Synthesis, Configuration, and Activity of Isomeric 2-Phenyl-2-(*N*-piperidinyl)bicyclo[3.1.0]hexanes at Phencyclidine and σ Binding Sites

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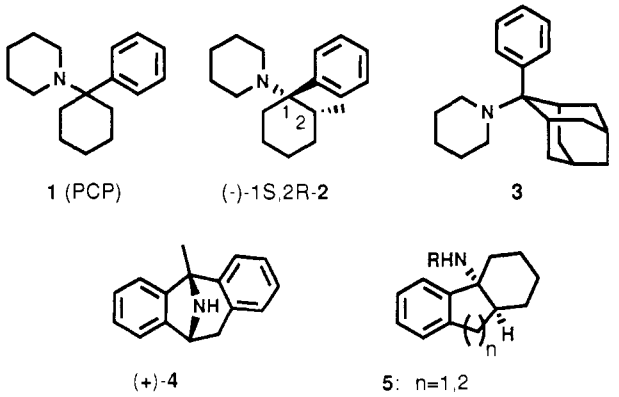
Received August 10, 1992

The novel semirigid derivatives (+)-*cis*-1-[2-phenyl-2-bicyclo[3.1.0]hexyl]piperidine [(+)-8], its enantiomer (-)-8, and (±)-*trans*-1-[2-phenyl-2-bicyclo[3.1.0]hexyl]piperidine [(±)-9] were synthesized as probes to investigate the mode of interaction of phencyclidine (PCP) with its binding site on the *N*-methyl-D-aspartate receptor complex. Each target compound was obtained in five steps starting from cyclopent-2-enone. (+)- and (-)-8 were obtained in greater than 98% optical purity through three recrystallizations from ethanol of the (*S*)-(+)- and (*R*)-(-)-mandelate salts of intermediate (±)-*cis*-2-phenyl-2-bicyclo[3.1.0]hexylamine ([(±)-16]. Crystallization of the (*R*)-(-)-mandelate salt afforded (1*R*,2*R*,5*S*)-(-)-16, whereas the (*S*)-(+)-mandelate salt afforded (1*S*,2*S*,5*R*)-(+)-16; the absolute configuration was determined by single-crystal X-ray analysis of (-)-16·(*R*)-(-)-mandelate. Single-crystal X-ray analysis of (±)-9-picrate confirmed its trans configuration and provided conformational data. (+)- and (-)-8 and (±)-9 were examined for their ability to interact with PCP and σ binding sites in vitro using [^{3}H]TCP and [^{3}H]pentazocine as radioligands. The binding was compared with that of PCP and contrasted with the rigid symmetrical phencyclidine derivatives *cis*- and *trans*-1-[3-phenyl-3-bicyclo[3.1.0]hexyl]piperidines (6 and 7). The results of the study indicated that the conformations of PCP represented by 6-9 are not optimal for potent interaction at either of these sites. Affinities ranged from 582 nM [(±)-9] to 29 000 nM [(+)-8] at PCP binding sites and from 1130 nM [(-)-8] to 16 300 nM (7) at σ sites. In this assay, PCP exhibited affinities of 64.5 nM at PCP and 1090 nM at σ sites. Qualitative correlation between the σ and PCP binding data suggests some similarities between these binding sites. An axial phenyl and equatorial piperidine ring with the nitrogen lone pair of electrons antiperiplanar to the phenyl ring has been postulated as the receptor-active conformation of PCP-like ligands at the PCP binding site. Comparison of the binding data of 7-9 with that of the previously described methylcyclohexyl-PCP derivatives allowed its rationalization in terms of this model. It is likely that the lowered affinity in this bicyclo[3.1.0]hexane series is a consequence of nonoptimal geometry (pseudoequatorial phenyl or pseudoboat) for binding as opposed to the presence of steric bulk which proved deleterious in the methylcyclohexyl-PCP derivatives.

Introduction

The drug of abuse phencyclidine (PCP, 1, Chart I) has elicited considerable interest during the past decade[1] because of its wide spectrum of activity ranging from the precipitation of bizarre psychomimetic effects in humans to anticonvulsant/neuroprotective activity in rodents.[2,3] PCP binds with high affinity to the PCP binding site associated with the *N*-methyl-D-aspartate (NMDA)/calcium channel complex and thereby noncompetitively inhibits the potential excitotoxic actions of glutamate.[4] Several classes of compounds including the dioxolane

Chart I



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0022-2623/92/1835-4704$03.00/0

anesthetics,[5] 2-methyl-1,1-diphenyl-3-amino-1-propanol (2-MDP),[6] MK-801,[3,7] 1,2-diphenylethylamines,[7e] 1,2,3,4-tetrahydroisoquinolines,[8] and certain (+)-opiates[9] (e.g. SKF 10,047) bind with high affinity to the PCP site.

Extensive structure–activity studies with PCP and its derivatives revealed that its binding properties are highly dependent on the conformation and substitution of the cyclohexyl moiety.[10] This problem has since been addressed through the synthesis of derivatives of PCP that favor certain conformations of the cyclohexyl ring.[11-13] Of the 10 isomeric methylcyclohexyl derivatives of PCP,[13] for example, the (1*S*,2*R*)-*trans*-2-methyl PCP isomer (−)-**2**[12] (Chart I) was found to be 5-fold more potent in vitro than PCP while all of the remaining methyl isomers were significantly less active.[12,13] It is likely that the preferred conformation of (−)-**2** is close to that required for strong interaction at the PCP binding site.[13]

The isomeric 4-*tert*-butylcyclohexyl derivatives of PCP possess either axial or equatorial conformations of the phenyl substituents.[10] The *cis*-4-*tert*-butyl isomer containing the preferred axial phenyl geometry, exhibited only weak PCP binding due to steric interference by the large *tert*-butyl substituent.[14] The trans isomer also displayed low affinity for the PCP binding site since it adopts an equatorial phenyl conformation which is not recognized by this site.[14] Rigid adamantyl derivative **3** of PCP, in which the phenyl ring simultaneously occupies axial and equatorial positions, was found to have no significant affinity for the PCP site but instead proved to be a potent muscarinic agent.[15] However, other structurally rigid 1-phenylcyclohexylamines such as (+)-MK-801 [(+)-**4**][3,7] and the tricyclic derivatives, **5**,[16,17] (Chart I) were found to be potent ligands for the PCP site and consequently potent non-competitive NMDA antagonists.

Unlike MK-801, PCP binds with moderate affinity to other CNS binding sites which include dopaminergic,[18] cholinergic,[15] and σ.[19] The functional role of the σ-binding site is poorly understood. σ sites are saturable, enantioselective binding sites that are distinct from opiate, dopaminergic, and PCP sites (see ref 20 for a review). σ-Binding sites have been the subject of intense interest in recent years because of their potential to offer new insights into the mechanisms of psychoses,[21] movement disorders,[22] and neurodegeneration[23] with which they have been implicated. Extensive structure–activity studies have led to the identification of several classes of ligands for the σ site.[20]

We recently reported the PCP and σ binding affinity of the bridged bicyclic PCP derivatives **6** and **7** (Chart II).[24] The rationale for these compounds was their "pseudoboat" conformations which we believed might favor interaction at the PCP site. Furthermore, unlike many studies involving conformational restriction of PCP, no new steric

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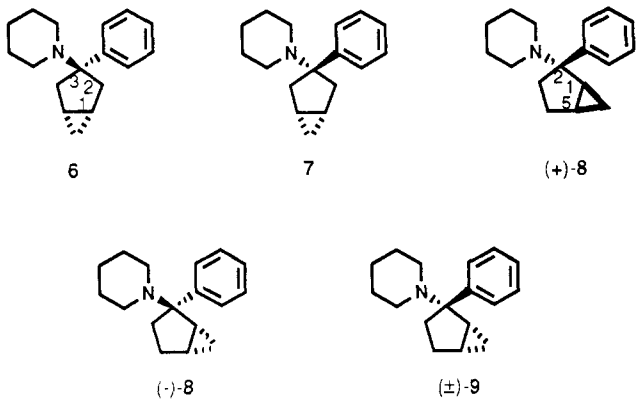
Chart II



bulk was added. However, **6** and **7** were found to bind with 7-fold lowered affinity compared with PCP to sites labeled by [^{3}H]TCP (rat brain) and 5–6-fold lowered affinity for σ sites ([^{3}H]SKF10,047, rat brain).[24] Surprisingly, when tested for ataxia in rats, they proved to be about equiactive to PCP. The results of the binding study suggest that **6** and **7** do not represent bound conformations of PCP at either the PCP or σ site. X-ray crystallographic analysis of **6** indicated the phenyl ring to be in an axial conformation which is preferred for strong interaction at the PCP binding site;[13] the lowered affinity of this compound is most likely due to steric hindrance from the cyclopropyl ring.

Since **6** and **7** only allow partial characterization of the bicyclo[3.1.0]hexane ring system at PCP and σ binding sites, we wished to synthesize and evaluate the remaining isomers [*cis*- and *trans*-2-phenyl-2-(*N*-piperidinyl)bicyclo-[3.1.0]hexanes] [(±)-**8** and (±)-**9** (Chart II] in order to complete the characterization of this ring system at these sites. We therefore report here the synthesis, absolute configuration and in vitro PCP and σ binding of enantiomeric *cis*-2-phenyl-2-(*N*-piperidinyl)bicyclo[3.1.0]hexanes [(+)- and (−)-**8**] and the trans isomer (±)-**9** using [^{3}H]-TCP[25] and the highly selective σ probe, [^{3}H](+)-pentazocine[26] in rat and guinea pig brain homogenates. Compounds **6**, **7**, and PCP were reevaluated under the same conditions to allow for internal comparison of the binding data. Additionally, we used computer-assisted molecular modeling (CAMM) to investigate the effect of ring restriction on the overall conformational preferences of these molecules. In this class of compounds, "cis" refers to a cis configuration between the phenyl and cyclopropyl moieties and "trans" refers to a trans relationship of these groups in accordance with established PCP nomenclature.[1,12]

Chemistry

cis- and *trans*-2-phenyl-2-(*N*-piperidinyl)bicyclo[3.1.0]-hexanes (**6** and **7**) were synthesized as described previously.[24] Isomers (+)- and (−)-**8** and (±)-**9** were obtained starting with commercially available (Aldrich) cyclopent-2-enone (**10**) (Scheme I). Thus, treatment of **10** with dimethylsulfoxonium methylide in DMSO[27] afforded bicyclo[3.1.0]penten-2-one [(±)-**11**] in 34% redistilled yield. Grignard reaction between (±)-**11** and PhMgBr gave a single alcohol (±)-**12** of undefined configuration in quantitative yield. Solvolysis of (±)-**12** with NaN_3/CF_3COOH[10] under equilibrium conditions formed a 9:1 mixture of azides (±)-**13** and (±)-**14** (IR 2102 cm^{-1}, N_3 str). Surprisingly, no styrene **15** was formed. Reduction of this azide mixture with $LiAlH_4$ in THF yielded a 9:1 mixture (GC, ^{1}H NMR) of amines (±)-**16** and (±)-**17** in 24% overall yield from (±)-**12**. These amines comigrated on TLC and were therefore chromatographically inseparable. Treatment of mixture (±)-**16**/(±)-**17** with 1,5-dibromopentane/K_2CO_3 in DMF[10] at 50 °C furnished an 85% yield of mixture (±)-**8** and (±)-**9** which proved to be separable by analytical TLC, in contrast to their precursors. Crystallization of the oxalate salt of (±)-**8**/(±)-**9** from hot 2-propanol afforded pure (±)-**8**·oxalate while crystallization of the perchlorate salt of amines recovered from the mother liquor afforded pure (±)-**9**.

Formation of the (*S*)-(+)-mandelate salt of mixture (±)-**16**/(±)-**17** (9:1) in boiling 100% EtOH gave (+)-**16**·(*S*)-(+)-mandelate which was also free of (±)-**17**. Two further recrystallizations under the same conditions furnished (+)-**16** (>98% enantiomeric purity, see below) in 45% yield. Similarly, recovery of the mixed bases from the mother liquors followed by three recrystallizations of the (*R*)-(−)-mandelate salt afforded (−)-**16** (>98% enantiomeric purity) in 47% yield. The enantiomeric purity of (+)- and (−)-**16** was assessed by ^{1}H NMR spectroscopy of the corresponding diastereomeric ureas **18** and **19** formed by reaction with enantiomerically pure (*S*)-(−)-α-methylbenzyl isocyanate in $CDCl_3$ (Scheme I).[28] Intermediates (+)- and (−)-**16** were readily converted to (+)- and (−)-**8** as for (±)-**8** above. Attempted optical resolution of (±)-**9** with several different optically active acids and different solvents proved unsuccessful. Further attempts to resolve (±)-**9** were discontinued due to limited amounts of this compound. The absolute configuration of (−)-**16** was determined as 1*R*,2*R*,5*S* through single-crystal X-ray analysis (see X-ray analysis section and Figure 1) of (−)-**16**·(*R*)-(−)-mandelate, thus defining the absolute configuration of the chiral "cis" products. The X-ray crystal structure of the picrate salt of (±)-**9** was also determined in order to confirm its "trans" geometry (see X-ray crystallographic section and Figure 2). The predominance of the cis isomer (±)-**13** in the HN_3 solvolysis of (±)-**12** under equilibrium conditions is good evidence that the N_3^- anion preferably attacks the intermediate planar carbonium ion (generated by the action of CF_3COOH on (±)-**13**) from the least-hindered face which in this case is trans to the cyclopropyl ring. The lack of styrene **15** suggests that the cyclopropyl ring does not participate to a great extent in delocalization of charge on the benzylic carbonium ion intermediate.

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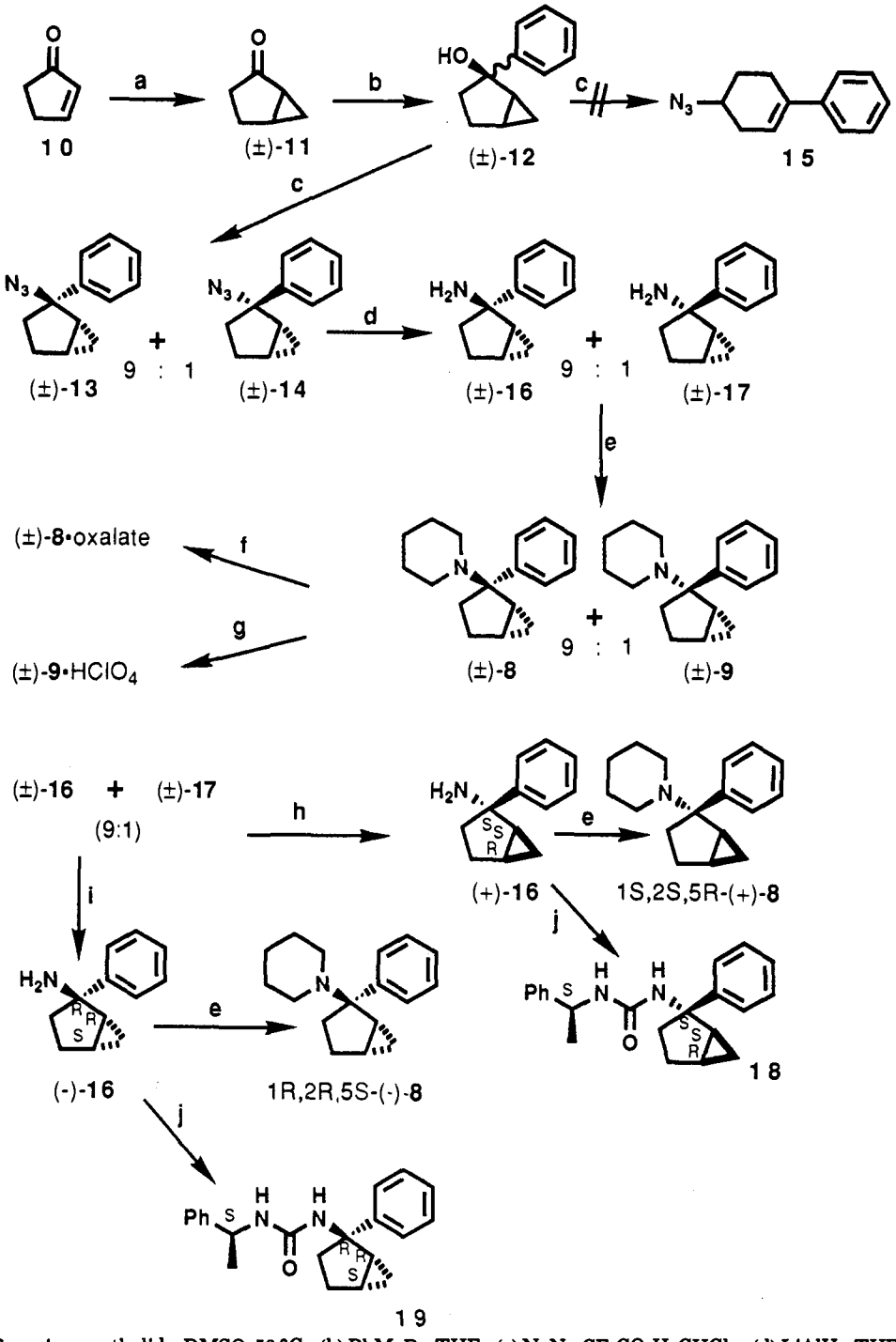
Scheme I. Synthesis of (+)- and (−)-8 and Diastereoisomer (±)-9 from Cyclopent-2-enone[a]



[a] (a) Dimethylsulfoxonium methylide, DMSO, 50 °C. (b) PhMgBr, THF. (c) NaN_3, CF_3CO_2H, $CHCl_3$. (d) $LiAlH_4$, THF, room temperature. (e) Pentane 1,5-dibromide, K_2CO_3, DMF, 50 °C. (f) Oxalic acid, 2-propanol. (g) Aqueous $HClO_4$, 2-propanol. (h) (*S*)-(+)-mandelic acid, EtOH. (i) (*R*)-(−)-Mandelic acid, EtOH. (j) (*S*)-(−)-α-methylbenzyl isocyanate, $CDCl_3$, room temperature.

Molecular Modeling

When substituted in the 3-position as in compound **6** and **7**, the bicyclo[3.1.0]hexane system can assume either a symmetrical pseudoboat or pseudochair conformation. When in the pseudoboat conformation, this will place either the phenyl or the (protonated) piperidine ring *in* close proximity to the cyclopropane ring. In **7**, this leads to strong repulsive forces between the piperidine and the cyclopropane rings, which will make the pseudochair conformation energetically preferred. This is supported by the molecular mechanics calculations (Table III), which show a strong preference for the pseudochair conformation. In contrast, **6** was found to occur in the pseudoboat conformation in the solid state, and ^1H NMR suggests the predominance of that conformation in solution as well. The energy difference between the pseudoboat and pseudochair conformation of **6**, as calculated with CHARMm, indicates no preference. In both the pseudoboat conformation of **6** and the pseudochair conformation of **7**, the protonated piperidine ring occupies the pseudoequatorial position. A similar preference is observed for almost all PCP derivatives with an unrestricted cyclohexane ring.[29] The conformational preferences for compounds **8** and **9** can be analyzed in a similar way. In **8**, calculations show the conformation with the piperidine ring in the pseudoaxial and the phenyl in pseudoequatorial

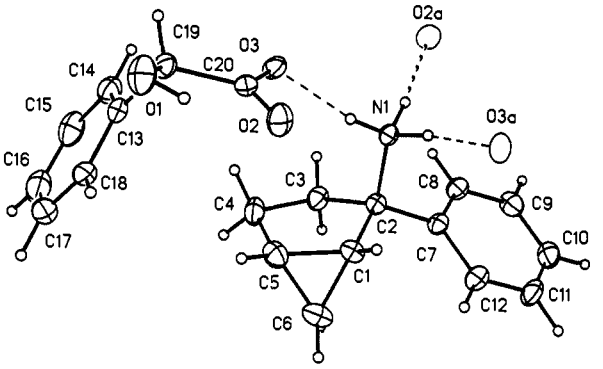


Figure 1. Thermal ellipsoid plot of (−)-16·mandalate drawn at the 20% probability level. The dashed bonds are hydrogen bonds, and O2a and O3a are symmetry-related atoms of O2 and O3.

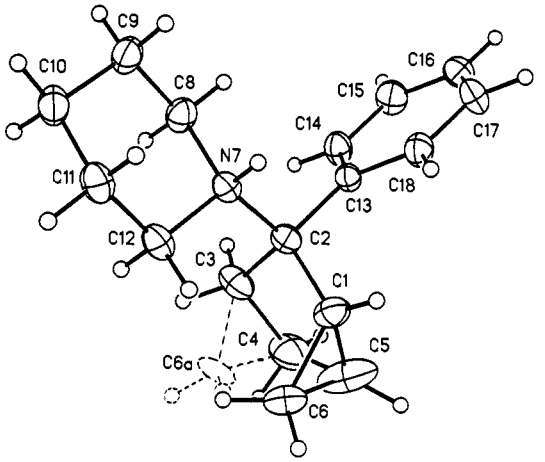


Figure 2. Thermal ellipsoid plot of (±)-9 cation. The dashed atoms represent the lower occupancy position for bridging.

position to be energetically favored, while the opposite preference is found in **9**. These results can be easily understood when the severe steric interaction between the phenyl (piperidine) ring and the neighboring cyclopropane ring in **8** (**9**) is taken into consideration. The preference of the axial phenyl conformation of **9** is found in the solid state as well. Although the antiperiplanar position of the protonated lone pair and phenyl ring is preferred in most simple PCP derivatives,[29] this seems not to be the case for **9**. Molecular mechanics calculations show that for **9** the gauche conformation with the protonated nitrogen lone pair syn relative to the cyclopropane ring is about 0.5 kcal/mol (Figure 3) lower in energy than the antiperiplanar conformation and 1.4 kcal/mol lower than the other gauche position.

Results and Discussion

Evaluation of PCP (**1**) and semirigid bicyclo[3.1.0]hexanes **6**, **7**, (+)-**8**, (−)-**8**, and (±)-**9** for their binding to PCP and σ sites in rat and guinea pig brain homogenates (Table I) revealed that the structurally rigid conformations of PCP represented by these compounds are not optimal for high affinity interaction at either PCP or σ-binding sites. Binding affinities at the PCP site ranged from 582 nM (9-fold reduction) for (±)-**9** to 29 000 nM (450-fold reduction) for (+)-**8**. Affinities at σ-binding sites ranged from 1130 nM for (−)-**8** (equipotent with PCP) to 16 300 nM (15-fold lowered) for **7**. Interestingly, with the exception of (−)-**8**, reductions in the binding affinity to PCP sites qualitatively followed the reductions in affinity at σ sites. Compound **8** exhibited a 3.5-fold enantioselectivity at PCP binding sites and a 6.5-fold enantioselectivity ratio and σ sites both in favor of the (−) isomer.

The conformation with the phenyl ring axial and the piperidine ring equatorial with the (protonated) lone pair antiperiplanar relative to the phenyl ring has been

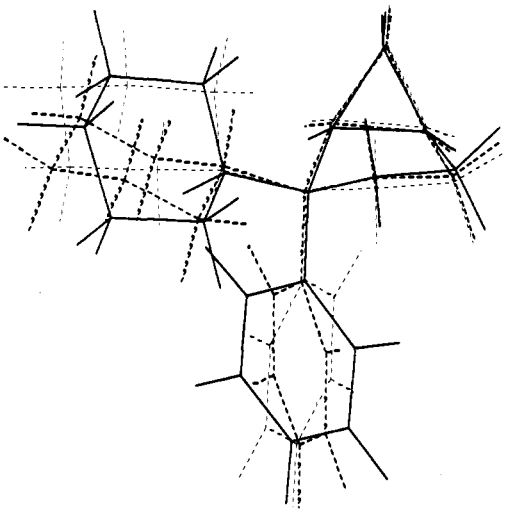
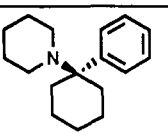
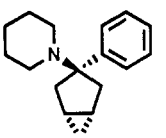
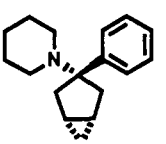
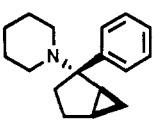
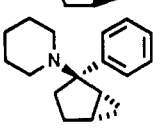
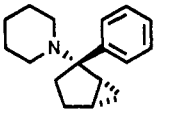


Figure 3. The three minimum-energy conformations of **9** (bicyclohexane part overlap) showing the different positions of the phenyl and piperidine rings. E = 98.56 kcal/mol (bold solid), E = 99.07 kcal/mol (bold dashed), and E = 99.94 kcal/mol (dashed).

Table I. Evaluation of the Binding of Bicyclo[3.1.0]hexylphencyclidine Derivatives at Phencyclidine ([^{3}H]TCP, Rat Brain) and σ ([^{3}H]-(+)-Pentazocine, Guinea Pig Brain) Binding Sites

compd no.	structure	K_i (nM)[a] [^{3}H]TCP	K_i (nM)[a] [^{3}H]-(+)-pentazocine
1 (PCP)		64.5 ± 10.5	1 090 ± 490
6		711 ± 17	3 720 ± 240
7		644 ± 16.1	16 300 ± 6 700
(+)-8		29 000 ± 4 250	7 280 ± 1 140
(−)-8		8 220 ± 1 130	1 130 ± 316
(±)-9		582 ± 58.2	4 450 ± 420

[a] Mean ± SEM of at least three experiments.

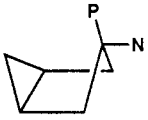
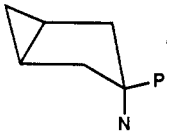
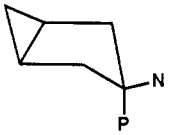
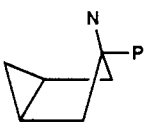
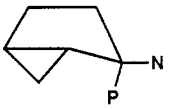
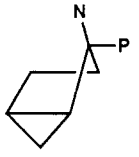
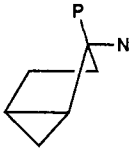
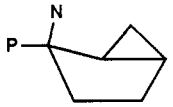
(29) Linders, J. T. M.; Jacobson, A. E. A conformational study of phencyclidine and its methyl congeners using the QUANTA/CHARMm potential energy function. Manuscript to be submitted to *J. Comput. Chem.* Also, see ref 13 above.

Table II. Crystal and Refinement Data

formula	$C_{12}H_{16}N^+ \cdot C_6H_7O_3^-$	$C_{17}H_{24}N^+ \cdot C_6H_2N_3O_7^-$
crystal system	orthorhombic	monoclinic
space group	$P2_12_12_1$	$P2_1/n$
a, Å	6.344 (2)	13.118 (4)
b, Å	16.493 (3)	11.542 (4)
c, Å	16.655 (3)	15.579 (6)
β, deg	90.0	108.79 (2)
V, Å^3	1742.6 (7)	2233.1 (13)
Z	4	4
formula weight	325.4	470.5
$F(000)$	696	992
ρ(calc), g cm^{-3}	1.240	1.399
T, °C	22	22
crystal dim., mm	0.10 × 0.15 × 0.45	0.12 × 0.35 × 0.44
λ, wavelength, Å	1.54178	1.54178
μ, absorption coef., cm^{-1}	6.65	8.78
2θ max., deg	115.0	115.0
scan speed, deg min.	variable 7 to 30	variable 7.5 to 30
2θ scan range, deg.	2.0 + $\Delta_{\alpha1\alpha2}$	2.0 + $\Delta_{\alpha1\alpha2}$
data collected, h,k,l	0 to 6, 0 to 18, 0 to 18	−14 to 12, −12 to 0, −16 to 12
unique data	1391	3036
R_{int}	na	0.012
unique data, $F_o > 3\sigma(F_o)$	1218	2360
standard refl	1.8% random variation	2.2% random variation
parameters refined	236	321
weighting function, g[a]	0.000 23	0.000 23
R,[b] wR,[c] S[d]	0.047, 0.047, 1.42	0.67, 0.80, 2.46
Fourier differences, e Å^{-3}	0.14, −0.19	0.20, −0.20

[a] $w^{-1} = \sigma^2(F_o) + gF_o^2$. [b] $\sum|\Delta|/\sum|F_o|$. [c] $\sum|(w\Delta^2)/\sum(wF_o^2)]^{1/2}$. [d] $[\sum w(\Delta^2)/(N_o - N_p)]^{1/2}$.

Table III. Energy Differences (ΔE, kcal/mol) between Pseudoaxial and Pseudoequatorial Phenyl Conformations for Protonated Bicyclohexane PCP Analogues 6–9 Calculated with CHARMm at $\epsilon = 80$[a]

compd	pseudoaxial conformation	ΔE (kcal/mol)	pseudoequatorial conformation
6		0.08	
7		1.48	
8		−5.26	
9		6.73	

[a] P = phenyl ring. N = protonated piperidine ring.

postulated as the receptor-active conformation.[30] The affinities for the PCP binding site of compounds 6–9 can be rationalized in terms of preferred conformations and

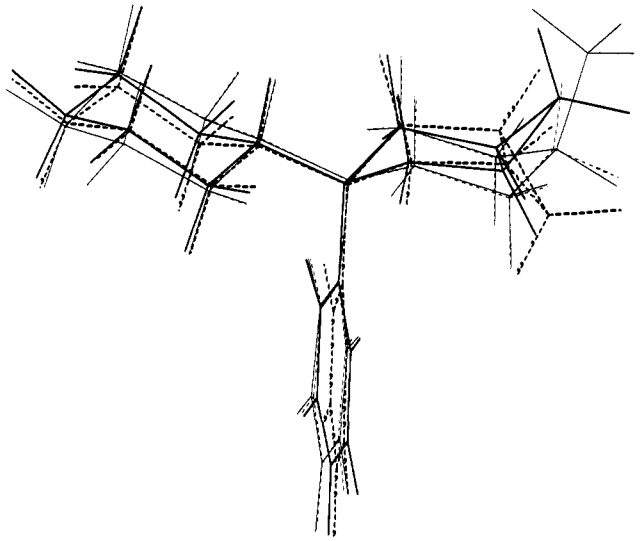


Figure 4. Overlap of bicyclohexane PCP derivatives 7 (bold solid) and 6 (bold dashed) with PCP (dashed), and *trans*-4-methyl-PCP (solid).

comparison with the postulated receptor-active conformation of PCP.

In its energetically preferred pseudochair conformation, 7 overlaps very well with PCP and *trans*-4-methyl-PCP, with the cyclopropyl methylene group occupying the same space as the methyl group in *trans*-4-methyl-PCP (Figure 4). The latter compound has an affinity of 617 nM,[12] which compares very well with the affinity found for 7. The low affinity of 6 can be explained by its low preference for the conformation with the phenyl group in a pseudoaxial position (Table III). Furthermore, it is likely that in the pseudoboat conformation, the cyclopropane group interferes with the receptor-essential volume.[31] In 8, the conformation with the piperidine ring in an axial position is even more preferable for reasons indicated earlier, and consequently this compound is without significant affinity for the PCP binding site. In contrast, 9 has some affinity for the PCP binding site, owing to its strong preference for the pseudoaxial phenyl conformation. The cyclopropane methylene group occupies a spatial position which is in between the methyl groups in *trans*-2- and *trans*-4-methyl-PCP (Figure 5). Furthermore, from X-ray analysis, it is clear that the piperidine ring is twisted away from the receptor-active position which has the protonated nitrogen lone pair antiperiplanar relative to the C–Ph bond.[30,32] In conclusion, the inactivity of these compounds is in agreement with data for methyl-substituted PCP derivatives and supports our recently developed model for the PCP binding site.[29,31]

Comparison of the overall conformation of (±)-9 to those observed in PCP,[33] PCP·HCl,[34] and 6[24] shows large differences in the conformation of the piperidine ring. A measure of this difference is the C(phenyl)–C(tertiary)–N–H torsion angle of −60.8, −174.1 (lone pair position),

(30) Geneste, P.; Kamenka, J.-M.; Ung, S. N.; Herrmann, P.; Goudal, R.; Trouiller, G. *Eur. J. Med. Chem.* **1979**, *14*, 301–308 (in French). Also, see: Eaton, T. A.; Houk, K. N.; Watkins, S. F.; Fronczek, F. R. Geometries and conformational processes in phencyclidine and a rigid adamantyl analogue: Variable-temperature NMR, X-ray crystallographic, and molecular mechanics studies. *J. Med. Chem.* **1983**, *26*, 479–492.

(31) Linders, J. T. M.; Mattson, M. V.; Furlano, D. C.; Jacobson, A. E. Manuscript in preparation.

(32) Chen, C.; Kozikowski, A. P.; Wood, P. L.; Reynolds, I. J.; Ball, R. G.; Pang, Y.-P. Synthesis and biological activity of 8a-phenyldecahydroquinolines as probes of PCP's binding conformation. A new PCP-like compound with increased in vivo potency. *J. Med. Chem.* **1992**, *35*, 1634–1638.

(33) Singh, P.; Jones, L. A.; Couch, R. Structure of 1-(1-phenylcyclohexyl)piperidine (PCP). *Acta Crystallogr.* **1988**, *C44*, 1976–1979.

(34) Argos, P.; Barr, R. E.; Weber, A. H. The crystal and molecular structure of 1-(1-phenylcyclohexyl)piperidine hydrochloride. *Acta Crystallogr.* **1970**, *B26*, 53–61.

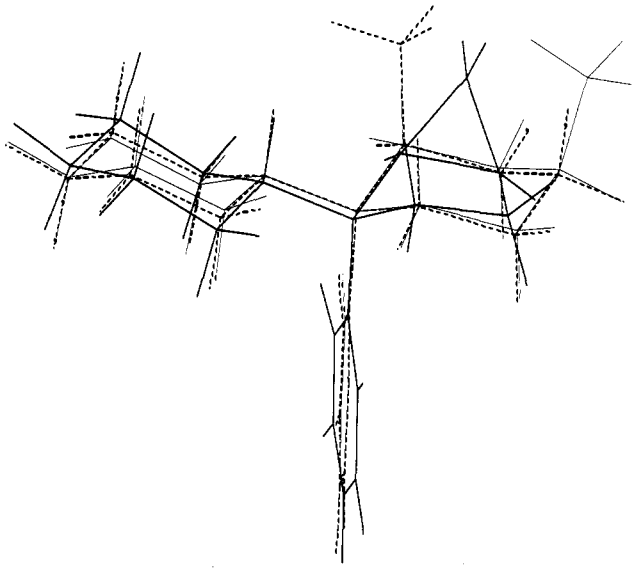


Figure 5. Overlap of **9** (bold solid) with *trans*-2 (bold dashed) and *trans*-4-methyl-PCP (solid).

−167.0, and −177.5° for (±)-**9** and the above listed compounds, respectively. The conformation for the piperidine ring in (±)-**9** is similar to the global energy minimum found by CHARMm calculation [C(phenyl)–C(tertiary)–N–H torsion angle −43°] although the energy difference with the antiperiplanar orientation is small (about 1 kcal/mol). The restriction of the conformation for (±)-**9** also results in significant differences in bond angles about C(2). Comparisons of these angles to equivalent angles in the listed compounds are C_p–C_t–N = 106.7 (3), 110.9 (1), 109.0 (4), and 109.0 (2), and N–C_t–C(bridged) = 111.4 (4) (major form), 107.7 (1), 107.8 (4), and 108.8° (2), respectively, for the largest of the differences.

In summary, it is likely that in this isomeric bicyclo[3.1.0]hexane series, affinities at the PCP binding site are significantly reduced due to nonoptimal (e.g. pseudoequatorial phenyl or pseudoboat conformations) geometry for binding as opposed to the addition of new steric bulk which proved deleterious to binding in the methylcyclohexyl- and adamantyl-PCP derivatives. Additionally, the bicyclo[3.1.0]hexane analogues of PCP can also be considered as alkyl-substituted derivatives of 1-(1-phenylcyclopentyl)-piperidine which exhibits significantly lower affinity for the PCP site than PCP. The data reported here conform with a molecular model that accounts for the PCP-binding properties of MK-801, the isomeric methylcyclohexyl-PCP derivatives, and related compounds.[29,31]

Experimental Section

Chemistry Materials and Methods. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Specific rotation determinations at the sodium D line were obtained in a 1-dM cell using a Perkin-Elmer 241-MC polarimeter. Elemental analyses were performed at Atlantic Microlabs, Atlanta, GA; where molecular formulae are indicated followed by the symbols of the elements, analyses were found to be within ±0.4% of the theoretical values for these elements. Chemical-ionization mass spectra (CIMS) were obtained using a Finnigan 1015 mass spectrometer. Electron-ionization mass spectra (EIMS) and high-resolution mass measurements (HRMS) were obtained using a VG-Micro Mass 7070F mass spectrometer. IR spectra were recorded from $CHCl_3$ solutions of compounds using a Bio-Rad FTS-45 FTIR spectrophotometer. ^1H NMR spectra were recorded from $CDCl_3$ solutions using a Varian XL-300 spectrometer; results are recorded as parts per million (ppm) downfield of the TMS signal. NMR and IR spectra were recorded from the free-base forms only of amines reported herein. Thin-layer chromatography (TLC) was performed on 250 μM Analtech GHLF silica gel plates. TLC solvent system A corresponds to concentrated aqueous NH_3/MeOH/$CHCl_3$ (1:9:90). No attempt was made to optimize the yields.

Molecular Modeling Studies. Molecular models were constructed on a Silicon Graphics 4D70GT workstation using Quanta 3.0 software,[35] which uses the CHARMm force field[36] for the minimization procedures. Starting geometries were obtained from X-ray coordinates (refs 12, 24, 34, and this paper) or by manual input, followed by further manipulation if necessary. To locate the local and global energy minima, the following procedure has been used.[29] For each structure, two possible starting conformations were generated with the phenyl either in a pseudoequatorial or pseudoaxial conformation on the bicyclohexane moiety. Calculations were performed on the protonated species, using a dielectric constant (ϵ) = 80, approximating aqueous surroundings. Both rotatable bonds were varied in 20-deg increments and each conformation was energy minimized using the adopted-basis Newton–Raphson routine. The minimum energy conformations and all conformations within 10 kcal/mol were subjected to a short molecular dynamics run (0.03 ps at 1000 K) and reminimized without constraints on the torsion angles using the Newton–Raphson method. Geometries were considered minimized with either the energy change between two subsequent structures was less than 0.001 kcal/mol or the RMS of the deviation in the geometry of two subsequent structures was less than 0.01.

Bicyclo[3.1.0]hexan-2-one [(±)-11]. In a 2000-mL three-necked round-bottom flask was placed NaH (97%) (23.1 g, 962 mmol, 1.1 equiv), and trimethylsulfoxonium iodide (211.7 g, 962 mmol, 1.1 equiv). Dry DMSO (750 mL) was added dropwise with motorized stirring over 15 min. Vigorous evolution of hydrogen occurred during the addition and a milky off-white suspension was formed. Following addition of the DMSO, a solution of cyclopent-2-enone (71.81 g, 875 mmol) in dry DMSO (100 mL) was added slowly to the milky suspension, with continued stirring. After an initial exotherm, the suspension dissolved resulting in a clear red solution. This was stirred for 2 h at 50 °C, cooled, and poured into water (1000 mL). The solution was extracted with ether (3 × 500 mL) and the combined organic extract was back-washed with water (2 × 500 mL) and brine (500 mL) and dried (Na_2SO_4). Evaporation of the solvent in vacuo afforded crude (±)-**11** as a yellow oil. Distillation in vacuo through a short Vigreux column afforded pure (±)-**11** (28.7 g, 34%): bp 60–65 (15 mmHg) [lit.[37] bp 57–59 °C (12 mmHg), lit[38] bp 69 °C (20 mmHg)]; ^1H NMR ($CDCl_3$) δ 1.80–2.21 (complex m, 3 H), 1.30–1.80 (complex m, 3 H), 1.20 (m, 1 H, cyclopropyl-CH_2), 0.93 (m, 1 H), cyclopropylCH_2).

(±)-2-Phenylbicyclo[3.1.0]hexan-2-ol [(±)-12]. The Grignard reagent generated by treatment of Mg turnings (43.6 g, 1.79 mol, 6.0 equiv) in THF (500 mL) with bromobenzene (89.6 g, 0.57 mol, 1.9 equiv) was cooled to 0 °C and to the stirred solution was added **10** (28.7 g, 0.3 mol). The solution was stirred for 10 min at 0 °C after which time a white precipitate formed. The reaction was quenched with excess saturated aqueous NH_4Cl (200 mL) followed by water (400 mL). The aqueous mixture was extracted with ether (500 mL) and the organic layer was separated and dried (Na_2SO_4), and the solvent was evaporated in vacuo to give (±)-**12** (52.0 g, quantitative) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 2 H, Ar*H*), 7.34 (m, 2 H, Ar*H*), 7.26 (m, 1 H, Ar*H*), 1.47–1.88 (complex m, 4 H), 1.22 (m, 2 H, cyclopropylCH), 0.75 (m, 1 H, cyclopropylCH_2), 0.61 (m, 1 H, cyclopropylCH_2); HRMS M^+ (calcd for $C_{12}H_{14}O$) 174.1045, found 174.1034 (M^+). No attempt was made to further purify or characterize this material. It was used directly for the next reaction step.

(35) QUANTA 3.0 Program (1990), Polygen Corporation, 200 Fifth Ave., Waltham, MA 02254.

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(38) Nelson, N. A.; Mortimer, G. A. Bicyclo[3.1.0]hexane derivatives. I. Synthesis of bicyclo[3.1.0]-2-hexanone and methyl bicyclo[3.1.0]-hexane-1-carboxylate. *J. Org. Chem.* **1957**, *22*, 1146–1153.

(±)-*cis*- and (±)-*trans*-2-Phenyl-2-bicyclo[3.1.0]hexylamine [(±)-16 and (±)-17]. To a stirred suspension of NaN_3 (58.3 g, 0.9 mol, 3 equiv) and (±)-12 (52 g, 0.3 mol) in hydrocarbon-stabilized $CHCl_3$ (1000 mL) was added dropwise at −10 °C CF_3COOH (92 mL, 1.2 mol, 4 equiv), and the solution was stirred overnight from −10 to 20 °C. The reaction was quenched by the addition of concentrated aqueous NH_3 solution (250 mL) and water (250 mL). The $CHCl_3$ layer was separated and dried (Na_2SO_4), and the solvent was evaporated in vacuo to give crude azides [(±)-13 and (±)-14] as a colorless oil (quantitative): IR ($CHCl_3$) 2102 cm^{-1} (v strong, N_3 str). No attempt was made to further purify this azide mixture. Mixture (±)-13/(±)-14 was dissolved in dry ether (500 mL) and added dropwise at 20 °C to a solution of $LiAlH_4$ in THF (400 mL of a 1.0 M solution, 0.4 mol, 1.3 equiv) during which time vigorous evolution of N_2 occurred. The reaction mixture was allowed to stir overnight at 20 °C (complete by TLC, solvent system A), cooled to 0 °C, and quenched by dropwise addition of water (15 mL), 15% aqueous NaOH (15 mL), and finally water (45 mL). The reaction mixture was stirred for 40 min at 20 °C and then the granular aluminum salts were filtered and the filter cake was washed with ether (100 mL). The filtrate was partitioned with 10% aqueous citric acid (500 mL), and the aqueous acidic layer was washed with ether (3 × 250 mL) and the combined organic extract was discarded. The aqueous layer was basified by addition of excess concentrated aqueous NH_3 solution and extracted with CH_2Cl_2 (2 × 250 mL). The combined CH_2Cl_2 extract was back-washed with water (250 mL) and dried (Na_2SO_4), and the solvent was evaporated in vacuo to give mixture (±)-16 and (±)-17 (9:1) as a colorless oil (12.54 g, 24% overall yield from (±)-12). Mixture (±)-16/(±)-17 (9:1) appeared as a single spot on TLC (solvent system A). Crystallization of the HBr salt from EtOAc afforded pure (±)-16·HBr: mp 206–207 °C dec; ^1H NMR ((±)-16 base in $CDCl_3$) δ 7.56 (m, 2 H, Ar*H*), 7.32 (m, 2 H, Ar*H*), 7.23 (m, 1 H, Ar*H*), 2.08 (m, 1 H), 1.83 (m, 2 H), 1.44–1.60 (complex m, 3 H), 0.61 (m, 1 H, cyclopropylCH_2), 0.24 (m, 1 H, cyclopropylCH_2); ^1H NMR [(±)-16·HBr in D_2O] δ 7.55–7.62 (m, 2 H, Ar*H*), 7.35–7.48 (m, 3 H, Ar*H*), 2.25 (dd, J_{gem} = 15 Hz, J_{vic} = 8.0 Hz, 1 H), 1.98–2.14 (m, 1 H), 1.85–1.98 (complex m, 2 H), 1.59–1.75 (m, 2 H, cyclopropaneCH), 0.74 (m, 1 H, cyclopropaneCH_2), 0.26 (m, 1 H, cyclopropaneCH_2); EIMS (M^+ calcd for $C_{12}H_{15}N$) 173, found 173 (M^+), 156 ($M^+ - NH_3$), 141 ($M^+ - NH_3 - CH_3$). Anal. (calcd for $C_{12}H_{16}BrN$) C, H, N.

Evaporation of the mother liquors and isolation of the free base by partitioning between 5% aqueous NaOH/$CHCl_3$ afforded mixed bases enriched in (±)-17: ^1H NMR ($CDCl_3$) δ 7.63 (m, 2 H, Ar*H*), 7.32 (m, 2 H, Ar*H*), 7.23 (m, 1 H, Ar*H*), 2.08 (m, 1 H), 1.71 (m, 2 H), 1.32–1.57 (complex m, 3 H), 0.54 (m, 2 H, cyclopropaneCH_2). No attempt was made to purify (±)-17 from this mixture because it could not be separated chromatographically. However, it was separated during the optical resolution step (see below) and was separable either chromatographically or via $HClO_4$ salt formation as its pentamethylene derivative (±)-9 (see below).

(±)-*cis*-1-[2-Phenyl-2-bicyclo[3.1.0]hexyl]piperidine [(±)-8]. To the mixed bases enriched in (±)-17 from above (5.36 g, 31.0 mmol) in dry DMF (100 mL) was added pentane 1,5-dibromide (8.55 g, 37.2 mmol, 1.2 equiv), and the reaction mixture was heated and stirred for 24 h at 52 °C. After this time, anhydrous K_2CO_3 (5.14 g, 37.2 mmol, 1.2 equiv) was added, and heating and stirring at this temperature were continued for a further 24 h when TLC (solvent system A) indicated the reaction to be complete. The reaction mixture was cooled and poured into cold water (300 mL), and the pH was adjusted to >9.5 by addition of 10% aqueous K_2CO_3. The resulting aqueous mixture was extracted with ether (3 × 150 mL), and the combined organic extract was back-washed with water (100 mL). The ethereal extract was washed well with 1.0 M aqueous citric acid (300 mL), and the aqueous layer was washed with a further 2 × 200 mL of ether. The combined ethereal washings were discarded, and the aqueous layer was basified by the addition of concentrated aqueous NH_3 and extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 extract was back-washed with water (100 mL) and dried (Na_2SO_4), and the solvent was evaporated to give the crude mixed bases (±)-8/(±)-9 as a yellow oil (6.31 g, 85%). This was dissolved in hot 2-propanol (50 mL) and treated with oxalic acid (2.36 g). Copious crystallization occurred to give (±)-8·oxalate (3.71 g, 36%): mp 151–152 °C; ^1H NMR ((±)-8 base in $CDCl_3$) δ 7.49 (m, 2 H, Ar*H*), 7.27 (m, 2 H, Ar*H*), 7.19 (m, 1 H, Ar*H*), 2.46 (m, 4 H, N(CH_2)$_2$), 2.17 (m, 1 H), 1.99 (m, 1 H), 1.43–1.80 (complex m, 8 H), 1.39 (m, 2 H, cyclopropaneCH), 0.55 (m, 1 H, cyclopropaneCH_2), −0.11 (m, 1 H, cyclopropaneCH_2); ^1H NMR ((±)-8·oxalate in D_2O) δ 7.53 (m, 2 H, Ar*H*), 7.39 (m, 3 H, Ar*H*), 3.33 (dm, J_{gem} = 12 Hz, 2 H), 2.89 (m, 2 H), 2.61 (m, 1 H), 2.05 (m, 2 H), 1.41–2.02 (complex m, 8 H), 1.28 (m, 1 H, cyclopropaneCH), 0.82 (m, 1 H, cyclopropaneCH_2), −0.089 (m, 1 H, cyclopropaneCH_2); EIMS (M^+ calcd for $C_{17}H_{23}N$) 241, found 154 (M^+ − piperidine − H_2); CIMS (MH^+ calcd for $C_{17}H_{23}N$) 242, found 242 (MH^+). Anal. (calcd for $C_{19}H_{25}NO_4 \cdot 0.33H_2O$) C, H, N.

(±)-*trans*-1-[2-Phenyl-2-bicyclo[3.1.0]hexyl]piperidine [(±)-9]. The mother liquors from the synthesis of (±)-8·oxalate above were converted to the free base by partitioning between aqueous 1.0 M NaOH and $CHCl_3$. This was dissolved in 2-propanol (20 mL) and treated with 70% aqueous $HClO_4$ to pH 3, and the crystals were filtered, washed twice with cold (0 °C) 2-propanol and once with ether and dried overnight at 60 °C in vacuo to give (±)-9·$HClO_4$ (1.76 g, 2.4% overall from (±)-12): mp 155–156 °C; ^1H NMR ($CDCl_3$) δ 7.53 (m, 2 H, Ar*H*), 7.32 (t, 2 H, J_{app} = 8 Hz, 2 H, Ar*H*), 7.23 (m, 1 H, Ar*H*), 2.46 (m, 4 H, piperidine N(CH_2)$_2$), 1.91 (m, 1 H), 1.55–1.74 (complex m, 4 H), 1.42–1.55 (complex m, 4 H), 1.33 (m, 2 H), 1.24 (m, 1 H, cyclopropaneCH), 0.66 (m, 1 H, cyclopropaneCH_2), 0.52 (m, 1 H, cyclopropaneCH_2); EIMS (M^+ calcd for $C_{17}H_{23}N$) 241, found 241 (M^+); CIMS (MH^+ calcd for $C_{17}H_{23}N$) 242, found 242 (MH^+). Anal. (calcd for $C_{17}H_{24}ClNO_4$) C, H, N.

(±)-9·picrate crystallized slowly from EtOH as large yellow prisms which proved suitable for single-crystal X-ray analysis (see X-ray section later): mp 151–152 °C dec. Anal. (calcd for $C_{23}H_{26}N_4O_7$) C, H, N.

Optical Resolution of (±)-16: *cis*-(1*S*,2*S*,5*R*)-(+)-2-Phenyl-2-bicyclo[3.1.0]hexylamine [(+)-16]. To a stirred solution of amines (±)-16/(±)-17 (9:1) (11.24 g, 65 mmol) in boiling EtOH (100 mL) was added a solution of (*S*)-(+)-mandelic acid (9.88 g, 65 mmol) in hot EtOH (100 mL). Crystallization occurred spontaneously following complete addition of the (*S*)-(+)-mandelic acid. The crystallization mixture was set aside to cool slowly to room temperature and then filtered, and the filter cake was washed twice with a little cold (0 °C) EtOH followed by ether and dried overnight in vacuo at 60 °C to yield (+)-16·(*S*)-(+)-mandelate (7.60 g, 80%). This material was recrystallized twice from hot EtOH (150 mL) to yield (+)-16·(*S*)-(+)-mandelate (4.28 g, 45%) as feathery needles: mp 191–192 °C; $[\alpha]_D$ = +68° (*c* 1.2, MeOH). Anal. (calcd for $C_{20}H_{23}NO_3$) C, H, N.

(+)-16 (base) obtained by partitioning this salt between aqueous 1.0 M KOH solution and $CHCl_3$ proved to be >98% enantiomerically pure (see below) as well as free of (±)-17. Evaporation of the mother liquor and isolation of the free amine as for (+)-16 afforded mixed bases 8.07 g (72%).

***cis*-(1*R*,2*R*,5*S*)-(−)-2-Phenyl-2-bicyclo[3.1.0]hexylamine [(−)-16].** A solution of mixed bases from the optical resolution above (8.07 g, 46.7 mmol) in EtOH (100 mL) was rapidly mixed with a solution of (*R*)-(−)-mandelic acid (7.10 g, 46.7 mmol) in EtOH (100 mL) at room temperature. Copious crystallization occurred after several seconds. The crystallization mixture was stirred occasionally and then filtered after 20 min at room temperature. The filter cake was washed twice with a little cold (0 °C) EtOH and finally ether and then oven-dried overnight in vacuo at 60 °C to yield (−)-16·(*R*)-(−)-mandelate (6.86 g, 72%). This material was recrystallized twice from hot EtOH as described above to give (−)-16·(*R*)-(−)-mandelate (4.43 g, 47%): mp 193–194 °C; $[\alpha]_D$ = −68° (*c* 1.51, MeOH). Anal. (calcd for $C_{20}H_{23}NO_3$) C, H, N.

Isolation of the free base as above for (+)-16 yielded (−)-16 base which was >98% enantiomerically pure (see below) as well as free of (±)-17.

(+)-*cis*-1-[2-Phenyl-2-bicyclo[3.1.0]hexyl]piperidine [(+)-8]. (+)-16 (1.06 g, 6.15 mmol obtained from 2.00 g of (+)-16·(*S*)-(+)-mandelate by partitioning between 1.0 M aqueous KOH/$CHCl_3$) in DMF (25 mL) was treated with pentane 1,5-dibromide (1.40 g, 6.1 mmol, 1.0 equiv) at 50 °C for 24 h followed by addition of K_2CO_3 (0.84 g, 6.1 mmol, 1.0 equiv). The reaction was continued for an additional 24 h at 50 °C as described above for (±)-8. The crude (+)-8 (1.38 g, 93%) was isolated as a pale yellow oil. This

was dissolved in hot 2-propanol (20 mL) and treated with oxalic acid (0.52 g). Crystallization occurred on cooling and scratching with a glass rod. The crystallization mixture was cooled to 4 °C, and the crystals were filtered, washed twice with 2-propanol (0 °C) followed by ether to give (+)-8·oxalate (1.48 g, 73%): mp 156–157 °C; $[\alpha]_D = +35°$ (c 1.4, MeOH). Anal. (calcd for $C_{19}H_{25}NO_4$) C, H, N.

(−)-*cis*-1-[2-Phenyl-2-bicyclo[3.1.0]hexyl]piperidine [(−)-8]. This was obtained from (−)-16·(*R*)-(−)-mandelate (2.00 g, 6.15 mmol) by the same procedure as for its enantiomer above; (−)-8·oxalate (1.45 g, 71%): mp 157.5–158.5 °C; $[\alpha]_D = -34°$ (c 1.08, MeOH). Anal. (calcd for $C_{19}H_{25}NO_4$) C, H, N.

1-[(*S*)-1-Phenyl-1-ethyl]-3-[(1*S*,2*S*,5*R*)-2-phenyl-2-bicyclo-[3.1.0]hexyl]urea (18). The base from (+)-16·(*S*)-(+)-mandelate (20.0 mg, 0.062 mmol) was dissolved in $CDCl_3$ (0.5 mL) and treated with optically pure (*S*)-(−)-α-methylbenzyl isocyanate[28] (9.46 μL, 0.067 mmol, 1.1 equiv). The solution was allowed to stand at room temperature for 20 min when TLC (solvent system A) indicated that the reaction was still incomplete. Brief heating (45 °C for 5 min) of the reaction mixture resulted in complete reaction to give 18 in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 7.58 (d, *J* = 7.1 Hz, 2 H, Ar*H*), 7.15–7.40 (complex m, 6 H, Ar*H*), 7.01 (d, *J* = 6.7 Hz, 2 H, Ar*H*), 4.99 (s, 1 H), 4.73 (m, 1 H), 4.46 (d, *J* = 7.1 Hz, 1 H), 1.72–1.94 (complex m, 4 H), 1.56 (m, 1 H), 1.41 (m, 1 H, cyclopropaneCH), 1.12 (d, *J* = 6.8 Hz, 3 H, CH_3), 0.61 (m, 1 H, cyclopropaneCH_2), 0.31 (m, 1 H, cyclopropaneCH_2); CIMS (MH^+ calcd for $C_{21}H_{24}N_2O$) 321, found 321 (MH^+); EIMS (M^+ calcd for $C_{21}H_{24}N_2O$) 320, found 320 (M^+), 215 (M^+ − $PhCHCH_2$), 172 (M^+ − $PhCH(CH_3)(NCO)$); HRMS (M^+ calcd for $C_{21}H_{24}N_2O$) 320.1889, found 320.1868 (M^+). The ^{1}H NMR spectrum exhibited <2% of the signals 1.21 (d, *J* = 6.8 Hz, 3 H, CH_3) corresponding to the diasteoisomer 19 thus indicating successful optical resolution.

1-[(*S*)-1-Phenyl-1-ethyl]-3-[(1*R*,2*R*,5*S*)-2-phenyl-2-bicyclo-[3.1.0]hexyl]urea (19). The base from (−)-16·(*R*)-(−)-mandelate (20.0 mg, 0.062 mmol) was treated as for its enantiomer above to give 19 in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 7.56 (d, *J* = 6.4 Hz, 2 H, Ar*H*), 7.15–7.40 (complex m, 6 H, Ar*H*), 6.88 (d, *J* = 5.9 Hz, 2 H, Ar*H*), 5.04 (s, 1 H), 4.75 (m, 1 H), 4.56 (d, *J* = 7.5 Hz, 1 H), 1.72–2.04 (complex m, 4 H), 1.53 (m, 1 H), 1.41 (m, 1 H, cyclopropaneCH), 1.21 (d, *J* = 6.8 Hz, 3 H, CH_3), 0.65 (m, 1 H, cyclopropaneCH_2), 0.32 (m, 1 H, cyclopropaneCH_2). The ^{1}H NMR spectrum exhibited <2% of the signals 1.12 (d, *J* = 6.8 Hz, 3 H, CH_3) corresponding to the diasteoisomer 18 thus indicating successful optical resolution.

Single-Crystal X-ray Analysis of (−)-16-(*R*)-(−)-Mandelate and (±)-9-Picrate. Optically pure (−)-16·(*R*)-(−)-mandelate obtained as above was dissolved in hot water (80 °C), and the solution was allowed to cool gradually to 20 °C. Large crystalline translucent rods formed overnight. The (±)-9·picrate was obtained in crystalline form by treatment of a solution of (±)-9 (20.0 mg, 0.083 mmol) in hot (80 °C) EtOH (100%) with picric acid (19.0 mg, 1.0 equiv). Slow overnight cooling of the solution to ambient temperature resulted in the formation of large yellow prisms. A single crystal of each was selected for data collection in the q/2q mode on a computer-controlled automated diffractometer (Siemens R3m/V). The space group determinations were based on observed extinctions, *E* value statistics, and structure solutions. The data were corrected for Lorentz and polarization effects but not for absorption. Both structures were solved by direct methods with the aid of the program SHELXTL[39] and refined by a full-matrix least squares.[39] The parameters refined include the coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Carbon hydrogens used a riding model in which the coordinate shifts of the carbons were applied to the attached hydrogens with C–H = 0.96 Å, H angles idealized, and U_{iso}(H) set at fixed values. The coordinates of hydrogens involved in hydrogen bonding and hydrogens on the bridged carbons were refined isotropically.

The determination of the absolute configuration of the (−)-16·(*R*)-(−)-mandelate was based on the known configuration of the mandelate anion. This established the configuration of the cation to be 1*R*,2*R*,5*S* as shown in Figure 1. The crystal structure of the (±)-9·picrate is shown in Figure 2. Here the cation is disordered with the cyclohexane ring bridged trans to the phenyl on opposite sides of the ring with occupancy ratios for the two possible bridging sites of 2:1. Additional experimental and structural analysis details are given in Table II, and tables of crystal coordinates, bond distances, and bond angles have been deposited with the Crystallographic Data Center, Cambridge, CB2 1EW, England.

Biological Materials and Methods. Phenylcyclidine (PCP) Binding. Following decapitation from male Sprague-Dawley rats (Taconic Farms, Germantown, NY), whole brains minus the cerebellum were rapidly removed and disrupted with 45 volumes of 5 mM Tris-HCl buffer (pH 7.4) using a Brinkman polytron (setting 6, 20 s). The homogenates were centrifuged at 20 000*g* for 20 min at 5 °C. The pellet was washed in fresh buffer and recentrifuged for a total of three times. The final resuspension was performed in 45 volumes of fresh assay buffer and kept on ice until needed.

Binding to homogenates was determined in a 1-mL incubation volume, consisting of 900 μL of tissue (containing approximately 0.8 mg of protein by Lowry analysis), 50 μL of [^{3}H]TCP (40.8 Ci/mmol; New England Nuclear, Boston, MA) for a final concentration of 2 nM, and 50 μL of buffer, test compound, or 10 μM TCP (for determination of nonspecific binding). After a 90-min incubation at 5 °C, the reaction was terminated by rapid filtration using a Brandel cell harvester (Brandel, Inc., Gaithersburg, MD) through #32 Schleicher and Schuell glass fiber filters which had been presoaked in 0.03% polylysine (Sigma Chemical Co., St. Louis, MO; molecular weight 150 000–300 000) for 2 h at 5 °C. The filters were washed with three 5-mL aliquots of ice-cold assay buffer and placed in counting vials with 4 mL of CytoScint ES scintillation cocktail (ICN Biomedicals, Inc., Irvine, CA) and allowed to stand overnight before counting in a Packard Tri-Carb 2200CA liquid scintillation counter (Packard Instrument Co., Downers Grove, IL).

The inhibition constant (K_i) was calculated using GraphPAD software (ISI Software, Philadelphia, PA) using a K_d for TCP of 16.5 nM as determined by Scatchard analysis. Each concentration was performed in triplicate, and the resulting values are expressed as the mean of three or more experiments.

σ-Ligand Binding. Male Hartley guinea pigs (Charles River, Kingston, NY) were decapitated and the whole brains plus cerebellum were rapidly removed and disrupted with 40 volumes of 50 mM Tris-HCl buffer (pH 8.0) using a Brinkman polytron (setting 6, 20 s). The homogenates were centrifuged at 27 000*g* for 20 min at 5 °C. The pellet was resuspended in the original volume with fresh assay buffer and recentrifuged for a total of three times. The final resuspension was kept on ice until needed. Binding to homogenates was determined in a 1-mL incubation volume, consisting of 900 μL of tissue, 50 μL of [^{3}H]-(+)-pentazocine[26] (51.7 Ci/mmol) for a final concentration of 3 nM, and 50 μL of buffer, test compound, or 10 μM (+)-pentazocine (for determination of nonspecific binding). After a 120-min incubation at 25 °C, the reaction was terminated by rapid filtration using a Brandel cell harvester (Brandel, Inc., Gaithersburg, MD) through #32 Schleicher and Schuell glass fiber filters which had been presoaked in 0.5% polyethylenimine at 25 °C during the incubation period. The filters were washed with three 5-mL aliquots of ice-cold 10 mM Tris buffer (pH 8.0) and placed in counting vials with 4 mL of CytoScint ES scintillation cocktail (ICN Biomedicals, Inc., Irvine, CA) and allowed to stand overnight before counting in a Packard Tri-Carb 2200CA liquid scintillation counter (Packard Instrument Co., Downers Grove, IL).

Data were analyzed using GraphPAD software (ISI Software, Philadelphia, PA) using a K_d for (+)-pentazocine of 3.4 nM as determined by Scatchard analysis. Each concentration was performed in triplicate, and the resulting values are displayed as the mean of three or more experiments.

Supplementary Material Available: Tables of crystallographic parameters, bond lengths, bond angles, and atomic coordinates for (±)-9·picrate (8 pages). Ordering information is given on any current masthead page.

(39) Sheldrick, G. M. (1980) SHELXTL80. An integrated system for solving, refining, and displaying crystal structures from diffraction data. Univ. of Göttingen, Federal Republic of Germany.