

methanol was added dropwise a solution of 3.1 g (10 mmol) of **4c** and 2.20 g (58 mmol) of NaBH₄ in 20 mL of methanol. Halfway through this addition, a second portion of 2.6 mL of 6 N H₂SO₄ was added to the reaction. The resulting mixture was stirred at room temperature for about 4 h. Analysis of the reaction mixture by TLC indicated the presence of mostly starting material. The pH of the reaction was adjusted to 4 (methyl orange) with 15% HCl. Additional formaldehyde was added (3.0 mL, 40 mmol), followed by 2.51 g (40 mmol) of NaCNBH₃. After 30 min, excess HCl was added, and the mixture was concentrated in vacuo. The residue was partitioned between CH₂Cl₂ and 5% NH₄OH. The organic layer was dried over MgSO₄ and evaporated. The residue was purified by MPLC (70% heptane, 29% EtOAc, 1% NH₄OH) to yield 0.50 g (15%) of **4f**: mp 89–93 °C; NMR (CDCl₃) δ 1.98–2.08 (2 H, m), 2.58–2.69 (6 H, m), 2.95 (6 H, s), 3.20–3.26 (4 H, m), 4.06 (2 H, t, *J* = 6.4 Hz), 6.30–6.41 (3 H, m), 6.84–6.98 (3 H, m), 7.11–7.33 (3 H, m); MS, *m/z* 339 (M, 71), 175 (100). Anal. (C₂₁H₂₉N₃O) C, H, N.

Pharmacological Methods. [³H]Haloperidol Receptor Binding Assay. The affinities of compounds for brain DA receptors were determined by standard receptor binding assays,¹³ according to methods described previously.²²

Effects on the Firing Rate of Substantia Nigra DA Neurons.¹⁴ The action potential of zona compacta DA cells was recorded in chloral anesthetized rats by using standard extracellular recording techniques. DA cells were identified by waveform and firing pattern and recording sites were verified histologically. Drugs were administered intraperitoneally via an indwelling catheter. Base-line firing rate was calculated by averaging the rate over the 2 min prior to drug injection. Drug effects were determined by averaging the response during the 1-min period of maximal inhibition. Drug-induced inhibition of firing was reversed with the DA antagonist haloperidol to confirm a DA agonist mechanism.

Inhibitions of spontaneous locomotor activity and motor coordination¹⁶ were carried out according to methods described previously.²²

Inhibition of GBL-Stimulated DA Synthesis.¹⁵ Compounds were administered to rats 1 h before sacrifice, and γ -butyrolactone (GBL, 750 mg/kg ip) and NSD 1015 (100 mg/kg ip) were administered 30 and 25 min, respectively, before sacrifice. Brain levels of dihydroxyphenylalanine (DOPA) were analyzed by HPLC with electrochemical detection.²³

Effects on Spontaneous Locomotion in Reserpinized Rat vs Normal Rat.¹⁸ Drugs were administered subcutaneously to normal rats treated with 5 mg/kg of reserpine 24 h prior to testing. Locomotor activity was measured for 30 min beginning immediately after drug administration as described previously.^{17,22}

Effects on Spontaneous Locomotion in 6-OHDA Lesioned Rats.¹⁹ Drugs were administered subcutaneously to rats treated at least one month previously with central injections of 6-hydroxydopamine (6-OHDA, 200 μ g icv) and systemic injections of pargyline (50 mg/kg ip) and desmethylimipramine (25 mg/kg ip) as described previously.²⁴ This treatment produced large selective depletion of brain DA (approximately 90%) as described previously²⁴ and as determined by brain DA determinations in representative animals. Locomotor activity was measured for 30 min beginning immediately after drug administration as described previously.^{17,22}

Sidman avoidance procedure²⁰ and **extrapyramidal side effect test**²¹ in mature squirrel monkeys were performed as described previously.²²

Acknowledgment. We wish to thank C. L. Christofersen, L. L. Coughenour, J. N. Wiley, and A. E. Williams for biological data.

Registry No. 2, 73966-53-7; 3, 85976-54-1; **4a**, 114597-68-1; **4a**·2HCl, 114597-69-2; **4b**, 114597-70-5; **4c**, 85868-45-7; **4d**, 114597-71-6; **4e**, 114614-34-5; **4f**, 114597-72-7; **5**, 621-42-1; **6**, 78702-97-3; **7a**, 114597-73-8; **7b**, 114597-74-9; **7c**, 78702-84-8; **7d**, 114597-75-0; **8c**, 10599-17-4; **8c**·2HCl, 93507-98-3; **9**, 78702-83-7; 1-bromo-3-chloropropane, 109-70-6; 1,2,3,6-tetrahydro-4-phenylpyridine dihydrochloride, 114597-76-1; 1-(2-pyridinyl)-piperazine, 34803-66-2; 1-phenylpiperazine, 92-54-6; *N*-propylphenethylamine, 27906-91-8.

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Synthesis, Pharmacological Action, and Receptor Binding Affinity of the Enantiomeric 1-(1-Phenyl-3-methylcyclohexyl)piperidines

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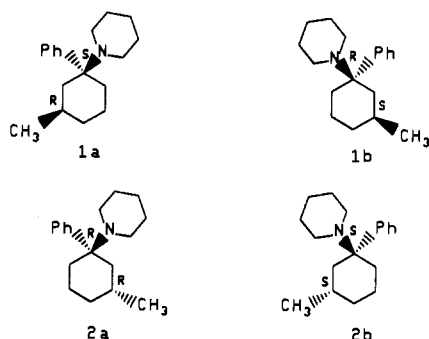
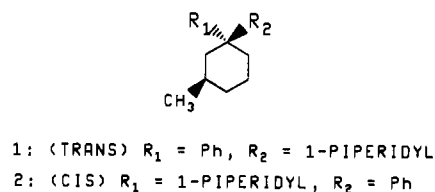
The cis and trans enantiomers of the 1-(1-phenyl-3-methylcyclohexyl)piperidines were prepared from either 3(*R*)- or 3(*S*)-methylcyclohexanone through the Bruylents reaction or a modified azide route, respectively. Separation of the intermediate amines **5** and **6** was achieved through chromatography or selective crystallization of a fumarate salt. The cis isomer **2b** had about one-third of the affinity of phencyclidine for the PCP receptor. The other isomers were less potent. There was a 40-fold difference between the binding affinity of the cis enantiomers **2a** and **2b** and a fourfold difference between the affinities of the trans enantiomers **1a** and **1b**. None of the compounds antagonized the stereotypy induced by phencyclidine in the rotarod assay in mice, after intraperitoneal introduction.

In 1981, Vincent et al.¹ examined the structure-activity relationships of various diastereomeric pairs of 1-(1-phenyl-2-methylcyclohexyl)piperidines and the 3-methyl and 4-methyl isomers. Those compounds having the methyl and phenyl group on the same side or "face" of the

cyclohexyl ring were referred to as cis compounds; those with methyl and phenyl on opposite sides were called trans.¹ For the purpose of simplicity we retain these definitions when referring to the diastereomers. Potentially important differences in the receptor binding and behavioral characteristics of some of these pairs of "facial" isomers were noted. For instance, while the affinities of the 3-methylcyclohexyl "cis" and 3-methylcyclohexyl "trans" diastereomers for the phencyclidine (PCP) receptor

(1) Vincent, J. P.; Vignon, J.; Kartolovski, B.; Lazdunski, M. *PCP (Phencyclidine): Historical and Current Perspectives*; Domino, E. F., Ed.; NPP Books: 1981; p 83.

Chart I

**Table I.** Binding Affinity of the Enantiomeric 1-(1-Phenyl-3-methylcyclohexyl)piperidines^a

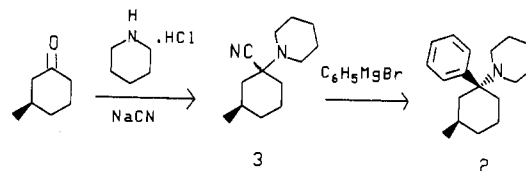
compound	K_i , μM	compound	K_i , μM
<i>trans</i> -1a	0.82 (± 0.03)	(+)-PCMP ^b	0.06 (± 0.007)
<i>trans</i> -1b	3.3 (± 0.96)	(-)-PCMP ^b	2.15 (± 0.61)
<i>cis</i> -2a	6.8 (± 0.54)	PCP ^c	0.06 (± 0.011)
<i>cis</i> -2b	0.17 (± 0.03)		

^a Displacement of [³H]TCP from tissue homogenate preparation of whole rat brain minus cerebellum. The K_i values were determined from displacement data run in triplicate and are the mean ($\pm$ standard deviation) of the results from at least three separate experiments. ^b 1-(1-Phenylcyclohexyl)-3-methylpiperidine. ^c Phencyclidine [1-(1-phenylcyclohexyl)piperidine].

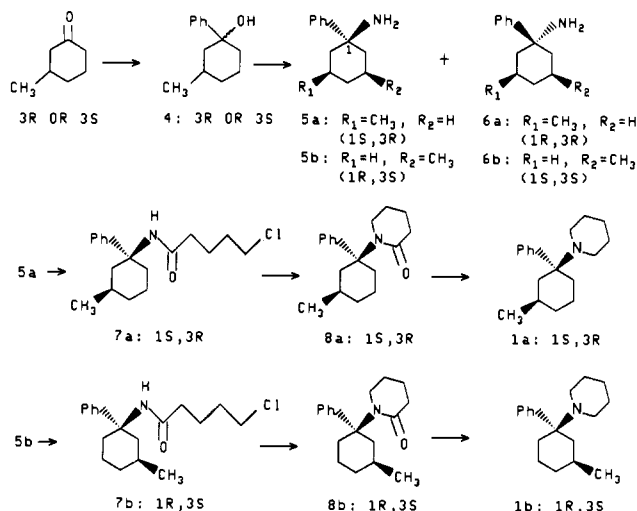
were found to be similar ($\text{IC}_{50} = 0.6 \mu\text{M}$) in a displacement assay, they showed a large difference in behavioral activity. The *trans* diastereomer was behaviorally active in the rotorod assay; the *cis* diastereomer was much less active. These findings suggested to us the possibility that one of the enantiomers in these diastereomers might have PCP antagonist activity and led us to examine more closely the 1-(1-phenyl-3-methylcyclohexyl)piperidine isomers through the preparation and isolation of the enantiomeric sets of "*trans*" (1a,b) and "*cis*" (2a,b) isomers (Chart I). We have determined their affinity for the PCP receptor and have made a preliminary assessment of their pharmacological activity using a rotorod assay.

Phencyclidine is a potent psychotomimetic agent that rivals heroin and cocaine in level of abuse. It is now generally accepted, on the basis of several lines of evidence, that at least some of the pharmacological effects of PCP are mediated through its interaction with the PCP receptor; however a specific receptor antagonist has yet to be identified. One of the generally accepted requirements for a "receptor" to be defined as such is that such a site should show stereospecificity of binding to the optical isomers of the ligand for which it is defined. Unfortunately, the achiral nature of PCP itself precludes it from being used for this purpose. While a number of agents that have been shown to be competitive with PCP at this site do show enantiomeric selectivity (dexoxadrol,² *N*-allyl-normetazocine,³ MK-8014⁴), they are structurally very

Scheme I



Scheme II



different from PCP. However, a pair of enantiomers from 1-(1-phenylcyclohexyl)-3-methylpiperidine (PCMP), which are structurally quite similar to PCP, were shown to have a distinct difference in binding (Table I) and behavioral action.⁵ We thought that the enantiomers of the *cis* and *trans* diastereomers of the 1-(1-phenyl-3-methylcyclohexyl)piperidines, which also retain a close structural resemblance to PCP, might prove to have affinity and stereoselectivity for the PCP receptor comparable to the aforementioned PCMP⁵ compounds.

Chemistry

The compounds were prepared from either 3(*R*)- or 3(*S*)-methylcyclohexanone. As has been shown,⁶ 3(*R*)-methylcyclohexanone is commercially available as optically pure material. The optically pure "unnatural" 3(*S*)-methylcyclohexanone was obtained by using a practical procedure developed in our laboratory.⁶ The "*cis*" enantiomers 2a and 2b were prepared from the amino nitrile derivatives 3 via the Bruylants reaction as described by Maddox⁷ (Scheme I). The Bruylants reaction is known to give only *cis* products. Thus, with pure 3(*R*)-methylcyclohexanone⁶ as the starting material, only the *R,R* compound 2a could be obtained. Similarly, the *S,S* compound 2b was the only compound obtained from the Bruylants reaction when pure 3(*S*)-methylcyclohexanone⁶ was used as the starting material. The "*trans*" derivatives 1a and 1b were prepared via a modification of the azide route of Geneste.⁸ Certain modifications were applied to

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this pathway, which, although requiring two additional synthetic steps, led to a more satisfactory overall yield. Scheme II shows the overall preparation. Phenyllithium was condensed with the appropriate cyclohexanone to give the tertiary alcohol 4. Treatment with sodium azide and trifluoroacetic acid followed by reduction of the resulting azide gave a 7:3 mixture of "trans" (5) to "cis" (6) amines. Since the reaction pathway gave both trans and cis compounds, the amino compounds 5a and 6a were obtained when 3(R)-methylcyclohexanone was the starting material, and 5b and 6b were obtained from 3(S)-methylcyclohexanone. Compounds 5a and 6a are diastereomers, as are 5b and 6b, and thus are easily purified and differentiated by GC and TLC. The amines 5a and 6a could be separated from their diastereomers 5b and 6b, respectively, by selective crystallization of the "trans" amine as its fumarate salt. The preparation of the piperidine ring, usually accomplished by the use of 1,5-dibromopentane, was found to proceed in considerably better yield (72% vs 41%) by the three-step process of N-acylation with 5-chloropropionyl chloride, followed by cyclization to the valerolactam and reduction to give trans-1-(1-phenyl-3-methylcyclohexyl)piperidine 1a or 1b. The "cis" amines 6a and 6b were not utilized since they lead to the cis compounds 2a and 2b, which had been obtained via the Bruylants reaction.

Results and Discussion

The receptor binding affinity of the enantiomers of the *trans*- and *cis*-1-(1-phenyl-3-methylcyclohexyl)piperidine (1a, 1b and 2a, 2b) assessed on the basis of competitive inhibition of tritiated 1-(2-thienylcyclohexyl)piperidine ($[^3\text{H}]\text{TCP}$) binding to rat brain tissues is shown in Table I. All of these compounds were shown to have less affinity for the PCP receptor than phencyclidine itself. When the binding affinities of the enantiomers 1a + 1b and 2a + 2b are averaged, the "racemic" values thus obtained are fairly similar for the "trans" and "cis" pairs, in agreement with the data of Vincent et al.¹ However, inspection of the binding data for the individual enantiomers reveals distinctly different binding affinities for the isomers in the "cis" and "trans" pairs. This is most pronounced for the "cis" compounds (2a, 2b), where the 3(S)-methylcyclohexyl enantiomer (2b) showed a 40-fold greater ability to displace $[^3\text{H}]\text{TCP}$ than did the 3(R)-methylcyclohexyl enantiomer (2a). Within the "trans" pair (1a, 1b) a smaller affinity difference (4 times) is found. The cis compounds 2a and 2b were somewhat less potent, although they were a little more enantiomerically selective, in binding to the PCP receptor than the PCMP isomers (Table I). The methyl substituent on the cyclohexane ring of PCP (in 2b) lessened the affinity of the molecule to the PCP receptor, unlike a methyl substituent on the piperidine ring of the PCP molecule (in the (+)-PCMP isomer), which had little or no effect on receptor binding, as compared with PCP itself (Table I). The enantiomerically selective binding of the *cis*-1-(1-phenyl-3-methylcyclohexyl)piperidines (2a and 2b) and the PCMP isomers lends credence to the presence of a distinct binding site for phencyclidine within a chiral matrix.

Vincent et al.¹ noted that the *cis*-1-(1-phenyl-3-methylcyclohexyl)piperidine mixture had affinity for the PCP receptor and that the *cis* mixture had little behavioral effect as measured by the rotorod assay. This led us to speculate on the possibility of antagonistic qualities residing within one of these enantiomers. Preliminary testing of compounds 2a and 2b against PCP with the rotorod assay, in mice (NIH colony, 20–25 g) injected intraperitoneally in doses representing up to 10 times the

PCP dose, indicated only potentiation of PCP stereotypy for both enantiomers. No antagonism of the stereotypy induced by PCP was noted.

Experimental Section

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were obtained on a Beckman 4230 spectrometer, CI mass spectra were obtained on a Finnigan 1015D mass spectrometer with NH_3 as the reagent gas, and ^1H NMR spectra were obtained on a Varian XL-300 spectrometer. GC was performed on a Hewlett-Packard 5880A instrument through a 12-m OV-1 capillary column, with a flame ionization detector. Optical rotations were obtained with a Perkin-Elmer 241MC polarimeter. All reported optical rotations were obtained on free bases dried under high vacuum. The free bases were obtained from their pure amine salt, after the salt had been crystallized to a constant melting point.

1-(1(R)-Phenyl-3(R)-methylcyclohexyl)piperidine (2a). Compound 2a was prepared in 54% overall yield from 3(R)-methylcyclohexanone according to the method used by Kalir et al.⁹ for the preparation of the racemic material. The final products were purified by recrystallization of the hydrochloride salts from ethyl acetate/hexane: mp 114–116 °C (HCl salt); TLC R_f 0.74 (2.5% $\text{MeOH}/\text{CHCl}_3/1\% \text{NH}_4\text{OH}$); (free base) $[\alpha]_D^{25} -35.1^\circ$ (*c* 3.75, CHCl_3); IR (neat) 2860, 1440, 1150, 1065, 945 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.3 (m, 5 H), 2.60 (dd, $J = 14.4, 14.4$ Hz, 2 H), 2.22 (m, 3 H), 1.95 (m, 1 H), 1.85 (ddd, $J = 13.2, 3.5, 3.5$ Hz, 1 H), 1.75 (d, $J = 14.1$ Hz, 1 H), 1.0–1.6 (m, 11 H), 0.91 (d, $J = 6.5$ Hz, 3 H); CI MS, m/z 258 ($\text{M} + \text{H}$)⁺. Anal. ($\text{C}_{18}\text{H}_{27}\text{N}\cdot\text{HCl}$) C, H, N.

1-(1(S)-Phenyl-3(S)-methylcyclohexyl)piperidine (2b). Compound 2b was prepared in 48% overall yield from 3(S)-methylcyclohexanone by using the procedure previously described for compound 2a: mp 114–115 °C (HCl salt); spectrally identical with 2a except for optical rotation; (free base) $[\alpha]_D^{25} +34.8^\circ$ (*c* 1.59, CHCl_3). Anal. ($\text{C}_{18}\text{H}_{27}\text{N}\cdot\text{HCl}$) C, H, N.

1-Phenyl-3(R)-methylcyclohexylamine (5a, 6a). Phenyllithium solution (1.1 equiv) was added dropwise at 0 °C to a solution of 3 g (26.7 mmol) of 3(R)-methylcyclohexanone in 50 mL of dry ether. After 10 min the reaction was carefully poured into a separatory funnel containing 150 mL of 0.1 N HCl. The organic layer was removed, dried with NaSO_4 , and concentrated to give 3.7 g (73%) of a mixture of isomeric 1-phenyl-3-methylcyclohexanols (4).

This mixture (19.5 mmol) was dissolved in 80 mL of chloroform, and an argon atmosphere was applied to the resulting solution. Powdered sodium azide (2.53 g, 39 mmol) was added, followed by 4.45 g (3.0 mL, 39 mmol) of trifluoroacetic acid. The violet mixture was stirred for 9 h, during which time the suspended solid material became a paste. The reaction was poured into a separatory funnel with 50 mL of water and 50 mL of saturated sodium bicarbonate solution. The organic layer was removed, dried (NaSO_4), and concentrated.

The concentrated material (4.0 g) was dissolved in 90 mL of dry ether, and 1.5 g of powdered lithium aluminum hydride was added in portions at 0 °C. The resulting mixture was then refluxed for 30 min. After cooling, 2 mL of ethyl acetate was added to the solution and the mixture was carefully poured into a separatory funnel containing 100 mL of 1.0 N HCl. The mixture was carefully shaken. The aqueous layer was returned to the funnel, aqueous ammonia was added until the mixture was basic to pH paper, and the resulting solution was extracted with ether (3×50 mL). The combined extracts were dried (NaSO_4) and concentrated to give 770 mg (21%) of isomeric amines. Gas chromatographic analysis (at 130 °C, retention times: 5a, 3.05 min, and 6a, 3.62 min) indicated a 7 to 3 ratio of 5 to 6. The separation of the diastereomers 5a and 6a (or 5b and 6b) could be successfully achieved either by column chromatography or by separation of 5a from the mixture by selective crystallization as its fumarate salt from ethyl acetate (see procedure below). Assignment of the relative stereochemistry of these compounds was made after conversion of the primary amines to the corresponding piperidines 1a and 2a and subsequent comparison of their ^1H NMR spectra with

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those of the known trans and cis racemates **1** and **2**.⁸ Their absolute stereochemistry and enantiomeric purity then followed from the previously established (>98%) enantiomeric purity of the 3(*R*)- and 3(*S*)-methylcyclohexanone.⁶ Since the reaction conditions employed were highly unlikely to affect the isolated chiral center of the 3-methylcyclohexanones, greater than 98% purity followed for the products. Diastereomeric purification of **5a** and **6a** was easily followed by TLC and GC. It was experimentally found that a 0.1% diastereomeric impurity was discernable by GC (see the experimental conditions below). Compounds **5a** and **6a** (and **5b** and **6b**) had less than 0.1% diastereomeric impurity.

Separation of the Diastereomeric Amines 1(*S*)-Phenyl-3(*R*)-methylcyclohexylamine (5a**) and 1(*R*)-Phenyl-3(*R*)-methylcyclohexylamine (**6a**).** A mixture of amines **5a** and **6a** (7:3 ratio, 1.0 g) was dissolved in 20 mL of EtOAc. A solution of 430 mg of fumaric acid (0.7 equiv) in 6 mL of hot methanol was added to produce a crystalline precipitate. After cooling, the precipitate (700 mg) was collected and recrystallized from 2-propanol to give 590 mg of **5a**·C₄H₄O₄ (59%): mp 220–221 °C; (free base) $[\alpha]_D^{25}$ –20.1° (c 0.77, methanol). Anal. (C₁₅H₁₉N·C₄H₄O₄) C, H, N. After conversion to the free base with concentrated NH₄OH, the mother liquor was separated by column chromatography (silical gel, 94% CHCl₃/5% MeOH/1% NH₄OH) to give 281 mg of **6a** and an additional 178 mg of **5a**.

In order to confirm that the GC assay method used for determination of diastereomeric purity during the separation of **5a** from **6a** (or **5b** from **6b**) was accurate to 0.1%, the following test was performed. A standard solution of **5a** (0.01 M) was prepared, and 0.05 mL of this solution was added to 10 mL of MeOH containing 94.5 mg of **6a**. This 0.1% "impurity" of **5a** in the **6a** was easily discerned by GC. The diastereomeric purity of **5a** and **6a** (and **5b** and **6b**) assures the diastereomeric purity of **1a** and **1b** since the reaction conditions employed could not have altered the stereochemistry.

1(*R*)-Phenyl-3(*S*)-methylcyclohexylamine (5b**).** The overall yield of **5b** and **6b** was 68%, and the same diastereomeric ratio of **5b** to **6b** was obtained as **5a** to **6a**. For **5b**·C₄H₄O₄: mp 171–173 °C; (free base) $[\alpha]_D^{25}$ 20.9° (c 0.77, methanol).

1(*R*)-Phenyl-3(*R*)-methylcyclohexylamine (6a**).** For **6a**·C₄H₄O₄: mp 203–204 °C; (free base) $[\alpha]_D^{25}$ –7° (c 0.024, methanol).

1(*S*)-Phenyl-3(*S*)-methylcyclohexylamine (6b**).** For **6b**·C₄H₄O₄: mp 201 °C; (free base) $[\alpha]_D^{25}$ +7° (c 0.024, methanol).

N-(1(*S*)-Phenyl-3(*R*)-methylcyclohexyl)-5-chlorovaleramide (7a**).** The fumarate salt of **5a** (0.49 g, 1.61 mmol) was dissolved in a two-phase mixture of 5 mL of CHCl₃ and 5 mL of saturated sodium carbonate solution. The mixture was rapidly stirred as 249 mg (1.61 mmol) of 5-chlorovaleryl chloride in 1.0 mL of CHCl₃ was added via syringe. After 20 min the CHCl₃ phase was removed by pipette, the aqueous layer was washed with another 2 mL of CHCl₃, and the combined organics were dried by passage through a short column of MgSO₄. Concentration of the filtrate gave 455 mg (92%) of the chloroamide **7a** as an oil: TLC *R*_f 0.47 (30% EtOAc/hexane); IR (neat) 3300, 3060, 2950, 2860, 1640, 1540, 1485 cm^{–1}; ¹H NMR (CDCl₃) δ 7.52 (d, *J* = 7.5 Hz, 2 H), 7.35 (dd *J* = 7.5 Hz, 2 H), 7.24 (m, 1 H), 5.44 (br, 1 H, NH), 3.48 (t, *J* = 6.1 Hz, 2 H), 2.68 (t, *J* = 14 Hz, 2 H), 2.05 (m, 4 H), 1.0–1.8 (m, 10 H), 0.91 (d, *J* = 6.7 Hz, 3 H); CI MS, *m/z* 308, 310.

N-(1(*R*)-Phenyl-3(*S*)-methylcyclohexyl)-5-chlorovaleramide (7b**).** The amide was obtained as an oil. The spectral data and MS were identical with those obtained with **7a**.

N-(1(*S*)-Phenyl-3(*R*)-methylcyclohexyl)-δ-valerolactam (8a**).** In a dry 25-mL side-arm flask containing an argon atmosphere, a quantity of sodium hydride (ca. 150 mg, 80% in oil) was washed twice with isooctane and then covered with 4 mL of dry ether. To this solution was added 450 mg of the chloroamide **7a** (1.4 mmol) in 4 mL of ether, and the resulting solution was refluxed until the starting material was undetectable by thin-layer chromatography (3 h). The solution was then cooled to room temperature, and the excess hydride destroyed by the addition of a few drops of water. The reaction mixture was filtered through a Celite pad, and the pad was subsequently washed with 10 mL of ether. The filtrate was concentrated to give 348 mg of the cyclic

amide **8** (92%). While the material was of sufficient purity to proceed with the reaction sequence, a portion of the mixture was purified by chromatography (30% EtOAc/hexane) to give pure **8** as an oil: TLC *R*_f 0.36 (30% EtOAc/hexane); (free base) $[\alpha]_D^{25}$ –15.1° (c 3.08, MeOH); IR 2945, 2870, 1643, 1455 cm^{–1}; ¹H NMR (CDCl₃) δ 7.48 (d, *J* = 7.5 Hz, 2 H), 7.30 (dd, *J* = 7.5, 7.5 Hz, 2 H), 7.19 (m, 1 H), 3.28 (t, *J* = 5.7 Hz, 2 H), 2.9 (m, 3 H), 2.24 (t, *J* = 6.6 Hz, 2 H), 1.0–2.05 (m, 10 H), 0.89 (d, *J* = 6.3 Hz, 3 H); CI MS, *m/z* 272. Anal. (C₁₈H₂₅NO) C, H.

N-(1(*R*)-Phenyl-3(*S*)-methylcyclohexyl)-δ-valerolactam (8b**).** Spectral data were identical with those of **8a**: $[\alpha]_D^{25}$ +15.4° (c 3.08, MeOH).

1-(1(*S*)-Phenyl-3(*R*)-methylcyclohexyl)piperidine (1a**).** The cyclic amide **8** (300 mg, 1.1 mmol) was dissolved in 18 mL of dry THF. Powdered lithium aluminum hydride (540 mg) was added in portions, and the mixture was refluxed for 1 h, cooled to 10 °C, and quenched by the successive addition of 0.54 mL of water, 0.54 mL of 1.0 N NaOH solution, and 1.1 mL of water. An additional 20 mL of ether was added, and the solution was stirred for 20 min, filtered through MgSO₄, and concentrated. The crude material was taken up in 10 mL of EtOAc, and 128 mg of fumaric acid in 3 mL of hot methanol was added. The mixture was then heated to dissolution and allowed to cool, giving 344 mg of fumarate salt of **1a** (84%): mp 197–198 °C dec; TLC *R*_f 0.10 (2.5% MeOH/CHCl₃/1% NH₄OH). Free base: $[\alpha]_D^{25}$ –32.3° (c 0.027, CHCl₃); ¹H NMR (CDCl₃) δ 7.3 (m, 5 H), 2.62 (m, 2 H), 2.28 (m, 3 H), 1.65 (ddd, *J* = 12.0, 3.0, 3.0 Hz, 1 H), 1.0–1.6 (m, 13 H), 0.89 (d, *J* = 7.1 Hz, 3 H); CI MS, *m/z* 258. Anal. (C₁₈H₂₇N·C₄H₄O₄) C, H, N.

1-(1(*R*)-Phenyl-3(*S*)-methylcyclohexyl)piperidine (1b**).** Fumarate salt, prepared as with **1a**, mp 196 °C dec. Compound **1b** was spectrally identical with **1a** except for optical rotation, $[\alpha]_D^{25}$ +33.5° (c 0.021, CHCl₃) (free base). Anal. (C₁₈H₂₇N·C₄H₄O₄) C, H, N.

Binding Studies. The displacement assays were performed as previously described by Jacobson et al.,¹⁰ with a tissue homogenate preparation of fresh whole rat brain minus cerebellum. Incubation was carried out at 5 °C with [³H]TCP as the radioligand. Rapid filtration was done through filters presoaked with 0.03% polylysine. The inhibition constant (*K_i*) for determination of the compound for the PCP receptor was calculated by using the Cheng-Prusoff equation,¹¹ employing our determined *K_d* for TCP (16.5 nM) from Scatchard analysis. Experiments were performed in triplicate, and 10 μM TCP was used for determination of nonspecific binding. The *K_i* values listed in Table I were the mean values (± standard deviation) from at least three separate experiments.

Acknowledgment. P.H., from the Food and Drug Administration, Rockville, MD 20857, was supported as an NIH Guest Worker. A.T. was supported by the National Institute on Drug Abuse through National Research Service Award No. 5F32 DAO5287-02. A.T. also gratefully acknowledges partial support from Key Pharmaceuticals Inc., G. D. Searle and Co., and the Committee on Problems of Drug Dependence. We thank N. F. Whittaker, LAC, NIDDK, NIH, for the mass spectral data.

Registry No. **1a**, 114760-75-7; **1a**·C₄H₄O₄, 114817-20-8; **1b**, 114760-76-8; **1b**·C₄H₄O₄, 114817-21-9; **2a**, 114760-65-5; **2a**·HCl, 114817-14-0; **2b**, 114760-66-6; **2b**·HCl, 114817-15-1; (*1S,3R*)-**4**, 114760-67-7; (*1R,3R*)-**4**, 114760-68-8; **5a**, 114760-69-9; **5a**·C₄H₄O₄, 114817-16-2; **5b**, 114760-71-3; **5b**·C₄H₄O₄, 114817-17-3; **6a**, 114760-70-2; **6a**·C₄H₄O₄, 114817-18-4; **6b**, 114760-72-4; **6b**·C₄H₄O₄, 114817-19-5; **7a**, 114693-38-8; **7b**, 114760-73-5; **8a**, 114693-39-9; **8b**, 114760-74-6; PCP, 77-10-1; (*3R*)-methylcyclohexanone, 13368-65-5; phenyllithium, 591-51-5; 5-chlorovaleryl chloride, 1575-61-7.

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