Structure-Anti-Parkinson Activity Relationships in the Aminoadamantanes. Influence of Bridgehead Substitution[1]

James G. Henkel,* Jeffrey T. Hane,

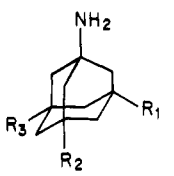
Section of Medicinal Chemistry and Pharmacognosy

and Gerald Gianutsos*

Section of Pharmacology and Toxicology, School of Pharmacy, U-92, University of Connecticut, Storrs, Connecticut 06268. *Received June 5, 1981*

A limited series of bridgehead alkyl-, dialkyl-, and trialkyl-substituted amantadines was synthesized and tested for potential anti-Parkinson activity as dopamine (DA) agonists. The compounds were evaluated using a battery of three murine bioassays, including stimulation of locomotor activity, induction of circling in animals with unilateral striatal lesions, and reversal of reserpine/α-methyltyrosine induced akinesia. Apparent mechanistic differences were seen between the methyl-substituted series and the ethyl-substituted series. While activities in both series increase with increasing liphophilicity, the methyl series (**1b–d**), as well as amantadine itself (**1a**), exhibits only indirect DA agonist activity, as evidenced by ipsilateral rotation in the circling model and no significant difference from control in reversal of akinesia. The ethyl series (**1e,f**) exhibits weak but reproducible direct DA agonist activity, as shown by contralateral rotation in the circling assay for **1e** and reversal of akinesia by **1e** and **1f**. The 3-*n*-propyl derivative (**1g**) was devoid of any DA agonist activity.

The antiviral substance amantadine (**1a**) has found use in the treatment of Parkinson's disease since Schwab et al.[2] fortuitously noted its clinical activity. Substantial investigative effort has been made in the past decade to elucidate its mechanism of action.[3-5] Although the consensus now seems to be that **1a** causes an indirect release



1a, $R_1 = R_2 = R_3 = H$
b, $R_1 = R_2 = CH_3$; $R_3 = H$
c, $R_1 = CH_3$; $R_2 = R_3 = H$
d, $R_1 = R_2 = R_3 = CH_3$
e, $R = C_2H_5$; $R_2 = R_3 = H$
f, $R_1 = R_2 = C_2H_5$; $R_3 = H$
g, $R_1 = n\text{-Pr}$; $R_2 = R_3 = H$

of neurotransmitter from intact dopaminergic (DA) neurons,[3] there is less well documented evidence for a minor postsynaptic DA component,[3] as well as an indirect serotonergic component.[5] Despite these efforts, the precise molecular mechanism of action of **1a** is not yet known. More recently, memantine (**1b**), a second more potent member of the class, has been found to be clinically useful. Interestingly, it possesses a pharmacological profile similar to, yet distinct from, that of **1a**, one which is reported to include a larger postsynaptic DA agonist component.[6-8] A major difference between the effects of **1a** and **1b** is the dramatic increase in locomotor stimulation produced by **1b**. This may be due to a mechanism not directly related to DA agonist properties.[9] As for **1a**, the mechanism of action of **1b** at the molecular level also remains cryptic. Although a very large number of adamantane derivatives have been investigated in connection with their potential antiviral properties, surprisingly few have been tested for anti-Parkinson activity. The only systematic studies reported to date are those of Chakribarti et al.,[10,11] in which a series of 2-substituted 1-adamantanealkanamines and 4-protoadamantanemethanamines was examined and found to possess potential anti-Parkinson activity. The most active analogues were shown to be approximately twice as active as **1a** in the reversal of reserpine-induced catalepsy. Menon and Clark also investigated a collection of 40 miscellaneous congeners of **1a** using stimulation of locomotor activity in mice as a bioassay and found a notable lack of activity.[12]

Hornykiewicz[13] has suggested that three criteria should be used for the design of improved drugs for the treatment of Parkinson's disease: (1) the drug should possess a profile dominated by postsynaptic dopaminergic agonist action, (2) the drug should be lipophilic enough to penetrate into the CNS without dependence on facilitated transport, and (3) the drug should show relative metabolic stability and be free of severe toxicity and other side effects. To date no class of drugs has more than partially met all of the criteria. L-Dopa, the current drug of choice,[14] possesses an unfavorable pharmacokinetic profile and a dependence upon intact DA neurons for its uptake and activation. Several directly acting newer drugs show promise, including the aporphines,[15] the ergot analogues,[16] and the aminotetralins,[17] but all have various undesirable side

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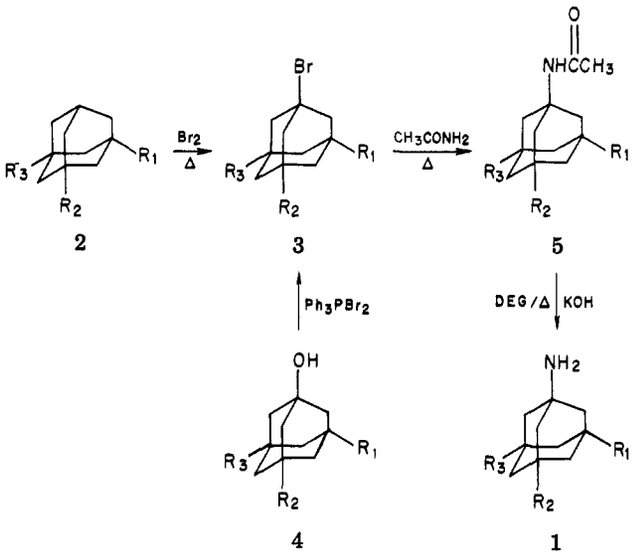
Scheme I



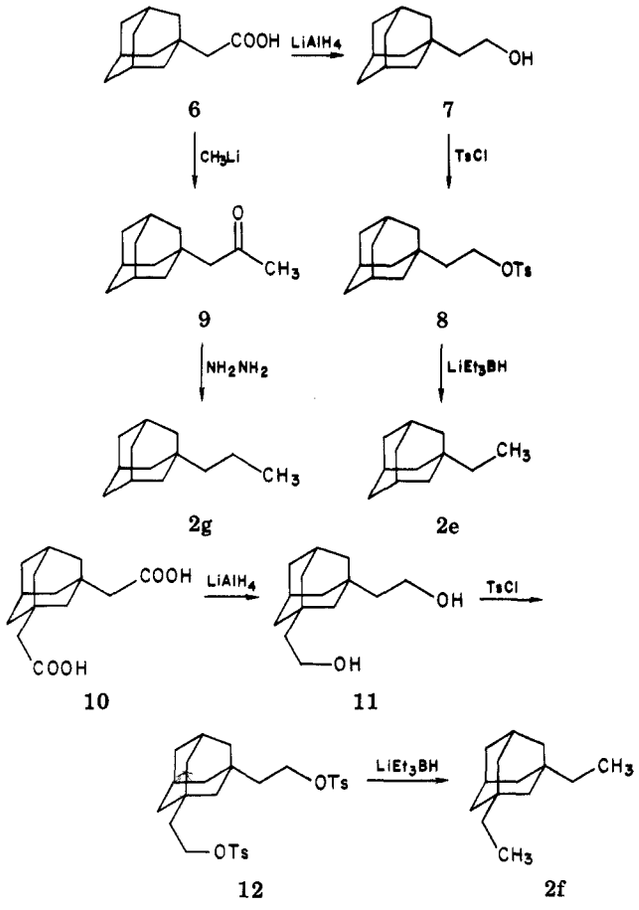
a, $R_1 = R_2 = R_3 = H$
b, $R_1 = R_2 = CH_3$; $R_3 = H$
c, $R_1 = CH_3$; $R_2 = R_3 = H$
d, $R_1 = R_2 = R_3 = CH_3$
e, $R_1 = C_2H_5$; $R_2 = R_3 = H$
f, $R_1 = R_2 = C_2H_5$; $R_3 = H$
g, $R_1 = n$-Pr; $R_2 = R_3 = H$

effects and/or pharmacokinetic instabilities.

The previously investigated amantadine congeners **1a** and **1b** offer the potential clinical advantages of metabolic stability,[18] relatively low toxicity,[19] and facile CNS penetrability but essentially no component of direct agonist action. To determine if such action may be present within the series, we have undertaken a program to explore the potential structure–anti-Parkinson activity profiles contained therein. Our initial efforts have been directed toward an examination of the contribution of lipophilicity.

Chemistry. The congeners chosen for examination consist of bridgehead alkyl-, dialkyl-, and trialkyl-substituted derivatives of **1a**, as represented by **1b–g**. The syntheses of these congeners were accomplished from either the corresponding hydrocarbon or the bridgehead alcohol using the general approach of Gerzon et al.[20] (Scheme I). Thus, treatment of **2e–g** with Br_2 afforded **3e–g** in excellent yield. Products **3c** and **3d** were formed from **4c** and **4d**, respectively, by treatment with Ph_3PBr_2. Each bridgehead halide **3c–g** was converted into the corresponding acetamide **5c–g**, which was then saponified to give the desired products **1c–g**. Each free base was isolated as the HCl salt. Memantine (**1b**) was obtained by direct amination of **2b** by the method of Kovacic and Roskos,[21] followed by conversion to its HCl salt. Although the latter pathway may appear to be more direct, we have found it unsuitable for the conversion of adamantanes containing alkyl groups other than methyl, due to the propensity of the higher homologues toward cationic rearrangements under the amination conditions.[21]

Scheme II



Hydrocarbons **2e–g** were synthesized from the respective adamantaneacetic and adamantanediacetic acids according to Scheme II. Alcohol **7** and diol **11** were formed by reduction of **6** and **10**, respectively. They were converted to the corresponding *p*-toluenesulfonates **8** and **12** and further reduced with $LiEt_3BH$ (Super Hydride, Aldrich) to **2e** and **2f**. Treatment of **6** with CH_3Li produced ketone **9**, which was subsequently reduced under Wolff–Kishner conditions to **2g**. Alcohols **4c** and **4d**, hydrocarbon **2b**, and amantadine (**1a**) were obtained commercially (Aldrich).

Biological Results

A number of behavioral and biochemical models have been used to assay potential anti-Parkinson activity. In this study we have utilized three behavioral models: (1) stimulation of spontaneous locomotor activity in mice,[22] (2) modification of circling behavior in mice with unilateral striatal lesions produced by 6-hydroxydopamine injection,[23] and (3) the reversal of reserpine/α-methyltyrosine induced akinesia in mice.[24] The results of the locomotor activity tests are shown in Table I. The large difference in activity between **1a** and **1b** is strikingly apparent. Amantadine was one of the least potent and least efficacious of the drugs tested, producing a 2.5-fold increase in motor activity at the optimal dose of 0.2 mmol/kg. On the other hand, memantine was at least equiactive with amphetamine, inducing a maximal 14-fold increase in motor counts over

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Table I. Effect of Amantadine Congeners on Locomotor Activity

compd	dose, mmol/kg	activity [a]
1a	0.05	87 (44)
	0.10	201 (68)
	0.20	243 (58)
	0.40	44 (13)
1b	0.0125	181 (76)
	0.025	264 (90)
	0.05	377 (108)
	0.10	916 (146)
	0.20	1378 (193)
1c	0.05	37 (19)
	0.10	144 (43)
	0.20	383 (67)
1d	0.025	148 (65)
	0.05	264 (41)
	0.10	351 (100)
	0.20	472 (165)
	0.40	*b*
1e	0.025	61 (15)
	0.05	147 (52)
	0.10	237 (75)
	0.15	432 (66)
	0.20	522 (66)
	0.30	368 (110)
1f	0.025	154 (52)
	0.05	383 (98)
	0.10	716 (163)
	0.20	478 (97)
1g	0.025	75 (11)
	0.05	75 (44)
	0.10	94 (40)
amphetamine	0.01	177 (61)
	0.02	562 (141)
	0.04	993 (232)

[a] Expressed as a percentage of control with standard errors in parentheses; each value represents the average results of a minimum of six mice. [b] Lethal.

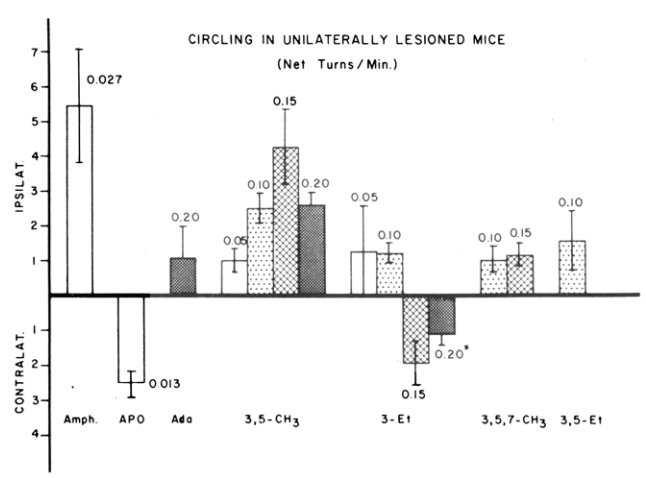

Figure 1. Circling behavior in unilaterally striatally lesioned mice. Doses of drug in millimoles per kilogram are denoted above each bar. Error bars represent 95% confidence limits for each dosage level. See Table II.

control, although it was approximately tenfold less potent. The remaining congeners produced intermediate locomotor activity profiles between those of **1a** and **1b**, with the exception of **1g**, which was uniformly inactive at doses up to 0.10 mmol/kg. Throughout the series, toxicity began to appear at doses in the range of 0.4–0.8 mmol/kg, manifested as a decrease in locomotor activity and the appearance of tremors and piloerection.

The results from stimulation of circling behavior in mice with unilateral striatal lesions provide further insight into

Table II. Induction of Circling Behavior in Unilaterally Striatally Lesioned Mice

compd	dose, mmol/kg	net turns/min [a]	*N*
1a	0.20	1.1 (0.9)	8
1b	0.05	1.0 (0.4)	10
	0.10	2.6 (0.5)	20
	0.15	4.3 (0.6)	10
	0.20	2.6 (0.4)	11
1d	0.10	1.0 (0.4)	7
	0.15	1.2 (0.4)	9
1e	0.05	1.3 (1.3)	8
	0.10	1.2 (0.3)	19
	0.15	2.0 (0.7) [b]	20
	0.20	1.2 (0.3) [b,c]	9
1f	0.10	1.6 (0.9)	14
amphetamine	0.027	5.5 (1.7)	24
APO	0.013	2.6 (0.4)	24

[a] Turning behavior expressed in a direction ipsilateral to the side of the 6-OHDA-induced lesion, except as noted; standard errors are indicated in parentheses. [b] Turning behavior contralateral to the lesion. [c] Toxicity observed in the form of preconvulsive signs.

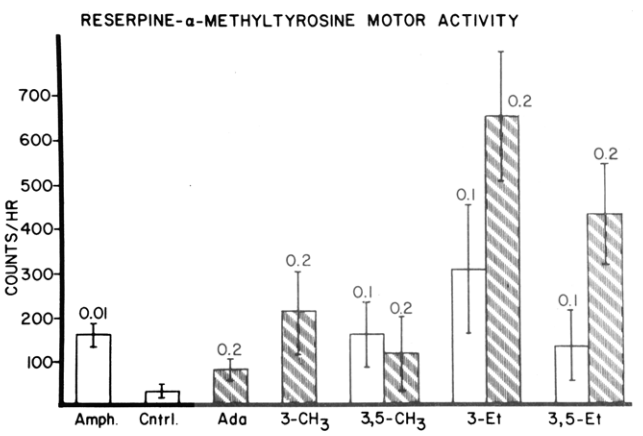

Figure 2. Reversal of reserpine/α-methyltyrosine induced akinesia in mice. The dose of drug in millimoles per kilogram is shown over each respective bar. Error bars denote the 95% confidence limits for each dosage level in three animals.

the activity profiles in the series. It is well established that postsynaptically acting DA agonists such as apomorphine (APO) cause turning behavior contralateral to the side of the lesion, while indirectly acting agonists (e.g., amphetamine) cause ipsilateral rotation.[23] Figure 1 and Table II present the activities of the more potent members of the series, along with those of amphetamine, APO, and **1a** for comparison. Memantine (**1b**) induced the most vigorous circling behavior among the experimental compounds. Based upon the resulting ipsilateral rotation, **1b** exerts its action in an indirect manner. Amantadine (**1a**), as well as trimethyl derivative **1d** and diethyl congener **1f**, also induced ispilateral circling in the test animals but were less potent than **1b**. Of special interest was 3-ethylamantadine (**1e**), which at low doses evoked weak ipsilateral circling but at higher doses caused contralateral circling. This action is supportive of a mixed mechanism of action, in which a direct postsynaptic DA agonist component plays a significant role.

To confirm this unusual behavior, several of the congeners were tested for the ability to reverse reserpine/α-methyltyrosine induced akinesia in mice. The results are shown in Figure 2, expressed as counts of spontaneous locomotor activity. Again **1e** showed a significant, although weak, ability to restore motor activity in catecholamine-depleted mice. Interestingly, diethyl derivative **1f** also

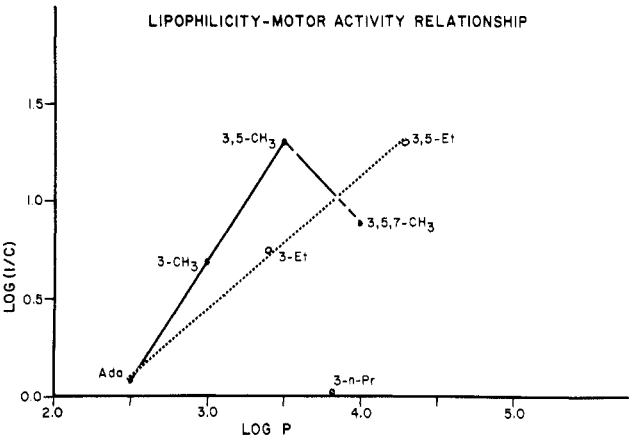

Figure 3. Lipophilicity (expressed as log P) vs. motor activity (expressed as log $1/C$) plot for methyl- and ethyl-substituted amantadine congeners.

Table III. Log P and pK_a Values for **1a-g**[a]

compd	pK_a	log P[b]
1a	10.63	2.44 (0.05)
1b	10.42	3.28 (0.04)
1c	10.56	3.01 (0.04)
1d	10.58	4.01[d]
1e	10.61	3.40 (0.12)
1f	c	4.36[d]
1g	c	3.76[d]

[a] Determined titrimetrically by the method of Clarke.[25] [b] Values in parentheses represent 95% confidence limits for the data. [c] Not determined. [d] Estimated by extrapolation of accompanying values.

showed the ability to stimulate motor activity at 0.2 mmol/kg, although the effect is not as strong as for **1e**. The methyl-substituted congeners (**1b** and **1c**) and amantadine itself produced levels of activity comparable to that of amphetamine and may be attributed to residual catecholamine release.

Discussion

Taken together, the results strongly support the existence of two separate dopaminergic mechanisms within the amantadine series: (1) the well-known indirect agonist effects of **1a** and **1b** and (2) a heretofore undescribed direct DA agonist component found in **1e** and to some extent in **1f**, although the effect in the latter substance is subject to a higher degree of uncertainty due to intervening toxicity. To examine the structure–motor activity effects from the results shown in Table I, the dose of drug necessary to produce a fourfold increase in motor activity was defined as the standard biological response. This level of activity represents a large enough difference from control levels to be reliable, yet is still within the range of efficacy of the derivatives of interest. Figure 3 shows a plot of motor activity (expressed as log $1/C$) vs. lipophilicity (expressed as log P) in this series. The log P values were determined titrimetrically using the method of Clarke[25] or were estimated using standard extrapolative techniques. They represent true octanol/water partition coefficients. Table III contains the pK_a and log P values for the series. While the number of data points is necessarily low, it appears that the lipophilicity–activity relationship for the bridgehead methyl series differs from that for the bridgehead ethyl series. The fact that the slopes of the lines are different supports the existence of different mechanisms of action when taken in the context of the other bioassay results.

Based upon the results obtained here, it appears that while lipophilicity contributes positively to anti-Parkinson activity, it clearly is not the sole determing factor within these amantadine congeners. For example, while **1b** and **1e** are isomeric and nearly isolipophilic, their profiles of action in all three bioassays are quite different. Even more striking is the differing behavior of the isomers **1d** and **1g**. While **1d** is a moderately active indirect DA agonist (within this context) that produces toxicity at lower than usual doses, **1g** is totally devoid of DA agonist activity at the doses tested. On this basis other structural factors must be contributing to DA agonist activity. Since the congeneric series was chosen to minimize any contribution due to electronic or polar effects, the factor that may best explain the observed activity is molecular shape.

The 3-ethyl substituent apparently contributes to direct DA agonist activity within the series in an unique way, since methyl substituents produce only indirect DA agonist effects and longer alkyl groups (e.g., n-propyl) appear to abolish activity. The reason for this apparent specificity is presently unknown. In seeking an explanation for this effect, one is tempted to speculate upon a possible superimposition of the direct DA agonist molecule (**1e**) and the active conformation of DA.[26] Reference to Dreiding models of **1e** and DA provides only a limited basis for common interaction, and on this basis the interaction that occurs is predicted to be quite weak. If such a potentially weak interaction does produce an in vivo DA agonist response, it may be rationalized, at least in part, on pharmacokinetic grounds. Unlike the other direct DA agonists, **1e** is expected to be highly metabolically stable, i.e., be only weakly affected by the metabolizing enzymes that inactivate APO, the ergot derivatives, and the aminotetralins. Further, **1e** is expected to easily penetrate into the CNS and reach appreciable concentration therein, compared to the classic DA agonists. These two factors may combine to produce a detectable DA agonist response despite what must be very weak receptor binding. This possibility is presently being considered, and in vitro bioassays are planned to address it.

In summary, we have investigated the potential anti-Parkinson activity of a series of amantadine alkyl congeners. Based on these in vivo bioassays, we have identified two weak but reproducible types of DA agonist activities, an indirect one within the bridgehead methyl-substituted series and a direct one within the bridgehead ethyl-substituted series. The activity within each series is dependent upon lipophilicity. Based on these results, other areas of substituent space are being explored, including a more in-depth look at the steric requirements at the 3-position and the influence of electronic or polar factors upon activity.

Experimental Section

Melting points were determined in an open or sealed glass capillary using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by Baron Consulting Co., Orange, CT. IR spectra were recorded on either a Beckman Acculab 3 or a Beckman MX620 instrument. NMR spectra were recorded on a Perkin-Elmer R24B spectrometer using tetramethylsilane as the internal standard. Mass spectra were determined on an AEI MS-902 instrument.

3,5-Dimethyl-1-aminoadamantane (1b) was prepared from 1,3-dimethyladamantane (Aldrich), NCl_3, and $AlCl_3$ by the method

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of Kovacic and Roskos[21] in 98% crude yield. The free base was converted to the HCl salt, which was recrystallized from EtOH–Et_2O, mp >310 °C (lit.[21] mp 290–295 °C).

3-Methyl-1-bromoadamantane (3c). To a stirred mixture of 12.007 g (45.8 mol) of Ph_3P and 30 mL of CH_3CN under N_2 was added 7.324 g (45.8 mmol) of Br_2. To this suspension was added 6.908 g (41.6 mmol) of 3-methyladamantan-1-ol (**4c**) (Aldrich) in 25 mL of CH_3CN. The mixture was heated to reflux for 30 h. The solvent was removed in vacuo, and the resulting oil was triturated with 5 portions of petroleum ether. The combined extracts were washed successively with 3 N HCl, H_2O, and 5% $NaHCO_3$ and then dried over $MgSO_4$. Evaporation of solvent afforded 9.10 g (96%) of a colorless oil that was distilled to give 8.124 g (85%) of **3c**, bp 95–97 °C (4 mm) [lit.[20] bp 65–67 °C (0.05 mm)]. The product became a low-melting soild upon standing at winter room temperature.

***N*-Acetyl-3-methyl-1-aminoadamantane (5c)** was prepared by the method of Gerzon et al.[27] Thus, 4.027 g (17.6 mmol) of **3c** and 10.306 g (176 mmol) of acetamide afforded 3.5 g of crude product, which was recrystallized from CH_2Cl_2–petroleum ether to afford 2.839 g (78%) of **5c**, mp 105.5–106.5 °C (lit.[20] mp 108–109 °C).

3-Methyl-1-aminoadamantane (1c) was prepared by the method of Gerzon et al.[27] using 1.500 g (7.25 mmol) of **5c** and 3.0 g (72.5 mmol) of NaOH in 25 mL of diethylene glycol. The resulting free base was not characterized but converted to the HCl salt to afford 1.423 g (97.5%) of product, which was recrystallized from CH_2Cl_2–Et_2O to give 1.108 g (76%) of **1c**·HCl, mp >325 °C (sublimes) (lit.[20] mp 295–300 °C).

3,5,7-Trimethyl-1-bromoadamantane (3d) was prepared in a manner identical with **3c** using 2.905 g (11.0 mmol) of Ph_3P and 1.767 g (11.0 mmol) of Br_2 in 25 mL of CH_3CN, to which was added 1.948 g (10.0 mmol) of **4d** (Aldrich). Subsequent workup gave 2.246 g (87%) of **3d** after recrystallization from MeOH, mp 99–100 °C (lit.[28] mp 101–102 °C).

***N*-Acetyl-3,5,7-trimethyl-1-aminoadamantane (5d)** was prepared in quantitative yield as described for **5c**, using 3.0 g (11.7 mmol) of **3d** and 7.0 g (119 mmol) of acetamide. Recrystallization from CH_2Cl_2–petroleum ether gave **5d**, mp 191–192 °C (lit.[27] mp 194–195 °C).

3,5,7-Trimethyl-1-aminoadamantane (1d) was prepared in a manner identical with **1c** using 2.74 g (10.7 mmol) of **5d** and 5.8 g (145 mmol) of NaOH in 50 mL of diethylene glycol. Workup and conversion to the HCl salt, followed by recrystallization from MeOH–Et_2O, afforded 2.18 g (89%) of **1d**·HCl, mp >325 °C (lit.[27] mp >300 °C).

2-(1-Adamantyl)ethyl *p*-Toluenesulfonate (8). To a stirred solution of 13.439 g (74.5 mmol) of 2-(1-adamantyl)ethanol (**7**; Aldrich) in 150 mL of dry pyridine at 0 °C was added 16.80 g (88.0 mmol) of freshly recrystallized TsCl in 50 mL of dry pyridine. After stirring for 2 h and standing overnight at 6 °C, the mixture was dumped into 400 mL of 10% HCl at 0 °C and extracted with 4 portions of Et_2O. The combined extracts were washed successively with cold 10% HCl, H_2O, and 5% $NaHCO_3$ and then dried over Na_2SO_4. Evaporation of solvent afforded 22.945 g (92%) of **8** as a very pale yellow oil: IR (neat) 1600, 1450, 1362, 1190, 1178 cm^{-1}; NMR ($CDCl_3$) δ 7.50 (dd, 4 H, C_6H_4), 4.07 (t, 2 H, α-CH_2), 2.42 (s, 3 H CH_3), 1.3–2.1 (m, 17 H, adamantyl + CH_2). The product was not purified further.

1-Ethyladamantane (2e). To a stirred solution of 8.145 g (24.4 mmol) of **8** in 35 mL of dry THF under N_2 at 0 °C was added dropwise 51 mL of 1 M $LiEt_3BH$ in THF (Aldrich). After the mixture was stirred at room temperature for 15 h, the excess hydride was destroyed with H_2O, followed by 20 mL of 3 N NaOH and careful dropwise addition of 20 mL of 30% H_2O_2 (vigorous reaction). The layers were separated, and the aqueous layer was extracted with 3 portions of petroleum ether. The combined extracts were washed with H_2O and dried over $MgSO_4$. The solvent was evaporated to yield 4.40 g of crude product, which was distilled to afford 3.292 g (82%) **2e**: bp 155–160 °C (97 mm) [lit.[20] bp 240 °C (745 mm)]. Considerable foaming occurred during distillation.

1-Bromo-3-ethyladamantane (3e). Under an N_2 atmosphere, 0.944 g (5.76 mmol) of **2e** was stirred with 10 mL of Br_2 for 4 h, over which time the temperature was increased to reflux. The heat was removed and the solution was stirred overnight. A 40-mL portion of CCl_4 was added, the mixture was poured into 120 mL of ice–H_2O, and enough solid Na_2SO_3 was added with vigorous stirring to decolorize the product. The layers were separated, and the aqueous phase was extracted with 3 portions of CCl_4. The combined extracts were washed with H_2O and then 5% $NaHCO_3$ and dried over $MgSO_4$. Evaporation of solvent yielded a yellow liquid, which was distilled to afford 1.263 g (90.3%) of **3e** as a colorless liquid that became a low-melting solid upon standing: bp 114–115 °C (3.5 mm) [lit.[30] sublime 85 °C (0.01 mm)].

***N*-Acetyl-3-ethyl-1-aminoadamantane (5e)** was prepared in a manner identical with **5c** using 1.205 g (4.96 mmol) of **3e** and 2.950 g (50 mmol) of acetamide to produce 1.004 g (91.6%) of **5e** after recrystallization from CH_2Cl_2–petroleum ether: mp 103.5–104.5 °C; IR (Nujol) 3270, 1640, 1555 cm^{-1}; NMR ($CDCl_3$) δ 5.40 (br s, 1 H, NH), 1.87 (s, 3 H, CH_3CO), 1.0–2.3 (m, 16 H, adamantyl + CH_2), 0.79 (t, 3 H, CH_3). Anal. ($C_{14}H_{23}NO$) C, H, N.

3-Ethyl-1-aminoadamantane (1e) was prepared in a manner analogous to **1c** using 858 mg (3.88 mmol) of **5e** and 1.5 g (39 mmol) of NaOH in 25 mL of diethylene glycol. The product was isolated as the HCl salt, which was recrystallized from CH_2Cl_2–Et_2O to give 0.539 g (64%) of **1e**·HCl: mp 271.5–272 °C; NMR ($CDCl_3$) δ 8.3 (br s, 3 H, NH_3^+), 1.0–2.3 (m, 16 H, adamantyl + CH_2), 0.80 (t, 3 H, CH_3). M_r Calcd for $C_{12}H_{21}N$: 179.1675. Found: 179.1676. Anal. ($C_{12}H_{22}NCl$) C, H, N.

1,3-Adamantanediethanol (11). A 5.00-g quantity of 1,3-adamantanediacetic acid (Aldrich) suspended in 50 mL of Et_2O was converted to the bis(methyl ester) with excess CH_2N_2 in Et_2O. A 4.129 g (14.7 mmol) portion of this diester in 50 mL of anhydrous Et_2O was carefully added to a suspension of 1.60 g (42 mmol) of $LiAlH_4$ in 100 mL of anhydrous Et_2O under N_2. After the mixture was stirred overnight, the excess $LiAlH_4$ was destroyed by the careful successive addition of 1.5 mL of H_2O, 4.5 mL of 15% aqueous KOH, and 1.5 mL of H_2O. After separation, the inorganic salts were washed with several portions of Et_2O. The extracts were combined, dried over $MgSO_4$, and evaporated to afford 2.759 g (83.5%) of **11** as colorless needles after recrystallization from CH_2Cl_2–Et_2O: mp 117–117.5 °C; IR (Nujol) 3240, 1042, 1030 cm^{-1}; NMR ($CDCl_3$) δ 3.70 (t, 4 H, CH_2O, J = 7.5 Hz), 2.02 (br s, 2 H, bridgehead H), 1.1–1.8 (m, 16 H, adamantyl + CH_3 + OH). Anal. ($C_{14}H_{24}O_2$) H; C: calcd, 74.95; found, 76.01.

1,3-Adamantanediethanol bis(*p*-toluenesulfonate) (12) was prepared in a manner identical with **8** using 7.028 g (36.9 mmol) of freshly recrystallized TsCl in 25 mL of dry pyridine and 3.942 g (17.6 mmol) of **11** in 25 mL of dry pyridine at 0 °C under N_2 to afford 9.061 g (96.8%) of **12** as a colorless oil: IR (neat) 1340, 1165, 950, 665 cm^{-1}; NMR ($CDCl_3$) δ 7.50 (dd, 8 H, C_6H_4), 4.07 (t, 4 H, CH_2O, J = 6.5 Hz), 2.43 (s, 6 H, $ArCH_3$), 1.93 (br s, 2 H, bridgehead H), 0.9–1.8 (m, 16 H, adamantyl + CH_2). The product was not purified further.

1,3-Diethyladamantane (2f) was prepared in a manner identical with **2e** using 8.880 g (16.7 mmol) of **12** in 25 mL of dry THF and 60 mL of 1.0 M $LiEt_3BH$ in THF to afford 2.869 g (89.5%) of **2f** as a colorless oil after workup and distillation: bp 100–102 °C (10 mm); IR (neat) 1440, 1370 cm^{-1}; NMR ($CDCl_3$) δ 2.0 (br s, 2 H, bridgehead H), 0.55–1.85 (m, 22 H, adamantyl + CH_2 + CH_3). M_r Calcd for $C_{14}H_{24}$: 192.1879. Found: 192.1883. The product was too volatile for microanalysis.

3,5-Diethyl-1-bromoadamantane (3f) was prepared by the same procedure as **3e** using 2.667 g (13.9 mmol) of **2f** and 25 mL of Br_2 to yield 3.154 g (83.8%) of **3f** after workup and distillation: bp 126–128 °C (3 mm); IR (neat) 1442, 1304, 725 cm^{-1}; NMR ($CDCl_3$) δ 1.65–2.4 (m, 7 H, bridgehead H + CH_2CBr), 0.5–1.6 (m, 16 H, C_2H_5 + remaining adamantyl). M_r Calcd for $C_{14}H_{23}$: 191.1801. Found: 191.1806. Anal. ($C_{14}H_{23}Br$) C, H.

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N-Acetyl-3,5-diethyl-1-aminoadamantane (5f) was prepared in a like manner to 5e using 3.154 g (11.64 mmol) of 3f and 6.87 g (116 mmol) of acetamide to produce 2.561 g (88.4%) of 5f after workup and recrystallization from CH_2Cl_2–petroleum ether: mp 117.5–118 °C; IR (Nujol) 3280, 1640, 1560 cm^{-1}; NMR ($CDCl_3$) δ 5.33 (br s, 1 H, NH), 2.13 (br s, 2 H, bridgehead H), 1.89 (s, 3 H, CH_3CO), 0.6–1.8 (m, 22 H, C_2H_5 + adamantyl). Anal. ($C_{16}H_{27}NO$) C, H, N.

3,5-Diethyl-1-aminoadamantane (1f) was prepared analogously to 1e using 2.474 g (9.936 mmol) of 5f and 4.0 g (100 mmol) of NaOH in 50 mL of diethylene glycol to produce 1.872 g (78%) of 1f·HCl after workup, conversion to the HCl salt, and recrystallization from CH_2Cl_2–Et_2O: mp 321–323 °C dec; NMR ($CDCl_3$) δ 8.3 (br s, 3 H, NH_3^+), 0.5–2.4 (m, 23 H, C_2H_5 + adamantyl). Anal. ($C_{14}H_{25}NCl$) C, H, N.

1-Adamantylacetone (9). To a stirred solution of 4.271 g (21.98 mmol) of 6 (Aldrich, recrystallized from Et_2O–petroleum ether) in 100 mL of dry THF was slowly added 28.6 mL of 1.6 M CH_3Li (low halide) in Et_2O. After 70 min, saturated aqueous NH_4Cl was added, followed by 10% aqueous KOH. The layers were separated, and the aqueous phase was extracted several times with Et_2O, then acidified, and reextracted with Et_2O. The extracts from alkaline solution were combined, dried over $MgSO_4$, and evaporated to give 3.40 g (80.4%) of 9 after distillation: bp 102–104 °C (2.2 mm) [lit.[30] bp 84–85 °C (0.6 mm)]; IR (neat) 1700, 1445, 1353 cm^{-1}; NMR ($CDCl_3$) δ 2.16 (s, 2 H, CH_2CO), 2.10 (s, 3 H, CH_3), 1.94 (br s, 3 H, bridgehead H), 1.5–1.8 (m, 12 H, adamantyl). 2,4-Dinitrophenylhydrazone: mp 142–143 °C (from EtOH) (lit.[30] mp 140 °C).

1-*n*-Propyladamantane (2g). To a mixture of 3.053 g (53.3 mmol) of KOH, 2.14 mL of 64% hydrazine in H_2O, and 25 mL of diethylene glycol was added 3.033 g (15.8 mmol) of 9. The mixture was heated to reflux for 18 h with separation of H_2O. The mixture was cooled, diluted with water, and extracted several times with petroleum ether. The extracts were combined, dried over $MgSO_4$, and evaporated to yield 1.742 g (62%) of 2g after distillation: bp 138–139 °C (25 mm) [lit.[31] bp 234 °C (atm)].

1-Bromo-3-*n*-propyladamantane (3g) was prepared from 2g in a manner identical with 3e using 1.694 g (9.50 mmol) of 2g and 20 mL of Br_2 to produce 1.760 g (71.8%) of 3g after workup and distillation: bp 127–128 °C (3.5 mm); IR (neat) 1451, 1304, 819, 678 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.4 (m, 18 H), 0.85 (t, 3 H, CH_3, J = 6 Hz). M_r Calcd for $C_{13}H_{21}$: 177.1643. Found: 177.1643. Anal. ($C_{13}H_{21}Br$) C, H.

N-Acetyl-3-*n*-propyl-1-aminoadamantane (5g) was synthesized according to the procedure used for 5c. Thus, 1.760 g (6.816 mmol) of 3g and 4.024 g (68.2 mmol) of acetamide afforded 1.093 g (68.2%) of 5g after workup and recrystallization from CH_2Cl_2–petroleum ether: mp 104–104.5 °C; IR (Nujol) 3258, 1640, 1550, 1300 cm^{-1}; NMR ($CDCl_3$) δ 5.5 (br s, 1 H, NH), 1.90 (s, 3 H, $COCH_3$), 1.0–2.1 (m, 18 H, adamantyl + CH_2), 0.85 (t, 3 H, CH_3, J = 6.0 Hz). Anal. ($C_{15}H_{25}NO$) C, H, N.

3-*n*-Propyl-1-aminoadamantane (1g) was prepared from 6g by the procedure used for 1c. Thus, 1.081 g (4.60 mmol) of 6g and 1.84 g (46 mmol) of NaOH in 40 mL of diethylene glycol afforded 633 mg of 1g after formation of the HCl salt and recrystallization from CH_2Cl_2–Et_2O: mp 251 °C dec; NMR ($CDCl_3$) δ 8.2 (br s, 3 H, NH_3^+), 0.7–2.4 (m, 18 H, adamantyl + CH_2), 0.85 (t, 3 H, CH_3, J = 6 Hz). M_r Calcd for $C_{13}H_{23}N$: 193.1832. Found: 193.1825. Anal. ($C_{13}H_{24}NCl$) C, H, N.

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Partition Coefficient Measurements. Into a 50-mL water-jacketed beaker maintained at 25.00 °C (±0.05 °C) was placed 20.00 mL of a solution of the amine HCl, accurately weighed to produce a concentration of ca. 0.5 mg/mL. The solution was stirred for 10 min to allow temperature equilibration, and the pH of the solution was recorded. To the stirred solution was added a 50.0-μL aliquot of standardized KOH solution (ca. 0.1 N). The solution was again allowed to equilibrate, and the new pH was recorded. The pK_a of the amine was calculated by the method of Clarke.[25] Using an identical apparatus and solution volumes, another determination was performed in the presence of a 4.0-mL aliquot of purified *n*-octanol. After each addition of standard KOH, the biphasic mixture was stirred vigorously, after which the layers were allowed to separate and the pH of the aqueous solution was recorded. The log P and pK_a parameters were calculated with the aid of an HP-41C calculator using programs translated from those of Clarke.[25]

Bioassay Methods. Motor activity was recorded in a Stoelting Activity Monitor. Six mice were placed one per cage (10 × 19 in.) above one of the recording channels. After a 20-min base-line period, the mice were removed, injected sc with the drug or vehicle, and returned to the monitor for 2 h. Activity "counts" were recorded at 30-min intervals.

The effect of drug on circling behavior was measured by counting the number and direction of turns over a 2-min period after the lesioned mouse was placed in a 3-L beaker. Only complete rotations were recorded. Tests were performed 60 min after sc injection of the drug (for the adamantanes and amphetamine) and 30 min after sc injection for APO. The lesion was made by slowly injecting 6-hydroxydopamine (16 μg in 4 μL of ice-chilled 0.1% ascorbic acid solution) into the right striatum of methoxyflurane-anesthetized mice as described by Pycock et al.[32] At least 1 week was allowed for recovery from surgery. At the conclusion of the experiment the mice were sacrificed and the DA content of the lesioned and intact striata were determined. Only mice exhibiting contralateral circling in response to APO, ipsilateral circling in response to amphetamine, and striatal DA reduced by at least 50% were used for analysis.

Akinesia was induced by an ip injection of reserpine (5 mg/kg), followed 5 h later by an ip injection of α-methyltyrosine methyl ester hydrochloride (equivalent to 250 mg/kg free base). Ten minutes after the second injection, the mice were allowed the 20-min warm-up period for activity and then injected sc with the drug. Analysis of randomly selected mice demonstrated that this treatment resulted in >90% depletion of brain DA.

Striatal DA concentrations were determined using the radioenzymatic method of Cuello et al.[33] This procedure depends on the enzymatic methylation of DA by [^{3}H]-*S*-adenosylmethionine (ICN Radiopharmaceuticals) using crude rat liver catechol *O*-methyltransferase (COMT).

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