and 0.9% NaCl, and injected ip or po (gavage) in a volume of 10 mL/kg (mice) or 5 mL/kg (rats). In testing performed by NINCDS, drugs were suspended or dissolved in 30% polyethylene glycol and injected in a volume of 10 mL/kg (mice) or 4 mL/kg (rats).

Animals. Male Swiss-Webster mice (22–32 g, Buckberg Labs, Tomkin Cove, NY, or Charles River, Portage, MI) were used for electroshock and ataxia experiments; male CF-1 mice (25–35 g, Charles River, Portage, MI, or Wilmington, MA) were used for threshold clonic seizures from pentylenetetrazol and for all testing from NINCDS. Male Sprague–Dawley rats (125–150 g, Charles River, Portage MI) were used for ataxia experiments, and somewhat larger rats (270–300 g) were used for implantation of hippocampal electrodes. All rodents were allowed free access to food and water prior to testing.

Maximal Electroshock. For mice, shocks were applied through earclip electrodes from a Ugo Basile (Milan, Italy) electroshock apparatus; 90-mA monophasic pulses of 1-ms duration, 100 Hz for 0.2 s. This stimulus intensity was approximately 4 times the threshold for tonic extensor seizures. In tests at the NINCDS, shocks were applied through corneal electrodes from a Wahlquist (Salt Lake City, UT) electroshock apparatus, 50-mA (zero to peak) sinusoidal current, 60 Hz for 0.2 s. In both cases, an anticonvulsant effect was scored if tonic extensor seizures (extension of the hindlimbs parallel to the body) were prevented.

Pentylenetetrazol Threshold Seizures. Pentylenetetrazol was dissolved in 0.9% NaCl and administered subcutaneously (10 mL/kg) at the dorsal part of the neck (85 mg/kg). Mice were observed for 30 min following injection. Prevention of all clonic seizures (≥5 s of forelimb clonus) was scored as an anticonvulsant effect.

Afterdischarge in Kindled Rats. Rats were anesthetized and stereotaxically implanted with paired wire electrodes in the dorsal hippocampus of the brain. At least 1 week after surgery, electrical stimuli were delivered to the implanted electrodes at 30-min intervals for a total of 8 h (biphasic pulses, 1 ms each phase, 500 μA peak-to-peak, 10 Hz for 10 s). Such intermittent stimulation was given for 8-h periods on each of four alternating days. At least 3 days later, rats were used for pharmacological testing. Each rat was tested for the threshold electrical stimulus to produce a focal seizure (afterdischarge). Beginning with a peak-to-peak stimulus of 40 μA (biphasic pulses, 1 ms each phase, 60 Hz for 1 s), the stimulus was incremented by 20% at intervals of 1 min until a focal afterdischarge (rapidly repeated high-voltage EEG spikes lasting for at least 3 s) occurred. The stimulus intensity that first caused an afterdischarge was taken as the untreated afterdischarge threshold. Following drug administration, each rat received an electrical stimulus at twice the mean untreated threshold. If no afterdischarge occurred, additional stimuli were given at 4, 6, and 8 times the untreated threshold until an afterdischarge was recorded.

Anticonvulsant effects were scored separately for each of the stimulus intensities (2, 4, 6, or 8 times the untreated threshold).

Measurement of Ataxia. Ataxia in mice is defined as the lowest dose level at which two or more animals ($N = 5$) fell from an inverted wire mesh screen[11] or, in NINCDS studies, from a rotating rod.[12] In rats, ataxia was evaluated by scoring uncoordinated locomotion on a flat surface (uneven gait in each of three trials) and by delayed righting responses (righting more than 1 s after being placed supine in each of three trials).

ED_{50} Determinations. Doses of drug causing 50% of the maximal effect were determined by quantal probit analysis for anticonvulsant and ataxia measurements.[13] For inhibition of spontaneous locomotion, ED_{50} was estimated graphically from log dose–response curves.

Acknowledgment. We thank Dr. F. A. MacKellar and his associates for IR and NMR spectra as well as for the elemental analyses; M. Vartanian, P. Mickevicius, and B. Stieber (Warner-Lambert) for pharmacological test results. The help of the Anticonvulsant Drug Discovery Program, Epilepsy Branch, NINCDS (H. J. Kupferberg and G. Gladding) in the pharmacological evaluation of several of these compounds is gratefully acknowledged.

Registry No. **1**, 55745-89-6; **1**·2HCl, 120144-91-4; **2**, 120145-32-6; **2**·3HCl, 120144-92-5; **3**, 120145-33-7; **3**·2HCl, 120144-93-6; **4**, 120144-94-7; **4**·$C_3H_4O_4$, 120144-95-8; **5**, 120145-34-8; **5**·2HCl, 120144-96-9; **6**, 120144-97-0; **6**·$C_3H_4O_4$, 120144-98-1; **7**, 120144-99-2; **8**, 120145-00-8; **8**·$C_3H_4O_4$, 120145-01-9; **9**, 120145-02-0; **9**·$C_3H_4O_4$, 120145-03-1; **10**, 120145-04-2; **10**·$C_3H_4O_4$, 120145-05-3; **11**, 120145-06-4; **11**·$C_3H_4O_4$, 120145-07-5; **12**, 120145-08-6; **12**·$C_3H_4O_4$, 120145-09-7; **13**, 120145-35-9; **13**·HCl, 120145-10-0; **14**, 120145-11-1; **14**·$C_3H_4O_4$, 120145-12-2; **15**, 120145-13-3; **15**·$C_3H_4O_4$, 120145-14-4; **16**, 120145-15-5; **17**, 120145-36-0; **17**·2HCl, 120145-16-6; **18**, 120145-17-7; **18**·$C_3H_4O_4$, 120145-18-8; **19**, 120145-19-9; **20**, 120145-20-2; $Br(CH_2)_2CH_3$, 106-94-5; $Br(CH_2)_3CH_3$, 109-65-9; $Br(CH_2)_4CH_3$, 110-53-2; $Br(CH_2)_6CH_3$, 629-04-9; $Br(CH_2)_7CH_3$, 111-83-1; $Br(CH_2)_9CH_3$, 112-29-8; cyanoacetamide, 107-91-5; 6-chloro-2-heptylpyridine, 120145-24-6; 1-bromohexane, 111-25-1; *N*-methylpiperazine, 109-01-3; homopiperazine, 505-66-8; morpholine, 110-91-8; piperidine, 110-89-4; 2-chloro-6-hexylpyridine, 109201-48-1; 2-octanone, 111-13-7; ethyl formate, 109-94-4; piperazine, 110-85-0; 2-chloro-6-nonylpyridine, 120145-26-8; 6-chloro-2-picoline, 18368-63-3; *n*-butylmercaptan, 109-79-5; 2-(butylthio)-6-chloropyridine, 87512-14-9; 2,6-dichloropyridine, 2402-78-0; 2-chloro-6-propylpyridine, 120145-21-3; 2-chloro-6-isopropylpyridine, 120145-22-4; 2-chloro-6-butylpyridine, 40273-58-3; 2-chloro-6-*tert*-butylpyridine, 97691-23-1; 2-chloro-6-pentylpyridine, 120145-23-5; 2-chloro-6-octylpyridine, 120145-25-7; 6-chloro-2-decylpyridine, 120145-27-9; 2-chloro-6-(2-phenylethyl)pyridine, 120145-28-0; 2-chloro-6-(cyclohexylmethyl)pyridine, 120145-29-1; 2-chloro-6-(tridecan-7-yl)pyridine, 120145-30-4; 2-chloro-4-heptylpyridine, 120145-31-5; (2-bromoethyl)benzene, 103-63-9.

(11) Swinyard, E. A.; Woodhead, J. H. In *Antiepileptic Drugs*; Woodbury, D. M., Ed.; Raven: New York, 1982; pp 111–126.
(12) Coughenour, L. L.; McLean, J. R.; Parker, R. B. *Pharmacol. Biochem. Behav.* **1977**, *6*, 351.
(13) Litchfield, J. T.; Wilcoxon, F. J. *Pharmacology* **1949**, *96*, 99.

Phencyclidine-like Effects of Tetrahydroisoquinolines and Related Compounds

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A series of 1,2,3,4-tetrahydroisoquinolines, tetrahydrothieno[2,3-c]pyridines, and related compounds were evaluated for their ability to inhibit binding of [^{3}H]-1-[1-(2-thienyl)piperidine and [^{3}H]-*N*-allylnormetazocine to phencyclidine (PCP) and σ receptors, respectively. A representative series of compounds was evaluated in behavioral assays to determine the ability of the compounds to induce PCP-like stereotyped behavior and ataxia. All of the compounds caused stereotyped behavior and ataxia, indicating their agonist actions at the PCP site.

Phencyclidine (PCP) was originally developed as a general anesthetic agent,[1] which was withdrawn from human use because of unwanted side effects, often resembling acute schizophrenia.[2] These observed side effects, how-

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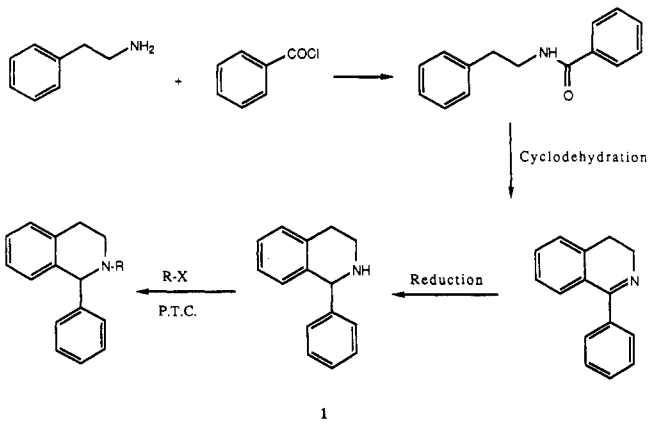
Scheme I



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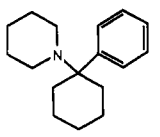
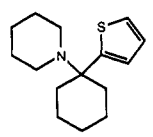
ever, have led to the speculation that PCP antagonists may be useful as antipsychotic agents. The development of a reliable binding assay for the PCP receptor and the correlation of PCP-like stereotyped behaviors of several standard compounds to their affinity at this binding site[3] have provided the pharmacological tools to screen for PCP receptor antagonists.

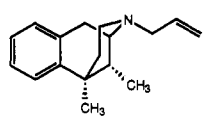
Compounds representing a wide variety of structures have been found to be agonists at the PCP receptor. 1-[1-(2-Thienyl)cyclohexyl]piperidine (TCP),[4] (+)-*N*-allylnormetazocine ((+)-NANM),[5] and MK-801[6] are a few of the prototypic agonists for this site.



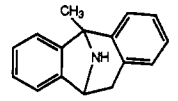
PCP



TCP



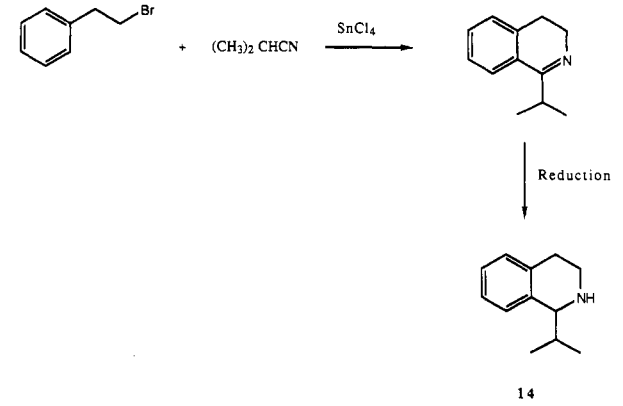
(+)-NANM



MK-801

MK-801 was originally identified in the early 1980s as a potent, orally active anticonvulsant that also possessed anxiolytic and central sympathomimetic properties.[7] Comparison of the rigid structure of MK-801 to the more flexible structure of PCP led us to believe that compounds containing a tetrahydroisoquinoline or isoindoline ring system may also interact with the PCP receptor. Such structures would be less flexible than PCP but more flexible than MK-801. Accordingly, a series of compounds containing these ring systems and the related tetrahydrothieno[2,3-*c*]pyridine system were prepared and evaluated for their receptor affinities.

Scheme II



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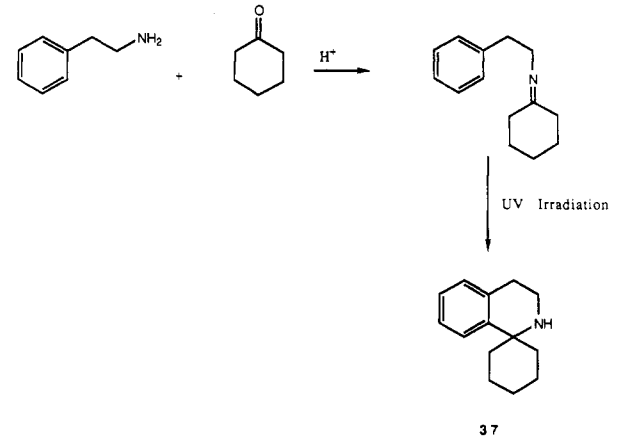
Scheme III



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Chemistry

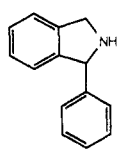
The majority of the compounds given in Table I were prepared by standard methods from the appropriate 2-arylethylamines and acid chlorides to prepare the intermediate amides which were cyclized by using the Bischler–Napieralski reaction[8] as outlined in Scheme I. The cyclodehydration step utilized either polyphosphoric acid or a mixture of phosphorus oxychloride and phosphorus pentoxide as the dehydrating agent. The reduction of the intermediate dihydroisoquinolines was achieved utilizing lithium aluminum hydride, sodium borohydride, or catalytic hydrogenation. Alkylation of the tetrahydroisoquinoline system was achieved by reaction with the appropriate alkylating agent under phase-transfer conditions.

Alternately, synthesis of the compounds containing alkyl groups at the C-1 position was often best achieved by employing a modified Ritter reaction[9] as outlined in Scheme II.

Compound **37** was prepared by UV irradiation of the intermediate imine as shown in Scheme III.

The syntheses of compounds **20–25**[10] were reported elsewhere. Compounds **18**,[11,12] **19**,[13] and **35**[14] were prepared by known procedures.

(1) Collins, V. J.; Gorospe, C. A.; Ronenstine, E. A. *Anesth. Analg. (N.Y.)* **1960**, *39*, 302.
(2) Greifenstein, F. D.; Yoshitake, J.; DeVauit, M.; Gajewski, J. E. *Anesth. Analg. (N.Y.)* **1958**, *37*, 283.
(3) Contreras, P. C.; Rice, K. C.; Jacobson, A. E.; O'Donohue, T. L. *Eur. J. Pharmacol.* **1986**, *121*, 9.
(4) Kalir, A.; Edery, H.; Pelah, Z.; Balderman, D.; Porath, G. *J. Med. Chem.* **1969**, *12*, 473.
(5) Zukin, S. R.; Zukin, R. S. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 5372.
(6) Wong, E. H. F.; Kemp, J. A.; Priestly, T.; Knight, A. R.; Woodruff, G. N.; Iversen, L. L. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 7104.
(7) Clineschmidt, B. V.; Martin, G. E.; Bunting, P. R. *Drug Devel. Res.* **1982**, *2*, 123.
(8) Bischler, A.; Napieralski, B. *Chem. Ber.* **1893**, *26*, 1903.
(9) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045.
(10) Ellefson, C. R.; *J. Org. Chem.* **1979**, *44*, 1533.
(11) Boyce, W. T.; Levine, R. *J. Org. Chem.* **1966**, *31*, 3807.
(12) Powell, B. F.; Overberger, C. G.; Anselme, J. P. *J. Heterocycl. Chem.* **1983**, *20*, 121.
(13) Pridgen, L. N.; Killmer, L. B.; Webb, R. L. *J. Org. Chem.* **1982**, *47*, 1985.
(14) Veber, D. F.; Lwowski, W. *J. Am. Chem. Soc.* **1964**, *86*, 4152.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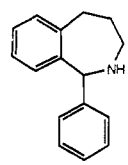
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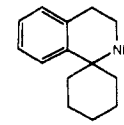
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Pharmacological Results and Discussion

The compound structures and results of the radioreceptor assays are summarized in Table I. This series of compounds was selected for preparation due to their structural similarity to MK-801, a potent and selective ligand for the PCP receptor. PCP and TCP are two potent, albeit less selective, ligands for the PCP receptor which, unlike MK-801, are less conformationally restrained. The compounds used in this study are more rigid than PCP or TCP, but less rigid than MK-801. It is interesting to note that compounds **1**, **13**, and **35**, which can be viewed directly as more flexible analogues of MK-801, are much less potent in displacing [^{3}H]TCP from its receptor. The loss of rigidity in the compounds also appears to diminish selectivity for the PCP site relative to the σ site as is indicated by comparable IC_{50} values for both sites shown by the latter three molecules. The higher affinity of TCP, relative to PCP, for the PCP site led to the preparation of compounds **10** and **28** to examine the effects of the thiophene ring in this series of compounds. In both cases, the affinity for both the PCP and σ site is less than that shown by the parent compound **1**.

Additionally, in the isoquinoline series, the presence of a second aromatic ring is preferred for interaction with the PCP site, but the position of this ring can vary. The presence of an aromatic group directly attached to the isoquinoline ring system at C-1, C-3, or C-8 (compounds **1**, **18**, and **20**) or separated by a methylene group at C-1 (compound **13**) is tolerated by the PCP receptor, while the presence of an aromatic ring at C-4 is not (compound **19**). Compound **19**, however, maintains affinity for the σ site, suggesting that there are subtle differences between the two binding sites in their requirements for the location of the aromatic ring. A large aromatic ring at C-1 (compound **11**) or para substituents on the C-1 phenyl (compounds **6–9**) diminishes activity at both sites, while an *o*-methoxy on the C-8 phenyl slightly increased affinity at both (compound **25** vs compound **20**).

The effects of alkylation of the nitrogen on selectivity and potency were also studied. In general, alkylation of the nitrogen diminished affinity for the PCP site in the compounds containing a phenyl ring at the C-1 position of the isoquinoline ring (compounds **1–5**). This effect was not paralleled in the case of the σ site, where no consistent effect of alkylation could be found. When the compound did not contain an aromatic substituent on the isoquinoline or thieno[2,3-*c*]pyridine ring, however, the presence of an *N*-allyl group increased the affinity of the compound at both sites relative to the corresponding compounds without an *N*-allyl group (compounds **17**, **27**, **34**). This effect of the *N*-allyl group is consistent with the fact that in the benzomorphan series,[15] *N*-allylnormetazocine and related compounds containing allyl groups have high affinity for the σ site and in a series of 3-phenylpiperidines[16] hydrophobic *N*-alkyl groups also enhanced affinity at this site. In terms of the PCP site, the preference for *N*-allyl substitution on the nitrogen of compounds with only one aromatic ring is consistent with the finding that in a series of related hexahydroindeno[2,1-*c*]pyridines[17] and benz[*f*]isoquinolines,[18] *N*-allyl substitution also enhanced affinity.

Several representative compounds were also evaluated for their ability to induce PCP-like stereotyped behavior and ataxia (Table II). These compounds were selected on the basis of their affinity for the PCP receptor (compounds **1**, **8**, **13**, and **25**), the position of the phenyl substituent (compounds **18** and **20**), and the incorporation of a thiophene ring (compounds **10** and **28**). All of the compounds selected for in vivo evaluation from this series elicited PCP-like behaviors, suggesting that it is unlikely that structural modifications based on MK-801 or the tetrahydroisoquinolines will lead to the discovery of compounds with affinity for the PCP receptor without eliciting PCP behaviors in animals. Since the induction of PCP-like stereotypy has been demonstrated to be an indicator of agonist activity at the PCP site,[3] it is also unlikely that further structural modifications in this series of compounds will lead to PCP antagonists.

Experimental Methods

^{1}H NMR spectra were taken on a Varian XL-300 spectrometer and were consistent with assigned structures. All distillations were done on a Kugelrohr apparatus. Melting points are uncorrected. Microanalysis were performed for the stated elements and were within 0.04% of the theoretical values for the stated empirical formulas. Synthetic and analytical data for compounds **20–25**[10] were reported previously.

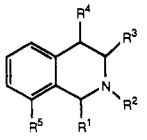
Synthesis. 1-Phenyl-1,2,3,4-tetrahydroisoquinoline (1). A mixture of phenylethylamine (6.0 g, 0.050 mol) in methylene chloride (50 mL) and 10% aqueous sodium hydroxide (50 mL) was stirred vigorously and treated dropwise with benzoyl chloride (6.0 g, 0.043 mol). After the addition, the mixture was stirred an additional 15 min and then poured into water (50 mL). The layers were separated, and the organic layer was washed with water, 5% aqueous HCl, and water. The solution was dried ($MgSO_4$) and the solvent removed. The solid residue was recrystallized from ethyl acetate to give the amide (8.9 g, 92%): mp 118–120 °C (lit. mp 117 °C).[19]

The amide (2 g, 0.0089 mol) was dissolved in $POCl_3$ (50 mL) and treated with P_2O_5 (5 g). The solution was heated to reflux for 2 h, cooled to room temperature, and cautiously poured onto ice (200 g). The aqueous mixture was washed with methylene chloride to remove the starting material and then made basic by the addition of concentrated aqueous ammonia. The resulting mixture was extracted with methylene chloride and the organic solution dried (Na_2SO_4) and concentrated to give an amber oil. The amber oil was distilled (140 °C at 0.3 mmHg) to provide a yellow oil (1 g). The oil was dissolved in 10 mL of absolute ethanol and hydrogenated for 10 h at 54 psi over PtO_2 catalyst. The catalyst was removed by filtration and the solvent removed. The residue was distilled (100 °C at 0.3 mmHg) to give 1 as a colorless oil which solidified upon standing (1 g, 54%): mp 73–75 °C (lit.[20] mp 70–75 °C); NMR ($CDCl_3$) δ 6.75–7.45 (series of res, 9 H, Ar), 5.4 (s, 1 H, CH), 2.95–3.4 (m, 4 H, CH_2).

2-(2-Ethoxyethyl)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (2). A mixture of 1 (2 g, 0.0096 mol), 2-bromoethyl ethyl ether (1.61 g, 0.0105 mol), K_2CO_3 (1 g), and potassium iodide (catalytic

(15) Tam, S. W. *Eur. J. Pharmacol.* **1985**, *109*, 33.
(16) Wikstrom, H.; Andersson, B.; Elebring, T.; Svensson, K.; Carlsson, A.; Largent, B. *J. Med. Chem.* **1987**, *30*, 2169.
(17) Cantrell, B. E.; Leander, J. D.; Mendelsohn, L. G.; Schoepp, D. D.; Hermann, R. B.; Zimmerman, D. M. 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 11–17.
(18) Zimmerman, D. M.; Woods, J. H.; Hynes, M. D.; Cantrell, B. E.; Reamer, M.; Leander, J. D. In *Phencyclidine and Related Arylcyclohexylamines: Present and Future Applications*; Kamenka, J. M., Domino, E. F., Geneste, P., Eds.; NPP Books: Ann Arbor, MI, 1983; pp 59–69.
(19) Nakajima, S. *J. Pharm. Soc. Jpn.* **1956**, *76*, 1008.
(20) Brodrick, C. I.; Short, W. F. *J. Chem. Soc.* **1949**, *2587*.

Table I. Inhibition of [^{3}H]TCP and [^{3}H]NANM Binding



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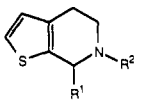

28-34

compd	R^1	R^2	R^3	R^4	R^5	IC_{50}, μM [^{3}H]TCP	IC_{50}, μM [^{3}H]NANM
PCP						0.091 ± 0.005[a]	0.53 ± 0.10
TCP						0.020 ± 0.006	0.24 ± 0.076
MK-801						0.0053 ± 0.0003	1.7 ± 0.5
(+)-NANM						0.76 ± 0.13	0.050 ± 0.012
1	Ph	H	H	H	H	1.9 ± 0.2	2.0 ± 0.6
2	Ph	$CH_2CH_2OCH_2CH_3$	H	H	H	8.2 ± 0.9	5.4 ± 0.4
3	Ph	CH_2CH_3	H	H	H	3.8 ± 0.2	1.3 ± 0.2
4	Ph	$CH_2CH{=}CH_2$	H	H	H	2.3 ± 0.4	1.3 ± 0.2
5	Ph	CH_3	H	H	H	24.0 ± 0.3	2.9 ± 0.9
6	*p*-ClC_6H_4	H	H	H	H	5.3 ± 1.3	3.4 ± 0.4
7	*p*-CH_3O-C_6H_4	H	H	H	H	2.5 ± 0.2	2.2 ± 0.6
8	*p*-F-C_6H_4	H	H	H	H	4.9 ± 0.2	1.8 ± 0.7
9	*p*-CH_3-C_6H_4	H	H	H	H	9.5 ± 0.1	5.6 ± 1.2
10	2-thienyl	H	H	H	H	7.6 ± 0.4	3.8 ± 0.8
11	2-naphthyl	H	H	H	H	>30	10.0 ± 1.1
12	2-naphthyl	$CH_2CH{=}CH_2$	H	H	H	NI[b]	11.0 ± 1.1
13	CH_2Ph	H	H	H	H	1.0 ± 0.2	0.43 ± 0.08
14	$CH(CH_3)_2$	H	H	H	H	11.0 ± 1.4	2.5 ± 1.2
15	$CH_2CH(CH_3)_2$	H	H	H	H	20.0 ± 2.0	5.0 ± 2.2
16	c-C_6H_{11}	H	H	H	H	12.0 ± 1.4	11.0 ± 7.8
17	c-C_6H_{11}	$CH_2CH{=}CH_2$	H	H	H	6.2 ± 0.2	3.1 ± 0.2
18	H	H	Ph	H	H	3.9 ± 0.2	2.6 ± 1.3
19	H	H	H	Ph	H	>30	4.2 ± 1.7
20	H	H	H	H	Ph	4.4 ± 1.2	2.7 ± 0.4
21	H	CH_2Ph	H	H	H	NI	7.8 ± 3.8
22	H	CH_3	H	H	H	>30	2.7 ± 0.5
23	H	CH_2Ph	CH_3	H	H	>30	3.2 ± 1.0
24	H	CH_3	CH_3	H	H	>30	2.6 ± 1.0
25	H	H	H	H	*o*-CH_3O-C_6H_4	0.9 ± 0.3	1.8 ± 0.4
26	CH_3	H	CH_3	H	H	>30	15.0 ± 2.4
27	CH_3	$CH_2CH{=}CH_2$	CH_3	H	H	5.4 ± 1.5	1.6 ± 0.2
28	Ph	H				8.8 ± 0.3	6.3 ± 0.2
29	Ph	$CH_2CH{=}CH_2$				NI	20.0 ± 5.7
30	CH_3	H				>30	11.0 ± 2.2
31	$CH(CH_3)_2$	H				17.0 ± 1.0	3.8 ± 0.2
32	$CH(CH_3)_2$	CH_3				17.0 ± 2.3	7.8 ± 2.2
33	$CH(CH_3)_2$	CH_2CH_3				12.0 ± 0.6	NI
34	$CH(CH_3)_2$	$CHCH{=}CH_2$				8.5 ± 0.7	5.0 ± 1.2
35						>30	>30
36						NI	NI
37						NI	NI

[a] Mean ± SEM for at least three experiments. [b] No detectable inhibition of binding at 30 μM.

Table II. Induction of PCP-like Behaviors

compd	ED_{50}, mg/kg stereotyped behavior	ED_{50}, mg/kg ataxia
PCP	4.7 (3.6–6.0)[a]	6.5 (4.9–8.4)
1	25 (18–37)	>20[b]
8	38 (29–51)	49 (36–38)
10	61 (43–88)	54 (39–76)
13	26 (20–35)	42 (31–59)
18	19 (14–25)	18 (14–23)
20	28 (21–38)	44 (32–64)
25	20 (14–29)	22 (16–32)
28	>50[c]	>50[c]

[a] Values in parentheses are 95% confidence intervals. [b] Compound insoluble at higher doses in injection medium. [c] Produced convulsions at 160 mg/kg.

amount) in acetone (50 mL) was heated to reflux for 20 h. The mixture was cooled, treated with 100 mL of H_2O, and extracted with methylene chloride. The organic solution was dried ($MgSO_4$), the solvent removed, and the residue distilled (100 °C at 0.05 mmHg) to provide **2** as a colorless oil (0.7 g, 26%): NMR ($CDCl_3$) δ 6.75–7.3 (series of res, 9 H, Ar), 4.65 (s, 1 H, CH), 2.5–3.5 (series of multiplets, 10 H, CH_2), 1.1 (t, 3 H, CH_3). Anal. ($C_{19}H_{23}NO$) C, H, N.

2-Ethyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (3). Compound 1 (1 g, 0.0048 mol) in a mixture of methylene chloride (25 mL) and 50% aqueous sodium hydroxide (3 mL) was treated with diethyl sulfate (0.62 mL, 0.0047 mol) and benzyltriethylammonium chloride (100 mg) and the resulting mixture stirred 22 h at room temperature. Water was added to the reaction mixture, and the layers were separated. The organic layer was washed with additional water and dried ($MgSO_4$), and the solvent was removed. The residue was distilled (80 °C at 0.2 mmHg) to obtain **3** as a colorless oil (0.8 g, 70%): NMR ($CDCl_3$) δ 6.6–7.3 (series of res, 9 H, Ar), 4.65 (s, 1 H, CH), 2.2–3.2 (series of multiplets, 6 H, CH_2), 1.0 (t, 3 H, CH_3). Anal. ($C_{17}H_{19}N$) C, H, N.

2-Allyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (4). Compound 1 (0.5 g, 0.0024 mol) in a mixture of methylene chloride (25 mL) and 50% aqueous sodium hydroxide (3 mL) was treated with allyl bromide (0.2 mL, 0.0017 mol) and benzyltriethylammonium chloride (100 mg) and the resulting mixture stirred 15 min at room temperature. Water was added to the reaction mixture, and the layers were separated. The organic layer was washed with additional water and dried ($MgSO_4$), and the solvent was removed. The residue was distilled (100 °C at 0.2 mmHg)

to obtain **4** as a colorless oil (0.1 g, 24%): NMR ($CDCl_3$) δ 6.6–7.3 (series of res, 9 H, Ar), 5.7–5.9 (m, 1 H, CH of alkene), 5.0–5.2 (m, 2 H, CH_2 in alkene), 4.5 (s, 1 H, CH in isoquinoline), 2.5–3.2 (series of multiplets, 6 H, CH_2), 1.0 (t, 3 H, CH_3). Anal. ($C_{17}H_{19}N$) C, H, N.

2-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (5). Compound **1** (0.8 g, 0.0038 mol) in a mixture of methylene chloride (25 mL) and 50% aqueous sodium hydroxide (3 mL) was treated with dimethyl sulfate (0.4 mL, 0.0042 mol) and benzyltriethylammonium chloride (100 mg) and the resulting mixture stirred 15 min at room temperature. Water was added to the reaction mixture, and the layers were separated. The organic layer was washed with additional water and dried ($MgSO_4$), and the solvent was removed. The residue was distilled (100 °C at 0.2 mmHg) to obtain **5** as a colorless oil (0.55 g, 65%): lit.[21] mp 72 °C; NMR ($CDCl_3$) δ 6.5–7.3 (series of res, 9 H, Ar), 4.2 (s, 1 H, CH), 2.5–3.3 (series of multiplets, 4 H, CH_2), 2.2 (s, 3 H, CH_3).

1-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (6). Phenylethylamine (12.6 mL, 0.1 mol) in methylene chloride (25 mL) was treated dropwise with a solution of *p*-chlorobenzoyl chloride (6.4 mL, 0.050 mol) in methylene chloride (25 mL). The resulting mixture was stirred 4 h at room temperature. The mixture was treated slowly with 5% $NaHCO_3$ solution (25 mL), the layers were separated, and the organic solution was washed with additional 5% $NaHCO_3$ solution, water, 5% aqueous HCl, and water. The organic layer was dried ($MgSO_4$) and the solvent removed. The resulting solid was recrystallized from ethyl acetate to give the amide (11.3 g, 87%): mp 138–141 °C (lit.[22] mp 134 °C).

The amide (1 g, 0.0039 mol) was placed in polyphosphoric acid (50 g) and heated with stirring to 140 °C for 4 h. The hot mixture was cautiously poured onto ice (200 g) and the mixture stirred 30 min. The aqueous mixture was washed with methylene chloride and then made basic by the addition of excess concentrated aqueous ammonia. The resulting mixture was extracted with ether. The ether solution was dried ($MgSO_4$) and the solvent removed to yield a yellow oil (0.92 mg), which was reduced directly. The oil was dissolved in anhydrous ether and treated with lithium aluminum hydride (141 mg). The mixture was heated to reflux for 20 h, then cooled in an ice bath, and treated slowly with 1 N HCl. The resulting layers were separated and the acid solution washed with ether. The acid layer was made basic by the addition of 50% aqueous NaOH and extracted with ether. The ether solution was dried ($MgSO_4$), the solvent removed, and the residue distilled (110 °C at 0.2 mmHg) to yield **6** as a colorless oil, which solidified upon standing (250 mg, 26% from amide): mp 65–67 °C (lit.[23] mp 233–236 °C for HCl salt); NMR ($CDCl_3$) δ 6.7–7.4 (series of res, 8 H, Ar), 5.1 (s, 1 H, CH), 2.75–3.4 (m, 4 H, CH_2), 2.0 (br s, 1 H, NH).

1-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (7). Phenylethylamine (12.6 mL, 0.1 mol) and *p*-methoxybenzoyl chloride (8.5 g, 0.050 mol) were used to prepare the precursor amide as described for compound **6**. The crude amide was recrystallized from ethyl acetate to give the product (11.3 g, 87%); mp 119–121 °C (lit.[23] mp 116–118 °C).

The amide (2 g, 0.0078 mol) was cyclized with $POCl_3$ and P_2O_5 and the cyclized product was hydrogenated as described for compound **1**. The resulting material was sublimed at 110 °C at 0.2 mmHg to give compound **7** as an off white solid (675 mg, 36%): mp 79–81 °C (lit.[23] mp 244–250 °C for HCl salt); NMR ($CDCl_3$) δ 6.7–7.3 (series of res, 8 H, Ar), 5.1 (s, 1 H, CH), 3.8 (s, 3 H, CH_3), 2.75–3.5 (m, 4 H, CH_2), 1.8 (br s, 1 H, NH).

1-(4-Fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (8). Phenylethylamine (12.6 mL, 0.1 mol) and *p*-fluorobenzoyl chloride (5.9 mL, 0.050 mol) were used to prepare the precursor amide as described for compound **6**. The crude amide was recrystallized from ethyl acetate to give the product (10.3 g, 85%): mp 127–130 °C (lit.[23] mp 123–124.5 °C).

The amide (1 g, 0.0041 mol) was cyclized with polyphosphoric acid as described for compound **6** to provide the intermediate as a yellow oil (1 g). The oil was dissolved in 10 mL of absolute ethanol and hydrogenated for 20 h at 30 psi over PtO_2 catalyst. The catalyst was removed by filtration and the solvent removed. The residue was distilled (110 °C at 0.2 mmHg) to give **8** as a pale yellow oil, which solidified upon standing (224 mg, 24%): mp 88–89 °C (lit.[23] mp 252–258 °C for HCl salt); NMR ($CDCl_3$) δ 6.7–7.4 (series of res, 8 H, Ar), 5.1 (s, 1 H, CH), 2.75–3.3 (m, 4 H, CH_2), 1.9 (br s, 1 H, NH).

1-(4-Methylphenyl)-1,2,3,4-tetrahydroisoquinoline (9). The intermediate amide (9.0 g, 75%) was prepared from 2-phenylethylamine (12.6 g, 0.100 mol) and *p*-toluyl chloride (6.6 mL, 0.050 mol) as described for compound **6**: mp 84–86 °C (lit.[23] mp 78–79 °C).

The amide (1.5 g, 0.0063 mol) was cyclized with $POCl_3$ and P_2O_5 and the cyclized product was hydrogenated as described for compound **1**. The residue was sublimed (100 °C at 0.2 mmHg) to yield **9** as a white solid (965 mg, 69%): mp 69–71 °C (lit.[23] mp 282–286 °C for HCl salt); NMR ($CDCl_3$) δ 6.7–7.4 (series of res, 8 H, Ar), 5.7 (s, 1 H, CH), 3.0–3.4 (m, 4 H, CH_2), 2.5 (br s, 1 H, NH), 2.3 (s, 3 H, CH_3).

1-(2-Thienyl)-1,2,3,4-tetrahydroisoquinoline (10). The intermediate amide (10.0 g, 87%) was prepared from 2-phenylethylamine (12.6 g, 0.100 mol) and 2-thiophenecarbonyl chloride (7.3 g, 0.050 mol) as described for compound **6**: mp 111–114 °C (lit.[24] mp 111–112 °C).

The amide (1.5 g, 0.0065 mol) was cyclized with $POCl_3$ and P_2O_5 as described for compound **1**. The cyclized product was reduced with lithium aluminum hydride as described for compound **6** and the crude product distilled (110 °C at 0.2 mmHg) to yield **10** as a yellow oil, which solidified upon standing (568 mg, 41%): mp 93–96 °C; NMR ($CDCl_3$) δ 6.9–8.0 (series of res, 7 H, Ar), 5.4 (s, 1 H, CH), 2.7–3.4 (m, 4 H, CH_2), 1.9 (br s, 1 H, NH). Anal. ($C_{13}H_{13}NS$) C, H, N.

1-(2-Naphthyl)-1,2,3,4-tetrahydroisoquinoline (11). The intermediate amide (26.0 g, 97%) was prepared from 2-phenylethylamine (12.6 g, 0.100 mol) and 2-naphthoyl chloride (19 g, 0.100 mol) as described for compound **1**: mp 134–136 °C (lit.[25] mp 133–134 °C).

The amide (10 g, 0.036 mol) was cyclized with $POCl_3$ and P_2O_5 as described for compound **1**. The cyclized product (6 g) was dissolved in ethanol (50 mL) and treated with sodium borohydride (2 g, 0.053 mol) and the solution heated to reflux for 16 h. The solution was cooled and treated with water (50 mL), and the mixture was extracted with ether. The organic solution was dried ($MgSO_4$), the solvent removed, and the crude product recrystallized from ethanol to yield **11** as white crystals (2 g, 21%): mp 94–95 °C; NMR ($CDCl_3$) δ 6.7–7.9 (series of res, 11 H, Ar), 5.3 (s, 1 H, CH), 2.8–3.4 (m, 4 H, CH_2), 2.0 (br s, 1 H, NH). Anal. ($C_{19}H_{17}N$) C, H, N.

2-Allyl-1-(2-naphthyl)-1,2,3,4-tetrahydroisoquinoline (12). Compound **12** was prepared from compound **11** (0.5 g, 0.0019 mol) and allyl bromide (1 mL, 0.010 mol) as described for compound **4**. The crude product was distilled (120 °C, at 0.04 mmHg) to give **12** as a viscous yellow oil (0.5 g, 88%): NMR ($CDCl_3$) δ 6.7–8.0 (series of res, 11 H, Ar), 5.8–6.0 (m, 1 H, CH of alkene), 5.1–5.3 (m, 2 H, CH_2 of alkene), 4.8 (s, 1 H, CH of isoquinoline), 2.6–3.4 (m, 6 H, CH_2). Anal. ($C_{22}H_{21}N$) C, H, N.

1-Benzyl-1,2,3,4-tetrahydroisoquinoline (13). A solution of 2-phenylethylamine (12 g, 0.100 mol), phenylacetic acid (13.6 g, 0.100 mol), and diethyl cyanophosphonate (17.9 g, 0.110 mol) in dimethylformamide (100 mL) was cooled in an ice bath and treated dropwise with triethylamine (10.1 g, 0.100 mol). The reaction mixture was stirred for 4 h in an ice bath and then allowed to warm to room temperature. Water was added to the solution to precipitate the amide. The crude amide was recrystallized from ethyl acetate to give a white solid: mp 91–93 °C (lit.[26] mp 94 °C).

The amide (10 g, 0.042 mol) was cyclized and the cyclization product reduced as described for compound **11**. The crude product was distilled (120 °C at 0.004 mmHg) to give **13** as a colorless oil (3 g, 32%): lit.[27] bp 120 °C (0.005 mmHg); NMR ($CDCl_3$) δ 7.05–7.4 (series of res, 9 H, Ar), 4.2 (dd, 1 H, CH), 3.1–3.3

(21) Brook, P. R.; Karrer, P. *Helv. Chim. Acta* **1957**, *40*, 260.
(22) McCoubrey, A. *J. Chem. Soc.* **1950**, 1833.
(23) Paul, R.; Coppola, J. A.; Cohen, E. *J. Med. Chem.* **1972**, *15*, 720.
(24) Kametani, T.; Sugahara, H. *Yakugaku Zasshi* **1963**, *83*, 1031.
(25) Berndt, D. C.; Faburada, A. L. *J. Org. Chem.* **1982**, *47*, 4167.
(26) Sugasawa, S.; Tsuda, T. *J. Pharm. Soc. Jpn.* **1935**, *55*, 194.

(dq, 2 H, benzylic CH_2), 2.7–2.9 (m, 4 H, CH_2), 1.95 (br s, 1 H, NH).

1-Isopropyl-1,2,3,4-tetrahydroisoquinoline (14). A mixture of 2-bromoethylbenzene (18.5 g, 0.100 mol), isobutyronitrile (25 mL, 0.167 mol), and $SnCl_4$ (10 mL, 0.085 mol) was heated to reflux 20 h. The soltuion was cooled, treated with water (50 mL), and washed with methylene chloride. The aqueous solution was cooled in an ice bath, made alkaline by the addition of concentrated aqueous ammonia, and extracted with methylene chloride. The organic solution was dried ($MgSO_4$) and the solvent removed to obtain a colorless oil. The oil was dissolved in ethanol (25 mL), treated with acetic acid (1 mL), and hydrogenated over PtO_2 at 55 psi for 16 h. The catalyst was removed by filtration and the filtrate extracted between 10% aqueous sodium hydroxide and methylene chloride. The organic solution was dried ($MgSO_4$), the solvent removed, and the residue distilled (80 °C at 0.02 mmHg) to give **14** as a colorless oil: lit.[27] bp 50 °C (0.001 mmHg); NMR ($CDCl_3$) δ 7.0–7.2 (m, 4 H, Ar), 3.9 (s, 1 H, CH of isoquinoline), 2.6–3.35 (series of multiplets, 4 H, CH_2), 2.35–2.4 (m, 1 H, CH of isopropyl), 1.5 (br s, 1 H, NH), 1.1 (d, 3 H, CH_3), 0.7 (d, 3 H, CH_3).

1-Isobutyl-1,2,3,4-tetrahydroisoquinoline (15).[28] The intermediate amide (10.0 g, 97%) was prepared from 2-phenylethylamine (6.3 g, 0.050 mol) and isovaleryl chloride (6.0 g, 0.050 mol) as described for compound **1**: mp 69–72 °C (lit.[29] mp 57–59 °C).

The amide (5 g, 0.024 mol) was cyclized with $POCl_3$ and P_2O_5 and the resulting product reduced as described for compound **11**. The crude product was distilled (60 °C at 0.03 mmHg) to yield **15** as a colorless oil (2 g, 44%): NMR ($CDCl_3$) δ 7.0–7.2 (m, 4 H, Ar), 3.95 (dd, 1 H, CH of isoquinoline), 2.7–3.3 (series of multiplets, 4 H, CH_2 of isoquinoline), 2.85 (m, 1 H, CH of isobutyl), 1.5–1.75 (m, 3 H, CH_2 of isobutyl and NH), 0.95 (dd, 6 H, CH_3).

1-Cyclohexyl-1,2,3,4-tetrahydroisoquinoline (16). The intermediate amide (22.4 g, 97%) was prepared from 2-phenylethylamine (12.6 g, 0.100 mol) and cyclohexanecarbonyl chloride (11.2 g, 0.100 mol) as described for compound **1**: mp 94–97 °C (lit.[29] mp 97–98 °C).

The amide (5 g, 0.0216 mol) was cyclized with polyphosphoric acid as described for compound **6** and the cyclized product reduced as for compound **11** to provide the crude product as a yellow oil. The crude material was distilled (100 °C at 0.1 mmHg) to provide **16** as a colorless oil (2.1, 46%): lit.[27] bp 120 °C (0.005 mmHg); NMR ($CDCl_3$) δ 7.07–7.2 (m, 4 H, Ar), 3.85 (d, 1 H, CH of isoquinoline), 2.6–3.3 (series of multiplets, 4 H, CH_2 of isoquinoline), 1.0–2.0 (series of multiplets, 11 H, CH and CH_2 of cyclohexyl).

2-Allyl-1-cyclohexyl-1,2,3,4-tetrahydroisoquinoline (17). Compound **17** was prepared from compound **16** (0.8 g, 0.0037 mol) and allyl bromide (1 mL, 0.010 mol) as described for compound **4**. The crude product was distilled (80 °C at 0.1 mmHg) to give **17** as a colorless oil (0.8 g, 84%): NMR ($CDCl_3$) δ 6.7–8.0 (m, 4 H, Ar), 5.8–6.0 (m, 1 H, CH of alkene), 5.1–5.3 (m, 2 H, CH_2 of alkene), 4.0 (d, 1 H, CH of isoquinoline), 2.6–3.4 (m, 6 H, CH_2). Anal. ($C_{18}H_{25}N$) C, H, N.

3-Phenyl-1,2,3,4-tetrahydroisoquinoline (18). 2-Cyanobenzyl phenyl ketone was converted to 3-phenylisocarbostyril by the method of Boyce and Levine.[11] The 3-phenylisocarbostyril was then converted to 3-phenyl-1,2,3,4-tetrahydroisoquinoline by the method of Powell et al.:[12] mp 43–45 °C (lit.[30] mp 45–48 °C); NMR ($CDCl_3$) δ 7.0–7.5 (m, 9 H, Ar), 4.0–4.2 (s, 3 H, C-3 and C-4 H's), 2.5 (m, 2 H, C-1 H's), 1.8 (s, 1 H, NH).

4-Phenyl-1,2,3,4-tetrahydroisoquinoline (19). Compound **19** was prepared by the method of Pridgen et al.:[13] mp (HCl salt) 223–225 °C (lit.[13] mp 224–225 °C; NMR ($CDCl_3$) δ 6.7–7.4 (m, 9 H, Ar), 4.2–4.4 (m, 3 H, C-3 and C-4 H's), 2.5 (s, 2 H, C-1 H's), 1.9 (s, 1 H, NH).

1,3-Dimethyl-1,2,3,4-tetrahydroisoquinoline (26). A solution of 1-phenyl-2-propanol (5 g, 0.0367 mol) and triethylamine (5.1 mL, 0.0367 mol) in anhydrous ethyl ether (40 mL) was treated dropwise with a solution of thionyl chloride (2 mL, 0.0274 mol). The resulting mixture was stirred at room temperature for 30 min and poured into water, and the layers were separated. The orgainc layer was washed with water and dried ($MgSO_4$), and the solvent was removed. The alkyl chloride (2.8 g, 66%) was purified by distillation (60 °C at 0.3 mmHg). The alkyl chloride (1.5 g, 0.010 mol) and $SnCl_4$ (10 mL, 0.085 mol) in acetonitrile (50 mL) were refluxed 20 h. The reaction was allowed to cool to room temperature and treated with methylene chloride (100 mL), followed by concentrated aqueous ammonia. The precipitate was filtered, the two layers of the filtrate were separated, and the organic layer was washed with water. The organic solution was dried ($MgSO_4$), the solvent removed, and the residue distilled (80 °C at 0.2 mmHg). The distillate was dissolved in ethanol and hydrogenated at 54 psi over PtO_2 for 20 h. The catalyst was removed by filtration, the solvent removed and the residue distilled (80 °C at 0.2 mmHg) to give **26** as a colorless oil (1.2 g, 61%): mp (HCl salt) 251–254 °C (lit.[31] mp 254 °C); NMR ($CDCl_3$) δ 7.0–7.2 (m, 4 H, Ar), 4.14 (m, 2 H, CH), 2.5–3.15 (m, 2 H, CH_2), 1.5 (d, 3 H, C-1 CH_3), 1.25 (d, 3 H, C-3 CH_3).

2-Allyl-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (27). Compound **17** was prepared from compound **26** (0.6 g, 0.003 mol) and allyl bromide (0.4 mL, 0.004 mol) as described for compound **4**. The crude product was distilled (60 °C at 0.1 mmHg) to give **27** as a colorless oil (40 mg, 6.6%): NMR ($CDCl_3$), δ 7.0–7.8 (m, 4 H, Ar), 5.8–6.0 (m, 1 H, CH of alkene), 5.1–5.3 (m, 2 H, CH_2 of alkene), 4.0–4.5 (m, 2 H, CH of isoquinoline), 2.6–3.1 (m, 2 H, CH_2), 1.0–1.5 (m, 6 H, C-1 and C-3 CH_3). Anal. ($C_{14}H_{19}N$) C, H, N.

1-Phenyl-1,2,3,4-tetrahydrothieno[2,3-*c*]pyridine (28). The intermediate amide (4 g, 0.017 mol) was prepared and cyclized by a previously reported method.[32] Reduction to the desired compound **28** was accomplished by the method described for compound **11**. The crude product was purified by sublimation (100 °C at 0.05 mmHg) to give **28** as a white solid (1.2 g, 32.2%): mp 201–202 °C; NMR ($CDCl_3$) δ 7.35–7.5 (m, 5 H, Ph), 6.9–7.25 (m, 2 H, Th), 5.25 (s, 1 H, CH), 2.75–3.5 (m, 4 H, CH_2), 2.0 (s, 1 H, NH). Anal. ($C_{13}H_{13}NS$) C, H, N.

2-Allyl-1-phenyl-1,2,3,4-tetrahydrothieno[2,3-*c*]pyridine (29). Compound **29** was prepared from compound **28** (1 g, 0.0046 mol) and allyl bromide (1 mL, 0.010 mol) as described for compound **4**. The crude product was distilled (80 °C at 0.05 mmHg) to give **29** as a colorless oil (0.5 g, 42.6%): NMR ($CDCl_3$) δ 7.3–7.5 (m, 5 H, Ph), 6.8–7.2 (m, 2 H, Th), 5.8–6.0 (m, 1 H, CH of alkene), 5.1–5.25 (m, 2 H, CH_2 of alkene), 4.65 (s, 1 H, CH of thienopyridine), 2.6–3.45 (m, 6 H, CH_2). Anal. ($C_{16}H_{17}NS$) C, H, N.

1-Methyl-1,2,3,4-tetrahydrothieno[2,3-*c*]pyridine (30).[33] Compound **30** was prepared from 3-(2-chloroethyl)thiophene (1 g, 0.0068 mol), acetonitrile (25 mL), and $SnCl_4$ (10 mL, 0.085 mol) as described for compound **14**, with the reduction following the method used for compound **11**. The crude product was distilled (80 °C at 0.05 mmHg) to provide **30** as a colorless oil: NMR ($CDCl_3$) δ 6.85–7.2 (m, 2 H, Ar), 4.15–4.3 (q, 1 H, CH), 3.0–3.45 (m, 4 H, CH_2), 1.8 (s, 1 H, NH), 1.55 (d, 3 H, CH_3).

1-Isopropyl-1,2,3,4-tetrahydrothieno[2,3-*c*]pyridine (31). Compound **31** was prepared from 3-(2-chloroethyl)thiophene (1 g, 0.0068 mol), isobutyronitrile (25 mL), and $SnCl_4$ (10 mL, 0.085 mol) as described for compound **14**, with the reduction following the method used for compound **11**. The crude product was distilled (80 °C at 0.05 mmHg) to provide **31** as a colorless oil: NMR ($CDCl_3$) δ 6.95–7.4 (m, 2 H, Ar), 4.2–4.5 (d, 1 H, CH of thienopyridine), 3.0–3.45 (m, 4 H, CH_2), 2.0 (m, 1 H, CH of isopropyl), 1.8 (br s, 1 H, NH), 1.3 (d, 6 H, CH_3). Anal. ($C_{10}H_{15}NS$) C, H, N.

1-Isopropyl-2-methyl-1,2,3,4-tetrahydrothieno[2,3-*c*]-pyridine (32). Compound **32** was prepared from compound **31** (0.5 g, 0.0028 mol) and dimethyl sulfate (0.26 mL, 0.0028 mol) as described for compound **5**. The crude product was distilled (80 °C at 0.05 mmHg) to provide **32** as a colorless oil (0.5 g, 91%):

(27) Seebach, D.; Lohmann, J. J.; Syfrig, M. A.; Yoshifur, M. *Tetrahedron* **1982**, *39*, 1963.
(28) Pirkle, W. H.; Welch, C. J.; Mahler, G. S. *J. Org. Chem.* **1984**, *49*, 2504.
(29) Cannon, J. G.; Webster, G. L. *J. Am. Pharm. Assoc. Sci. Ed.* **1958**, *47*, 353.
(30) Gabriel, S. *Chem. Ber.* **1885**, *18*, 3470.
(31) Robinson, R. A. *J. Org. Chem.* **1951**, *16*, 1911.
(32) Herz, W. *J. Am. Chem. Soc.* **1951**, *73*, 352.
(33) Parcor. Ger. Patent 2628045, 1977; *Chem. Abstr.* **1977**, *86*, 171429.

NMR ($CDCl_3$) δ 6.7–7.3 (m, 2 H, Ar), 3.35 (d, 1 H, CH of thienopyridine), 2.7–3.2 (m, 4 H, CH_2), 2.45 (s, 3 H, CH_3 on N), 2.0 (m, 1 H, CH of isopropyl), 1.3 (dd, 6 H, CH_3 of isopropyl). Anal. ($C_{11}H_{17}NS$) C, H, N.

1-Isopropyl-2-ethyl-1,2,3,4-tetrahydrothieno[2,3-*c*]pyridine (33). Compound **33** was prepared from compound **31** (0.5 g, 0.0028 mol) and diethyl sulfate (0.29 mL, 0.0031 mol) as described for compound **3**. The crude product was distilled (100 °C at 0.05 mmHg) to provide **33** as a colorless oil (0.4 g, 68%): NMR ($CDCl_3$) δ 6.7–7.3 (m, 2 H, Ar), 3.35 (d, 1 H, CH of thienopyridine), 2.2–3.2 (m, 6 H, CH_2), 1.3 (dd, 6 H, CH_3 of isopropyl), 1.0 (t, 3 H, CH_3 of ethyl). Anal. ($C_{12}H_{19}NS$) C, H, N.

2-Allyl-1-isopropyl-1,2,3,4-tetrahydrothieno[2,3-*c*]pyridine (34). Compound **34** was prepared from compound **31** (0.5 g, 0.0028 mol) and allyl bromide (1 mL, 0.010 mol) as described for compound **4**. The crude product was distilled (100 °C at 0.05 mmHg) to give **34** as a colorless oil (0.5 g, 80%): NMR ($CDCl_3$) δ 6.8–7.2 (m, 2 H, Ar), 5.8–6.0 (m, 1 H, CH of alkene), 5.1–5.2 (m, 2 H, CH_2 of alkene), 3.35–3.45 (d, 1 H, CH of thienopyridine), 2.3–3.3 (series of m, 4 H, CH_2), 1.85–2.0 (m, 1 H, CH of isopropyl), 1.05 (d, 6 H, CH_3). Anal. ($C_{16}H_{17}NS$) C, H, N.

1-Phenylisoindoline (35). 1-Phenylisoindoline was synthesized by a previously reported method:[14] mp 53–55 °C (lit.[14] mp 54.5–55 °C); NMR ($CDCl_3$) δ 6.95–7.4 (m, 9 H, Ar), 5.55 (s, 1 H, CH), 4.3–4.5 (m, 2 H, CH_2).

1-Phenyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (36). The intermediate amide was prepared from 3-phenyl-1-propylamine (13.5 g, 0.100 mol) and benzoyl chloride (14.1 g, 0.100 mol) as described for compound **1** and isolated as a colorless oil (24 g), which was not purified further. The amide (5 g, 0.018 mol) was cyzliced with polyphosphoric acid as described for compound **6** and the cyclized product reduced as for compound **11** to provide the crude product as a yellow oil. The crude material was distilled (100 °C at 0.3 mmHg) to provide **36** as a colorless oil (0.5 g, 11%): NMR ($CDCl_3$) δ 6.6–7.4 (series of res, 9 H, Ar), 5.2 (s, 1 H, CH), 2.9–3.5 (m, 4 H, CH_2), 1.55–1.95 (m, 3 H, NH and CH_2). Anal. ($C_{16}H_{17}N$) C, H, N.

Spiro[cyclohexane-1,1′(2*H*)-isoquinoline] (37). A solution of cyclohexanone (9.8 g, 0.100 mol), phenylethylamine (12.1 g, 0.100 mol), and *p*-toluenesulfonic acid (250 mg) in cyclohexane (100 mL) was heated to reflux and the heating continued until 1 equiv of H_2O collected in a Dean–Stark trap. The solvent was removed from the reaction mixture and the residue distilled (140 °C at 0.3 mmHg) to provide the intermediate imine (19 g, 95%) as a colorless oil. The imine (1 g) was dissolved in chloroform (3 mL) and placed in a closed quartz crucible. The solution was irradiated with a 450-W sunlamp for 15 h. The solvent was removed and the residue distilled (100 °C at 0.2 mmHg) to yield the product as a colorless oil (0.5 g, 50%) after the removal of lower boiling material (60 °C at 0.2 mmHg): lit.[34] mp (HCl salt) 268–269 °C.

Pharmacological Methods. Radioreceptor Assays. Crude membrane homogenates were prepared from rat whole brain as previously described.[3] Incubation tubes were prepared in triplicate containing varying concentrations of displacing ligand, 0.1 mL of tissue homogenate, 2 nM of [^{3}H]TCP or 6 nM of [^{3}H]-(+)-NANM, and buffer (5 mM of Tris·HCl, pH 7.4) to bring the final volume to 0.5 mL. After the tubes were incubated for 1 h at room temperature, the contents of the tubes were filtered through Schleicher & Shuell no. 32 filters, which were presoaked for 1 h in 0.05% polyethylenimine. The tubes were rinsed twice and the filters rinsed once with 5 mL of Tris buffer. IC_{50} values were calculated from inhibition curves with use of least-squares analysis and converted to apparent K_i values by the method of Cheng and Prusoff.[35]

Behavioral Assays. Male Sprague-Dawley rats were placed individually into rat cages and allowed to acclimate to the new environment for at least 1 h. Drugs were dissolved in saline or sodium acetate buffer and administered ip in a volume of 1 mL/kg. The animals were rated with a rating scale described by Sturgeon et al.[36] and the ratings determined at the time of peak effect were used to generate dose–response curves. Briefly, the stereotyped behavioral rating scale is (0) inactive or in-place nonrepetitive activity, (1) sniffing, grooming, or rearing more frequently than control, (2) nondirectional movements, occasional reciprocal forepaw treading, frequency of sniffing, rearing, and grooming greater than (1), (3) turning or backpeddling, (4) rapid and continuous turning, backpeddling, assuming a praying posture, and gagging, and (5) dyskinetic extension and flexion of limbs, head and neck, weaving greater than (4). The ataxia rating scale is (0) inactive or coordinated movements, (1) awkward or jerky movements or loss of balance while rearing, (2) moderate rate of falling, (3) frequent falling or partial impairment of antigravity reflexes, (4) cannot move beyond a small area, may support weigth on stomach or haunches, and (5) unable to move except for twitching movements. ED_{50} values were determined with use of at least 21 rats and a computerized Finney analysis.[37]

Registry No. **1**, 22990-19-8; **2**, 120086-31-9; **3**, 120086-32-0; **4**, 120086-33-1; **5**, 7149-64-6; **6**, 112891-30-2; **7**, 59224-74-7; **8**, 120086-34-2; **9**, 112891-31-3; **10**, 120086-35-3; **11**, 120086-36-4; **12**, 120086-37-5; **13**, 19716-56-4; **14**, 77796-20-4; **15**, 113721-80-5; **16**, 87443-64-9; **17**, 120086-38-6; **18**, 78318-00-0; **19**, 75626-12-9; **20**, 69381-55-1; **21**, 13605-95-3; **22**, 1612-65-3; **23**, 120086-39-7; **24**, 54365-72-9; **25**, 120086-40-0; **26**, 120086-41-1; **27**, 120086-42-2; **28**, 120086-43-3; **29**, 120086-44-4; **30**, 62539-83-7; **31**, 120086-45-5; **32**, 120086-30-8; **33**, 120086-46-6; **34**, 120086-47-7; **35**, 35392-51-9; **36**, 120086-48-8; **37**, 89248-68-0; $C_6H_5(CH_2)_2NH_2$, 64-04-0; $C_6H_5(CH_2)_2NHCOC_6H_5$, 3278-14-6; $CH_2(Br)CH_2OCH_2CH_3$, 592-55-2; $BrCH_2CH{=}CH_2$, 106-95-6; Cl-*p*-C_6H_4COCl, 122-01-0; $C_6H_5(CH_2)_2NHCOC_6H_4$-*p*-Cl, 39887-24-6; CH_3O-*p*-C_6H_4COCl, 100-07-2; F-*p*-C_6H_4COCl, 403-43-0; CH_3-*p*-C_6H_4, 874-60-2; $C_6H_5(CH_2)_2NHCOC_6H_4$-*p*-OCH_3, 6346-07-2; $C_6H_5(CH_2)_2NHCOC_6H_4$-*p*-F, 33799-96-1; $C_6H_5(CH_2)_2NHCOC_6H_4$-*p*-CH_3, 38925-77-8; $C_6H_5CH_2CO_2H$, 103-82-2; $CH_3CH_2P(O)(CN)OCH_2CH_3$, 2942-58-7; $C_6H_5(CH_2)_2NHCOCH_2C_6H_5$, 5460-60-6; $C_6H_5(CH_2)_2Br$, 103-63-9; $(CH_3)_2CHCH_2C{\equiv}N$, 78-82-0; $C_6H_5(CH_2)_2NHCOCH_2CH(CH_3)_2$, 53181-99-0; $C_6H_5(CH_2)_2NHCO$-*c*-C_6H_{11}, 53182-00-6; *c*-$C_6H_{11}COCl$, 2719-27-9; NCC_6H_4-*o*-$CH_2COC_6H_5$, 10517-64-3; $C_6H_5CH_2CH(OH)CH_3$, 698-87-3; $NH_2(CH_2)_3C_6H_5$, 108-94-1; $C_6H_5(CH_2)_3NHCOC_6H_5$, 35960-75-9; $C_6H_5(CH_2)_2N{=}(C_6H_{10}$-*c*), 6115-05-5; 1-phenyl-3,4-dihydroisoquinoline, 52250-50-7; 2-thiophenecarbonyl chloride, 5271-67-0; 2-naphthoyl chloride, 2243-83-6; *N*-(2-thiophenecarbonyl)phenylethylamine, 75690-78-7; *N*-(2-naphthoyl)phenylethylamine, 82740-61-2; 1-isopropyl-3,4-dihydroisoquinoline, 71611-83-1; isovaleryl chloride, 108-12-3; 1-cyclohexyl-3,4-dihydroisoquinoline, 65071-52-5; 3-phenylisocarbostyril, 7115-13-1; 1-phenyl-2-chloropropane, 10304-81-1; 3-(2-chloroethyl)thiophene, 7136-58-5; 1-phenyl-4,5-dihydro-3*H*-2-benzazepine, 56900-75-5; cyclohexanol, 108-94-1; phencyclidine, 77-10-1.

(34) Parke, Davis & Co. Brit. Patent 871,327, 1965; *Chem. Abstr.* **1961**, *56*, 462.

(35) Cheng, Y. C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.

(36) Sturgeon, R. D.; Fessler, R. G.; Meltzer, H. Y. *Eur. J. Pharmacol.* **1979**, *59*, 169.

(37) Finney, D. J. *Statistical Methods in Biological Assay*, 2nd ed.; Hafner Publishing Co.: New York, 1964.