Articles

Synthesis of 8-Aryltetrahydroisoquinolines as Dopamine Antagonists and Evaluation for Potential Neuroleptic Activity

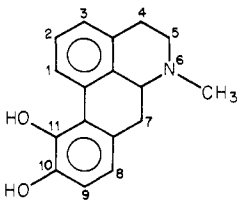
Charles R. Ellefson,* Kathleen A. Prodan, Linda R. Brougham, and Arni Miller

G. D. Searle and Company, Chicago, Illinois 60680. *Received February 11, 1980*

The synthesis of 8-(methoxyphenyl)-1,2,3,4-tetrahydroisoquinolines using aryloxazolines as key intermediates is described. Nucleophilic displacement on an *o*-methoxyphenyloxazoline by an aryl Grignard reagent, followed by electrophilic substitution at the other ortho position, provided a specific route to the properly substituted benzene intermediates necessary for conversion to the tetrahydroisoquinolines. These compounds and 8-phenyl- and 2-methyl-8-phenyl-1,2,3,4-tetrahydroisoquinolines, which are ring-opened analogues of apomorphine, were found to be dopamine antagonists by in vitro dopamine receptor studies. In vivo evaluation, however, did not substantiate potential usefulness as antipsychotic agents when they were compared with standard neuroleptic agents.

The dopamine hypothesis of schizophrenia[1] has developed from a concept that neuroleptics exert their action by blocking brain dopamine receptors. The theory has benefited from considerable indirect evidence,[2] direct in vitro receptor binding evidence,[3] and direct evidence for abnormalities in brain dopamine receptors of schizophrenics.[4] The development of the in vitro dopamine receptor assays, which can differentiate between dopamine agonists and antagonists, has provided a relatively convenient assay for evaluation of new compounds synthesized as potential antipsychotic agents.

One approach toward looking for new neuroleptics has been to synthesize compounds modeled after known clinically useful drugs. However, since all known clinically effective antipsychotic agents are dopamine antagonists, our approach was to synthesize compounds modeled after the known dopamine agonist apomorphine, 1, anticipating



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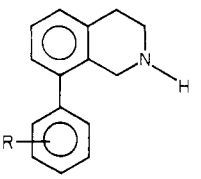

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that the modifications would result in compounds which lack intrinsic activity but would still compete with dopamine for its receptor and thereby block its actions. Our objective was to prepare some 8-aryltetrahydroisoquinolines, 2, which are analogues of apomorphine in which the C-7 methylene bridge is absent. These compounds maintain the integrity of the phenethylamine portion of 1 and keep the aromatic ring and the nitrogen of the dopamine portion in the same relative positions; however, the aryl group can rotate and is not held in an orientation that is generally planar with the rest of the molecule as in 1. Others[5a,b] have shown that disruption of the phenethylamine portion of apomorphine resulted in decreased emetic activity (agonist activity); however, these compounds were not evaluated for antagonist activity. It has also been reported[5c] that 1,2,3,4-tetrahydroisoquinoline and its *N*-methyl and *N*-propyl analogues (i.e., rigid phenethylamine analogues) were found to be dopamine antagonists with behavioral effects similar to some neuroleptics.

The first goal of this approach was to develop a model synthesis of 8-phenyl-1,2,3,4-tetrahydroisoquinoline. As reported previously,[6] that was accomplished using aryloxazolines as key intermediates. In that synthesis, electrophilic substitution of 2-biphenyloxazoline at the position ortho to the oxazoline allowed further elaboration to the tetrahydroisoquinolines. Another application of the oxazoline chemistry that has been developed by Meyers and Mihelich[7] was used for the synthesis of the corresponding methoxybiphenyloxazolines which were needed for extension of the synthesis to the oxygenated analogues. The synthesis begins with a nucleophilic displacement of an *o*-methoxyphenyloxazoline by an aryl Grignard reagent. The overall result is that a nucleophilic displacement on an *o*-methoxyphenyloxazoline, followed by electrophilic substitution at the other ortho position, provides a convenient, specific route to the necessary 1,2,3-trisubstituted benzene intermediates that are useful for preparing the 8-(methoxyphenyl)tetrahydroisoquinolines.

Chemistry. The general synthesis of the 8-(methoxyphenyl)tetrahydroisoquinolines is outlined in Scheme I. The conversion of *o*-anisic acid to the oxazoline, 3,[8] pro-

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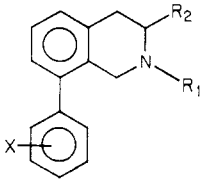
Table I. Biological Evaluation of 10-12



compd	R_1	R_2	X	salt	IC_{50}[a] [^{3}H]DA	IC_{50}[a] [^{3}H]HP	ratio[b]	CAR[c]	rel CNS act.[d]	LD_{50}
10a	$CH_2C_6H_5$	H	H	HCl	$>10^{-4}$	6.2×10^{-8}		I	–	158
10b	$CH_2C_6H_5$	CH_3	H	HCl	$>10^{-4}$	4×10^{-7}		A (40), I (10)	+	227
10c	$CH_2C_6H_5$	H	o-CH_3O	HCl	3.4×10^{-5}	2.7×10^{-7}	126	I	–	>160
10d	$CH_2C_6H_5$	H	m-CH_3O	HCl	1.9×10^{-5}	6.4×10^{-8}	297	I	–	>320
11a	H	H	H	HCl	1.2×10^{-4}	1.5×10^{-6}	80	A (20), I (10)	–	82
11b	H	CH_3	H	HCl	$>10^{-4}$	7.5×10^{-7}		I (5, 20)	–	146
11c	H	H	o-CH_3O	HCl	$>10^{-4}$	1.3×10^{-5}		A (10, 40)	++	81
11d	H	H	m-CH_3O	HCl	3.6×10^{-5}	6.5×10^{-7}	55	A (40), I (10)[e]	++	<160
12a	CH_3	H	H	$(CHCO_2H)_2$	6.6×10^{-5}	2.7×10^{-8}	2400	A (40), I (10)	+++	<320
12b	CH_3	CH_3	H	HBr	3.5×10^{-4}	1.8×10^{-6}	194	I	++	<320
12c	CH_3	H	o-CH_3O	HCl	8.8×10^{-5}	6.6×10^{-7}	133	A (40), I (10)[e]	–	81
12d	CH_3	H	m-CH_3O	HCl	2.5×10^{-5}	8.5×10^{-8}	294	A (40), I (10)[e]	+	156
chlorpromazine					2.5×10^{-6}	3.4×10^{-8}	74		+++	
clozapine					8×10^{-6}	1.8×10^{-7}	44		+++	
haloperidol					5×10^{-7}	1.8×10^{-9}	278		+++	
apomorphine					5×10^{-9}	1×10^{-7}	0.05			
dopamine					6.4×10^{-8}	1.7×10^{-6}	0.038			

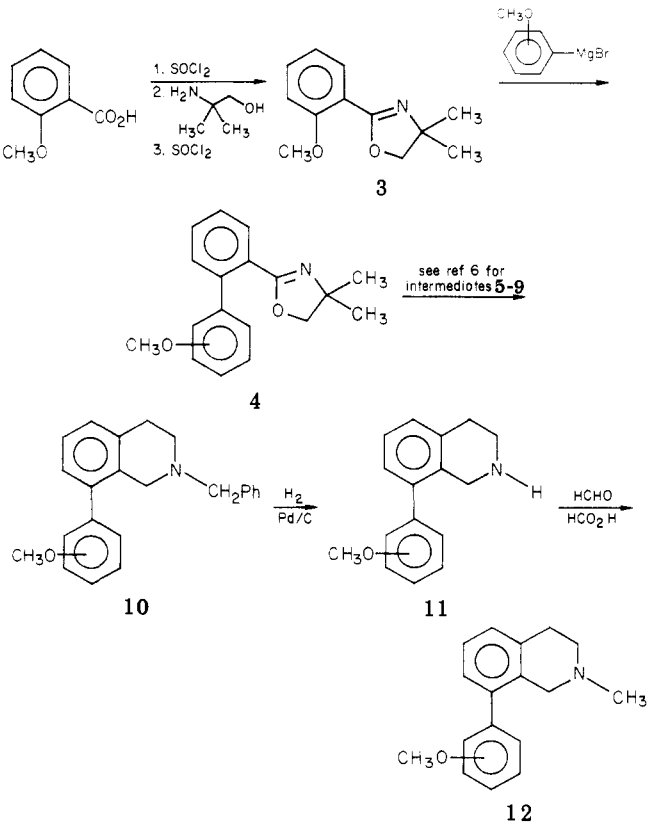
[a] Molar drug concentrations which inhibit specific binding of 5 nM [^{3}H]dopamine or 1.6 nM [^{3}H]haloperidol by 50%. [b] IC_{50} [^{3}H]DA/IC_{50} [^{3}H]HP. [c] Active, A, or inactive, I, at the doses (mg/kg) indicated. [d] See Experimental Section for explanation and description of assays. Activities shown or inactivity, I, at the designated doses (mg/kg) were observed as follows: 10a, He (32), I (2); 10b, He, Ro (45), I (2); 10c, Ma (32), I (2); 10d, I (64, 4); 11a, Ma (16), I (1); 11b, Ma (29), I (1); 11c, Ma, St, Pa, Ro, Am (16), I (1); 11d, Ma, Ro, Am (32), Pa (2); 12a, Ma, St, He, Ho, Ta, Ro (64), I (3); 12b, Ma, He, Ho, Ta, Ro (64), I (3); 12c, I (16, 1); 12d, Pa, He (32), I (2). Chlorpromazine St, Ho, Ta, Ro (36), He, Se (36, 2), Am (2). Halperidol He, Ho, Ta, Se (20), Ro, Am (20, 2), Me (2). Clozapine, He, Ho, Se, Ro, Am (10), Ta (10, 1). [e] Depression was observed at the 40 mg/kg dose.

vided a labile *o*-methoxy group[7] which was utilized to prepare the appropriately substituted biphenyloxazolines, **4**. Reaction of **3** with methoxyphenyl Grignard reagents resulted in displacement of the methoxy group producing **4**. Procedures for the conversion of **4** to *N*-benzyltetrahydroisoquinolines, **10**, 8-(methoxyphenyl)-1,2,3,4-tetrahydroisoquinolines, **11**, and the *N*-methyl compounds, **12**, were essentially the same as previously reported in ref 6.

Biological Results. Biological evaluation of the 8-aryltetrahydroisoquinolines is summarized in Table I. The compounds were evaluated in vitro in a dopamine receptor binding assay for their ability to displace two labeled ligands, [^{3}H]dopamine ([^{3}H]DA) and [^{3}H]haloperidol ([^{3}H]HP). According to other investigators,[3b] the use of these two ligands differentiates between agonist and antagonist states of the dopaminergic receptor; i.e., a high (greater than 1) [^{3}H]DA/[^{3}H]HP IC_{50} ratio indicates an antagonist. All of the 8-aryltetrahydroisoquinolines were found to be antagonists on the basis of these in vitro results. The most potent compound, **12a**, was comparable to chlorpromazine in this regard. The *N*-alkyl compounds (**10** and **12**) appeared to be more potent than the unsubstituted compounds (**11**) at displacing tritiated haloperidol. The effect of the methoxy substituents did not appear to be significant; however, in each case the *m*-methoxy compounds (**10d**, **11d**, and **12d**) were more potent than the *o*-methoxy compounds (**10c**, **11c**, and **12c**).

These results indicated that the title compounds were dopamine antagonists and suggested potential for neuroleptic activity. Results of in vivo evaluation, however, failed to substantiate antipsychotic activity. The compounds were tested for their effect on conditioned avoidance (CAR) behavior in naive male rats. A significant decrease in avoidance responses would indicate potential

Scheme I



(8) The oxazoline, **3**, was reported previously in ref 7; however, no properties were given.

as a central nervous system depressant or tranquilizer (antipsychotic). Six of these compounds were active at the high dose but only one (**11c**) was active at the low dose tested. CAR activity did not correlate with the in vitro receptor results (note, **11c** was the weakest displacer of tritiated haloperiodol). For several of the compounds, activity at the high dose was accompanied by an observation of depression.

The compounds were also tested in a battery of 16 assays for potential central nervous system effects. Since it would be too cumbersome to describe and detail all of these results, Table I contains a column for relative CNS activity for these compounds. All of the standard compounds had common activity in six of the assays (He, Ho, Ta, Se, Ro, Am). Of the 8-aryltetrahydroisoquinolines, **12a** and **12b** showed activity in four of these (He, Ho, Ta, Ro), but they did not have activity against amphetamine lethality, which was considered necessary for antipsychotic potential. Only two compounds (**11c** and **11d**) protected the animals from amphetamine lethality, but they did not have the other activities in common with the standards.

Of all of these compounds, **12a** has the most CNS effects and was the most potent in the receptor assays. It's lack of activity against amphetamine lethality and it's activity at only the high dose in CAR indicate low potential as an antipsychotic agent, however.

Our original hypothesis that 8-aryltetrahydroisoquinolines would be good candidates for dopamine antagonists and as potential antipsychotic agents seemed to be encouraging on the basis of the in vitro receptor assays. However, in vivo evaluation of these compounds has not substantiated their potential as neuroleptics.

Experimental Section

Synthetic and analytical data for the 8-phenyl- and 2-methyl-8-phenyltetrahydroisoquinolines were reported previously.[6] Procedures for the preparation of **3**, **4**, **10–12**, and other intermediates (6–9 of ref 6) were essentially the same as those reported;[6] therefore, only analytical data are reported herein. NMR (Varian A-60D) and IR (Beckman IR 12) were consistent with all structures. Melting points were determined in open capillary tubes in a Mel-Temp apparatus.

2-(2-Methoxyphenyl)-4,4-dimethyloxazoline (3)[8] was prepared from *o*-anisic acid via *N*-(2-hydroxy-1,1-dimethyl)-2-methoxybenzamide [83%; mp 125–129 °C; IR ($CHCl_3$) 1645 cm^{-1}; NMR ($CDCl_3$) δ 1.41 (s, 6 H), 3.67 (s, 2 H), 3.97 (s, 3 H), 5.1 (br s, 1 H), 6.85–7.63 (m, 4 H), 8.05–8.30 (dd, 1 H). Anal. ($C_{12}H_{17}NO_3$) C, H, N] yielding 83% of white crystals: mp 67–73 °C; IR ($CHCl_3$) 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (s, 6 H), 3.89 (s, 3 H), 4.08 (s, 2 H), 6.78–7.85 (m, 4 H). Anal. ($C_{12}H_{15}NO_2$) C, H, N.

4,4-Dimethyl-2-[2′-methoxy(1,1′-biphenyl)-2-yl]oxazoline (4c). A solution of 79.2 g (0.423 mol) of *o*-bromoanisole in 200 mL of dry tetrahydrofuran was added dropwise with rapid stirring to 11.6 g (0.475 mol) of magnesium turnings in 220 mL of dry tetrahydrofuran. The mixture was stirred at reflux for 1.75 h, then a solution of 30.0 g (0.146 mol) of **3** in 200 mL of dry tetrahydrofuran was added, and stirring at ambient temperature was continued overnight. The reaction was quenched with saturated aqueous ammonium chloride; the organic layer was dried over anhydrous sodium sulfate. Removal of the solvent gave 60 g of yellow liquid that was chromatographed by low pressure chromatography (LPC) on a Woelm silica gel column using a 5–10% EtOAc/toluene gradient. This yielded 30.1 g (73%) of yellow oil that solidified on standing: IR ($CHCl_3$) 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (s, 6 H), 3.70 (s, 3 H), 3.74 (s, 2 H), 6.73–7.50 (m, 7 H), 7.73–7.97 (m, 1 H). Anal. ($C_{18}H_{19}NO_2$) H, N; C: calcd, 76.84; found, 77.25.

4,4-Dimethyl-2-[3′-methoxy(1,1′-biphenyl)-2-yl]oxazoline (4d). Following the procedure for **4c**, 128 g (0.683 mol) of *m*-bromoanisole, 186 g (0.765 mol) of magnesium turnings, and 50.0 g (0.244 mol) of **3**, after LPC (Woelm silica gel, 10–15% EtOAc/toluene gradient), produced 55 g of yellow oil that contained a small amount of toluene and was used without further purification: IR ($CHCl_3$) 1663 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (s, 6 H), 3.80 (s, 5 H), 6.72–7.83 (m, 8 H).

4,4-Dimethyl-2-[3-(2-hydroxyethyl)-2′-methoxy(1,1′-biphenyl)-2-yl]oxazoline (5c). The product was purified by LPC (Woelm silica gel, 40–65% EtOAc/toluene gradient), yielding 26.2 g (63.4%) of clear amber oil: NMR ($CDCl_3$) δ 1.28 (s, 6 H), 3.03 (t, 2 H), 3.70 (s, 2 H), 3.76 (s, 3 H), 3.95 (t, 2 H), 4.36 (br, 1 H), 6.76–7.60 (m, 7 H).

4,4-Dimethyl-2-[3-(2-hydroxyethyl)-3′-methoxy(1,1′-biphenyl)-2-yl]oxazoline (5d). Following LPC (Woelm silica gel, 45% EtOAc/toluene), 63% of pale yellow crystals, mp 76–79 °C, were obtained. Recrystallization from EtOAc/hexane gave white crystals: mp 82–84 °C; IR ($CHCl_3$) 1658 and 3325 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (s, 6 H), 2.96 (t, 2 H), 3.74 (s, 2 H), 3.78 (s, 3 H), 3.89 (t, 2 H), 4.53 (br, 1 H), 6.73–7.58 (m, 7 H). Anal. ($C_{20}H_{23}NO_3$) C, H, N.

3,4-Dihydro-8-(2-methoxyphenyl)-1*H*-2-benzopyran-1-one (6c). Beige crystals, mp 152–155 °C, were obtained (84%) and recrystallized from EtOAc/hexane, producing white crystals: mp 155–156 °C; IR ($CHCl_3$) 1732 cm^{-1}; NMR ($CDCl_3$) δ 2.98 (m, 2 H), 3.70 (s, 3 H), 4.47 (m, 2 H), 6.75–7.78 (m, 7 H). Anal. ($C_{16}H_{14}O_3$) C, H.

3,4-Dihydro-8-(3-methoxyphenyl)-1*H*-2-benzopyran-1-one (6d). A crude off-white solid (90%) was recrystallized from EtOAc/hexane, giving slightly beige crystals: mp 120–121.5 °C; IR ($CHCl_3$) 1740 cm^{-1}; NMR ($CDCl_3$) δ 3.06 (t, 2 H), 3.84 (s, 3 H), 4.52 (t, 2 H), 6.76–7.71 (m, 7 H). Anal. ($C_{16}H_{14}O_3$) C, H.

***N*-Benzyl-3-(2-hydroxyethyl)-2-(2′-methoxybiphenyl)-carboxamide (7c).** Recrystallization from EtOAc/hexane yielded 70% of flocculant white crystals: mp 94–95 °C; IR ($CHCl_3$) 1645, 3380 cm^{-1}; NMR ($CDCl_3$) δ 2.91 (t, 2 H), 3.46 (s, 3 H), 3.86 (m, 2 H), ~3.9 (br, 1 H), 4.21 (d, 2 H), 6.29 (t, 1 H), 6.64–7.75 (m, 12 H). Anal. ($C_{23}H_{23}NO_3$) C, H, N.

***N*-Benzyl-3-(2-hydroxyethyl)-2-(3′-methoxybiphenyl)-carboxamide (7d).** Recrystallization from EtOAc/hexane yielded 79% of off-white crystals: mp 111–111.5 °C; IR ($CHCl_3$) 1645, 3360, 3435 cm^{-1}; NMR ($CDCl_3$) δ 2.91 (t, 2 H), 3.78 (s, 3 H), 3.87 (t, 2 H), ~3.8 (br, 1 H), 4.30 (d, 2 H), 5.89 (br, 1 H), 6.69–7.52 (m, 7 H). Anal. ($C_{23}H_{23}NO_3$) C, H, N.

3,4-Dihydro-8-(2-methoxyphenyl)-2-(phenylmethyl)-1-(2*H*)-isoquinolinone (9c). The mesylate, **8c**, was prepared as a thick paste [NMR ($CDCl_3$) δ 2.84 (s, 3 H), 3.18 (t, 2 H), 3.58 (s, 3 H), 4.26 (d, 2 H), 4.54 (t, 2 H), 6.35 (t, 1 H), 6.63–7.86 (m, 12 H)] and converted in 72% yield to nearly colorless crystals: mp 152–153.5 °C; IR ($CHCl_3$) 1652 cm^{-1}; NMR ($CDCl_3$) δ 2.89 (m, 2 H), 3.44 (t, 2 H), 3.70 (s, 3 H), 4.70 (s, 2 H), 6.81–7.60 (m, 12 H). Anal. ($C_{23}H_{21}NO_2$) C, H, N.

3,4-Dihydro-8-(3-methoxyphenyl)-2-(phenylmethyl)-1-(2*H*)-isoquinolinone (9d). The crude mesylate, a cream-colored solid [mp 83–86 °C; NMR ($CDCl_3$) δ 2.85 (s, 3 H), 3.12 (t, 2 H), 3.75 (s, 3 H), 4.28 (d, 2 H), 4.49 (t, 2 H), 5.75 (t, 1 H), 6.67–7.58 (m, 12 H)] yielded 59% of yellow-tan crystals: mp 132.5–135 °C; IR ($CHCl_3$) 1655 cm^{-1}; NMR ($CDCl_3$) δ 2.87 (t, 2 H), 3.51 (t, 2 H), 3.80 (s, 3 H), 4.69 (s, 2 H), 6.74–7.56 (m, 12 H). Anal. ($C_{23}H_{21}NO_2$) C, H, N.

1,2,3,4-Tetrahydro-8-(2-methoxyphenyl)-2-(phenylmethyl)isoquinoline (10c) Hydrochloride. The free amine, a clear oil [NMR ($CDCl_3$) δ 2.52–3.10 (m, 4 H), 3.26–3.73 (m, 4 H), 3.61 (s, 3 H), 6.16–7.56 (m, 12 H)], was dissolved in ether and treated with isopropanolic HCl, yielding 9.99 g (96%) of white solid. Recrystallization from EtOH/Et_2O gave white crystals, mp 213–215 °C. Anal. ($C_{23}H_{24}ClNO$) C, H, N.

1,2,3,4-Tetrahydro-8-(3-methoxyphenyl)-2-(phenylmethyl)isoquinoline (10d) Hydrochloride. Following the procedure used for **10c**, and recrystallization from EtOH/Et_2O, yielded 86% of white crystals, mp 199–202 °C. Anal. ($C_{23}H_{24}ClNO$) C, H, N.

1,2,3,4-Tetrahydro-8-(2-methoxyphenyl)isoquinoline (11c) Hydrochloride. White crystals (91%) were recrystallized from EtOH/Et_2O: mp 209.5–210.5 °C; NMR (CD_3OD) 3.44 (d, J = 5 Hz, 2 H), 3.77 (s, 3 H), 4.03 (d, J = 5 Hz, 2 H), 6.97–7.62 (m, 7 H), other CH_2 under CD_3 interference. Anal. ($C_{16}H_{18}ClNO$) C, H, N.

1,2,3,4-Tetrahydro-8-(3-methoxyphenyl)isoquinoline (11d) Hydrochloride. White crystals (96%) were recrystallized from EtOH: mp 192.5–193.5 °C; NMR ($CDCl_3$) of free base (**11d**) δ

1.68 (s, 1 H), 2.66–3.31 (m, 4 H), 3.78 (s, 3 H), 3.84 (s, 2 H), 6.55–7.46 (m, 7 H). Anal. ($C_{16}H_{18}ClNO$) C, H, N.

1,2,3,4-Tetrahydro-8-(2-methoxyphenyl)-2-methylisoquinoline (12c) Hydrochloride. A clear colorless free amine (12c) [NMR ($CDCl_3$) δ 2.30 (s, 3 H), 2.50–3.14 (m, 4 H), 3.26 (s, 2 H), 3.71 (s, 3 H), 6.79–7.53 (m, 7 H)] was dissolved in ether and treated with isopropanolic hydrochloric acid, yielding 3.1 g of white powder that was recrystallized from EtOH/Et_2O yielding 2.9 g (89%) of white crystals, mp 212–213 °C. Anal. ($C_{17}H_{20}ClNO$) C, H, N.

1,2,3,4-Tetrahydro-8-(3-methoxyphenyl)-2-methylisoquinoline (12d) Hydrochloride. The free amine 12d [NMR ($CDCl_3$) δ 2.31 (s, 3 H), 2.46–3.16 (m, 4 H), 3.39 (s, 2 H), 3.76 (s, 3 H), 6.66–7.46 (m, 7 H)] was isolated as the hydrochloride and recrystallized from EtOH/Et_2O, yielding 2.23 g (91%) of white crystals, mp 196.5–197.5 °C. Anal. ($C_{17}H_{20}ClNO$) C, H, N.

Receptor Binding Studies. Calf caudate nuclei were dissected from freshly obtained brains and stored frozen at −76 °C. As needed, caudate tissue was homogenized and prepared following procedures outlined by Creese and co-workers.[3b]

Receptor-binding studies were performed as reported in the literature[2f,3b,c,e] with slight modifications. A typical sample contained 2 mL of caudate membrane homogenate (10 mg of original tissue/mL) in a final ligand concentration of either 2.5 nM [^{3}H]dopamine or 1.6 nM [^{3}H]haloperidol. Test compounds were added as 20-μL aliquots from stock solutions prepared in absolute ethanol or 0.1% ascorbic acid. Samples were incubated in triplicate at 37 °C for 10 min.

Immediately following all incubations, proteins were recovered on Whatman GF/B glass-fiber filters under reduced pressure. Trapped membranes were solubilized off the filters using 1 mL of NCS tissue solubilizer (Amersham/Searle Corp.) at 50 °C for 1 h. The pH was adjusted by adding 0.1 mL of glacial acetic acid, 10 mL of PCS (Amersham/Searle Corp.) was added, and the samples were analyzed for membrane-bound radioactivity using a Mark II liquid scintillation counter (Searle Analytical, Inc.).

Nonspecific binding was measured in the presence of 10^{-5} M (+)-butaclamol for the [^{3}H]dopamine studies and 10^{-4} M nonradiolabeled dopamine for the [^{3}H]haloperidol studies. IC_{50} values were determined from log probit using four to six concentrations of each compound.

Conditioned Avoidance Response in Trained Rat (CAR). The apparatus consisted of a shuttle box divided into two compartments and enclosed in a sound-attenuating chamber. The floor of the shuttle box was an electrifiable grid. Following intraperitoneal injection of the vehicle or the drug, the rat was placed into the shuttle cage and was allowed to acclimate for approximately 1 min. A 5-s conditioned stimulus, consisting of a tone and light, preceded a 0.2-mA footshock delivered to the grid floor of the cage. The shock was automatically terminated after 30 s if the rat failed to respond. A shuttle response during the conditioned stimulus prevents the onset of the shock and was scored as an avoidance response. If no escape response was made, an escape failure was scored. Each conditioned stimulus presentation was separated by a 15-s interval, and a response during this interval was scored as an intertrial interval response and results in the onset of the shock and the conditioned stimulus until the rat returned to the other side. Each rat was presented with 100 trials (i.e., 100 conditioned stimulus presentations) which took approximately 30 min. Each rat was trained to an average criterion of ≥85 avoidance responses per 100 trial session when administered vehicle control solution. Eight CD F strain male albino rats per dose were tested, and each rat's performance under the drug treatment was compared to its previous performance under vehicle control treatment by means of a Student's t test ($p < 0.05$, two tailed). Drugs were evaluated 30 min postinjection.

Compounds which did not alter avoidance response or intertrial interval responses were considered inactive. Compounds which significantly decreased avoidance responses were considered as central nervous system depressants or transquilizers (neuroleptics). Test compounds were assayed at 5 and 20 mg/kg. Drugs currently in clinical use as tranquilizers showed activity in this test.

LD_{50}. Lethal doses (to a maximum of 320 mg/kg) were determined 0.5 h post intraperitoneal administration of test compounds to groups of ten individually housed male Charles River mice per dose level. The LD_{50} was calculated using the method of Litchfield and Wilcoxon.[9]

Relative CNS Activity. The compounds were evaluated in a battery of the 16 standard assays listed below. For each assay, groups of male Charles River mice were administered intraperitoneal doses of test compound approximating 20 and 1% of the LD_{50} (maximum dose of 64 mg/kg). Details for each assay are not included herein (references to related procedures are noted), and the results should be used for a qualitative and not a quantititative estimation of a compound's effects. Table I (footnote *d*) summarizes the activities for each test compound and standard substance. The assays, number of animals, and abbreviations used in Table I for activities observed were: antagonism of maximal electroshock seizures,[10] 6, Ma; antagonism of minimal electroshock seizures,[10] 6; antagonism of metrazole-induced seizures,[11] 6, Me; antagonism of strychnine-induced seizures, 6, St; conditioned response–passive avoidance,[12] 6, Pa; inhibition of oxotremorine-induced seizures,[13] 6; antagonism of RO4-1284-induced ptosis,[14] 6; inhibition of barbiturate sleeping time,[15] 6; potentiation of barbiturate sleeping time,[15] 6, He; analgesia (hot-plate test),[16] 6, Ho; analgesia (tail-clip test),[17] 6, Ta; rotating-rod test for motor coordination,[18] 6, Ro; potentiation of amphetamine-induced lethality,[19] 10; inhibition of amphetamine-induced lethality,[19] 10, Am; blockade of physostigmine-induced lethality, 10, Ph; antagonism of morphine-induced analgesia,[20] 6.

No activity was observed for the tested compounds in the above assays without an abbreviation. Relative CNS activity was rated as: +++, for activity in ≥6 assays; ++, for activity in 4–5 assays; +, for activity in 2–3 assays; −, for activity in ≤1 assay.

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