were weighed during the course of the experiment and the percentage change of body weight and lethality was used as an indication of drug toxicity. The sensitivity of ascitic neoplasms to these agents was based on the increase in median survival time and the number of long-term (>60 days) survivors achieved by the different treatments.

Procedures of Biochemical Studies. The procedure for extraction of cytidine/deoxycytidine deaminase up to the thymidine affinity column was performed as described.[17] Subsequently, the enzyme preparation was eluted in the void volume of a Blue Sepharose CL-6B column equilibrated with buffer (0.2 M Tris-HCl, pH 7.5, 2 mM dithiothreitol, and 10% glycerol). The fractions containing deaminase activity were pooled and applied to a DE-52 anion exchange column. The purified enzyme, which eluted in a gradient of increasing ionic strength (0 to 0.5 M KCl), was desalted by using G-25 Sephadex before use.

The procedure for quantitating the activity of dCyd deaminase using [2-^{14}C]-dCyd as substrate has been described.[17] The kinetic analysis was performed by using three fixed concentrations of radiolabeled dCyd against four concentrations of each analogue. Inhibition was competitive. The data were fit to the rate equation for competitive inhibition using a nonlinear least-squares computer program.

Acknowledgment. This investigation was supported by PHS Grants CA-45410 and AI-29430 (to T.S.L.), CA-44358 (to Y.C.C.), and CA-05262 (to W.H.P.) awarded by the National Institutes of Health, DHHS, and Grant CH-452 (to W.R.M.) from the American Cancer Society. We thank Ms. Diane Mozdziesz and Kim Krauss for their excellent technical assistance. We also acknowledge the support of the Northeast NMR Facility at Yale University for the high-resolution NMR spectra, made possible by a grant from the Chemical Division of the National Science Foundation (Grant No. CHE-7916210).

Supplementary Material Available: Tables V-IX of the final atomic parameters, anisotropic thermal parameters, bond lengths and angles, torsion angles, and details of hydrogen bonds in the crystal structure of compound **23**·HCl (5 pages). Ordering information is given on any current masthead page.

Synthesis, Stereochemistry, and Biological Activity of the 1-(1-Phenyl-2-methylcyclohexyl)piperidines and the 1-(1-Phenyl-4-methylcyclohexyl)piperidines. Absolute Configuration of the Potent *trans*-(−)-1-(1-Phenyl-2-methylcyclohexyl)piperidine†

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The (−)- and (+)-isomers of the *cis*- and *trans*-Ph/Me 1-(1-phenyl-2-methylcyclohexyl)piperidines have been synthesized and the achiral *cis*- and *trans*-Ph/Me 1-(1-phenyl-4-methylcyclohexyl)piperidines were prepared, and their in vitro [displacement of [^{3}H]TCP (1-[1-(2-thienylcyclohexyl)]piperidine) from the PCP (1-(1-phenylcyclohexyl)piperidine) binding site] and in vivo (rotarod assay) activities determined. The 1-(1-phenyl-2-methylcyclohexyl)piperidine isomers were resolved by classical crystallization procedures, through the diastereomeric salts obtained with *d*- and *l*-10-camphorsulfonic acid. The relative stereochemistry of the *cis*- and *trans*-Ph/Me 1-(1-phenyl-2-methylcyclohexyl)piperidines and the achiral *cis*- and *trans*-Ph/Me 1-(1-phenyl-4-methylcyclohexyl)piperidines was established by using ^{13}C and ^{1}H NMR. Both (−)-*trans*-1-(1-phenyl-2-methylcyclohexyl)piperidine ((−)-**2**) and (+)-*trans*-1-(1-phenyl-2-methylcyclohexyl)piperidine ((+)-**2**) were examined by single-crystal X-ray analysis, and the absolute configuration of (−)-**2** was determined to be 1*S*,2*R*. The (−)-**2** was found to be about five times more potent than PCP in vitro and twice as potent in vivo. It is the most potent of all of the simple methyl-substituted cyclohexyl PCP isomers and is among the most potent PCP-like compounds which have been synthesized. It was nine times more potent in vitro and four times more potent in vivo than (+)-**2**. The racemic *cis*-1-(1-phenyl-2-methylcyclohexyl)piperidine (**3**), and its enantiomers ((+)-**3** and (−)-**3**), were essentially inactive in vitro and in vivo. The *cis*-Ph/Me 1-(1-phenyl-4-methylcyclohexyl)piperidine (**18**) was more potent than *trans*-Ph/Me 1-(1-phenyl-4-methylcyclohexyl)piperidine (**17**), but considerably less potent than (−)-**2**. The enantioselectivity observed at the PCP binding site for (−)-**2** could indicate that this site can discriminate between enantiotopic edges of the achiral PCP (choosing the *pro*-1-*S* edge), as does the μ-opioid receptor in the prodine series of opioids. Benzimidoyl or benzoyl group replacement of the phenyl ring in the 1-(1-phenyl-2-methylcyclohexyl)piperidine series gave compounds which showed little in vitro and in vivo activity.

Several studies have described stereoselective, saturable phencyclidine (1, 1-(1-phenylcyclohexyl)piperidine, PCP) binding sites in the brain of animals of many species.[1-4] PCP has a wide spectrum of activity which directly or indirectly involves dopaminergic and cholinergic neurotransmitters, as well as excitatory amino acid neurotrans-

† Dedicated to Prof. G. B. Marini Bettolo on the occasion of his 75th birthday.

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∥ Naval Research Laboratory.

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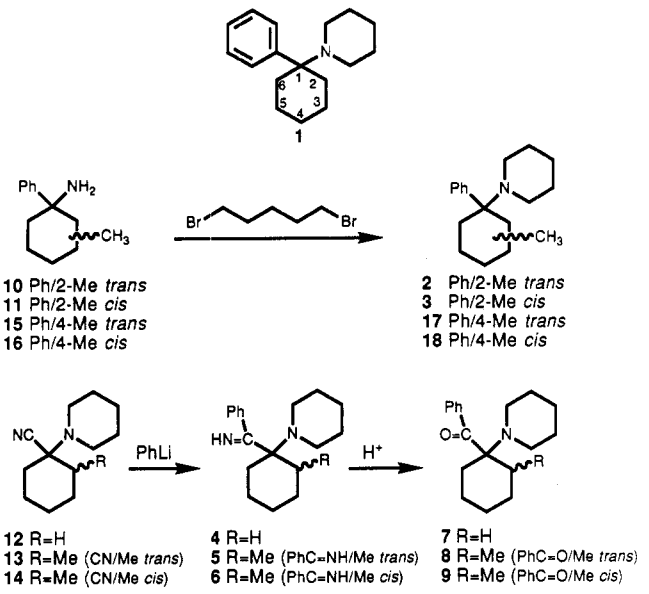
0022-2623/91/1834-2615$02.50/0

Scheme I



mitters.[5,6] There has recently been increased interest in the molecular characteristics of PCP-like compounds which induce these actions,[7,8] since some PCP-like compounds have been found to exhibit neuroprotective and anticonvulsant properties in animal models.[9,10] This could possibly occur through their actions as noncompetitive antagonists at the PCP binding site in excitatory amino acid ion channels regulated by the NMDA receptor complex.[11-13] The determination of the relative stereochemistry and absolute configuration of the relatively simple methyl-substituted cyclohexyl PCP isomers, and their activity in vitro and in vivo, should aid the more quantitative structure–activity correlations of the PCP-like molecules.

The *trans*- and *cis*-Me/Ph stereochemistry of the 2-, 3-, and 4-methylcyclohexane ring derivatives of PCP has attracted considerable attention because of an apparent relationship between their molecular configuration and biological activity.[14-17] Throughout this paper, for consistency with the published work of Vincent et al.,[16] and others,[14-15,17] our trans and cis designations refer to the relative position of phenyl and methyl on the cyclohexane chair ring.[18] Studies of each of the racemic isomeric pairs by Geneste et al.,[14] Kamenka et al.,[15] and Vincent et al.[16] showed that the isomer with an axial phenyl ring and an equatorially oriented piperidine ring geminally substituted on the cyclohexane ring in the chair conformation possessed structural and spatial features necessary for efficient interaction with the PCP binding site; the interaction appeared to be independent of the orientation assumed by a methyl substituent on the cyclohexane ring. More extensive theoretical work,[7,8] using computer-assisted molecular modeling with more complex PCP-like compounds, has recently delineated the molecular characteristics necessary for PCP-like activity; the PCP pharmacophore has been proposed.

Vincent et al.[16] noted that of the six methyl diastereomers, the racemic *trans*-1-(1-phenyl-2-methylcyclohexyl)piperidine (**2**) and the achiral *cis*-1-(1-phenyl-4-methylcyclohexyl)piperidine (**18**) (Scheme I) were the only ones which were found to be nearly equipotent with PCP in vivo and in vitro. Recently, the racemic *cis*- and *trans*-1-(1-phenyl-3-methylcyclohexyl)piperidine isomers were resolved and their in vitro activities determined.[17] Thurkauf et al. found that all four of the (+)- and (−)-*trans*- and -*cis*-1-(1-phenyl-3-methylcyclohexyl)piperidine compounds were less potent than PCP in vitro.[17] The most potent isomer was the *cis*-(+)-1-(1-phenyl-3-methylcyclohexyl)piperidine, and that compound was only one third as potent as PCP in vitro. The *cis*-(+)-1-(1-phenyl-3-methylcyclohexyl)piperidine was noted to have the 1*S*,3*S* configuration at the two centers of asymmetry.[17]

It seemed worthwhile, then, to resolve the racemate in the 1-(1-phenyl-2-methylcyclohexyl)piperidine series in order to see whether its enantiomers are selective in their interaction with the PCP site and to determine their potency in vitro and in vivo. The achiral *cis*- and *trans*-(1-phenyl-4-methylcyclohexyl)piperidine were resynthesized[14] for comparison purposes. As mentioned, the enantiomers of *trans*- and *cis*-1-(1-phenyl-3-methylcyclohexyl)-piperidine[17] have been found to show enantioselectivity in vitro, as have the enantiomers of 1-(1-phenylcyclohexyl)-3-methylpiperidine (PCMP).[3] We have, thus, resolved the *trans*- and *cis*-1-(1-phenyl-2-methylcyclohexyl)piperidines (**2** and **3**) and have determined their binding affinity to the PCP binding site and their in vivo activity on the rotarod test. We have found that the (−)-*trans*-1-(1-phenyl-2-methylcyclohexyl)piperidine ((−)-**2**) is about five times more potent than PCP in vitro (K_i= 11 nM vs 53 nM, respectively) and two times as potent in vivo; it is the most potent of the simple PCP derivatives with a methyl-substituted cyclohexane ring, and there is about 1 order of magnitude in enantioselectivity, at the PCP binding site, between (−)- and (+)-*trans*-1-(1-phenyl-2-methylcyclohexyl)piperidine. We have also prepared compounds in which the phenyl ring has been replaced with a benzimidoyl or benzoyl group, and have

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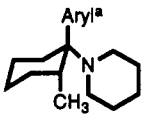
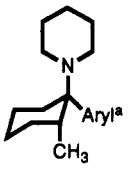
(18) As noted by the reviewer, the cis/trans designation are carryovers from past literature, and are ambiguous. Usually, cis/trans refers to the two highest priority groups. Unfortunately, the compounds discussed in this paper have appeared in the literature with cis/trans defined by the methyl/phenyl groups on the cyclohexane chair ring, and we have retained that reference system to avoid confusion. According to IUPAC recommendations (*J. Org. Chem.* **1970**, *35*, 2855), (−)-**2** should be named *r*-1-(1-phenyl-*c*-2-methylcyclohexyl)piperidine.

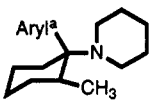
Table I. ^{13}C NMR Chemical Shifts of PCP Analogues (Bases) in $CDCl_3$



A *trans*



B *cis*



C *cis*

	configuration and preferred conformation								
		A	B		A	B (65%)		A	C
carbon	1	2	3	4	5	6	7	8	9
C-1	60.76	63.51	63.08	66.45	67.10	68.88	70.56	70.02	73.56
C-2	33.54	30.55	31.49	29.44	31.46	34.01	28.71	30.94	34.94
C-3	22.27	26.92	25.84	23.14	31.02	28.99	23.13	27.79	30.36
C-4	26.36	19.79	20.49	26.33	20.48	22.20	26.04	20.07	24.02
C-5	22.27	22.80	21.64	23.14	23.46	22.92	23.13	23.76	22.75
C-6	33.54	28.91	27.30	29.44	28.04	26.17	28.71	30.94	27.71
α	46.40	46.01	46.36	46.47	46.08	46.75	47.15	46.22	47.74
β	27.05	27.04	27.30	27.20	27.21	27.28	26.86	27.02	26.94
γ	24.91	25.15	25.33	25.31	25.45	25.40	25.07	25.31	25.23
q	140.33	137.43	141.15	142.38	143.40	144.62	138.32	140.01	141.59
o	127.22	127.31	127.06	128.09	128.23	127.96	129.85	129.47	129.12
m	127.06	127.31	126.74	127.69	127.79	127.14	127.66	127.65	127.68
p	125.17	125.68	125.59	128.59	127.75	128.18	131.43	130.63	131.00
C—Me		13.70	15.73		15.96	16.50		15.60	17.56
C=NH				182.10	181.91	183.57			
C=O							204.04	202.57	205.37

[a] Aryl = phenyl, benzimidoyl, or benzoyl. Configurations (trans/cis) and preferred conformations are indicated at the top of the table. Preferred conformations, unless otherwise indicated, exceed 80%.

compared their activity with the corresponding phenyl analogues. Conformational assignments of the new compounds were made by using ^{13}C spectra; complementary evidence was obtained through the chemical shift of the secondary (*sec*) methyl group in ^1H NMR spectra. The absolute configuration of both (-)- and (+)-*trans*-1-(1-phenyl-2-methylcyclohexyl)piperidine ((-)-**2** and (+)-**2**) have been determined by X-ray crystallography and (-)-**2** was found to have the 1*S*,2*R* configuration.

Chemistry

trans- and *cis*-1-(1-phenyl-2-methylcyclohexyl)amines **10** and **11** were obtained through the azide route of Geneste et al.[14,19] in the ratio of about 4:1 (*trans*-**10**/*cis*-**11**), as judged from ^1H NMR integration data (^1H NMR *sec*-methyl) of the total product. The *trans*-amine **10**, the major product of the reaction, was easily separated from **11** by crystallization of its hydrochloride salt. The *cis*-amine **11** was isolated from the enriched mother liquor by column chromatography. Reaction of 1,5-dibromopentane and the *trans*-amine **10** proceeded slowly and provided incomplete conversion to *trans*-1-(1-phenyl-2-methylcyclohexyl)piperidine (**2**). A modified procedure provided **2** in an 80% yield by using ethanol as the solvent and KI as catalyst. The amine **11** was similarly converted to *cis*-1-(1-phenyl-2-methylcyclohexyl)piperidine (**3**). The two isomers, **2** and **3**, were resolved by a classical crystallization procedure through the diastereomeric salts obtained with *d*- and *l*-10-camphorsulfonic acid.

trans- and *cis*-1-(1-benzimidoyl-2-methylcyclohexyl)-piperidine (**5** and **6**) were obtained by addition of phenyllithium to the isomeric mixture of 1-(1-piperidinyl)-2-methylcyclohexanecarbonitriles **13** and **14**. The imino compounds **5** and **6** were separated by column chromatography and were found to be quite stable as their hydrochloride salts. Acid hydrolysis of the imino group at reflux temperature gave the benzoyl derivatives, the *trans*- and *cis*-1-(1-benzoyl-2-methylcyclohexyl)piperidines, **8** and **9**, respectively. The 2-methyl group apparently had a stabilizing effect on the imino group, sterically interfering with the approach of the hydrolytic agent; the desmethyl analogue 1-(1-benzimidoylcyclohexyl)piperidine (**4**) was, however, readily converted to 1-(1-benzoylcyclohexyl)-piperidine (**7**) in acidic medium at room temperature. The achiral *trans*- and *cis*-Ph/Me 1-(1-phenyl-4-methylcyclohexyl)piperidines (**17** and **18**) were prepared similarly to **2** and **3**.

Stereochemistry

The relative configuration and preferred conformation of the new compounds (bases and hydrochloride salts) in solution were determined by ^{13}C spectral analysis. Assignment of cis and trans configurations and preferred conformations for the new compounds were derived mainly from the following considerations:

(1) Additivity parameters for axial and equatorial methylcyclohexane[20,21] were added to the chemical shifts of the parent desmethyl analogue and compared with experimental data. As usually found in alicyclic compounds, a substantial shift difference between the stereoisomers, especially at the γ-C, was indicative of a predominance of the methyl in the axial rather than the equatorial position.

(2) The ^{13}C shifts observed in 2-methyl-substituted compounds were indicative of a predominance of the methyl in an axial, rather than an equatorial position (Tables I and II). The empirical effects of an axial or equatorial C-2 methyl on the C-2 and C-6 atoms were modified by the shielding influence of the geminal C-1 substituents, and the chemical shifts of these two carbon atoms (C-2 and C-6) were less indicative of stereochemistry.

An analysis of the intermediate *trans*- and *cis*-amines **10** and **11** showed that both had the same orientation of

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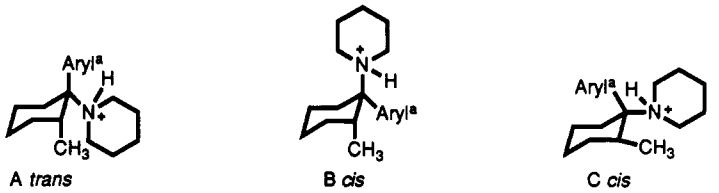
Table II. ^{13}C NMR Chemical Shifts of PCP Analogues (Hydrochlorides) in D_2O



	configuration and preferred conformation							
		A	B	A	C		A	C
carbon	1	2	3	5	6	7	8	9
C-1	72.31	74.62	75.84	76.30	77.79	77.26	79.64	82.15
C-2	31.73	31.44	32.36	34.05	37.85	30.72	33.84	38.29
C-3	23.35	29.82	27.57	30.61	31.39	22.87	30.19	31.63
C-4	25.29	18.75	19.71	21.26	24.91	24.50	19.82	24.95
C-5	23.35	23.06	21.11	22.05	22.91	22.87	22.40	23.28
C-6	31.73	25.06	25.96	27.90	26.46	30.72	26.16	25.70
α	48.32	49.14	49.67	52.24	52.06	50.73	52.76	53.03
		47.84	48.62		47.00		52.04	47.97
β	24.11	23.92	24.04	25.33	25.17	24.24	24.45	24.34
		23.45						24.04
γ	22.33	22.13	22.06	22.76	23.05	22.13	22.23	22.52
q	131.56	131.20	133.92	138.79	141.30	139.92	139.39	141.85
o	130.49	130.49	130.10	129.78	129.94	129.90	129.94	130.15
m	129.90	129.63	129.55	127.95	127.04	127.92	128.50	126.64
p	130.49	130.49	130.59	131.24	130.73	133.78	133.74	133.04
C—Me		13.64	16.69	14.48	16.13		14.16	15.92
C=NH				180.88	179.84			
C=O						305.80	203.94	206.68

[a] Aryl = phenyl, benzimidoyl, or benzoyl. Configurations (trans/cis) and preferred conformations are indicated at the top of the table. Preferred conformations exceed 80%.

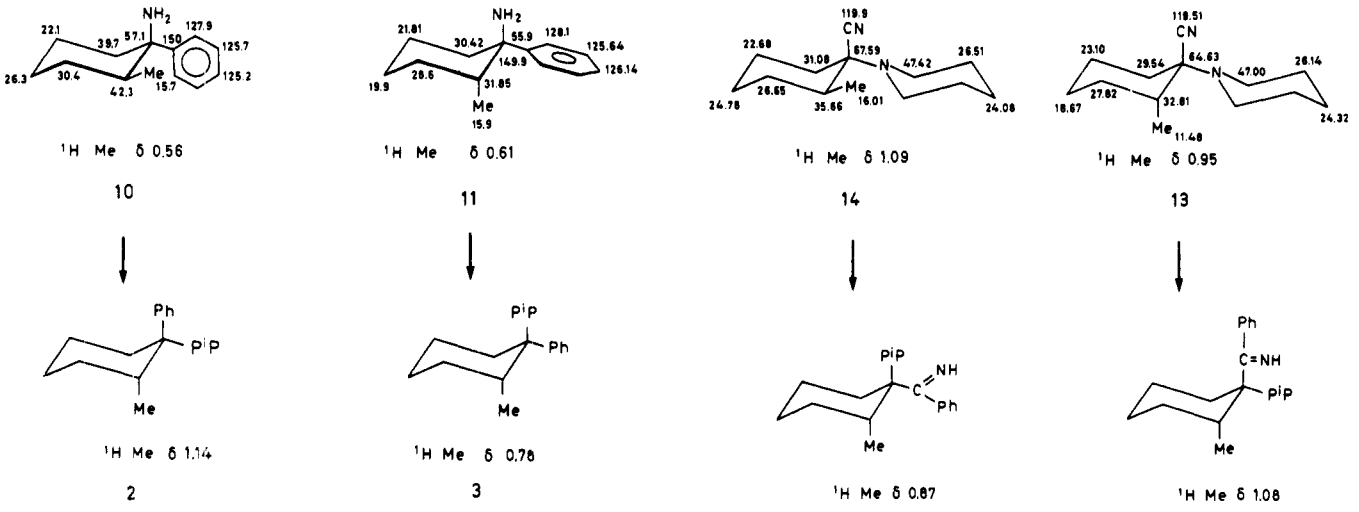


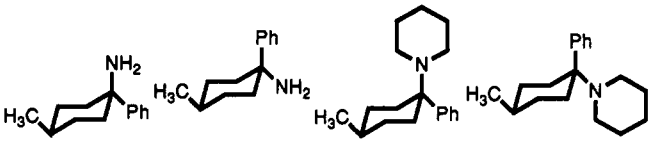
Figure 1. Preferred conformation and ^{13}C spectral chemical shifts (δ) of *trans*-Ph/Me 1-(1-phenyl-2-methylcyclohexyl)amine (*trans*-**10**) and *cis*-Ph/Me 1-(1-phenyl-2-methylcyclohexyl)amine (*cis*-**11**) (major and minor isomer of the reaction) and their respective derivatives *trans*- and *cis*-1-(1-phenyl-2-methylcyclohexyl)piperidine, **2** and **3**, respectively.

Figure 2. Preferred conformation and ^{13}C spectral chemical shifts (δ) of major (*cis*-CN/Me 1-(1-piperidinyl)-2-methylcycohexanecarbonitrile, **14**) and minor (*trans*-CN/Me 1-(1-piperidinyl)-2-methylcyclohexanecarbonitrile, **13**) isomer of the reaction and their respective derivatives *cis*-1-(1-benzimidoyl-2-methylcyclohexyl)piperidine (**6**) and *trans*-1-(1-benzimidoyl-2-methylcyclohexyl)piperidine (**5**).

the geminal substituents on C-1 and that the C-2 methyl was equatorially oriented in **10** and axially oriented in **11** (Figure 1). Cyclization of the amino group of **10** gave *trans*-1-(1-phenyl-2-methylcyclohexyl)piperidine (**2**) as the sole compound. Substitution of the amino group with the bulkier piperidine ring caused a conformational change in **2** to relieve the steric strain in the congested surrounding of the substituents. The *cis*-amine **11** was converted to the *cis*-1-(1-phenyl-2-methylcyclohexyl)piperidine (**3**) without change of conformation. Correlation of ^{13}C chemical shifts of the cyclohexane ring and their conformations were reported for the racemic hydrochlorides of 1-(1-phenyl-2-methylcyclohexyl)piperidine, 1-(1-phenyl-3-methylcyclohexyl)piperidine, and the achiral 1-(1-phenyl-4-methylcyclohexyl)piperidine by Kamenka et al.[15] and Geneste et al.[14] Since compounds **2** and **3** were also prepared for the resolution work, their full spectra (bases and hydrochloride salts) were also recorded to provide useful correlative data for signal assignment (Tables I and II). The ^{13}C chemical shift parameters of the 4-methyl series are reported in Table III. It is evident that the bases **15**, **16**, and **18** maintain the same conformational preference when protonated (hydrochloride salts). However, the base **17** undergoes complete inversion upon protonation.

The relative stereochemistry of the *trans*- and *cis*-CN/Me 1-(1-piperidinyl)-2-methylcyclohexanecarbonitrile

Table III. ^{13}C NMR Chemical Shifts of *trans*- and *cis*-Ph/Me 1-(1-Phenyl-4-methylcyclohexyl)amines (15 and 16) and Piperidines (17 and 18) and Their Bases ($CDCl_3$) and Hydrochlorides (D_2O)[a]



15 16 17 18

carbon	15	15·HCl	16	16·HCl	17	17·HCl[b]	18	18·HCl
C-1	53.09	58.66	53.99	58.31	59.22	72.37	61.93	72.06
C-2	38.96	34.26	38.33	34.26	33.27	26.29	33.21	31.62
C-3	30.64	29.36	31.49	30.83	30.10	28.70	31.58	31.62
C-4	31.73	30.42	31.76	31.83	32.51	26.29	32.58	31.93
C-5	30.64	29.36	31.49	30.80	30.10	28.70	31.58	31.62
C-6	38.96	34.26	38.33	34.26	33.27	26.29	33.21	31.62
α					46.52	48.28	46.80	48.49
β					27.23	24.07	27.17	24.09
γ					25.06	22.27	25.00	22.22
q	151.22	141.63	147.20	137.35	142.42	131.13	138.81	131.41
o	128.29	129.94	128.72	130.39	127.25	130.45	128.03	130.51
m	124.95	125.81	126.02	128.08	126.33	129.87	127.47	129.97
p	126.31	129.54	126.34	130.14	125.92	130.45	125.95	130.51
C-Me	22.23	21.11	21.20	21.51	22.25	17.86	21.77	21.59

[a] Configurations (*trans*- and *cis*-Ph/Me) and preferred conformations are indicated at the top of the table. Preferred conformations, unless otherwise indicated, exceed 80%. [b] Compound 17·HCl exists almost completely in the reverse conformation.

(13 and 14) has been established as indicated in Figure 2; the isomers differ in the configuration of the C-2 methyl group. Addition of phenyllithium to the nitrile group of 14 caused a conformational change in the resulting *cis*-1-(1-benzimidoyl-2-methylcyclohexyl)piperidine (6), to relieve steric strain. This conformational change was also noted in compound 2, which was prepared from *trans*-amine 10.

In the benzimidoyl and benzoyl series some factors, perhaps the hindered rotation around Ph—CO and Ph—C=NH, the presence of an equatorial C-2 methyl, and/or protonation of the piperidine nitrogen, led to asymmetric environments for the two apparently equivalent α-carbons of the piperidine ring; they differed by 5 ppm (broad signals) in *cis*-1-(1-benzimidoyl-2-methylcyclohexyl)-piperidine hydrochloride (6·HCl) and 5 ppm (sharp signals) in *cis*-1-(1-benzoyl-2-methylcyclohexyl)piperidine hydrochloride (9·HCl). Signal duplication of the α-piperidine carbons was still evident in *trans*-1-(1-benzoyl-2-methylcyclohexyl)piperidine hydrochloride (8·HCl), 2·HCl, and 3·HCl, where an axial C-2 methyl was present, but the differences were much less than those observed with the equatorial 2-methyl (Table II). In two cases this effect was also observable with the β-piperidine carbons (9·HCl, $\Delta\delta$ = 0.3 ppm; 2·HCl, $\Delta\delta$ = 0.47 ppm).

Small but consistent differences in chemical shifts helped in the attribution of the relative position of the C-1 substituents. As expected,[22] the quaternary carbon of an axial phenyl was shifted upfield by approximately 3 ppm from the resonance of its equatorial counterpart (compare C-q for 2/3, 16/15, and 18/17 (as bases)). The C-1 was at higher field when the piperidine ring was axial (compare 5/6 as bases); a small upfield shift was also observed for the aromatic quaternary carbon bonded to the axial imino group. Differences were also seen in the chemical shift of the carbonyl group in the two isomers, but these differences may be due in part to the γ-effect of the C-2 methyl which was axial in 8 (base) and equatorial in 9 (base). The preferred conformation of each isomer is shown in Tables I–III.

The para carbon of the phenyl ring suffered a consistent downfield shift on going from the base to the hydrochloride salt. In the base the signal was upfield relative to the meta and ortho carbon atoms, in the hydrochloride salt it was downfield (Tables I–III). The para carbon signal was easily identified, having about half of the intensity of the ortho and meta carbons.

Specific assignment of signals to the ortho and meta carbon atoms was obtained from the observation of the splitting pattern of the aromatic region in gated decoupled spectra (Figure 3). The relative position of ortho and meta carbons remained unchanged when the bases were protonated. Chemical shift variation of the aromatic carbons on PCP-like compounds as a function of the solvent was interpreted as being due to an increase in the population of the conformer with axial phenyl and equatorial piperidine (the biologically active conformation).[23] Here, the observed chemical shift variation of the aromatic carbons between bases and hydrochloride salts may also be accounted for in terms of solvation effects. Protonation of the piperidine nitrogen and its hydration increase the size of the cationic head and its nonbonded interactions, thus favoring a shift toward the form with an axial phenyl and an equatorial piperidine.

Further support for the deductions made from ^{13}C spectra came from the analysis of the ^1H C-2 methyl chemical shift. When Ph/Me have the orientations shown in 3, 10, or 11 (Figure 1), either the equatorial or axial methyl can experience the shielding influence of the aromatic ring and resonate at a higher field than in the isomers with an axial phenyl.[24]

Biological Results

The binding affinities of the tested compounds and their ataxic effects on the rotarod assay are summarized in Table IV. In reasonable agreement with an earlier report,[16] the racemic *trans*-1-(1-phenyl-2-methylcyclohexyl)piperidine (2) was found to be twice as potent as PCP in vitro and about equipotent with PCP in vivo, while its cis relative

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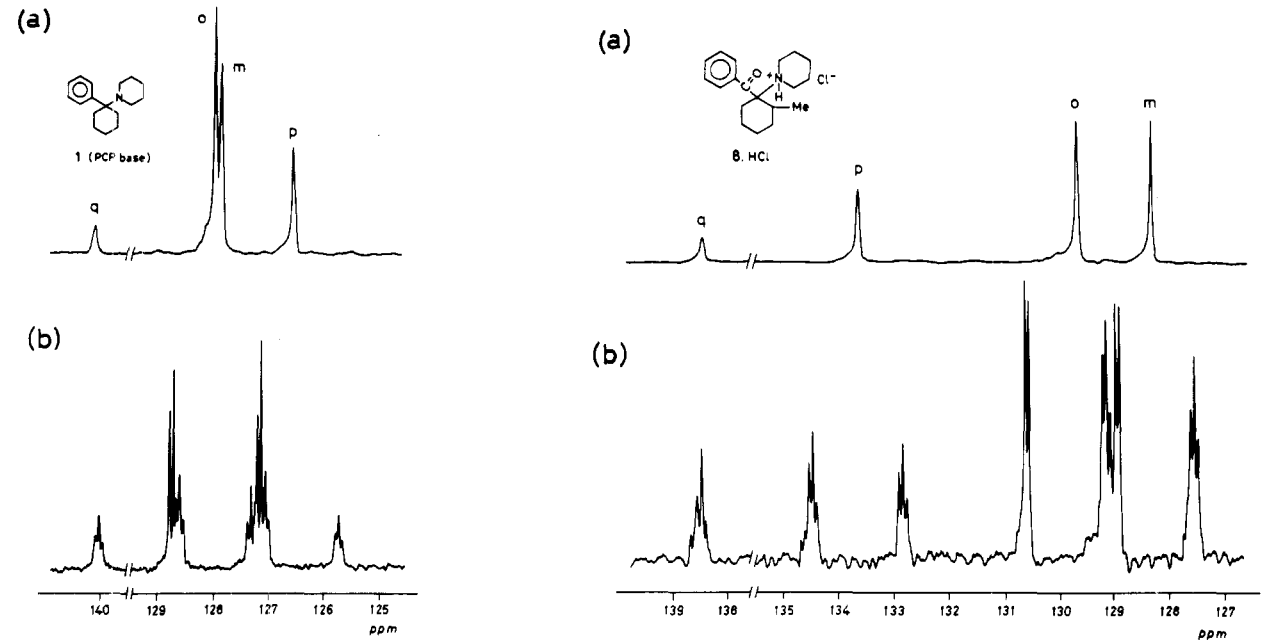

Figure 3. Aromatic region of ^{13}C NMR spectra (Bruker AM 400) of PCP (1) as the base in $CDCl_3$, and *trans*-1-(1-benzoyl-2-methylcyclohexyl)piperidine (8) as the hydrochloride salt in D_2O: (a) broad band proton decoupled, and (b) gated decoupled (decoupler off during acquisition time and on during pulse delay) spectra.

Table IV. The in Vitro and in Vivo Effects of 1-(1-Phenyl-2-methylcyclohexyl)piperidines (Diastereomers, Enantiomers, and Analogues) and the 1-(1-Phenyl-4-methylcyclohexyl)piperidines

compd[a]	K_i, nM[b]	rotarod ED_{50}[c]
1 (PCP)	53	4.0 (2.7–5.9)
2	25	3.3 (2.2–4.7)
(+)-2	100	7.5 (5.4–10.5)
(−)-2	11	1.9 (1.4–2.6)
3	7400	>150
(+)-3	2940[d]	>100
(−)-3	2180	>100
4	31000[d]	>100
5	23000[d]	>100
6	4700[d]	>100
17	617	>150
18	166	5.5 (2.9–10.0)

[a] Hydrochloride salts were administered in aqueous solution. When only the free base was available a suspension of the amine in water was treated with an equivalent amount of 1 N HCl and diluted to volume with water. [b] Determined by displacement of [^{3}H]TCP (1-[1-(2-thienylcyclohexyl)]piperidine), from a tissue homogenate preparation of fresh whole rat brain minus cerebellum. Experiments were performed in triplicate and the K_i values are from the mean of two separate experiments, except where indicated. The IC_{50} values were converted to K_i by using the Cheng–Prusoff equation[33] with the experimentally determined K_d = 16.5 nM for [^{3}H]TCP. TCP (10 μM) was used for the determination of nonspecific binding. [c] ED_{50} determined from four dose levels with eight mice per dose (mg/Kg, sc injection). Parenthesized numbers are confidence limits obtained from probit analysis. [d] Results from a single experiment run in triplicate.

(3) had little affinity for the PCP binding site and did not induce motor incoordination in mice at doses up to 150 mg/kg. No deaths were observed at this dose. The in vitro and in vivo activity of the racemate 2 can be mainly attributed to the levo enantiomer. The (−)-2 was about nine times more potent in vitro than (+)-2, indicative of the enantioselectivity of the PCP binding site, and two to three times more potent in vivo. In the rotarod assay, (−)-2, which was two times as potent as PCP, was at least 50 times more potent than the cis enantiomers (+)-3 and (−)-3. These cis enantiomers, like the racemate 3, were found to be relatively inactive in vitro and in vivo. In the 4-methyl series, the achiral trans isomer (17) had little activity in vivo and was at least 1 order of magnitude less potent than PCP in vitro. The cis isomer (18) was about one-third as potent in vitro and essentially equipotent in vivo with PCP (Table IV). Although the in vivo data for 17 and 18 are in accord with those formerly reported,[16] these compounds were found to be considerably less potent in vitro than previously reported. Previously, 18 was found to be twice as potent as PCP in vitro, and 17 was half as potent as PCP.

X-ray Determination of Absolute Configuration

The (−)-2 and (+)-2 hydrobromide hemihydrate salts were examined to determine their absolute configuration. The diffraction data includes Friedel pairs for the portion of the data $2\theta < 45°$ and the method used was based on the method suggested by D. Rogers.[25] The parameter η which multiplies all $\Delta f''$ values (imaginary component of anomalous scattering factor) in the expression $f_o^{anom} = f_o + \Delta f' + i\eta\Delta f''$ refines to values of $\eta = 1.28$ (5) and 1.26 (7) for (−)-2 and (+)-2, respectively. The correct choice of hand would give positive values near 1.0 and an incorrect choice values near −1.0. The results give the absolute configuration as (−)-2 1*S*,2*R* and (+)-2 1*R*,2*S*.

Discussion

As shown in Tables I and II, the racemate 2 (either as the base or hydrochloride salt) has the two geminal substituents in the spatial relationship necessary to elicit PCP-like activity. Since introduction of a 2-methyl group in PCP affords enantiomers ((+)-2 and (−)-2) which exhibit large potency differences it is possible that the PCP binding site can discriminate between the enantiotopic edges of the achiral PCP molecule (*pro*-1-*S* and *pro*-1-*R*) in the same way as the opioid receptor does in the prodine series.[26] If the PCP binding site and the μ-opioid receptor interact with ligands with the same stereospecificity, (−)-2, the active enantiomer for the PCP site, should have the 1*S*,2*R* configuration, since this configuration corresponds to the 4*S*,3*R* configuration of (+)-α-prodine (the active enantiomer for the μ-opioid receptor). Spectroscopic data

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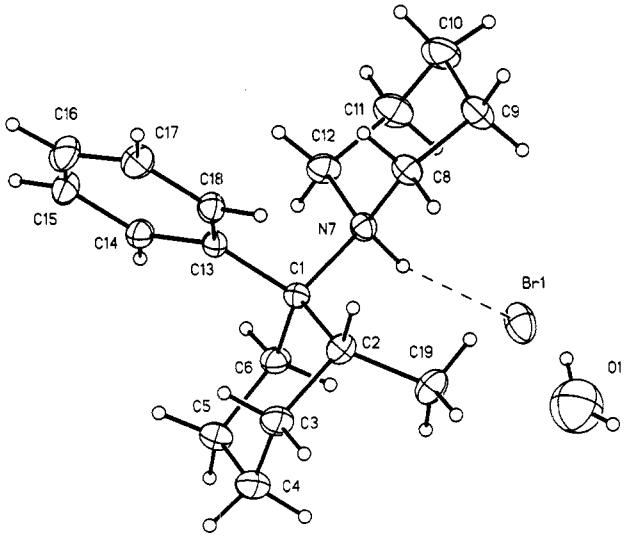

Figure 4. Thermal ellipsoid plot drawn from experimental coordinates of *trans*-(-)-1-(1-phenyl-2-methylcyclohexyl)piperidine [(-)-2] hydrobromide hemihydrate solvate. Thermal ellipsoids are drawn at the 20% probability level. Dotted line indicates intermolecular hydrogen bond. Compound (+)-2, which differs by chirality, is not shown but is numbered similarly.

could not determine the "correct edge" for introduction of a 2-methyl group, but X-ray crystallographic determination of (+)-2 and (-)-2 solved the dilemma.

Compound (-)-2, shown in Figure 4, and (+)-2 are in space groups $P4_32_12$ and $P4_12_12$, respectively, and should differ only by hand. The RMS deviation of the fit of the two structures to one another when inverted for hand is 0.017 Å. The piperidine and cyclohexane rings are in the usual chair conformation with the piperidine ring equatorial and the phenyl and methyl substituents in an axial position with respect to the cyclohexane. The exocyclic C–N bonds are unusually long, 1.569 (6) and 1.581 (8) Å, respectively, due to steric stain, and significantly longer than the endocyclic C–N bonds which average 1.508 (9) Å. Similar values occur in the protonated piperidine of PCP hydrochloride[27] with values of 1.550 (7) and 1.508 (8) Å for the exocyclic and average endocyclic bonds. The corresponding values in PCP are 1.490 (2) and 1.455 (2) Å.[28] The active enantiomer, (-)-2, was found to have the 1*S*,2*R* configuration. Compound (+)-2 was found to have the 1*R*,2*S* configuration, as expected. The two structures were "isostructural" after inversion with a RMS deviation of less than 0.02 Å.

We have, thus, succeeded in obtaining the enantiomeric 1-(1-phenyl-2-methylcyclohexyl)piperidine compounds in the cis and in the trans series, and we have determined the absolute configuration of (-)-*trans*-1-(1-phenyl-2-methylcyclohexyl)piperidine ((-)-2), one of the most potent simple PCP analogues known. The much more complex, structurally rigid, 10,11-dihydroxy-5-methyl-5*H*-dibenzo[*a*,*d*]-cyclohepten-5,10-imine (Dizocilpine, (+)-MK801) is, in our hands, about half as potent as (-)-2 in displacement studies, when [^{3}H]TCP was used as the radioligand (K_i = 24 nM). The spectroscopic and X-ray crystallographic data which we have obtained may help to establish the concept of the "enantiotopic edge", for biological activity in the PCP series. This "edge" has now been determined to be *pro-S*.

A replacement of the phenyl moiety of PCP by a benzimidoyl group markedly reduced binding affinity by 2–3 orders of magnitude (**4**, **5**, and **6**). Compounds with a benzoyl instead of a phenyl group were completely inactive. The insertion of a carbon atom (C=NH, C=O) between the phenyl ring and the quaternary cyclohexyl carbon (**5** and **8**) apparently altered the optimum[7,8] spatial position in three-dimensional space of the nitrogen atom in the piperidine ring for PCP-like biological activity. A similar effect was observed by replacing the phenyl by a benzyl group.[29]

Experimental Section

Melting points were determined with a Büchi-Tottoli apparatus. Elemental analyses were performed at the Microanalytical Section of the Istituto Superiore di Sanità. Optical rotations were obtained from 1% solutions in methanol with a Perkin-Elmer 141 polarimeter and a 1-dm microcell. ^{13}C NMR spectra were recorded on a Varian XL 100 or a Bruker AM 400 spectrometer operating at 25.2 MHz or at 100.61 MHz, respectively, with broad-band proton decoupling. Chemical shifts (δ) are reported in parts per million downfield from TMS. In D_2O, chemical shifts were measured relative to the dioxane signal as an internal standard (δ = 67.4) and are quoted relative to TMS. Routinely run ^{1}H NMR spectra, used during the course of the syntheses for product characterization, were obtained with a Varian T-60 spectrometer. In the "gated experiments" the spectra were obtained by using a pulse-modulated broad-band proton decoupling sequence, with the decoupler turned off during data acquisition periods and applied only during the delay time; the pulse repetition time was 2.5 s. Purity of each compound was checked by TLC (SiO_2, F-254). Developing solvents were (A) chloroform–methanol–ammonia (90:9:1); (B) hexane–ethyl acetate (2:1); (C) chloroform–methanol–ammonia (95:5:0.5); (D) dichloromethane–cyclohexane (2:1); (E) hexane–ethyl acetate (9:1). Spots were detected by exposure to iodine vapor or by spraying with Dragendorff's reagent.

PCP (**1**) and the nitrile **12** were prepared according to the literature.[29] The ^{13}C NMR spectrum of **12** has been published.[24,30]

***trans*- and *cis*-Ph/Me 1-(1-Phenyl-2-methylcyclohexyl)-amines (10 and 11).** Solid sodium azide (36.0 g, 0.56 mol) was added to a chloroform (100 mL) solution of a mixture of isomeric 1-phenyl-2-methylcyclohexanols (27 g, 0.14 mol), which was obtained by treating 2-methylcyclohexanone with phenyllithium.[31] The mixture was cooled in an ice bath, and concentrated H_2SO_4 (33 mL, d 1.81) was added dropwise, with vigorous magnetic stirring. The cold mixture was stirred for 6 h, poured onto ice, and made alkaline with aqueous ammonia. The chloroform layer was separated, and the aqueous solution was extracted with chloroform. The combined chloroform extracts were washed with water, dried and concentrated to afford a crude oil (29.4 g). This crude azide was dissolved in dry ether (20 mL) and added dropwise to a stirred suspension of LAH (7.8 g) in dry ether (250 mL) cooled with an ice bath. The mixture was refluxed 1 h and stirred at room temperature overnight. Excess LAH in the ice-cold mixture was carefully decomposed by dropwise addition of water (8 mL), followed by 8% NaOH (16 mL), and the white suspension was filtered to remove inorganic salts. The ethereal solution was dried and evaporated, and the oily residue was distilled. The fraction collected at 68–72 °C (0.08 mmHg) gave 19 g of isomeric amines, in an approximate ratio of 4:1 (*trans*-**10**/*cis*-**11**), from integration data of the ^{1}H sec-Me signals (TLC, solvent B: **10**, R_f 0.39; **11**; R_f 0.18). The mixture was treated with ethanolic HCl and diluted with ether, precipitating a solid. One crystallization from ethanol/water gave pure **10**·HCl, mp > 260 °C (sublimation occurred in the capillary). Anal. ($C_{13}H_{20}ClN$) C, H, N. The residue from the mother liquors (as the free base) was chromatographed on silica gel with use of hexane with an increasing concentration of ethyl acetate, from 1% to 2.5%, as the elution system. The cis

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isomer 11 was the slower running component. It was converted to its hydrochloride salt, mp > 260 °C (sublimation occurred in the capillary). Anal. ($C_{18}H_{20}ClN$) C, H, N.

***trans*- and *cis*-Ph/Me 1-(1-Phenyl-2-methylcyclohexyl)-piperidines (2 and 3).** A mixture of the *trans*-amine 10 (8.0 g, 42 mmol), 1,5-dibromopentane (9.8 g, 44 mmol), KI (0.1 g), and K_2CO_3 (23.0 g, 0.17 mol) in absolute ethanol (150 mL) was stirred and refluxed under N_2 (very slow bubbling). The reaction proceeded slowly (TLC, solvent B); it took approximately 1 week to almost completely convert the starting amine to product. After cooling, the solvent was removed in vacuo and the mixture partitioned between ether and water. Drying and evaporation of the ether left a solid which was dissolved in a minimum of hot petroleum ether (bp 30–50 °C). After overnight refrigeration, 2 was isolated (4.2 g), mp 83–85 °C (lit.[14] mp 84–85 °C); 2·HCl, mp 222–223 °C. Anal. (base and HCl salt) ($C_{18}H_{27}N$; $C_{18}H_{28}ClN$) C, H, N. An additional amount of 2 (4.5 g) was obtained by chromatography of the concentrated mother liquor on silica gel, with hexane containing 1.5% ethyl acetate as eluent (total yield 80%). The second fraction from the column chromatography contained the residual starting amine 10 (2 g).

The cis isomer 3 was obtained from 11, similarly, mp 55 °C (lit.[14] mp 57–58 °C); 3·picrate, mp 164–165 °C, from ethanol. Anal. (base and picrate salt) ($C_{18}H_{27}N$; $C_{24}H_{30}N_4O_7$) C, H, N.

Optical Resolution of *trans*-(±)-1-(1-Phenyl-2-methylcyclohexyl)piperidine (2). The racemate 2 (2.5 g, 9.7 mmol) and *d*-10-camphorsulfonic acid monohydrate (2.5 g, 10.0 mmol) were each dissolved in warm acetone, and the solutions were mixed. The solvent was decanted from the crystals which separated overnight at room temperature. Two crystallizations from acetone-ethanol gave the optically pure (+)-2·10-camphorsulfonate (0.8 g), mp 221 °C; $[\alpha]^{22}_D$ +33.0°. The base was regenerated from an aqueous solution of the salt with ammonia and extracted with ether. Evaporation of the solvent gave (+)-2: mp 84–85 °C; $[\alpha]^{22}_D$ +8.0°. Anal. ($C_{18}H_{27}N$) C, H, N. The hydrobromide salt was prepared and recrystallized from 2-propanol, to give (+)-2·HBr: mp 190–192 °C; $[\alpha]^{22}_D$ +20.65°. Anal. ($C_{18}H_{27}N$·HBr) C, H, N.

The mother liquor from the resolution was concentrated, the residue was basified with aqueous ammonia and extracted with ether, and the solvent was evaporated to give a crude base. Treatment with an equivalent amount of *l*-10-camphorsulfonic acid and crystallization as above gave 0.7 g of (−)-2 as the salt: mp 219–220 °C; $[\alpha]^{22}_D$ −32.6°. The salt was treated with ammonia and extracted with ether to give, after evaporation of the solvent, (−)-2: mp 84–85 °C; $[\alpha]^{22}_D$ −8.5°. Anal. ($C_{18}H_{27}N$) C, H, N. The hydrobromine salt was prepared and recrystallized from 2-propanol, to give (−)-2·HBr: mp 190–191 °C; $[\alpha]^{22}_D$ −20.61°. Anal. ($C_{18}H_{27}N$·HBr) C, H, N.

Optical Resolution of *cis*-(±)-1-(1-Phenyl-2-methylcyclohexyl)piperidine (3). Resolution was achieved similarly to that of 2, to give (+)-3·10-camphorsulfonate: mp 184–185 °C; $[\alpha]^{22}_D$ +25.9°. (+)-3: mp 55 °C; $[\alpha]^{22}_D$ +18.0°. Anal. ($C_{18}H_{27}N$) C, H, N. (−)-3·10-camphorsulfonate: mp 184–186 °C, $[\alpha]^{22}_D$ −24.6°. (−)-3: mp 55 °C; $[\alpha]^{22}_D$ −18.4°. Anal. ($C_{18}H_{27}N$) C, H, N.

***trans*- and *cis*-CN/Me 1-(1-Piperidinyl)-2-methylcyclohexanecarbonitrile (13 and 14).** Piperidine (17 g, 0.2 mol), on crushed ice (approximately 50 g), was neutralized with concentration HCl to pH 3–4. 2-Methylcyclohexanone (22 g, 0.2 mol) was added to this solution, followed by a solution of KCN (14.4 g, 0.22 mol) in water (30 mL), with stirring. The reaction proceeded very slowly at room temperature. The mixture was heated (oil bath, 50–55 °C) until TLC (solvent D) indicated the complete conversion of the starting ketone (approximately 8 days). The mixture was diluted with water and extracted with ether, and the ethereal solution was washed with 10% HCl (three times). The aqueous acidic solution was made alkaline with aqueous ammonia and extracted with ether. The ethereal solution was evaporated and the residual oil distilled (70–78 °C, 0.1 mmHg) to give a mixture of nitriles 13 and 14 (21.8 g, TLC showed one spot with several solvent systems). ^1H NMR ($CDCl_3$) of the product showed two doublets for the *sec*-Me of the two compounds: δ 0.95 (J = 7 Hz) for the minor isomer 13, and δ 1.09 (J = 6.5 Hz) for the major isomer 14, in the ratio of 1:2.5.

A sample was converted to the HCl salt. Fractional crystallization from ethanol–ether gave 14·HCl, mp 143 °C. Anal. ($C_{13}H_{25}ClN_2$) C, H, N. The second isomer, 13·HCl, was obtained from the mother liquor on standing, mp 134–135 °C. Anal. ($C_{13}H_{25}ClN_2$) C, H, N.

***trans*- and *cis*-1-(1-Benzimidoyl-2-methylcyclohexyl)-piperidine (5 and 6).** The isomeric mixture of 13 and 14 which was obtained as above (20 g, 0.1 mol) was added dropwise with stirring to a cooled solution of phenyllithium in ether, prepared from Li (4.4 g, 0.63 g-atom) and bromobenzene (45 g, 0.29 mol). The mixture was stirred overnight at room temperature and then added to crushed ice (the excess Li was removed by filtration through cotton gauze or glass wool). The mixture was extracted with ether, and the dried ethereal solution was evaporated to give an yellow oil. Distillation of the oil gave, after removing the lower boiling fraction, a mixture of 5 and 6 (17 g, bp 118–125 °C, 0.04 mmHg). Integration of the two *sec*-Me signals showed *trans*-5 and *cis*-6 in the approximate ratio of 1:1.5–2, respectively. The isomers were separated by column chromatography on silica gel packed with hexane and eluted with hexane, with increasing concentrations of ethyl acetate from 1% to 2.5%. TLC (solvent E, R_f 0.6) showed that the initial isomer eluted was 5. A hydrochloride salt was prepared to give 5·HCl (recrystallized from 2-propanol–ether), mp 195–196 °C. Anal. ($C_{19}H_{29}ClN_2$) C, H, N. The second eluted isomer was 6 (TLC solvent E, R_f 0.33). A hydrochloride salt was prepared to give 6·HCl (recrystallized from 2-propanol–ether), mp 199–201 °C. Anal. ($C_{19}H_{29}ClN_2$) C, H, N.

1-(1-Benzimidoylcyclohexyl)piperidine (4). 1-(1-Piperidinyl)cyclohexanecarbonitrile[29] (4.3 g, 25.6 mmol) was dissolved in ether and added dropwise to a cooled, stirred, solution of phenyllithium in ether which had been prepared from Li (1.3 g, 0.19 g-atom) and bromobenzene (8.6 g, 5.5 mmol). The mixture was stirred for 4 h at room temperature and poured onto crushed ice, filtering the excess Li through cotton gauze or glass wool. The ether extract was dried and evaporated to give 4 as an oil, which crystallized on standing (89% yield), mp 81–82 °C (petroleum ether). Anal. ($C_{18}H_{28}N_2$) C, H, N. Compound 4 was completely converted to 1-(1-benzoylcyclohexyl)piperidine (7) in strong acid, at room temperature.

***trans*- and *cis*-1-(1-Benzoyl-2-methylcyclohexyl)-piperidine (8 and 9).** Compound 5 was hydrolyzed with 3 N HCl by refluxing for 10 h. The product was made alkaline with aqueous ammonia and extracted with ether, and the ethereal extracts were evaporated to give 8, as an oil, in almost theoretical yield. A hydrochloride salt was prepared, mp 202–203 °C (from ethanol–ether). Anal. ($C_{19}H_{28}ClNO$) C, H, N.

cis-1-(1-Benzoyl-2-methylcyclohexyl)piperidine (9) was obtained similarly from 6 and characterized as the hydrochloride salt, mp 175–176 °C (from ethanol), and as the hydrogen sulfate salt, mp 230–232 °C. Anal. ($C_{19}H_{28}ClNO$ and $C_{19}H_{29}NO_5S$) C, H, N. Both 8 and 9 gave the same R_f in TLC.

1-(1-Benzoylcyclohexyl)piperidine (7). The desmethyl analogue 7 precipitated as the hydrochloride salt by treating 4 with ethereal HCl. Crystallization from ethanol gave 7·HCl, mp 185–188 °C dec. Anal. ($C_{18}H_{26}ClNO$) C, H, N. The salt was converted to the free base 7, mp 79–80 °C (petroleum ether). Anal. ($C_{18}H_{25}NO$) C, H, N.

***trans*- and *cis*-Ph/Me 1-(1-Phenyl-4-methylcyclohexyl)-amines (15 and 16).** Preparation followed that of *trans*- and *cis*-Ph/Me 1-(1-phenyl-2-methylcyclohexyl)piperidines (2 and 3). However, on distillation of the oily residue from the ethereal solution, the fraction collected at 65–77 °C (0.1 mm) gave the isomeric amines. The ^1H NMR ($CDCl_3$) of the mixture showed an apparent singlet at δ 1.00 for the methyl signal of the major isomer 15 and a doublet at δ 0.80 (J = 5 Hz) for the minor isomer 16. The approximate ratio was 3:1. A sample was treated with excess ethereal HCl and the resultant hydrochlorides fractionally crystallized to give 15·HCl, mp 224–226 °C (from ethanol–ether). Anal. ($C_{13}H_{20}ClN$) C, H, N. For 16·HCl, mp >260 °C (sublimation). Anal. ($C_{13}H_{20}ClN$) C, H, N. The remaining distilled isomeric mixture was used for the next step.

***trans*- and *cis*-Ph/Me 1-(1-Phenyl-4-methylcyclohexyl)-piperidines (17 and 18).** The isomeric mixture of 15 and 16 (17 g, 90 mmol) was dissolved in absolute ethanol (150 mL). 1,5-Dibromopentane (23 g, 0.1 mol), KI (0.2 g), and K_2CO_3 (17 g, 0.12 mol) were added, and the mixture was stirred and refluxed for 6 days. The ethanol was removed in vacuo and the residue partitioned between water and ether. Drying and evaporation

of the organic solvent left an oil which was distilled. The fraction collected at 100–102 °C (0.01 mmol) was an isomeric mixture with the trans isomer **17** preponderant. The ^{1}H NMR spectrum of the total base gave two signals for the *sec*-methyl. A broad singlet at δ 0.97 was observed for the major isomer **17** and a symmetrical doublet (δ 0.72, (J = 5 Hz) for the minor isomer **18**. The trans/cis isomers were formed in the approximate ratio of 3:1. Separation was attained through column chromatography on silica gel with hexane containing 5% ethyl acetate as eluent. The first isomer eluted was **17**, mp 59–60 °C (lit.[14] mp 61–62 °C). It was converted to the hydrochloride salt, mp 208–209 °C (from ethanol–ether) (lit.[14] mp 210–213 °C). Anal. ($C_{18}H_{28}ClN$) C, H, N. The second eluted isomer was **18**, mp 45–46 °C (lit.[14] mp 42–43 °C). It was converted to the hydrochloride salt, mp 201–202 °C (from ethanol) (lit.[14] mp 200–201 °C). Anal. ($C_{18}H_{28}ClN$) C, H, N.

Single-Crystal X-ray Analysis of (-)- and (+)-*trans*-1-(1-Phenyl-2-methylcyclohexyl)piperidine [(-)-2 and (+)-2] Hydrobromide Hemihydrate Solvate. Crystals of the (-)- [and (+)-] enantiomers of the hydrobromide salt of **2** were examined under equivalent conditions, parameters for the (+)-enantiomer, where different, are indicated by brackets. Clear 0.21 × 0.32 × 0.46 [0.32 × 0.35 × 0.42] mm crystals, $C_{18}H_{28}N^+Br^-\cdot{}^1/_2H_2O$, FW = 347.3, were selected for data collection. Data was collected on a computer-controlled diffractometer with an incident beam graphite monochromator (Nicolet R3m/V with Cu Kα radiation, λ = 1.54178 Å, T = 295 K). A least-squares refinement using 25 centered reflections within 50 < 2θ < 74° gave the tetragonal $P4_32_12$ [$P4_12_12$] cell, a = 10.269 (1) [10.271 (1)], c = 34.023 (7) [34.028 (9)] Å, with V = 3587.8 (9) [3589.7 (14)] Å^3, Z = 8, and d_{calc} = 1.286 [1.285] gm/cm^3. A total of 3875 [3846] reflections were measured in the $\theta/2\theta$ mode to $2\theta_{max}$ = 120°, of which there were 2677 [2682] independent reflections (Friedel's not merged). Corrections were applied for Lorentz and polarization effects. A semiempirical absorption correction based on the φ-dependence of 11 reflections with χ ca. 90° was applied, μ = 3.083 mm^{-1} and maximum and minimum transmission was 0.94 and 0.54 [0.86 and 0.57], respectively. The structure was solved by direct methods with the aid of the program SHELXTL[32] and refined with a full matrix least-squares.[32] The 191 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, and C–H = 0.96 Å, H angles idealized and U_{iso}(H) = 1.1U_{eq}(C) (1.2U_{eq} for methyl hydrogens), except for the hydrogen bonded to the nitrogen and in the water solvate, which were refined isotropically. The final R values for the 2454 [2440] observed reflections with $F_o > 3\sigma(|F_o|)$ were R = 0.043 [0.055], and wR = 0.051 [0.068], where $w = 1/[\sigma^2(|F_o|) + g(F_o)^2]$ and g = 0.000 23. The goodness of fit parameter was 1.67 [2.01] and final difference Fourier excursions were 0.71 and –0.89 [0.93 and –0.62] eÅ^{-3}.

Binding Studies. The displacement assays were performed as previously described,[4] with, however, a tissue homogenate preparation of fresh whole rat brain minus cerebellum. Incubation was carried out at 5 °C with [^{3}H]TCP (1-[1-(2-thienylcyclohexyl)]piperidine) as the radioligand. Rapid filtration was carried out through filters presoaked with 0.03% polylysine. The inhibition constant (K_i, Table IV) for determination of the affinity of the compound for the PCP binding site was calculated by using the Cheng–Prusoff equation,[33] with use of predetermined K_d for TCP (16.5 nM) from Scatchard analysis. Experiments were performed in triplicate and are the mean values from two separate experiments, except where indicated in Table IV. Cold TCP (10 μM) was used for the determination of nonspecific binding.

Rotarod Assay. Ataxia was measured in mice by using a "Rotarod treadmill" (Biological Research Apparatus U. Basile, 21025 Comerio, Varese, Italy), following the method of Kalir et al.[34] for PCP-like compounds. Swiss, male, 22–28 g mice were trained to cling and walk on a rod, which was divided into 5 sections and which rotated at 16 rpm. Trained mice were injected sc with an aqueous solution of the examined compounds. The number of animals which were, or were not, able to stay on the rod more than 60 s (lesser times were also noted) was recorded at 15 min intervals over 1 h. Mice strongly effected by a PCP-like drug fell from the rotating rod quickly and repeatedly. Eight mice were used at each of the four doses which were chosen from exploratory experiments. The ED_{50} was determined as the dose that included the fall of half of the animals from the rotarod system.

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Registry No. (±)-**2**·HCl, 134005-77-9; (+)-**2**·D-10-camphorsulfonate, 134107-21-4; (+)-**2**, 134053-32-0; (+)-**2**·HBr·$^1/_2H_2O$, 134107-22-5; (-)-**2**·L-10-camphorsulfonate, 134107-23-6; (-)-**2**, 134053-33-1; (-)-**2**·HBr·$^1/_2H_2O$, 134107-24-7; (±)-**3**, 134005-78-0; (±)-**3**·picrate, 134005-87-1; (+)-**3**·D-10-camphorsulfonate, 134005-88-2; (+)-**3**, 134005-89-3; (-)-**3**·L-10-camphorsulfonate, 134005-91-7; (-)-**3**, 134005-90-6; **4**, 16283-47-9; **5**, 134005-79-1; **5**·HCl, 134005-94-0; **6**, 134005-80-4; **6**·HCl, 134005-95-1; **7**, 13441-36-6; **7**·HCl, 13430-12-1; **8**, 134005-81-5; **8**·HCl, 134005-96-2; **9**, 134005-82-6; **9**·HCl, 134005-97-3; **9**·H_2SO_4, 134005-98-4; **10**, 125801-96-9; **11**, 129329-46-0; **11**·HCl, 125801-97-0; **13**, 134005-83-7; **13**·HCl, 134005-93-9; **14**, 134005-84-8; **14**·HCl, 134005-92-8; **15**, 55040-01-2; **15**·HCl, 125801-99-2; **16**, 55040-02-3; **16**·HCl, 125802-00-8; **17**, 29084-52-4; **17**·HCl, 134005-99-5; **18**, 55040-03-4; **18**·HCl, 134006-00-1; (*cis*)-1-phenyl-2-methylcyclohexanol, 134005-85-9; (*cis*)-1-(1-phenyl-2-methylcyclohexyl)azide, 125802-39-3; 1,5-dibromopentane, 111-24-0; piperidine, 110-89-4; 2-methylcyclohexanone, 583-60-8; bromobenzene, 108-86-1; 1-(1-piperidinyl)cyclohexanecarbonitrile, 3867-15-0; (±)-1-phenyl-4-methylcyclohexanol, 63007-45-4; (*trans*)-1-phenyl-2-methylcyclohexanol, 134005-86-0; (*trans*)-1-(1-phenyl-2-methylcyclohexyl)azide, 125802-38-2.

Supplementary Material Available: Tables of atomic coordinates, bond lengths, bond angles, anisotropic displacement coefficients, and H atom coordinates for compounds (-)-**2** and (+)-**2** (18 pages). Ordering information is given on any current masthead page. Tables of atomic coordinates and bond lengths and angles have been deposited with the Crystallographic Data Centre, Cambridge University Chemical Laboratory, Cambridge CB2 1EW, England.

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