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Adamantanealkanamines as Potential Antidepressant and Anti-Parkinson Agents†

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Various adamantanealkanamines were prepared and their activity in antagonizing reserpine-induced hypothermia was compared with nortriptyline. A structure–activity relationship in respect of the substitution on the adamantane ring and the nature of the alkanamino side chain is discussed. Norepinephrine responses *in vivo* as well as *in vitro* are potentiated at low doses with only one compound, *N*,α-dimethyl-2-phenyl-1-adamantaneethanamine (**52**). However, unlike the tricyclic antidepressants, **52** fails to block the pressor response to tyramine in the cat. The anti-Parkinson activity of some of these potent amines in reversing the reserpine-induced catalepsy in rats was evaluated and compared with amantadine.

While screening adamantane derivatives for biological activity, it was found that certain adamantanealkanamines antagonized reserpine hypothermia in mice, indicating possible antidepressant activity. The present paper describes the synthesis and evaluation of antidepressant properties, in terms of reserpine antagonism, of these amines. The anti-Parkinson properties of some of the amines, as determined by reversal of reserpine-induced catalepsy in rats, are also described. The compounds concerned are adamantanes substituted on the 1 position with an alkyl (2–4 carbon atom, straight/branched) amino group. In some of the compounds, the other nuclear positions of adamantane are also substituted with methyl, phenyl, halo, or hydroxyl groups. Adamantane derivatives substituted on the 2 position with an aminopropylidene group, analogous to amitriptyline or nortriptyline, and their corresponding reduction products are also described. It is interesting to note that these amines bear structural resemblance to the tricyclic antidepressants in respect of their nonplanar fused ring structure being replaced by the adamantane ring system. It is also possible that the pronounced lipophilic nature of the adamantane group may facilitate access of these amines into the brain and cerebrospinal fluid.[2]

Chemistry. 1-Adamantanealkanamines II and VI were obtained by procedures as represented in Scheme I.

(i) Reductive Amination of the Appropriate Ketones I (Method A). The preparation of these ketones was effected either by reacting an acid chloride with diethylethoxymagnesium malonate and subsequent hydrolysis and decarboxylation as described in our earlier paper[3] or by the reaction of an acid with MeLi. The latter procedure is preferred as it reduces the number of steps and also gives excellent yields.

(ii) Reduction of an Amide with $LiAlH_4$ (Method C). The amides were obtained by reacting an acid chloride III with the appropriate amine or, where a lengthening of the alkyl chain was intended, through an Arndt–Eistert synthesis, as in the case of V.

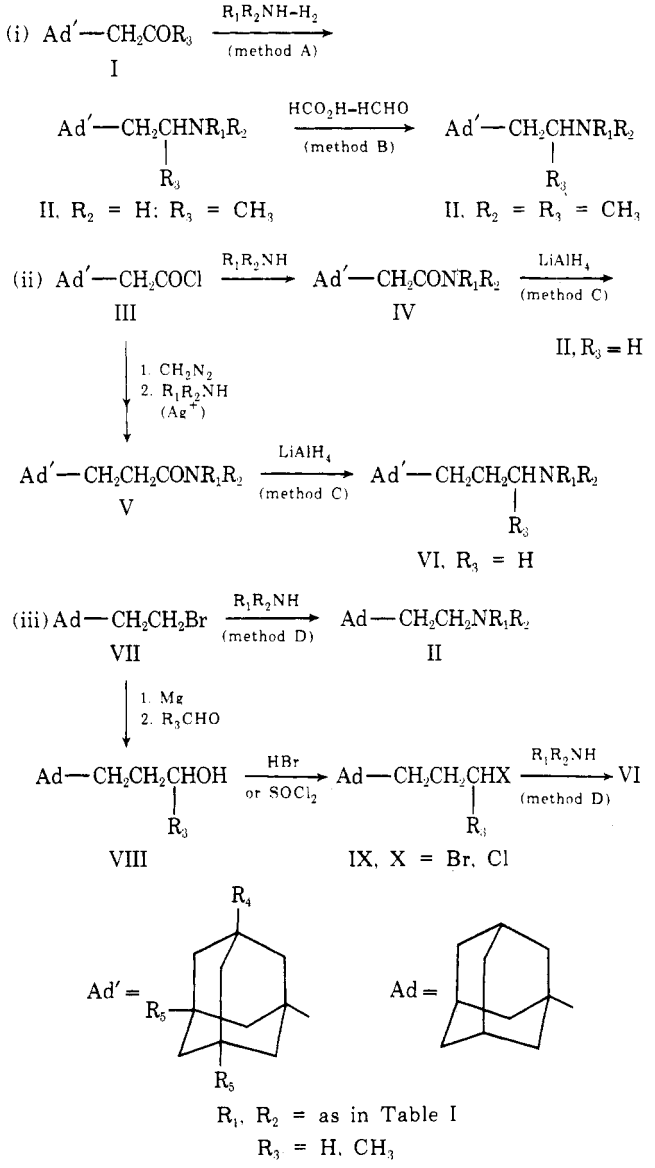
(iii) Reaction of an Alkyl Halide with an Appropriate Amine (Method D). The starting 1-(2-bromoethyl)adamantane VII was obtained according to the procedure described by Stetter, *et al.*[4] When the magnesium Grignard reagent of this bromide was allowed to react with formaldehyde, acetaldehyde, or ethylene oxide, the corresponding higher alkanols VIII were obtained. These alkanols on reaction with either HBr or $SOCl_2$ produced the corresponding alkyl halides IX.

N-Methyl-1-adamantanepropanamine was also prepared by an alternative route as follows. 1-Adamantanepropanonitrile was obtained in almost quantitative yield by reacting VII with NaCN in DMSO. This nitrile on reaction with dimethoxycarbonium fluoroborate[5] yielded the corresponding nitrilium salt, which on reduction with $NaBH_4$ produced the desired amine.

1,2-Disubstituted adamantane derivatives were obtained by using intramolecular free-radical reactions.[3,6] We described[3] the reaction of 1-adamantaneethanol with $Pb(OAc)_4$ to give adamantano[2,1-*b*]tetrahydrofuran (octahydro-4*H*-3a,7:5,9-dimethanocycloocta[*b*]furan). This

† Part VII of the series, Chemistry of Adamantane. For part VI, see ref 1.

Scheme I



reaction was successfully extended to 1-adamantanepropanol to give adamantano[2,1-*b*]tetrahydropyran X (octahydro-5*H*-4a,8:6,10-dimethano-2*H*-cyclooctа[*b*]pyran) in good yield (Scheme II). This ether was cleaved by BF_3 in Ac_2O and the resulting diacetate on alkaline hydrolysis produced the corresponding diol XI, which on reaction with HBr or $SOCl_2$ afforded the respective dihalide XII. Halogen substituted on the 2 position of adamantane has been found relatively resistant to the usual nucleophilic displacement or toward solvolysis under basic conditions.[3] Thus a selective displacement of the chain halogen in such dihalides was possible by reacting XII with an amine in anhydrous benzene or dioxane to obtain the haloamines XIII almost exclusively. However, when the reaction was carried out with an ethanolic solution of methanamine, some 2-hydroxy-*N*-methyl-1-adamantanepropanamine (**22**, Table I) was also obtained. We also found that during methylation of 2-bromo-*N*,α-dimethyl-1-adamantaneethanamine (**51**) with HCO_2H and HCHO, the nuclear bromine suffered a partial solvolysis to give some 2-hydroxy-*N*,α-dimethyl-1-adamantaneethanamine (**45**) along with the desired product. Displacement of this nuclear halogen in XIII by a phenyl group was effected by using $AlCl_3$ as a catalyst to produce the corresponding phenyl-substituted derivatives XIV. The appearance of the single proton nmr signal (δ 2.4-3.2) indicates that the phenyl ring is substituted on the 2 position and not on a tertiary position, as would be expected in the possible rearranged product.[1]

2-Chloro-*N*-methyl-1-adamantaneethanamine (**11**) was obtained by the application of the Hofmann-Loeffler-Freytag reaction on the *N*-chloroamine derived from *N*-methyl-1-adamantaneethanamine. This haloamine on reaction with benzene (excess) in the presence of $AlCl_3$ produced *N*-methyl-2-phenyl-1-adamantaneethanamine (**12**). Compound **52**, *N*,α-dimethyl-2-phenyl-1-adamantaneethanamine, was similarly prepared, which on catalytic reduction afforded the corresponding cyclohexyl derivative **56**.

The haloamine XIII (X = Cl; R_1 = H; R_2 = CH_3) was also prepared by an alternative route. 2-Chloro-1-adamantaneethanol[3] (XV) was oxidized with $KMnO_4$ to give the corresponding acid XVI. This was then converted to the homologous amine XIII as described in Scheme I (ii). Methylation of secondary amines with HCO_2H and HCHO (method B) was used to prepare some of the tertiary amines.

2-(3-Aminopropylidene)adamantane derivatives were prepared using the route as represented in Scheme III. The lithio derivative of 2-(3-bromopropoxy)tetrahydro-2*H*-pyran was allowed to react with adamantanone to give 2-[3-(tetrahydro-2*H*-pyran-2-yloxy)propyl]-2-adamantanol XVII. Dehydration of the latter in refluxing acetic anhy-

Scheme II

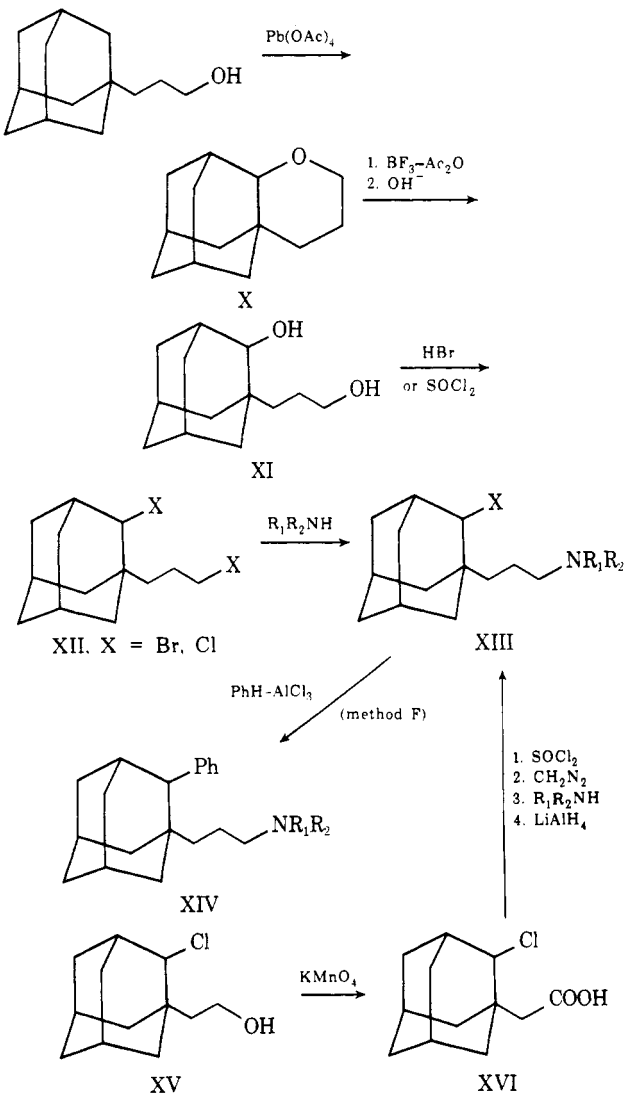
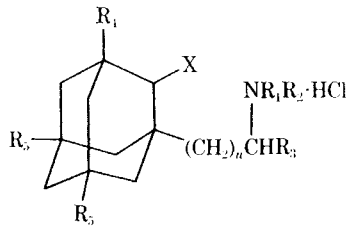


Table I



No.	n	NR_1R_2	R_3	R_4	R_5	X	Method	Yield, %	Mp, °C	Purifcn solvent	Formula[a]	Analyses[b]	LD_{50}[c] ip	LD_{50}[c] po	Reserpine hypothermia[d] sc	Reserpine hypothermia[d] po
1	1	NH_2	H	H	H	H	C	86	>350	EtOH–Et_2O	$C_{12}H_{21}N$	H, N; C[e]	NT	NT	0 (20)	NT
2	1	NHMe	H	H	H	H	C	44	275–277	EtOH–Et_2O	$C_{13}H_{23}N$	C, H, N, Cl	150	400	+ (20)	+ (20)
							D	48	277	EtOH–Et_2O						
3	1	NMe_2	H	H	H	H	C	66	259	EtOH–Et_2O	$C_{14}H_{25}N$	C, H, N, Cl	150	150	+ (20)	+ (20)
							D	36	259	EtOH–Et_2O						
4	1	NHEt	H	H	H	H	D	47	290	*i*-PrOH	$C_{14}H_{26}N \cdot H_2O$	C, H, N, Cl	150	300	0 (20)	NT
5	1	$NHCH_2CH_2OH$	H	H	H	H	D	34	286	$CHCl_3$–hexane	$C_{14}H_{25}NO$	C, H, N, Cl, O	150	200	0 (20)	NT
6	1	$NHCH_2CH_2Ph$	H	H	H	H	D	75	242–243	C_6H_6–hexane	$C_{20}H_{29}N$	C, H, N	NT	NT	0 (20)	NT
7	1	c-NC_4H_8	H	H	H	H	D	53	269	EtOH–*i*-Pr_2O	$C_{16}H_{27}N$	C, H, N	100	300	+ (10)	++ (20)
8	1	c-NC_5H_{10}	H	H	H	H	D	55	268	*i*-PrOH–hexane	$C_{17}H_{29}N$	C, H, N, Cl	150	200	+ (20)	NT
9	1	c-$N(CH_2CH_2)_2NMe$[f]	H	H	H	H	D	48	236	MeOH–Et_2O	$C_{17}H_{30}N_2$[f]	C, H, N, Cl	300	600	0 (20)	NT
10	1	$N(CH_2CH_2)_2O$	H	H	H	H	D	47	247	MeOH–C_6H_6	$C_{16}H_{27}NO$	C, H, N, Cl, O	300	600	0 (20)	NT
11	1	NHMe	H	H	H	Cl	E	52	260	*i*-PrOH–hexane	$C_{13}H_{22}ClN$	C, H, N	150	400	++ (10)	++ (20)
12	1	NHMe	H	H	H	Ph	F	35	175	*i*-PrOH–hexane	$C_{19}H_{27}N$	C, H, N	100	400	+ (10)	++ (20)
13	1	NMe_2	H	H	H	Ph	B	73	218–222	*i*-PrOH–hexane	$C_{20}H_{29}N$	C, H, N	300	800	++ (10)	++ (20)
14	1	NMe_2	H	$(CH_2)_2$-NMe_2	H	H	D	41	301	EtOH–Et_2O	$C_{16}H_{30}N_2$[f]	C, H, N, Cl	150	1600	0 (20)	NT
15	2	NH_2	H	H	H	H	C	48	291–294	*i*-PrOH–petrol	$C_{13}H_{23}N$	C, H, N, Cl	150	600	0 (20)	0 (40)
16	2	NHMe	H	H	H	H	D	79	238	C_6H_6–hexane	$C_{14}H_{25}N$	C, H, N	200	600	++ (10)	++ (20)
17	2	NMe_2	H	H	H	H	D	84	264–265	CH_2Cl_2–hexane	$C_{15}H_{27}N$	C, H, N, Cl	150	600	+ (10)	++ (40)
							C	55	260–262	*i*-PrOH–petrol						
							B	25	259–262	*i*-PrOH–petrol						
18	2	NHEt	H	H	H	H	D	25	267	CH_2Cl_2–C_6H_6–hexane	$C_{15}H_{27}N$	C, H, N, Cl	200	600	++ (10)	++ (20)
19	2	$NHCMe_3$	H	H	H	H	D	35	275	*i*-PrOH–hexane	$C_{17}H_{31}N$	C, H, N, Cl	150	600	0 (20)	NT
20	2	c-NC_4H_8	H	H	H	H	D	60	245	*i*-PrOH–hexane	$C_{17}H_{29}N$	C, H, N, Cl	150	200	++ (20)	0 (80)
21	2	c-NC_5H_{10}	H	H	H	H	D	75	274	*i*-PrOH–hexane	$C_{18}H_{31}N$	C, H, N, Cl	150	300	0 (20)	NT
22	2	NHMe	H	H	H	OH	*g*	21	177	$CHCl_3$–C_6H_6–hexane	$C_{14}H_{25}NO$	C, H, N, Cl, O	150	300	+ (20)	+ (80)
23	2	NHMe	H	H	H	Cl	D[*g*]	51	205–206	C_6H_6–hexane	$C_{14}H_{25}ClN$	C, H, N	NT	NT	++ (10)	++ (20)
							C	30	203	*i*-PrOH–petrol						
24	2	NMe_2	H	H	H	Br	*g*	63	213–214	C_6H_6–hexane	$C_{15}H_{26}BrN$	C, H, N	150	400	++ (20)	++ (20)
25	2	NHMe	H	H	H	Ph	F	22	120	C_6H_6–hexane	$C_{20}H_{29}N$	C, H, N	200	>1600	+ (20)	0 (20)
26	2	NMe_2	H	H	H	Ph	F	75	155	C_6H_6–hexane	$C_{21}H_{31}N$	C, H, N, Cl	150	800	++ (20)	+ (20)
27	1	NH_2	Me	H	H	H	A	64	291	EtOH–dioxane	$C_{13}H_{23}N$	C, H, N, Cl	600	NT	+ (20)	0 (80)
28	1	NHMe	Me	H	H	H	*h*						150	300	+ (10)	+ (40)
29	1	NMe_2	Me	H	H	H	B	52	215–217	*i*-PrOH–EtOAc	$C_{15}H_{27}N$	C, H, N	200	250	+ (20)	+ (80)
30	1	$NHCH(CH_3)_2$	Me	H	H	H	A	50	225–226	*i*-PrOH	$C_{16}H_{29}N$	C, H, N, Cl	150	400	+ (10)	+ (40)
31	1	$NMeCH(CH_3)_2$	Me	H	H	H	B	63	190–193	*i*-PrOH–petrol	$C_{17}H_{31}N$	C, H, N, Cl	100	300	+ (10)	0 (80)
32	1	$NHCH_2Ph$	Me	H	H	H	A	45	197–199	H_2O	$C_{20}H_{29}N$	C, H, N, Cl	150	600	0 (20)	NT

33	1	$NMeCH_2Ph$	Me	H	H	H	B	68	214–216	*i*-PrOH–petrol	$C_{21}H_{31}N$	C, H, N, Cl	300	600	0 (20)	NT
34	1	$NH(CH_2)_2OH$	Me	H	H	H	A	56	130–132	*i*-PrOH–petrol	$C_{15}H_{27}NO$	H, N; C[i]	150	600	+ (10)	0 (40)
35	1	$NMe(CH_2)_2OH$	Me	H	H	H	B	71	173–175	*i*-PrOH–petrol	$C_{16}H_{29}NO$	C, H, N	150	400	+ (20)	++ (80)
36	1	c-NC_4H_8	Me	H	H	H	A	54	214–215	*i*-PrOH–petrol	$C_{17}H_{29}N$	C, H, N, Cl	100	300	+ (10)	+ (80)
37	1	c-$N(CH_2CH_2)_2$-$N(CH_2)_2OH$[f]	Me	H	H	H	A	46	279–283	MeOH	$C_{19}H_{34}N_2O$[f]	C, H, N, Cl	150	400	0 (20)	NT
38	1	$NMeCH_2COC_6H_4Cl$	Me	H	H	H	*i*	74	100 dec	*i*-PrOH–petrol	$C_{22}H_{30}ClNO$	C, H, N, Cl, O	600	>1600	++ (10)	+ (20)
39	1	NHMe	Me	Me	Me	H	A	88	253–255	Dilute HCl	$C_{17}H_{31}N$	C, H, N, Cl	35	400	0 (20)	NT
40	1	NMe_2	Me	Me	Me	H	B	86	206–208	*i*-PrOH–petrol	$C_{18}H_{33}N$	C, H, N, Cl	150	300	+ (20)	0 (80)
41	1	NHMe	Me	Br	H	H	A	17	185–187	*i*-PrOH–petrol	$C_{14}H_{24}BrN$	C, H, N	150	400	0 (20)	NT
42	1	NHMe	Me	OH	H	H	A	37	201–203	EtOH–Et_2O	$C_{14}H_{25}NO$	C, H, N, Cl	100	600	0 (20)	NT
43	1	NHMe	Me	CH_3 | ($CH_2CHNHMe$)	H	H	A	76	314–316	EtOH	$C_{18}H_{34}N_2$[f]	C, H, N, Cl	200	600	0 (20)	NT
44	1	NMe_2	Me	CH_3 | (CH_2CHNMe_2)	H	H	B	58	268–271	*i*-PrOH–petrol	$C_{20}H_{38}N_2$[f]	C, H, N, Cl	75	1200	0 (20)	NT
45	1	NMe_2	Me	H	H	OH	B[a]	20	255–257	*i*-PrOH	$C_{15}H_{27}NO$	C, H, N, Cl	NT	NT	0 (20)	NT
46	1	NHMe	Me	H	H	Cl	*h*						85	250	+ (20)	+ (20)
47	1	NMe_2	Me	H	H	Cl	B	73	195–197	*i*-PrOH–EtOAc	$C_{15}H_{26}ClN$	C, H, N, Cl	100	175	+ (20)	+ (20)
48	1	$NHCH(CH_3)_2$	Me	H	H	Cl	E	83	188–191	*i*-PrOH–petrol	$C_{16}H_{28}ClN$	C, H, N, Cl	150	150	+ (20)	+ (40)
49	1	NHMe	Me	Me	Me	Cl	E	89	250–251	*i*-PrOH–Et_2O	$C_{17}H_{30}ClN$	C, H, N, Cl	100	400	+ (20)	0 (80)
50	1	NMe_2	Me	Me	Me	Cl	B	72	176–178	*i*-PrOH–petrol	$C_{18}H_{32}ClN$	C, H, N, Cl	150	400	+ (20)	0 (80)
51	1	NHMe	Me	H	H	Br	E	64	184–188	*i*-PrOH–petrol	$C_{14}H_{24}BrN$	C, H, N, Br, Cl	150	300	+ (10)	++ (40)
52	1	NHMe	Me	H	H	Ph	F	63	200	EtOH–Et_2O	$C_{20}H_{29}N$	C, H, N, Cl	75	250	+ (10)	+ (20)
53	1	NMe_2	Me	H	H	Ph	B	30	186–190	*i*-PrOH–EtOAc	$C_{21}H_{31}N$	C, H, N	NT	NT	+ (20)	0 (80)
54	1	NHMe	Me	Me	Me	Ph	F	42	234–237	EtOH–petrol	$C_{23}H_{35}N$	C, H, N, Cl	50	1200	0 (20)	0 (80)
55	1	NMe_2	Me	Me	Me	Ph	B	40	213–216	EtOH–EtOAc	$C_{24}H_{37}N$	C, H, N, Cl	NT	NT	+ (10)	0 (80)
56	1	NHMe	Me	H	H	c-C_6H_{11}	*g*	79	193–196	*i*-PrOH–petrol	$C_{20}H_{35}N$	C, H, N, Cl	25	>1600	++ (20)	+ (40)
57	1	NMe_2	Me	H	H	c-C_6H_{11}	B	50	214–216	*i*-PrOH–petrol	$C_{21}H_{37}N$	C, H, N, Cl	NT	NT	0 (20)	NT
58	3	NHMe	H	H	H	H	D	37	195	C_6H_6–hexane	$C_{15}H_{27}N$	C, H, N, Cl	75	800	++ (10)	++ (20)
59	3	NMe_2	H	H	H	H	D	41	230–231	*i*-PrOH–hexane	$C_{16}H_{29}N$	C, H, N	150	400	++ (10)	++ (40)
60	2	NHMe	Me	H	H	H	D	26	189–191	C_6H_6–hexane	$C_{15}H_{27}N$	C, H, N, Cl	75	400	0 (20)	NT
							A	31	188–190	*i*-PrOH–petrol						
61	2	NMe_2	Me	H	H	H	D	39	219	C_6H_6–hexane	$C_{16}H_{29}N$	C, H, N, Cl	75	400	+ (20)	++ (20)

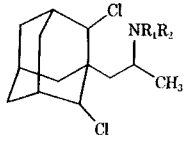
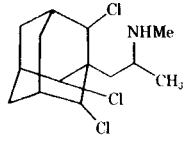
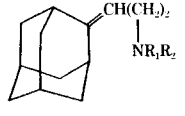
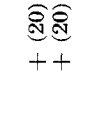
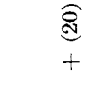
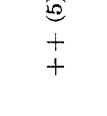
Structure		NR_1R_2										
62		NHMe	E[k]	65	204–205	*i*-PrOH–hexane	$C_{14}H_{23}Cl_2N$	C, H, N, Cl	150	300	+ (20)	++ (40)
63		NMe_2	B	48	216–218	*i*-PrOH–petrol	$C_{15}H_{25}Cl_2N$	C, H, N, Cl	NT	NT	+ (20)	+ (40)
64			E[l]	10	247–250	*i*-PrOH–petrol	$C_{14}H_{22}Cl_3N$	H, N; C,[m] Cl[m]	NT	NT	0 (20)	NT
65		NHMe	D	59	204–206	*i*-PrOH–EtOAc	$C_{14}H_{23}N$	C, H, N	150	200	+ (10)	0 (80)
66		NMe_2	D	52	238	*i*-PrOH–EtOAc	$C_{15}H_{25}N$	C, H, N	150	300	++ (20)	+ (40)

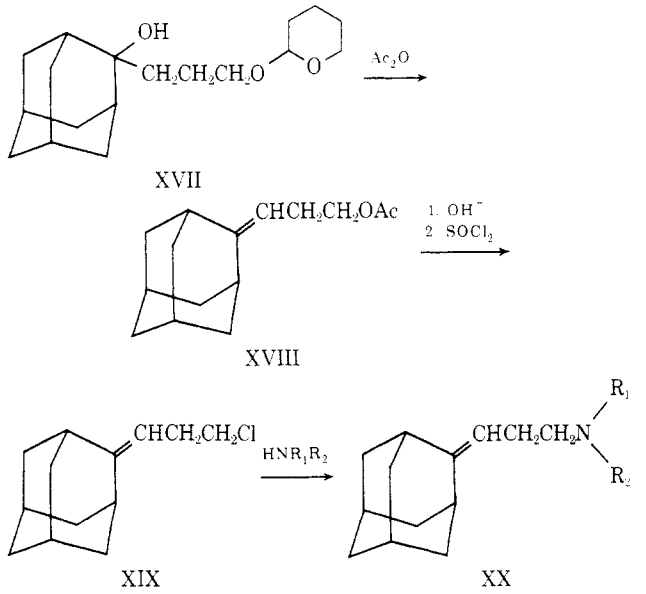
Table I (*continued*)

No.	n	Structure	NR_1R_2	Method	Yield, %	Mp, °C	Purifcn solvent	Formula[a]	Analyses[b]	LD_{50}[c] ip	LD_{50}[c] po	Reserpine hypothermia[d] sc	Reserpine hypothermia[d] po
67			NHMe	*g*	56	230–232	*i*-PrOH–EtOAc	$C_{14}H_{25}N$	C, H, N			+ (20)	+ + (40)
68			NMe_2	*g*	54	246	*i*-PrOH–EtOAc	$C_{15}H_{27}N$	Cl	150	400	+ (20)	+ (80)
69				*n*	86	220–222	*i*-PrOH–petrol	$C_{15}H_{27}NO$	C, H, N, Cl	300	400	+ (20)	+ (40)
70		 (nortriptyline hydrochloride)								85	325	+ + (5)	+ + (20)

[a] All compounds contain 1 mol of HCl unless otherwise stated. [b] Unless otherwise indicated, all analyses were within ±0.4% of the theoretical values. [c] Figures represent approximate LD_{50} (mg/kg) in mice; NT = not tested. [d] Symbols represent activity as follows: 0 = no effect; + = temperature index (TI) 5–10; + + = TI > 10; NT = not tested. Doses (mg/kg) are shown in parentheses. Temperature index is defined in Pharmacological Methods. [e] C: calcd, 66.72; found, 67.4. /2 mol of HCl. [f] See Experimental Section. [g] See ref 3. [h] Prepared by alkylation of **28** with *p*-chlorophenacyl bromide. [i] C: calcd, 65.78; found, 63.84. [k] Prepared from **46** by method E. [l] Prepared from **62** by method E. [m] C: calcd, 48.44; found, 49.34. Cl: calcd, 40.85; found, 39.61. The compound probably contained 15–20% of **51**. [n] Prepared by $LiAlH_4$ reduction of 1-(1-adamantyl)-3-(*N*,*N*-dimethylamino)-propan-1-one: F. N. Stepanov and R. A. Myrsina, *Zh. Org. Khim.*, **2**, 644 (1966). Petrol was petroleum spirit, bp 60–80°, and hexane was *n*-hexane.

dride gave 2-[3-(acetyloxy)propylidene]adamantane XVIII, which on alkaline hydrolysis and subsequent reaction with $SOCl_2$ yielded the corresponding 2-(3-chloropropylidene)adamantane XIX. This on reaction with the appropriate amine (method D) produced the desired amine XX, which on catalytic hydrogenation afforded the corresponding reduction products.

Scheme III



Results and Discussion

The compounds were tested for acute toxicity in mice. Potential antidepressant activity was assessed using the reversal of reserpine-induced hypothermia as an index.[7] The results of the acute toxicity and reserpine hypothermia tests are given in Table I, and for comparative purposes we have similarly tested nortriptyline hydrochloride (**70**). None of the adamantanealkanamines showed activity comparable to that of **70** by the subcutaneous route but by the oral route compounds **7**, **11–13**, **16**, **18**, **23**, **24**, **58**, and **61** were equally potent and their oral toxicity was similar or, in some cases, less than that of **70**. This would indicate good oral absorption for these compounds.

In the series of compounds shown in Table I in which n = 1 and R_3, R_4, and R_5 = H, optimum activity was obtained with Cl or Ph at the 2 position of adamantane as in compounds **11**, **12**, and **13**. When the length of the side chain was increased (n = 2 and R_3, R_4, and R_5 = H), good activity was seen with the secondary amines **16** and **18** and was retained with a halogen at the 2 position of adamantane (**23** and **24**). In this instance the 2-Ph analogs (**25** and **26**) showed slightly reduced activity. Compounds substituted at the 3 position of adamantane with Br or OH were inactive.

Compounds substituted with an α-Me at R_3, where n = 1, have a side chain analogous with that of amphetamine. Gross observation of the animals treated with these compounds did not reveal the characteristic stimulant effects of the amphetamines and activity against reserpine was generally low. The corresponding 2-substituted adamantanes **46**, **47**, **51**, and **52** appeared more active than the unsubstituted analogs **28** and **29**. Methyl substitution at R_4 and R_5 in the adamantane ring[8] as in compounds **39**, **40**, **49**, **50**, **54**, and **55** did not appear advantageous.

The n-butanamines (n = 3) **58** and **59** were both of interest showing similar activity to the analogous propanamines **16** and **17**. Adamantanepropanamine substituted with OH at the γ position (**69**) was only slightly active.

Adamantane derivatives **65**, **66**, **67**, and **68** substituted at the 2 position with side chains analogous to nortriptyline and amitriptyline showed only moderate activity. Multisubstitution with halogen on the adamantane ring, as in compounds **62**, **63**, and **64**, did not improve activity.

It is known[9] that reserpine-induced hypothermia can be reversed by pharmacological agents other than antidepressants, and this makes it necessary to test agents active on this test in other systems before concluding that the activity is due to an antidepressant action. It is generally accepted[10] that antidepressant drugs potentiate norepinephrine responses, probably by interfering with reuptake into storage vesicles in sympathetic nerves. They also block catecholamine release induced by indirectly acting sympathomimetics such as tyramine. We have studied some of the more active adamantanealkanamines *in vivo* on the cardiovascular system of the anaesthetized cat and *in vitro* on the rat isolated vas deferens preparation. Norepinephrine responses *in vivo* and *in vitro* are potentiated at low concentrations with only one of the adamantanealkanamines we have tested, and this compound **52** fails to block the pressor response to tyramine in the cat. The lack of activity in this respect should not preclude this compound being further investigated for antidepressant activity, as iprindole, which is clinically active as an antidepressant, is similarly without effect in blocking the peripheral effects of indirectly acting sympathomimetic amines.[11]

Potential anti-Parkinson activity of some of the relevant interesting compounds was assessed using the reversal of reserpine-induced catalepsy as an index.[12] The results of the reversal of reserpine-induced catalepsy in rats (Table II) show that several adamantane derivatives possess activity which is equivalent to or better than amantadine. In most of the cases, significant activity was only observed when the adamantane ring was substituted in the 2 position by halogen or phenyl groups. Compound **11** was found to be most active. The activity appears to diminish with the lengthening of the basic side chain.

Table II

Compd no.	Reversal of reserpine catalepsy[a] 20 mg/kg po	40 mg/kg po	Compd no.	Reversal of reserpine catalepsy[a] 20 mg/kg po	40 mg/kg po
2	NT	0	**52**	±	++
7	0	0	**53**	NT	0
11	±	+++	**56**	NT	0
12	0	++	**62**	+	++
13	0	++	**23**	0	±
28	NT	0	**58**	0	±
46	0	+	**61**	0	±
47	+	+	**67**	0	++
51	+	++	Amantadine	0	+

[a]Symbols represent activity as follows: 0 = no effect; ± = marginal effect; + = significant effect; ++ = marked effect; +++ = approaching complete reversal. NT = not tested.

Experimental Section

Melting points were determined on a Kofler block under microscopic magnification or in capillary tubes and are uncorrected. The structures of all compounds were supported by ir and nmr spectra measured with Perkin-Elmer 457 and Varian A-60A instruments, respectively. Where analyses are indicated only by symbols of the elements, the results obtained for these elements were within ±0.4% of the theoretical values unless otherwise stated.

1-(1-Adamantyl)-2-propanones (I). 1. 1-(3,5,7-Trimethyl-1-adamantyl)-2-propanone [bp 88–90° (0.7 mm). *Anal.* ($C_{16}H_{26}O$) C, H] and 1,1′-(1,3-adamantyl)bis-2-propanone [bp 139–142° (0.7 mm). *Anal.* ($C_{16}H_{24}O_2$) H; C: calcd, 77.38; found, 76.54] were prepared in yields of 62 and 66%, respectively, by the method previously described for 1-(1-adamantyl)-2-propanone.[3]

2. A solution of the adamantaneacetic acid in Et_2O was treated dropwise with 2.05 equiv of a 2 *M* solution of MeLi in Et_2O, causing evolution of gas. The mixture was heated under reflux for 15 min, then washed (saturated NH_4Cl, dilute Na_2CO_3, and H_2O), dried, and evaporated to give the ketones I as oils which were purified by distillation or, in some cases, used without purification.

Adamantanealkanamine Hydrochlorides II. Method A. The 1-(1-adamantyl)-2-propanones were reductively aminated as previously described for **28**[3] to give II (R_2 = H; R_3 = CH_3).

Method B. The secondary amines II (R_2 = H) (0.005 mol of free base) were dissolved in 90% HCO_2H (5 ml) and 40% HCHO (5 ml) and heated on a steam bath for 4 hr. The solutions were evaporated and the residues in dilute NaOH were extracted with Et_2O. The extracts were washed, dried, and evaporated to give the oily tertiary amines II (R_2 = R_3 = CH_3) which were converted to their hydrochlorides by treatment with HCl in Et_2O.

This procedure, when carried out on the 2-bromo compound **51**, gave a mixture from which the 2-hydroxy compound **45** was isolated by crystallization.

1-Adamantaneacetamides IV. A solution of 1-adamantaneacetyl chloride (5.85 g, 0.0275 mol) in Et_2O was added dropwise to a stirred saturated solution of $MeNH_2$ in Et_2O at 0° and further $MeNH_2$ gas was passed into the mixture. After the mixture was allowed to stand overnight, H_2O was added and the Et_2O layer was washed (dilute HCl, H_2O, dilute $NaHCO_3$, H_2O), dried (Na_2SO_4), and evaporated to give *N*-methyladamantane-1-acetamide (5.3 g, 93%). Recrystallization from petroleum spirit gave mp 116–118°. *Anal.* ($C_{13}H_{21}NO$) C, H, N. *N,N*-Dimethyladamantane-1-acetamide [mp 60–62°. *Anal.* ($C_{14}H_{23}NO$) C, H, N] was similarly prepared.

1-(2-Chloro-1-adamantyl)-3-diazo-2-propanone. Crude 2-chloro-1-adamantaneethanol[3] (12.5 g, 0.058 mol) was dissolved in Me_2CO (200 ml) and finely ground $KMnO_4$ (9.2 g, 0.058 mol) was added in small portions over 45 min causing gentle reflux. The mixture was stirred for a further 1 hr, the Me_2CO was evaporated and the residue was extracted with H_2O. Acidification of the H_2O solution, Et_2O extraction, evaporation, and crystallization from Me_2CO–petroleum spirit gave 2-chloro-1-adamantaneacetic acid (3.8 g), mp 147–150°. *Anal.* ($C_{12}H_{17}ClO_2$) C, H, Cl. Treatment of this acid with $SOCl_2$ gave the acid chloride which, without purification, was treated with CH_2N_2 as previously described[6] to give the diazo ketone as a yellow solid (3.2 g): ir (film) 2110 (CN_2) and 1635 cm^{-1} (C=O); used without further examination.

1-Adamantanepropanamides V. A mixture of 30% $MeNH_2$ solution (5 ml) and 10% $AgNO_3$ solution (2 ml) was added to a stirred solution of 1-(1-adamantyl)-3-diazo-2-propanone[6] (2 g, 0.0092 mol) in dioxane (10 ml) at 70°. When evolution of gas had ceased, further $MeNH_2$ solution (5 ml) was added and the mixture was heated to 90–100° for 2 hr. The mixture was allowed to stand overnight at room temperature and then filtered; the filtrate was evaporated to give *N*-methyladamantane-1-propanamide (1 g, 50%), mp 102–105°. *Anal.* ($C_{14}H_{23}NO$) C, H, N.

Adamantane-1-propanamide [mp 136–139°. *Anal.* ($C_{13}H_{21}NO$) C, H, N] and 2-chloro-*N*-methyladamantane-1-propanamide [mp 110–112°. *Anal.* ($C_{14}H_{22}ClNO$) C, H, Cl, N] were similarly prepared. *N,N*-Dimethyladamantane-1-propanamide was similarly prepared and used without further purification.

Adamantanealkanamine Hydrochlorides II (R_3 = H). Method C. The amides IV and V were reduced with $LiAlH_4$ (THF or dioxane) and worked up in the usual way.

1-(3-Chloropropyl)adamantane (IX, R_3 = H; X = Cl). $SOCl_2$ (2.5 ml) was added dropwise to a solution of 1-adamantanepropanol[13] (5.0 g, 0.026 mol) in pyridine (25 ml); the solution was heated on a steam bath for 30 min and was then poured onto ice. Extraction with Et_2O gave IX (R_3 = H; X = Cl) as a crude oil which was used without further purification.

1-(3-Bromobutyl)adamantane (IX, R_3 = CH_3; X = Br). A solution of 1-(2-bromoethyl)adamantane[4] (24.1 g, 0.1 mol) in THF (150 ml) was added over 45 min to Mg turnings (2.55 g). The mixture was stirred for 15 min and then cooled at <10° while a solution of MeCHO (11.5 ml) in THF (25 ml) was added. The mixture was stirred for a further 30 min, diluted with ice-cold 10% H_2SO_4, and extracted with $CHCl_3$. The extract was washed (dilute H_2SO_4, saturated $NaHCO_3$), dried ($MgSO_4$), and evapo-

rated to leave an oil which was purified by chromatography on a silica gel column (*n*-hexane–CH_2Cl_2) to give 1-adamantanebutan-3-ol (VIII, R_3 = CH_3): 16.2 g (78%); bp 97–98° (0.25 mm); mp 46–51°. *Anal.* ($C_{14}H_{24}O$) C, H. VIII (R_3 = CH_3) (10.5 g, 0.05 mol) was heated under gentle reflux with 48% HBr (25 ml) and concentrated H_2SO_4 (5 ml) for 2.5 hr. Extraction with $CHCl_3$ gave IX (R_3 = CH_3; X = Br) as an oil which was used without further purification.

1-(4-Bromobutyl)adamantane. 1-Adamantanebutan-4-ol [bp 115–118° (0.35 mm)] was prepared in a similar manner using ethylene oxide instead of MeCHO and was similarly converted to crude 1-(4-bromobutyl)adamantane.

1-Adamantanealkanamine Hydrochlorides II (R_3 = H) and VI. Method D. The 1-(haloalkyl)adamantane VII, IX, or XII was heated overnight with a solution of the appropriate amine in EtOH either under reflux or in a sealed vessel at 60–80° and the product was isolated in the usual way.

***N*-Methyl-1-adamantanepropanamine Hydrochloride (16).** A solution of 1-(2-bromoethyl)adamantane (95 g, 0.4 mol) in DMSO (750 ml) was added over 45 min to a stirred suspension of NaCN (19.5 g) in DMSO (165 ml) at 60–80°; the mixture was heated at 100–110° for 2 hr and then poured onto ice to precipitate 1-adamantanepropanonitrile (74.2 g, 99%). Sublimation at 90° (2 mm) gave the pure compound, mp 49–49.5°. *Anal.* ($C_{13}H_{19}N$) C, H, N. A solution of this nitrile (18.9 g, 0.1 mol) and dimethoxycarbonium fluoroborate[5] (33.2 g, 0.2 mol) in CH_2Cl_2 (100 ml) was heated under reflux (N_2 cover) for 18 hr. EtOH (10 ml) was added and the CH_2Cl_2 was removed under vacuum. The residue was dissolved in dry *i*-PrOH, $NaBH_4$ (20 g) was added in portions, and the mixture was stirred for 3 hr at 0° and worked up in the usual manner to give a crude HCl salt which was purified by chromatography on a neutral Al_2O_3 column (CH_2Cl_2–MeOH) to give compound **16** (6.7 g, 34%).

Octahydro-5*H*-4a,8:6,10-dimethano-2*H*-cycloocta[*b*]pyran (X). 1-Adamantanepropanol[13] (VIII, R_3 = H), mp 44°, prepared as described above for VIII (R_3 = CH_3), was oxidized with $Pb(OAc)_4$ in PhH as previously described[3] for the ethanol to yield X, bp 63–64° (0.05 mm). *Anal.* ($C_{13}H_{20}O$) C, H.

2-Hydroxy-1-adamantanepropanol (XI). The cyclic ether X was cleaved with BF_3·Et_2O in Ac_2O as previously described[3] for the furan derivative to give XI, mp 105–106° (from *i*-Pr_2O). *Anal.* ($C_{13}H_{22}O_2$) C, H, O.

2-Bromo-*N,N*-dimethyl-1-adamantanepropanamine Hydrochloride (24). The diol XI (5.0 g) was heated under gentle reflux with 60% HBr (15 ml) and concentrated H_2SO_4 (3.5 ml) for 2.5 hr. The solution was diluted with H_2O and extracted with $CHCl_3$; the extract was washed ($NaHCO_3$), dried, and evaporated to give crude 2-bromo-1-(3-bromopropyl)adamantane (8.0 g, 100%) (XII, X = Br). This dibromo compound was stirred with $CaCO_3$ (4 g) in dioxane (50 ml) containing Me_2NH (7 ml) under a Dry Ice condenser for 20 hr. Usual work-up gave compound **24.**

2-Chloro-*N*-methyl-1-adamantanepropanamine Hydrochloride (23) and 2-Hydroxy-*N*-methyl-1-adamantanepropanamine Hydrochloride (22). The diol XI (9.4 g) was heated for 10 min with $SOCl_2$ (4 ml) and pyridine (2 drops) in refluxing PhH (100 ml). The solvent was evaporated and a solution of the residue in CH_2Cl_2 was passed down a silica column to give crude 2-chloro-1-(3-chloropropyl)adamantane (XII, X = Cl) (9.2 g, 83%). This crude dichloro compound was allowed to react with $MeNH_2$ (method D) to give a crude HCl salt which on chromatography on a Florisil column was separated into compound **23** (1.2 g, 12%) and compound **22** (0.52 g, 6%).

2-Halo-1-adamantaneethanamine Hydrochlorides. Method E. These compounds were prepared by the method previously described[3] for compound **46.**

2-Phenyl-1-adamantanealkanamine Hydrochlorides. Method F. A solution of compound **11** free base (7.2 g, 0.032 mol) in dry PhH (50 ml) was added dropwise to a stirred suspension of $AlCl_3$ (6.3 g) in dry PhH (150 ml) at reflux under N_2. The mixture was heated under reflux for 2 hr and then poured onto a mixture of ice and dilute HCl (200 ml). Normal work-up gave an oil which was distilled, bp 122–130° (0.08 mm), to give compound **12** (free base) (2.97 g, 35%). This was converted to the HCl salt, recrystallized from *i*-PrOH–*n*-hexane: compound **12** (2.50 g) mp 175°; ir (KBr) 750, 730, and 700 cm^{-1}; nmr ($CDCl_3$) δ 2.77 ppm (br s, CHPh). *Anal.* ($C_{19}H_{28}ClN$) C, H, N. The dechlorinated compound **2** was also obtained from the distillation as the free base, bp 59–62° (0.08 mm) (0.64 g, 10%). Compounds **13, 25, 26, 52,** and **54** were similarly prepared.

2-Cyclohexyl-*N*,α-dimethyl-1-adamantaneethanamine Hydrochloride (56). A solution of compound **52** free base (1.4 g, 0.0047 mol) in AcOH (50 ml) was hydrogenated over PtO_2 (0.3 g of Adams catalyst). The catalyst was removed by filtration and usual work-up gave the desired compound.

2-[3-(Tetrahydro-2*H*-pyran-2-yloxy)propyl]-2-adamantanol (XVII). A solution of 2-(3-bromopropoxy)tetrahydro-2*H*-pyran[14] (98.0 g, 0.44 mol) in dry Et_2O (240 ml) was added dropwise over 1 hr to a suspension of lithium shavings (5.38 g, 0.78 g-atom) in dry Et_2O (400 ml), stirred at −15° under nitrogen. The mixture was stirred for a further 1 hr and then cooled to −30° while adamantanone (31.6 g, 0.21 mol) in Et_2O (320 ml) was added over 0.5 hr. Stirring at −30° was continued for a further 0.5 hr; then the temperature was allowed to rise to −10°. H_2O (200 ml) was added and the mixture stirred for a short while. The organic phase was separated, washed with H_2O, and dried ($MgSO_4$). Removal of Et_2O *in vacuo* gave an oil (100.5 g). Chromatography on 1200 g of basic alumina, using PhH–petroleum spirit (75:25) to develop the column and PhH–EtOAc (95:5) as eluent, afforded 46.9 g (76%) of a clear oil, sufficiently pure for the next stage.

2-(3-Acetyloxypropylidene)adamantane. 2-[3-(Tetrahydro-2*H*-pyran-2-yloxy)propyl]-2-adamantanol (16.8 g, 0.57 mol) was heated under reflux in Ac_2O (170 ml) for 4 days. Evaporation *in vacuo* and distillation of the residue afforded XVIII as a clear oil: yield 9.5 g (71%); bp 94–101° (0.4 mm).

2-(3-Chloropropylidene)adamantane (XIX). Compound XVIII (29.6 g, 0.154 mol) was hydrolyzed by heating under reflux with KOH (17.1 g) in a mixture of EtOH (250 ml) and H_2O (62 ml). After 1 hr, EtOH was removed *in vacuo* and the residue extracted with Et_2O. The extract was washed (H_2O), dried ($MgSO_4$), and evaporated to give a brown oil, which gave pure 2-(3-hydroxypropylidene)adamantane on distillation: yield 20.6 g (85%); bp 94–96° (0.2 mm).

A solution of $SOCl_2$ (8.9 ml, 0.122 mol) in PhH (100 ml) was added to this alcohol (19.6 g, 0.102 mol) in PhH (100 ml) and the mixture was heated on a boiling H_2O bath for 10 min. Evaporation afforded an oil which was eluted from a 25-cm column of neutral alumina with petroleum spirit. Removal of solvent *in vacuo* afforded pure XIX as a clear oil: yield 17.1 g (80%).

***N*-Methyl-2-adamantanepropanamine Hydrochloride (67).** A solution of compound **65** (2.2 g) in EtOH (100 ml) was hydrogenated over Pt (0.1 g of Adams catalyst). The catalyst was removed by filtration and the filtrate was evaporated to give a white solid which was recrystallized from EtOAc-*i*-PrOH to give **67.** ***N,N*-Dimethyl-2-adamantanepropanamine hydrochloride (68)** was similarly prepared from **66.**

Pharmacological Methods. 1. Acute Toxicity. The compounds were formulated in 0.9% wt/v NaCl solution or as suspensions in 0.5% wt/v sodium carboxymethylcellulose. They were administered to pairs of albino mice (CFW) weighing 19–21 g in doses usually ranging from 100 to 1600 mg/kg orally and 50–800 mg/kg intraperitoneally and observed over 48 hr for mortalities and other gross behavioral changes. LD_{50} values were approximated from the results. In most cases deaths appeared to have been caused by clonic convulsions accompanied by marked central depression.

2. Reserpine-Induced Hypothermia. Groups of five mice (CFW) weighing 19–21 g were placed individually in cages (6 × 4 in.) and injected with 4 mg/kg of reserpine subcutaneously in a volume of 0.2 ml. The reserpine was prepared as an injection solution[15] and diluted with distilled H_2O prior to use; 2 hr after the reserpine injection, the rectal temperature of each mouse was measured with a thermocouple (Sierex, Type RM6). Immediately following this, drugs were dosed to the groups of mice at 10 and 20 mg/kg subcutaneously and further temperature recordings were made at 15-min intervals for up to 1.5 hr. Usually, two compounds (four groups) were tested in each experiment and a group of control mice were dosed with saline by the same route. Compounds active subcutaneously were tested orally at 20, 40, and 80 mg/kg.

In order to simplify the recording of results, a temperature index assessment[16] has been used. Taking as a base the mean initial temperature for each group, the mean temperature changes from this figure at 15, 30, 45, 60, 75, 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 −8 to −16, while drugs were considered active if the TI was greater than five units hyperthermic from the control results. If the control group TI was less than −8 or greater than −16, the experiment was repeated.

3. Reserpine-Induced Catalepsy. The rats (female Wistar), weighing 180–200 g, were injected subcutaneously with 5 mg/kg of reserpine solution[15] on the evening prior to the test. Later (17 hr)

they were tested for catalepsy using the following methods. (i) One hind leg was placed on a 3-cm high cork. (ii) One hind leg was placed on a 9-cm high cork. (iii) Rats were placed with their feet on parallel bars. (iv) Rats were placed with their feet on a vertical grid (⅜ in. mesh). The rats were considered cataleptic if no movement occurred within about 20 sec and each rat was given a score of 2 on each test. If a rat moved immediately after being placed on an object, as mentioned above, but then remained immobile, a score of 1 was given. Rats showing a high degree of catalepsy (score 7 or 8) were split into groups of four and each group dosed orally with the compounds, using a dose volume of 1 ml per rat. The rats were retested for catalepsy at intervals over the following 5.5 hr. The degree of reversal of the catalepsy induced by the compounds was assessed from the time course of the catalepsy over the 5.5-hr period. Amantadine was also tested in a similar manner for comparative purposes. The results are recorded in Table II.

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Synthesis and Structure–Activity Relationships of a Series of Antibacterially Active 5-(5-Nitro-2-furfurylidene)thiazolones, 5-(5-Nitro-2-furylpropenylidene)thiazolones, and 6-(5-Nitro-2-furyl)-4*H*-1,3-thiazinones

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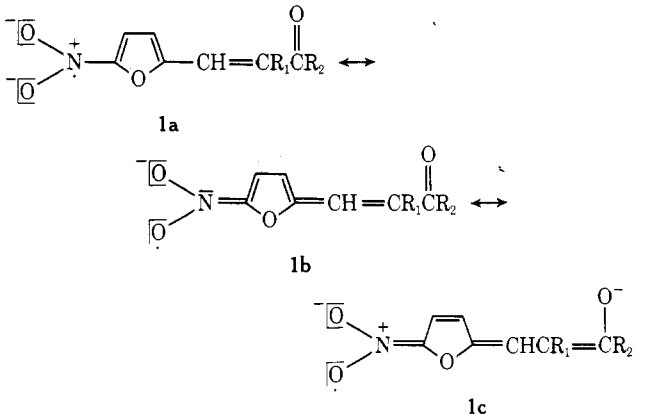
A series of 5-(5-nitro-2-furfurylidene)thiazolones, 5-(5-nitro-2-furylpropenylidene)thiazolones, and 6-(5-nitro-2-furyl)-4*H*-1,3-thiazinones was synthesized and their antibacterial activity against *Staph. aureus*, *β-haem. streptococcus*, *E. coli*, *K. aerogenes*, and *P. vulgaris* was determined. Many of the new nitrofurans showed a very high activity against all five bacteria *in vitro* and were up to 60 times as active as nitrofurantoin. The new nitrofurans were inactive in *in vivo* chemotherapeutic tests with *Sal. typhimurium* and *Sal. gallinarum*. Structure-activity studies showed that the 2-substituent may increase the antibacterial activity of a 5-nitrofuran compound by facilitating the reduction of the nitro group. Bulky substituents in the 2 position adversely affect the activity against the gram-negative bacteria, probably by sterically inhibiting the penetration of the nitrofuran into the bacteria.

5-Nitrofurans substituted at the 2 position with a wide variety of substituents are active against bacteria.[1,2] The nitro group is essential for the activity, whereas the influence of the 2-substituent on the activity is not completely understood. Nitrofurans are shown to interfere with several reductive enzyme systems in the bacteria[1,3] and there may be a correlation between the reduction potential of the nitro group and the antimicrobial activity. Sasaki[4] studied the polarographic half-wave potential for a series of nitrofurans and found that the antibacterial activity increased when the reduction potential became less negative.

The inductive and resonance effects of a substituent in the 2 position influence the half-wave potential of the nitro group. Nitrofurans with a conjugated carbonyl group in the 2 position should be easily reduced since the radical anion **1**, formed during the initial reduction step, can be stabilized by conjugation[5] (**1a–c**, Scheme I).

In our search for nitrofurans with high antibacterial activity a series of nitrofurans with a conjugated carbonyl in the 2 position has been synthesized and examined for antibacterial activity (Table I). The relationship between antibacterial activity, half-wave potentials, partition coefficients, and steric effect has been studied.

Scheme I



1a

1b

1c

Chemical Results. I. 5-(5-Nitro-2-furfurylidene)- and 5-(5-Nitro-2-furylpropenylidene)thiazolin-4-ones (2–5). (a) Synthesis. The nitrofurans in series 2–4 (Table I)