
(+)-12	H	Me	OMe	*n*-Pr	H	*b*	31	265–266.5	B	$C_{15}H_{23}NO\cdot HCl$
(−)-12	H	Me	OMe	*n*-Pr	H	*b*	37	267–268	B	$C_{15}H_{23}NO\cdot HCl$
(±)-13	H	Me	OH	*n*-Pr	H	V	65	244–245	B	$C_{14}H_{21}NO\cdot HCl\cdot{}^3/_4H_2O$
(+)-13	H	Me	OH	*n*-Pr	H	V	66	284–285	B	$C_{14}H_{21}NO\cdot HCl$
(−)-13	H	Me	OH	*n*-Pr	H	V	70	284–285	B	$C_{14}H_{21}NO\cdot HCl$
(±)-14	H	Me	OMe	*n*-Pr	*n*-Pr	IV	66	215–216	B	$C_{18}H_{29}NO\cdot HCl$
(+)-14	H	Me	OMe	*n*-Pr	*n*-Pr	IV	94	*c*	*d*	$C_{18}H_{29}NO\cdot HCl$
(−)-14	H	Me	OMe	*n*-Pr	*n*-Pr	IV	70	*c*	B	$C_{18}H_{29}NO\cdot HCl$
(±)-15	H	Me	OH	*n*-Pr	*n*-Pr	V	91	254–256	C	$C_{17}H_{27}NO\cdot HCl\cdot{}^1/_2H_2O$
(+)-15	H	Me	OH	*n*-Pr	*n*-Pr	V	89	200–202	C	$C_{17}H_{27}NO\cdot HCl$
(−)-15	H	Me	OH	*n*-Pr	*n*-Pr	V	85	200–201.5	C	$C_{17}H_{27}NO\cdot HCl$
16	Me	Me	OMe	H	H	I	68	226.5–227.5	B	$C_{13}H_{19}NO\cdot HCl$
17	Me	Me	OMe	*n*-Pr	H	II	54	231–233	B	$C_{16}H_{25}NO\cdot HCl$
18	Me	Me	OMe	*n*-Pr	*n*-Pr	IV	86	*e*		$C_{19}H_{31}NO$
19	Me	Me	OH	*n*-Pr	*n*-Pr	V	47	204–206	B	$C_{18}H_{29}NO\cdot HCl\cdot{}^1/_4H_2O$

[a] Recrystallization solvents: A, EtOH; B, EtOH–ether; C, MeOH–ether. [b] See the Experimental Section. [c] This compound is very hygroscopic, and no reproducable melting point was obtained. [d] No recrystallization. [e] Oil.

chemically well-defined C3-methylated derivatives of **1** (**7–19**; Table I). Compounds **7**, **9–11**, **13–15**, and **19** have been investigated pharmacologically by use of biochemical and behavioral tests in rats. In addition, the affinity of the active compounds **11** and **15** for [^{3}H]-8-OH-DPAT labeled 5-HT_{1A} binding sites were evaluated in vitro. Interestingly, all of the compounds appear to be less potent as 5-HT-receptor agonists than the lead compound **1**. In fact, several of the compounds lack ability to stimulate 5-HT receptors, and a few have dopaminergic components in their activity profiles. However, **11** and **15** interact more stereoselectively with 5-HT (5-HT_{1A}) receptors than **1**.



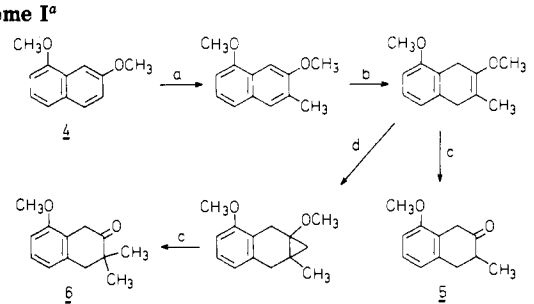
(2*S*,3*S*)-**11**: R^1 = H; R^2 = CH_3
(2*S*,3*R*)-**15**: R^1 = CH_3; R^2 = H
(2*S*)-**19**: R^1 = R^2 = CH_3

In order to investigate if conformational factors might be responsible for the stereoselectivity of **11** and **15**, and for the inactivity of **19**, we have also studied the conformational preferences of these compounds by use of molecular mechanics (MMP2) calculations and NMR spectroscopy.

Chemistry

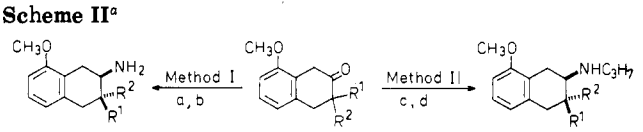
Syntheses. The 2-aminotetralin derivatives were prepared from 8-methoxy-3-methyl-2-tetralone (**5**) or 8-methoxy-3,3-dimethyl-2-tetralone (**6**), which are available from 1,7-dimethoxynaphthalene (**4**) by facile synthetic routes (Scheme I).[9] The syntheses of the 2-aminotetralin

Scheme I[a]



[a] Reagents: (a) *n*-C_4H_9Li, CH_3I; (b) Na, C_2H_5OH; (c) H^+; (d) $Zn(C_2H_5)_2$, CH_2I_2.

Scheme II[a]



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

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Table II. ^{1}H NMR Spectral Data of Four 8-Hydroxy-2-(dipropylamino)tetralins in CD_3OD

	chemical shifts, δ							
compd	H_{1eq}	H_{1ax}	H_2	H_{3eq}	H_{3ax}	H_{4eq}	H_{4ax}	C_3Me
1·HBr	3.22	2.77	3.74	2.31	1.89	≈2.95	≈2.95	
11·HCl	3.10	2.89	3.54		2.26	2.94	2.61	1.20
15·HCl	3.27	2.70	3.72	2.70		2.73	3.11	1.01
19·HCl	3.16	3.01	3.71			2.62	2.86	1.17 (ax) 1.29 (eq)

	coupling constants (J, Hz)									
compd	$J_{1ax,1eq}$	$J_{1ax,2ax}$	$J_{1eq,2ax}$	$J_{2ax,3ax}$	$J_{2ax,3eq}$	$J_{3ax,4ax}$	$J_{3ax,4eq}$	$J_{3eq,4ax}$	$J_{3eq,4eq}$	$J_{4ax,4eq}$
1·HBr	−16.2	11.6	5.8	11.8	3.0					
11·HCl	−16.5	9.0	6.0	8.8		9.8	4.7			−16.1
15·HCl	*a*	11.5	3.0		6.0			4.5	2.5	−16.5
19·HCl	−17.5	9.0	6.0							−16.8

[a] Not determined.

derivatives, which followed known procedures,[10] are outlined in Scheme II.

trans-2-Amino-8-methoxy-3-methyltetralin (**7**) was prepared from the oxime of **5** by reduction with sodium in 2-propanol (method I). This reaction produced a mixture of cis and trans isomers in a 1:9 ratio (^{1}H NMR) from which the pure trans isomer **7** was obtained by fractional crystallization of the hydrochlorides. Racemic **7** was resolved into the enantiomers by fractional crystallization of the diastereomeric salts obtained with the enantiomers of 5,5-dimethyl-2-hydroxy-4-phenyl-1,3,2-dioxaphosphorinane 2-oxide.[11] Compound **7** was N-propylated by acylation followed by reduction (method III) and N,N-dipropylated by alkylation with iodopropane (method IV) to afford compounds **8** and **10**, respectively. The enantiomers of **8** and **10** were prepared from (+)- or (−)-**7**, respectively, by use of the same procedure.

cis-8-Methoxy-3-methyl-2-(*n*-propylamino)tetralin (**12**) was obtained by reductive amination of **5** (method II); the catalytic hydrogenation (palladium on carbon) of the intermediate imine afforded a 85:15 mixture (capillary GC) of cis and trans stereoisomers **12** and **8**. Pure **12** was obtained by fractional crystallization of the hydrochlorides. Compound **12** was resolved into the enantiomers by fractional crystallization of the diastereomeric di-*p*-toluoyltartrates. N-Alkylation of (±)-**12**, (+)-**12**, and (−)-**12** by use of method IV gave compounds (±)-**14**, (+)-**14**, and (−)-**14**, respectively.

3,3-Dimethyl-8-methoxy-2-(di-*n*-propylamino)tetralin (**18**) was obtained by reductive amination of tetralone **6** (method II) followed by N-alkylation of the resulting secondary amine (method IV). The primary amine **16** was prepared from **6** by use of method I.

The phenols presented in Table I were prepared from the corresponding methoxy-substituted derivatives with use of aqueous 48% HBr (method V).

NMR Spectroscopy. High-resolution ^{1}H NMR spectral data of compounds **11**·HCl, **15**·HCl, and **19**·HCl in CD_3OD are shown in Table II.[12] For comparison, previously reported ^{1}H NMR data for **1**·HBr, which assumes mainly half-chair conformations with a pseudoequatorial nitrogen substituent in CD_3OD,[12c] are also included in Table II.

The 400-MHz ^{1}H NMR spectra were complicated to interpret due to nonequivalence of the *N*-*n*-propyl groups[13] and several overlapping resonances. Thus, although COSY spectroscopy allowed unambiguous assignments of all proton resonances, several coupling constants remain undetermined. Nevertheless, the large dipseudoaxial coupling constants $J_{1ax,2ax}$ in **11**·HCl, **15**·HCl, and **19**·HCl indicate that these compounds prefer to assume half-chair conformations with pseudoequatorial nitrogen substituents (i.e., similar solution conformations as **1**·HBr).[12c] This conclusion is supported by the large value of $J_{2ax,3ax}$ in **11**·HCl and by the small value of $J_{3eq,4eq}$ in **15**·HCl, which is typical for a dipseudoequatorial coupling constant. The COSY spectrum of **15**·HCl, in which detection of long range couplings was optimized, revealed a small *W* coupling[14] between the C3-methyl group and H_{4ax}, which provides additional support for the suggested predominating solution conformation of **15**·HCl. The assignment of resonances due to the C3-methyl groups and the C4-hydrogens of **19**·HCl was corroborated by the observation of a similar *W* coupling between one of the C3-methyls ($C3\text{-}Me_{ax}$) and one of the C4-hydrogens (H_{4ax}) in the COSY spectrum. The above *W* couplings were confirmed by decoupling experiments.

In NMR spectroscopy of flexible molecules, observed vicinal coupling constants are weighted averages of cou-

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(11) Ten Hoeve, W.; Wynberg, H. *J. Org. Chem.* **1985**, *50*, 4508–4514.

(12) For other NMR spectral studies of 2-aminotetralin derivatives, see (a) Karlén, A.; Johansson, A. M.; Kenne, L.; Arvidsson, L.-E.; Hacksell, U. *J. Med. Chem.* **1986**, *29*, 917–924. (b) Johansson, A. M.; Karlén, A.; Grol, C. J.; Sundell, S.; Kenne, L.; Hacksell, U. *Mol. Pharmacol.* **1986**, *30*, 258–269. (c) Arvidsson, L.-E.; Karlén, A.; Norinder, U.; Sundell, S.; Kenne, L.; Hacksell, U. *J. Med. Chem.* **1988**, *31*, 212–221. (d) Nichols, D. E.; Jacob, J. N.; Hoffman, A. J.; Kohli, J. D.; Glock, D. J. *J. Med. Chem.* **1984**, *27*, 1701–1705. (e) De Jong, A. P.; Fesik, S. W.; Makriyannis, A. *J. Med. Chem.* **1982**, *25*, 1438–1441. (f) Johansson, A. M.; Nilsson, J. L. G.; Karlén, A.; Hacksell, U.; Svensson, K.; Carlsson, A.; Kenne, L.; Sundell, S. *J. Med. Chem.* **1987**, *30*, 1135–1144. (g) Johansson, A. M.; Nilsson, J. L. G.; Karlén, A.; Hacksell, U.; Sanchez, D.; Svensson, K.; Hjort, S.; Carlsson, A.; Sundell, S.; Kenne, L. *J. Med. Chem.* **1987**, *30*, 1827–1837.

(13) In ^{13}C NMR spectra (22.5 MHz, CD_3OD, 37 °C) of **11**·HCl, **15**·HCl, and **19**·HCl, resonances due to one or several of the *N*-propyl carbons have different chemical shifts or exhibit coalescence. In contrast, dynamic ^{13}C NMR experiments indicate that rotation around the C2–N bond in **1**·HBr is fast on the NMR time scale.

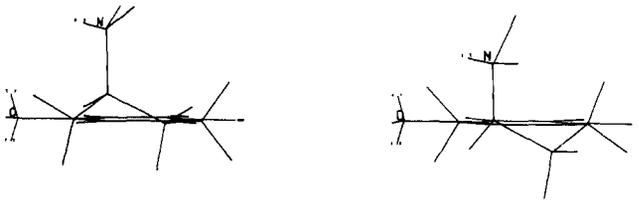
(14) See, for example: Becker, E. D. *High Resolution NMR. Theory and Chemical Applications*, 2nd ed.; Academic: New York, 1980; p 104.

pling constants from various conformations at equilibrium. Thus, the smaller values of $J_{1ax,2ax}$ and $J_{2ax,3ax}$ in 11·HCl, as compared to those in 1·HBr, indicate that the preference for half-chair conformations with a pseudoequatorially located nitrogen substituent is less pronounced in 11·HCl.

Molecular Mechanics Calculations. To identify conformations of low energy of the compound 1 analogues (2*S*,3*S*)-11, (2*S*,3*R*)-15, and (2*S*)-19, we have applied a minor modification[12b] of a strategy which has been described in detail elsewhere.[12a] Two conformational parameters, the tetralin inversion angle Φ and the dihedral angle τ(C1, C2, N, NH or electron pair) (τ_N), are particularly useful when characterizing the different conformations. At least two torsion angles have to be used to unambiguously define the conformation of the nonaromatic ring of tetralin derivatives. Therefore, we prefer to use a single parameter, Φ, when defining tetralin conformations. Ideally, the tetralin inversion angle Φ is simply calculated from eq 1 where τ_{obsd} is the observed value and

$$\Phi = \arccos(\tau_{obsd}/\tau_{max}) \quad (1)$$

τ_{max} is the maximal value (64.73°) of the torsion angle τ(C1, C2, C3, C4). For example, in (2*R*)-8-hydroxy-2-aminotetralin, conformation a has τ_{obsd} = 53.74°. equation 1 gives Φ = 33.88° when this value is inserted. Conformation b has a similar τ_{obsd} value (56.20°) but differs considerably from conformation a. Inspection of the tetralin inversion



a b

wheel in ref 12c reveals that conformation b belongs to the western hemisphere of the wheel (conformation a belongs to the eastern hemisphere). To obtain Φ values of geometries in the western hemisphere, the calculated value has to be subtracted from 360°. Thus, the Φ value of conformation b is obtained as follows: Φ = 360° − arc cos (56.20°/64.73°) = 330.25°. 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 on the tetralin inversion wheel (cf. ref 12a and 12c). Φ is configurationally dependent, and enantiomeric conformations differ in Φ values with ±180°.[12a] In (2*R*)-2-aminotetralin, a half-chair conformation with a pseudoequatorial amino group corresponds to Φ = 180° while a half-chair conformation with a pseudoaxially oriented amino group corresponds to Φ = 0°.[12c] 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.[12a-c,f,g]

In the present investigation, we have identified four low-energy conformations of (2*S*,3*S*)-11 and (2*S*,3*R*)-15, respectively, and 22 conformations of (2*S*)-19 within 2.5 kcal/mol of the respective global minimum (geometries and relative steric energies of low-energy conformations are given in Table III). Thus, the conformational mobility of 11 and 15 appears to be considerably lower than that of 1[12c] and 19. Boltzmann distributions were calculated on the basis of the steric energies of the identified low-energy conformations of the compounds. Figure 1 shows that (2*S*,3*S*)-11, (2*S*,3*R*)-15, and (2*S*)-19, like (2*R*)-1,[12c]

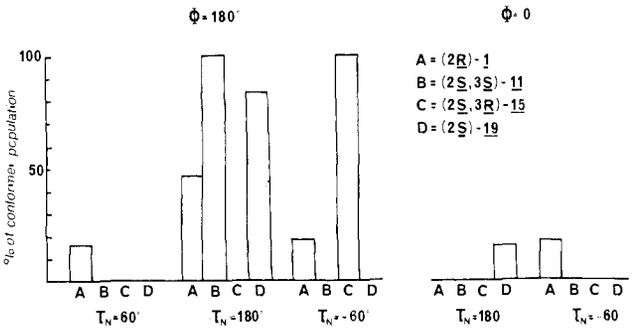


Figure 1. Conformational distribution of (2*R*)-1, (2*S*,3*S*)-11, (2*S*,3*R*)-15, and (2*S*)-19. The probability of existence of each conformation (at 37 °C) was estimated from a Boltzmann distribution based on calculated (MMP2) steric energies. The bars represent the relative amount of staggered rotamers of the dipropylamino group. Only conformations with Φ values around 0° and 180° seem to be populated.

preferentially assume Φ values around 180° and that they, unlike (2*R*)-1,[12c] prefer to assume only one of the three possible dipropylamino group rotamers in tetralin conformations with Φ values around 180°. The restricted rotation around the C2–N bond in these C3-methylated derivatives, and their preference for half-chair conformations with pseudoequatorial nitrogen substituents, was also demonstrated in the ^1H and ^{13}C NMR studies (vide supra).

X-ray Crystallography. The absolute configurations of (+)-11·HBr and (−)-15·HBr were determined by X-ray crystallography to be 2*S*,3*S* and 2*R*,3*S*, respectively. The molecular conformations of (−)-15·HBr and the two independent molecules A and B of (+)-11·HBr are shown in Figure 2. Crystal data for (+)-11·HBr and (−)-15·HBr are given in Table IV, and the atomic fractional coordinates are listed in Tables V and VI. The atom numbering is shown in the formula of (2*R*)-1.

Conformation A of (+)-11·HBr and the molecular conformation of (−)-15·HBr were similar to minimum-energy MMP2 conformations (see Figure 2). However, conformation B of (+)-11·HBr was found to correspond to a MMP2 conformation with a relative steric energy of 3.3 kcal/mol above the global minimum (Figure 2). The difference in preferred conformations in the crystal (X-ray crystallography) and in vacuo (MMP2) may be due to hydrogen bonding in the crystal and/or packing forces.

Pharmacological Results

Biochemistry and Behavior in Vivo. It is well-known that agonists at 5-HT, DA, and NE receptors inhibit the synthesis and utilization of the corresponding monoamine.[15] Thus, the monoamine synthesis can be used as an indicator of pre- and postsynaptic receptor activation. In the present study, the synthesis of 5-HT, DA, and NE was measured indirectly by determining the accumulation of 5-hydroxytryptophan (5-HTP) in various brain parts and of 3,4-dihydroxyphenylalanine (DOPA) in DA-predominant (corpus striatum, limbic system) and NE-predominant (brain stem, hemispheres) brain regions following L-aromatic amino acid decarboxylase inhibition.[16] The rats were not pretreated with reserpine.

(15) Andén, N.-E.; Carlsson, A.; Häggendal, J. *Annu. Rev. Pharmacol.* **1969**, *9*, 119–134.
(16) Carlsson, A.; Davis, J. N.; Kehr, W.; Lindqvist, M.; Atack, C. V. *Naunyn Schmiedeberg's Arch. Pharmacol.* **1972**, *275*, 153–168.
(17) Compare: Hacksell, U.; Arvidsson, L.-E.; Johansson, A. M.; Nilsson, J. L. G.; Sanchez, D.; Lindberg, P.; Wikström, H.; Svensson, K.; Hjorth, S.; Carlsson, A.; Ask, A.-L.; Ögren, S.-O. *Acta Pharm. Suec.* **1986**, *23*, 77–90.

Table III. Geometrical Parameters[a] for Low-Energy Conformations of (2*S*,3*S*)-11, (2*S*,3*R*)-15, and (2*S*)-19

conformation	τ_1, deg	Φ, deg	τ_N, deg	τ_A, deg	τ_B, deg	τ_A', deg	τ_B', deg	rel steric energy, kcal/mol
				(2*S*,3*S*)-11				
A	−64	180[b]	180	−167	170	52	170	0.0
B	−64	180[b]	−179	−166	170	55	55	0.1
C	−63	180[b]	180	−168	54	53	170	0.1
D	−63	180[b]	−179	−168	53	56	55	0.1
				(2*S*,3*R*)-15				
A	−61	160	−60	178	170	−62	−178	0.0
B	−61	160	−60	−178	56	−61	−179	0.4
C	−60	159	−65	64	179	−178	−171	0.0
D	−60	159	−65	64	179	179	−57	0.4
				(2*S*)-19				
A	−65	170[b]	37	−51	−169	163	−170	2.5
B	−65	175[b]	37	−55	−54	161	−53	2.5
C	−62	180[b]	−144	−171	170	−68	−179	0.8
D	−61	180[b]	−144	−169	55	−67	−179	0.8
E	−66	160[b]	177	−177	169	52	169	0.3
F	−66	160[b]	177	−176	168	54	56	0.5
G	−66	160[b]	179	−171	54	53	169	0.5
H	−63	168	−168	−162	53	59	−106	2.4
I	−66	165[b]	179	−170	52	56	56	0.4
J	−61	161	−172	−134	180	172	−174	1.5
K	−61	160	−173	−132	175	167	−62	2.2
L	−62	165	−165	−157	172	64	167	0.2
M	−63	165	−168	−156	173	68	58	0.5
N	−62	164	−164	−160	52	64	167	0.0
O	−62	165	−167	−159	53	67	59	0.2
P	−62	165	−162	88	−175	166	−177	2.4
Q	59	0[b]	−147	−171	170	−67	−178	1.2
R	59	0[b]	−147	−168	54	−66	−179	1.3
S	53	25[b]	−169	−169	168	56	166	0.9
T	54	25[b]	−170	−168	168	61	56	1.2
U	54	25[b]	−169	−167	53	58	166	0.9
V	54	25[b]	−169	−167	52	62	56	1.0

[a] For definitions, see ref 12a. [b] Approximate Φ value estimated by comparison with relevant conformations of C2-unsubstituted tetralin.

Table IV. Crystal Data for (+)-11·HBr and (−)-15·HBr and Final Parameters Regarding the Refinement of the Correct (C) and the Erroneous (E) enantiomers

	(+)-11·HBr	(−)-15·HBr
configuration	(2*S*,3*S*)	(2*R*,3*S*)
crystal dim, mm	0.55 × 0.13 × 0.02	0.62 × 0.07 × 0.02
formula	$C_{17}H_{27}NO$·HBr	$C_{17}H_{27}NO$·HBr
mol wt	342.33	342.33
space group	$P2_1$	$P2_1$
a, Å	7.741 (1)	8.694 (1)
b, Å	18.358 (3)	9.254 (3)
c, Å	12.243 (1)	10.900 (2)
β, deg	98.47 (1)	101.61 (1)
V, Å^3	1720.74	859.96
Z	4	2
D_{calcd}, g cm^{-3}	1.321	1.323
μ, cm^{-1}	35.5	35.5
R(C),[a] R(C)$_w$[b]	0.038, 0.046	0.039, 0.048
R(E), R(E)$_w$	0.047, 0.058	0.047, 0.060
M(refl)[c]	5532	2710
N(refl)[d]	5312	2463
N(var)[e]	351	180
S(C),[f] S(E)	0.672, 0.826	1.051, 1.316
σ(C)[g]	0.756	0.607

[a] R is the sum of ΔF's over the sum of F's used in the refinement. [b] R_w is the weighted R value. [c] The number of measured reflections. [d] The number of reflections used in the refinement. [e] The number of variables. [f] $S = [\sum w(|F_o| - |F_c|)^2/(N(\text{refl}) - N(\text{var}))]^{1/2}$. [g] An approximation of the standard deviation of an observation of unit weight.

Stimulation of postsynaptic 5-HT and DA receptors was studied in rats in which the presynaptic monoamine stores had been depleted by reserpine pretreatment. Behavioral observations were made, particularly with regard to motility, gnawing, and sniffing (DA syndrome) and to flat body posture and foreleg movements (5-HT syndrome).[18]

The effects of the tested compounds on the monoamine synthesis in rats are shown in Table VII. Compounds (±)-**9**, (−)-**13**, and (±)-**14** did not appear to affect rat brain monoamine synthesis whereas (±)-**7** and (±)-**10** only slightly decreased the 5-HT synthesis rate. The effects due to treatment with (±)-**7** probably arose through indirect mechanisms; a series of related methoxy-substituted primary 2-aminotetralin derivatives has been found to exhibit similar biochemical effects via indirect mechanisms, such as increased release of 5-HT.[17] The DOPA, but not the 5-HTP accumulation, was reduced in the corpus striatum and in the limbic system by (+)-**13**. This effect was not seen in reserpine-pretreated rats,[19] indicating that it is not due to a direct action on DA receptors.

The racemic trans-C3-methyl-substituted derivative of **1**, (±)-**11** (50 μmol/kg, sc), elicited a syndrome characterized by flat body posture and forepaw treading in reserpine-pretreated rats.[19] It also dose-dependently and significantly decreased 5-HTP levels in nonreserpinized rats treated with the decarboxylase inhibitor NSD 1015 (Table VII). In addition, the concentration of DA was decreased and the concentration of homovanillic acid (HVA; data presented in ref 19) was increased, whereas the accumulation of DOPA was not significantly changed by (±)-**11** in the rats treated with NSD 1015. One of the enantiomers, (+)-**11**, produced all the behavioral and biochemical effects observed after the racemate. No behavioral or biochemical changes indicating a 5-HT receptor stimulation were observed following (−)-**11**. The concen-

(18) Jacobs, B. L. *Life Sci.* **1976**, *19*, 777–786.
(19) For a more detailed discussion of the pharmacology of the enantiomers of **11** and **15**, see: Björk, L.; Mellin, C.; Hacksell, U.; Anden, N.-E. *Eur. J. Pharmacol.* **1987**, *143*, 55–63.

Table V. Fractional Coordinates of the Non-Hydrogen Atoms of (2*S*,3*S*)-11·HBr

atom	*x*	*y*	*z*
Br1	−0.2038 (1)	−0.5003 (−)	0.7677 (1)
Br2	−0.1770 (1)	−0.2683 (1)	0.2954 (1)
	Molecule A		
C1	0.3733 (7)	−0.4549 (3)	0.5245 (4)
C2	0.1961 (6)	−0.4850 (2)	0.5428 (4)
C3	0.1658 (7)	−0.5636 (3)	0.5076 (4)
C4	0.1801 (7)	−0.5689 (3)	0.3857 (5)
C4a	0.3348 (6)	−0.5294 (2)	0.3491 (4)
C5	0.3845 (7)	−0.5466 (3)	0.2485 (4)
C6	0.5202 (7)	−0.5083 (3)	0.2115 (4)
C7	0.6021 (7)	−0.4522 (3)	0.2745 (4)
C8	0.5531 (6)	−0.4359 (3)	0.3747 (4)
C8a	0.4192 (6)	−0.4749 (2)	0.4146 (4)
Cα	0.2920 (7)	−0.5069 (6)	0.7491 (5)
Cβ	0.2639 (−)	−0.5293 (−)	0.8473 (−)
Cγ	0.3892 (8)	−0.5822 (3)	0.9083 (4)
Cα′	0.1460 (7)	−0.3901 (3)	0.6847 (4)
Cβ′	0.0114 (7)	−0.3521 (3)	0.6027 (4)
Cγ′	−0.0234 (8)	−0.2757 (3)	0.6372 (5)
C3-CH_3	−0.0111 (8)	−0.5924 (3)	0.5272 (5)
N1	0.1642 (5)	−0.4704 (2)	0.6603 (3)
O1	0.6280 (5)	−0.3812 (2)	0.4406 (3)
	Molecule B		
C1	0.3729 (6)	−0.3189 (3)	0.0333 (4)
C2	0.2476 (5)	−0.2664 (2)	0.0773 (3)
C3	0.1062 (6)	−0.2380 (2)	−0.0151 (3)
C4	0.2050 (7)	−0.1916 (2)	−0.0886 (4)
C4a	0.3496 (6)	−0.2320 (2)	−0.1317 (4)
C5	0.4044 (7)	−0.2119 (3)	−0.2307 (4)
C6	0.5295 (7)	−0.2514 (3)	−0.2727 (4)
C7	0.5992 (6)	−0.3122 (3)	−0.2201 (4)
C8	0.5471 (6)	−0.3340 (3)	−0.1217 (4)
C8a	0.4244 (5)	−0.2933 (2)	−0.0757 (3)
Cα	0.1330 (6)	−0.3788 (2)	0.1726 (3)
Cβ	−0.0036 (7)	−0.4022 (3)	0.0802 (4)
Cγ	−0.0425 (8)	−0.4825 (3)	0.0895 (4)
Cα′	0.2999 (5)	−0.2825 (2)	0.2821 (3)
Cβ′	0.3071 (6)	−0.2011 (2)	0.3096 (4)
Cγ′	0.3971 (8)	−0.1921 (4)	0.4284 (5)
C3-CH_3	−0.0340 (8)	−0.1925 (3)	0.0274 (5)
N1	0.1763 (5)	−0.2979 (2)	0.1777 (3)
O1	0.6087 (4)	−0.3959 (2)	−0.0670 (3)

Table VI. Fractional Coordinates of the Non-Hydrogen Atoms of (2*R*,3*S*)-15·HBr

atom	*x*	*y*	*z*
Br	0.2061 (1)	0.0105 (13)	0.3527 (1)
C1	0.5777 (6)	−0.2719 (14)	0.2964 (5)
C2	0.4373 (6)	−0.3750 (14)	0.2743 (4)
C3	0.3595 (6)	−0.3846 (14)	0.1365 (4)
C4	0.4819 (6)	−0.4471 (13)	0.0687 (4)
C4a	0.6263 (6)	−0.3538 (14)	0.0841 (4)
C5	0.7139 (6)	−0.3449 (14)	−0.0096 (4)
C6	0.8411 (6)	−0.2541 (15)	0.0045 (5)
C7	0.8866 (6)	−0.1720 (14)	0.1118 (5)
C8	0.8032 (6)	−0.1836 (14)	0.2061 (5)
C8a	0.6704 (5)	−0.2715 (14)	0.1938 (4)
Cα	0.1644 (8)	−0.3954 (15)	0.3261 (6)
Cβ	0.1572 (10)	−0.5568 (15)	0.3395 (6)
Cγ	−0.0103 (9)	−0.6077 (15)	0.2937 (8)
Cα′	0.4003 (6)	−0.3520 (14)	0.4940 (4)
Cβ′	0.3066 (7)	−0.2948 (14)	0.5852 (5)
Cγ′	0.4000 (8)	−0.3066 (15)	0.7182 (5)
C3-CH_3	0.2963 (7)	−0.2417 (15)	0.0786 (5)
N	0.3254 (5)	−0.3289 (13)	0.3587 (3)
O	0.8448 (4)	−0.1074 (14)	0.3160 (4)

trations of DA and HVA were however influenced by (−)-11 in a similar way to that seen after (±)- and (+)-11 (Table VII and ref 19).

When given to reserpine-pretreated rats, the racemic cis-C3-methylated derivative of 1, (±)-**15** (50 μmol/kg, sc),

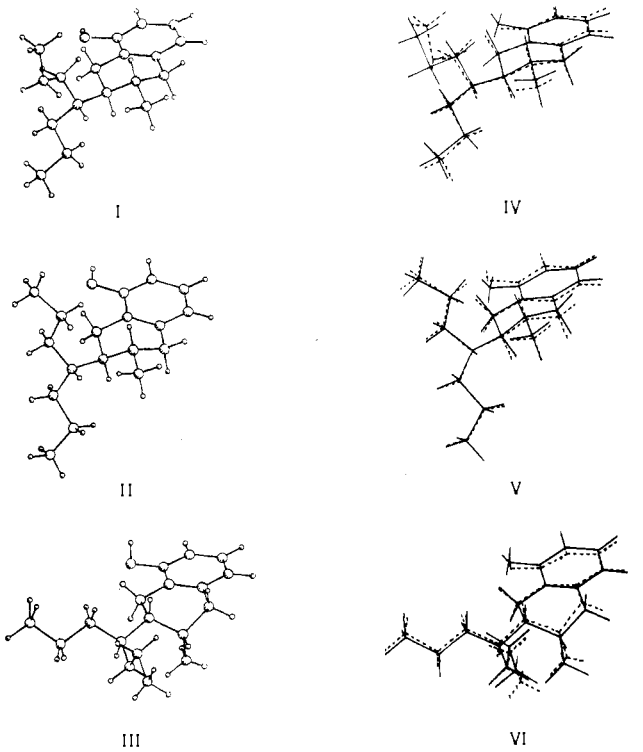


Figure 2. Molecular conformation of the two independent molecules A and B of (+)-11·HBr (I and II, respectively) and of (−)-15·HBr (III). The two conformations of (+)-11·HBr have similar conformations (A: $\Phi = 190°$, $\tau_N = -174°$. B: $\Phi = 155°$, $\tau_N = -154°$) and differ mainly with respect to the conformations of the *N*-*n*-propyl groups. A computer generated best fit (IV) of the carbon, oxygen, and nitrogen atoms of conformation A (dashed lines) with the MMP-generated conformation of lowest energy (solid lines; $\Phi = 180°$, $\tau_N = 180°$) gave an average distance between fitted atoms of 0.17 Å. Conformation B is not similar to any of the low-energy MMP2 conformations of (+)-11. MMP2 minimization of conformation B gave a conformation with a relative steric energy, 3.3 kcal/mol ($\Phi = 165°$; $\tau_N = -165°$), above the global MMP2 minimum. The computer generated best fit (V) of this MMP2 conformation (solid lines) with conformation B (dashed lines) gave an average distance between fitted atoms of 0.19 Å. The molecular conformation of (−)-15·HBr (III: $\Phi = 335°$, $\tau_N = 53°$) is similar to one of the minimum-energy MMP2 conformations of (−)-**15** ($\Phi = 340°$, $\tau_N = 60°$; the enantiomer of conformation A of (2*S*,3*R*)-**15**). The best fit (VI) of this MMP2 conformation (solid lines) and the X-ray conformation (dashed lines) gave an average distance between fitted atoms of 0.22 Å.

produced increased locomotor activity, occasionally combined with sudden jerks. In addition, the rats exhibited weak stereotyped head and forelimb movements. 5-Hydroxytryptaminergic components in the behavior were barely detectable. The biochemical effects of (±)-**15** were complex (Table VII); the 5-HTP levels were decreased in the corpus striatum and in the hemispheres, and the DA levels were decreased and the HVA[19] levels were increased in the corpus striatum and in the limbic system.

Compound (+)-**15** powerfully decreased the DA and increased the HVA[19] levels in the corpus striatum and the limbic system. It also somewhat enhanced the accumulation of DOPA in normal and reserpine-treated rats. The 5-HTP accumulation was not clearly changed by (+)-**15** in any brain region of normal (Table VII) or reserpine-pretreated (see ref 19) rats. The behavior induced by (+)-**15** (50 μmol/kg, sc) in reserpinized rats was similar to that after the racemate. This effect was not significantly counteracted by haloperiodol-treatment (1 mg/kg, i.e., 2.7 μmol/kg, ip), indicating that it is not caused by stimulation of postsynaptic DA receptors. Taken together, the bio-

Table VII. Effects on in Vivo Accumulations of 5-HTP and DOPA and on the Concentration of DA in Rat Brain[a]

compd	dose (μmol/kg)	5-HTP,[b] ng/g		DOPA,[b] ng/g		DA,[b] ng/g	
		striatum	limbic	striatum	limbic	striatum	limbic
(±)-7	66	90.2 ± 18.9	106 ± 10.4*	823 ± 10.2*	356 ± 10.5	6863 ± 206*	1243 ± 64.1
(±)-9	59	101 ± 9.7	155 ± 12.1	1047 ± 70.0	400 ± 16.4	5877 ± 427	1215 ± 43.7
(+)-9	59	67.4 ± 1.5*	125 ± 3.0	957 ± 63.5	426 ± 24.6	4249 ± 120	1030 ± 64.5
(−)-9	59	105 ± 7.8	169 ± 5.2	978 ± 59.3	340 ± 19.7*	5588 ± 245	975 ± 32.5
(±)-10	48	61.3 ± 7.9*	145 ± 9.2	979 ± 87.0	389 ± 42.3	5833 ± 468	1225 ± 104
(±)-11	50	27.1 ± 6.3**	79.3 ± 16.9**	792 ± 106	348 ± 14.5	3871 ± 323*	775 ± 57.4**
(+)-11	22	56.4 ± 4.4**	89.5 ± 6.0**	959 ± 53.0	400 ± 20.7	4089 ± 164**	839 ± 24.0**
	2.2	87.3 ± 3.6	144 ± 2.7	1008 ± 42.0	389 ± 11.2	5158 ± 200	1067 ± 46.0
(−)-11	43	117 ± 8.6	136 ± 10.9	1039 ± 27.8	381 ± 17.3	4181 ± 8.8**	800 ± 6.5**
(±)-13	59	69.0 ± 9.7	98.1 ± 15.8**	633 ± 43.5**	283 ± 18.9**	4530 ± 153	1058 ± 18.5
(+)-13	59	101 ± 4.0	140 ± 5.2	525 ± 26.5**	271 ± 11.7**	5133 ± 302	1186 ± 46.5
	5.9	104 ± 13.1	131 ± 10.2	1013 ± 45.8	365 ± 14.1	5924 ± 139	1292 ± 141
(−)-13	59	103 ± 8.5	151 ± 13.4	932 ± 56.4	365 ± 14.6	5365 ± 154	1148 ± 25.6
(±)-14	48	88.8 ± 16.2	141 ± 18.9	1078 ± 80.8	414 ± 19.4	6465 ± 476	1342 ± 86.8
(±)-15	50	57.8 ± 7.1**	138 ± 9.2	1059 ± 44.9	436 ± 16.6	2935 ± 134**	678 ± 43.9**
(+)-15	50	115 ± 11.1	197 ± 10.9	1157 ± 84.1	507 ± 21.1*	2758 ± 67.7**	609 ± 33.4**
(−)-15	50	45.8 ± 4.2**	88.3 ± 9.9**	1001 ± 66.6	396 ± 26.2	5282 ± 380	1065 ± 43.7
	25	65.4 ± 3.7**	120 ± 7.4**	1241 ± 123	521 ± 25.7**	4751 ± 158	1094 ± 49.0
	2.5	96.6 ± 4.7	163 ± 6.9	1080 ± 26.4	463 ± 12.2*	4439 ± 260	1133 ± 50.5
(±)-19	48	90.0 ± 9.2	158 ± 14.1	982 ± 94.8	362 ± 38.9	5417 ± 236	1125 ± 72.4
control		103 ± 5.6	161 ± 7.5	1111 ± 36.3	398 ± 7.5	5518 ± 198	1125 ± 39.3

[a] Nonreserpinized animals were injected with test drug sc 60 min and NSD 1015 (573 μmol/kg, ip) 30 min before death. [b] The values are means ± SEM (n = 17–19 and 3–7 in the control and experimental groups, respectively). Statistics: one-way ANOVA followed by Dunnett's t test: (** $p < 0.01$, (*) $p < 0.05$ vs control.

Table VIII. Potencies of Selected 8-Hydroxy-2-(di-*n*-propylamino)tetralins at 5-HT_{1A} Binding Sites[a]

compound	IC_{50}, nM	slope	N
(±)-1·HBr	3.98 ± 0.33	1.05 ± 0.03	6
(±)-11·HBr	129 ± 26.3	0.80 ± 0.09	3
(+)-11·HBr	60.5 ± 7.03	0.86 ± 0.03	3
(−)-11·HBr	1680 ± 139	1.09 ± 0.09	3
(±)-15·HCl	774 ± 27.8	1.09 ± 0.09	3
(+)-15·HCl	2420 ± 305	0.98 ± 0.19	3
(−)-15·HCl	486 ± 58.9	0.89 ± 0.07	3

[a] IC_{50} and slope values are expressed as the mean ± SEM for N separate experiments. Comparison of the slopes by one-way ANOVA showed no significant differences between any of the slope values ($p > 0.05$).

chemical and functional experiments do not give a good explanation for the effects of (+)-**15** on DA systems.[19] The antipode, (−)-**15** (50 μmol/kg, sc) elicted a clear-cut 5-HT syndrome in reserpinized rats and caused a decline in the 5-HT synthesis without significantly affecting the DA synthesis in any of the brain areas studied.

The half-maximal decrease in the accumulation of 5-HTP, in nonpretreated rats, was achieved following about 5 μmol/kg of (+)-**11** and 20 μmol/kg of (−)-**15**. Thus, these compounds are considerably less potent than (±)-**1** (the corresponding ED_{50} value appears to be around 0.1 μmol/kg, sc).[3a]

Affinity for 5-HT_{1A} Binding Sites in Vitro. Since compound **1** itself has significant selectivity for the 5-HT_{1A}-receptor subtype,[4,5] the enantiomers of **11** and **15** were evaluated for their direct effects on 5-HT_{1A} binding sites for comparison with the in vivo biochemical and behavioral 5-hydroxytryptaminergic effects. In agreement with the in vivo studies, (+)-**11** and (−)-**15** were found to be the active enantiomers at the 5-HT_{1A} sites (Table VIII), being 28 and 5 times more potent than their respective antipodes. Although (−)-**11** and (+)-**15** had measurable affinity for the 5-HT_{1A} sites as determined by the binding assay, their potencies were relatively low, which probably accounts for the inability to find measurable 5-hydroxytryptaminergic effects of these enantiomers after in vivo administration. Also in agreement with the in vivo results was the finding that (±)-**1** was more potent at the binding sites than either (+)-**11** or (−)-**15**. The rank order of potencies for (±)-**1**, (+)-**11**, and (−)-**15** at the binding sites corresponded to that for decreasing the accumulation of 5-HTP. Thus, the results from the binding assays, in general, correlated well with the in vivo results, lending support to the idea that these in vivo tests measure activation of 5-HT_{1A} receptors.

Structure–Activity Relationships

The present series of 5-hydroxytryptaminergic compounds shows some similarities with the compound **1** analogues, which have been previously described by Arvidsson et al.[1b,8] In both series, potency appears to decrease with methylation of the phenolic functionality and with removal of one or both of the N-substituents. Similar to the C1-methylated compound **2**,[8] the C3-methylated **11** and **15** interact more stereoselectively with 5-HT receptors than **1**. However, whereas (1*S*,2*R*)-**2** is equipotent to 2*R*-**1**,[8] the 5-HT agonists (2*S*,3*S*)-(+)-**11** and (2*R*,3*S*)-(−)-**15** seem to be considerably less potent.

Consideration of conformational and steric properties in a series of dopaminergic C1-, C2-, or C3-methyl-substituted 5-hydroxy-2-(di-*n*-propylamino)tetralins has allowed rationalization of the structure–activity relationships.[12b,f,g] Such an analysis is more complicated in the present series of 8-hydroxylated 2-aminotetralins since no obvious relationship has been observed between the absolute configuration at C2 and the 5-HT receptor activating ability;[12c] for example, (2*R*)-**1** is only twofold more potent than (2*S*)-**1**[1a] and the cis-methyl-substituted 5-HT receptor agonists (2*R*,3*S*)-(−)-**15** and (1*S*,2*R*)-**2** are heterochiral[20] at C2. In addition, *it does not appear to be possible to strictly define an optimal N-electron pair (N–H) orientation for 5-HT_{1A}-receptor agonists.*[12c]

It has been proposed that 5-HT_{1A}-receptor agonists should have the nitrogen located close to the plane of the aromatic ring.[12c] Thus, the inactivity of the trans derivative **3** might be due to its reluctance to assume half-chair conformations with a pseudoequatorial dipropylammonium substituent.[12c] However, the inability of

(20) The term heterochiral is used to denote compounds with a different sense of chirality.

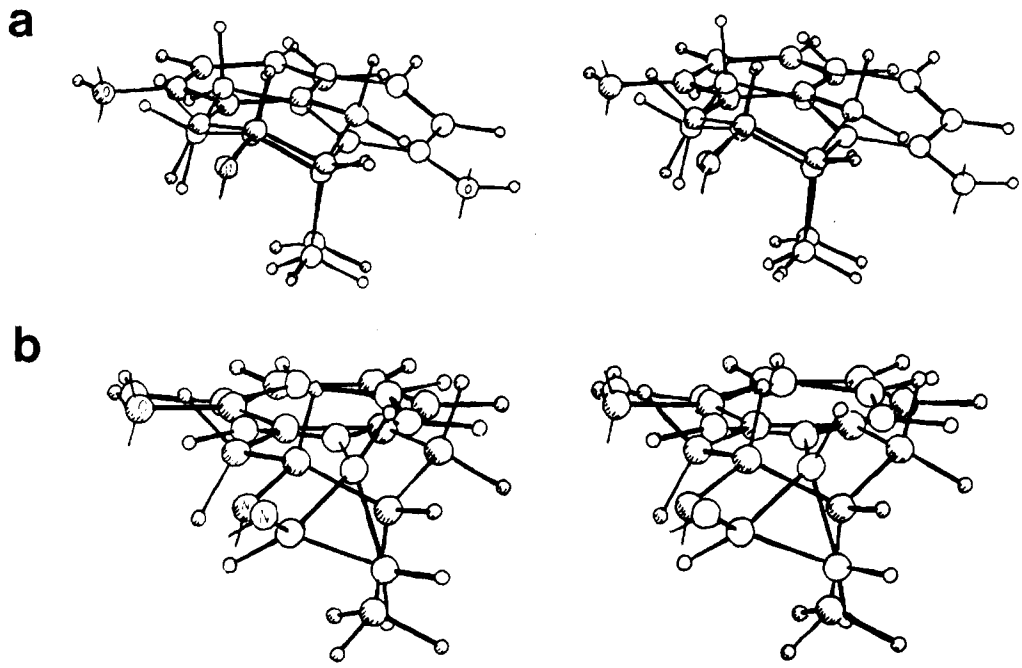


Figure 3. Computer-generated stereo pairs of (a) the 2-aminotetralin fragments of the minimum energy (MMP2) conformations of (1*S*,2*R*)-**2** and (2*R*,3*S*)-**15** [mean distance between fitted atoms (C4a, C5, N, and N-electron pair) was 0.06 Å; this fit was based on a structural comparison with *d*-LSD (not shown)] and (b) the 2-aminotetralin fragments of (1*R*,2*S*)-**20** and (2*R*,3*S*)-**15**. The nitrogens, the oxygens, and the midpoints of the aromatic rings were included in the fitting procedure, which gave a mean distance between fitted atoms = 0.47 Å.

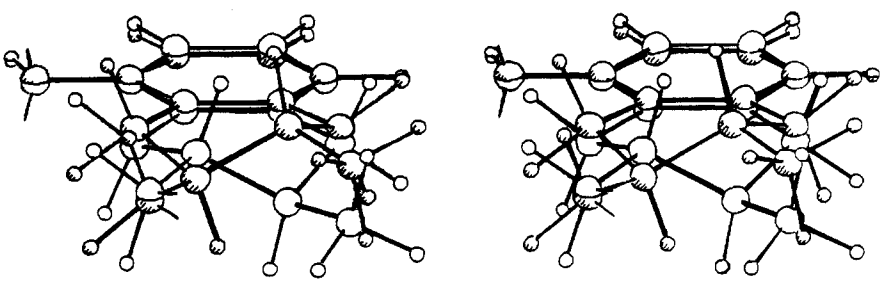
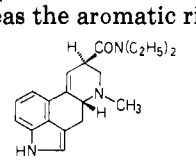


Figure 4. Computer-generated stereo pair of the best fit of the two enantiomers of the minimum-energy conformation (MMP2) of **11**. For clarity, the propyl groups are omitted. The nitrogens, the oxygens, and the midpoint of the aromatic rings were included in the fitting procedure.

(1*R*,2*S*)-**2**, (2*R*,3*R*)-(−)-**11**, (2*S*,3*R*)-(+)-**15**, and (±)-**19** to stimulate 5-HT receptors must be due to other factors since these compounds preferentially assume half-chair conformations with pseudoequatorial nitrogen substituents. For example, the stereoselectivity of **15** may be rationalized by assuming that the pseudoaxial C3-methyl of the inactive/weakly potent (2*S*,3*R*)-**15** occupies space that is part of the 5-HT-receptor essential volume. The pseudoaxial methyl substituent of the active 2*R*,3*S* enantiomer does not seem to have a detrimental influence on the 5-HT-receptor interaction.

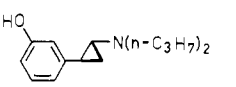
It is interesting to compare the stereoselectivity of **15** with that of **2** since the active enantiomers [(2*R*,3*S*)-**15** and (1*S*,2*R*)-**2**] are heterochiral. This might indicate that they interact differently with 5-HT receptors and suggests a structural comparison in which the aromatic ring of (1*S*,2*R*)-**2** assumes a position similar to that of the benzene ring of *d*-LSD whereas the aromatic ring of (2*R*,3*S*)-**15** is



d-LSD

located at the pyrrole moiety of LSD. In such a structural fit the methyl groups of (1*S*,2*R*)-**2** and (2*R*,3*S*)-**15** assume almost identical spatial positions (see the structural comparison in Figure 3a).

Alternatively, **15** can be compared with the hydroxylated phenylcyclopropane derivative **20**, which was recently reported to be a potent and stereoselective 5-HT receptor agonist:[21] The methyl group of (2*R*,3*S*)-**15** and the cyclopropane methylene group of (1*R*,2*S*)-**20** coincide when the hydroxyl groups; the aromatic rings and the nitrogens of "5-HT receptor active" conformations[12c] are fitted (Figure 3b).



(1R,2S)-20

It is noteworthy that none of the above comparisons appears to provide a satisfactory rationale for the stereoselectivity of **11** or for the inactivity of (±)-**19**; for example, the difference in overall shape of the enantiomers of **11** in "5-HT receptor active" conformations (Figures 4 and 5a) is only slightly larger than that between the enantiomers of **1** (Figure 5b). This contrasts to the large dif-

(21) Arvidsson, L.-E.; Johansson, A. M.; Hacksell, U.; Nilsson, J. L. G.; Svensson, S.; Hjort, S.; Magnusson, T.; Carlsson, A.; Lindberg, P.; Andersson, B.; Sanchez, D.; Wikström, H.; Sundell, S. *J. Med. Chem.* **1988**, *31*, 92–99.

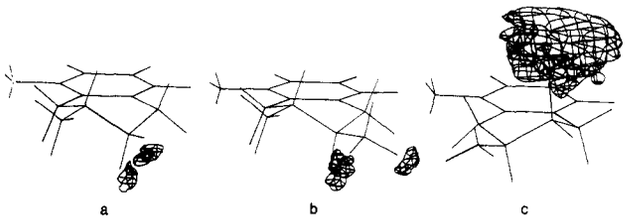


Figure 5. Structural comparison of enantiomeric pairs of the aminoanalogues of (a) 1 (conformation E; ref 12c), (b) 11 (conformation A), and (c) 15 (conformation A) constructed by use of the "set map" option of CHEM-X (developed and distributed by Chemical Design Ltd., Oxford). The excess van der Waals volume of the less potent/inactive enantiomer was obtained by the following: (i) A computer-generated best fit (the center of the aromatic rings, the oxygens, and the nitrogens were included in the fit) of the respective enantiomers of 1, 11, and 15. (ii) Generation of the combined van der Waals volumes of the fitted enantiomeric pairs. (iii) Subtraction of the van der Waals volume of the more potent enantiomer from the combined volumes. (iv) The excess volumes thus obtained were displayed at the 0.8 countoring level by using 24^3 grid points. The excess volume correponds to that volume that is unique for the less potent enantiomer. The excess volume and stick models of the less potent/inactive enantiomers are shown in Figures a–c (the other enantiomer is not shown for clarity).

ference in overall shape between the enantiomers of the stereoselective **15** (Figure 5c). Thus, we have not been able to rationalize all results in the present investigation. Studies that define additional parameters of critical importance for 5-HT_{1A}-receptor activation (such as the rotamer distribution of the dipropylamino substituent and/or the conformational preferences of the *N*-propyl substituents) should increase the understanding of the complex structure–activity relationships presented here.

Experimental Section

Chemistry. General Comments. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. 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, ^1H NMR spectra were recorded on a JEOL GX-400 spectrometer with 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. Pulse sequences used for COSY spectroscopy were obtained from the GX-400 software. IR spectra (recorded on a Perkin-Elmer 157 G spectrometer) and mass spectra[22] (recorded at 70 eV on a 9000 LKB spectrometer with use of a direct-insertion probe) were all in accordance with the assigned structures. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter. The elemental analyses (C, H, and N), which were performed by Micro Kemi AB, Uppsala, Sweden, were within ±0.4% of the theoretical values. 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. For the determinations of percent diastereomeric excess, capillary GC was performed on a Carlo Erba 4200 instrument equipped with an SE 54 column (10 m).

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

***trans*-2-Amino-8-methoxy-3-methyltetralin (7). Method I.** A mixture of 8-methoxy-3-methyl-2-tetralone (**5**; 30.0 g, 157.7 mmol),[9] hydroxylamine hydrochloride (21.9 g, 315.4 mmol), and sodium acetate (42.7 g, 520.4 mmol) in ethanol (300 mL) was heated under reflux for 2 h. The ethanol was evaporated in vacuo, and the residue was partitioned between ether and water. The dried (magnesium sulfate) ether layer was concentrated in vacuo, affording yellowish, slightly oily crystals, which were rinsed with ether. The 8-methoxy-3-methyl-2-tetralone oxime thus obtained was used in the next step without further purification.

To a solution of the above oxime (32.0 g, 155.9 mmol) in dry 2-propanol (2000 mL), kept at gentle reflux under nitrogen, were added thin slices of sodium (137 g, 6000 mmol). When the addition of sodium was complete (7 h), the heating was interrupted and water 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, to afford a product of 80% diastereomeric excess (as indicated by ^1H NMR). Ethereal hydrogen chloride was added to an ethereal solution of the oily residue, and the resulting precipitate was recrystallized from ethanol several times to give pure **7**·HCl in 39% yield as calculated from **5**: ^1H NMR (methanol-d_4) δ 7.22–6.98 (m, 1 H), 6.83–6.60 (m, 2 H), 3.81 (s, OMe), 3.43–2.38 (m, 5 H), 2.28–1.75 (m, 1 H), 1.17 (d, 3 H, C3-Me); mass spectrum, m/z 191 (88%, M^+), 174 (64%, $M^+ - NH_3$), 159 (87%).

***cis*-8-Methoxy-3-methyl-2-(*n*-propylamino)tetralin (12). Method II.** A mixture of 8-methoxy-3-methyl-2-tetralone (**5**; 25.0 g, 131.4 mmol),[9] *n*-propylamine (15.6 g, 263.0 mmol), and *p*-toluenesulfonic acid monohydrate (5 mg) in dry benzene (1500 mL) was heated to reflux under nitrogen in a Dean–Stark apparatus. More *n*-propylamine (15.6 g) was added after 48 h. The heating was interrupted after 4 days, and the volatiles were evaporated in vacuo. The residue was quickly dissolved in dry methanol (400 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 three portions of aqueous 1 M HCl. The combined aqueous layers were alkalinized with aqueous 5 M sodium hydroxide and extracted several times with ether. The combined ether layers were dried (potassium carbonate), filtered, and concentrated. Ethereal hydrogen chloride was added to an ethereal solution of the resulting oil (consisting of 85% of **12** and 15% of **8** according to GC analysis), and the resulting mixture of diastereomeric hydochlorides was recrystallized several times from ethanol to give 16.5 g (47%) of pure **12**·HCl: ^1H NMR (methanol-d_4) δ 7.26–7.00 (m, 1 H), 6.82–6.60 (m, 2 H), 3.82 (s, OMe), 3.73–3.46 (m, 1 H), 3.40–2.37 (m, 7 H), 2.05–1.55 (m, 2 H), 1.06 (t, 3 H), 0.99 (d, 3 H, C3-Me); mass spectrum, m/z 233 (100%, M^+), 204 (83%, $M^+ - C_2H_5$), 175 (87%, $M^+ - NHC_3H_7$).

***trans*-8-Methoxy-3-methyl-2-(*n*-propylamino)tetralin (8). Method III.** A solution of propionyl chloride (1.22 g, 13.18 mmol) in dry ether (10 mL) was added to a cold solution of **7** (1.26 g, 6.59 mmol) and triethylamine (1.33 g, 13.18 mmol) in dry ether (120 mL) kept under nitrogen. The reaction mixture was stirred for 2 h at room temperature, dichloromethane (50 mL) was added, and the mixture was extracted, first with aqueous 1 M HCl and then with aqueous 1 M sodium hydroxide. The organic layer was dried (magnesium sulfate), filtered, and concentrated. The resulting amide was dissolved in dry tetrahydrofuran (150 mL) and added to a suspension of lithium tetrahydroaluminate (1.6 g, 42 mmol) in dry tetrahydrofuran (100 mL) under nitrogen. The reaction mixture was stirred and heated under reflux for 16 h and was then quenched by addition of water and aqueous 15% sodium hydroxide. The resulting precipitate was filtered off, and the filtrate was dried (potassium carbonate), filtered, and concentrated. The crude amine was converted into the hydrochloride and recrystallized from ethanol–ether to afford 1.20 g (68%) of pure **8**·HCl: ^1H NMR (methanol-d_4) δ 7.26–7.09 (m, 1 H), 6.80–6.65 (m, 2 H), 3.83 (s, 3 H, OMe), 3.50–1.55 (m, 10 H), 1.17 (d, 3 H, C3-Me), 1.04 (t, 3 H); mass spectrum, m/z 233 (96%, M^+), 204 (76%, $M^+ - C_2H_5$), 175 (100%, $M^+ - NHC_3H_7$).

***cis*-8-Methoxy-3-methyl-2-(di-*n*-propylamino)tetralin (14). Method IV.** 1-Iodopropane (0.97 g, 5.73 mmol) was added to a stirred mixture of compound **12**·HCl (0.7 g, 2.59 mmol), potassium carbonate (2.0 g, 14.47 mmol), and acetonitrile (15 mL). The mixture was stirred at 50 °C under nitrogen. Two 1-g portions of potassium carbonate and 0.49 g of 1-iodopropane were added during the next 2 days. After 3 days the heating was interrupted, and ether was added. The reaction mixture was filtered, and the volatiles were evaporated. The oily residue was purified on an

(22) Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, J. L. G.; Wikström, H.; Lindberg, P.; Sanchez, D. *Biomed. Mass Spectrom.* 1981, *8*, 90–92.

alumina column with ether–petroleum ether (1:19) as eluant. The amine was converted into the hydrochloride and recrystallized from ethanol–ether, yielding 0.53 g (66%) of pure **14**·HCl: ^{1}H NMR (methano-d_4) δ 7.27–7.02 (m, 1 H), 6.86–6.52 (m, 2 H), 3.84 (s, OMe), 3.90–3.56 (m, 1 H), 3.48–2.98 (m, 6 H), 2.88–2.47 (m, 3 H), 2.05–1.52 (m, 4 H), 1.20–0.92 (m, 9 H); mass spectrum, m/z 275 (40%, M^+), 246 (96%, $M^+ - C_2H_5$), 175 (100%, $M^+ - NC_6H_{14}$).

***cis*-8-Hydroxy-3-methyl-2-(di-*n*-propylamino)tetralin (15). Method V.** A solution of compound **14**·HCl (0.150 g, 0.48 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 etheral solution of the residue, and the precipitate was recrystallized from ethanol–ether to afford 130 mg (91%) of pure **15**·HCl: ^{1}H NMR (methanol-d_4) δ 7.10–6.88 (m, 1 H), 6.70–6.50 (m, 2 H), 3.88–3.56 (m, 1 H), 3.48–2.42 (m, 9 H), 2.07–1.52 (m, 4 H), 1.20–0.90 (m, 9 H); mass spectrum, m/z 261 (37%, M^+), 232 (100%, $M^+ - C_2H_5$), 161 (84%, $M^+ - NC_6H_{14}$).

Resolution of Racemic *trans*-8-Methoxy-3-methyl-2-aminotetralin (7). (–)-5,5-Dimethyl-2-hydroxy-4-phenyl-1,3,2-dioxaphosphorinane 2-oxide[11] (16.0 g, 66.1 mmol) was added to a hot solution of (±)-**7** (12.6 g, 66.1 mmol) in 96% ethanol (600 mL) and water (150 mL). The solution was stirred overnight at room temperature, and the precipitated salt was collected. The salt was then recrystallized (with stirring) five times from ethanol–water. The free amine was liberated and precipitated from ether as the hydrochloride. One recrystallization from ethanol–ether afforded 2.17 g (29%) of (+)-**7**·HCl.

(–)-**7**·HCl was obtained by fractional crystallization of the diastereomeric salts formed from the free amine recovered from the combined mother liquors and (+)-5,5-dimethyl-2-hydroxy-4-phenyl-1,3,2-dioxaphosphorinane 2-oxide.[11] After five recrystallizations, the amine was liberated, and the hydrochloride was prepared and recrystallized to give 2.53 g (34%) of (–)-**7**·HCl.

The enantiomeric excess of the primary amines (+)- and (–)-**7** was determined indirectly, as follows: The sample to be investigated [(+)- or (–)-**7**·HCl; 20 mg, 74.1 μmol] was mixed with water (0.2 mL) and aqueous 1 M sodium hydroxide (0.2 mL). A solution of (*R*)-2-methoxy-2-phenylacetyl chloride (111.2 μmol) [prepared from (*R*)-2-methoxy-2-phenylacetic acid (18.5 mg, 111.2 μmol) and thionyl chloride (2.0 mL), by stirring at room temperature for 2 h followed by evaporation of volatiles] in dichloromethane (0.5 mL) was added with vigorous stirring at room temperature. The stirring was interrupted after 1 h, and the organic layer was separated, dried (magnesium sulfate), filtered, and concentrated. ^{1}H NMR spectra (acetone-d_6) of the 2-methoxy-2-phenylacetamides of (+)- and (–)-**7** showed no diastereomeric impurities. GC analysis of the crude amides indicated that the diastereomeric excess was >96%.

Resolution of Racemic *cis*-8-Methoxy-3-methyl-2-(*n*-propylamino)tetralin (12). (–)-Di-*p*-toluoyl-L-tartaric acid (29.8 g, 77.1 mmol) was added to a hot solution of (±)-**12** (18.0 g, 77.1 mmol) in ethanol (300 mL) and water (30 mL). The solution was allowed to stand overnight 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 base was converted to the hydrochloride. One recrystallization from ethanol–ether afforded 3.14 g (31%) of (–)-**12**·HCl.

The free amine isolated from the mother liquors in the resolution of (–)-**12** was treated with (+)-di-*p*-toluoyl-D-tartaric acid as described above. After three recrystallizations of the salt from ethanol–water, the amine was liberated, and the hydrochloride was prepared and recrystallized to give 3.90 g (37%) of (+)-**12**·HCl.

The percent enantiomeric excess in (+)- and (–)-**12** was determined indirectly, by the same procedure as described above for the determination of the diastereomeric excess in the *O*-methylmandeloyl amides of (+)- and (–)-**7**, to be larger than 96% (GC analysis); ^{1}H NMR spectra (benzene-d_6) of the crude diastereomeric amides prepared from (+)- and (–)-**12**·HCl, respectively, showed no diastereomeric impurities.

The percent enantiomeric excess in (+)- and (–)-**11** and in (+)- and (–)-**15** was determined directly, by HPLC analysis, by use of an optically active counter ion in the eluent, to be ≥96%, respectively (detection limit of the method).[23]

Optical Rotations. The resolved compounds presented in Table I have the following optical rotations ($[\alpha]^{22}_D$, methanol, *c* 1.0): (+)-**7**, +76.5°; (–)-**7**, –79.9°; (+)-**7**, +54.3°; (–)-**8**, –54.5°; (+)-**9**, +53.8°; (–)-**9**, –54.2°; (+)-**10**, +79.6°; (–)-**10**, –78.2°; (+)-**11**, +67.0°; (–)-**11**, –65.5°; (+)-**12**, +37.6°; (–)-**12**, –37.3°; (+)-**13**, +38.2°; (–)-**13**, –37.8°; (+)-**14**, +58.1°; (–)-**14**, –57.7°; (+)-**15**, +60.2°; (–)-**15**, –60.1°.

Molecular Mechanics Calculations. The structural modeling was preformed by use of the interactive computer graphics programs MIMIC (methods for interactive modeling in chemistry)[24] and CHEM-X. The structural comparisons shown in Figures 2–4 were performed by use of the least-squares fitting routine in MIMIC. Calculations were preformed on VAX 11/780 and MICROVAX II computers by using Allinger's MMP2 force field[25] to which had been added parameters for the phenol[26] and amino groups.[27] Computational times ranged from 1 to 30 min/minimization.

Absolute Configuration Determination by Single-Crystal X-ray Analysis of (+)-11·HBr and (–)-15·HBr. Crystals of (+)-**11**·HBr and (–)-**15**·HBr were grown from ethanol solutions. The dimensions of the crystals used for data collection are given in Table IV together with additional crystal data. Intensities for (+)-**11**·HBr and (–)-**15**·HBr were recorded on an Enraf-Nonius CAD4F-11 diffractometer. The lattice parameters were determined from angular settings of 25 reflections. The crystals were irradiated with monochromatized Cu Kα radiation, and the $\theta/2\theta$ scan method was used. Three standard reflections, which were checked every 2 h, indicated a slight decay (2% and 5% for (–)-**15**·HBr and (+)-**11**·HBr, respectively) of the crystals. The measured intensities were rescaled to account for this decay. For each compound, two sets of independent reflections with $1 < \theta < 60°$ were measured. In all, 2710 and 5532 reflections were measured, and of these, 2463 and 4964 with $I > 3\sigma(I)$ were considered observed for (–)-**15**·HBr and (+)-**11**·HBr, respectively. The intensities were corrected for Lorentz and polarization effects but not for extinction or absorption.

The structures were solved by a combination of the Patterson heavy-atom method and direct methods by using the program DIRDIF.[28] Methyl and hydroxyl hydrogen positions were determined from Fourier difference synthesis maps, and the remaining hydrogen atoms were included at expected positions. The methyl hydrogen positions of (+)-**11**·HBr having C–H distances ranging from 0.83 to 1.40 Å were repositioned at idealized bond lengths and angles. Corresponding C–H distances for (–)-**15**·HBr ranged from 0.91 to 1.22 Å, which was accepted. The non-hydrogen atom parameters were refined by the full-matrix least-squares method with anisotropic temperature factors. The hydrogen atoms were assigned a common temperature factor ($B = 5$ Å^2). The hydrogen atom parameters were not refined. Carbon atom C15 of molecule A in (+)-**11**·HBr did not respond correctly to the refinement. The C14–C15 distance became much too short (1.17 Å) and the U_{22} and U_{33} values became very large (about 0.3) A Fourier difference synthesis map provided no conclusive evidence for whether this was caused by disorder or by highly anisotropic motion of C15. The position of C15, obtained from the Fourier difference synthesis, was kept fixed during the later part of the refinement. In order to determine the absolute configurations, anomalous dispersion factors were introduced for the non-hydrogen atoms.[29] Two sets of unique reflections ($h,k,\pm l$ and $h,-k,\pm l$) were used in the refinement, and nonobserved reflections were allowed to contribute when $F_{calcd} > F_{obsd}$. The final residuals for the correct

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(24) Liljefors, T. *J. Mol. Graphics* **1983**, *1*, 111–117.
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(26) Dodziuk, H.; von Voithenberg, H.; Allinger, N. L. *Tetrahedron* **1982**, *38*, 2811–2819.
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(C) and erroneous (E) enantiomers of the two compounds are given in Table IV. By use of Hamilton's test,[30] the $R(E)_w/R(C)_w$ ratios for both structures were sufficiently great to reject the (E) enantiomer at the 0.005 significance level. The form factors used were those by Cromer and Mann.[31] The weighting scheme used in the latter part of the refinement was $w = 1/[1 + (|F_o| - A)/B]^2$[32] where the constants (A, B) were (9, 15) and (18, 19) for (-)-15·HBr and (+)-11·HBr, respectively. All calculations were performed on a DEC-system-10 computer with use of mainly the X-ray 72 program system.[33]

Pharmacology. Materials and Methods. Male Sprague–Dawley rats (Alab, Stockholm) weighing 170–230 g were used. Reserpine and haloperidol were dissolved in a minimal quantity of glacial acetic acid and made up to volume with 5.5% glucose solution. The other substances were dissolved in aqueous 0.9% sodium chloride plus a minimal amount of aqueous 2 M hydrogen chloric acid and moderate heating when required. Throughout, injection volumes were 5 mL/kg.

Biochemistry. Substances to be tested were given as the hydrochlorides or hydrobromides, subcutaneously in the neck region, to rats not pretreated with reserpine. In a few cases, the substance was also given to reserpine pretreated (5 mg/kg, i.e., 8 μmol/kg, sc, 4 h before) rats. The aromatic L-amino acid decarboxylase inhibitor (3-hydroxybenzyl)hydrazine hydrochloride (NSD 1015; 100 mg/kg, i.e., 573 μmol/kg, ip) was given 30 min later.[16] After another 30 min, the rat was killed by decapitation. The brain was removed and immediately dissected on an ice-cooled Petri dish into four parts: the corpus striatum, the limbic system, the rest of the hemispheres including the cerebellum, and the brain stem. The brain parts were frozen on dry ice. The tissue was homogenized in 0.1 M perchloric acid containing glutathione, EDTA, and α-methyl-DOPA (internal standard). DOPA, DA, HVA, 5-HTP, and 5-HT were determined by means of HPLC (ion-pair, reversed-phase) with electrochemical detection. The concentrations were calculated by comparing the peak heights of the compound and the internal standard in the sample and in an external standard solution. The values were corrected for the recovery of the internal standard.

Locomotor Activity. The locomotor activity was studied by means of a motility meter (Motron Productions, Stockholm) consisting of a 32 × 40 × 25 cm plastic cage containing 40 photocells in the floor and a bulb in the ceiling and placed in a sound-proof box. Light-beam interruptions were registered by an external counting device. Reserpine and the DA receptor blocking agent haloperidol were given 4 and 1 h prior to the testing, respectively. The substances to be tested were injected subcutaneously immediately before the rats were placed in the motility meter. The locomotor activity was registered for each 5-min period during 2 h. The animals were continuously observed through a semitransparent window.

5-HT_{1A} Binding Assay. The measurement of 5-HT_{1A} binding sites, with use of [^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetralin ([^{3}H]-8-OH-DPAT; New England Nuclear Corp., Boston, MA), was carried out essentially as described previously.[34] Male Sprague–Dawley rats (150–225 g; Harlan Sprague–Dawley, Indianapolis, IN) were decapitated, and the brains were rapidly chilled and dissected to obtain the cerebral cortex dorsal to the rhinal sulcus. The tissue was homogenized in 40 volumes of ice-cold Tris·HCl buffer (50 mM, pH 7.4 at 22 °C) with a Brinkmann Polytron (setting 5 for 15 s), and the homogenate was centrifuged at 48000*g* for 10 min. The resulting pellet was then resuspended in the same buffer, and the centrifugation and resuspension process was repeated three additional times to wash the membranes. Between the second and third washes the resuspended membranes were incubated for 10 min at 37 °C to facilitate the removal of endogenous 5-HT.[35] The final pellet was resuspended in the buffer to a final concentration of 10 mg of tissue (original wet weight)/mL for use in the binding assay. To each assay tube the following were added: 0.1 mL of drug dilution (or water if no competing drug was added), 0.9 mL of [^{3}H]-8-OH-DPAT in buffer (containing Tris, $CaCl_2$, and pargyline to achieve final assay concentrations of 50 mM, 3 mM, and 100 μM, respectively, pH 7.4), and 1 mL of resuspended membranes. The final concentration of [^{3}H]-8-OH-DPAT in the assays was 1 nM. The tubes were incubated for 15 min at 37 °C, and the incubations were terminated by vacuum filtration through Whatman GF/B filters (pretreated by soaking for 2 h in a 0.1% v/v solution of polyethyleneimine and then dried), followed by two 4-mL rinses with ice-cold 50 mM phosphate buffer. The filters were dried, and the radioactivity bound to the filters was measured by liquid scintillation spectrometry. Specific [^{3}H]-8-OH-DPAT binding was defined as the difference between binding in the absence and presence of 10 μM 5-HT. IC_{50} and slope values from the competition assays were determined by nonlinear regression analysis by using the program PCNONLIN and the four-parameter logistic function described by De Lean et al.[36]

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Supplementary Material Available: X-ray data, consisting of positional and thermal parameters for the hydrogen atoms of (+)-11·HBr and (-)-15·HBr (3 pages). Ordering information is given on any current masthead page.

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