# Molecular Analysis of Hexahydro-1*H*-indeno[1,2-*b*]pyridines: Potential Antidepressants

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Biological tests indicate hexahydro-1*H*-indeno[1,2-*b*]pyridines to be potential human antidepressants with additional stimulating properties. Two diastereomeric series with H_{4a},H_5-trans,H_{4a},H_{9b}-cis and H_{4a},H_5-cis,H_{4a},H_{9b}-cis configurations have been tested biologically. The results revealed that the H_{4a},H_5-cis,H_{4a},H_{9b}-cis series and the ortho-substituted 5-phenyl H_{4a},H_5-trans,H_{4a},H_{9b}-cis compounds lack activity. Neither the conformation with lowest potential energy nor any other electron-derived parameter correlate with these data. The only relevant difference between the active and the inactive compounds detected thus far is the rotational barrier of the phenyl in the 5-position. The conclusion was reached that certain conformations, which do not resemble those of lowest potential energy, cannot be adopted by the inactive compounds. Therefore, the interaction of the drug with the binding site, responsible for its biological activity, appears to be governed by a dynamic process. This process is characterized by a transformation of the conformation of lowest potential energy to one with an energy content above the minimum.

The easy accessibility[1] of 2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridines with the H_{4a},H_5-trans,H_{4a},H_{9b}-cis (1) and H_{4a},H_5-cis,H_{4a},H_{9b}-cis configuration (2) made it possible to perform intensive studies on structure–activity relationships of these two diastereomeric series.[2] Compounds related to 1 were found to be strong tetrabenazine antagonists with stimulating properties, activity being almost independent of the substituents introduced into the aromatic ring at the 5-position. The only exception was the lack of activity of compounds bearing a substituent in the ortho position of the phenyl ring (1, R^1 = 2-CH₃). In addition we found that compounds related to 2 lack activity, independent of R^1. Compound 2 (R^1 = 4-NH₂) is the only exception to this rule; however, it is assumed that the special character of the amino group in comparison to other substituents overrules any other common geometrical derived parameter that may explain the inactivity of this series. Because of the almost clear-cut structure–activity relationships, the current study was undertaken to find relevant molecular parameters that might correlate with the experimental biological data and that could explain the biological findings.

1			2
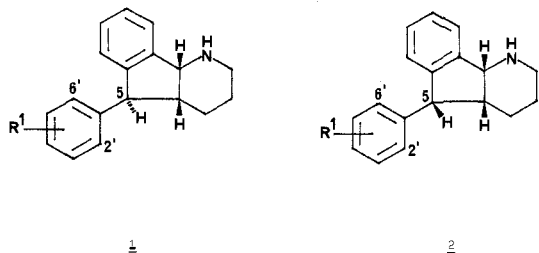
Method. Conformational analyses of the compounds selected was done with the computer program SCRIPT.[3] The main features of SCRIPT are as follows: generation of three-dimensional structures from the two-dimensional representation of a given compound, calculation of the

energies of the generated conformers, energy minimization of these conformers, and a manipulation phase in which one can analyse precisely the geometry of the final structures.

The initial generation of the three-dimensional structures is based primarily on the division of the molecules into chain and ring fragments. These main parts are described by sets of torsion angles that allow the calculation of all conformational states for the chain and the ring fragments. The combinatory product of the conformational diagrams for rings and chains produces all possible conformational diagrams of the molecule. From these diagrams the three-dimensional coordinates are calculated with use of numerical values for atomic distances, valency angles, and torsion angles.

After constructing the three-dimensional conformers, it is possible to calculate the corresponding molecular energies. The energy is the sum of stretching, bending, torsional, van der Waals, electrostatic, and hydrogen-bonding energy terms. Each of the conformers generated initially is now relaxed with respect to all its degrees of internal freedom in order to reach the corresponding minimum on the conformational potential surface. By definition, minimum conformational energy is reached when the sum of stretching, bending, torsional, van der Waals, electrostatic, and hydrogen-bonding energies does not change during an iteration step more than the preselected convergence criteria. In a typical procedure 5000 iteration steps and a convergence criteria of 0.01 kcal/mol were selected. As an example, the total energy gain during a minimization procedure as the sum of the different terms is listed in Table I for compound 1 (R^1 = 4-CH₃) and compound 2 (R^1 = 4-CH₃). For further details of the program see ref 3.
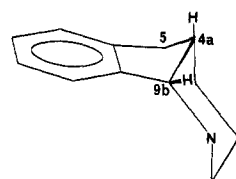
Generation of the Conformers. For the calculations three compounds were selected from each of the diastereomeric series bearing methyl groups in the para, meta, or ortho position. With a chair conformation for the piperidine ring, the program generates two conformations for the condensed three system (Figure 1, conformations 1 and 2).

The differences between these two possible conformations can easily be seen. C-5 and C-9b take in each case a position in the same plane as the benzo ring, whereas
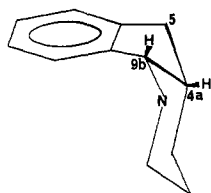
(1) R. Kunstmann, U. Lerch, and K. Wagner, *J. Heterocycl. Chem.*, 18, 1437 (1981).

(2) R. Kunstmann, U. Lerch, H. Gerhards, M. Leven, and U. Schacht *J. Med. Chem.*, 27, 432 (1984).

(3) N. C. Cohen, P. Colin, and G. Lemoine, *Tetrahedron*, 37, 1711 (1981).

Table I. Energy (kcal/mol) of Initial and Relaxed Conformers with Respect to the Different Terms Used in SCRIPT

	compound 1: H_{4a},H_5-trans,H_{4a},H_{9b}-cis; 4'-CH_3			compound 2: H_{4a},H_5-cis,H_{4a},H_{9b}-cis; 4'-CH_3		
	initial	relaxed	gain	initial	relaxed	gain
bond	29.57	1.07	28.5	29.57	1.11	28.64
valency	31.74	12.63	19.11	31.80	14.50	17.30
torsion	5.44	5.45	-0.01	5.45	5.69	-0.24
van der Waals	11.7	7.27	4.43	181.00	7.42	173.58
sp^2	0	0	0	0	0	
dipolar	0	0	0	0	0	
H bond	0	0	0	0	0	
total	78.45	26.42	52.03	247.82	28.72	219.1

conformer 1

conformer 2

Figure 1. The two possible conformations for the hexahydro-1H-indeno[1,2-b]pyridine skeleton.

C-4a will be found above (conformation 1) or below (conformation 2) this plane. Thus, the central cyclopentene is in an envelope conformation.

The aromatic ring at position five can rotate and the program generates conformations in which this substituent is staggered with respect to H-5, C-4a, or C-5a (Figure 2).

Because of the two edges of the phenyl ring, this results in six conformational possibilities for the phenyl at position 5, which, in combination with the two possible conformers of the condensed ring system, leads to 12 possible conformations for the whole molecule. If R^1 = 2- or 3-CH_3, these conformations are distinguishable. In the case of R^1 = H or 4-CH_3, pairs of these conformations are identical, reducing the number of possible conformers to six.

Selection of Conformers To Be Minimized. For a comprehensive study, a minimization of all the initially generated conformers is necessary. This corresponds to 60 minimization procedures for the six compounds selected for this study. In order to reduce the number of experiments to be carried out, a pilot study with compound 1 (R^1 = 4-CH_3) was performed. All six possible conformations were minimized. Independent of the initial position of the phenyl ring before minimization described by the torsion angle 6'-1'-5-5a (see Figure 2A-C), its position after minimization was the same for all conformers (Figure 2A). We thus decided to exclude those conformers from further consideration that are characterized by a position of the 5-phenyl ring as illustrated in Figures 2B and 2C.

Results

(a) Relative Potential Energies after Relaxation. With respect to the starting conformation 1 and 2 (Figure
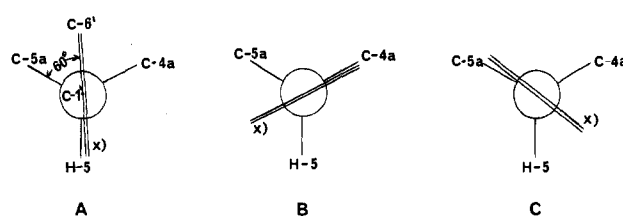
x) plane of phenyl ring in position 5

Figure 2. Possible conformation for phenyl ring in position 5.
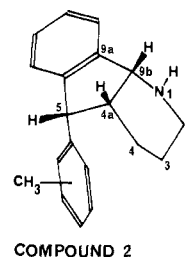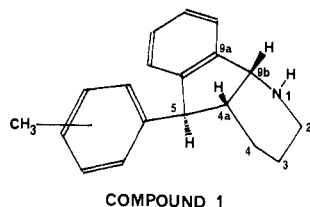
1), the energies of the relaxed structures differed in each case by about 3 kcal/mol. Without exception, lowest potential energy was reached starting with conformers 1. This was true in both series 1 and 2 and was independant of the position of the substituent R^1.

The ortho- and meta-substituted compounds have two preferred orientations for their aromatic ring in position 5. The substituent was either staggered to C-4a and C-5a or eclipsed to H-5 (see Figure 2A). In the ortho-substituted cases, lowest energy values after relaxation were found when the substituent was eclipsed to H-5. The energy difference between these two relaxed conformers with the preferred orientations of the aromatic ring was in this case $\sim$2 kcal/mol. This finding can be explained by there being less steric interaction between H-5 and the methyl group than between the methyl group and the hydrogen atoms at C-4. Significant energy differences between the minimized conformations of the meta-substituted compounds were not encountered.

The geometrical analysis described below refers only to that conformer of each compound having the lowest potential energy after relaxation. Therefore all conformers belonging to the conformer 2 family are omitted. In addition, those conformers of the ortho- and meta-substituted compounds that have their substituent R^1 staggered to C-4a and C-5a (Figure 2A) are neglected. This simplification in the presentation of the results is well justified, because the salient conclusions can be drawn already from the six selected three-dimensional structures. When all conformers were included into the geometrical analyses, no additional information on geometry or conformational dynamic behavior of the compounds in this series could be extracted.

(b) Geometrical Parameters. The minimization procedure for the selected conformers afforded the results summarized in Table II. To characterize the conformation of the three-ring skeleton, the torison angles of the cyclopentene and piperidine ring were chosen. The envelope conformation of the five-membered central ring is demonstrated by a value between 0° and 1.5° for the angle 5-5a-9a-9b, which indicates that these atoms will be found in the same plane. Atom C-4a will be located symmetrically above this plane in all compounds as indicated by the almost identical absolute values for the corresponding

Table II. Selected Geometrical Features of Compounds 1 and 2

COMPOUND 1

COMPOUND 2

	calculated values						
	compound 1			compound 2			
	H_{4a},H_5-trans,H_{4a},H_{9b}-cis			H_{4a},H_5-cis,H_{4a},H_{9b}-cis			X-ray
geom feature	para[a]	meta[a]	ortho[a]	para[a]	meta[a]	ortho[a]	data[b]
torsion angle (deg), cyclopentene ring							
5-5a-9a-9b	1.5	1.5	1.2	1.1	0.5	0.7	5.5
5a-9a-9b-4a	-15.6	-15.6	-15.2	-15.5	-14.9	-15.2	-18.7
9a-9b-4a-5	24.1	24.0	23.9	24.0	23.7	24.3	33.9
9b-4a-5-5a	-23.1	-23.0	-23.0	-23.1	-23.1	-23.7	-36.2
4a-5-5a-9a	13.4	13.4	13.5	13.6	14.0	14.0	26.7
torsion angle (deg), piperidine ring							
1-2-3-4	-60.0	-59.9	-59.3	-57.7	-57.7	-57.6	-59.9
2-3-4-4a	53.4	53.2	52.5	52.4	50.8	51.1	50.6
3-4-4a-9b	-43.6	-43.4	-43.5	-45.8	-43.4	-44.4	-43.8
4-4a-9b-1	39.7	39.4	40.6	43.4	42.2	43.8	43.1
4a-9b-1-2	-46.7	-46.5	-48.0	-49.6	-50.0	-51.3	-51.9
9b-1-2-3	57.0	57.1	57.6	57.3	58.2	58.6	61.0
torsion angle (deg), ring fusion cyclopentene-piperidine							
9a-9b-4a-4	155.5	155.8	157.0	160.8	160.1	161.5	162.5
1-9b-4a-5	-97.1	-92.3	-92.5	-93.4	-94.2	-93.5	-85.6
angle (deg) between the plane of: (a) phenyl ring A[c] and phenyl ring B[c]	76.1	76.3	76.6	85.3	86.4	84.1	66.3
(b) phenyl ring A[c] and piperidine ring (1-3-4a)	141.3	141.0	138.8	49.9	50.8	51.8	140.1
(c) phenyl ring B[c] and piperidine ring (1-3-4a)	129.0	128.4	127.4	125.5	124.2	123.9	127.6
dist in (Å) between N-1 and plane of: (a) phenyl ring A[c]	1.0	1.0	0.9	-2.1	-2.0	-2.2	1.2
(b) phenyl ring B[c]	-1.4	-1.4	-1.4	-1.4	-1.3	-1.4	-1.2

[a] Refers to the position of the CH_3 group. [b] The X-ray analysis has been performed on 1-methyl-5-phenyl-1,2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridine mandelate[6] (H_{4a},H_5-trans,H_{4a},H_{9b}-cis configuration). [c] A refers to the phenyl ring in position 5; B refers to the condensed benzo ring.

torsion angles (-15°, +13° and +24°, -23°, respectively). The chair conformation of the piperidine ring follows from the alternating values for the six torsion angles. Two more torsion angles describing the fusion of the carbo- and heterocyclic rings are also included in Table II. Ball–stick drawings (Figure 3) illustrate the relaxed conformations of compound 1 (R^1 = 4-CH_3) and compound 2 (R^1 = 4-CH_3).

For further characterization, the relative position of the 5-phenyl ring with respect to the ring skeleton was examined. Selected results are listed in Table II. Angles between different planes and the relative position of the nitrogen to each of the aromatic planes were calculated. In order to calculate angles including the nonplanar piperidine ring, the atoms N-1, C-3, and C-4a were chosen to define the plane for the piperidine ring.

(c) CNDO Calculations.[4] Qualitative results of the CNDO/2 calculations are summarized in Table III. The Cartesian coordinates that were obtained as a result after the minimization procedure by SCRIPT were used in this calculation. In each column the symbol x indicates those atoms where significantly high coefficients of either HOMO
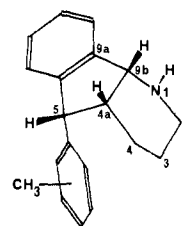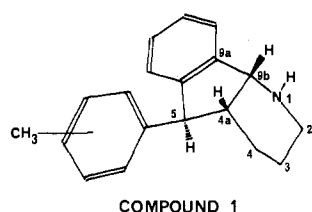
or LUMO in either direction p_x, p_y, or p_z were found. The three atoms that exhibit highest values are marked with three x's.

(d) Energy Profile for the Rotation of the 5-Substituents. In Figure 4 the energy profile calculated by SCRIPT resulting from the variation of the torsion across the C-1'-C-5 bond is illustrated. All other dihedral angles are held fixed at the value for the global minimum. We started with the conformation of lowest potential energy and went on by calculating the energies after changing the torsion angle stepwise by 15° in clockwise direction until we completed a 360° rotation. This calculation was performed for each of the six compounds. The energy profiles for meta- and para-substituted compounds were found to be identical, independent of the relative configuration of H_{4a} and H_5. Therefore, only one curve for either H_{4a},H_5-trans, meta- or para- substituted compounds and H_{4a},H_5-cis, meta- or para-substituted compounds are shown.

Discussion

As can be seen from Table II, identical values for the three-ring skeleton in both series 1 and 2 are obtained. Comparison of the torsion angles indicates the identical envelope conformation for the central five-membered ring

(4) G. A. Segal, *QCPE*, No. 91 (1966).

Table III. CNDO/2 Calculations[a]

COMPOUND 1

COMPOUND 2

	compound 1						compound 2					
	H_{4a},H_5-trans,H_{4a},H_{9b}-cis						H_{4a},H_5-cis,H_{4a},H_{9b}-cis					
	HOMO			LUMO			HOMO			LUMO		
	para[b]	meta[b]	ortho[b]	para[b]	meta[b]	ortho[b]	para[b]	meta[b]	ortho[b]	para[b]	meta[b]	ortho[b]
$C_{1'}$	xxx	x	x	xxx	x	x	xxx	x	x	xxx	xxx	xxx
$C_{2'}$	x			x			x			xxx		xxx
$C_{3'}$			x		xxx		x			x	x	
$C_{4'}$	xxx	xxx	x	xxx	xxx	xxx	xxx			xxx	xxx	x
$C_{5'}$				xxx						x		xxx
$C_{6'}$		x		x	xxx		xxx			x	xxx	
C_{5a}	xxx	xxx	xxx		x			xxx	xxx			
C_6	x					x						
C_7						xxx		x	x			x
C_8		xxx	xxx		x			xxx	xxx			
C_9						x						
C_{9a}		x	xxx			xxx		xxx	xxx		x	x
N_1								x	x			
C_{4a}	x		x				x				x	
C_5	x	x	x				x	x	x			

[a] Atoms with detectable amount of HOMO or LUMO; atoms with considerably high coefficients for either HOMO or LUMO (x); the three atoms in one column with the highest portion for HOMO or LUMO (xxx). [b] Refers to the position of the CH_3 group.

skeleton. In addition, the piperidine ring takes the identical chair conformation in each of the examined structures. The fusion of both rings is almost indistinguishable, which is seen from the two selected torsion angles describing this structural feature, 155° to 160° and −92° to −97°. This basic conformation is obviously not changed by the introduction of substituents into the ortho, meta, or para position of the aromatic ring in position 5.

The data from an X-ray analysis[6] are in good agreement with the calculated values. The calculated chair conformation of the piperidine ring is almost completely reproduced in the X-ray data. Differences between calculated and experimental data exist only for the cyclopentene ring. Whereas the calculated values suggest a pure envelope conformation, a distorted envelope comformation is shown in the X-ray data. Because of the overall identity in both series 1 and 2 with respect to the conformation of the basic ring skeleton, no conclusion can be drawn on this basis to explain the different biological results.

Differences between the active trans and the inactive cis series are seen in the relation between the aromatic ring in the 5-position and the indeno[1,2-b]pyridine ring (Table II). Most striking is the angle between the piperidine ring and the 5-phenyl ring within the trans and cis series, which are about 140° and 50°, respectively. The second difference results from the location of the nitrogen with respect to this aromatic ring. It is located on different sides of the aromatic plane (about +1.0 and −2.0 Å, respectively). This means that the nitrogen in the cis series is located within the roof, which is formed by the planes defined by the two

aromatic rings, whereas in the trans series the nitrogen is on top of this roof (Figure 5). The values in both series for the angle between the condensed phenyl ring and the piperidine ring (about 124–129°) and the location of the nitrogen below the plane of the condensed phenyl ring (about −1.4 Å) only reflect the identity of the indeno[1,2-b]pyridine ring system in both series. The difference in conformation between the cis and trans series (angle between the planes defined by the 5-phenyl ring and piperidine ring, location of the nitrogen within or on top of the roof defined by the aromatic rings) could account, in part, for the different biological activity of the two diastereomeric series. However, because of the inactivity of compound 1 (R^1 = 2-CH_3) and the lack of any variations in geometrical properties for compounds 1 (R^1 = 2-, 3-, 4-CH_3), this explanation cannot be fully correct.

Assuming that the interaction at the receptor site can only be brought about at such atoms where the coefficients for HOMO or LUMO or the charge is reasonably high, these parameters were examined for the molecules in question. The results indicate (Table III) that the atoms with the highest coefficient for HOMO or LUMO are located in the aromatic rings of the diphenylmethane moiety and, not surprisingly, the highest charge is located at the nitrogen. It is interesting to note that in both series some amount of HOMO is located at C-5. Because of the lack of accuracy of such empirical methods, one should not overstress these results. Yet, they are comparable with those summarized in Table II. Together they suggest that receptor interaction takes place at the aromatic rings, the nitrogen, and possibly at C-5. The difference between the two series would then be due to the shielding of H-5 and the nitrogen against an attack in the cis series, therefore suggesting the importance of these parts of the molecule for activity. But again, this conclusion would not account

(5) Convention of Klyne and Prelog: W. Klyne and V. Prelog, *Experientia*, **16**, 521 (1960).

(6) R. Kunstmann, E. F. Paulus, H. Gerhards, P. Witte, U. Schacht, M. Leven, unpublished results.
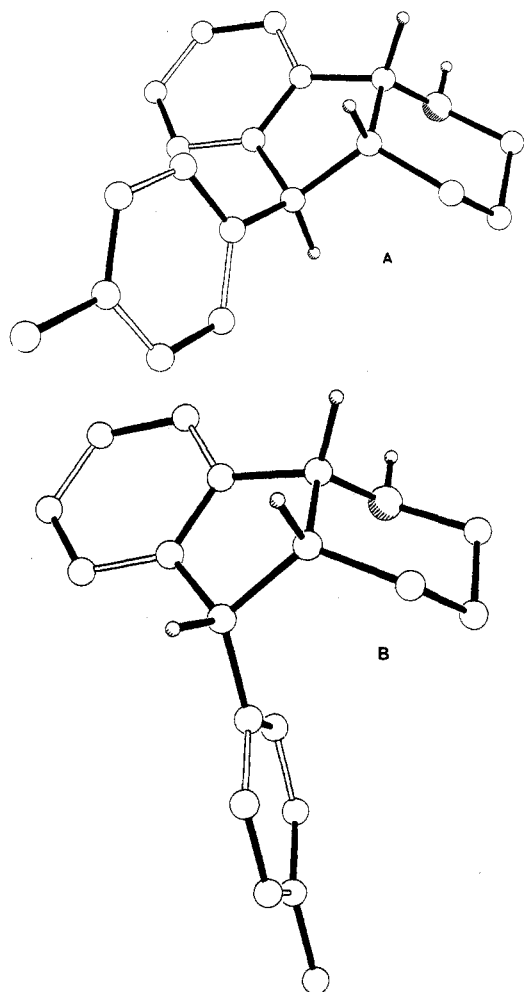
Figure 3. Ball–stick drawing of relaxed conformations (A = compound 1 (R^1 = 4-CH_3), B = compound 2 (R^1 = 4-CH_3)).

for the lack of activity for the ortho-substituted species 1 (R^1 = 2-CH_3).

Good agreement between activity and a molecular parameter was only achieved by comparing the rotational energies across the C-1′ and C-5 axis. It is seen easily from Figure 4 that compounds 1 with para and meta substitution need much less additional energy to rotate the phenyl ring around this C bond than compound 1 (R^1 = 2-CH_3) and all cis compounds.[7]

It is concluded that the reason for inactivity of the latter compounds is either the inability of these compounds to attain a conformation that is the active one at the receptor site or that, during the formation of the drug–receptor complex, a conformational change is required which cannot be adopted by the inactive compounds. It would appear

(7) We have to keep in mind that the only variable in the calculation of the energy of the rotational barrier, shown in Figure 4, is the torsion angle 6′-7′-5-4a. Thus, the energy values used in Figure 4 do not refer to a relaxed conformation. The results listed in Table I indicate that during a minimization procedure the gain in absolute energy might go up to more than several hundreds of kilocalories/mole. This gain in energy would easily compensate the calculated barrier for compounds 1 with para and meta substituents. Because of the relative high amount of the additional necessary energy for compound 1 (R^1 = 2-CH_3) and all cis compounds to overcome this rotational barrier, even a relaxation of the transient stages would leave these compounds in the range of an unsurmountable barrier. From there we conclude a free rotation of the phenyl ring for compounds 1 with para and meta substituents and a severe rotational barrier for compound 1 (R^1 = 2-CH_3) and for all cis compounds.

TORSION ANGLE (6′-1′-5-4A)
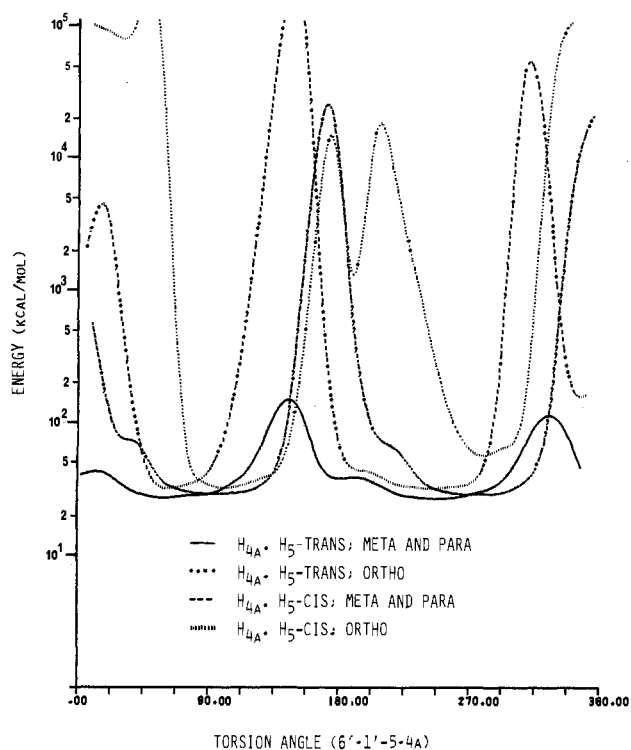
Figure 4. Relative energy profiles for the rotation of phenyl ring in position 5. All other dihedral angles are held fixed at the value for the global minimum. The torsion angle is considered as positive when it is measured clockwise from the front substituent (C-6′) to the rear substituent (C-4a).[5]
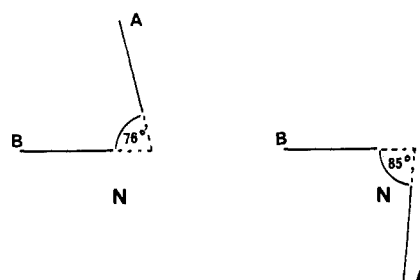
Figure 5. Angle between the planes defined by the aromatic rings and relative positive of the "N" atom (A = aromatic ring in position 5, B = aromatic ring being part of the ring skeleton).

that, during the interaction between the drug and the binding site, a conformational change reflected by a rotation of the aromatic ring at position 5 is required. Such a conformational change can be brought about in the para- and meta-substituted series 1 but is impossible for the ortho-substituted compound 1 and all compounds 2. The geometries of the conformations with lowest potential energy either do not resemble the active conformation at the receptor site or are not involved in the formation of the drug–receptor complex. Therefore, a dynamic process affecting the conformation of the drug molecule in the course of its interaction with its binding site is required.

Experimental Section

The conformational calculations were done with program SCRIPT running on a Univac 90-80 with a Tektronix 4014 as graphical display. HOMO and LUMO calculations were done with a CNDO/2 program again on a UNIVAC 90-80 computer.

Registry No. p-1, 88823-36-3; m-1, 88823-37-4; o-1, 88763-17-1; p-2, 88763-12-6; m-2, 88763-15-9; o-2, 88687-15-4.