Synthesis and Biological Activity of 8a-Phenyldecahydroquinolines as Probes of PCP's Binding Conformation. A New PCP-like Compound with Increased in Vivo Potency

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The synthesis and chemical resolution of cis- and trans-fused 8a-phenyldecahydroquinolines 3 and 4 are described together with the affinity of the four optically pure compounds for the PCP recognition site of the NMDA receptor complex. These compounds were also evaluated for their antagonistic effects on cGMP levels in male Swiss Webster mice, and (-)-4 was found to exhibit in vivo potency comparable to that of MK-801. The results of the binding studies are interpreted in terms of a preferred orientation of PCP's N-H bond in binding to its NMDA receptor-associated recognition site.

Introduction

To better pursue the search for highly selective and potent noncompetitive antagonists (or open-channel blockers) of the *N*-methyl-D-aspartate (NMDA) receptor, compounds that may prove useful as neuroprotective agents or as probes for characterization of the NMDA receptor, it is essential to learn more about PCP's binding conformation and the topography of its associated recognition sites. We have recently described the high binding affinity of an aromatic ring-constrained analogue of PCP, the aminohexahydrofluorene 1.[1] This structurally more rigid PCP-like analogue provides support for the axial-phenyl, $\phi \approx 90°$, binding conformation of PCP (see structure 1). It may be assumed that the aromatic ring of PCP is involved in a herringbone or π-type interaction with an aromatic group provided by an appropriately positioned amino acid residue present within the PCP binding domain.

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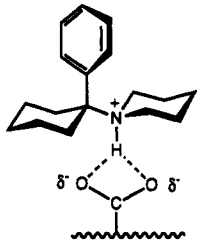
Because PCP will exist predominantly in protonated form at physiological pH, a second likely interaction between PCP-H^+ and its recognition site is a charge-reinforced ligand–receptor hydrogen bond, possibly to a carboxylate residue as illustrated in 2. In the event that such



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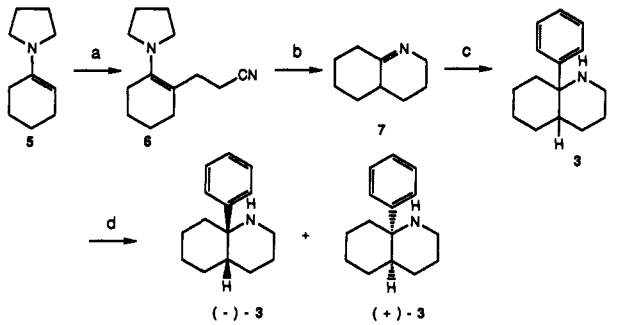
a hydrogen bonding interaction actually exists, then the orientation of the N–H bond relative to, for instance, the cyclohexyl–phenyl bond should be crucial to binding affinity. Should PCP-H^+ actually bind to its recognition site in the lowest energy conformation as determined from molecular mechanics calculations,[2] then this N–H bond should optimally be situated antiperiplanar to the phenyl ring. To gain more concrete evidence for this preference, we prepared the cis- and trans-fused 8a-phenyldecahydroquinolines 3 and 4 in their optically pure forms. The process of incorporating the amino group into a ring which is fused to the existing cyclohexane ring serves to fix the relation of the N–H group relative to the C–phenyl bond. In this paper we provide details on the synthesis of these compounds in their optically pure forms. The affinities of these compounds in binding to the PCP site of the NMDA receptor complex are provided together with in

Scheme I[a]



[a] (a) H_2C=CHCN, 1,4-dioxane, reflux, 1.5 h (87%); (b) 1. $LiAlH_4$, Et_2O, room temperature, 30 min; 2. H_2O, 100 °C, 1 h (50%); (c) PhLi, Et_2O, reflux, 2 h (50%); (d) 1. fractional crystallization of camphanic acid amides; 2. KO-*t*-Bu, H_2O, Et_2O, room temperature, 3 days (66%); PhLi, Et_2O, room temperature, 45 min (96%).

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(1) (a) Kozikowski, A. P.; Pang, Y. P. Structural determinants of affinity for the phencyclidine binding site of the *N*-methyl-D-aspartate receptor complex: discovery of a rigid phencyclidine analogue of high binding affinity. *Mol. Pharmacol.* **1990**, *37*, 350–357. (b) Also, see: Casalotti, S. O.; Kozikowski, A. P.; Fauq, A.; Tückmantel, W.; Krueger, K. E. Design of an irreversible affinity ligand for the phencyclidine recognition site on the *N*-methyl-D-aspartate-type glutamate receptors. *J. Pharmacol. Exp. Ther.* **1992**, *260*, 21–28.

(2) 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. Also, see: Carroll, F. I.; Brine, G. A.; Boldt, K. G.; Mascarella, S. W.; Moreland, C. G.; Sumner, S. J.; Burgess, J. P.; Stejskal, E. O. Solid state conformation of phencyclidine and phencyclidine analogs. In *Sigma and Phencyclidine-Like Compounds as Molecular Probes in Biology*; Domino, E. F., Kamenka, J.-M., Eds.; NPP Books: Ann Arbor, MI, 1988; pp 91–106. Manallack, D. T.; Beart, P. M. Quantitative conformational analyses predict distinct receptor sites for PCP-like and σ drugs. *Eur. J. Pharmacol.* **1987**, *144*, 231–235.

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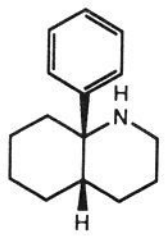
Table I. Optical Rotations and Binding Data for Compounds 3 and 4

compd	optical rotation: $[\alpha]^{25}_D$, deg [c (g/100 mL), solvent]	IC_{50} (nM)	nH
(+)-3	+21.8 (0.57, $CHCl_3$)	158.7 ± 24	0.96 ± 0.04
(−)-3	−19.3 (0.56, $CHCl_3$)	467.4 ± 52	1.05 ± 0.07
(+)-4	+3.3 (1.05, $CHCl_3$)	94.6 ± 28	1.12 ± 0.11
(−)-4	−3.6 (0.85, $CHCl_3$)	66.3 ± 9.7	1.19 ± 0.19
PCP		35[a]	
MK-801		1.4[a]	

[a] Data taken from ref 1a.

vivo measurements of their effects on cGMP levels in mice. The results of the binding experiments are interpreted in terms of a preferred orientation of PCP's N–H bond.



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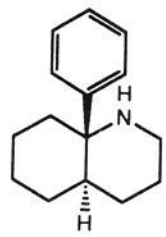

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Synthesis

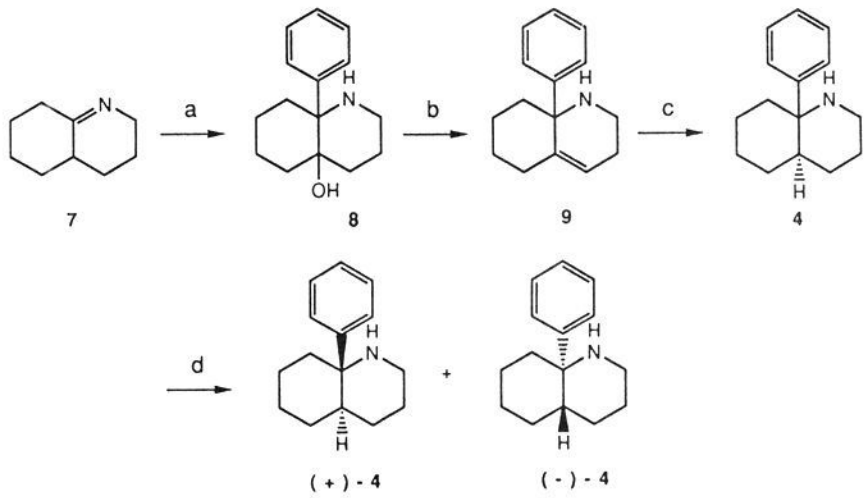
The cis-fused quinoline **3** was synthesized by reacting the enamine **5** with acrylonitrile (Scheme I), reducing the nitrile to amine, and then refluxing with a sodium hydroxide solution to generate $\Delta^{1,8a}$-octahydroquinoline **7**.[3] This cyclic imine was reacted in turn with phenyllithium to provide solely the cis-fused quinoline **3**.[4] Chemical resolution of compound **3** was accomplished by fractional crystallization of the derived camphanic acid amides followed by a two step amide cleavage protocol[5] to provide (+)-**3** and (−)-**3** (for optical rotations, see Table I). The determination of absolute stereochemistry of these isomers was described previously.[5] These compounds were converted to their hydrochloride salts in order to facilitate biological testing.

The trans-fused quinoline **4** was synthesized in a novel fashion by reacting the hydroperoxide derived from **7** by air oxidation with phenyllithium in ether (Scheme II). The resulting cis-fused quinoline **8** was reacted with sulfuric acid to provide the octahydroquinoline **9**, which was reduced exclusively to the desired trans-fused quinoline **4** by use of Adam's catalyst in methanol. Racemic **4** was resolved by fractional crystallization of its tartaric acid salts. The absolute stereochemistry of the enantiomers were assigned on the basis of an X-ray structural analysis of the (+)-tartaric acid salt of (−)-**4** (supplementary material). The hydrochloride salts of (+)- and (−)-**4** were used for biological testing.

Molecular Mechanics Studies

From molecular mechanics studies (conformational analyses were performed by using the systematic conformational search program SS1 in conjunction with the Tripos SYBYL program and the MM2 force field available in MACROMODEL[6]), the cis-compound **3** can exist either in conformer **3a** or **3b**, with **3a** being 2.5 kcal/mol (MM2 energy) lower in energy than **3b**. Conformer **3b** constains an incorrect N–H bond orientation to satisfy the binding model proposed in **2**, while conformer **3a** possesses the "favored" anti orientation. However, in this conformer an unfavorable steric interaction is likely to be incurred between the "carboxylate" acceptor group and the cyclohexane ring in satisfying model **2**. Conformer **3a** can also be viewed from the perspective of possessing an equatorial phenyl group on the cyclohexane ring, and thereby it fails to satisfy the structural requirements for PCP binding as delineated previously.[1] Compound **4**, on the other hand, will exist in the conformation depicted below, and thus it expresses the favored "anti" orientation (also, see Figure 1). On the basis of the proposed model **2**, one would anticipate that one of the enantiomers of **4** should bind with higher affinity than the enantiomeric forms of **3**.

Scheme II[a]



[a] (a) 1. O_2, EtOAc, room temperature (32%); 2. PhLi, Et_2O, reflux, 2 h; 3. H_2O (64%); (b) H_2SO_4, CH_2Cl_2, room temperature, 5 h (91%); (c) H_2, PtO_2, MeOH, 40 h (49%); (d) fractional crystallization of L-tartaric acid salt.

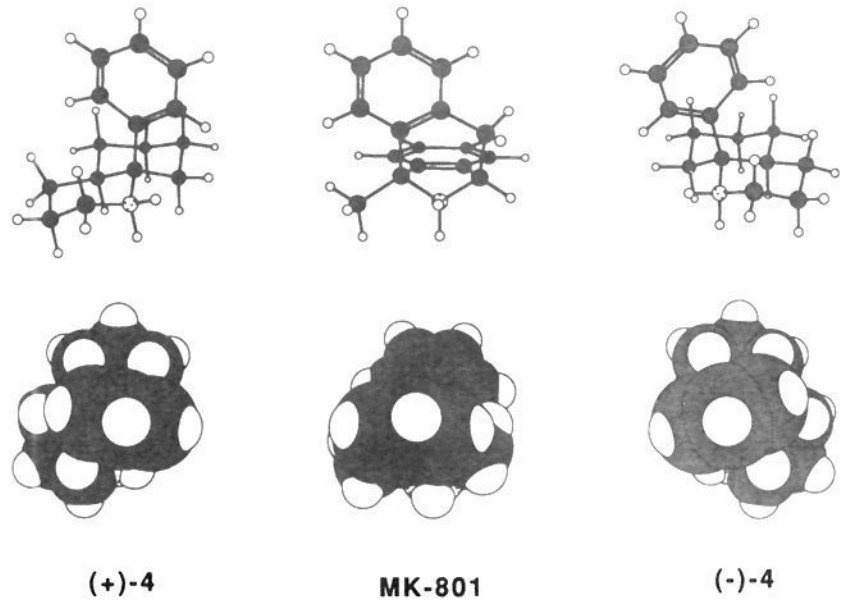


Figure 1. CPK and ball and stick models of (+)-**4**, (−)-**4**, and MK-801.

Biological Studies

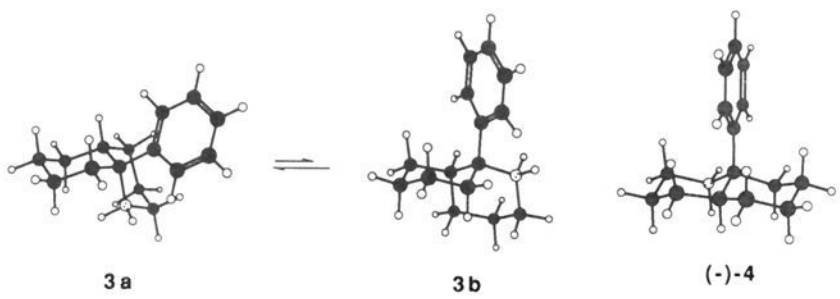
To test the proposed model **2**, binding assays were performed using [^{3}H]dizocilpine ([^{3}H]MK-801), a high affinity ligand which is selective for the PCP recognition

(3) Cohen, L. A.; Witkop, B. Transannular reaction of peptides. The peptide nitrogen in a 10-membered ring. *J. Am. Chem. Soc.* **1955**, *77*, 6595–6600.

(4) Godefroi, E. F.; Simanyi, L. H. Angularly arylated decahydroquinolines, hexahydroindolines and octahydropyrindines. *J. Org. Chem.* **1962**, *27*, 3882–3885.

(5) Kozikowski, A. P.; Chen, C.; Ball, R. G. An unusual fragmentation process discovered during the course of cleavage of a camphanic acid amide. *Tetrahedron Lett.* **1990**, *31*, 5869–5872.

(6) The SS1 program developed by Dr. Yuan-Ping Pang at the Mayo Clinic Jacksonville scans all the energy-minimized conformations which are initially generated by rotating all possible rotatable bonds of a molecule at user defined increments. SYBYL (V5.41) program: Tripos Associates, Inc., 1699 S. Hanley Road, Suite 303, St. Louis, MO 63144 and MACROMODEL (V3.1X): Professor W. C. Still, Department of Chemistry, Columbia University, New York.



sites on the NMDA receptor complex.[7] This assay system is now widely used in characterizing diverse modulators of the NMDA receptor complex, and moreover, it also provides a good prediction of functional activity (i.e., agonist, antagonist, or partial agonist activity) in in vitro as well as in vivo assay systems. The (+)-isomer of **3** exhibited an IC_{50} of 158.7 ± 24 nM in this assay, while the (−)-isomer was less potent (IC_{50} = 467.4 ± 52 nM). On the other hand, (+)-**4** exhibited an IC_{50} of 94.6 ± 28 nM while that of (−)-**4** is 66.3 ± 9.7 nM. The binding data together with Hill coefficients are presented in Table I. The IC_{50} values for PCP and MK-801 are also provided for comparison.

These four PCP analogues were also tested in male Swiss Webster mice for their antagonist effects on cGMP levels according to the method of Wood et al.[8] The in vivo cerebellar cGMP measurement provides a biochemical index of cerebellar Purkinje cell activity, which has been shown previously to be modulated by excitatory amino acid inputs. Phencyclidine-like ligands exhibit a noncompetitive antagonism of NMDA receptor agonist activity in this neuronal system. In this assay, (+)-MK-801 decreased cGMP with an ED_{50} of 0.3 mg/kg, subcutaneous administration, and a Hill number of 0.57. Surprisingly, in the same assay, (−)-**4** was found to be 48-fold more potent (ED_{50} = 0.16 mg/kg, subcutaneous administration, see Figure 2) than its (+)-isomer. For both the (+)- and (−)-enantiomers, the pseudo Hill numbers for the logit-log dose regressions were significantly less than unity (0.42 for the (+)-isomer and 0.29 for the (−)-isomer), data which are consistent with noncompetitive inhibition at the NMDA receptor complex. The cis-isomers **3** were also tested and found to decrease basal cGMP levels by 10 to 20% but with no dose–response relationship.

Discussion

Since the binding affinity of (−)-**4** is higher than that of (+)- or (−)-**3**, we believe that this result provides support for the anti N–H/C–phenyl relation displayed in **2**. The fact that (−)-**4** binds with lower affinity than PCP may result from the following: (a) possible steric interactions between the rigidifying three-carbon chain of **4** and certain residues comprising the PCP recognition site, or (b) the fact that ϕ deviates from the preferred value of 90° (in the gmec of **4**, ϕ was found to be about 53°). Somewhat surprising, however, is the relatively small binding difference observed between the (+)- and (−)-isomers. In order to gain some understanding of the close binding affinities of these compounds, overlays of (+)- and (−)-**4** with MK-801 were carried out by manual fitting which was monitored

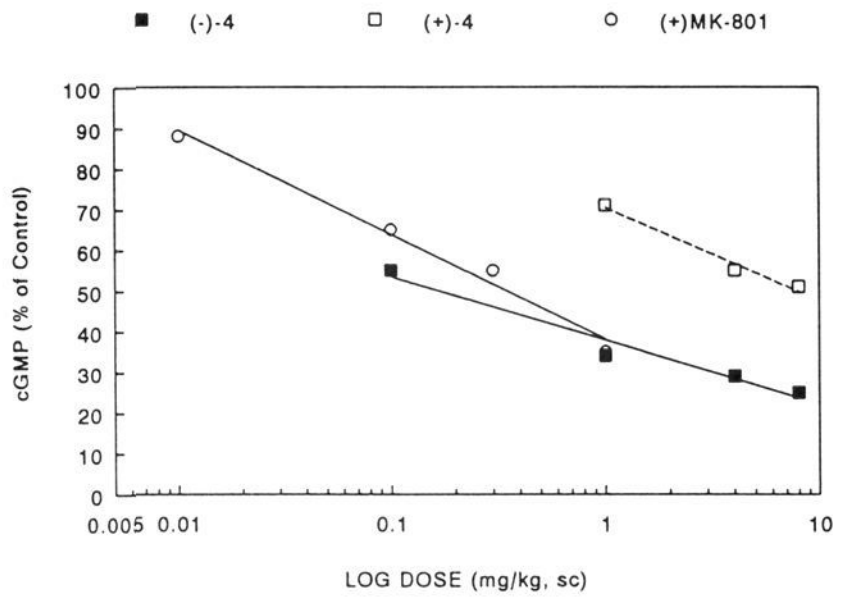


Figure 2. Decreases in cerebellar cGMP elicited by subcutaneous administration of (+)-MK-801, (−)-**4**, and (+)-**4**. The ED_{50} (mg/kg, sc) values and Hill numbers were 0.3 and 0.57 for (+)-MK-801, 0.16 and 0.29 for (−)-**4**, and 7.8 and 0.42 for (+)-**4**.

by a Field-Fit energy calculation available in SYBYL.[6] The overlay study revealed a relatively small difference between the (+)- and (−)-isomers in terms of their three-dimensional correspondence with MK-801. Similarities among the three structures are readily apparent from the CPK and ball and stick models displayed in Figure 1, and such similarities serve to rationalize the observed binding affinities.

The larger stereoselectivity of action observed for (+)- and (−)-**4** in the in vivo cGMP assay as compared to the relatively small difference found in the binding assay may relate to differential uptake, adsorption, distribution, and/or metabolism as well as a possible action at other undefined CNS receptors. Although further work is needed to discover the actual source of this differential activity, it is of interest to note that (−)-**4** displays higher in vivo potency in the cGMP assay than does PCP,[8] which has an ED_{50} of 5 mg/kg in this assay. Indeed, (−)-**4** has a potency (ED_{50} = 0.16 mg/kg) which is similar to that of (+)-MK-801 (ED_{50} = 0.3 mg/kg).

In conclusion, the series of compounds reported herein provide evidence for the anti-orientation of the N–H and C–phenyl bonds in the binding of PCP to its recognition site.[9] The novel ligand (−)-**4** binds with an affinity close to that of PCP and additionally it exhibits excellent in vivo potency as a noncompetitive antagonist of the NMDA receptor complex. Further study of (−)-**4** in animal models of ischemia would therefore appear warranted.

Experimental Section

THF and Et_2O were distilled from sodium benzophenone ketyl prior to use. Benzene and toluene were distilled from CaH_2 prior to use. CH_2Cl_2 was dried by passage through a column of activity I neutral alumina and stored over 4-Å molecular sieves. Solvents used for chromatography were purchased in 5-gal drums, redistilled in all-glass apparatus, and stored in glass bottles. Silica gel 60 (Merck, 70–230 mesh, or 230–400 mesh for flash chromatography) was used for column chromatography. TLC was performed on Merck silica gel 60F-254 (0.25 mm, precoated on glass). Other reagents were used as supplied, or purified as noted. ^1H and ^{13}C NMR spectra were recorded at 300.13 and 75.47 MHz on a Bruker AC-300, respectively, with $CDCl_3$ or C_6D_6 as the internal standard. Infrared spectra were obtained on a Mattson

(7) Reynolds, I. J.; Murphy, S. N.; Miller, R. J. ^3H-labeled MK-801 binding to the excitatory amino acid receptor complex from rat brain is enhanced by glycine. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 7744–7748.

(8) Wood, P. L.; Steel, D.; McPherson, S. E.; Cheney, D. L.; Lehmann, J. Antagonism of N-methyl-D-aspartate evoked increases in cerebellar cGMP and striatal ACh release by phencyclidine receptor agonists: Evidence for possible allosteric coupling of NMDA and PCP receptors. *Can. J. Physiol. Pharmacol.* **1987**, *65*, 1923–1927.

(9) The hydrogen bonding model proposed herein is consistent with the notions developed for ligand interactions with the NMDA receptor ion channel using benzoazabicyclo[x.y.z]alkanes. Leeson, P. D.; Carling, R. W.; James, K.; Smith, J. D.; Moore, K. W.; Wong, E. H. F.; Baker, R. *J. Med. Chem.* **1990**, *33*, 1296–1305.

2020 FT-IR, low resolution mass spectra on a Hewlett-Packard 5971A spectrometer, and high resolution mass spectra on a VG 70-SE double focusing magnetic sector spectrometer. Elemental analyses were obtained from Oneida Research Services, Inc., Whitesboro, NY.

***cis*-8a-Phenyldecahydroquinoline (3).** To a solution of compound **7** (5.8 g, 42 mmol) in 10 mL of ether was added 106 mL of 1.35 M phenyllithium in ether, and the mixture was refluxed for 2 h under a nitrogen atmosphere. The mixture was chilled in ice water and quenched with water. The ether solution was decanted, and the aqueous solution was extracted with ether. The combined ethereal extracts were washed with water and dried over magnesium sulfate. After evaporation, the residual oil was submitted to flash chromatography on silica gel deactivated with ammonia gas using 10% ethyl acetate–hexane as eluent to afford 4.5 g (50%) of **3** as an oil: IR (thin film) 3347, 3070, 3051, 3017, 2934, 2867, 1455, 756, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2–7.5 (m, 5 H), 2.83 (m, 1 H), 2.7 (m, 1 H), 2.35 (m, 1 H), 2.1–1.8 (m, 1 H), 1.1–1.85 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 148.2, 128.5, 126.0, 125.7, 58.2, 44.0, 42.1, 35.7, 27.2, 26.6, 22.5, 21.3; mass spectrum *m/z* 215 (M^+), 186, 172, 158, 138, 104, 91, 77, 55, 43. Anal. ($C_{15}H_{21}N$) C, H, N.

***cis*-4a-Hydroxy-8a-phenyldecahydroquinoline (8).** To a solution of 4a-hydroperoxy-$\Delta^{8,8a}$-octahydroquinoline (20.8 g, 0.123 mol) in 250 mL of ether was added 250 mL of 1.2 M phenyllithium in ether. The solution was refluxed under a nitrogen atmosphere for 2 h, cooled in ice water, and quenched in water. The aqueous solution was extracted with ether, and the combined organic extracts were washed with water and dried over sodium sulfate. After concentration, the crude oil was submitted to flash chromatography on silica gel using first 10% and then 33% ethyl acetate–hexane as eluent to give 18.2 g (64%) of compound **8**: mp 90.5–91.5 °C; IR (KBr) 3216 (b), 3051, 3016, 2913, 2853, 1489, 1443, 1140, 1034, 995, 812, 752, 700, 542 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.94 (d, 2 H, *J* = 8.0 Hz), 7.31 (t, 2 H, *J* = 7.7 Hz), 7.19 (t, 1 H, *J* = 7.3 Hz), 2.5–2.9 (b, 3 H), 1.2–2.05 (b, 13 H); ^{13}C NMR ($CDCl_3$) δ 146.3, 128.7 (2 C), 127.9 (2 C), 125.9, 77.2, 73.4, 62.0, 41.1, 35.4 (2 C), 24.6, 21.6 (2 C); mass spectrum *m/z* 231 (M^+), 214, 202, 188, 175, 160, 154, 145, 132, 119, 104, 91, 86, 77, 55.

8a-Phenyl-$\Delta^{4,4a}$-octahydroquinoline (9). To a solution of compound **8** (18.2 g, 78.8 mmol) in 150 mL of methylene chloride at 0 °C was added 21 mL of concentrated sulfuric acid, and the mixture was stirred at room temperature for 5 h. The solution was basified with 6 N sodium hydroxide solution, and the aqueous solution was extracted with methylene chloride. The combined organic extracts were dried over sodium sulfate. After concentration, the crude oil was submitted to flash chromatography on silica gel deactivated with ammonia gas using first 10% and then 33% ethyl acetate–hexane as eluent to give 15.3 g (91%) of compound **9** as an oil: IR (thin film) 3277, 3080, 3052, 3022, 2928, 2855, 1599, 1491, 1447, 1350, 1120, 1016, 937, 853, 756, 700, 663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2–7.45 (m, 5 H), 5.76 (t, 1 H, *J* = 2.4 Hz), 2.7 (m, 1 H), 2.55 (m, 1 H), 1.9–2.1 (m, 4 H), 1.45–1.7 (m, 4 H), 1.1–1.45 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 143.9, 140.7, 128.0 (2), 127.4 (2), 126.3, 121.3, 59.5, 39.6, 37.4, 33.9, 27.9, 26.2, 22.8; mass spectrum *m/z* 213 (M^+), 198, 184, 156, 122, 104, 83, 77, 67, 40.

***trans*-8a-Phenyldecahydroquinoline (4).** A mixture of compound **9** (0.379 g, 1.78 mmol) and platinum(IV) oxide (0.19 g) in 90 mL of methanol was stirred under a hydrogen atmosphere at room temperature for 40 h. The reaction solution was filtered and washed with methanol. After concentration, the crude oil was submitted to flash chromatography over silica gel deactivated with ammonia gas using ethyl acetate as eluent to afford 0.189 g (49%) of compound **4** as an oil. IR (thin film) 3285, 3060, 3047, 2922, 2851, 1487, 1445, 1113, 758, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–7.6 (m, 5 H), 2.65 (m, 1 H), 2.3 (m, 1 H), 2.0 (m, 3 H), 1.8 (m, 2 H), 1.3–1.7 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 144.8, 129.3 (2 C), 127.6 (2 C), 125.7, 59.5, 48.3, 44.3, 41.8, 30.6, 28.5, 28.0, 27.1, 22.4; exact mass calcd for $C_{15}H_{21}N$ 215.1674, found 215.1674; mass spectrum *m/z* 215 (M^+), 186, 172, 158, 138, 132, 104, 91, 77, 67, 41. Anal. ($C_{15}H_{21}N$) C, H, N.

***cis*-(±)-*N*-[(4′,7′,7′-Trimethyl-3′-oxo-2′-oxabicyclo[2.2.1]-heptyl)-1′-carbonyl]-8a-phenyldecahydroquinoline.** (1*S*)-(−)-Camphanic chloride (3.64 g, 16.8 mmol) was slowly added to a solution of compound **3** (3.62 g, 16.8 mmol) and pyridine (2.00 g, 25.2 mmol) in 44 mL of methylene chloride and 22 mL of ether at 0 °C. After the addition, the temperature of the reaction was raised to room temperature, and stirring was continued for 3 h. The solution was filtered and washed with methylene chloride. The filtrate was concentrated, and the residue was submitted to flash chromatography on silica gel deactivated with ammonia gas using 20% ethyl acetate–hexane as eluent to give 3.23 g (49%) of the 3-amide. The racemate was separated by four fractional crystallizations from 10% ethyl acetate–hexane. The crystals of the first fractional crystallization were recrystallized to give the (−)-3-amide. The mother liquor of the first fractional crystallization was evaporated and recrystallized to give the (+)-3-amide.

(−)-3-amide: mp 191.5–192.5 °C; $[\alpha]^{25}_D$ −348.8° (*c* 1.27 g/100 mL, $CHCl_3$); IR (KBr) 3057, 2955, 2928, 2895, 1788, 1645, 1446, 1412, 1390, 1373, 1331, 1267, 1165, 1124, 1101, 1047, 1018, 920, 760, 704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15 (m, 5 H), 3.95 (d, 1 H, *J* = 14 Hz), 3.3 (dd, 1 H, *J* = 14, 4 Hz), 2.82 (td, 1 H, *J* = 8.7, 4.0 Hz), 2.5 (m, 1 H), 2.3 (dd, 1 H, *J* = 12, 4 Hz), 1.2–2.25 (m, 14 H), 1.3 (s, 3 H), 1.12 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.0, 170.6, 146.2, 128.7, 126.5, 126.3, 93.6, 68.7, 56.4, 54.1, 45.1, 42.0, 39.5, 32.0, 30.2, 28.3, 26.6, 25.8, 24.3, 20.4, 18.6, 17.0, 9.9; exact mass calcd for $C_{25}H_{33}NO_3$ 395.2460, found 395.2460; mass spectrum *m/z* 395 (M^+), 352, 336, 318, 302, 242, 214, 198, 172, 157, 129, 109, 91, 83, 67.

(+)-3-amide: mp 153.5–154.5 °C; $[\alpha]^{25}_D$ +116.0° (*c* 1.87 g/100 mL, $CHCl_3$); IR (KBr) 3055, 2995, 2963, 2932, 2893, 2866, 1778, 1641, 1496, 1446, 1410, 1394, 1369, 1329, 1269, 1165, 1122, 1097, 1045, 924, 762, 704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44 (dtt, 5 H, *J* = 7.2, 5.1, 4.5 Hz), 3.8 (dt, 1 H, *J* = 14, 2.7 Hz), 3.2 (t, 1 H, *J* = 8 Hz), 2.9 (d, 1 H, *J* = 12 Hz), 2.55 (m, 1 H), 2.34 (m, 1 H), 1.3–2.2 (m, 14 H), 1.1 (s, 6 H), 0.9 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.9, 169.3, 145.9, 128.3, 126.9, 126.1, 94.1, 67.2, 54.8, 54.4, 43.7, 40.3, 36.9, 33.1, 29.3, 28.2, 26.2, 24.1, 21.7, 17.7, 17.6, 9.7; exact mass calcd for $C_{25}H_{33}NO_3$ 395.2460, found 395.2460; mass spectrum *m/z* 395 (M^+), 352, 336, 318, 302, 242, 214, 198, 172, 157, 129, 109, 91, 83, 67.

(4a*R*,8a*R*)-*cis*-*N*-Formyl-8a-phenyldecahydroquinoline. A mixture of (+)-3-amide (0.244 g, 0.62 mmol), potassium *tert*-butoxide (0.555 g, 4.9 mmol), and 44.5 μL of water in 30 mL of ether was stirred at room temperature for 3 days. The mixture was filtered and washed with ether. The filtrate was concentrated, and the residual oil was submitted to flash chromatography over silica gel deactivated with ammonia gas using 20% ethyl acetate–hexane as eluent to give 78.1 mg (52%) of the title compound as an oil: $[\alpha]^{25}_D$ +96.9° (*c* 0.78, $CHCl_3$); IR (thin film) 3058, 2930, 2859, 2700, 1655, 1495, 1447, 1379, 1260, 1236, 1180, 1122, 1101, 754, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.5 (s, 1 H), 7.2–7.4 (m, 5 H), 4.4 (d, 1 H, *J* = 12.8 Hz), 2.5 (m, 2 H), 2.27 (d, 1 H, *J* = 14.4 Hz), 1.20–1.95 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 163.1, 145.3, 129.1, 127.1, 125.5, 64.3, 39.7, 38.0, 37.6, 27.1, 26.3, 26.0, 22.6, 19.5; exact mass calcd for $C_{16}H_{21}NO$ 243.1623, found 243.1623; mass spectrum *m/z* 243 (M^+), 214, 200, 198, 172, 157, 144, 129, 104, 91, 77, 55, 43.

(4a*S*,8a*S*)-*cis*-*N*-Formyl-8a-phenyldecahydroquinoline. A mixture of the (−)-*N*-formyl-3 (0.175 g, 0.44 mmol), potassium *tert*-butoxide (0.40 g, 1.78 mmol), and 31.9 μL of water in 20 mL of ether was stirred at room temperature for 3 days. The mixture was filtered and washed with ether. The filtrate was concentrated, and the residual oil was submitted to flash chromatography on silica gel deactivated with ammonia gas using 33% ethyl acetate–hexane as eluent to give 71 mg (66%) of (−)-3-formyl as an oil: $[\alpha]^{25}_D$ −78.8° (*c* 0.67 g/100 mL, $CHCl_3$); IR (thin film) 3058, 2930, 2859, 2700, 1655, 1495, 1447, 1379, 1260, 1236, 1180, 1122, 1101, 754, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.5 (s, 1 H), 7.2–7.4 (m, 5 H), 4.4 (d, 1 H, *J* = 12.8 Hz), 2.5 (m, 2 H), 2.27 (d, 1 H, *J* = 14.4 Hz), 1.20–1.95 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 163.1, 145.3, 129.1, 127.0, 125.5, 64.3, 39.7, 38.0, 37.6, 27.1, 26.3, 26.0, 22.6, 19.5; exact mass calcd for $C_{16}H_{21}NO$ 243.1623, found 243.1623; mass spectrum *m/z* 243 (M^+), 214, 200, 198, 172, 157, 144, 129, 104, 91, 77, 55, 43.

(4a*S*,8a*S*)-*cis*-8a-Phenyldecahydroquinoline [(−)-3]. At 0 °C and under a nitrogen atmosphere, the (−)-*N*-formyl derivative (57.6 mg, 0.24 mmol) was dissolved in 5 mL of ether, and 0.58 mL of 1.225 M phenyllithium in 75:25 benzene–ether was added. Then the temperature was raised to room temperature, and the mixture was stirred for 45 min. The reaction solution was cooled to 0 °C and quenched with water. The aqueous solution was

extracted with ether, and the combined extracts were dried over sodium sulfate. After concentration, the residual oil was submitted to flash chromatography on silica gel deactivated with ammonia gas using 10% ethyl acetate–hexane as eluent to give 49 mg (96%) of (−)-**3** as an oil: $[\alpha]^{25}_D$ −19.3° (*c* 0.56 g/100 mL, $CHCl_3$); IR (thin film) 3347, 3070, 3051, 3017, 2934, 2867, 1455, 756, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2–7.5 (m, 5 H), 2.83 (m, 1 H), 2.7 (m, 1 H), 2.35 (m, 1 H), 1.8–2.1 (m, 1 H), 1.1–1.85 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 148.2, 128.5, 126.0, 125.7, 58.2, 44.0, 42.1, 35.7, 27.2, 26.6, 26.0, 22.5, 21.3; mass spectrum *m/z* 215 (M^+), 186, 172, 158, 138, 104, 91, 77, 55, 43. Anal. ($C_{15}H_{21}N$) C, H, N.

(4a*R*,8a*R*)-*cis*-8a-Phenyldecahydroquinoline [(+)-3]. At 0 °C and under a nitrogen atmosphere, the (+)-*N*-formyl derivative (61.2 mg, 0.25 mmol) was dissolved in 5 mL of ether, and 0.62 mL of 1.225 M phenyllithium in 75:25 benzene–ether was added. After the addition, the temperature was raised to room temperature, and the mixture was stirred for 45 min. The reaction solution was cooled to 0 °C and quenched with water. The aqueous solution was extracted with ether, and the combined extracts were dried over sodium sulfate. After concentration, the residual oil was submitted to flash chromatography on silica gel deactivated with ammonia gas using 10% ethyl acetate–hexane as eluent to afford 47.9 mg (89%) of (+)-**3** as an oil: $[\alpha]^{25}_D$ +21.8° (*c* 0.57 g/100 mL, $CDCl_3$); IR (thin film) 3347, 3070, 3051, 3017, 2934, 2867, 1455, 756, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2–7.5 (m, 5 H), 2.83 (m, 1 H), 2.7 (m, 1 H), 2.35 (m, 1 H), 1.8–2.1 (m, 1 H), 1.1–1.85 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 148.2, 128.5, 126.0, 125.7, 58.2, 44.0, 42.1, 35.7, 27.2, 26.6, 26.0, 22.5, 21.3; mass spectrum *m/z* 215 (M^+), 186, 172, 158, 138, 104, 91, 77, 55, 43. Anal. ($C_{15}H_{21}N$), C, H, N.

Optical Resolution of *trans*-8a-Phenyldecahydroquinoline (4). A mixture of **4** (2.10 g, 9.7 mmol) and L-tartaric acid in 25 mL of methylene chloride and 10 mL of methanol was stirred at room temperature for 6 h. The solvent was removed, and the residue was recrystallized from methanol. After several recrystallizations, the (+)-salt was obtained. The mother liquor of the first recrystallization was concentrated, and the residue was made alkaline with 6 N sodium hydroxide solution. The recovered **4** (0.87 g, 4.0 mmol) and D-tartaric acid (0.61 g, 4.0 mmol) were converted to the (−)-salt which was purified by several recrystallizations from methanol. The (+)- and (−)-salts were converted to (−)-**4** and (+)-**4** with 6 N sodium hydroxide solution. The optical purity of (+)-**4** and (−)-**4** was checked by ^{13}C NMR. The ^{13}C NMR samples were prepared as follows: (±)-**4** (52.00 mg), C_6D_6 (0.4 mL), Eu(hfc)$_3$ [0.25 mL of a 241.2 mg/mL solution in C_6D_6]; (+)-**4** (53.34 mg), C_6D_6 (0.4 mL), Eu(hfc)$_3$ [0.25 mL of a 241.2 mg/mL solution in C_6D_6]; (−)-**4** (55.58 mg), C_6D_6 (0.4 mL), Eu(hfc)$_3$ [0.25 mL of a 241.2 mg/mL solution in C_6D_6]. The samples were heated at 65 °C for 1 h prior to measurement. In the chemical shift region between 27.5 to 28.5 ppm, (±)-**4** exhibited two separate peaks, but (+)-**4** and (−)-**4** exhibit only a single peak.

(+)-Salt: mp 162.0–163.0 °C; $[\alpha]^{25}_D$ +27.2° (*c* 1.48 g/100 mL, CH_3OH).

(−)-Salt: mp 163.5–164.5 °C; $[\alpha]^{25}_D$ −28.0° (*c* 1.50 g/100 mL, CH_3OH).

(4a*R*,8a*S*)-*trans*-8a-Phenyldecahydroquinoline [(+)-4]: $[\alpha]^{25}_D$ +3.3° (*c* 1.05 g/100 mL, $CHCl_3$); IR (thin film) 3285, 3060, 3047, 2922, 2851, 1487, 1445, 1113, 758, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–7.6 (m, 5 H), 2.65 (m, 1 H), 2.3 (m, 1 H), 2.0 (m, 3 H), 1.8 (m, 2 H), 1.3–1.7 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 144.8, 129.3, 127.6, 125.7, 59.5, 48.3, 44.3, 41.8, 30.6, 28.5, 28.0, 27.1, 22.4; exact mass calcd for $C_{15}H_{21}N$ 215.1674, found 215.1674; mass spectrum *m/z* 215 (M^+), 186, 172, 158, 138, 132, 104, 91, 77, 67, 41. Anal. ($C_{15}H_{21}N$) C, H, N.

(4a*S*,8a*R*)-*trans*-8a-Phenyldecahydroquinoline [(−)-4]: $[\alpha]^{25}_D$ −3.6° (*c* 0.85 g/100 mL, $CHCl_3$); IR (thin film) 3285, 3060, 3047, 2922, 2851, 1487, 1445, 1113, 758, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–7.6 (m, 5 H), 2.65 (m, 1 H), 2.3 (m, 1 H), 2.0 (m, 3 H), 1.8 (m, 2 H), 1.3–1.7 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 144.8, 129.3, 127.6, 125.7, 59.5, 48.3, 44.3, 41.8, 30.6, 28.5, 28.0, 27.1, 22.4; exact mass calcd for $C_{15}H_{21}N$ 215.1674, found 215.1674; mass spectrum *m/z* 215 (M^+), 186, 172, 158, 138, 132, 104, 91, 77, 67, 41. Anal. ($C_{15}H_{21}N$) C, H, N.

Radioligand Binding Assay. Radioligand binding studies were carried out in accord with the published protocols of Reynolds et al.[7]

cGMP Assay. Male Swiss Webster mice (20 g) were administered drugs subcutaneously and sacrificed by focussed microwave irradiation of the skull 30 min later. The cerebellum was removed, polytroned in 1 N HCl, and centrifuged at 35000*g* for 30 min, and an aliquot of the supernatant dried in a Savant Speed Vac. The dried extract was processed for measurement of cGMP using a commercial RIA kit (Advanced Magnetics) as previously described (ref 8).

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Registry No. (±)-**3**, 131556-11-1; (+)-**3**, 132562-03-9; (+)-**3**-camphanamide, 131615-09-3; (+)-**3**-formyl, 131556-10-0; (−)-**3**, 131615-08-2; (−)-**3**-camphanamide, 131556-12-2; (−)-**3**-formyl, 131556-13-3; (±)-**4**, 139973-43-6; (+)-**4**, 139973-44-7; (+)-**4**·D-tartaric acid, 139973-45-8; (−)-**4**, 139973-46-9; (−)-**4**·L-tartaric acid, 139973-47-0; **7**, 139870-90-9; **8**, 139870-91-0; **9**, 139870-92-1; 4a-hydroperoxy-1,2,3,4,4a,5,6,7-octahydroquinoline, 139870-93-2.

Supplementary Material Available: X-ray structure data report for the (+)-tartaric acid salt of **4** including methods of data collection and data reduction with references, a table of experimental details, and tables of interatomic bond distances and angles and positional and thermal parameters (16 pages). Ordering information is given on any current masthead page.