Adamantane and Protoadamantanealkanamines as Potential Anti-Parkinson Agents[1]

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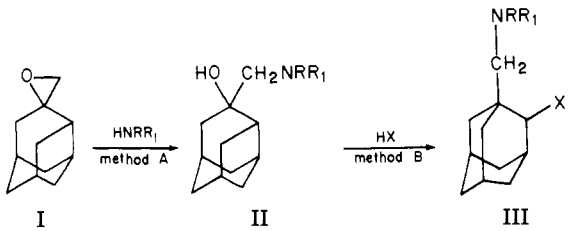
The synthesis of 2-halo-1-adamantanemethanamines, 4-protoadamantanemethanamines, and 4-protoadamantaneamines is described. The anti-Parkinson activity of these amines in terms of reversal of reserpine-induced catalepsy in rats has been evaluated and compared with amantadine. 2-Bromo- and 2-chloro-1-adamantanemethanamines are shown to be twice as active as amantadine.

The deficiency of striatal dopamine is implicated in Parkinson's disease. The reduced level of this biogenic amine can be restored by the use of L-Dopa. Optimum response to L-Dopa therapy is often limited by its associated side effects. Amantadine (1-aminoadamantane), among other drugs, has been widely assessed clinically. Although in some cases[2] it has shown remarkable effect, in most patients the degree of improvement is slight. In animal experiments amantadine enhances catecholamine metabolism and causes increased dopamine release in response to the nerve impulse. It does not, however, cause direct stimulation of dopamine receptors.[3] Thus there is a need for a suitable agent, which should be effective preferably by causing direct stimulation of the receptors. 1,3-Dimethyl-5-aminoadamantane (D-145) has been reported to activate the central dopaminergic receptors. It thus differs from amantadine but acts in many respects like apomorphine.[4] Since a slight structural change from 1-aminoadamantane to its dimethyl analogue (D-145) can profoundly influence the pharmacological profile, we became interested in simple but novel adamantane and protoadamantaneamines.

In a previous paper,[5a] we reported the potential anti-Parkinson properties of certain 2-substituted 1-adamantaneethanamines and higher alkanamines. Significant activity was observed in most cases when adamantane was substituted by a halogen at the 2 position. The activity seemed to decrease with the lengthening of the basic side chain. These amines were obtained via insertion reactions.[5] The activity of the lower analogues, 1-adamantanemethanamines, could not be evaluated then due to their inaccessibility by these methods. Recently we have developed a direct and convenient route to these amines.[6] In the present report we describe the synthesis of these 2-substituted 1-adamantanemethanamines and also of various protoadamantaneamines. The activities of these amines in respect of reserpine antagonism in mice and anti-Parkinson activity in terms of reversal of reserpine-induced catalepsy in mice and rats have been evaluated.

Chemistry. 2-Substituted 1-adamantanemethanamines were prepared by the route presented in Scheme I. The nucleophilic opening of the 4-protoadamantanespiro-oxirane[6] (I) with the appropriate amines led to the cleavage of the ring, as expected, at the least substituted terminal carbon to give the aminols II. These, in turn, were rearranged by mineral acids to give the corresponding 2-substituted 1-adamantanemethanamines III. The substitution at the 2 position was determined by the nature of the acid employed. Aqueous acids led to 2-hydroxy-1-adamantanemethanamines, whereas anhydrous acids (HBr, HCl) gave the corresponding 2-halo analogues. The NMR spectra of the 2-substituted 1-adamantanemethanamines revealed a low-field signal (δ 4.7–5.2) due to the proton at the 2 position geminal to the halogen. It is interesting to note that this absorption is consistently at δ ~0.5 lower field than in the corresponding higher alkanamines.[5] This shift is presumably due to the closer proximity of the charged nitrogen atom in these molecules. The difficulty in displacing the halogen atom by a phenyl group using a Friedel–Crafts process, as described in the cases of higher alkanamines,[5a] can also be explained in terms of steric factors. However, 2-phenyl 1-adamantanemethanamine (**6**) was obtained in poor yield by rearrangement of the aminol 18 in benzene using boron trifluoride etherate as catalyst. Use of metal halide catalysts gave the 2-halo compounds exclusively.

Scheme I



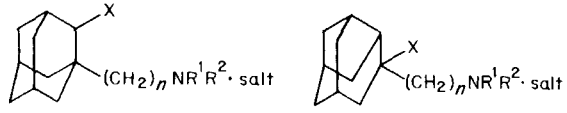
4-Protoadamantaneamines and 4-protoadamantanemethanamines were obtained by reductive amination of 4-protoadamantanone[7] (method C) and 4-protoadamantanecarboxaldehyde[1] (method D), respectively.

Pharmacology. The compounds were tested for acute toxicity in mice both orally and intraperitoneally and approximate LD_{50} values are recorded in Table I. Potential antidepressant properties were examined using the reversal of reserpine-induced hypothermia as an index in mice. Potential anti-Parkinson activity was assessed using the reversal of reserpine-induced catalepsy as an index in mice as well as in rats. The relevant methods are described in our earlier paper.[5a] The reserpine antagonism in mice has now been extended to evaluate catalepsy (see the Experimental Section). The results (Table I) were compared with amantadine and compound **2**, found to be the most active derivative in the 2-substituted 1-adamantaneethanamine series.[5a] The reversal of reserpine-induced catalepsy in rats shows that 2-halo-1-adamantanemethanamines (**1**, **3**, and **5**) are markedly more active than amantadine. They retain the activity similar to compounds **2** and **4**. In line with our observation on the higher alkanamine series, the halogen substituent at the 2 position of adamantane seems to be critical for activity. The 2-bromo derivative **3** is slightly more active than its 2-chloro analogue **1**. On the other hand, the 2-bromo analogue (**4**) of **2** showed diminished activity. The phenyl substitution at the 2 position (**6**) did not show any advantage. The secondary amines appear to be better than the tertiary amines. A complete reversal of catalepsy was observed with one compound (**3**). Some moderate degree of activity in antagonizing the reserpine-induced hypothermia was observed in certain protoadamantaneamines but their anticataleptic activity was only marginal.

Experimental Section

Unless mentioned otherwise, the relevant salts of the amines

Table I. Adamantanealkanamines 1-8 and Protoadamantanealkanamines 9-20



1-8 9-20

No.	n	NR^1R^2	X	Salt	Method	Yield, %	Mp, °C	Formula	Analyses	LD_{50}[d] po	LD_{50}[d] ip	Reserpine, mice, sc[e] Hypothermia[f]	Reserpine, mice, sc[e] Catalepsy[g]	Reserpine, rats, po,[e] catalepsy[a,g]
1	1	NHMe	Cl	HCl	B	20	216-226	$C_{12}H_{20}ClN\cdot HCl$	C, H, N, Cl	1.20	0.60	0 (0.02)	0 (0.02)	4 (0.16)
2	2	NHMe	Cl	HCl	*a*					1.50	0.60	2 (0.04)	3 (0.15)	4 (0.15)
3	1	NHMe	Br	HCl	B	46	269-272	$C_{12}H_{20}BrN\cdot HCl$	C, H, N	1.00	1.00	1 (0.17)	3 (0.17)	5 (0.14)
4	2	NHMe	Br	Maleate	*b*	23	171-173	$C_{13}H_{22}BrN\cdot C_4H_4O_4$	C, H, N, Br	1.60	0.40	1 (0.04)	0 (0.08)	3 (0.11)
5	1	NMe_2	Br	HCl	B	35	185	$C_{13}H_{22}BrN\cdot HCl\cdot 0.5H_2O$	C, H, N	1.30	0.50	0 (0.13)	0 (0.13)	4 (0.13)
6	1	NHMe	Ph	HCl	*c*	4	225	$C_{18}H_{25}N\cdot HCl\cdot 0.5H_2O$	C, H, N	N.T.	N.T.	1 (0.07)	0 (0.07)	0 (0.14)
7	1	$N(CH_2CH_2)_2NMe$	Br	2HBr	B	40	246-249	$C_{16}H_{27}BrN_2\cdot 2HBr$	C, H, N	1.20	0.60	0 (0.13)	0 (0.13)	0 (0.08)
8	1	$N(CH_2CH_2)_2NMe$	OH	2HCl	*c*	80	240-245	$C_{16}H_{28}N_2O\cdot 2HCl$	C, H, N, Cl	1.20	0.90	1 (0.15)	0 (0.15)	N.T.
9	0	NH_2	H	HCl	C	76	310-325	$C_{10}H_{17}N\cdot HCl$	C, H, N, Cl	3.20	0.80	0 (0.16)	0 (0.16)	N.T.
10	0	NHMe	H	HCl	C	32	282	$C_{11}H_{19}N\cdot HCl$	C, H, N	2.00	0.70	0 (0.20)	1 (0.20)	N.T.
11	0	$NHCH_2Ph$	H	HCl	C	57	233-236	$C_{17}H_{23}N\cdot HCl$	C, H, N, Cl	0.70	0.50	2 (0.09)	3 (0.09)	1 (0.07)
12	0	$NH(CH_2)_2Ph$	H	HCl	C	24	295-300	$C_{18}H_{25}N\cdot HCl$	C, H, N, Cl	1.00	0.30	1 (0.09)	3 (0.09)	0 (0.14)
13						24	290-295	$C_{18}H_{25}N\cdot HCl$	C, H, N, Cl	0.50	0.20	1 (0.03)	2 (0.07)	1 (0.14)
14	0	$NH(CH_2)_2OH$	H	HCl	C	74	261-264	$C_{12}H_{21}NO\cdot HCl$	C, H, N	2.60	0.60	0 (0.11)	0 (0.11)	N.T.
15	0	$NHCH_2$-*p*-C_6H_4Cl	H	HCl	C	85	245-247	$C_{17}H_{22}ClN\cdot HCl$	C, H, N, Cl	1.90	0.60	1 (0.16)	0 (0.16)	N.T.
16	1	NHMe	H	Maleate	D	37	148-149	$C_{12}H_{21}N\cdot C_4H_4O_4$	C, H, N	1.00	0.50	1 (0.14)	0 (0.14)	N.T.
17	1	$NHCH_2Ph$	H	Maleate	D	28	154-155	$C_{18}H_{25}N\cdot C_4H_4O_4$	C, H, N, O	0.50	0.20	0 (0.05)	0 (0.05)	N.T.
18	1	NHMe	OH	Maleate	A	58	160-162	$C_{12}H_{21}NO\cdot C_4H_4O_4$	C, H, N, O	3.90	1.90	0 (0.32)	0 (0.32)	N.T.
19	1	NMe_2	OH	HCl	A	48	250	$C_{13}H_{23}NO\cdot HCl\cdot {}^1/_3H_2O$	C, H, N, Cl	1.60	1.20	0 (0.20)	0 (0.20)	N.T.
20	1	$N(CH_2CH_2)_2NMe$	OH	2HCl	A	65	232-234	$C_{16}H_{28}N_2O\cdot 2HCl$	C, H, N, Cl	2.40	0.90	1 (0.07)	0 (0.15)	N.T.
Amantadine										2.10	1.10	1 (0.21)	0 (0.21)	2 (0.21)

[a] See ref 5a. [b] Prepared as described for compound 2. [c] See Experimental Section. [d] Figures represent approximate LD_{50} (mmol/kg) in mice; N.T. = not tested. [e] Doses (mmol/kg) are shown in parentheses. [f] Activity: 0 = no effect; 1 = temperature index (TI) 5-10; 2 = TI > 10. [g] Activity: 0 = no effect; 1 = marginal effect; 2 = significant effect, 3 = marked effect; 4 = approaching complete reversal; 5 = complete reversal, N.T. = not tested.

were crystallised from *i*-PrOH–*n*-hexane. Melting points were determined on a Kofler block under microscopic magnification or in capillary tubes and are not corrected. The structures of the compounds are supported by ir and NMR spectra measured with Perkin-Elmer 457 and Varian A-60A spectrometers, respectively. Where analyses are indicated by symbols of the elements, the results were within ±0.4% of the theoretical values unless otherwise stated.

4-(4-Methyl-1-piperazinyl)methylprotoadamantan-4-ol Dihydrochloride (20) (Method A). To a solution of 4-protoadamantanespirooxirane (1.64 g, 0.01 mol) in ethanol (40 ml) was added 4-methylpiperazine (5 g, 0.05 mol). The solution was heated under reflux for 18 h, diluted with water, and extracted with CH_2Cl_2. The organic phase was washed with water several times, dried ($MgSO_4$), and evaporated under vacuum at 50° to give an oil (2.5 g). This in ethereal solution was converted to the hydrochloride salt (2.2 g): mp 232–234°; ir (KBr) 3400 cm^{-1}; NMR δ ($CDCl_3$–Me_2SO-d_6) 3.37 (2 H, CCH_2N–), 2.84 (3 H, NCH_3).

2-Hydroxy-1-(4-methyl-1-piperazinyl)methyladamantane Dihydrochloride (8). A solution of the above aminol **20** as the base (0.75 g) in dioxane (10 ml) and 10% aqueous sulfuric acid (2 ml) was heated on a steam bath for 2 h. The solution was diluted with water, neutralized with 5 N NaOH to pH ~10, and extracted with CH_2Cl_2 to give the base as a gum. This was converted to its hydrochloride: mp 240–245° dec; ir (KBr) 3380, 1065 cm^{-1}; NMR δ (D_2O) 3.95 (1 H, CHOH), 3.21, 3.50 (2 H, CCH_2N–), 3.03 (3 H, NCH_3).

2-Bromo-1-(4-methyl-1-piperazinyl)methyladamantane Dihydrobromide (7) (Method B). To a solution of the aminol **20** as the base (1.3 g, 0.005 mol) in glacial acetic acid (30 ml), cooled in an ice–salt bath, was added dropwise with stirring a solution of HBr in acetic acid (40 ml of 50% w/v). The mixture was stirred for 24 h and most of the acetic acid removed under vacuum at ~60° to give a white solid (1 g), which was crystallized from ethanol: mp 246–249° dec; NMR δ ($CDCl_3$–Me_2SO-d_6) 5.2 (1 H, –CHBr).

***N*-Methyl-2-phenyl-1-adamantanemethanamine Hydrochloride (6).** To a solution of the free base of aminol 18, converted from its salt 18 (4.78 g, 0.015 mol), in benzene (100 ml) was added freshly distilled BF_3 etherate (10.5 ml). The mixture was refluxed for 20 h. The usual workup gave an oil (3 g), which was converted to the hydrochloride salt. Chromatography on Sorbsil M60 eluting with Et_2O–$CHCl_3$–MeOH–0.88 NH_4OH (50:30:18:2) gave the pure compound **6** (0.4 g): mp 225°; NMR δ ($CDCl_3$) 3.30 (1 H, –CHPh).

4-Protoadamantaneamines (Method C). *N*-Phenylethyl-4-protoadamantaneamines (12 and 13). A solution of 4-protoadamantanone[7] (3 g, 0.02 mol) and phenylethylamine (2.7 g, 0.022 mol) in dry benzene (100 ml) containing a trace of *p*-toluenesulfonic acid was refluxed (Dean-Stark) for 16 h. The solution was evaporated to dryness and the residue dissolved in ethanol (100 ml). The pH of the solution was adjusted to ~6 with glacial AcOH and hydrogenation carried out at 60 psi over PtO_2 (0.2 g). Removal of the catalyst and evaporation of the solution under vacuum gave the amines (5.2 g, 90%) as a mixture of endo and exo epimers. These were separated by chromatography on Sorbsil M60 by elution with EtOAc–CH_2Cl_2 (20:80) followed by MeOH–CH_2Cl_2 (20:80) to give the corresponding bases **12** (1.4 g, 24%) and **13** (1.3 g, 24%), respectively. GLC showed both isomers to be 90% pure and the rest consisted of the other isomer. These bases were converted to their respective hydrochloride salts and crystallized. Separation of the isomers was not attempted in other cases.

4-Protoadamantanemethanamines (Method D). 4-Protoadamantanecarboxaldehyde, prepared by acid-catalyzed isomerization of 4-protoadamantanespirooxirane,[1] was reductively aminated in the usual manner to give 4-protoadamantanemethanamines.

Antagonism of Reserpine-Induced Hypothermia and Catalepsy in Mice. The experiment was carried out in groups of five mice (CFW) by a modification of the method described earlier[5a] for the reversal of reserpine hypothermia.

The animals were injected subcutaneously (sc) with 4 mg/kg of reserpine[8] and after 2.5 h their rectal temperature was measured and their degree of catalepsy assessed. Immediately following this, drugs were given sc and further temperature and catalepsy readings were made at 30-min intervals for up to 1.5 h.

Catalepsy was evaluated using the following two tests: (a) a hind limb of the mouse was placed on a 1.5 cm high cork and (b) the mouse was placed on a vertical grid. A score of 1 was recorded in each test if the mouse did not move from its initial position for 20 s, and a score of 0.5 was given for any mouse making only a slight movement. In all tests the control group scored 9 or 10 at each of the three time intervals. The activity of compounds was assessed on the scores obtained on at least one time interval.

In order to simplify the recording of reserpine hypothermia antagonism, the "temperature index" assessment[9] was used. Taking as a base the mean initial temperature of each group, the mean temperature changes from this figure at 30, 60, and 90 min were summed and termed the "temperature index" (TI).

Using this system, mice given reserpine alone gave temperature indices in the range of –5 to –15. Drugs were considered active if the TI was greater than 5 units hyperthermic from the control results. If the reserpine-treated control group gave a TI less than –5 or greater than –15, the experiment was repeated.

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References and Notes

(1) Part 10 of the series. For part 9, see J. K. Chakrabarti, T. M. Hotten, D. M. Rackham, and D. E. Tupper, to be published.
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