was evaporated to dryness and the residue chromatographed on a CHP-20P column (200-mL bed volume, 1-in.-diameter column) eluting with a linear gradient of H_2O (100%)/CH_3CN (100%). The product-containing fractions were pooled and evaporated. The residue was taken up in water, filtered (millipore), and lyophilized to give disodium salt **15a** (0.310 g, 60%) as a white solid: mp 190–200 °C; TLC (*i*-PrOH/concentrated NH_4OH/H_2O, 4:2:1) R_f 0.52; ^{13}C NMR (D_2O) δ 22.5, 23.4, 24.6, 25.8 (138), 29.1, 31.5, 32.1 (17), 34.7, 40.7, 47.5, 62.1 (CH), 70.8 (CH, 5), 156.7 (C), 171.0 (C), 179.0 (C); ^1H NMR (D_2O) δ 1.15–2.10 (14 H, m), 2.40 (2 H, t), 3.01 (2 H, t), 3.35 (1 H, m), 3.55 (1 H, m), 4.07 (1 H, dd), 4.68 (1 H, m), 7.12 (5 H, m); $[\alpha]_D$ −49.1° (*c* 0.57, H_2O). Anal. ($C_{21}H_{31}N_4O_6PNa_2 \cdot 0.3H_2O$) C, H, N, P.

Guanidino phosphonates **15b** (28% from **8b**) and **15c** (16% from **8q**) were also prepared by this method.

In Vitro Inhibition of Angiotensin Converting Enzyme from Rabbit Lung. The conditions for the assay of inhibition of ACE are those we reported previously[7] in which hippuric acid liberated from the synthetic substrate hippurylhistidylleucine by rabbit lung ACE is quantitated by a spectrophotometric method (see ref 7 for details).

Angiotensin Converting Enzyme Inhibitor Screen in Vivo. Male Sprague–Dawley rats (225–275 g) were equipped with indwelling abdominal aorta and vena caval catheters by using a modification of the method of Weeks and Jones.[20] The animals were allowed to recover for at least 2 weeks before experimentation, during which time they were housed individually and maintained on rat chow and tap water ad libitum. On the day of experimentation aortic blood pressures were monitored directly by pressure transducers and recorded on a Beckman Dynograph. The venous catheter was used for drug injections. During all experiments the rats were conscious and unrestrained in their cages. Pressor responses were obtained for angiotensin I (310 ng/kg, iv) and angiotensin II (100 ng/kg iv) before administration of the compounds. For intravenous testing, compounds were administered in 0.1 mL of water or 5% $NaHCO_3$, and angiotensin I and II pressor responses were evaluated for up to 70 min. For oral testing, compounds were administered in 0.1 mL of water, 5% $NaHCO_3$, or 1% agar suspension and angiotensin I and II pressor responses were evaluated for up to 280 min. Maximum percent inhibition was determined as the mean of the responses for four animals per dose. The dose required to produce 50% inhibition of the response (ED_{50}) was estimated by interpolation of a plot of maximum inhibition versus dose.

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Structural Factors of Importance for 5-Hydroxytryptaminergic Activity. Conformational Preferences and Electrostatic Potentials of 8-Hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) and Some Related Agents

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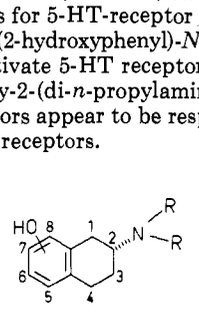
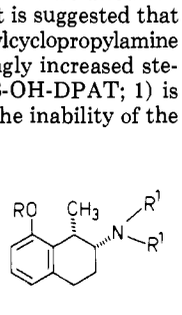
The conformational characteristics of two series of 5-hydroxytryptamine (5-HT) receptor agonists, monophenolic N,N-dialkylated 2-aminotetralins and *trans*-2-phenylcyclopropylamines, have been studied by a combination of experimental (NMR spectroscopy) and theoretical (molecular mechanics and MNDO calculations) methods. In addition, molecular electrostatic potentials have been calculated for selected conformations and the absolute configuration of the potent 5-HT-receptor agonist (+)-*cis*-8-hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin (**2**) has been determined, by X-ray crystallography of the synthetic precursor, to be 1*S*,2*R*. Results obtained are discussed in terms of conformational, steric, and electronic requirements for 5-HT-receptor activation. It is suggested that different conformations of the 5-HT-receptor agonists (1*R*,2*S*)-2-(2-hydroxyphenyl)-*N*,*N*-di-*n*-propylcyclopropylamine [(1*R*,2*S*)-**4**] and its 3-hydroxy isomer (1*R*,2*S*)-**5** are able to activate 5-HT receptors. The strongly increased stereoselectivity of **2**, **4**, and **5** as compared to that of 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT; **1**) is rationalized on the basis of steric factors. Conformational factors appear to be responsible for the inability of the *trans*-C1-methyl-substituted derivative of **1** to activate 5-HT receptors.

8-Hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT; **1**) is a potent centrally active 5-hydroxytryptamine (5-HT) receptor agonist[1,2] with high selectivity for $5\text{-}HT_{1A}$-binding sites.[3,4] The *R* enantiomer of **1** is twofold more potent than the antipode.[1,5] Introduction of a *cis*-C1-methyl group in **1** led to the 5-HT agonist (+)-**2**,[6] which was found to be approximately equipotent to **1**. Interestingly, (−)-**2** and trans isomer (±)-**3** were found to be inactive.[6]

It has been shown that also monophenolic N,N-dialkylated derivatives of *trans*-2-phenylcyclopropylamine possess 5-HT receptor stimulating properties.[7] These compounds displayed high stereoselectivity, thereby being





(2R)-**1**: 8-OH; R = n-C_3H_7
(2R)-**6**: 7-OH; R = n-C_3H_7
(2R)-**10**: 8-OH; R = CH_3

(1S,2R)-**2**: R = H; R^1 = n-C_3H_7
(1S,2R)-**7**: R = CH_3; R^1 = n-C_3H_7
(1S,2R)-**11**: R = H; R^1 = CH_3

similar to the *cis*-C1-methylated derivative of **1**. The 5-HT-receptor activity of **4** and **5** resides in the 1*R*,2*S* en-

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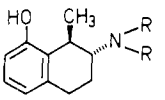
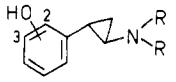
antiomers; the antipodes were found to be at least 100 times less potent.[7]



(1R,2R)-3: R=n-C3H7
(1R,2R)-12: R=CH3



(1R,2S)-4: 2-OH; R=n-C3H7
(1R,2S)-5: 3-OH; R=n-C3H7
(1R,2S)-8: 2-OH; R=CH3
(1R,2S)-9: 3-OH; R=CH3

Some of these observations are not readily interpreted in terms of structure–activity relationships; e.g., (a) why is 1 weakly stereoselective when **2**, **4**, and **5** demonstrate a considerable stereoselectivity, (b) why are (1*R*,2*S*)-**4** and **5** equipotent when 1 is at least 100-fold more potent than the 7-hydroxy isomer **14** as a 5-HT-receptor agonist, and (c) why is (±)-**3** inactive? In the present investigation, we have studied the conformational preferences and the electrostatic potentials of compounds **1**–**5** in order to find out if conformational and/or electronic factors may be of importance for the 5-HT-receptor activities of these compounds. In addition, we have determined the absolute configuration of (+)-**2** by X-ray crystallography of the synthetic precursor (+)-**7**. The conformational preferences of **1**–**3** were studied by use of force field calculations (MMP2)[8] and ^1H and ^{13}C NMR spectroscopy, whereas conformational properties of the *trans*-2-phenylcyclopropylamines **4** and **5** were examined by use of MNDO calculations.[9] Molecular electrostatic potentials were calculated for model compounds of **1**–**5** (**10**–**12**, **8**, and **9**, respectively) by use of the ab initio STO-3G method.[10]

Experimental Section

The syntheses of compounds **1**–**5** have been previously reported.[1,5,7]

Absolute Configuration Determination of (+)-7·HCl by Single-Crystal X-ray Analysis. Crystals of (+)-**2**·HCl or (+)-**2**·HBr were not suitable for X-ray analysis. Instead, (+)-**7**·HCl,[6] which is the synthetic precursor of (+)-**2**, was subjected to X-ray analysis.

Crystals of (+)-**7**·HCl were grown from a methanol–ether solution, and a crystal with the dimensions 0.46 × 0.15 × 0.05 mm was used for data collection with an Enraf-Nonius CAD4F-11 diffractometer. The angular settings of 25 reflections ($6° < \theta < 38°$) were measured to calculate the lattice parameters. Intensity data for reflections within one hemisphere and with $\theta < 60°$ were collected by the $\theta/2\theta$ scan method by use of monochromatized Cu Kα radiation. Three intensity control reflections, which were measured every 2 h, indicated a decay of the crystal by 34%. The measured intensities were rescaled to account for this decay. A total of 3135 reflections were recorded, and of these, 2091 reflections with $I > 3\sigma(I)$ were considered observed. All intensities were corrected for Lorentz and polarization effects but not for absorption or extinction.

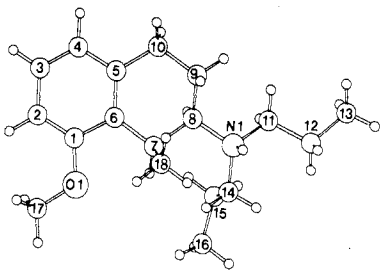


Figure 1. X-ray crystal structure of (+)-**7**·HCl; molecular structure and atom labeling scheme.

Crystal data: molecular formula $C_{18}H_{29}NO{\cdot}HCl{\cdot}CH_3OH$, M_r 343.939; space group, $P2_1$; unit cell, a = 9.868 (2) Å, b = 7.394 (3) Å, c = 13.759 (3) Å, and β = 96.80 (2)°; V = 997 Å^3, Z = 2, D_{calcd} = 1.146 g cm^{-3}, μ(Cu Kα) = 17.6 cm^{-1}.

The structure was solved by a combination of Patterson heavy atom method and direct methods using the program DIRDIF,[11] which provided the non-hydrogen atom positions. The positions of the hydrogen atoms (except those of the methyl groups and of the methanol molecule which were omitted) were calculated to be at expected positions. Refinement was carried out by the full-matrix least-squares method, using anisotropic temperature factors for the non-hydrogen atoms. The hydrogen atoms were assigned a common isotropic temperature factor (B = 5 Å^2). The hydrogen atom parameters were not refined.

In order to determine the absolute configuration of (+)-**7**·HCl, we introduced anomalous dispersion factors[12] 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 was finished, the residuals for the 1*S*,2*R* and 1*R*,2*S* enantiomers were calculated to be R = 0.082 and R = 0.108 (R_w = 0.091 and R_w = 0.121), respectively. When Hamilton's test[13] is used, the ratio $R_w(1R,2S)/R_w(1S,2R)$ = 1.330 is sufficiently great to reject the 1*R*,2*S* enantiomer at the 0.005 significance level. Furthermore, among the 74 Bijvoet pairs for which $|F_c(h,k,l) - F_c(h,-k,l)| > 1.0$, 67 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 refinement was $w = 1/(1 + ((|F_o| - 6)/5)^2)$.[14] The form factors used were those given by Cromer and Mann.[15] All calculations have been performed on a DEC-system-10 computer using mainly the X-ray 72 program system.[16]

The molecular conformation and atomic labeling scheme[17] for (+)-**7**·HCl is shown in Figure 1.

Molecular Mechanics Calculations of 2-Aminotetralins. The force field calculations (MMP2)[8] on **1**–**3** (free bases) were performed as previously described for other 2-aminotetralins.[18]

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Table I. Geometrical Parameters[a] for Low-Energy Conformations of (2*R*)-1, (1*S*,2*R*)-2, and (1*R*,2*R*)-3

conformation	Φ,[b] deg	τ_N,[c] deg	τ_A,[d] deg	τ_B,[e] deg	$\tau_{A'}$,[f] deg	$\tau_{B'}$,[g] deg	rel steric energy, kcal/mol
				(2*R*)-1			
A	200[h]	55	−49	−170	176	−170	0.6
B	200[h]	55	−50	−170	173	−55	0.9
C	200[h]	54	−52	−57	175	−170	1.0
D	200[h]	53	−55	−59	171	−53	1.1
E	175[h]	176	−173	169	53	171	0[i]
F	175[h]	177	−173	169	55	57	0.4
G	180[h]	176	−171	54	53	171	0.2
H	175[h]	177	−170	53	53	56	0.4
I	165	−56	178	170	−61	−178	0.6
J	165	−56	−179	57	−60	−179	1.0
K	165	−64	63	178	−177	−171	0.7
L	165	−64	63	179	180	−57	1.2
M	25[h]	−61	177	171	−64	−177	0.9
N	25[h]	−60	−179	56	−64	−178	1.2
O	25[h]	−66	62	180	180	−170	0.6
P	25[h]	−67	62	−179	176	−56	0.7
				(1*S*,2*R*)-2			
A	197	−55	179	170	−61	−179	0[j]
B	197	−54	−177	56	−61	180	0.3
C	198	−60	63	177	−176	−171	0.2
D	198	−61	63	178	−179	−58	0.8
				(1*R*,2*R*)-3			
A	155[h]	46	−52	−168	170	−170	0.7
B	155[h]	47	−53	−168	168	−54	0.7
C	155[h]	47	−55	−55	170	−170	0.9
D	155[h]	47	−56	−55	167	−53	0.7
E	150[h]	28	66	175	171	−171	2.5
F	138	−55	−179	170	−64	179	2.1
G	138	−54	−177	57	−64	178	2.5
H	137	−55	70	−178	180	−172	2.4
I	20[h]	61	−52	−172	171	−169	2.1
J	25[h]	61	−54	−172	168	−54	2.4
K	25[h]	61	−55	−58	170	−169	2.5
L	25[h]	−61	176	170	−63	−176	0.3
M	25[h]	−60	180	57	−63	−178	0.6
N	25[h]	−66	61	179	−179	−170	0[k]
O	25[h]	−67	61	−179	176	−56	0.1
P	25[h]	−61	−103	179	−59	−173	2.4

[a] Only conformations with τ(C8a, C8, O, H) $\approx$ 180° are included, and conformations with energies larger than 2.5 kcal/mol above the respective global minima have been omitted. [b] Tetralin inversion angle (see Figure 2). [c] $\tau_N = \tau$(C1, C2, N, electron pair). [d] $\tau_A = \tau$(C2, N, C_α, C_β). [e] $\tau_B = \tau$(N, C_α, C_β, C_γ). [f] $\tau_{A'} = \tau$(C_2, N, $C_{\alpha'}$, $C_{\beta'}$). [g] $\tau_{B'} = \tau$(N, $C_{\alpha'}$, $C_{\beta'}$, $C_{\delta'}$). [h] Approximate Φ value estaimated by comparison with relevant conformations of C2-unsubstituted tetralin. [i] Steric energy = 13.6 kcal/mol. [j] Steric energy = 17.4 kcal/mol. [k] Steric energy = 17.4 kcal/mol.

The structural modelling was performed by use of the interactive computer graphics program MIMIC (methods for interactive modelling in chemistry).[19] Calculations were performed on VAX 11/780 and Microvax II computers by use of Allinger's MMP2 force field[8] to which had been added parameters for the phenol[20] and amino groups.[21] The force field parameters used in the present investigation have been used in several previous studies of phenolic 2-aminotetralin derivatives.[18] They have been found to reproduce X-ray geometries as well as conformational preferences in solution with satisfactory accuracy.[18] Computational times ranged from 1 to 30 min/minimization.

The tetralin inversion angle Φ (Figure 2)[18a] defines the conformation of the nonaromatic ring of tetralin derivatives; for example, Φ is around 180° when the nonaromatic ring of a (2*R*)-2-aminotetralin assumes a half-chair conformation with a pseudoequatorial amino substituent.[18] It should be noted that the tetralin inversion angle Φ is dependent on the configuration, that is, enantiomeric conformations of (2*R*)- and (2*S*)-2-aminotetralin differ in the Φ values by ±180°. The conformation of the dipropylamino group is described by the following torsion angles:[17,22] $\tau_N = \tau$(C1, C2, N, N-electron pair or N–H) defines the direction of the N-electron pair or the N–H bond. 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 one of the *N*-propyl groups.[18a,b] The conformation of the other *N*-propyl group is given by $\tau_{A'} = \tau$(C2, N, $C_{\alpha'}$, $C_{\beta'}$) and $\tau_{B'} = \tau$(N, $C_{\alpha'}$, $C_{\beta'}$, $C_{\gamma'}$).[18a,b]

NMR Spectroscopy. ^{1}H NMR spectra were recorded at 400 MHz on a JEOL GX-400 spectrometer at 25 °C using 0.1 M CD_3OD solutions of the hydrobromide of 1 and the hydrochlorides of 2 and 3. Chemical shifts were measured relative to internal tetramethylsilane. Apparent coupling constants were measured from expanded (1–2 Hz/cm) spectra. The assignments of protons were verified by decoupling experiments. However, the spectrum of 1·HBr was complex due to overlap of several multiplets. Thus, in order to fully assign the protons of 1·HBr, two-dimensional homonuclear (^{1}H–^{1}H; COSY) and heteronuclear (^{13}C–^{1}H) shift correlation experiments were performed.[23] In addition, chemical

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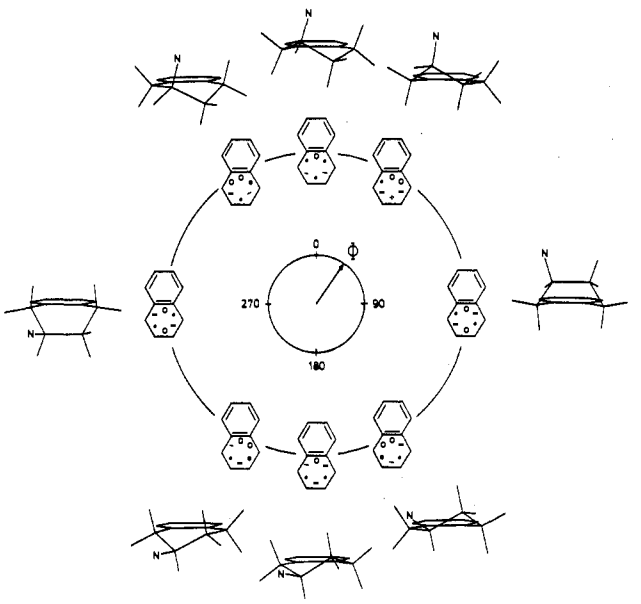


Figure 2. Tetralin inversion wheel that defines the relationship between tetralin ring conformation and the tetralin inversion angle Φ. The eight inserted tetralin structures correspond to conformations with Φ = 0°, 30°, 90°, 150°, 180°, 210°, 270°, and 330°, respectively. Each of the tetralin conformations is characterized by the signs (inserted) of the relevant torsion angles. Perspective drawings of eight conformations of a (2*R*)-2-aminotetralin moiety are shown outside the corresponding tetralin conformations. It should be noted that, for (2*S*)-2-aminotetralin, a half-chair conformation with a pseudoequatorial amino group corresponds to Φ = 0°.

shift values for some of the protons of 1·HBr were determined from the *J*-resolved two-dimensional spectrum. Pulse sequences used for the two-dimensional NMR experiments were obtained from the GX-400 software.

MNDO Calculations of *trans*-2-Phenylcyclopropylamines. High-quality force field parameters for the (phenylcyclopropyl)amino moiety were not available to us during the course of this study. Instead, we performed MNDO calculations on compounds (1*R*,2*S*)-**8** and (1*R*,2*S*)-**9**, which served as model compounds for (1*R*,2*S*)-**4** and (1*R*,2*S*)-**5**, respectively. The calculations were performed on a VAX 11/730 computer by use of the MOPAC (MNDO SCF-MO) program package.[9,24] Minimized structures were obtained by full relaxation of several trial geometries, which were generated by the use of perception routines of the LHASA program.[25] A nonlinear least squares gradient minimizer[26] was used for location of transition states. Two conformations were obtained by a computer-generated best fit of (1*R*,2*S*)-**8** and (1*R*,2*S*)-**9** with (2*R*)-**1** (conformation I, Table I).

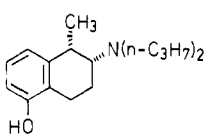
Calculations of Molecular Electrostatic Potentials of 2-Aminotetralins and *trans*-2-Phenylcyclopropylamines. It has been implied that 5-HT, LSD, and other tryptamine derivatives exert their pharmacological effect through formation of charge-transfer complexes.[27] This idea has been criticized.[28] However, the electronic properties of tryptamine derivatives seem to be of importance for their interaction with 5-HT receptors.[28] For example, Weinstein and co-workers[29] suggested that tryptamine derivatives will be differently oriented on the 5-HT receptor depending on the aromatic substitution pattern of the indole nucleus and that the interaction is electrostatic in nature but not of charge-transfer type. They arrived at this suggestion via a series of ab initio calculations on tryptamine derivatives. In particular, the molecular electrostatic potentials for the compounds were studied in a parallel plane 1.6 Å from the plane of the indole ring system, that is, at approximately half the interplanar distance between the indole nucleus of 5-HT[30] or skatole[31] and the benzene ring of the picrate ion in the picrate complex of 5-HT or skatole. Weinstein et al.[29] also found that the molecular electrostatic potentials for protonated and neutral forms of 5-HT are almost identical when 5-HT is interacting with a negative group. These results formed the bases for our calculations.

Model compounds **8**–**12** served as simplified analogues to (1*R*,2*S*)-**4**, (1*R*,2*S*)-**5**, (2*R*)-**1**, (1*S*,2*R*)-**2**, and (1*R*,2*R*)-**3**, respectively, in the calculations of the molecular electrostatic potentials. Geometrical parameters for the 1*R*,2*S* enantiomers of **8** and **9** were taken from MNDO-calculated conformations. The coordinates for (2*R*)-**10**, (1*S*,2*R*)-**11**, and (1*R*,2*R*)-**12** were obtained from MMP2-minimized conformations of (2*R*)-**1**, (1*S*,2*R*)-**2**, and (1*R*,2*R*)-**3**. Molecular electrostatic potentials were also calculated for the corresponding conformations having the hydroxyl group rotated 180°. In addition, the electrostatic potential surface for 5-HT was calculated. The coordinates for 5-HT were obtained from the MNDO-calculated best fit of the benzene moiety, the nitrogen, and the N-electron pair of 5-HT with the corresponding structural elements of conformation I of (2*R*)-**1**. The atoms, except for those included in the fitting procedure, were minimized at the MNDO level with respect to all internal coordinates. All calculations were performed on the free bases.

The ab initio molecular electrostatic potential surfaces were obtained by the GAUSSIAN 80 program (UCSF version)[10] at the STO-3G level. The calculations were performed on a VAX 11/785 or a VAX 8600 computer. In general, the electrostatic potentials were studied in a parallel plane 1.6 Å below and above the aromatic ring.

Results

X-ray Crystallography. The absolute configuration of (+)-**7** and thereby that of (+)-**2** was found to be 1*S*,2*R* (Figure 2). The torsion angle τ(C7, C8, C9, C10) = −64.5° corresponds to a tetralin inversion angle (Φ) of 205° (cf. Figure 1); that is, compound (+)-**7**·HCl adopts a slightly distorted half-chair conformation with the dipropylammonium substituent in a pseudoequatorial position. The direction of the N–H bond is given by the torsion angle τ_N, which is −69.6°. A similar conformation of the 5-hydroxy isomer, (1*S*,2*R*)-**13**·HCl, has been observed in the solid state.[18b]



13

Molecular Mechanics Calculations of 2-Aminotetralins. The results from the molecular mechanics calculations are given in Table I. The numbers of low-energy conformations (within 2.5 kcal/mol of the global minimum)[32,33] of compounds **1**, **2**, and **3** were found to be

(24) *Quantum Chem. Program Exchange*, Program No. 455.
(25) Pensak, D. A.; Corey, E. J. *ACS Symp. Ser.* **1977**, *No. 61*, 1. The conformer generator has been developed by the LHASA group at Leeds and is implemented in LHASA version 6-2.
(26) Optional minimizer available within the MOPAC program package.
(27) See, for example: Karreman, G.; Isenberg, I.; Szent-Györgyi, A. *Science (Washington, D.C.)* **1959**, *130*, 1191. Snyder, S. H.; Merril, C. R. *Proc. Natl. Acad. Sci. U.S.A.* **1965**, *45*, 258. Kang, S.; Green, J. P. *Nature (London)* **1970**, *226*, 645. Green, J. P. In *Molecular Basis of Some Aspects of Mental Activity*; Walaas, O., Ed.; Academic: New York, 1967; p 95. Green, J. P.; Kang, S. In *Molecular Orbital Studies in Chemical Pharmacology*; Kier, L. B., Ed., Springer-Verlag: New York, 1970; p 105.
(28) Gupta, S. P.; Singh, P.; Bindal, M. C. *Chem. Rev.* **1983**, *83*, 633.
(29) Weinstein, H.; Osman, R.; Green, J. P.; Topiol, S. In *Chemical Applications of Atomic and Electrostatic Potentials*; Politzer, P., Truhlar, D. G., Eds.; Plenum: New York, 1981; p 309.
(30) Thewalt, U.; Bugg, C. E. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1972**, *B28*, 82.
(31) Hanson, A. W. *Acta Crystallogr.* **1964**, *17*, 559.

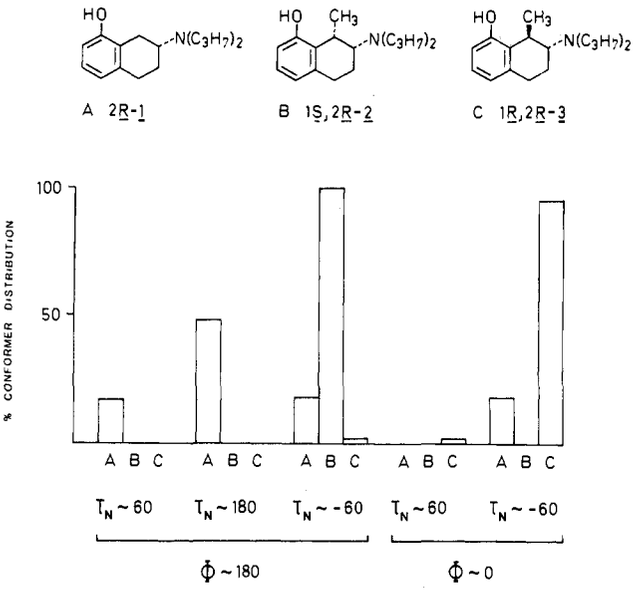


Figure 3. Conformational distribution of (2*R*)-**1**, (1*S*,2*R*)-**2**, and (1*R*,2*R*)-**3**. The probability of existence of each conformation (at 37 °C) was estimated from a Boltzmann distribution based on the steric energies in Table I.[33] For definitions of τ_N and Φ, see text.

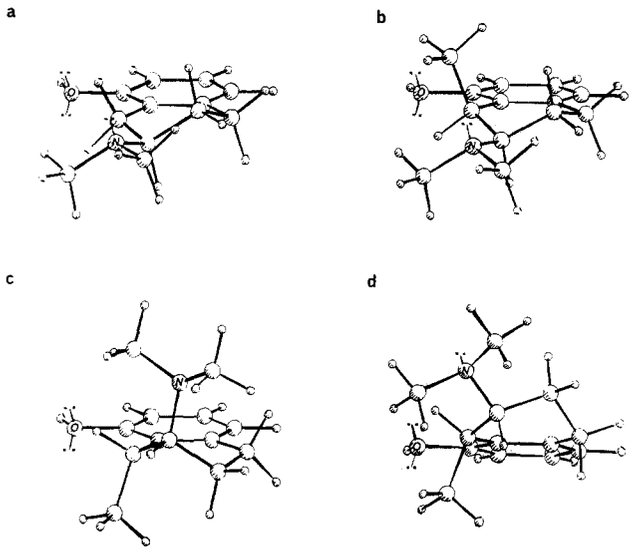


Figure 4. Graphical ball and stick representations of the energetically acessible conformations I of (2*R*)-**1** (a), A of (1*S*,2*R*)-**2** (b), and N and F of (1*R*,2*R*)-**3** (c and d, respectively) (for geometrical parameters and relative steric energies defining these conformations, see Table I). For clarity, only the 8-hydroxy-2-(dimethylamino)tetralin moieties are shown. In the projections shown, the nonaromatic rings are oriented toward the viewer.

16, 4, and 16, respectively. Compounds (2*R*)-**1** and (1*S*,2*R*)-**2** preferentially adopt Φ values around 180° (compare Table I and Figures 3 and 4). In contrast, the

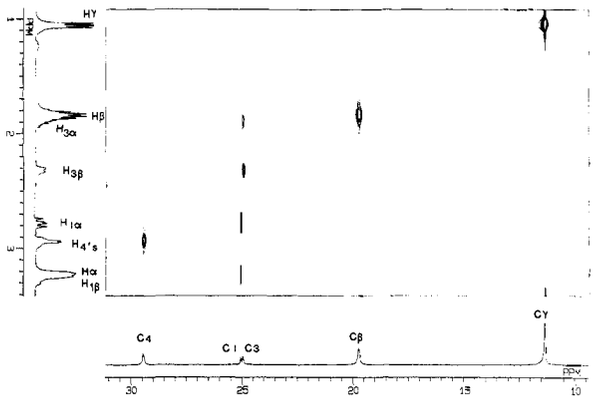


Figure 5. Partial ^{13}C–^{1}H NMR chemical shift correlation spectrum (aliphatic region) of 8-hydroxy-2-(di-*n*-propylamino)-tetralin hydrobromide (**1**·HBr) in CD_3OD.

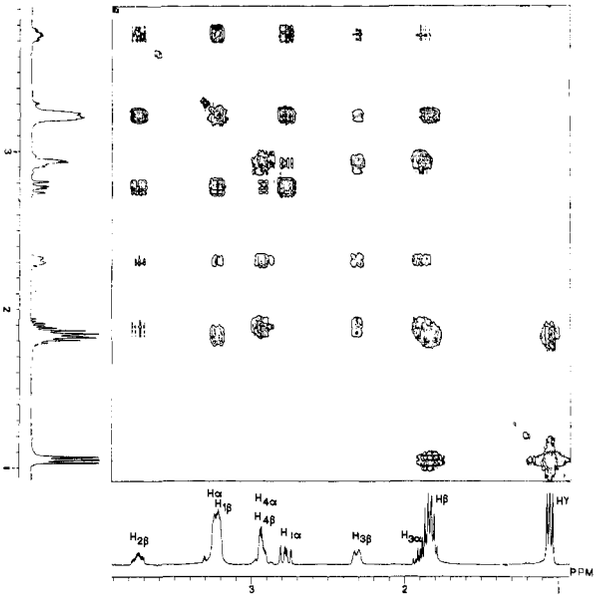


Figure 6. Partial COSY spectrum (aliphatic region) of 8-hydroxy-2-(di-*n*-propylamino)tetralin hydrobromide (**1**·HBr) in CD_3OD.

preferred conformations of (1*R*,2*R*)-**3** were found to have Φ values around 0° (Table I and Figures 3 and 4).[33] Previous force field calculations on hydroxylated 2-aminotetralins[18,34] have given results that are similar to those obtained here.

The solid-state conformation of (+)-**7** is similar to the MMP2-minimized conformation C of (1*S*,2*R*)-**2**: A best fit of the common carbon, oxygen, and nitrogen atoms of (+)-**7** and (1*S*,2*R*)-**2** in these conformations gave an average distance between fitted atoms of 0.18 Å.

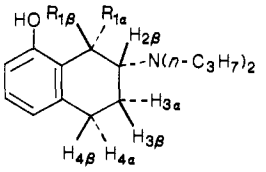
Although both (2*R*)-**1** and (1*S*,2*R*)-**2** preferentially adopt conformations with Φ values around 180°, they differ with respect to the preferred rotamer of the dipropylamino group (i.e., the τ_N values differ; compare Table I). τ_N values around 60° and 180° are energetically unfavorable in conformations of (1*S*,2*R*)-**2** with Φ values around 180°; in such conformations, there is a severe repulsion between the C1-methyl group and one of the α-methylene groups of the dipropylamino substituent. Similarly, conformations with $\Phi \approx 0°$ and $\tau_N \approx -60°$ are disfavored in (1*S*,2*R*)-**2** due

(32) Conformations with energies >2.9 kcal/mol above the global minimum of 2-(dimethylamino)- and >2.7 kcal/mol above that of 2-(diethylamino)tetralin derivatives were discarded (cf. ref 18b).

(33) In MMP2 conformations A–E of (1*R*,2*R*)-**3** (Table I), the geometry of C8 was observed to be perturbed [τ(C4a, C8a, C8, O) = −169° ± 1°]. These conformations have the oxygen positioned ≈0.2 Å from the plane of the aromatic ring. Such geometries differ considerably from those normally observed in MMP2 calculations and X-ray crystallography [τ(C4a, C8a, C8, O) = 180° ± 1°]. Therefore, conformations A–E were excluded when the Boltzmann distribution of the conformations of (1*R*,2*R*)-**3** was calculated.

(34) (a) Kocjan, D.; Hadzi, D. *J. Pharm. Pharmacol.* **1983**, *35*, 780. (b) Kocjan, D.; Solmajer, T.; Hodoscek, M.; Hadzi, D. *Int. J. Quantum Chem.* **1983**, *23*, 1121. (c) Froimowitz, M.; Neumeyer, J. L.; Baldessarini, R. J. *J. Med. Chem.* **1986**, *29*, 1570. (d) Liljefors, T.; Wikström, H. *J. Med. Chem.* **1986**, *29*, 1896.

Table II. ^{1}H NMR Spectral Data of the 2-Aminotetralin Derivatives 1·HBr, 2·HCl, and 3·HCl in CD_3OD



	chemical shifts, δ (ppm)						
compd	$H_{1\alpha}$	$H_{1\beta}$	$H_{2\beta}$	$H_{3\alpha}$	$H_{3\beta}$	$H_{4\alpha}$	$H_{4\beta}$
1·HBr	2.77	3.22	3.74	1.89	2.31	~2.95	~2.95
2·HCl		3.68	3.58	2.13	2.20	3.03	2.95
3·HCl	3.54		3.77	2.39	*a*	~2.8	~2.8

	coupling constants J, Hz										
compd	$J_{1\alpha,1\beta}$	$J_{1\alpha,2\beta}$	$J_{1\beta,2\beta}$	$J_{2\beta,3\alpha}$	$J_{2\beta,3\beta}$	$J_{3\alpha,3\beta}$	$J_{3\alpha,4\alpha}$	$J_{3\alpha,4\beta}$	$J_{3\beta,4\alpha}$	$J_{3\beta,4\beta}$	$J_{4\alpha,4\beta}$
1·HBr	−16.2	11.6	5.8	11.8	3.0	*b*	*b*	*b*	*b*	*b*	*b*
2·HCl			4.4	12.4	3.0	−12.0	6.5	11.4	2.0	6.4	−17.2
3·HCl		2.2		6.4	8.6	−13.7	5.5	5.5	*b*	*b*	*b*

[a] Obscured. [b] Not determined.

to unfavorable interactions between the C1-methyl group and the hydroxyl group. Peri interactions between the 8-hydroxy group and the C1-methyl group are also avoided in the trans isomer (1*R*,2*R*)-**3** since this compound preferentially adopts conformations with Φ values around 25° (Figure 4).[33] The conformers F–H of (1*R*,2*R*)-**3** (Table I) represent a small conformer population with $\Phi \approx 140°$ and $\tau_N \approx -60°$. In these conformations, the tetralin ring adopts a skew-boat conformation (Figure 4).

NMR Spectroscopy. ^{1}H NMR (400 MHz) spectral data of compounds 1·HBr, 2·HCl, and 3·HCl are presented in Table II. ^{13}C–^{1}H shift correlation and COSY spectra of 1·HBr are shown in Figures 5 and 6, respectively.

It has been previously shown that several 2-aminotetralins preferentially adopt half-chair conformations with pseudoequatorial nitrogen substituents in solution.[18] The observation of a large (dipseudoaxial) $J_{2\beta,3\alpha}$ in the ^{1}H NMR spectra of 1·HBr and 2·HCl and the large $J_{3\alpha,4\beta}$ in the spectrum of 2·HCl indicates that also these compounds assume similar conformations in solution. This conclusion is supported by the small $J_{1\beta,2\beta}$ in the spectra of 1·HBr and 2·HCl. Furthermore, in the spectrum of 2·HCl (Table II) and also in the COSY spectrum of 1·HBr (Figure 5), a four-bond coupling ($^4J_{1\beta,3\beta}$ = 1.5 Hz in 2·HCl) was observed. This *W* coupling[35] establishes that $H_{1\beta}$ and $H_{3\beta}$ assume pseudoequatorial positions in solution, that is, that the dipropylammonium groups of 1·HBr and 2·HCl are pseudoequatorially dispositioned.

No large vicinal coupling constants were observed in the spectrum of 3·HCl. This may reflect a time average of equilibrating tetralin ring conformations. Similar conclusions have been drawn on the basis of ^{1}H NMR spectral data of (1*S*,2*S*)-5-hydroxy-1-methyl-2-(dipropylamino)-tetralin hydrochloride.[18b] The small $J_{1\alpha,2\beta}$ in 3·HCl appears to indicate a preference for conformations with dipseudoaxial C1 and C2 substituents. The results obtained by molecular mechanics calculations on compound (1*R*,2*R*)-**3** tend to support this interpretation (compare Figure 3).

MNDO Calculations of *trans*-2-Phenylcyclopropylamines. MNDO calculations identified one minimum-energy conformation of model compound (1*R*,2*S*)-**8** [A, τ(C2, C1, C1′, C2′) = τ_1 = −138°, τ(C1′, C2′, N, N-electron pair) = τ_N = −35°] and two low-energy conformations of (1*R*,2*S*)-**9** (A, τ_1 = −133°, τ_N = −35°; B, τ_1 = 50°, τ_N = −35°) which were close in energy.[17] In these conformations, the steric interactions between the adjacent rings are minimal. The identified conformations of (1*R*,2*S*)-**8** and (1*R*,2*S*)-**9** differ from the conformations of (1*R*,2*S*)-**4** (τ_1 = 92°, τ_N = −37°) and (1*R*,2*S*)-**5** (τ_1 = 121°, τ_N = −46°) that have been observed by X-ray crystallography.[7] The energy barriers to rotation about C1–C1′ (τ_1) are 3.7 and 1.5 kcal/mol for (1*R*,2*S*)-**8** and (1*R*,2*S*)-**9**, respectively. Thus, a multitude of energetically accessible conformations of **8** and **9** can be envisaged.

Two energetically less favored conformations were obtained by computer-generated best fits of (2*R*)-**1** (conformation I) with (1*R*,2*S*)-**8** (B, τ_1 = −151°, τ_N = −136°, relative energy = 2.3 kcal/mol) and (1*R*,2*S*)-**9** (C, τ_1 = 29°, τ_N = 157°, relative steric energy = 1.2 kcal/mol). However, these conformations of (1*R*,2*S*)-**8** and (1*R*,2*S*)-**9** also should be accessible. Selected conformations of (1*R*,2*S*)-**8** and (1*R*,2*S*)-**9** are depicted in Figure 7.

Calculations of Molecular Electrostatic Potentials. Electrostatic potential maps of **8**–**12** and 5-HT are shown in Figure 8. The electrostatic potential below the aromatic ring was negative in all compounds. A local negative minimum was also produced by the oxygen atom. The electrostatic potential maps produced above and below the aromatic region were very similar.

The local minimum below the aromic region was distorted from the center of the benzene ring toward C5 and C6 in both the 2-aminotetralins and the *trans*-2-phenylcyclopropylamines. Rotation of the hydroxyl group by 180° in (2*R*)-**10** (Figure 8a) resulted in a positional shift of the local minimum due to the oxygen atom (Figure 8b) and also a small shift of the minimum in the aromatic region. The electrostatic potential pattern below the aromatic region was also changed. Similar effects were found in the electrostatic potential maps of the hydroxy group rotamers of (1*R*,2*S*)-**8**, (1*R*,2*S*)-**9**, (1*S*,2*R*)-**11**, and (1*R*,2*R*)-**12**. It is noteworthy that a change in τ_1 from 29° to −133° in (1*R*,2*S*)-**9** only had a minor influence on the electrostatic potential pattern below the aromatic ring (cf. Figure 8g,h).

Discussion

Pharmacological Background. Compound **1** exerts a variety of pharmacological effects that probably are related to interactions with 5-HT receptors. We have previously shown that the compound dose-dependently decreases brain 5-HTP levels and produces the 5-HT motor syndrome in the rat.[1,2,5] Subsequent studies have revealed that **1** has high affinity for 5-HT_1 sites, but low affinity

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

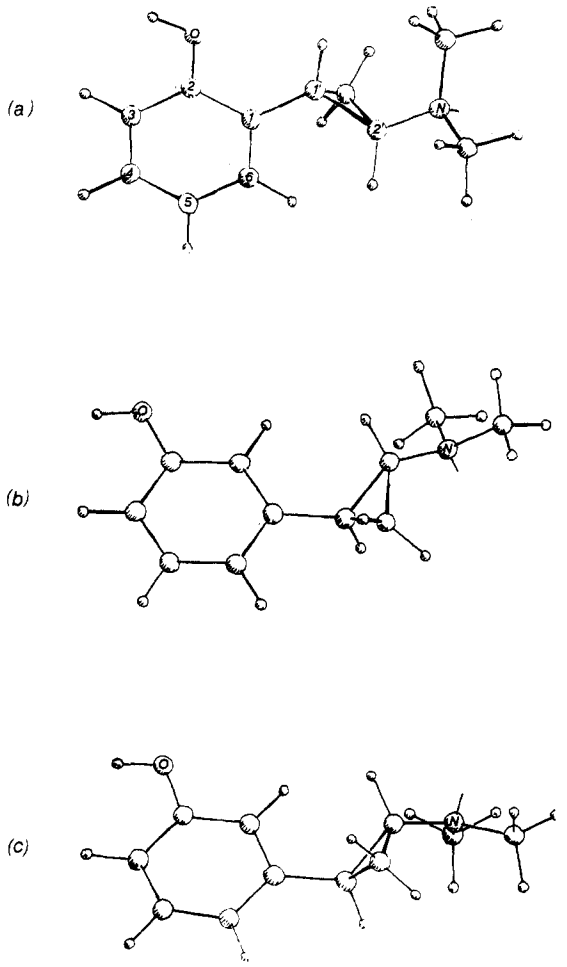
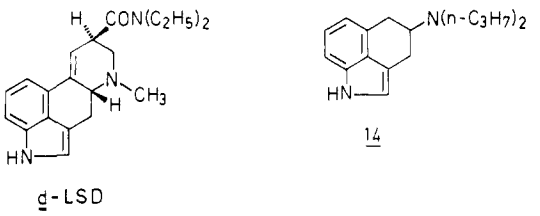


Figure 7. Numbering scheme and computer-generated ball and stick projections of selected MNDO conformations of (a) (1*R*,2*S*)-**8** (conformation B), (b) (1*R*,2*S*)-**9** (conformation B), and (c) (1*R*,2*S*)-**9** (conformation C). Definitions of the various conformations are given in the text.

for 5-HT_2 sites.[3,4] It is also of interest that compound 1 seems to be an agonist of high potency (comparable to that of LSD) at the electrophysiologically defined somatodendritic 5-HT autoreceptors; low doses of the agent (2–10 μg/kg iv) inhibited the firing rate of 5-HT neurons in the dorsal raphe of the rat.[36] In accordance with the pharmacological effects of 1, the other 5-HT-receptor agonists (1*S*,2*R*)-**2**,[6] (1*R*,2*S*)-**4**, and (1*R*,2*S*)-**5**[5] dose-dependently decrease brain 5-HTP levels and produce parts of the 5-HT motor syndrome in the rat. In addition, compounds 1, **2**, **4**, and **5** facilitate male rat sexual behavior.[37] The *O*-methyl derivatives of these compounds show a similar pharmacological profile although they are four to six times less potent than their phenolic analogues.

Two other 5-HT agonists are also relevant to the discussion. The ergoline derivative *d*-LSD dose-dependently decreases brain 5-HTP levels,[2] inhibits the firing rate of 5-HT neurons in the dorsal raphe,[38] produces the 5-HT motor syndrome in the rat,[39] and has a high affinity for 5-HT_1 sites.[40] Interestingly, compound 14 (TVX R1531) exhibits high potency and selectivity (vs 5-HT_2 sites) for 5-HT_1 sites, produces the 5-HT motor syndrome in the rat, and facilitates male rat sexual behavior.[41,42] Thus, these two agents and 1, (1*S*,2*R*)-**2**, (1*R*,2*S*)-**4**, and (1*R*,2*S*)-**5** have several pharmacological actions in common.



Structure–Activity Relationships. It is of particular interest that the four low-energy conformations of the potent 5-HT agonist (1*S*,2*R*)-**2** have similar Φ (≈200°) and τ_N values (≈−60°) (Table I) and that other conformations have relative steric energies larger than 2.7 kcal/mol. In the low-energy conformations of (1*S*,2*R*)-**2**, the nitrogen atom is fairly close to the plane of the aromatic ring (distance between the nitrogen and the plane of the aromatic ring; N–ArP distance ≈ 0.6 Å). At least one of these conformations ought to represent a "receptor-active conformation" since (1*S*,2*R*)-**2** is a 5-HT-receptor agonist of high potency. Support for this suggestion comes from conformational analysis of LSD which has been performed by use of X-ray diffraction techniques,[43] ^1H NMR spectroscopy,[44] and molecular mechanics calculations (QCFF/PI).[45] The results, which are in good agreement, demonstrate that the tetralin moiety of LSD preferentialy assumes a half-chair conformation with a pseudoequatorial N_6 substituent (N–ArP ≈ 0.4 Å). Similarly, (2*R*)-**1**, (1*S*,2*R*)-**2**, (1*R*,2*S*)-**7**, and (1*R*,2*S*)-**8** (and thereby the enantiomers) as well as **14**[46] can assume conformations with short N–ArP distances. In contrast, N–ArP distances are considerably longer (>1.8 Å) in the inactive **3**, which preferentially adopts conformations with pseudoaxial C1 and C2 substituents. Thus, the conformational preferences of **3** appear to prohibit an effective 5-HT-receptor interaction. However, the N–ArP distance seems to be only one of several critical parameters for 5-HT-receptor activation since also the inactive enantiomers of **2**, **4**, and **5** are able to adopt short N–ArP distances.

The *O*-methyl derivatives of the 5-HT agonists discussed here are only four to six times less potent than their phenolic analogues (**1**, **2**, 4, and **5**).[6,7] Thus, the hydrogen bond donating ability of the hydroxy group does not seem to be of critical importance in the receptor interaction. The high potency of methoxylated tryptamine derivatives supports this suggestion.[47] Furthermore, Weinstein et al.[29]

(36) Fallon, S. L.; Kim, H. S.; Welch, J. *Abstr. Soc. Neurosci.* **1983**, *9*, 716. DeMontigny, C.; Blier, P.; Chaput, Y. *Neuropharmacology* **1984**, *23*, 1511.
(37) Personal communication from K. Larsson, Department of Psychology, University of Göteborg, Sweden.
(38) Haigler, H. J.; Aghajanian, G. K. *J. Pharmacol. Exp. Ther.* **1974**, *188*, 688.
(39) Silbergeld, E. K.; Hruska, R. E. *Psychopharmacology (Berlin)* **1979**, *65*, 233.
(40) Peroutka, S. J.; Lebowitz, R. M.; Snyder, S. H. *Science (Washington, D.C.)* **1981**, *212*, 827.
(41) Glaser, T.; Dompert, W. U.; Allen, G.; Traber, J. Poster presented at the 6th European Winter Conference on Brain Research, Avoriaz (France), March 9–15, 1986.
(42) Spencer, D. G., Jr.; Glaser, T.; Schuurman, T.; Traber, J. *Abstr. Soc. Neurosci.* **1984**, *10*, 1072.
(43) (a) Baker, R. W.; Chothia, C.; Pauling, P.; Weber, H. P. *Science (Washington, D.C.)* **1972**, *178*, 614. (b) Baker, R. W.; Chothia, C.; Pauling, P.; Weber, H. P. *Mol. Pharmacol.* **1973**, *9*, 23.
(44) Bailey, K.; Grey, A. A. *Can. J. Chem.* **1972**, *50*, 3876.
(45) Kidric, J.; Kocjan, D.; Hadzi, D. *Period. Biol.* **1983**, *85* (Suppl. n2), 127.
(46) Hibert, M.; McDermott, I.; Middelmiss, D.; Fozard, J. Poster presented at the 6th European Winter Conference on Brain Research, Avoriaz (France), March 9–15, 1986.

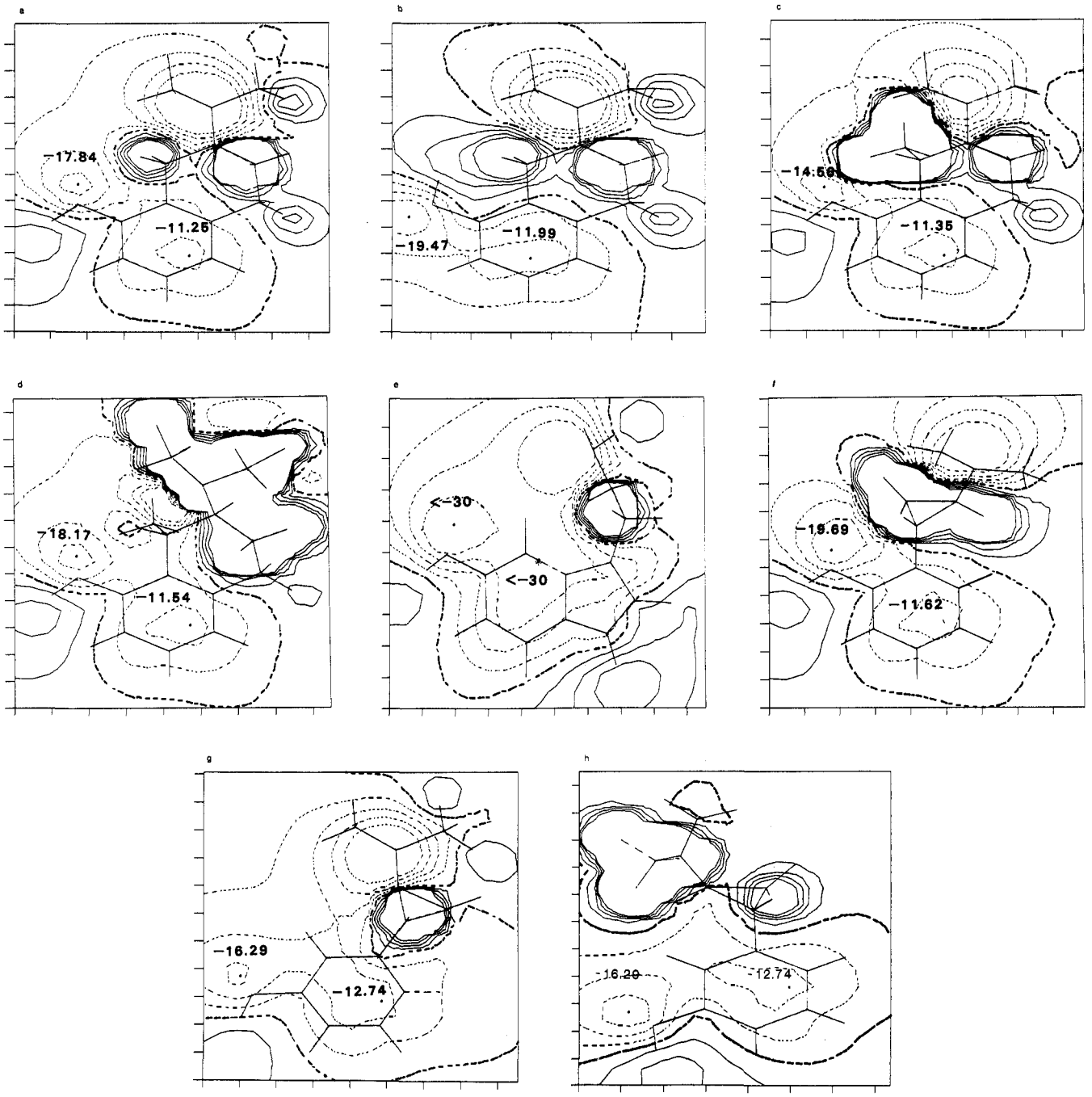


Figure 8. Molecular electrostatic potential maps of (a) (2*R*)-**10** (Φ = 197°, τ_N = −56°), (b) (2*R*)-**10** (same conformation as in a, but the hydroxyl group is rotated 180°), (c) (1*S*,2*R*)-**11** (Φ = 163°, τ_N = −55°), (d) (1*R*,2*R*)-**12** (Φ = 138°, τ_N = −55°), (e) 5-HT (conformation obtained from best fit with conformation I of (2*R*)-**1**), (f) (1*R*,2*S*)-**8** (conformation B), (g) (1*R*,2*S*)-**9** (conformation B), and (h) (1*R*,2*S*)-**9** (conformation C). Potentials were calculated in a plane 1.6 Å below the plane of the aromatic ring. Heavy dashed lines correspond to zero, light dashed lines to negative, and solid lines to positive potentials. Curves are shown in increments of 5 kcal/mol.

have shown by MEP calculations that the C9–C10 double bond of LSD produces electrostatic potentials that are similar to that of the 5-hydroxy group in 5-HT. In terms of electrostatic potential patterns, the oxygen atom at C8 in compounds **1**, **2**, and their O-methylated analogues seems to correspond to the oxygen atom at C5 in 5-HT (cf. Figure 8a,e).

The possible importance of the N–O distance becomes apparent when the potent 5-HT agonist **1** is compared with its much less potent 7-hydroxylated isomer **6**. In conformations of (2*R*)-**6** having low steric energies (Φ values around 180°), the N–O distance is considerably longer (7.4 Å) than in corresponding conformations of (2*R*)-**1** (5.2 Å). Compound **6** is at least 200 times less potent than **1** as a 5-HT-receptor agonist,[48] and this potency difference might thus be related to the different N–O distances in the two compounds. However, the regioisomeric *trans*-2-phenylcyclopropylamines (1*R*,2*S*)-**4** and (1*R*,2*S*)-**5**, which appear to be equipotent as 5-HT-receptor agonists, have similarly different N–O distances. This apparent discrepancy can be resolved by assuming that different conformations of

(47) For a review on 5-HT-receptor agonists and antagonists, see: Arvidsson, L.-E.; Hacksell, U.; Glennon, R. A. *Prog. Drug Res.* **1986**, *30*, 365.

(48) The ED_{50} value of **14**·HCl in the 5-HTP accumulation assay is around 10 μmol/kg. Personal communication from K. Svensson, Department of Pharmacology, University of Göteborg, Sweden.

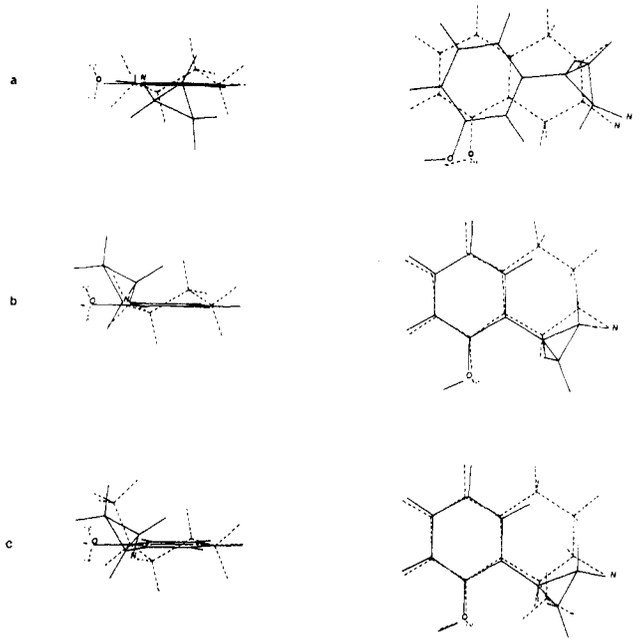


Figure 9. Computer-generated best fits of conformation I of (2*R*)-**1** (dashed lines) with conformation B of (1*R*,2*S*)-**4** and conformation C of (1*R*,2*S*)-**5** (b and a, respectively) and of conformation A of (1*S*,2*R*)-**2** (dashed lines) with conformation B of (1*R*,2*S*)-**4** (c). The nitrogens, the oxygens, and the midpoints of the aromatic rings were included in the fitting procedure. The mean distances between fitted atoms were 0.47 Å (a), 0.08 Å (b), and 0.06 Å (c). Two perspectives are shown of each fit: To the left, C4a and C8a of the tetralin moiety are in the plane of the paper and the nonaromatic ring is oriented toward the viewer. To the right, the plane of the aromatic ring of the tetralin is parallel with the plane of the paper. For clarity, the N-substituents have been omitted.

(1*R*,2*S*)-**4** and (1*R*,2*S*)-**5** exhibit 5-HT-receptor activity. Such conformations, which are depicted in Figures 7 and 9, should differ mainly with respect to τ_1; (1*R*,2*S*)-**4** is thought to be active in conformations having τ_1 around −150° (N–O distance ≈ 5.4 Å) whereas (1*R*,2*S*)-**5** would have to assume conformations with τ_1 around 30° in order to minimize the N–O distance (N–O distance ≈ 6.3 Å). It is noteworthy that these conformations of the model compounds of (1*R*,2*S*)-**4** (**8**) and (1*R*,2*S*)-**5** (**9**) produce electrostatic potentials above the aromatic ring that are similar to that of (2*R*)-**10** (Figure 8) and that they give good fits with (2*R*)-**1** (Figure 9).

The τ_N value is around −60° in the four low-energy conformations of (1*S*,2*R*)-**2** and in conformations I–L of (2*R*)-**1**. Furthermore, *d*-LSD preferentially assumes a similar relative orientation of the N-electron pair (N–H bond).[43-45] However, it does not appear to be possible to *strictly define* a "5-HT receptor active" direction of the N-electron pair (N–H bond) due to the low stereoselectivity of the potent **1**. Low-energy conformations should be responsible for the biological activity of both enantiomers of **1** since these are highly potent. It is impossible to get a perfect fit between two *enantiomeric* low-energy conformations of **1** as long as the oxygens, the nitrogens, the aromatic rings, and the electron pairs are included in the fit. It is, however, possible to get a fairly good, but not perfect, fit of two *different* local minimum-energy conformations of (2*R*)-**1** and (2*S*)-**1** which includes the oxygens, the aromatic rings, the nitrogens, and the N-electron pairs (Figure 10; note the different orientations of the N-electron pairs).

If we assume that a "5-HT receptor activating" pharmacophore is best described by the relative positions of

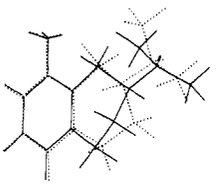
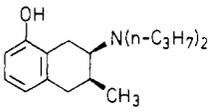


Figure 10. Computer-generated best fit of conformation K of (2*R*)-**1** (dotted lines) and a conformation of (2*S*)-**1** (solid lines) corresponding to the enantiomer of conformation I of (2*R*)-**1**. The nitrogens, the N-electron pairs, the oxygens, and the midpoints of the aromatic rings were included in the fitting procedure. Mean average distance between fitted atoms = 0.14 Å.

the aromatic oxygen substituent, the aromatic ring, and the nitrogen atom, the following conclusions can be drawn: The approximate equipotency of (2*R*)-**1** and (1*S*,2*R*)-**2** demonstrates that the steric bulk of the C1-methyl group of (1*S*,2*R*)-**2** does not interfere with a proper alignment with the 5-HT receptor(s). Similarly, the methylene group of the cyclopropane ring of (1*R*,2*S*)-**4**, which may be located in a similar spatial position (compare Figure 9), does not appear to present a steric obstacle. In addition, the steric bulk of the cyclopropane ring in (1*R*,2*S*)-**5**, which protrudes "below" the plane of the aromatic ring (Figure 9), does not considerably decrease the activity. However, the high stereoselectivities of **2**, **4**, and **5** indicate that, with (2*R*)-**1** as common frame of reference, the space below the C1-position (on the *re* face of the ring) and that above the C3-position (on the *si* face of the ring) of (2*R*)-**1** are part of the 5-HT receptor essential volume. This hypothesis is supported by the recent finding[49,50] that (2*R*,3*S*)-8-hydroxy-2-(di-*n*-propylamino)tetralin [(2*R*,3*S*)-**15**], in which the C3-methyl substituent preferentially is pseudoaxially located,[49] is a 5-HT-receptor agonist whereas the antipode is inactive.



(2R, 3S)-**15**

The alternative possibility that *the relative direction of the nitrogen lone pair of electrons (the N–H bond) is of strict importance* for the interactions between 5-HT receptors and their agonists implies that the enantiomers of **1** assume different orientations at 5-HT receptors. In order to obtain a perfect fit between local minimum-energy conformations of the enantiomers of **1**, *which includes the N-electron pairs*, different faces of the enantiomers have to be compared. That is, one or several of the three pharmacophore groups/atoms discussed above might be irrelevant for the biological activity. This line of thinking is illustrated in Figure 11, which shows three extreme fittings of (2*R*)-**1** and (2*S*)-**1**. However, the fitting of the oxygens, the nitrogens, and the lone pairs of electrons (Figure 11a) seems uninteresting from a biological point of view since it does not agree with the pronounced stereoselectivity of **2**; if the nitrogens, the N-electron pairs, and the oxygens of the enantiomers of **2** are fitted, the C1-methyls would assume almost the same spatial positions. Thus, this structural comparison would not rationalize the inactivity of (1*R*,2*S*)-**2**.

(49) Mellin, C.; Björk, L.; Karlēn, A.; Johansson, A. M.; Sundell, S.; Kenne, L.; Andēn, N.-E.; Hacksell, U., submitted to *J. Med. Chem.*

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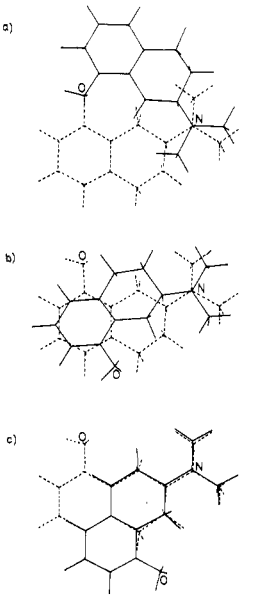

Figure 11. Extreme computer-generated best fits of conformation I of (2*R*)-1 (dashed lines) with the enantiomeric conformation of (2*S*)-1 (solid lines): (a) fit of the nitrogens, the N-electron pairs, and the hydroxyl groups; (b) fit of the nitrogens, the N-electron pairs, and the midpoints of the aromatic rings; (c) fit (C4a, C5, nitrogens, and N-electron pairs were fitted) based on a structural comparison with *d*-LSD (see text).

The other two extreme fittings of the enantiomers of 1 (Figure 11) are more attractive. When only the aromatic rings, the nitrogens, and the N-electron pairs are included in the fit, the main difference between the structures is the different location of the phenolic groups. The third mode of fitting (Figure 11) is based on the assumption that the aromatic ring of (2*R*)-1 would interact with the same portion of the 5-HT receptors as the benzene ring of **14** or *d*-LSD, whereas the benzene ring of (2*S*)-1 would assume a relative location similar to that of the pyrrole ring of 14 or *d*-LSD. This structural comparison is contradicted by several reports which indicate that the pyrrolethylamine moiety is the dopaminergic pharmacophore of LSD and related ergolines.[51] It is noteworthy, however, that the two latter modes of fitting seem to rationalize both the low stereoselectivity of 1 and the opposite stereoselectivities of **2** and **15**;[49,50] when (2*R*,3*S*)-**15** is fitted with (1*S*,2*R*)-**2** as above, the C3-methyl group of (2*R*,3*S*)-**15** adopts a similar relative position as the C1-methyl group of (1*S*,2*R*)-**2**.[49]

Additional studies of stereochemically well-defined 5-HT-receptor agonists should make it possible to assess the relevance of these structural comparisons.

Acknowledgment. The financial support from the Swedish Natural Science Research Council, Centrala Försöksdjursnämnden, and Stiftelsen Bengt Lundkvists Minne is gratefully acknowledged. We thank Dr. Tommy Liljefors and Dr. Robert E. Carter for providing access to the MIMIC program.

Registry No. **1**, 80300-09-0; **2**, 109062-25-1; **3**, 111001-22-0; **4**, 110901-82-1; **5**, 110901-84-3; **7**·HCl, 110271-10-8.

Supplementary Material Available: Positional and thermal parameters, bond lengths, and bond angles (2 pages). Ordering information is given on any current masthead page.

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Studies on Prodrugs. 7. Synthesis and Antimicrobial Activity of 3-Formylquinolone Derivatives

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Received April 30, 1987

Several 3-formylquinolone derivatives (**8a–c**) were synthesized to assay the antibacterial activity both in vitro and in vivo. In vitro, all of the compounds **8a–c** showed lower activity than that of the corresponding 3-carboxyl compounds **1a–c**, and in vivo, they showed higher activity than that of compounds **1a–c**. After oral administration of 3-formyl compounds **8a–c** to mice, the compounds were rapidly metabolized into 3-carboxyl compounds **1a–c**. In particular, the 3-formyl derivative (**8a**) of norfloxacin (NFLX, **1a**) gave a 2-fold higher serum level than that of NFLX and functioned as a prodrug of NFLX.

In 1979, norfloxacin (NFLX, 1a) was synthesized as a new quinolone by Koga et al.[1] Several related new quinolones, including ciprofloxacin (CPFX, **1b**)[2] and pefloxacin (PFLX, **1c**),[3] have also been developed. On comparison with conventional compounds[4] such as nalidixic acid, piromidic acid, and pipemidic acid, the new quinolones exhibited marked and broad antibacterial activities against Gram-positive and Gram-negative bacteria.[2,3,5] Although NFLX is strongly active in test systems in vitro, it was found there was still room for improvement in the activity after oral administration.[6] We have applied a prodrug technique to NFLX and have recently reported N-masked NFLX prodrugs (**2**[7] and **3**[8], Chart I) to propose that both an increase of oral absorbability by N-masked

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