activity in the presence of 1 μM phentolamine. Filtration and counting procedures have been described.[42] The concentration of compound that inhibited specific binding by 50% (IC_{50}) was obtained from linear regression analysis of log-probit transforms of the data obtained with three to five concentrations of each compound.

Acknowledgment. We are grateful to Drs. W. T. Comer and H. C. Stanton for quotidian discussion, D. J. Mann and M. Pohl for preparation of the manuscript, and L. E. Allen, E. M. Ashworth, J. A. Becker, D. K. Hyslop, W. Lobeck, R. A. Winnecke, and R. E. Yeager for technical assistance. The X-ray analysis of buspirone hydrochloride was performed by the Molecular Structure Corp., College Station, TX.

Registry No. 1, 36505-84-7; 2, 83928-56-7; 3, 57648-88-1; 4, 83928-57-8; 5, 57648-86-9; 6, 80827-69-6; 6 (base), 80827-68-5; 7, 80827-60-7; 7 (base), 80827-70-9; 8, 83928-58-9; 8 (base), 83928-70-5; 9, 83928-59-0; 9 (base), 83928-71-6; 10, 21090-07-3; 11, 21225-87-6; 12, 21102-94-3; 13, 21102-96-5; 14, 21103-03-7; 15, 21103-05-9; 16, 21103-20-8; 17, 21103-18-4; 18, 83928-60-3; 18 (base), 83947-21-1; 19, 21103-08-2; 20, 22684-83-9; 21, 21098-22-6; 22, 83928-61-4; 22 (base), 83928-72-7; 23, 83928-62-5; 23 (base), 83928-73-8; 24, 83928-63-6; 24 (base), 83947-20-0; 25, 83928-64-7; 25 (base), 83928-74-9; 26, 83928-65-8; 26 (base), 83928-75-0; 27, 83928-66-9; 27 (base), 83928-76-1; 28, 83928-67-0; 28 (base), 83928-77-2; 29, 83928-68-1; 29 (base), 83928-78-3; 30, 83928-69-2; 31, 25024-93-5; 32, 25024-94-6; 3,3-tetramethyleneglutaric anhydride, 5662-95-3; 4-(2-pyrimidinyl)-1-piperazinebutanamine, 33386-20-8; 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione, 80827-62-9; 1-(2-pyrimidinyl)piperazine, 20980-22-7.

Theoretical Conformational Studies of Some Dopamine Antagonistic Benzamide Drugs: 3-Pyrrolidyl- and 4-Piperidyl Derivatives

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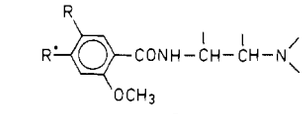
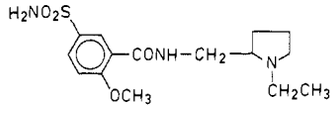
Model derivatives of 3-pyrrolidyl- and 4-piperidyl-*o*-methoxybenzamides, as representatives of neuroleptic substituted benzamide drugs, have been investigated by theoretical conformational analysis. Folded conformers of 2-methoxy-*N*-(1-methyl-3-pyrrolidyl)benzamide have the lowest energy, but extended conformers are only a few kilocalories per mole less stable. As regards the piperidyl derivative, it has been found that folded conformers are of much higher energy than extended ones. These and previous results are discussed in terms of the pharmacologically active conformers of substituted benzamide drugs and of possible modes of interaction with the dopamine receptor.

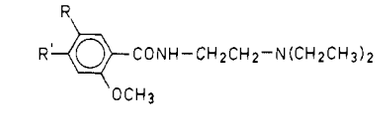
Substituted o-methoxybenzamide drugs (substituted o-anisamides, orthopramides) are a group of dopamine (DA) receptor antagonists having the general structure I.



I



II



III R = Cl, R' = NH_2

IV R = SO_2CH_3, R' = H

Representative drugs from this class are mainly centrally active and are used as neuroleptics [e.g., sulpiride (II)], antiemetics [e.g., metoclopramide (III)], or against various forms of dyskinesia [e.g., tiapride (IV)]. The mechanism of action of these compounds is not fully understood, but it is generally accepted that they act selectively as DA antagonists on a population of DA receptors not linked to adenylate cyclase.[1-6] Such a selectivity must be accounted for by molecular structural properties, including physicochemical properties and stereochemical features. As a result of this working hypothesis, topographical and conformational features of orthopramide drugs are of considerable interest for an understanding of their receptor selectivity and its rational improvement. Stereoselective activity has been observed for (−)-sulpiride and (−)-sultopride.[1]

Our laboratory has previously reported the conformational behavior of metoclopramide (III)[7] and sulpiride (II)[8] as examined by theoretical (PCILO) methods. Metoclopramide is thus believed to have only limited conformational freedom due to two intramolecular H bonds acting as conformational "locks" and favoring folded forms. The studies with sulpiride have also revealed that the minimum energy conformer is a folded, intramolecularly H-bonded form ($N^+/O=$ distance 2.56 Å), with extended conformers being only 3–4 kcal/mol less stable.

The distance between the basic nitrogen atom and the center of the aromatic ring, which is believed to be a crucial feature of dopamine agonistic and antagonistic activity, is very close to 5 Å in the fully extended dopamine molecule.[9] This is at least 1 Å shorter than the corresponding

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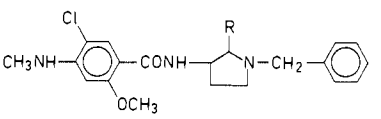
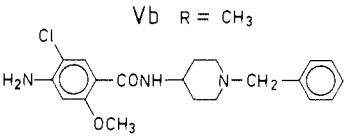
distance in the folded metoclopramide molecule[7] (5.95 Å) or in sulpiride[8] (6.2 and 7.2 Å, respectively, for the folded and extended conformers). Topographical differences thus exist between dopamine and orthopramides, but only preliminary conclusions can be drawn regarding their significance at the receptor level.

Substituted benzamide drugs can be subdivided into five classes according to the nature of the linkage between the two nitrogen atoms: aminoethyl (e.g., III), 2-pyrrolidyl (e.g., II), 3-pyrrolidyl (e.g., V), 4-piperidyl (e.g., VI), and



Va R = H

Vb R = CH_3

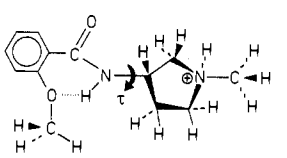


VI

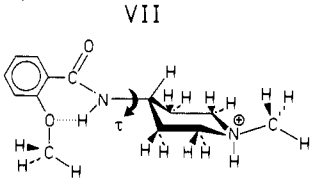
piperazyl derivatives.[10] In the present work, model derivatives of 3-pyrrolidyl- and 4-piperidylbenzamides are investigated by theoretical conformational analysis. Typical representatives of the former class are YM-08050 (Va)[11] and YM-09151-2 (Vb)[12] and of the latter class clebopride (VI).

Methods

Model compounds VII and VIII were used for the study of the



VII



VIII

conformational behavior of V and VI. The choice of these model molecules is dictated by the assumption that the conformation of the basic side chain is influenced only negligibly by aromatic substituents in the 4- and 5-positions. This assumption is proved correct by the identical H–H coupling constants seen in the NMR spectra of metoclopramide (III) and its corresponding model o-anisamide (Anker and Testa, unpublished). The two molecules VII and VIII were taken in their protonated form, which is predominant under physiological conditions. The methoxybenzamide moiety was constructed by standard geometry[13] and fixed in a planar conformation as shown (VII, VIII), which corresponds to its energy minimum as demonstrated by preliminary calculations.[7] An alternate conformation is conceivable with the methoxy oxygen H bonding to the N^+–H group of the side chain.

Table I. Topographical Features of 2-Methoxy-*N*-(1-methyl-3-pyrrolidyl)benzamide (VII)

pyrrolidine conformation[a]	τ, deg	ΔE, kcal/mol	N^+/arom center, Å	N^+/O=, Å	N^+ out of arom plane, Å
1 (C_2 up)	0	9.67	5.80	2.73	-1.61
	75	4.89	5.76	2.45	1.18
2 (N_1 up)	60	6.13	6.92	3.66	0.74
3 (C_4 up)	30	3.29	5.98	2.48	-0.62
4 (planar)	45	15.7	6.53	3.07	0.23
5 (C_3 up)	0	6.03	7.07	3.86	-0.62
	45	5.39	7.06	3.81	0.40
6 (N_1 down)	45	1.00	6.25	2.72	0.18
7 (C_3 down)	30	0.58	5.75	2.24	-0.64
	60	0.00	5.75	2.22	0.57
8 (half-chair)	60	16.2	6.39	3.78	0.72

[a] Conformers 1-3 and 5-7 are envelope forms (one ring atom out of the plane of the four other ones); the half-chair conformer 8 has C_3 above and C_4 below the plane of the three other ring atoms. The 1-methyl and 3-anisamidyl substituents are in equatorial or isoclinal positions.

Such a conformation, however, involves a virtual nine-membered ring that is expected to be markedly less stable than the virtual six-membered ring.[7] Also, Dreiding models show that the minimum O–N^+ distance would be ca 3.5 Å, corresponding to a weak H bond.

The remaining degrees of conformational freedom in the two molecules VII and VIII are the torsion angle τ, i.e., the angle C(O)–N–C–C, and the many dihedral angles of the saturated heterocycles. To approach this problem, we have first calculated the full geometry of a number of low-energy conformers of pyrrolidine and piperidine using a force-field method, as detailed later. These force-field geometries were then used as input for quantum mechanical calculations of the complete molecules VII and VIII, where only the torsion angle τ was varied. This torsion angle τ, defined according to Klyne and Prelog,[14,15] is shown for its zero value in VII and VIII; in the calculations, it was varied in 30° steps or in 5° steps in the vicinity of energy minima. The quantum mechanical method used in this work is an all-valence-electron semiempirical procedure, the PCILO method[16] (perturbative configuration interactions using localized orbitals).

The five-membered pyrrolidine ring has considerable conformational freedom within its steric limits. It has been shown for cyclopentane that the envelope and half-chair conformers populate a pseudorotational circuit that is essentially of constant strain and, hence, without well-marked energy minima and maxima.[17] Complete pseudorotational circuits have been explored for several five-membered rings,[17,18] the energy differences between the possible conformers being small (0–5 kcal/mol). We have used Allinger's MMI force-field method[19,20] to find a number of low-energy conformers of IX (supplementary material) by systematically exploring several plausible starting conformers with either a hydrogen or a methyl or both on the nitrogen atom, setting the program free to move all atoms. This procedure has led to the minimum-energy conformers 1, 2, 3, 6, and 8 (Tables I and II). (For Table III, see paragraph at the end of the paper concerning Supplementary Material.)

When the full molecule VII is considered, it becomes of interest to examine the entire range of permissible N^+/aromatic center distances, in particular the folded and extended conformers which in the case of sulpiride correspond to energy minima.[8] We have therefore included three additional conformers of IX in the

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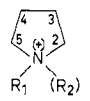
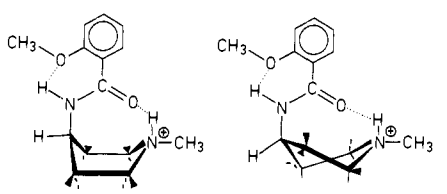


IX

calculations, namely, conformers 4, 5, and 7, imposing a fixed conformation (four or five coplanar heavy atoms) to the MMI program and letting it optimize the geometrical elements. Conformer 4 is the planar pyrrolidine ring, while conformer 5 must belong to the fully extended molecule VII and conformer 7 must belong to the most folded form of molecule VII (Supplementary Material).

For compound VIII, three conformations of the piperidine ring were considered (a chair, a boat, and a twist-boat form), and their geometry was optimized and fully calculated by the MMI program (supplementary material). The chair form is depicted in VIII. The boat and twist-boat forms in saturated six-membered rings are of higher energy than the chair form.[21] In the case of the complete molecule VIII, however, it cannot a priori be ruled out that a possible intramolecular H bond might stabilize a boat or twist-boat conformation of the piperidine ring, as shown in Xa and Xb, respectively. For each conformer of the piperidine ring,



Xa Xb

two positions (equatorial and axial) of the anisamidyl moiety were considered. The methyl substitutent was taken only in its equatorial position.

Results

2-Methoxy-*N*-(1-methyl-3-pyrrolidyl)benzamide (VII). Allinger's MMI force-field method has been applied successfully to many hydrocarbons.[19] Our calculations have confirmed the limited energy variations involved in the conformational behavior of pyrrolidines. The relative energies of IX calculated by the MMI method range from 0.00 to 3.83 kcal/mol depending on (imposed) conformation and on the substituents R_1 and R_2. Five conformers were calculated when the program was left free to move all atoms. Three additional conformers were calculated following some geometrical restrictions as previously explained. The full geometries of the eight conformers thus generated are reported in Table III (Supplementary Material). Our search procedure may have missed some interesting conformers of the pyrrolidine ring; these, however, should not enlarge the range of conformational energies obtained once the full molecule VII is considered.

Each of the eight pyrrolidine conformers was used in turn to construct molecule VII. Each time the torsion angle was rotated from 0 to 360°, and the conformational energy was calculated by the PCILO method. The eight curves of potential energy vs. the torsion angle are shown in Figure 1. For all curves an energy minimum is seen for values of τ between 30 and 90°. The pyrrolidine conformations 6 and 7, which correspond to folded conformers of molecule VII, lead to the lowest energy. Noteworthy is the fact that the pyrrolidine conformation 5, which corresponds to extended conformers of molecule VII, leads to an energy minimum that is only a few kilocalories per mole above the global minimum.

Some notable features of molecule VII are presented in Table I. The global minimum corresponds to the shortest

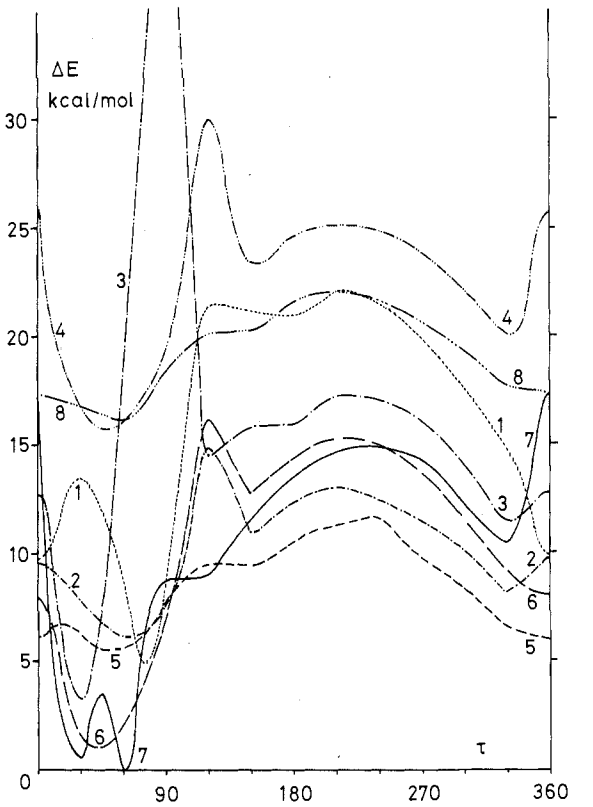


Figure 1. The conformational behavior of 2-methoxy-*N*-(1-methyl-3-pyrrolidyl)benzamide (VII) as a function of the torsion angle τ for various predetermined conformations of the pyrrolidine ring: 1, envelope C_2 up; 2, envelope N_1 up; 3, envelope C_4 up; 4, planar; 5, envelope C_3 up; 6, envelope N_1 down; 7, envelope C_3 down; 8, half-chair C_3 up C_4 down.

distance between N^+ and the center of the aromatic ring, with the $N^+/O=$ distance implying a strong intramolecular H bond.[22] It must be noted that $N^+/O=$ distances of 2.22 or 2.24 Å as seen in Table I are certainly unrealistically short. Clearly, the PCILO method underestimates here the optimal distance for a H bond; this is due to the neglect of diatomic overlap integrals, which results in an overemphasis of attractive nonbonded interactions.

Besides the preferred conformer, other folded conformers in Table I are just a few kilocalories per mole less stable. Extended conformers exhibiting a N^+/aromatic center distance of ca. 7 Å are less stable by 5–6 kcal/mol. This energy difference when considered by itself may seem considerable, but it is not a meaningful one due to three causes of uncertainty: (1) hydration factors are not taken into account (see Discussion); (2) the PCILO method itself has its shortcomings, as mentioned in the previous paragraph; and (3) no geometry optimization has been undertaken, which would influence energy differences and, in particular, remove some bad interactions (see also later).

2-Methoxy-*N*-(1-methyl-4-piperidyl)benzamide (VIII). The full geometries of the chair, one boat, and one twist-boat conformation of the *N*-methylpiperidinium cation, as calculated by Allinger's MMI force-field method, are given in Table IV (Supplementary Material). As with other saturated six-membered rings, this cation shows a higher energy for the boat form (6.36 kcal/mol) and for the twist-boat form (5.23 kcal/mol) relative to the minimum energy chair conformer. Each of these three conformations was then used in turn to construct the full molecule VIII by attachment of the anisamidyl moiety

(21) Reference 15, pp 113–115.

(22) Reference 15, pp 27–30.

Table II. Topographical Features of 2-Methoxy-*N*-(1-methyl-4-piperidyl)benzamide (VIII)

no.	piperidine geometry[a]		τ, deg	ΔE, kcal/mol	N^+/arom center, Å	$N^+/O=$, Å	N^+ out of arom plane, Å
	piperidine conformation	anisamidyl position					
1	chair	eq	0	6.55	7.88	5.59	0.02
			180	0	7.63	4.32	−0.02
2	chair	ax	90	30.88	6.15	4.14	−2.91
			270	36.71	6.18	4.24	2.91
3	boat	eq	180	10.58	7.67	4.67	0.07
4	boat	ax	120	28.76	5.14	2.74	−2.28
			240	28.76	5.14	2.74	2.28
5	twist-boat	eq	180	8.64	7.70	4.66	0.02
6	twist-boat	ax	120	29.47	5.25	2.75	−2.28

[a] The 1-methyl substituent is in the equatorial position.

either in the 4-equatorial or the 4-axial position.

The six curves of potential energy vs. the torsion angle, as calculated by the PCILO method, are shown in Figure 2. The three forms with the equatorial anisamidyl moiety are of the lowest energy, with the chair form as the preferred one. All these three forms display an energy minimum for $\tau = 180°$, with only limited variation in energy as a function of τ. Of much higher energy are the three forms with an axial anisamidyl moiety. Two local energy minima are seen, namely, for $\tau = 90$–120 and 240–$270°$. When the anisamidyl moiety is axial, the chair conformation is no longer of lower energy as compared to the boat and twist-boat forms. This is due to the fact that the latter conformers, as opposed to the chair isomer, form an intramolecular H bond (Xa and Xb), which has a marked stabilizing effect. From geometrical considerations, one would expect the energy curves for the chair and boat forms to be symmetrical with respect to the position $\tau = 180°$. This not always so, due to minor errors in the C–C(4)–H valency angle as calculated by the force-field program.

Some notable topographical features of compounds VIII are present in Table II, showing that the preferred conformations are extended ones (distance from N^+ to aromatic center larger than 7.5 Å). Folded conformations are less stable by ca. 30 kcal/mol. This energy difference is, for example, seen between the chair conformers having the anisamidyl moiety in an equatorial and an axial position, respectively. Such an energy difference appears considerable, despite the fact that the bulk anisamidyl moiety in the 4-axial position experiences severe steric interactions with the axial hydrogens on C-2 and C-6 and with C-3 and C-5. Certainly geometry optimizations would have alleviated some of the tensions in the axial conformers, resulting in a decrease of the energy difference but with certitude not to an inversion of sign. From these arguments we conclude that compound VIII, and hence clebopride, must exist practically exclusively as extended conformers under normal conditions.

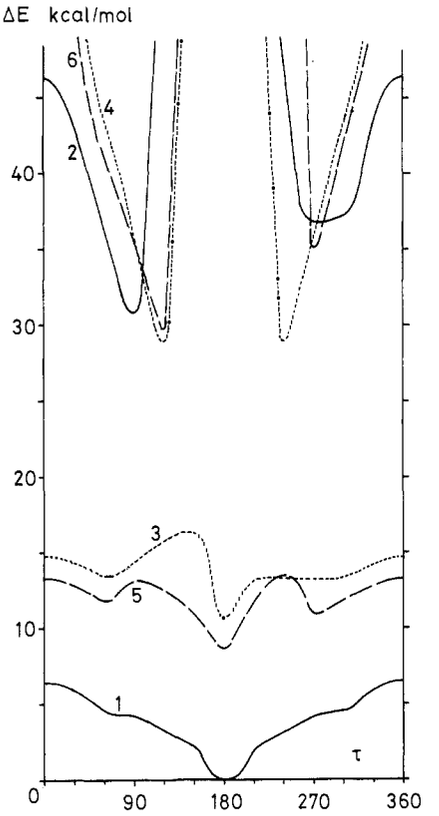


Figure 2. The conformational behavior of 2-methoxy-*N*-(1-methyl-4-piperidyl)benzamide (VIII) as a function of the torsion angle τ for various predetermined conformations of the piperidine ring: 1, chair, anisamidyl in equatorial position; 2, chair, anisamidyl in axial position; 3, boat, anisamidyl in equatorial position; 4, boat, anisamidyl in axial position; 5, twist-boat, anisamidyl in equatorial position; 6, twist-boat, anisamidyl in axial position.

Discussion

Several years ago, the conformational requirements for interaction with central DA receptors were formulated in two ways: (a) an "S-shaped" arrangement of the four-atom sequence linking the aromatic ring and the basic nitrogen[23] and (b) the dopamine overlap hypothesis,[24] which is based on the fact that the solid-state conformer of chlorpromazine[25] nearly overlaps the extended form of dopamine. Thus, it is believed that the distance from the basic nitrogen to the center of the (or an) aromatic ring is crucial.

It is interesting now to look closely at the topographical features of the substituted benzamides so far studied. Our quantum mechanical calculations show a preferred folded conformer for metoclopramide,[7] a small energy difference between folded and extended conformers of pyrrolidyl derivatives (e.g., sulpiride[8] and YM-08050), and a preferred extended conformation for clebopride. A discrepancy thus exists, which may be, at least in part, an artifact of neglecting solvation factors and of the PCILO method itself. As already discussed, the PCILO method overemphasizes attractive interactions between nonbonded atoms, in particular H bonds, and predicts too stable folded conformations. Regarding solvation factors, it might be expected that in an aqueous environment a competition exists between the intramolecular H bond and hydration

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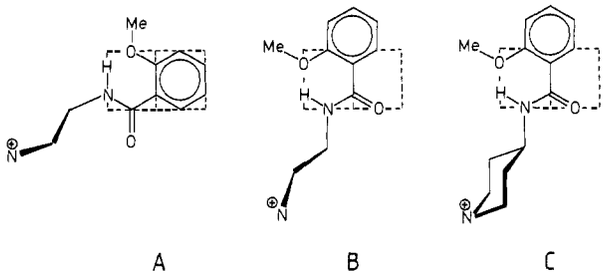

Figure 3. Possible modes of interaction of benzamide drugs with the topographical model of the dopamine receptors:[29] A and B, two possible modes; C, interaction of clebopride-like compounds.

of the cationic head, thus rendering more stable the extended form of metoclopramide. Preliminary NMR results in our laboratory confirm this explanation. Further, it can be noted that the distance between N^+ and the aromatic center in clebopride (ca. 7.6 Å), which is a rather rigid member of the benzamide series, is the same as that found in what are believed to be the active forms of butyrophenones.[26,27]

In contrast, other well-known neuroleptics show a smaller distance for this topographical feacture, e.g., butaclamol; from this and other rigid analogues, topographical features of a dopamine receptor have been derived.[28,29] Of relevance in the present context are the presence in this model of two phenyl binding sites, an α and a β region, located at a distance of 5.1 and 6.4 Å, respectively, from the nitrogen binding site.[29]

Clearly all neuroleptic orthopramides cannot exist with their basic nitrogen only 5.1 Å away from the center of the aromatic ring, as evidenced in the present and previous[7,8] studies. However, all these compounds exhibit a virtual six-membered ring stabilized by the strong intramolecular H bond between the amide N–H group and the methoxy O atom.[7] We speculate that this virtual cycle binds to the α region of the topographical dopamine receptors.[28,29] This mode of binding leaves the binding site of the phenyl ring undefined. The latter, indeed, can be conceived to interact with the β region (Figure 3A) or with another, as yet not recognized, region above the α and β region (Figure 3B). This latter mode of binding appears as more probable, since it is the only one compatible with the conformational behavior of clebopride (Figure 3C). Furthermore, the β region as originally derived binds a phenyl ring devoid of electron-donating substituents, whereas such substituents are necessary for orthopramides to be active.

We thus believe that the mode of binding of orthopramides to the topographical dopamine receptor[29] is that shown in Figure 3B,C. If this assumption is later proven correct, the topographical dopamine receptor will have to be completed by an additional aromatic binding site. At the present state, it may be correctly argued that preferred conformations may be different from receptor-recognized conformations despite a strong thermodynamic handicap. Work in progress (Jenner, Marsden, van de Waterbeemd, and Testa, in preparation) indicates that once log P has been accounted for, substituted benzamides of the pyrrolidine and piperidine series have a higher affinity for the D-2 receptor than analogues in the aminoalkyl series.

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Supplementary Material Available: Full geometries, as calculated by the MMI program, of the various conformers of pyrrolidine (Table III) and *N*-methylpiperidine (Table IV) used in the present study (4 pages). Ordering information is given on any current masthead page.

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