with minor modifications as described in ref 21.

Acknowledgment. We thank A. Mosimann and R. Labhart for their skillful technical assistance and our collegues and their collaborators in the Physical Chemistry Department and the Analytical Laboratory for their help in measuring and interpreting the spectra and performing the elemental analysis, respectively. We are further grateful to Dr. F. Braunschweiger and F. Seemann for the supply of ample quantities of intermediates.

Registry No. (±)-1, 69367-50-6; (±)-**2**, 101403-04-7; (±)-**2**·HCl, 78598-56-8; (±)-**3**, 101403-05-8; (−)-(*S*)-**3**, 88322-07-0; (+)-(*R*)-**3**, 101540-25-4; (±)-**3**·HCl, 78598-52-4; (±)-**4**, 101403-06-9; (±)-**4**·HCl, 78598-54-6; (±)-**5**, 78615-30-2; (±)-**5**·$^1/_2$nd, 78615-31-3; (±)-**6**, 78598-46-6; (±)-**6**·HCl, 78598-48-8; (±)-**7**, 99755-60-9; (±)-**7**·HCl, 101403-00-3; (±)-**8**, 101403-07-0; (±)-**8**·HCl, 101403-01-4; (±)-**9**, 101403-08-1; (±)-**9**·HCl, 78598-61-5; (±)-**10**, 101403-09-2; (±)-**10** (5-mesylate), 101403-16-1; (±)-**10**·HCl, 78598-62-6; (±)-**11**, 78598-65-9; (±)-**11**·$^1/_2$nd, 78598-66-0; (±)-**12**, 78598-47-7; (−)-(*S*)-**12**, 78598-85-3; (±)-**12**·fu, 78598-51-3; (±)-**13**, 101403-10-5; (±)-**13**·HCl, 78598-63-7; (±)-**14**, 78598-58-0; (±)-**15**, 78598-59-1; (±)-**15** (dimesylate), 101403-15-0; (±)-**16**, 101403-02-5; (±)-**17**, 78598-83-1; (±)-**18**, 78598-79-5; (±)-**18**·$^1/_2$nd, 78598-80-8; (±)-**19**, 101403-11-6; (±)-**19**·HCl, 78598-53-5; (±)-**20**, 101403-12-7; (±)-**20**·HCl, 78598-78-4; (±)-**21**, 78598-72-8; (±)-**21**·pm, 101403-03-6; (±)-**22**, 101403-13-8; (±)-**22**·HCl, 78598-70-6; (±)-**23**, 101403-14-9; (±)-**23**·HCl, 78598-71-7; (±)-**III** (R = Pr), 78598-91-1; (−)-(*S*)-**III** (R = $CH_2C_6H_5$), 58349-23-8; (−)-(*S*)-**III** (R = Pr), 101403-24-1; (+)-(*R*)-**III** (R = Pr), 101403-25-2; (±)-**IV** (R = Pr), 78598-89-7; (±)-**IV** (R = Et), 101403-19-4; (±)-**IV** (R = Me), 101403-20-7; (−)-(*S*)-**IV** (R = Pr), 101470-23-9; (+)-(*R*)-**IV** (R = Pr), 101470-24-0; (±)-**V** (R = Pr, X = NH_2, *n* = 2), 101403-17-2; (±)-**V** (R = Pr, X = NH_2, *n* = 3), 101403-18-3; (±)-**V** (R = Pr, X = $NHSO_2NEt_2$, *n* = 2), 101403-21-8; (±)-**V** (R = Pr, X = SMe, *n* = 3), 78598-90-0; (±)-**V** (R = Pr, X = OH, *n* = 3)·$^1/_2$nd, 78598-88-6; (±)-**V** (R = Pr, X = Cl, *n* = 3), 78598-49-9; (±)-**V** (R = Pr, X = Cl, *n* = 3)·$^1/_2$nd, 78598-50-2; (±)-**V** (R = Pr, X = SO_2Me, *n* = 3), 101403-22-9; (−)-(*S*)-**V** (R = $CH_2C_6H_5$, X = CH_3), 101403-23-0; (−)-(*S*)-**V** (R = Pr, X = OH, *n* = 3), 101470-25-1; (−)-(*S*)-**V** (R = Pr, X = Cl, *n* = 3), 101470-26-2; (−)-(*S*)-**V** (R = Pr, X = SMe, *n* = 3), 101470-27-3; $C_6H_5CH_2OCONHCH_2CO_2H$, 1138-80-3; $C_6H_5CH_2OCONHCH_2CONH_2$, 949-90-6; $H_2NCH_2CH_2NH_2$, 107-15-3; $Br(CH_2)_3CN$, 5332-06-9; $I(CH_2)_3OH$, 627-32-7.

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Conformational Analysis of the Dopamine-Receptor Agonist 5-Hydroxy-2-(dipropylamino)tetralin and Its C(2)-Methyl-Substituted Derivative

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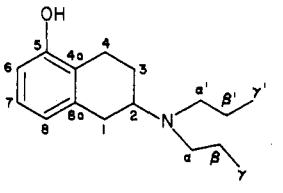
The conformational preferences of the dopamine (DA) receptor agonist 5-hydroxy-2-(di-*n*-propylamino)tetralin (1) and the DA-inactive 5-hydroxy-2-methyl-2-(di-*n*-propylamino)tetralin (2) have been studied by use of molecular mechanics (MMP2) calculations and NMR spectroscopy. A good agreement is demonstrated between the experimentally determined (by NMR) and the calculated (by MMP2) conformational distribution of 1 and 2. In addition, there is a good agreement between bond distances and bond angles in the X-ray structure of the hydrobromide of 1 and those in the corresponding MMP2 conformation. Results obtained demonstrate that the energetically preferred conformations of 1 and 2 are different: Compound 1 preferentially adopts half-chair conformations with a pseudoequatorial nitrogen substituent whereas the low-energy conformations of compound 2 have a pseudoaxial nitrogen substituent. However, the results also indicate that the difference in conformational preferences is too small to account for the dopaminergic inactivity of 2. Therefore it is suggested that the steric bulk of the C(2)-methyl group per se prevents a proper alignment of (2*S*)-2 with DA receptors.

5-Hydroxy-2-(di-*n*-propylamino)tetralin (1)[1] is a well-established dopamine (DA) receptor agonist in vivo[1a,b] and in vitro.[2] Due to its potency and selectivity for DA receptors, compound 1 has served as the lead compound in several structure–activity relationship (SAR) studies.[3] As part of an ongoing investigation of the effects of introduction of methyl substituents in the nonaromatic ring of 1,[4] we synthesized and tested racemic 5-hydroxy-2-methyl-2-(di-*n*-propylamino)tetralin (2),[5] the C(2)-methyl-substituted derivative of 1. Compound 2 exhibits a complex pharmacological profile:[5] (a) It reverses reserpine-induced akinesia, but this effect is not blocked by pretreatment with the DA-receptor antagonist haloperidol. (b) It increases the synthesis rate of 5-hydroxytryptamine but does not affect that of DA. (c) It raises the body temperature in rats. Notably, neither racemic 2 nor the enantiomers of 2[6] appear to act on DA receptors. Thus, the introduction of a C(2)-methyl substituent in 1 completely changes the pharmacological profile.



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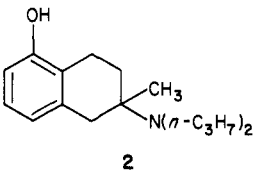

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(1) (a) McDermed, J. D.; McKenzie, G. M.; Phillips, A. P. *J. Med. Chem.* **1975**, *18*, 362. The dopaminergic activity resides almost entirely in the 2*S*-(−) enantiomer of 1: (b) McDermed, J. D.; McKenzie, G. M.; Freeman, H. S. *Ibid.* **1976**, *19*, 547 (synthesis). (c) Giesecke, J. *Acta Crystallogr., Sect. B* **1980**, *36*, 110 (X-ray crystallography).
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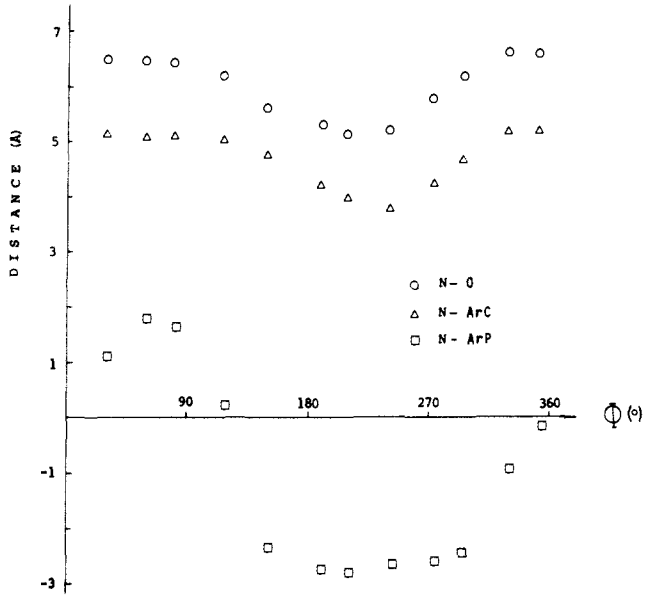


Figure 1. Plot illustrating the relationship between the tetralin inversion angle ϕ and key intramolecular distances[9] in a (2*S*)-2-amino-5-hydroxytetralin derivative. Distances are calculated from selected conformations along the tetralin inversion path. ArC is the center of the aromatic ring and ArP is the plane of the aromatic ring.

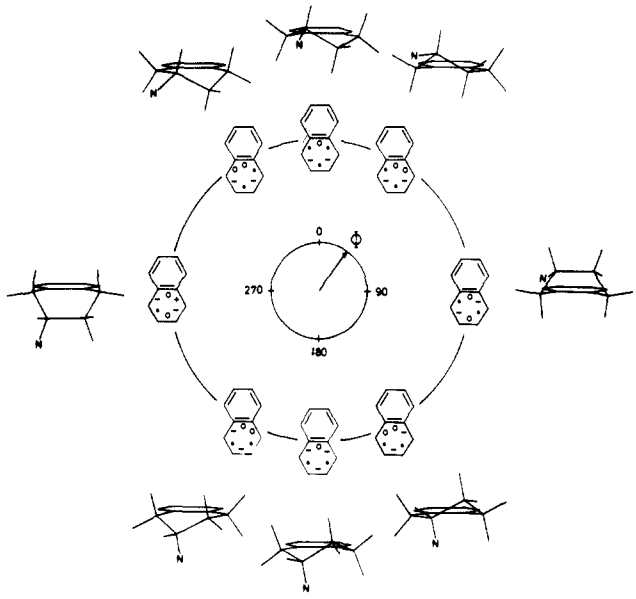
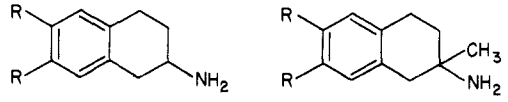


Figure 2. Tetralin inversion wheel that defines the relationship between tetralin ring conformation and the tetralin inversion angle ϕ. The eight inserted tetralin structures correspond to conformations with ϕ = 0°, 30°, 90°, 150°, 180°, 210°, 270°, and 330°, respectively. Each of the tetralin conformations is characterized by the signs (inserted) of the relevant torsion angles.[32] Perspective drawings of eight conformations of a (2*S*)-2-aminotetralin moiety are shown outside the corresponding tetralin conformations. It should be noted that, for (2*R*)-2-aminotetralin, a half-chair conformation with a pseudoequatorial amino group corresponds to ϕ = 180°.

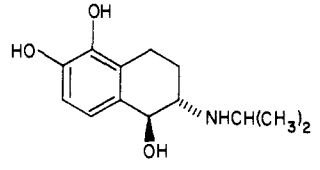
One or several of at least three conformational or steric differences between **1** and **2** might be responsible for the DA inactivity of **2**: (a) the steric bulk of the C(2)-methyl group may prevent a proper alignment of **2** with DA receptors; (b) the solution conformations of the nonaromatic ring of **2** may be different from that of **1**; (c) actual low-energy conformations of the dipropylammonium substituents of **1** and **2** may be different.

In order to find out if any of these factors is more likely to dominate, we have now studied the conformational preferences of **1** and **2** by use of ^1H and ^{13}C NMR spectroscopy and extensive molecular mechanics (MMP2) calculations. During the course of our work, Nichols et al.[7] reported the synthesis and pharmacological evaluation of racemic 6,7-dihydroxy-2-methyl-2-aminotetralin (**4a**), the C(2)-methyl-substituted derivative of ADTN (**3a**). In contrast to **3a**, compound **4a** was found to be inactive as a DA_1-type DA agonist.[7] Therefore, we have included MMP2 calculations also on compounds **3c** and **4c** (which serve as model compounds[8] for **3a** and **4a**, respectively) in the present study.



3a, R = OH
3b, R = OCH_3
3c, R = H

4a, R = OH
4b, R = OCH_3
4c, R = H



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Results and Discussion

Definition of Conformational Parameters. Conformational parameters of particular interest in the present investigation are (a) the conformation of the nonaromatic ring, to which certain key intramolecular distances[9] are

(3) See, for example: (a) Hacksell, U.; Svensson, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Wikström, H.; Lindberg, P.; Sanchez, D. *J. Med. Chem.* **1979**, *22*, 1469. (b) Feenstra, M. G. P.; Rollema, H.; Dijkstra, D.; Grol, C. J.; Horn, A. S.; Westerink, B. H. C. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1980**, *313*, 213. (c) Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, J. L. G.; Wikström, H.; Lindberg, P.; Sanchez, D.; Hjorth, S.; Carlsson, A.; Paalzow, L. *J. Med. Chem.* **1981**, *24*, 429. (d) Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H. *Ibid.* **1981**, *24*, 923.

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(8) Test calculations (MMP2) performed on compound **3a** indicate that the two hydroxyl groups do not significantly affect the conformation of the nonaromatic ring. In addition, PCILO calculations on protonated phenethylamine, tyramine, and DA have revealed only minor differences in the conformational characteristics of these compounds: Pullman, B.; Coubeils, J.-L.; Courriere, Ph.; Gervois, J.-P. *J. Med. Chem.* **1972**, *15*, 17.

related (Figure 1) and (b) the conformation of the dipropylammonium (or dipropylamino) substituent, that is, the relative orientation of the ammonium hydrogen (or the lone pair of electrons on the nitrogen)[10] as well as the conformation and relative spatial orientation of each of the *N*-propyl groups.[11]

The construction of a tetralin inversion wheel[12] (see Figure 2) enables one to define the conformation of the nonaromatic ring of any tetralin derivative by use of the tetralin inversion angle ϕ. Ideally, this parameter is simply calculated from eq 1 where τ_{obsd} is the observed value and

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

τ_{max} is the maximal value (64.73°) of the torsion angle $\tau(C_1,C_2,C_3,C_4)$.[13] However, in some conformations of 1 and 2, 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 C(2)-unsubstituted tetralin (see Figure 2). Due to the inherent symmetry (C_{2v}) of the tetralin molecule, the inversion wheel contains two degenerate boats (ϕ = 90° and ϕ = 270°, see Figure 2). Two pairs of degenerate skew boats (that is, conformations with all except one carbon atom in the same plane) with *P* (ϕ = 150° and ϕ = 210°) and *M* helicity (ϕ = 30° and ϕ = 330°), respectively, are also present in the inversion wheel. However, introduction of a C(2)-substituent destroys the symmetry of the tetralin moiety and now *eight different* conformations emerge (see the conformational drawings outside the inversion wheel in Figure 2), all of which are defined by their positions on the inversion wheel, that is, by the tetralin inversion angle ϕ. It should be noted that the tetralin inversion angle is configuration dependent. Therefore, in the present study we have used ϕ only to describe conformations of (2*S*)-2-aminotetralin derivatives.

Five parameters are needed to describe the conformation of the dipropylammonium (dipropylamino) group: The torsion angle[14] $\tau_N = \tau(C_1,C_2,N,H \text{ or electron pair})$ defines the relative direction of the N–H bond or the electron pair. The torsion angles $\tau_A = \tau(C_2,N,C_\alpha,C_\beta)$ and $\tau_B = \tau(N,C_\alpha,C_\beta,C_\gamma)$ define the conformation of the *N*-propyl group, which in a clockwise sense is next to the N–H bond (N-electron lone pair) when viewing along the C(2)–N bond. Similarly, the conformation of the second *N*-propyl group is defined by $\tau_{A'} = \tau(C_2,N,C_{\alpha'},C_{\beta'})$ and $\tau_{B'} = \tau(N,C_{\alpha'},C_{\beta'},C_{\gamma'})$.

Molecular Mechanics Calculations. Results from quantum mechanical and force field calculations on 2-aminotetralin derivatives have already appeared in the literature.[15] However, in these previous studies, no attempt was made to identify all available low-energy conformations. In the present study we have performed full energy minimization with respect to all internal coordinates. For the calculations we utilized the MMP2 program developed by Allinger;[16] specifically, the 1980 force field,[17] to which parameters for the phenol group[18] have been added and in which updated amine parameters[19] have been implemented, was used. Throughout, calculations were performed on the free bases although the 2-aminotetralins probably interact with DA receptors in their protonated form.[20] There is, however, a good agreement between the geometry of (2*R*)-1·HBr as observed by X-ray crystallography and the calculated geometry of the corresponding nonprotonated conformation (vide infra). In addition, the conformational preferences of protonated and nonprotonated 2-aminotetralins in solution appear to be very similar (compare for example **3b** and **3c**·HCl in Table IV) and calculations performed on 2-aminotetralins[15b] and phenethylamines[21] indicate that conformational differences between protonated and nonprotonated species in the gaseous state are small.

Compounds 1 and 2 possess a considerable amount of conformational flexibility; the tetralin ring is only semirigid; that is, a number of tetralin conformations are possible. In addition, the hydroxyl and amino groups can rotate around the C(5)–O and C(2)–N bonds, respectively, and the mobility of the two *N*-*n*-propyl groups further increase the conformational flexibilities of 1 and 2. Thus, a very large number of potential low-energy conformations of 1 and 2 can be envisaged. To deal with this problem, we adopted the following strategy: To each of the eight tetralin conformations in Figure 2, to which had been added the proper C(2)- and C(5)-substituents, a 2-dimethylamino substituent was added in three different ways so that τ(C1,C2,N,N – electron pair) = 60°, 180°, and –60°. The starting geometry of the hydroxyl groups of 1 and 2 was always set at $\tau(C_{4a},C_5,O,H)$ = 180°.[22] The resulting 24 "starting geometries" were then minimized and conformations with energies >3.4 kcal/mol above the global minimum were discarded. To each of the residual conformations, two methyl groups were then added so that the nine possible staggered "2-(diethylamino)tetralin geometries" were formed from each 2-(dimethylamino)-tetralin conformation. These new "starting geometries" were minimized and conformations with energies > 3.2 kcal/mol above the global minimum were discarded. The MIMIC program[23] contains a conformational mapping option and it would have been facile to construct conformational maps when searching for the low-energy 2-(diethyl-

(9) For discussions on important intramolecular distances in DA-receptor agonists, see for example ref 3c and Seeman, P. *Pharmacol. Rev.* **1980**, *32*, 229.
(10) The importance of the direction of the lone pair of electrons on the nitrogen has been frequently discussed. For a review, see: Kaiser, C.; Jain, T. *Med. Res. Rev.* **1985**, *5*, 145.
(11) One of the *N*-propyl groups of 1 appears to participate in receptor binding: see ref 3a.
(12) The term pseudorotation is not strictly applicable to the tetralin ring inversion process since it implicates a continuous change of dihedral angles to that each ring atom sequentially takes up each of the possible ring positions. See: Hendrickson J. B. *J. Am. Chem. Soc.* **1964**, *86*, 4854.
(13) Compare: Vanhee, P.; Tavernier, D.; Baas, J. M. A.; van de Graaf, B. *Bull. Soc. Chim. Belg.* **1981**, *90*, 697.
(14) For definitions of torsion angle and related concepts, see: Klyne, W.; Prelog, V. *Experientia* **1960**, *16*, 521.
(15) (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) Grol, C. J.; Rollema, H. *J. Pharm. Pharmacol.* **1977**, *29*, 153.
(16) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.
(17) Allinger, N. L.; Yuh, Y. *Quantum Chem. Program Exchange* **1980**, *12*, 395.
(18) Dodziuk, H.; von Voithenberg, H.; Allinger, N. L. *Tetrahedron* **1982**, *38*, 2811.
(19) Profeta, S., Jr.; Allinger, N. L. *J. Am. Chem. Soc.* **1985**, *107*, 1907.
(20) The dimethylsulfonium analogue of DA possesses DA agonistic properties: Andersson, K.; Kuruvilla, A.; Uretsky, N.; Miller, D. D. *J. Med. Chem.* **1981**, *24*, 683.
(21) Weintraub, H. J. R.; Hopfinger, A. J. *J. Theor. Biol.* **1973**, *41*, 53.
(22) Test calculations have shown that conformations with $\tau(C_{4a},C_5,O,H) \approx 0°$ consistently have energies 0.2–0.5 kcal/mol above those of the corresponding conformations with $\tau(C_{4a},C_5,O,H) \approx 180°$.
(23) Liljefors, T. *Mol. Graphics* **1983**, *1*, 111.

amino)tetralin conformations. However, most of the energetically favored geometries would not have been identified since the program locks the conformations of the rotating moieties when working in this mode. Actually, when certain rotamers of a 2-(dimethylamino)- or 2-(diethylamino)tetralin derivative are minimized, both the geometry of the tetralin ring and the value of τ_N change considerably. However, neither the conformation of the tetralin ring nor the value of τ_N is changed appreciably when the terminal methyl groups of a 2-(di-*n*-propylamino)tetralin derivative are rotated. Therefore, the construction of the 2-(di-*n*-propylamino)tetralin "starting geometries", which were used for the final energy minimization, was based on information from conformational maps of the low-energy 2-(diethylamino)tetralin conformations to which terminal methyl groups had been added (one to six 2-(di-*n*-propylamino)tetralin "starting geometries" were identified in each conformational map). By use of this approach we have identified 28 low-energy conformations (within 3.0 kcal/mol of the global minimum) of **1** and 33 low-energy conformations of **2** (see Table I). Four additional low-energy conformations of (2*S*)-**2** (FF, GG, HH, and II; Table I) were identified by minimization of all possible staggered "2-(dipropylamino)tetralin geometries" formed by addition of methyl groups to the 2-(diethylamino)tetralin conformations of (2*S*)-**1** and (2*S*)-**2**, which were found to have energies less than 0.5 kcal/mol above the respective global minimum.

Interestingly, the energetically most favorable conformations of **1** and **2** differ considerably with respect to attained tetralin inversion angles; compound (2*S*)-**1** appears to preferentially adopt ϕ values around 0° whereas compound (2*S*)-**2** preferentially adopts ϕ values around 180° (compare Table I and Figure 3). An indication of the quality of the present calculations is obtained by comparing observed geometrical parameters from X-ray crystallography of (2*R*)-**1**·HCl with structural data from the corresponding calculated conformation (Table II).

Calculations were also performed on 2-aminotetralin (**3c**) and on 2-amino-2-methyltetralin (**4c**) by applying essentially the same strategy as that described above. Results obtained (Table III) are in agreement with previous QCFF/PI and PCILO calculations performed on 2-aminotetralin[15a,b] but disagree with the large difference in energy (8.7 kcal/mol) between "axial" and "equatorial" ADTN (**3c**) that has been reported by Grol and Rollema.[15c]

NMR Spectroscopy. High-resolution ^{1}H NMR spectral data of compounds **1**·HCl and **2**·HCl in CD_3OD are shown in Table IV. Use of 400-MHz spectroscopy allowed analysis of the spectra by first-order approximations. Assignments and coupling constants were verified by spin-decoupling experiments, COSY spectroscopy, and spin–spin simulation. Also included in Table IV are previously reported spectral data for three other 2-aminotetralin derivatives (**3b**, **3c**·HCl, and **5**·HBr), which assume mainly half-chair conformations in solution.[7,24,25]

It is noteworthy that the coupling constants in **1**·HCl, **2**·HCl, **3b**, **3c**·HCl, and **5**·HBr (Table IV) are similar in magnitude regardless of ring substitution, N-substitution, ionization state of the nitrogen, or the solvent used. compounds **1**·HCl, **3b**, **3c**·HCl, and **5**·HBr appear to preferentially assume half-chair conformations with pseudoequatorial nitrogen substituents as indicated by the large dipseudoaxial coupling constants $J_{1ax,2ax}$ and $J_{2ax,3ax}$. This conclusion is further supported by the large $J_{3ax,4ax}$ value in compounds **1**·HCl, **3b**, and **5**·HBr. For compound **2**·HCl the coupling constants in Table IV offer less information: The C(2)-hydrogen is substituted with a methyl group and thus the structurally informative coupling constants with the C(1)- and C(3)-hydrogens are not available. However, a four-bond coupling constant ($^4J \approx 1$ Hz) between one of the C(1)-hydrogens and a C(3)-hydrogen was observed in the spectrum of **2**·HCl. Such long-distance couplings occur when two distant hydrogens are arranged in a *W* conformation.[26] Thus, the presence of this *W* coupling establishes the two interacting hydrogens as H_{1eq} and H_{3eq}, respectively, and also the conformation of the tetralin moiety as a half-chair. The half-chair tetralin conformation of **2**·HCl is further inferred from the large value of $J_{3ax,4ax}$ (Table IV). However, on the basis of the above ^{1}H NMR data, no conclusion can be drawn regarding the preferred conformation (pseudoequatorial or pseudoaxial) of the dipropylammonium substituent of **2**·HCl. Therefore a 2D-NOESY spectrum of **2**·HCl was recorded. In this NMR experiment, the intensities of cross peaks are related to the distance between nuclei. The 2D-NOESY spectrum of **2**·HCl shows that the C(2)-methyl hydrogens interact strongly with H_{1ax} and H_{3ax}. This is consistent only with a pseudoequatorial disposition of the C(2)-methyl substituent since the distance between a pseudoaxial C(2)-methyl and H_{1ax} and H_{3ax}, respectively, would be too large to account for the observed strong interactions.

In the report on the DA_1 inactivity of compound **4a**, Nichols et al.[7] presented ^{1}H NMR data for the *O*,*O*-dimethyl derivative **4b**. No dipseudoaxial coupling constants were present in the spectrum of **4b**. This was suggested to indicate the presence of two equally populated equilibrating tetralin conformations ($\phi \approx 0°$ and $\phi \approx 180°$).[7] It is thus apparent that N,N-dipropylation changes the conformational equilibrium considerably in C(2)-methyl-substituted 2-aminotetralins whereas that of C(2)-nonmethylated analogues is much less affected (compare also data in Tables I and III).

The ^{13}C NMR spectra of **1**·HCl and **2**·HCl in CD_3OD were also recorded; chemical shifts for resonances due to C(1)–C(4) are shown in Table V. The ^{13}C NMR assignements were verified by use of 2D chemical shift correlation spectroscopy. Recently, Morin et al.[27] reported ^{13}C chemical shift parameters for methyl substituents in tetralin derivatives. The parameters were obtained by a least-squares regression analysis of the ^{13}C NMR spectra of a large series of methyl-substituted tetralins.[27] The result of addition of the ^{13}C chemical shift parameters for a pseudoaxial C(2)-methyl group to the observed chemical shifts of **1**·HCl is interesting (Table V); the calculated chemical shift of C(4) is δ 18.4 whereas the observed chemical shift of C(4) of **2**·HCl is δ 22.05; that is, C(4) experiences a much smaller shielding (γ effect) than what would be expected if the C(2)-methyl substituent was pseudoaxially located. This indicates that the dipropylammonium group of **2**·HCl predominantly is pseudoaxially oriented and supports our results from the NOESY experiment and the molecular mechanics calculations.

Comparison of Conformational Distribution of 1, 2, 3c, and 4c. There is a good agreement between the experimentally determined (by NMR) and theoretically calculated (by MMP2) conformational preferences of

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(25) Motohashi, M.; Mizuta, E.; Nishikawa, M. *Chem. Pharm. Bull.* 1981, *29*, 1501.
(26) See, for example: Jackman, L. M.; Sternhell, S. "Applications of NMR Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon: Oxford, 1969.
(27) Morin, F. G.; Horton, W. J.; Grant, D. M.; Dalling, D. K.; Pugmire, R. J. *J. Am. Chem. Soc.* **1983**, *105*, 3992.

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

conf	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*S*)-5-Hydroxy-2-(di-*n*-propylamino)tetralin ((2*S*)-1)				
A	344	57	61	178	−178	−170	0.5[h]
B	344	56	60	179	179	−57	1.0
C	344	64	177	171	−63	−179	0.6
D	345	65	180	57	−63	−179	1.1
E	0	65	43	175	−63	170	2.8
F	353	−178	88	−176	167	−176	2.9
G	357	178	−171	173	134	180	2.8
H	356	177	−172	172	137	−60	3.0
I	0[i]	−176	−52	−171	174	−170	0[j,k]
J	15[i]	178	−57	98	171	−168	2.9
K	0[i]	−177	−54	−57	173	−169	0.4
L	0[i]	−176	−52	−170	173	100	2.6
M	0[i]	−177	−53	−170	171	−54	0.2
N	0[i]	−177	−56	−56	170	−53	0.4
O	342	−160	−170	170	−67	−171	2.7
P	343	−162	−61	−174	−64	−171	2.6
Q	343	−162	−61	−57	−64	−171	3.0
R	15[i]	−51	83	−179	168	−174	3.0
S	15[i]	−56	−176	170	49	170	0.4
T	15[i]	−55	−173	55	50	170	0.7
U	15[i]	−55	−176	169	52	57	0.9
V	15[i]	−53	−171	53	55	56	0.9
X	0[i]	−31	−171	172	−66	−174	2.5
Y	0[i]	−31	−170	55	−64	−175	2.8
Z	205[i]	60	64	177	−178	−171	0.8
AA	205[i]	60	64	178	179	−57	1.1
BB	205[i]	66	180	170	−62	180	0.6
CC	205[i]	66	−176	56	−62	179	0.7
			(2*S*)-5-Hydroxy-2-methyl-2-(di-*n*-propylamino)tetralin ((2*S*)-2)				
A	0[i]	61	81	176	171	−172	2.4
B	0[i]	61	82	178	170	−58	2.8
C	0[i]	66	−129	180	174	−174	1.9
D	0[i]	60	−119	180	168	−175	1.9
E	0[i]	66	−135	59	176	−173	2.2
F	0[i]	50	−98	−57	159	−175	2.8
G	0[i]	59	−114	177	163	−63	2.4
H	350[i]	56	−175	175	129	180	2.2
I	350[i]	62	−163	63	115	−178	2.8
J	350[i]	54	−178	174	136	−59	2.6
K	18	77	−170	170	−69	−173	1.8
L	18	77	−168	55	−68	−173	2.0
M	0[i]	41	67	172	168	−169	2.1
N	0[i]	40	66	173	166	−54	2.3
O	0[i]	−171	−131	180	177	−175	2.9
P	0[i]	−158	−170	170	−70	−173	2.4
Q	0[i]	−158	−168	56	−69	−174	2.7
R	22	−76	69	172	168	−170	2.6
S	22	−77	68	173	165	−55	2.8
T	12	−62	−175	175	129	179	2.6
U	12	−40	−170	170	−68	−173	2.2
V	12	−40	−168	55	−67	−174	2.4
X	205[i]	62	87	−178	168	−174	0.8
Y	205[i]	62	88	−175	165	−58	0.4
Z	205[i]	65	−138	179	178	−174	0.5
AA	205[i]	63	−136	174	169	−61	1.0
BB	200[i]	74	−56	−167	178	−168	1.9
CC	200[i]	74	−57	−166	172	−54	1.8
DD	195[i]	59	−166	175	119	179	0.0[l]
EE	195[i]	59	−165	64	117	−178	0.1
FF	195[i]	64	−158	174	98	52	0.3
GG	195[i]	55	−173	170	138	−58	0.4
HH	195[i]	65	−159	66	94	51	0.9
II	195[i]	55	−168	61	136	−60	0.8
JJ	200[i]	74	−169	170	−68	−172	0.1
KK	200[i]	75	−167	55	−68	−172	0.0[l]
LL	200[i]	74	−165	−102	−66	−171	2.7

[a] Only conformations with $\tau(C_{4a},C_5,O,H) \simeq 180°$ are included and conformations with energies larger than 3 kcal/mol above the respective global minima have been omitted. [b] Tetralin inversion angle (see Figure 2). [c] $\tau_N = \tau(C_1,C_2,N,\text{electron pair})$. [d] $\tau_A = \tau(C_2,N,C_\alpha,C_\beta)$. [e] $\tau_B = \tau(N,C_\alpha,C_\beta,C_\gamma)$. [f] $\tau_{A'} = \tau(C_2,N,C_{\alpha'},C_{\beta'})$. [g] $\tau_{B'} = \tau(N,C_{\alpha'},C_{\beta'},C_{\gamma'})$. [h] Conformation that corresponds to the X-ray structure of the A molecule of (2*R*)-1·HCl (ref 1c). [i] Approximate ϕ value estimated by comparison with relevant conformations of C(2)-unsubstituted tetralin. [j] Steric energy = 13.7 kcal/mol. [k] Conformation that corresponds to the B molecule of (2*R*)-1·HCl (ref 1c). [l] Steric energy = 19.5 kcal/mol.

Table II. Comparison between Observed[a] and Calculated[b] Geometrical Parameters of (2*R*)-5-Hydroxy-2-(di-*n*-propylamino)tetralin ((2*R*)-1)

bond length, Å			valence angle, deg			torsion angle, deg		
	obsd	calcd		obsd	calcd		obsd	calcd
C(7)–C(8)	1.36	1.39	C(7)–C(8)–C(8a)	122	120	C(8)–C(8a)–C1–C(2)	168	167
C(8)–C(8a)	1.40	1.40	C(4a)–C(8a)–C(8)	118	119	C(8a)–C(1)–C(2)–N	166	168
C(4a)–C(8a)	1.41	1.40	C(1)–C(8a)–C(8)	120	118	C(1)–C(2)–C(3)–C(4)	–64	–62
C(1)–C(8a)	1.50	1.51	C(1)–C(8a)–C(4a)	122	122	C(2)–C(3)–C(4)–C(4a)	53	52
C(4)–C(4a)	1.51	1.51	C(2)–C(1)–C(8a)	114	116	C(3)–C(4)–C(4a)–C(8a)	–21	–19
C(2)–C(3)	1.51	1.54	C(1)–C(2)–C(3)	109	107	C(1)–C(2)–N–$C_{\alpha'}$	–165	–174
C(3)–C(4)	1.54	1.53	C(1)–C(2)–N	108	112	C(2)–N–C_{α}–C_{β}	–177	178
C(1)–C(2)	1.55	1.54	C(3)–C(2)–N	112	113	C(2)–N–$C_{\alpha'}$–$C_{\beta'}$	–71	–61
C(2)–N	1.53	1.49	C(2)–C(3)–C(4)	110	111	N–C_{α}–C_{β}–C_{γ}	–176	170
N–C_{α}	1.52	1.48	C(3)–C(4)–C(4a)	113	113	N–$C_{\alpha'}$–$C_{\beta'}$–$C_{\gamma'}$	–173	–178
N–$C_{\alpha'}$	1.51	1.47	C(2)–N–C_{α}	111	111			
C_{α}–C_{β}	1.52	1.54	C(2)–N–$C_{\alpha'}$	115	113			
$C_{\alpha'}$–$C_{\beta'}$	1.52	1.54	C_{α}–N–$C_{\alpha'}$	112	112			
C_{β}–C_{γ}	1.50	1.54	N–C_{α}–C_{β}	114	116			
$C_{\beta'}$–$C_{\gamma'}$	1.52	1.54	N–$C_{\alpha'}$–$C_{\beta'}$	113	116			
			C_{α}–C_{β}–C_{γ}	113	112			
			$C_{\alpha'}$–$C_{\beta'}$–$C_{\gamma'}$	109	111			

[a] Observed values from the X-ray crystal structure of molecule A of (2*R*)-1·HCl (ref 1c). [b] Calculated values (MMP2) for the enantiomer of conformation A of (2*S*)-1 (Table I).

Table III. Geometrical Parameters for Low-Energy Conformations of (2*S*)-**3c** and (2*S*)-**4c**

conf	ϕ,[a] deg	τ_N,[b] deg	rel steric energy, kcal/mol
	(2*S*)-2-Aminotetralin ((2*S*)-**3c**)		
A	354	60	0.0[c]
B	358	–177	0.2
C	356	–59	0.2
D	80	63	4.2
E	82	–176	4.5
F	76	–58	4.4
G	191	59	0.9
H	195	176	1.2
I	195	–68	1.1
J	290	61	4.2
K	288	–179	4.4
L	288	–61	4.2
	(2*S*)-2-Amino-2-methyltetralin ((2*S*)-**4c**)		
A	17	60	0.5
B	16	180	0.6
C	16	–59	0.6
D	106	64	4.1
E	105	–175	4.2
F	100	–54	4.2
G	191	58	0.0[d]
H	195	173	0.2
I	195	–68	0.2
J	282	60	4.0
K	280	179	3.9
L	282	–61	3.8

[a] Tetralin inversion angle (see Figure 2). [b] $\tau_N = \tau(C_1,C_2,N,$-electron pair). [c] Steric energy = 0.6 kcal/mol. [d] Steric energy = 1.8 kcal/mol.

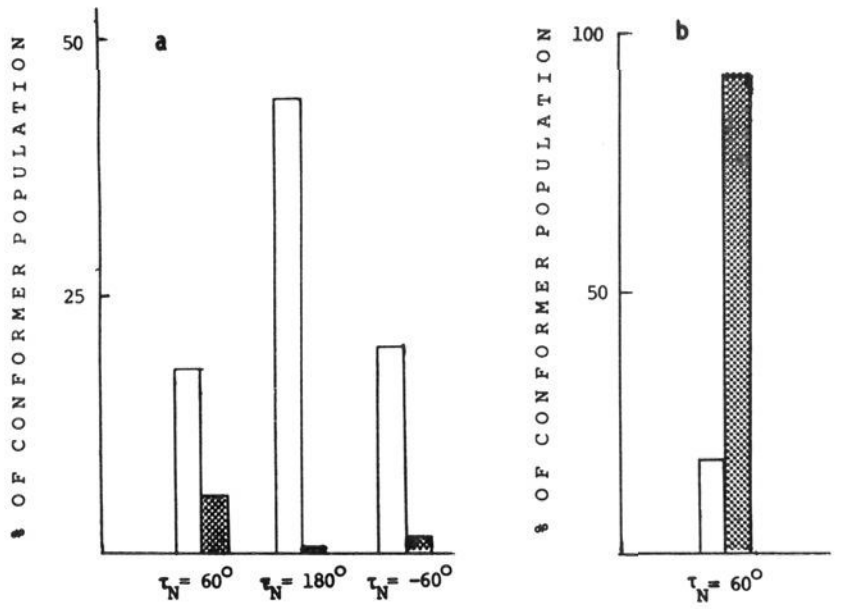

Figure 3. Conformational distribution of (2*S*)-1 (unfilled bars) and (2*S*)-2 (shaded bars). The probability of existence of each conformation (at 37 °C) was estimated from a Boltzman distribution based on the steric energies in Table I. (a) Distribution of dipropylamino group rotamers in conformations having ϕ values around 0°. (b) Distribution of conformations having ϕ values around 180°. In this case only one dipropylamino group rotamer ($\tau_N \approx 60°$) appears to be populated. For definitions of τ_N and ϕ, see text.

compounds **1**, **2**, **3c**(**3b**), and **4c**(**4b**) (vide supra). Further, the agreement between bond distances and bond angles in the X-ray structure of **1**·HCl and those in the corresponding MMP2 conformation (Table II) is impressive. Thus, the following MMP2-based (Tables I and III) comparison of the conformational distributions of **1**, **2**, **3c**, and **4c** can be made with considerable confidence: (a) Preferred ϕ values for (2*S*)-**1** and (2*S*)-**2** are around 0° and 180°, respectively (Table I and Figure 3). However, a significant part of the conformer populations of (2*S*)-**1** and (2*S*)-**2** will assume ϕ values around 180° and 0°, respectively, since these latter conformations represent local minima with energies < 2 kcal/mol above the respective global minimum (compare Figure 3). For compounds **3c** and **4c**, the energy differences between tetralin conformations with ϕ values around 0° and 180° are much smaller (<1 kcal/mol), and thus these compounds will easily adopt both conformations in solution. Accordingly, the suggestions of Nichols et al.[7] as to the conformational distribution of **4a** are supported by the present results. (b) The three staggered rotamers of the dipropylamino groups of (2*S*)-**1** and (2*S*)-**2** (having τ_N values around 60°, 180°, and –60°, respectively) appear to be populated in conformations with ϕ values around 0°. The corresponding rotamers of **3c** and **4c** have about equal energies. (c) Some relative spatial orientations that are perfectly accessible for the *N*-*n*-propyl groups of **1** are less accessible for the *N*-*n*-propyl groups of **2**. This must be due to the steric influence from the C(2)-methyl substituent.

Structure–Activity Relationship Implications. A dose of 10 nmol/kg of compound **1** induces a half-maximal decrease of the limbic and striatal Dopa levels in reserpinized rats.[3a] In contrast, compound **2** does not significantly affect the Dopa levels when given in doses of 60

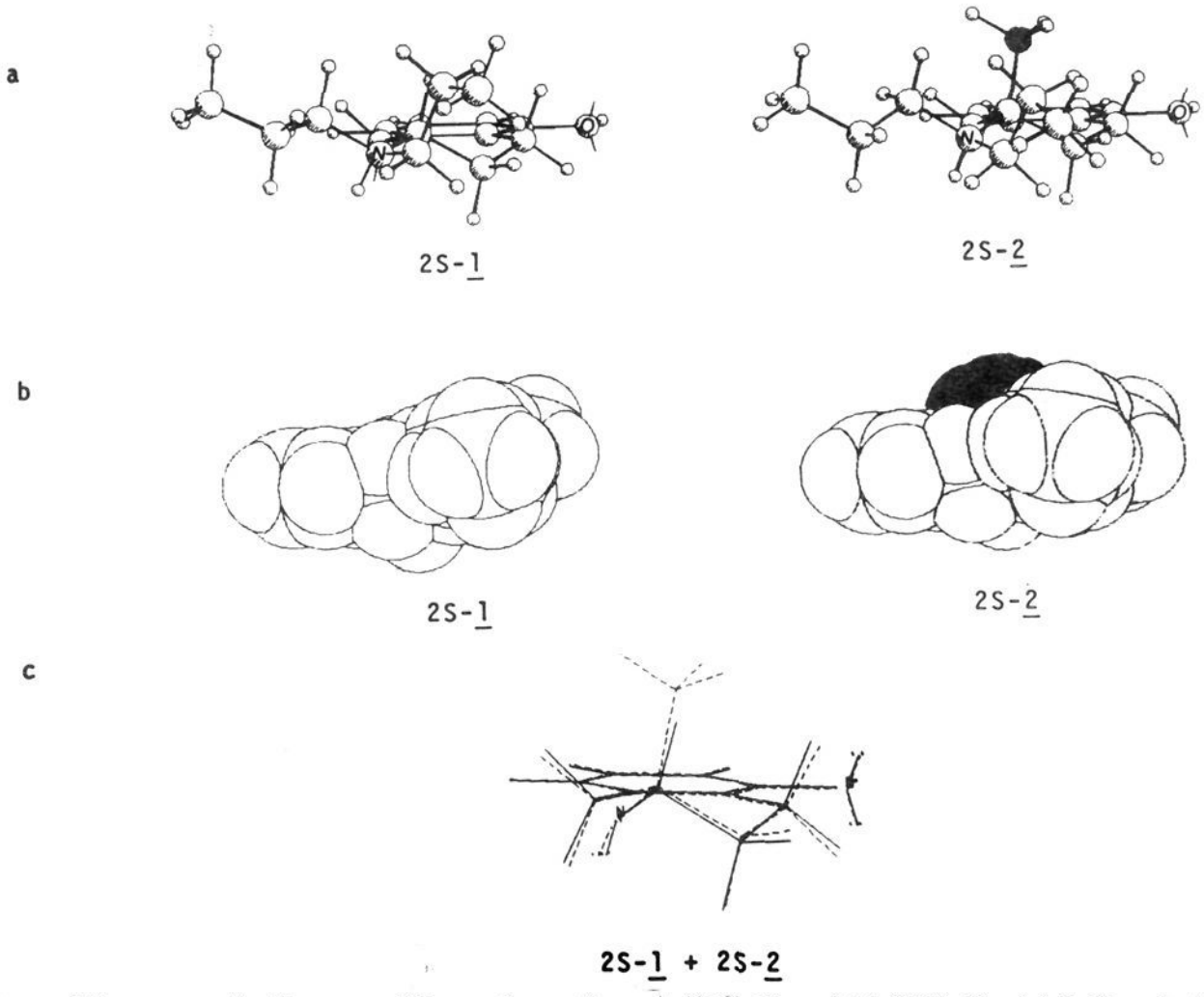

Figure 4. Comparison of the energetically accessible conformations A ((2*S*)-**1**) and M ((2*S*)-**2**). (a) Ball and stick representations. (b) van der Waals representations oriented so that the C(7) and C(8a) atoms are in the plane of the paper, the plane of the aromatic rings are perpendicular to the plane of the paper, and the hydroxyl groups are oriented away from the reader. For clarity, the C(2)-methyl group of M ((2*S*)-**2**) is shaded. (c) Computer-generated best fit of all carbon, oxygen, and nitrogen atoms of the 2-(dipropylamino)tetralin moieties of conformations A ((2*S*)-**1**) and M ((2*S*)-**2**). For clarity, the propyl groups have been omitted. The perspective is similar to that in (a). Mean distance between fitted atoms = 0.18 Å.

Table IV. ^{1}H NMR Spectral Data of Five 2-Aminotetralin Derivatives That Assume Mainly Half-Chair Conformations

		chemical shifts, δ						
compd	solvent	H_{1ax}	H_{1eq}	H_{2ax}	H_{3ax}	H_{3eq}	H_{4ax}	H_{4eq}
1·HCl	CD_3OD	~3[a]	~3[a]	3.69	1.89	2.33	2.64	~3[a]
2·HCl	CD_3OD	3.14	3.05[b]		1.97	2.25	2.61	3.04[b]
3b[c]	$CDCl_3$	2.47	2.89	3.14	1.55	1.94	2.76	2.78
3c·HCl[d]	D_2O	2.91	3.17	3.69	1.89	2.25	2.97	2.97
5·HBr[e]	D_2O	4.8		3.4	1.95	2.42	2.85	3.0

	coupling constants (J, Hz)										
compd	$J_{1ax,1eq}$	$J_{1ax,2ax}$	$J_{1eq,2ax}$	$J_{2ax,3ax}$	$J_{2ax,3eq}$	$J_{3ax,3eq}$	$J_{3ax,4ax}$	$J_{3ax,4eq}$	$J_{3eq,4ax}$	$J_{3eq,4eq}$	$J_{4ax,4eq}$
1·HCl	*f*	9.3	4.5	10.5	2.5	−10.5	10.5	5.6	5.8	3.0	−16
2·HCl	−15.2					−12.0	12.0	6.4	6.0	3.0	−18.0
3b	−15.8	9.2	4.8	9.9	3.0	−12.7	9.9	5.9	4.9	4.7	−15.7
3c·HCl	*g*	9.8	5.0	9.7	3.6	*g*	*g*	*g*	*g*	*g*	*g*
5·HBr		8.5		11.3	3.5	−13.4	9.9	6.3	5.6	4.1	−17.4

[a] Obscured. [b] Estimated from COSY spectrum. [c] From ref 7. [d] From ref 24. [e] From ref 25. [f] Not determined. [g] Not reported.

Table V. ^{13}C NMR Spectral Data of **1**·HCl and **2**·HCl

	chemical shifts,[a] δ			
compd	C(1)	C(2)	C(3)	C(4)
1·HCl[b]	30.85	61.89	24.95	23.69
2·HCl[b]	38.54	68.84	30.51	22.05
c	38.6	64.9	32.7	18.4

[a] Assignments have been verified by use of 2D chemical shift correlation spectroscopy. [b] Methanol-d_4 was used as solvent. [c] Calculated chemical shifts obtained by addition of observed chemical shifts of **1**·HCl and chemical shift parameters for a pseudoaxial C(2)-methyl substituent (ref 27).

μmol/kg.[5] Accordingly, there is a larger than 6000-fold potency difference between **1** and **2**. Most likely, the inactivity of **2** is not due to a different conformational distribution as compared to that of **1** since the energy differences between DA-active[28] ($\phi \approx 0°$) and DA-inactive ($\phi \approx 180°$) conformations of (2*S*)-**2** are rather small and since the three staggered dipropylamino-group rotamers appear to be energetically allowed in conformations of (2*S*)-**2** with ϕ values around 0° (Table I and Figure 3). This infers that the steric bulk of the C(2)-methyl group per se prevents a proper alignement of (2*S*)-**2** with central DA receptors; as demonstrated in Figure 4, an excellent fit is obtained when the 2-(dipropylamino)tetralin moieties of (2*S*)-**1** and (2*S*)-**2** are superimposed in their "DA-active conformations" (A and M, respectively ; these conforma-

(28) That the DA-active conformation of a (2*S*)-2-aminotetralin corresponds to $\phi \approx 0°$ is supported by a large variety of data. For reviews, see: Cannon, J. G. *Ann. Rev. Pharmacol. Toxicol.* **1983**, *23*, 103, and Cannon, J. G. In *CRC Handbook of Stereoisomers: Drugs in Psychopharmacology*; Smith, D. F., Ed.; CRC Press: Boca Raton, FL, 1984; p 117.

tions are also superimposable on the 2-aminotetralin moieties of low-energy conformations of the potent DA-receptor agonists (6a*R*)-apomorphine and (4a*S*,10b*S*)-*trans*-7-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline.[29] A similar conclusion was drawn in the report on the DA_1 inactivity of **4a**,[7] and our MMP2 calculations support the suggestion that **4a** is capable of assuming a "DA-active conformation". In order to rationalize the detrimental effect of the C(2)-methyl group, Nichols et al.[7] proposed a DA_1-receptor geometry "that may either be a groove or a slot into which the agonist fits or one where the receptor may fold in on the agonist during the process of receptor activation". In our opinion, the present results and those of Nichols et al.[7] can equally well be explained by assuming that the approach of (2*S*)-**1** and (2*R*)-**3a** (the DA-active enantiomers of **1** and **3**[30]) to the respective DA receptors is from the unsubstituted faces of the tetralin rings.[31]

(29) Wikström, H.; Andersson, B.; Sanchez, D.; Lindberg, P.; Arvidsson, L.-E.; Johansson, A. M.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1985**, *28*, 215.

(30) It has been demonstrated that the 2*R* enantiomer of **3a** is the more potent antipode: McDermed, J. D.; Freeman, H. S. In "Advances in Dopamine Research"; Kohsaka, M.; Shohmori, T.; Tsukada, Y.; Woodruff, G. N., Eds.; Pergamon: Oxford, 1981; p 179.

(31) It has been suggested that the approach of (*R*)-apomorphine to the DA receptor occurs from the corresponding face of the aporphine ring: Camerman, N.; Chan, L. Y. Y.; Camerman, A. *Mol. Pharmacol.* **1979**, *16*, 729.

Experimental Section

The syntheses of compounds **1** and **2** have been previously reported.[3a,5] The structural modelling was performed by use of the interactive computer graphics program MIMIC (methods for interactive modelling in chemistry).[23] Calculations were performed on a VAX 11/780 computer using Allingers MMP2 force field[17] to which had been added parameters for the phenol[18] and amino groups.[19] Computational times ranged from 1 to 30 min/minimization.

^1H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz or 22.5 MHz on JEOL GX-400 and FX-90Q spectrometers using 0.1 M CD_3OD solutions of the hydrochlorides at 25 °C. Chemical shifts were measured relative to internal tetramethylsilane. Apparent coupling constants were measured from expanded (1–2 Hz/cm) spectra and refined by use of the JEOL FASNO 5 NMR spectrum simulation program. Pulse sequences used for COSY, NOESY (mixing time 0.35 s.), and C–H shift correlation two-dimensional experiments were obtained from the GX-400 software.

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Registry No. (*S*)-**1**, 68643-08-3; (*S*-**1**·HCl, 58349-19-2; (*S*)-**2**, 101626-89-5; (*S*)-**2**·HCl, 101626-90-8; **3b**, 67445-12-9; (*S*)-**3c**·HCl, 21880-88-6; **3c**, 21880-87-5; (*S*)-**4c**, 101418-84-2; **5**·HBr, 78943-51-8.

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Synthesis, Antimalarial Activity, and Quantitative Structure–Activity Relationships of Tebuquine and a Series of Related 5-[(7-Chloro-4-quinolinyl)amino]-3-[(alkylamino)methyl][1,1′-biphenyl]-2-ols and N^{ω}-Oxides[1,2]

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A series of 5-[(7-chloro-4-quinolinyl)amino]-3-[(alkylamino)methyl][1,1′-biphenyl]-2-ols and N^{ω}-oxides was prepared from the substituted 1-phenyl-2-propanones proceeding through the 5-nitro[1,1′-biphenyl]-2-ols, the corresponding amino, and acetamido derivatives to the *N*-[5-[(alkylamino)methyl]-6-hydroxy[1,1′-biphenyl]-3-yl]acetamides and final condensation with 4,7-dichloroquinoline or the *N*-oxide. In a quantitative structure–activity relationship study first run on 28 and later expanded to 40 substituted phenyl analogues and their N^{ω}-oxides, increasing antimalarial potency vs. *Plasmodium berghei* in mice was found to be correlated with decreasing size ($\sum$MR) and electron donation ($\sum\sigma$) of the phenyl ring substituents. A significant correlation with N^{ω}-oxidation could not be demonstrated. Initial high activity against *P. berghei* infections in mice led to expanded studies that demonstrated in addition excellent activity against resistant strains of parasite, activity in primate models, and pharmacokinetic properties apparently allowing protection against infection for extended periods of time even after oral administration. Such properties encourage the clinical trial of a member of this class in man.

The ability of the malaria parasite to counteract man's efforts at its eradication by modulating its existence in some, still unknown, manner so that it is resistant to most known drugs remains a major problem for the chemotherapist. Our efforts to devise a solution to this problem led us to return to the well-explored 4-aminoquinolines.

The early classic work of Burckhalter[3] and colleagues on the modification of the bialamicol (**1**) structure led to the development of amodiaquine[4] (**2**). Recent efforts[5] on

(1) This is paper 60 of a series on antimalarial drugs. For paper 59, see: Werbel, L. M.; Hung, J.; McNamara, D.; Ortwine, D. F. *Eur. J. Med. Chem.* **1985**, *20*, 363.

(2) This investigation was supported by U.S. Army Medical Research and Development Command Contracts DADA-17-72-C-2077 and DAMD-17-79-C-9115. This is Contribution No. 1765 to the U.S. Drug Development Program.

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