Articles

Conformation-Activity Study of 4-Phenylpiperidine Analgesics

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A conformational study of various 4-phenylpiperidine analgesics (the prodines, ketobemidone, meperidine, and 1,3,4-trimethyl-4-phenylpiperidines) has been performed with Allinger's Molecular Mechanics II (MM2) program. Phenyl equatorial conformations were found to be preferred for the prodines, ketobemidone, and meperidine. For ketobemidone and meperidine, however, phenyl axial conformations were computed to be only 0.7 and 0.6 kcal/mol higher in energy. It was suggested that phenyl axial conformers can explain the potency-enhancing effect of a phenyl *m*-hydroxy group in these two compounds. In contrast, phenyl axial conformers were computed to be relatively unfavorable for the prodines, being 1.9, 2.8, and 3.4 kcal/mol higher in energy for 3-demethyl-, α-, and β-prodine, respectively. In addition, relative concentrations of an analgesic conformation can be related to the potencies of the three prodines. A phenyl axial conformer was computed to be preferred by 0.7 kcal/mol for the 3-demethyl compound of 1,3,4-trimethyl-4-phenylpiperidine, with phenyl equatorial conformers preferred by 1.3 and 3.3 kcal/mol for the α and β compounds. Phenyl axial conformers were unexpectedly found to be especially destabilized by a 3-methyl group in the β configuration due to the steric crowding of the three piperidine substituents. Detailed comparisons were made between the computed structures and those observed by X-ray crystallography.

The initial hypothesis regarding analgesic 4-phenylpiperidines was that it might be necessary for the phenyl group to be in an axial position on the piperidine ring, since rigid multicyclic analgesics such as morphine are constrained to that conformation.[1] Over the years, however, nuclear magnetic resonance,[2-4] X-ray crystallography,[5-12] and semiempirical quantum mechanical calculations[13] have shown that compounds related to meperidine and the prodines generally have their phenyl group in an equatorial position, though an equatorial methyl group in the 2 position can stabilize a phenyl axial conformation.[14-17] Moreover, it has been shown that compounds in which the phenyl ring is constrained to be in an equatorial position can be potent analgesics as well.[18-21] Using this and other data relating parallel changes in analgesic activity with changes in N-substituents, Portoghese postulated that there were two distinct classes of opiates that have different modes of interaction when they bind to opiate receptors.[22-24] More recently, it has been shown that both classes of analgesics interact with the same receptor but appear to bind to different portions of it.[25]

It is well known that the potency of multicyclic analgesics, such as morphine, which are constrained to be in a phenyl axial conformation, are generally increased by a phenyl *m*-hydroxy group.[26,27] Conversely, an *N*-allyl or related group generally converts these compounds from agonists to antagonists.[28] This is in sharp contrast to allylprodine in which a phenyl hydroxy group abolishes its potent analgesic activity, and an *N*-allyl group does not lead to antagonism.[25] Similarly, in 1,3,4-trialkyl-4-phenylpiperidines, a phenyl *m*-hydroxy group and a 3-methyl group in the β configuration results in a class of very potent pure opiate antagonists in which an *N*-allyl group decreases antagonist potency.[29]

(1) A. H. Beckett and A. F. Casy, in "Progress in Medicinal Chemistry", Volume 4, G. P. Ellis and G. B. West, Eds., Butterworths, London, 1965, pp 171–218.
(2) A. F. Casy, *Tetrahedron*, **22**, 2711 (1966).
(3) A. F. Casy, *J. Med. Chem.*, 11, 188 (1968).
(4) A. J. Jones, A. F. Casy, and K. M. J. McErlane, *Can. J. Chem.*, **51**, 1782 (1973).
(5) G. Kartha, F. R. Ahmed, and W. H. Barnes, *Acta Crystallogr.*, **13**, 525 (1960).
(6) F. R. Ahmed, W. H. Barnes, and L. D. M. Masironi, *Acta Crystallogr.*, **16**, 237 (1963).
(7) F. R. Ahmed and W. D. Barnes, *Acta Crystallogr.*, **16**, 1249 (1963).
(8) H. van Koningsveld, *Recl. Trav. Chim. Pays-Bas*, **89**, 375 (1970).
(9) W. H. DeCamp and F. R. Ahmed, *Acta Crystallogr., Sect. B*, **28**, 1791 (1972).
(10) K. Hayakawa and M. N. G. James, *Can. J. Chem.*, **51**, 1535 (1973).
(11) P. S. Portoghese, Z. S. D. Gomaa, D. L. Larson, and E. Shefter, *J. Med. Chem.*, **16**, 199 (1973).
(12) P. S. Portoghese and E. Shefter, *J. Med. Chem.*, **19**, 55 (1976).
(13) G. H. Loew and J. R. Jester, *J. Med. Chem.*, 18, 1051 (1975).
(14) A. F. Casy and K. M. J. McErlane, *J. Chem. Soc., Perkin Trans. 1*, 726 (1972).
(15) A. J. Jones, C. P. Beeman, A. F. Casy, and K. M. J. McErlane, *Can. J. Chem.*, **51**, 1790 (1973).
(16) A. F. Casy, J. E. Coates, and C. Rostron, *J. Pharm. Pharmacol.*, **28**, 106 (1976).
(17) W. H. DeCamp and F. R. Ahmed, *Acta Crystallogr., Sect. B*, **28**, 1796 (1972).
(18) E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 1197 (1955).
(19) N. B. Eddy, *Chem. Ind. (London)*, 1462 (1959).
(20) E. E. Smissman and M. Steinman, *J. Med. Chem.*, **9**, 455 (1966).
(21) P. S. Portoghese, A. A. Mikhail, and H. J. Kupferberg, *J. Med. Chem.*, 11, 219 (1968).
(22) P. S. Portoghese, *J. Med. Chem.*, **8**, 609 (1965).
(23) P. S. Portoghese, *J. Pharm. Sci.*, **55**, 865 (1966).
(24) P. S. Portoghese, *Acc. Chem. Res.*, 11, 21 (1978).
(25) P. S. Portoghese, B. D. Alreja, and D. L. Larson, *J. Med. Chem.*, **24**, 782 (1981).
(26) J. Hellerbach, O. Schnider, H. Besendorf, B. Pellmart, N. B. Eddy, and E. L. May, "Synthetic Analgesics", Pergamon Press, Oxford, 1966.
(27) J. Reden, M. F. Reich, K. C. Rice, A. E. Jacobson, A. Brossi, R. A. Streaty, and W. A. Klee, *J. Med. Chem.*, **22**, 256 (1979).
(28) S. Archer and L. S. Harris, *Prog. Drug Res.*, **8**, 261 (1965).
(29) D. M. Zimmerman, R. Nickander, J. S. Horng, and D. T. Wong, *Nature (London)*, **275**, 332 (1978).

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Recently, a detailed molecular explanation has been offered to account for this divergence of structure–activity relationships.[25] It was noted that the enkephalins, which are the endogeneous equivalent to the opiates, contain both tyrosine, which has a phenyl hydroxy group, and phenylalanine, which does not. It was proposed that phenolic opiates, such as morphine, bind to the tyrosine (T) subsite, whereas analgesics, such as allylprodine, in which a phenyl hydroxy group is detrimental, bind to the phenylalanine (P) site.

Another significant feature of the prodines is that the two edges of the piperidine ring are not equivalent, in that a 3-substituent on the *pro*-4*S* side is invariably more potent than the equivalent substitution on the *pro*-4*R* side.[30-35] This has been explained in terms of a receptor preferred orientation of the phenyl and propionoxy groups that is induced by the presence of a 3-substituent.[11,12,30]

This research was undertaken to further clarify the energy differences between phenyl equatorial and phenyl axial conformers in various 4-phenylpiperidines. Presumably, if a phenyl axial conformation is energetically favored for a particular compound, its structure–activity relationships should be more similar to morphine-like compounds. One compound that was examined in great detail is ketobemidone, which is equipotent with morphine even though it contains a phenyl *m*-hydroxy group.[36] Similarly, the analgesic activity of meperidine can be enhanced with this addition.[37] This suggests that phenyl axial conformations may be important for their activity. Other compounds that were examined are 3-demethyl-, α-, and β-prodine. Finally, calculations were performed on 1,3,4-trimethyl-4-phenylpiperidine with and without the 3-methyl group, since it has been found that potent antagonism is only associated with a methyl group in the β configuration (cis 3-methyl, 4-phenyl).[29]

The conformational energy calculations were performed with the recently released MM2 (Molecular Mechanics II) program[38] developed by Allinger and his co-workers. Independent observers have confirmed that the predecessor of this program is capable of computing quantitative thermodynamic values for hydrocarbons for which there is an abundance of data with which to parameterize the method.[39] The parameterization has been extended to encompass the most commonly occuring atomic groupings. This method of computing conformational energies using potential functions offers a distinct speed advantage over even semiempirical quantum mechanical methods.[40,41] Thus, one can minimize the potential energy with respect to all internal coordinates of a molecule,[41] which was not done in the quantum mechanical study of meperidine and the prodines.[13]

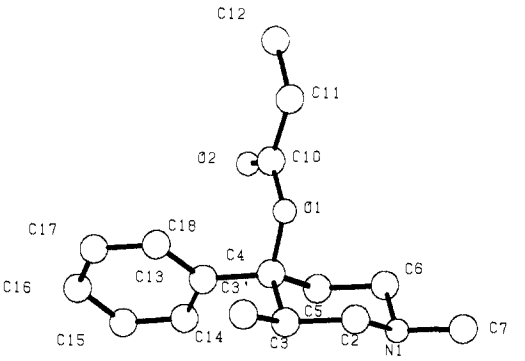

Figure 1. Molecular structure of the more active stereoisomer of α-prodine showing the atom numbering convention used in this work. For meperidine, the C10 and O1 atoms are interchanged. For ketobemidone, the O1 atom is omitted. For the 1,3,4-trimethyl-4-phenylpiperidines, the propionoxy group is replaced by a methyl group denoted C4′.

In this work, we are focusing on the role of conformation in the ability of 4-phenylpiperidines to act as opiate agonists and antagonists. Of course, a number of other factors, such as metabolism or distribution, can be significant as well. In addition, the placement of specific functional groups in a substrate may also play a key role in its ability to bind to a specific receptor site. Conformation would be important in the latter for conformationally flexible opiates, such as the 4-phenylpiperidines.

One aspect of this work that should be discussed is the relevance of these calculations to the analgesic effects of the compounds. Since the opiate receptor environment may very well have an effect on the conformation of a substrate, all low energy conformations should be considered as being potentially significant. However, as the energy of a conformation increases, it becomes increasingly unlikely that it is a requirement for binding to the receptor, since there would be an energy penalty paid for assuming that conformation. This should tend to result in decreased potency for the compound. A somewhat analogous situation arises in comparing our results with those of X-ray crystallography, since there are intermolecular packing forces in the latter that may have a significant conformational effect. It is, therefore, somewhat reassuring that our results in this work and previously[42] are in accord with those of X-ray crystallography in that conformations observed by the latter are generally computed to have relatively low energies (<1 kcal/mol) despite very different molecular environments. This suggests that the intrinsic conformational tendencies of the molecules may be more important than environmental effects, though the latter may cause a particular conformation to be preferred under certain conditions.

Methods

Conformational energy calculations were performed with the recently released MM2 (Molecular Mechanics II) program[38] rather than the MM1 program[43] used previously with methadone and related compounds.[42] This is an improved and reparameterized version of the MM1 program. All calculations were performed with the supplied data set except for one torsional parameter for the prodines that was not available. This was for the carbonyl carbon–ether oxygen–saturated carbon–unsaturated carbon, which is an unusual linkage. Because of a lack of experimental data, this was taken to be the same as for carbonyl carbon–ether ox-

(30) D. L. Larson and P. S. Portoghese, *J. Med. Chem.*, **16**, 195 (1973).
(31) K. H. Bell and P. S. Portoghese, *J. Med. Chem.*, **16**, 203 (1973).
(32) K. H. Bell and P. S. Portoghese, *J. Med. Chem.*, **16**, 589 (1973).
(33) K. H. Bell and P. S. Portoghese, *J. Med. Chem.*, **17**, 129 (1974).
(34) D. S. Fries and P. S. Portoghese, *J. Med. Chem.*, **17**, 990 (1974).
(35) D. S. Fries and P. S. Portoghese, *J. Med. Chem.*, **19**, 1155 (1976).
(36) M. R. Johnson and G. M. Milne, in "Burger's Medicinal Chemistry", Part III, 4th ed., M. E. Wolff, Ed., Wiley, New York, 1981, p 704.
(37) A. H. Beckett and A. F. Casy, in "Progess in Medicinal Chemistry", Volume 2, G. P. Ellis and G. B. West, Eds., Butterworths, London, 1962, p 62.
(38) N. L. Allinger and Y. H. Yuh, *QCPE*, **13**, 395 (1980).
(39) E. M. Engler, J. D. Andose, and P. von R. Schleyer, *J. Am. Chem. Soc.*, **95**, 8005 (1973).
(40) M. Froimowitz and P. J. Gans, *J. Am. Chem. Soc.*, **94**, 8020 (1972).
(41) B. R. Gelin and M. Karplus, *J. Am. Chem. Soc.*, **97**, 6996 (1975).
(42) M. Froimowitz, *J. Med. Chem.*, **25**, 689 (1982).
(43) N. L. Allinger, *QCPE*, **13**, 318 (1976).

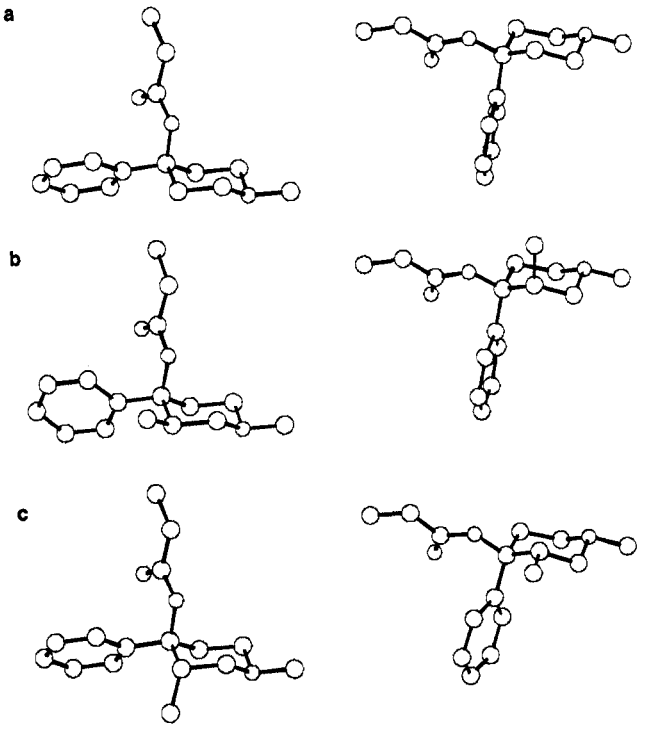

Figure 2. Lowest energy phenyl equatorial and phenyl axial conformers for the prodines. Relative steric energies are (a) 10.5 and 12.4 kcal/mol for 3-demethylprodine, (b) 12.9 and 15.7 kcal/mol for α-prodine, and (c) 13.2 and 16.6 kcal/mol for β-prodine.

ygen–saturated carbon–saturated carbon, which was available in the parameter set. For most torsional parameters, this is usually a reasonable approximation.[44] The force constant and bond length for the C–C bonds in the phenyl ring were set to 8.0667 md/Å and 1.3937 Å as prescribed. The steric energy was minimized with respect to all internal coordinates as the program is set up to do.

In our previous work on methadone-like compounds,[42] an electrostatic potential function was included for some of the calculations to mimic possible hydrogen bonding. This was not done for the present compounds, since the polar groups are well separated in space from each other. A possible hydrogen bond could occur if the piperidine ring were in a boat conformation in which the amine nitrogen approachs a carbonyl oxygen. However, in ketobemidone, boat conformations were found to be so unfavorable as to make this unlikely.

The atomic numbering system is the same as that used in the crystal structures of prodine-like compounds[11,12] in order to facilitate comparison with them. This is illustrated in Figure 1 with α-prodine. In meperidine, the C10 and O1 atoms are interchanged, while in ketobemidone the O1 atom is omitted. In the 1,3,4-trimethyl-4-phenylpiperidines, the propionoxy group is replaced by a methyl group denoted by C4′.

The piperidine ring was placed in a chair conformation with the *N*-methyl group in an equatorial position for all calculations, except where noted. For all compounds with a 3-methyl substitution, it was put on the *pro*-4*S* edge of the piperidine ring, since it has been shown that this invariably leads to more potent compounds.[30-35] Both phenyl equatorial and phenyl axial conformations were examined. For the prodines, the τ(C12–C11–C10–O1), τ(C10–O1–C4–C5), and τ(C14–C13–C4–O1) dihedral angles were varied as well. The first two were systematically varied with gauche and trans initial starting conformations. τ(C14–C13–C4–O1) was initially set to 90 and 180° for those compounds in which there proved to be two possible conformations of the phenyl ring. τ(C11–C10–O1–C4) was set to 180° for all calculations, since there is a strong preference for that value with hindered rotation about the C10–O1 bond.[45] The same procedure

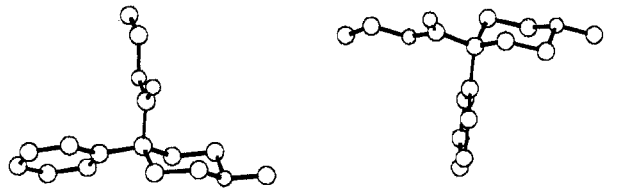

Figure 3. Lowest energy phenyl equatorial and phenyl axial conformers for meperidine. Relative steric energies are 13.3 and 13.9 kcal/mol.

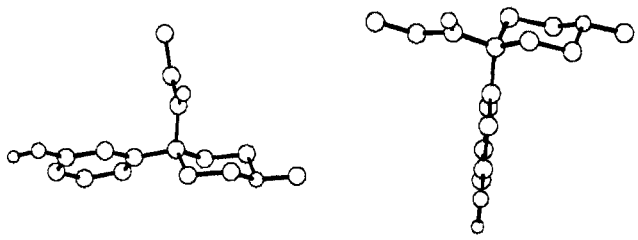

Figure 4. Lowest energy phenyl equatorial and phenyl axial conformers for ketobemidone. Relative steric energies are 11.9 and 12.6 kcal/mol.

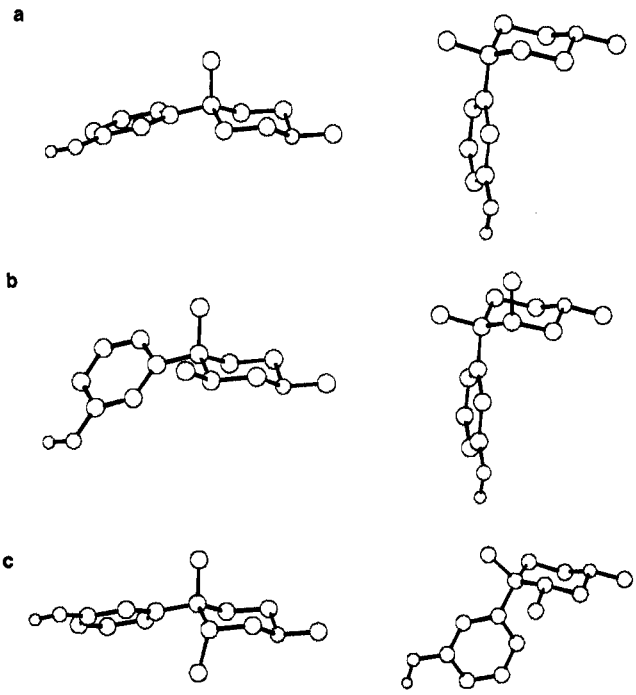

Figure 5. Lowest energy phenyl equatorial and phenyl axial conformers for 1,3,4-trimethyl-4-phenylpiperidines. Relative steric energies are (a) 12.4 and 11.7 kcal/mol for 3-demethyl compound, (b) 14.9 and 16.2 kcal/mol for α compound, and (c) 15.1 and 18.4 kcal/mol for β compound.

was followed for meperidine and ketobemidone, except that boat conformations of the piperidine ring were examined for the latter as well. In ketobemidone and the 1,3,4-trimethyl-4-phenylpiperidines, all calculations were performed with a phenyl *m*-hydroxy group, which does not have a significant conformational effect.

The following convention has been used for dihedral angles: τ(A–B–C–D) is the angle between the planes A–B–C and B–C–D, with the eclipsed form being defined as 0°. Looking along A–B–C–D, a clockwise rotation of the plane B–C–D is considered positive.

All computations were performed on a Perkin-Elmer 3220 superminicomputer. The figures were initially prepared on a TEKTRONIX 4010 graphics terminal using the PLUTO program

(44) N. L. Allinger, personal communication.

(45) N. L. Allinger and S. H. M. Chang, *Tetrahedron*, **33**, 1561 (1977).

Table I. Energy-Minimized Dihedral Angles and Intramolecular Geometrical Parameters of Lowest Energy Phenyl Equatorial and Phenyl Axial Conformations for the Prodines[a]

	3-demethylprodine		α-prodine			β-prodine			
	Ph equat	Ph axial	Ph equat	Ph axial	HCl[b]	Ph equat	Ph axial	HCl[c]	HBr[d]
τ(C12-C11-C10-O1)	179	-179	-177	-178	171	-179	-178	-80	-175
τ(C11-C10-O1-C4)	179	177	180	177	-178	179	177	176	178
τ(C10-O1-C4-C5)	78	77	71	77	60	77	74	63	64
τ(C10-O1-C4-C3)	-168	-170	-174	-168	176	-167	-173	179	180
τ(O1-C4-C5-C6)	61	166	59	166	57	61	160	55	53
τ(C4-C5-C6-N1)	58	-56	59	-53	60	57	-50	58	58
τ(C5-C6-N1-C2)	-58	56	-57	55	-61	-57	55	-58	-56
τ(C5-C6-N1-C7)	179	179	179	179	176	179	178	180	180
τ(C6-N1-C2-C3)	57	-59	57	-60	59	58	-61	58	56
τ(N1-C2-C3-C4)	-57	62	-57	60	-55	-57	62	-56	-55
τ(C3'-C3-C4-C13)			-58	-161	-60	51	-52	55	56
τ(C10-O1-C4-C13)	-49	-50	-54	-49	-65	-48	-51	-63	-63
τ(O1-C4-C13-C14)	127	115	151	118	152	128	133	138	147
N1-Ph center, Å	5.7	4.9	5.8	4.9	5.7	5.8	5.1	5.7	5.7
N1-Ph plane, Å	1.3	2.6	0.8	2.5	0.8	1.2	2.0	1.0	0.9
steric energy, kcal/mol	10.5	12.4	12.9	15.7		13.2	16.6		

[a] The dihedral angles that are found by X-ray crystallography are included for comparison. The crytallographic results were recomputed from the fractional coordinates given in the cited references and are for the more active enantiomer only. [b] Reference 5. [c] Reference 6. [d] Reference 7.

Table II. Energy-Minimized Dihedral Angles and Intramolecular Geometrical Parameters of Lowest Energy Phenyl Equatorial and Phenyl Axial Conformations for Meperidine

	Ph equat	Ph axial
τ(C12-C11-O1-C10)	179	-177
τ(C11-O1-C10-C4)	178	177
τ(Q1-C10-C4-C5)	56	68
τ(Q1-C10-C4-C3)	173	-178
τ(C10-C4-C5-C6)	65	172
τ(C4-C5-C6-N1)	61	-57
τ(C5-C6-N1-C2)	-59	56
τ(C5-C6-N1-C7)	178	179
τ(C6-N1-C2-C3)	56	-58
τ(N1-C2-C3-C4)	-55	62
τ(O1-C10-C4-C13)	-68	-57
τ(C10-C4-C13-C14)	125	107
N1-Ph center, Å	5.8	4.8
N1-Ph plane, Å	1.3	2.7
steric energy, kcal/mol	13.3	13.9

with the plotting commands in the TEKTRONIX PLOT10 package. Pen and paper plots of the figures were then made on a Nicolet ZETA 1553 plotter, which has software that converts PLOT10 output to ZETA output.

Results

The dihedral angles that describe the lowest energy phenyl equatorial and phenyl axial conformations are listed in Table I for the prodines, Table II for meperidine, Table III for ketobemidone, and Table IV for the 1,3,4-trimethyl-4-phenylpiperidines. These are also illustrated in Figures 2–5. It should be noted that all compounds without a 3-methyl substitution actually have two conformations with identical energies due to the symmetry of the piperidine ring. However, only the one that is favored by the 3-substituent on the *pro*-4*S* edge of the piperidine ring is actually listed in the tables.

Prodines. In all of these compounds, the phenyl equatorial conformation is found to have a significantly lower energy than the phenyl axial one. The energy difference was 1.9 kcal/mol for the 3-demethyl compound, 2.8 kcal/mol for α-prodine, and 3.4 kcal/mol for β-prodine (Table I). Trans values of τ(C12–C11–C10–O1) were found to be preferred, but gauche values were only 0.3–0.5 kcal/mol higher in energy.

Table III. Energy-Minimized Dihedral Angles and Intramolecular Geometrical Parameters of Lowest Energy Phenyl Equatorial and Phenyl Axial Conformations for Ketobemidone

	Ph equat	Ph axial
τ(C12-C11-C10-C4)	168	174
τ(C11-C10-C4-C5)	57	64
τ(C11-C10-C4-C3)	174	177
τ(C10-C4-C5-C6)	65	173
τ(C4-C5-C6-N1)	61	-57
τ(C5-C6-N1-C2)	-59	56
τ(C5-C6-N1-C7)	178	179
τ(C6-N1-C2-C3)	56	-58
τ(N1-C2-C3-C4)	-55	62
τ(C11-C10-C4-C13)	-67	-61
τ(C10-C4-C13-C14)	123	105
N1-Ph center, Å	5.7	4.8
N1-Ph plane, Å	1.4	2.8
steric energy, kcal/mol	11.9	12.6

Meperidine. Two possible orientations of the phenyl ring were found for the phenyl equatorial conformation with τ(C14–C13–C4–C10) = 120 and 176°. The energy of the latter was computed to be 1.1 kcal/mol higher than the former. The phenyl equatorial conformation was 0.6 kcal/mol more stable than the phenyl axial one (Table II). As with the prodines, trans values of τ(C12–C11–O1–C10) were preferred, but gauche values were only slightly higher in energy (0.0–0.1 kcal/mol).

Ketobemidone. The phenyl equatorial conformation was computed to be 0.7 kcal/mol more stable than the phenyl axial one (Table III). The energies of conformations with the piperidine ring in a boat conformation were also computed. However, they were found to have steric energies of 5.7 kcal/mol or higher than the phenyl equatorial–chair conformation and, therefore, do not seem significant. Trans values of τ(C12–C11–C10–C4) were preferred by 1.5 kcal/mol or more.

1,3,4-Trimethyl-4-phenylpiperidines. The lowest energy conformation of the phenyl ring was found to be more variable with these compounds. For the 3-demethyl compound, τ(C4′–C4–C13–C14) ≃ 90° was preferred over ~180° for both the phenyl equatorial and phenyl axial conformations. However, for the α compound, the latter orientation of the phenyl ring was favored by 0.4 kcal/mol for the phenyl equatorial conformation but could not be

Table IV. Energy-Minimized Dihedral Angles and Intramolecular Geometrical Parameters of Lowest Energy Phenyl Equatorial and Phenyl Axial Conformations for 1,3,4-Trimethyl-4-phenylpiperidines

	1,3,4-trimethyl-4-phenylpiperidine					
	3-demethyl-		α-		β-	
	Ph equat	Ph axial	Ph equat	Ph axial	Ph equat	Ph axial
τ(C4'-C4-C5-C6)	72	176	68	173	70	155
τ(C4'-C4-C5-C2)	-72	-176	-67	-172	-69	-152
τ(C4-C5-C6-N1)	56	-60	56	-55	55	-51
τ(C5-C6-N1-C2)	-58	56	-57	56	-57	59
τ(C5-C6-N1-C7)	178	180	179	179	180	-178
τ(C6-N1-C2-C3)	58	-56	58	-60	58	-59
τ(N1-C2-C3-C4)	-56	60	-56	60	-56	50
τ(C4'-C4-C13-C14)	90	89	180	109	111	178
N1-Ph center, Å	5.7	4.7	5.7	4.9	5.8	5.2
N1-Ph plane, Å	1.6	2.9	0.1	2.6	1.4	0.0
steric energy, kcal/mol	12.4	11.7	14.9	16.2	15.1	18.4

found for the phenyl axial one. For the β compound, the latter could not be found for the phenyl equatorial conformation, but it is favored by 0.7 kcal/mol for the phenyl axial one. For the 3-demethyl compound, the phenyl axial conformation is actually found to be preferred by 0.7 kcal/mol over the phenyl equatorial one (Table IV). However, for the α and β compounds, the phenyl equatorial conformations are 1.3 and 3.4 kcal/mol lower in energy.

Discussion

The equilibrium distribution of phenyl equatorial and phenyl axial conformations is found to be quite variable, depending on the specific 4-phenylpiperidine and the absence or presence of a substituent in the 3-position. For ketobemidone and meperidine, the energy difference between the two conformers is relatively small (0.7 and 0.6 kcal/mol) and there should still be a sizable population of phenyl axial conformers present. With an energy difference of 0.6 kcal/mol, the concentration of the phenyl axial conformer would be 37% of the phenyl equatorial conformer at 298 K when the Boltzmann factor is used, if one assumes no significant entropic or solvation differences between the two. For the prodines, however, the equilibrium distribution should be strongly shifted to the phenyl equatorial conformer, since the smallest energy difference that was found was 1.9 kcal/mol for the 3-demethyl compound, while it was even greater (2.8 and 3.4 kcal/mol, respectively) for the α and β compounds. For the 3-demethyl derivative of the 1,3,4-trimethyl-4-phenylpiperidines, the phenyl axial conformer was actually found to be preferred by 0.7 kcal/mol, although this situation is reversed for the α and β compounds.

The above results would appear to account for the behavior of ketobemidone, which is a potent analgesic even though it contains a phenyl *m*-hydroxy group. Similarly, this substitution has been found to increase the potency of meperidine. Our results suggest that this could be due to their binding to the opiate receptor in a phenyl axial conformation, which would make their structure–activity relationships more similar to that of morphine than to the prodines. This would then be in line with the different modes of interaction hypothesis of Portoghese. It should be noted, however, that both ketobemidone and meperidine are still different from morphine-type analgesics, since *N*-allyl groups do not convert them to antagonists.[22,46] This may be due to the preponderance of phenyl equatorial conformers present. The smaller difference between the two conformers for these two compounds relative to the prodines appears to be related to having a carbonyl group adjacent to the piperidine ring rather than an ether group.

The issue of whether a phenyl axial conformation is required for compounds with a phenyl hydroxy group is further confused, however, by the analgesic potency of the phenylmorphans.[47] These compounds contain a phenyl hydroxy group and yet appear to be constrained to a phenyl equatorial conformation. The major difference between the prodines and phenylmorphan may be the presence and orientation of the propionoxy group in the former, which may have a complementary binding site in the receptor.

Ketobemidone appears to have an intrinsic affinity for the opiate receptor that is several orders of magnitude greater than that of meperidine[48,49] despite structural and energetic similarities (Figures 3 and 4). The affinity of meperidine for the opiate receptor is one of the weakest for a known analgesic,[50] and its potency is apparently bolstered by its enhanced ability to penetrate the brain.[51] Ketobemidone, of course, does contain a phenyl *m*-hydroxy group that generally enhances activity and, probably, binding to the receptor as well. While a similar substitution for meperidine only increases its in vivo potency by 50%,[37] this might be due to a combination of decreased brain penetration and increased affinity for the receptor. Another factor that may have some significance is the relative rigidity of the ethyl ketone group in ketobemidone relative to the carbethoxy group in meperidine, since gauche values of the latter are only 0.0–0.1 kcal/mol higher in energy. It is possible that this increased conformational flexibility may entropically interfere with binding to the receptor if such binding requires a specific conformation of the carbethoxy group.[52]

The effect on conformation of a methyl group in the 3-position of the 4-phenylpiperidines in somewhat surprising. It was found for both the prodines and the 1,3,4-trimethyl-4-phenylpiperidines that the energy difference between the phenyl equatorial and phenyl axial

(46) T. Oh-ishi and E. L. May, *J. Med. Chem.*, **16**, 1376 (1973).
(47) H. H. Ong, T. Oh-ishi, and E. L. May, *J. Med. Chem.*, **17**, 133 (1974).
(48) R. S. Wilson, M. E. Rogers, C. B. Pert, and S. H. Snyder, *J. Med. Chem.*, **18**, 240 (1975).
(49) C. B. Pert, S. H. Snyder, and P. S. Portoghese, *J. Med. Chem.*, **19**, 1248 (1976).
(50) C. B. Pert and S. H. Snyder, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 2243 (1973).
(51) E. Kutter, A. Hertz, H. Teschemacher, and R. Hess, *J. Med. Chem.*, **13**, 801 (1970).
(52) P. A. Kollman, in "The Basis of Medicinal Chemistry", Part I, 4th ed., M. E. Wolff, Ed., Wiley, New York, 1980, p 313.

conformations was the smallest for the 3-demethyl compound and greatest for the β compound. In the past, it has been assumed that the energy difference should be *smallest* for the β compound, since the 3-substituent would be put into a generally favored equatorial position in a phenyl axial conformation.[23] The reason for the computed result appears to be steric crowding. In the phenyl equatorial conformation of a β compound, the substituents in the 3- and 4-positions will be in axial conformations but on opposite sides of the piperidine ring (Figure 2c). In the phenyl axial conformation, however, the 3-substituent is placed between the 4-substituent and the phenyl ring. The resultant crowding appears to outweigh the expected advantage of having two substituents in a favorable equatorial position.

It should be noted that qualitatively similar results were obtained in the PCILO quantum mechanical calculations for meperidine and the prodines. The energy differences between phenyl equatorial and phenyl axial conformers were found to increase in the order meperidine, 3-demethylprodine, α-prodine, and β-prodine.[13] However, the energy differences were computed to be 3–9 times greater than here. The apparent reason for this is that there was not full minimization of the energy with respect to all internal coordinates in that study. Since the geometries that were chosen for the calculations were from phenyl equatorial crystal structures,[13] this would appear to have favored those conformations in a greatly exaggerated manner. It should be noted that the energy differences computed here appear to be more in line with experimental values.[53]

The results for the prodines are consistent with the idea that a 3-substituent induces a receptor preferred orientation of the phenyl and propionoxy groups. Indeed, it appears to be possible to relate potency differences between 3-demethyl-, α-, and β-prodine to conformational factors. As was noted above, with the absence of a 3-substituent, there are actually two distinct conformers with identical energies due to the symmetry of the piperidine ring. In addition to the phenyl equatorial conformer listed in Table I for 3-demethylprodine, the second one is characterized by having τ(C10–O1–C4–C5) = 168°, τ(C10–O1–C4–C3) = −77°, and τ(C14–C13–C4–O1) = 53°. If only the first conformer can bind to the receptor, the effective concentration of the analgesically active conformer will only be 50% of the actual concentration of 3-demethylprodine. With the introduction of a 3-substituent, the symmetry of the piperidine ring is disrupted and the two conformers no longer have identical energies. For α-prodine, the energy difference is computed to be 0.5 kcal/mol. If the Boltzmann factor is used and one assumes no significant entropic or solvation effects, 70.0% of the α-prodine molecules will have the correct conformation at 298 K. For β-prodine, the energy difference rises sharply to 3.7 kcal/mol, so that virtually all of the molecules are now in the correct conformation. Thus, the effective concentration of the receptor-preferred conformer accounts for the potency differences of these three compounds (Table V). Previously, it had been found that metabolism or distribution could not fully account for the potency differences.[54]

The computed results for the prodines also suggest that the relative inactivity of the α-compound with the opposite stereochemistry is due to the substituent on the *pro*-4*R* edge blocking access to the receptor site. Since the less

Table V. Correlation of the Relative Potencies of 3-Demethylprodine, α-Prodine, and β-Prodine with the Relative Concentration of Their Analgesic Conformation[a]

	ED_{50}, mg/kg	rel potency[b] after brain penetration	energy difference, kcal/mol	rel concn of analgesic conformation
3-demethylprodine	1.00	1.00	0.0	1.00
(3*R*,4*S*)-α-prodine	1.45	1.24	0.5	1.40
(3*S*,4*S*)-β-prodine	5.21	1.77	3.7	2.00

[a] Differences in brain penetration have been adjusted for. Energy differences are between the two conformers that have identical energies when the piperidine ring does not contain a substituent in the 3-position. The analgesic conformation is assumed to be the one that is favored by a substitution on the *pro*-4*S* edge of the piperidine ring. See text. [b] Reference 54.

active stereoisomer of α-prodine should contain an effective concentration of 30% of the correct conformer, its very high ED_{50} (22.4 mg/kg)[30] can only be due to a steric effect at the receptor. Similarly, the high potency of a 3-allyl group with the α configuration appears to be the result of a receptor-related events as has been suggested.[31]

It was noted above that the 1,3,4-trimethyl-4-phenylpiperidine compounds are potent opiate antagonists when they contain a 3-methyl group with the β configuration, while the same substitution with the α configuration only results in very weak antagonism. It is clear from Table IV that both the α and β compounds should prefer a phenyl equatorial conformation, particularly the latter. However, one conformational difference between the two diastereomers is the preferred orientation of the phenyl ring. For the α compound, the two low-energy phenyl equatorial conformers have τ(C4′–C4–C13–C14) = 180° (Figure 5b) and 50° (not show), with the latter being 0.4 kcal/mol higher in energy. For the β compound, the equivalent dihedral angle is 111°. The latter conformation of the phenyl ring is much more similar to that found in a semirigid compound like morphine[55] and may, therefore, account for the significant differences in antagonist potency. The 3-demethyl compound has very different conformational properties in that it prefers a phenyl axial conformation by 0.7 kcal/mol.

Some intramolecular geometrical parameters were computed for the various equilibrium structures, and these are also listed in Tables I–IV. For the prodines, meperidine, and ketobemidone, conformations in which the phenyl ring is equatorial are characterized by having nitrogen–phenyl center distances of 5.7–5.8 Å with nitrogen–phenyl plane distances of 0.8–1.4 Å. The equivalent distances for phenyl axial conformers are 4.8–5.1 and 2.0–2.8 Å. In a recent review of the crystal structures of opiates, the equivalent distances were found to be 4.0–4.6 and 0.7–1.7 Å for compounds that are constrained to be in a phenyl axial conformation.[56] As can be clearly seen, the intramolecular geometrical parameters of flexible phenyl axial conformers vary somewhat from those constrained to that conformation by multicyclic ring systems. This suggests that small differences in geometry should not be interpreted as necessarily being significant, since flexibility due to bond

(53) E. L. Eliel, in "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, 1962, p 236.
(54) M. M. Abdel-Monem, D. L. Larson, H. J. Kupferberg, and P. S. Portoghese, *J. Med. Chem.*, 15, 494 (1972).
(55) G. Hite, personal communication.
(56) A. Horn and J. R. Rodgers, *J. Pharm. Pharmacol.*, 29, 257 (1977).

stretching and bending are possible in the substrate and receptor as well. Lumping all phenyl axial conformers together, the geometry would then be characterized as having a nitrogen–phenyl center distance of 4.3–5.1 Å and a nitrogen–phenyl plane distance of 0.7–2.8 Å.

The 1,3,4-trimethyl-4-phenylpiperidines are somewhat different from the above compounds in that the phenyl ring was occasionally found to prefer a distinctly different conformation with τ(C4′–C4–C13–C14) $\simeq$ 180°. This did not significantly affect the nitrogen–phenyl center distance but does have an appreciable effect on the nitrogen–phenyl plane distance (~0.0 Å).

The results of X-ray crystallographic studies of α- and β-prodine have been included in Table I to facilitate a detailed comparison between the computed and observed geometries. The crystal structure of meperidine was not included, since it appears to be very approximate with a rather high disagreement factor.[8] The observed structures of α- and β-prodine in the crystal state are in reasonably good agreement with the computed geometries. The HCl salt of β-prodine was found to have a gauche value of 80° for τ(C12–C11–C10–O1). Our results indicate that this conformation would only be 0.5 kcal/mol above the global minimum. Another feature in which there is some variability is in the dihedral angle, which describes the tilt of the phenyl ring. There is very good agreement for α-prodine with a computed value of τ(O1–C4–C13–C14) = 151° as opposed to 152°. For β-prodine, there is more of a discrepancy with computed values of 128 and 127° as opposed to 138 and 147°.

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Effects of Conformationally Restricted 4-Piperazinyl-10*H*-thienobenzodiazepine Neuroleptics on Central Dopaminergic and Cholinergic Systems[1]

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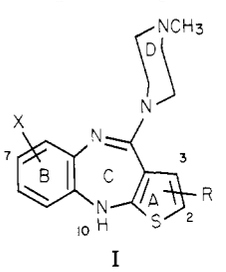
The levels of antidopaminergic and anticholinergic activities of neuroleptics, 4-piperazinyl-10*H*-thienobenzodiazepines, are modulated by imposing steric impedence to the piperazine ring. The optimum situation in favor of the anticholinergic action is reached in compound **5**, 2,3-dimethyl-7-fluoro-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine, where a maximum activity (equivalent to hyoscine), as measured by the [^{3}H]QNB receptor binding assay, is obtained. The structure–activity relationships found highlight the importance of certain spatial dispositions of the distal piperazine nitrogen (electron lone pair) with respect to the tricyclic system. The evidence for molecular topography of these compounds is presented from X-ray, NMR, and other physical data. The conformational aspects for correspondence to the relevant receptors are discussed.

The antipsychotic activity, as well as the extrapyramidal side effects (EPS), of neuroleptic drugs is correlated with their ability to block central dopaminergic transmission. Most of the biochemical and pharmacological tests have been designed to recognize agents that produce such antidopaminergic effects. For example, neuroleptics typically increase dopamine (DA) turnover, compete with DA receptor ligands for membrane binding sites, induce catalepsy, and block a conditioned avoidance response (CAR) in trained animals. In the striatum, the dopaminergic neurons from the substantia nigra form inhibitory synapses with cholinergic interneurons. Thus, a reduction in the dopaminergic input to these neurons results in an increased release of acetylcholine.[2] This leads, in turn, to catalepsy in animals and extrapyramidal symptoms (drug-induced Parkinsonism) in man.[3] Support for this view is derived from the fact that centrally acting anticholinergic agents alleviate these symptoms without interfering with the antipsychotic actions of the neuroleptics. In fact, neuroleptics, which possess anticholinergic properties (clozapine, thioridazine), produce a reduced incidence of EPS in the clinic.[4] Several lines of evidence[5] indicate that neuroleptics produce their antipsychotic action by blocking DA receptors in the mesolimbic area of the brain. Neuroleptics differ widely in their ability to block central cholinergic muscarinic receptors. Thus, in order to achieve a maximum reduction in side effects, it is important to obtain a correct balance of the antidopaminergic and anticholinergic activities.

Recently, we have reported[6] a series of thienobenzodiazepines (I) possessing neuroleptic activity, as demonstrated by their ability to inhibit a CAR and to produce



I

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[‡] Lilly Research Laboratories.

(1) Part 5 of the series Heteroarenobenzodiazepines. For Part 4, see J. K. Chakrabarti, J. F. Fairhurst, N. J. A. Gutteridge, L. Horsman, I. A. Pullar, C. W. Smith, D. J. Steggles, D. E. Tupper, and F. C. Wright, *J. Med. Chem.*, **23**, 884 (1980).
(2) P. L. McGeer, E. C. McGeer, and T. Hattori, *Biochem. Psychopharmacol.*, **16**, 397 (1977).
(3) O. Hornykiewicz, *Handb. Neurochem.*, **7**, 464 (1972).
(4) D. DeMaio, *Arzneim.-Forsch.*, **22**, 919 (1972).
(5) N.E. Andén and G. Stock, *J. Pharm. Pharmacol.*, **25**, 346 (1973); G. Bartholini, *ibid.*, **28**, 429 (1976); B. Costall and R. J. Naylor, *Eur. J. Pharmacol.*, **40**, 9 (1976).
(6) J. K. Chakrabarti, L. Horsman, T. M. Hotten, I. A. Pullar, D. E. Tupper, and F. C. Wright, *J. Med. Chem.*, **23**, 878 (1980).

0022-2623/82/1825-1133$01.25/0