hydrochloride which analyzed satisfactorily. The benzaldehyde hydrazone **19** was made in 50% AcOH at 50–60° and the formamido derivative **20** was prepd by refluxing the crude **18** with 97% HCO_2H for 0.5 hr. Excess HCO_2H was removed *in vacuo*, the residue was basified with cold dil NaOH soln, and the product was removed by filtration and purified by recrystn.

7-Chloro-4-(4-amino-1-piperazinylamino)quinoline (21) and 1,4-Bis(7-chloro-4-quinolylamino)piperazine (22).—A mixt of 4,7-dichloroquinoline (15.0 g, 0.075 mole), 1,4-diaminopiperazine dihydrate (30.4 g, 0.2 mole), 60 ml of ethoxyethanol, and a cryst of KI was refluxed overnight. The solvent was removed under reduced pressure, the residue was basified with NaOH soln, and the solid was collected by filtration and washed with H_2O. The solid was taken up in hot EtOH and filtered. The filtrate was evapd to dryness and the residue was recrystd.

The solid insol in EtOH (**22**) was crystd from AcOH, as it happened to be practically insol in all other solvents. The crystd product retained some AcOH which was difficult to remove. The anal. sample was dried at 110° under high vacuum for 24 hr.

7-Chloro-4-(4-formamido-1-piperazinylamino)quinoline (23).—A mixt of **21** (5.56 g, 0.02 mole), 100 ml of HCO_2Et, and 20 ml of 99% HCO_2H was refluxed for 4 hr. Excess HCO_2Et and HCO_2H were removed under reduced pressure (bath temp not exceeding 50°), the residue was treated with dil NaOH, and the white solid was collected by filtration and purified by crystn.

7-Chloro-4-(4-benzylideno-1-piperazinylamino)quinoline (24).—A mixt of **21** (5.56 g, 0.02 mole) and PhCHO (3.2 g, 0.03 mole) in 50 ml of 50% AcOH was warmed on a steam bath for 0.5 hr. The solvent was removed under reduced pressure and the residue was treated with dil K_2CO_3 soln. The aq layer was decanted. The semisolid mass, when triturated with Et_2O, gave a fine powder which was collected by filtration and crystd.

7-Chloro-4-(4-methylamino-1-piperazinylamino)quinoline (25).—**23** (1 g) was reduced with 1.0 g of LAH in 300 ml of anhyd Et_2O over a period of 18 hr. The color of the mixt turned greenish. The mixt was then refluxed for 5 hr more, decompd with satd Na_2SO_4 soln, and filtered and the filtrate, on evapn, gave 150 mg of cryst product which was purified by crystn.

7-Chloro-4-(4-benzoylamino-1-piperizinylamino)quinoline (26) was prepd in 52.7% yield from the reaction of **23** with BzCl using the usual Schotten–Baumann reaction condns.

***N*-Acetyl-*N'*-methyl-*N'*-[3-methyl-3-(7-chloro-4-quinolylamino)propyl]hydrazine (6).**—Compd **5** (3.0 g) was dissolved in 30 ml of Ac_2O at room temp and the soln was warmed at 60° for 5 min. Excess Ac_2O was removed under reduced pressure, keeping the bath temp below 60°. On addn of H_2O to the residue a clear soln was obtained. This was basified with cold NaOH soln and the product was extd with Et_2O. The ext was dried (K_2CO_3), filtered, and concd until crystn started.

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Antiviral Agents. 2.[1] Structure–Activity Relationships of Compounds Related to 1-Adamantanamine

PAUL E. ALDRICH, * EDWARD C. HERMANN, WALTER E. MEIER, MARVIN PAULSHOCK, WILLIAM W. PRICHARD, JACK A. SNYDER, AND JOHN C. WATTS

The Industrial Biochemicals and Central Research Departments, Experimental Station, E. I. du Pont de Nemours & Co., Wilmington, Delaware

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The antiviral activity toward influenza A S-14 (swine) of a number of compounds related to 1-adamantanamines has been determined. Among these compounds are N- and C-alkylated 1-adamantanamines, 1-adamantanemethylamines, and homoadamantanamines.

Extensive laboratory studies[2,3] and clinical reports[3,4] have established the prophylactic effect of 1-adamantanamine·HCl (amantadine·HCl) (**1**) toward influenza A virus strains. More recently, clinical investigators have found a therapeutic effect with amantadine·HCl[5,6] and with rimantadine·HCl[6] (α-methyl-1-adamantanemethylamine·HCl, **58**) in patients with naturally occurring influenza A_2 respiratory illness. Inhibition of rubella,[7] Rous sarcoma,[8,9] and Esh sarcoma viruses has also been reported. Amantadine·HCl more recently has been demonstrated to benefit patients suffering from Parkinson's disease.[10] Meanwhile, others[11] have disclosed results from drugs that include the adamantane moiety.

No systematic study of the effect of structural variations of 1-adamantanamine upon antiviral activity has

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(9) A. M. Wallbank, R. E. Matter, and N. G. Klinikowski, *Science*, **152**, 1760 (1966).

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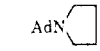
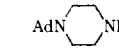
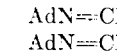
(11) (a) K. Gerzon, D. J. Tobias, Sr., R. E. Holmes, R. E. Rathburn, and R. W. Kattan, *J. Med. Chem.*, **10**, 603 (1967); (b) K. Gerzon, E. V. Krumkolns, R. L. Brindle, F. J. Marshall, and M. Root, *ibid.*, **6**, 760 (1963); (c) R. T. Rapola, R. J. Kraay, and K. Gerzon, *ibid.*, **8**, 580 (1965); (d) K. Gerzon and D. Kau, *ibid.*, **10**, 189 (1967).

TABLE I

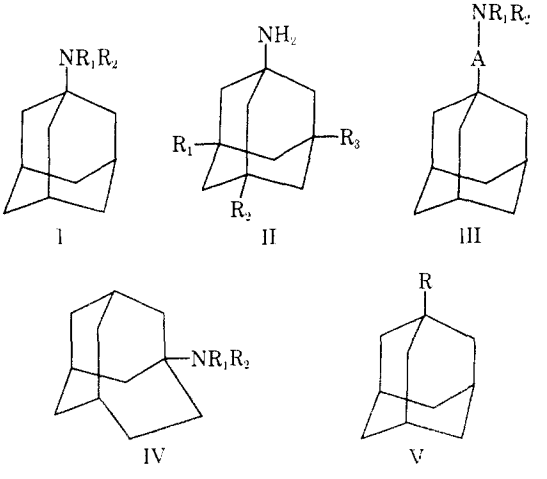
No.	Structure	AVI$_{50}$,[a] mg/kg	Formula	Analysis	Mp, °C	Reference or method of prep[b]
1	AdNH$_2$·HCl	4.6	$C_{10}H_{17}N$·HCl		367 dec	*c*
2	AdNHCH$_3$·HCl	3.3	$C_{11}H_{19}N$·HCl	C, H, N	250–251	B
3	AdNHEt·HCl	3.7	$C_{12}H_{21}N$·HCl	C, H, N, Cl	319–324 dec	C[d]
4	AdNH-*n*-Pr·HCl	8.0	$C_{13}H_{23}N$·HCl	C, H	342 dec	C[d]
5	AdNHCH(CH$_3$)$_2$·HCl	6.1	$C_{13}H_{23}N$·HCl	C, H, N	289	B
6	AdNH-*n*-Bu·HCl	16	$C_{14}H_{25}N$·HCl	C, H, N	293–295	C[d]
7	AdNHCH$_2$CH(CH$_3$)$_2$·HCl	17	$C_{14}H_{25}N$·HCl	C, H	325	B
8	AdNHCH(CH$_3$)Et·HCl	13	$C_{14}H_{25}N$·HCl	C, H, N	286–288	B
9	AdNH(CH$_2$)$_5$CH$_3$·HCl	>32[e]	$C_{16}H_{29}N$·HCl	C, H[f]	281	C
10	AdNH(CH$_2$)$_{11}$CH$_3$·HCl	>200[e]	$C_{22}H_{41}N$·HCl	C, H[f]	202	C[d]
11	AdNHCH$_2$CH=CH$_2$·HCl	3.4	$C_{13}H_{21}N$·HCl	C, H	325–328	A
12	AdNHCH$_2$C≡CH·HCl	12	$C_{13}H_{19}N$·HCl	C, H, N[f]	264–266	A
13	AdNHCH$_2$CH$_2$OH	26	$C_{12}H_{21}NO$·0.5H$_2$O	C, H, N[f]	99[g]	
14	AdNH(CH$_2$)$_3$OH·HCl	36	$C_{13}H_{23}NO$·HCl	C, H, N	218–211	A
15	AdNH(CH$_2$)$_2$NH$_2$·2HCl	>100[e]	$C_{12}H_{22}N_2$·2HCl	C, H, N	294–296	
16	AdNHCH$_2$CH$_2$COOCH$_3$·HCl	200[e]	$C_{14}H_{23}NO_2$·HCl	C, H, N	236 dec	A
17	AdNHCH$_2$C$_3$H$_5$·HCl	25	$C_{14}H_{23}N$·HCl	C, H, N	309–311	C[d]
18	AdNHC$_6$H$_{11}$·HCl	>32[e]	$C_{16}H_{27}N$·HCl	C, H, N	322	B
19	AdNHC$_6$H$_5$·HCl	>200[e]	$C_{16}H_{21}N$·HCl	C, H, N	279–280 dec	
20	AdNHCH$_2$C$_6$H$_5$	>200[e]	$C_{17}H_{23}N$	C, H	*h*	
21	AdNHCH$_2$CH$_2$C$_6$H$_5$·HCl	>18[e]	$C_{18}H_{25}N$·HCl	C, N[i]	233–236	B
22	AdNHCHC$_6$H$_5$·HCl	>200[e]	$C_{23}H_{27}N$·HCl	H, N[j]	253–255	A
23	AdNHBr·HBr	8.7	$C_{10}H_{16}NBr$·HBr	C, H, N, Br	217	
24	AdNHOH·HCl	48	$C_{10}H_{17}NO$·HCl	C, H, Cl	192–195	
25	AdN(CH$_3$)$_2$O	80	$C_{12}H_{23}NO$[k]	*l*	130–132	
26	AdN(CH$_3$)$_2$·HCl	4.8	$C_{12}H_{21}N$·HCl·0.33H$_2$O	C, H, N	250 (subl)[k]	
27	AdN(C$_2$H$_5$)$_2$·HCl	2.9	$C_{14}H_{25}N$·HCl	C, H[f]	248 dec	C[d]
28	AdN-*n*-Pr$_2$·HCl	13	$C_{16}H_{29}N$·HCl	C, H, N	215–218	
29	AdN(CH$_3$)CH$_2$CH=CH$_2$·HCl	6.3	$C_{14}H_{23}N$·HCl	C, H, N	186–189	A
30	AdN(CH$_2$CH=CH$_2$)$_2$·HCl	8.6	$C_{16}H_{25}N$·HCl	C, H	385 (subl)	A
31	AdN(CH$_3$)CH$_2$CH$_2$OH·HCl	26	$C_{13}H_{23}NO$·HCl	C, H, N	215–217	
32	AdN(CH$_2$CH$_2$OH)$_2$	>200[e]	$C_{14}H_{25}NO_2$	C, H, N	115.4–116.4	
33	AdN(CH$_3$)CH$_2$CH$_2$NH$_2$·HCl	61	$C_{13}H_{24}N_2$·HCl	C, H, N	190–193	
34	AdN(CH$_3$)CH$_2$CH$_2$Cl·HCl	19	$C_{13}H_{22}ClN$·HCl	C, H, Cl	198	
35	AdN(CH$_2$CH$_2$Cl)$_2$·HCl	>200[e]	$C_{14}H_{23}NCl_2$·HCl	C, H, Cl	226–228 dec	
36		>200[e]	$C_{12}H_{15}N$	C, H, N	*m*	
37		11	$C_{14}H_{23}N$·HCl·0.25H$_2$O	C, H, N	274–279	C[d]
38		>56[e]	$C_{14}H_{24}N_2$·2HCl·H$_2$O	C, H, Cl, N	309–311 dec	B
39	AdN=CH$_2$	17	$C_{11}H_{17}N$	C, H, N	125–127	
40	AdN=CHC$_6$H$_5$	5.3	$C_{17}H_{21}N$	C, H	58.5–60.0	
41	AdN(CH$_3$)$_3$ClO$_4$	41	$C_{13}H_{24}ClNO_4$	C, H	288–290 dec	

[a] See text for definition. [b] See Experimental Section. [c] Reported: mp >360° (H. Stetter, J. Mayer, M. Schwarz, and K. Wulff, *Chem. Ber.*, **93**, 226 (1960)), 320° (E. V. Krumkalns and W. Pfeiffer, *J. Med. Chem.*, 11, 1103 (1968)). [d] Prepd from the appropriate carboxamide of 1-AdNH$_2$ in the following yields: **4**, 53; **6**, 24; **9**, 51; **10**, 69; **17**, 31; **27**, 33; **3**, prepd from AdNHCOOCH$_3$ (H. Stetter, J. Moyer, M. Schwarz, and K. Wulff, *Chem. Ber.*, **93**, 226 (1960)), 69% yield; **37**, prepd for **91**, 54%. [e] Highest dose level tested. [f] Anal. of free base. [g] Reported, mp 110° (N. V. Philips' Gloeilampenfabrieken, Netherlands Application 6,410,363; *Chem. Abstr.*, **65**, 3769*e* (1966)). [h] Bp 91° (0.13 mm). [i] H: calcd, 8.98; found, 8.43. [j] C: calcd, 78.05; found, 77.47. [k] Sealed capillary. [l] Isolated as a hydrate; see Experimental Section. [m] Bp 60.5° (0.09 mm).

been published.[12] This paper reports the effect of such variations on inhibition of influenza A S-15 (swine) in mice.

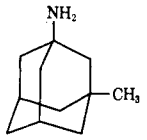
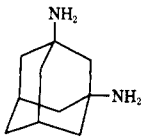
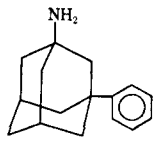
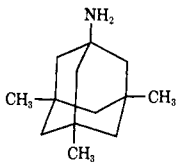
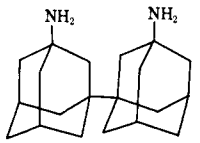
Structure–Activity Relationships.—Structural variations of **1** are classified for purposes of discussion into five types as illustrated by structures I–V.

Variations in I (Table I).—The simplest variations of **1** from the preparative viewpoint were *N*-mono- and dialkyl derivatives. Examples of these products and



(12) The antiviral effects have been published of *N*-(1-adamantyl)urea [N. V. Phillips' Gloeilampenfabrieken, Netherlands Application 6,408,765, Feb 1, 1966], adamantyloxycarboxylic acids [J. R. Geigy A.-G., Netherlands Application 6,515,007, March 7, 1966], 2-aminoadamantane [George W. Smith, U. S. Patent 3,257,456, June 21, 1966], 1-hydrazinoadamantane [CIBA, Ltd., French Patent 1,491,581, Aug 11, 1967], and 1-adamantylguanidines [H. W. Geluk, J. Schut, and J. L. M. A. Schlatmann, *J. Med. Chem.*, **12**, 712 (1969)].

TABLE II

No.	Structure		AVI_{50},[a] mg/kg	Formula	Mp, °C	Reference or method of prepn[b]
42		·HCl	8.9	$C_{11}H_{24}N \cdot HCl$	340 (subl)	*c*
43		·HCl	>200[d]	$C_{10}H_{18}N_2 \cdot 2HCl$	315	*e*
44		·HCl	>200[d]	$C_{16}H_{21}N \cdot HCl$	325–326	*f*
45			>200[d]	$C_{13}H_{23}N \cdot HCl$	360 (subl)	*g*
46		·2HCl	>200[d]	$C_{20}H_{32}N_2 \cdot 2HCl$[h]	420	

[a] See text for definition. [b] See Experimental Section. [c] L. Gerzon, E. V. Krumkolns, R. L. Brindle, F. J. Marshall, and M. Root, *J. Med. Chem.*, **6**, 760 (1963). [d] Highest dose level tested. [e] H. Stetter and C. Wulff, *Chem. Ber.*, **93**, 1366 (1960); G. W. Smith and H. D. Williams, *J. Org. Chem.*, **26**, 2207 (1961). [f] F. N. Stepanov and Yu I Sebrodol'skii, *Sint. Prir. Soedin., Ikh Analogov Fragmentov*, 97 (1965); *Chem. Abstr.*, **65**, 627*f* (1965). [g] K. Gerzon, D. J. Tobias, Sr., R. E. Holmes, R. E. Rathburn, and R. W. Kattan, *J. Med. Chem.*, **10**, 603 (1967). [h] *Anal.* C, H, N.

their biological activities are presented in Table I.[13,14] Some quarternary compounds are also included in this table.

None of the N-substituted derivatives of **1** were significantly more active than **1** itself. Compounds with comparable activity were the *N*-Me (**2**), the *N*,*N*-Me_2 (**26**), the *N*-allyl (**11**), the *N*-Et (**3**), and the *N*,*N*-Et_2 (**27**) derivatives. In general, as the size of the substituent (or substituents) increased, the activity diminished. The presence of functional groups such as OH, NH_2, Cl, and $COOCH_3$ on the alkyl moiety, *e.g.*, **13–16** and **31–35**, reduced activity. The quarternary derivatives **25** and **41** were very weakly active.

Variations in II (Table II).—Substituents at one or more of the other tertiary positions of **1** affected activity adversely. While 3-methyl-1-adamantanamine·HCl (**42**) was mildly active, other members of this series were inactive. Thus, this kind of substitution was highly detrimental to activity.

Variations in III (Table III).—The insertion of moiety "A" of one or more carbons between N and adamantane nucleus of **1** was explored. Insertion of a single C, itself substituted or unsubstituted, led to compounds of good activity. One of these, α-methyl-1-adamantanemethylamine·HCl (**58**, rimantadine·HCl), was found by Tsunoda and coworkers to be more effective than **1** *in vitro* against influenza A/Japan 305 virus.[7b] Protection in mice and ferrets was also demonstrated.

Rimantadine, unlike amantadine, possesses a center of asymmetry and thus provided an opportunity to prepare and test the optical antipodes. Resolution *via* the diamides from (+)- and (−)-tartranil gave (−)-α-methyl-1-adamantanemethylamine and (+)-α-methyl-1-adamantanemethylamine, respectively. The HCl salts were essentially equipotent with the racemic compound.

Further substitution at the α position of the adamantanemethylamines, *e.g.*, α,α-dimethyl-1-adamantanemethylamine·HCl (**64**), or substitution with an Et group, *e.g.*, α-ethyl-1-adamantanemethylamine·HCl (**61**), retained activity. On the other hand, N-alkylation with groups larger than Me usually decreased activity sharply.

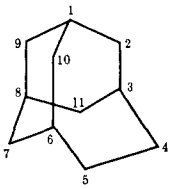
Variations in IV (Table IV).—The adamantane skeleton has been expanded to the tricyclo[4.3.1.1.^{3,8}]undecane (homoadamantane) system.[15,16] The 3-amino

(13) Ad, a convenient symbol for the 1-adamantyl group, has been used throughout this article.

(14) Many of the compounds listed in the tables are the subject of U. S. patents: (a) M. Paulshock and J. C. Watts, U. S. Patent 3,310,469, 1967; (b) T. L. Cairns, U. S. Patent 3,397,233 1968; (c) W. W. Prichard, U. S. Patent 3,352,912, 1967.

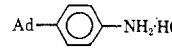
(15) H. Stetter and P. Goebel, *Chem. Ber.*, **96**, 550 (1963).

(16) The numbering system is as follows:



In this paper all derivatives of homoadamantane are substituted at the 3 position.

TABLE III

No.	Structure	AVI_{50},[a] mg/kg	Formula	Analysis	Mp, °C	Reference or method of prepn[b]	Precursor[c]	% yield
47	$AdCH_2NH_2 \cdot HCl$	2.9	$C_{11}H_{19}N \cdot HCl$		324–328[d]	*e*		
48	$AdCH_2NHCH_3 \cdot HCl$	1.6	$C_{12}H_{21}N \cdot HCl$	C, H, N	324.5–325[d]	C	$AdCONHCH_3$	60
49	$AdCH_2NHCH_2CH_3 \cdot HCl$	69	$C_{13}H_{23}N \cdot HCl$	C, H, N	356	C	AdCONHEt	91
50	$AdCH_2NHCH_2CH_2CH_3 \cdot HCl$	68	$C_{14}H_{25}N \cdot HCl$	C, H, N	342	C	AdCONHPr	83
51	$AdCH_2NHCH_2C_3H_5 \cdot HCl$	24	$C_{15}H_{25}N \cdot HCl$	C, H, N		C	$AdCH_2COC_3H_5$	
52	$AdCH_2NHCH_2C_6H_{11} \cdot HCl$	>32[f]	$C_{18}H_{31}N \cdot HCl$	N		C	$AdCH_2NHCOC_6H_{11}$	
53	$AdCH_2NHC_5H_9 \cdot HCl$	48	$C_{16}H_{27}N \cdot HCl$	N		C	$AdCONHC_5H_9$	92
54	$AdCHNHC_6H_{11} \cdot HCl$	>200[f]	$C_{17}H_{29}N \cdot HCl$	N		C	$AdCONHC_6H_{11}$	65
55	$AdCH_2N(CH_3)_2 \cdot HCl$	4.9	$C_{13}H_{23}N \cdot HCl \cdot 0.33H_2O$	C, H, N	254	C	$AdCON(CH_3)_2$	70
56	$AdCH_2N(CH_3)CH_2CH_3 \cdot HCl$	12	$C_{14}H_{25}N \cdot HCl \cdot 0.5H_2O$	C, H, N	25	C	$AdNH_2N(CH_3)Ac$	75
57	$AdCH_2N(CH_2CH_3) \cdot HCl$	11	$C_{15}H_{27}N \cdot HCl$	C, H, N	240–241	C	$AdCONEt_2$	70
58	(±)-$AdCH(CH_3)NH_2 \cdot HCl$	1.4	$C_{12}H_{21}N \cdot HCl$	C, H, N	373–375[d]			
59	(−)-$AdCH(CH_3)NH_2 \cdot HCl$	1.4	$C_{12}H_{21}N \cdot HCl$		400–402[d]			
60	(+)-$AdCH(CH_3)NH_2 \cdot HCl$	1.4	$C_{12}H_{21}N \cdot HCl$		400–402[d]			
61	$AdCH(CH_2CH_3)NH_2 \cdot HCl$	4.2	$C_{13}H_{23}N \cdot HCl$	H, N[g]	278–282[d]			
62	$AdCH(CH_3)NHCH_3 \cdot HCl$	3.3	$C_{13}H_{23}N \cdot HCl$			C	$AdCH(CH_3)NHCOOCH_3$	65
63	$AdCH(CH_3)N(CH_3)_2 \cdot HCl$	3.8	$C_{14}H_{25}N \cdot HCl \cdot H_2O$	C, H, N	266–268			
64	$AdC(CH_3)_2NH_2 \cdot HCl$	1.7	$C_{13}H_{23}N \cdot HCl$	C, H, N				
65	$AdC(CH_3)_2NHCH_3 \cdot HCl$	3.6	$C_{14}H_{25}N \cdot HCl$	C, H, N	282–283			
66	$AdC(CH_3)_2NHCH_2CH_3 \cdot HCl$	5.8	$C_{15}H_{27}N \cdot HCl$	H, N[h]				
67	$AdC(CH_3)_2N(CH_3)_2 \cdot HCl$	9.8	$C_{15}H_{27}N \cdot HCl$	C, H, N	215–217			
68	$AdCH_2CH_2NH_2$	>18[f]		C, H	*i*			
69		>200[f]	$C_{21}H_{21}N \cdot HCl$		260–263	*j*		

[a] See text for definition. [b] See Experimental Section. [c] Amides were prepd from the corresponding amine and acid chloride or anhydride. [d] Sealed capillary. [e] H. Stetter and P. Goebel, *Chem. Ber.*, **96**, 550 (1962). [f] Highest level tested. [g] C: calcd, 67.99; found, 68.55. [h] C: calcd, 69.90; found, 69.33. [i] Bp 119° (6 mm). [j] See preparation of **19**.

TABLE IV

No.	Structure[a]	AVI_{50},[b] mg/kg	Formula	Analysis	Mp, °C	Reference or method of prepn[c]	Precursor[d]	% yield
70	$HAdNH_2 \cdot HCl$	3.5	$C_{11}H_{19}N \cdot HCl$	C, H, N, H_2O[e]	205–206.5	C		
71	$HAdNHCH_3 \cdot HCl$	13	$C_{12}H_{21}N \cdot HCl$	C, H, N	225–226	C	$HAdNHCOOCH_3$	34
72	$HAdNHCH_2CH_3 \cdot HCl$	13[f]	$C_{13}H_{23}N \cdot HCl$	C, H, N	345–350 dec	C	$HAdNHA_c$	75
73	$HAdN(CH_3)_2 \cdot HCl$	13[f]	$C_{13}H_{23}N \cdot HCl$	C, H, N	276 dec			
74	$HAdN(CH_2CH_3)_2 \cdot HCl$	13[f]	$C_{15}H_{27}N \cdot HCl$	C, H, N	239–241 dec			
75	$HAdCH_2NH_2 \cdot HCl$	3.4	$C_{12}H_{21}N \cdot HCl$	C, H, N	352–352.5	C	$HAdCONH_2$	
76	$HAdCH(CH_2)NH_2 \cdot HCl$	5.0	$C_{13}H_{23}N \cdot HCl \cdot 0.25H_2O$	C, H, N	362–364			
77	$HAdC(CH_3)_2NH_2 \cdot HCl$	1.9	$C_{14}H_{25}N \cdot HCl$	C, H, N	370–372[g]			
78	$HAdC(CH_3)_2NHCH_3 \cdot HCl$	14	$C_{15}H_{27}N \cdot HCl$	C, H, N	261–262			

[a] A convenient symbol for the 3-homoadamantyl group is HAd. [b] See text for definition. [c] See Experimental Section. [d] Amides were prepd from the corresponding amine and acid chloride or anhydride. [e] By Karl Fischer titration. [f] Highest dose level tested. [g] Sealed capillary.

and 3-methylamino derivatives[17] were active antiviral agents (*e.g.*, **70**, **75**, and **77**, Table IV).

Other Variations.—Replacement of the amino group of **1** by H, OH, SH, CN, COOH, Cl, or Br gave inactive compounds. Furthermore, acyl derivatives of **1** (Table V) were usually much less active than **1** itself, indicating the importance of a basic nitrogen for activity.[18] At present we have no information allowing us to rationalize the activity of the exceptional glycyl derivative **81**.

Method of Preparation.—Many of the *N*-monoalkyl- and *N*,*N*-dialkyladamantanamines of Table I were prepared by three general methods.

A. Alkylation of 1-Adamantanamine.—This method

$$AdNH_2 \xrightarrow{R_1X} AdNHR_1 \xrightarrow{R_2X} AdNR_2R_2$$

suffered from the usual difficulty that mixtures resulted. However, separation of products was somewhat simplified by the fact that 1-adamantanamine rapidly formed an insol salt when moist CO_2 was passed into its solutions. The salt was then easily removed by filtration, and the mono- and dialkyl derivatives were then separated by distn. The best example of this method was the preparation and separation of *N*-allyl- (**11**) and *N*,*N*-diallyl-1-adamantanamine (**30**).

(17) A convenient symbol for the 3-homoadamantyl group is HAd.

(18) The antiviral effects of higher acyl derivatives of 1-aminoadamantane have been reported: C. Runti and T. Sciortino, *Farmaco Ed. Sci.*, **23**, 106 (1968).

TABLE V

No.	Structure	AVI_{50},[a] mg/kg	Formula	Analysis	Mp, °C	Reference or method of prepn[b]
79	AdNHCHO	28	$C_{11}H_{17}NO$		139.4–141.5	*c*
80	$AdNHCOCH_3$	>200[d]	$C_{12}H_{19}NO$		149–149.5	*e*
81	$AdNHCOCH_2NH_2$	5.6	$C_{12}H_{20}N_2O \cdot HCl$	C, H, N	237.5–239.5	
82	$AdNHCONHNH_2$	>18[d]	$C_{11}H_{19}N_3O \cdot HCl$	C, H, N	175–176	
83	$AdNHCOOCH_2CH_3$	24	$C_{13}H_{21}NO_2$	N	90.4–91.3	
84	AdNHCONH-*p*-C_6H_4Cl	>200[d]	$C_{17}H_{21}ClN_2O$	N	245.5–246	
85	$AdNHCOCH_2C_6H_5$	96	$C_{18}H_{23}NO$		177–178.5	
86	AdNHCONHAd	>200[d]	$C_{21}H_{32}N_2O$		301[f]	*f*
87		>200	$C_{14}H_{21}NO$	C, H, N	99.6–100.4	

[a] See text for definition. [b] See Experimental Section. [c] W. Haaf, *Angew. Chem.*, **73**, 144 (1961). [d] Highest dose level tested. [e] C. Runti and T. Sciortino, *Farmaco Ed. Sci.*, **23**, 106 (1968). [f] Reported [H. Stetter and C. Wulff, *Chem. Ber.*, **95**, 2302 (1962)] mp 312°.

B. Alkylation of Amines with 1-Bromoadamantane.

$$AdBr + HNR_1R_2 \longrightarrow AdNR_1R_2$$

—The unusual bridgehead reactivity of 1-adamantane derivatives such as 1-bromoadamantane has been documented.[19] We were, therefore, attracted by the possibility of a direct SN1 route to the bridgehead amines. It appeared necessary primarily to find the appropriate kinetic conditions for ionization of the 1-bromoadamantane. Heating 1-bromoadamantane with lower molecular weight amines, *e.g.*, NH_3 and $MeNH_2$, at 180–220° in an autoclave provided yields of 80–90% of the corresponding 1-adamantanamine. When the amine precursor was more lipophilic and when steric hindrance intervened, yields were much lower. Presumably, the lower dielectric constant of the lipophilic amines disfavored the ionization of the bromoadamantane. The direct amination of 1-bromoadamantane has been reported by others.[20]

C. Reduction of *N*-(1-Adamantyl)carboxamides and carbamic Acid Esters with LAH.—When applicable,

$$AdN(R_1)COR_2 \xrightarrow{LaH} AdNR_1CH_2R_2$$

this method gave good yields and easily purified products; it was well suited to both lower and higher alkyl derivatives. The amide precursors were made by 3 routes.

1.

$$AdBr + RCN \xrightarrow{H_2SO_4} AdNHCOR \quad (1)$$
R = H or alkyl (Ritter reaction)

This reaction provided a useful route to secondary amides.[21]

2. A Modified Ritter Reaction.—Would substitution of amides for the nitriles in reaction 1 lead to *N*-adamantylamides? Ritter has reported that the H_2SO_4-catalyzed reaction of olefins with amides failed[21b] and thus inferred that amides were not intermediates in the Ritter reaction. We have found that the reaction of 1-bromoadamantane with primary and secondary amides succeeds in the presence of Ag_2SO_4.

$$AdBr \xrightarrow[RNHCOR']{Ag_2SO_4} AdNRCOR' \quad (2)$$
(R and R′ = H or alkyl)

For example, $HCONH_2$, $CH_3CONHMe$, pyrrolidin-2-one, and caprolactam reacted with 1-bromoadamantane in the presence of Ag_2SO_4 to give the corresponding *N*-(1-adamantyl)amides. The preparation of *N*-(1-adamantyl)pyrrolidin-2-one (**87**) is described in the Experimental Section.

3. Acylation of 1-Adamantanamines.—Standard methods of acylating adamantanamines were used.

$$AdNHR \xrightarrow{R'COCl\ [or\ (R'CO)_2O]} AdNRCOR' \quad (3)$$
(R = H or alkyl; R′ = alkyl or alkoxy)

1-Adamantanemethylamine was prepared by the method of Stetter and Goebel.[15] Preparation of the *N*-alkyl derivatives paralleled those of the *N*-alkyl adamantanamines. The α-Me and α-Et adamantanemethylamines resulted from LAH reduction of the appropriate oxime (reaction 4).

$$AdCOR \xrightarrow{H_2NOH} AdC(R)=NOH \xrightarrow{LAH} AdCHRNH_2 \quad (4)$$
(R = Me, Et)

α,α-Dimethyl-1-adamantanemethylamine was obtained *via* a Grignard reaction followed by a Ritter reaction and hydrolysis (eq 5).

$$AdCOCl \xrightarrow{MeMgBr} AdC(CH_3)_2OH \xrightarrow[H_2SO_4]{HCN} AdC(CH_3)_2NHCHO \xrightarrow{NaOH} AdC(CH_3)_2NH_2 \quad (5)$$

1-(2-Aminoethyl)adamantane (**68**) was prepared from 1-(2-bromoethyl)adamantane[22] (**6**).

$$AdCH_2CH_2Br \xrightarrow{NaN_3} AdCH_2CH_2N_3 \xrightarrow{H_2/Pt} AdCH_2CH_2NH_2 \quad (6)$$

Homoadamantanamine **70** was prepared from homoadamantanecarboxylic acid[23] (**7**).

$$HAdCOOH \xrightarrow[pyridine]{CH_3OCOCl} HAdCOOCOOCH_3 \xrightarrow{NaN_3} HAdCON_3 \xrightarrow{heat} HAdNCO \xrightarrow{CH_3OH} HAdNHCOOCH_3 \xrightarrow{NaOH} HAdNH_2 \quad (7)$$

Antiviral Testing.—The antiviral $dose_{50}$ (AVI_{50}) screen was devised to offer a quantitative comparison of the antiviral activity of a series of compounds tested at different times. The AVI_{50} dose is the amount of compd in milligrams per kilogram which causes a 3.2-

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(20) (a) E. V. Krumkalns and W. Pfeiffer, *J. Med. Chem.*, **11**, 1103 (1968); (b) F. N. Stepanov and Z. E. Stolyarov, *Zh. Org. Khim.*, **5** (3), 537 (1969).

(21) (a) H. Stetter, J. Mayer, M. Schwarz, and K. Wulff, *Chem. Ber.*, **93**, 226 (1960); (b) J. J. Ritter and P. P. Minieri, *J. Amer. Chem. Soc.*, **70**, 4045 (1948); (c) J. J. Ritter and J. Kalish, *ibid.*, **70**, 4049 (1948).

(22) H. Stetter and P. Goebel, *Chem. Ber.*, **95**, 1039 (1962).

(23) H. Stetter, M. Schwarz, and A. Hirschhorn, *ibid.*, **92**, 1629 (1959).

TABLE VI

No.	Alkyl halide	AdNR1R2 R1	AdNR1R2 R2	Bp, °C (mm)	% yield
11	CH_2=$CHCH_2Br$	H	CH_2=$CHCH_2$	55–58 (0.1)	38
12	HC≡CCH_2Br	H	HC≡CCH_2	150–153 (22)	32
13	$HOCH_2CH_2CH_2Br$	H	$HOCH_2CH_2CH_2$		10
14	$HOCH_2CH_2CH_2Br$	H	$CH_3O_2CCH_2CH_2$		
16	$CH_3O_2CCH_2CH_2Br$	H	$CH_3O_2CCH_2CH_2$		
22	$(C_5H_6)_2CHCl$	H	$(C_5H_6)_2CH$		
29	CH_2=$CHCH_2Br$	CH_3	CH_2CH=CH_2[a]	128–132 (9)	65
30	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	CH_2=$CHCH_2$[b]	78 (0.05)	8

[a] N-Methyl-1-adamantanamine was used in place of 1-adamantanamine to prep this compd. [b] Compd **30** was obtd as a by-product from the prepn of 11.

fold decrease in the infectivity of a standard 20-LD_{50} dose of infecting virus to mice.[24]

Other Data.—Drug dynamics and the metabolic fate of **1**[25] and the toxicologic and pharmacologic properties[26] have been reported elsewhere. The mode of action of **1** has been studied.[27]

Experimental Section

Many compounds listed in the tables and in this section were prepared by general procedures listed below as methods A, B, C, and D. Where no general procedure is listed, specific procedures are given in this section. Melting points were determined in capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Boiling points are uncorrected. Ir spectra were determined with a Perkin-Elmer 137 spectrophotometer. Nmr spectra were determined with a Varian A-60 spectrophotometer using Me_4Si as an internal standard. Compds in Tables I–IV also have anal. results listed in the tables. Where elemental analyses are indicated only by symbols, analytical results were within ±0.4% of the theoretical values.

Method A.—A mixt of 0.2 mole of 1-adamantanamine·HCl (1), 0.20 mole of the appropriate alkyl halide, and 0.60 mole of $NaHCO_3$ in 500 ml of EtOH was refluxed until no more CO_2 was evolved. The insol material was filtered off, and the filtrate was evapd. The residue was distributed between 10% aq NaOH and Et_2O. The Et_2O soln was dried (NaOH or K_2CO_3) and evapd.

The residue was dissolved in 300 ml of 90% EtOH, and CO_2 was bubbled into the soln until all unchanged 1-adamantanamine was pptd as the insol carbonate. The ppt was filtered off, and the filtrate was evapd. The residue was either distd or dissolved in Et_2O and treated with anhyd HCl to give the salt. Compds prepared by this method are listed in Table VI.

Method B.[28]—A mixt of 0.06 mole of 1-bromoadamantane and 0.30 mole of the appropriate amine were heated in a 145-ml stainless steel bomb at 215° for 6 hr at autogeneous pressure. The product was poured into a mixt of 250 ml of 2 *N* HCl and 200 ml of Et_2O. The aq layer was sepd and made alkaline with 200 ml of 50% aq NaOH. The mixt was extd with Et_2O, and the ext was dried (K_2CO_3) and evapd to give an oil, which could be distd. Compds prepd by this method are listed in Table VII.

Method C.—A soln of 0.1 mole of 1-acylaminoadamantane or adamantane-1-carboxamide and 0.15 mole of LAH in 100 ml of anhyd $(MeOCH_2)_2$ was heated at 120° for 2 hr under N_2. After cooling, the mixt was treated with sufficient H_2O to decomp excess LAH and hydrate the resulting salts. The salts were filtered off and washed with solvent. The filtrate was evapd. The residue was either distd or dissolved in Et_2O and treated with anhyd HCl to afford the HCl salt. Compds prepd by this method are listed in Tables I, III, and IV.

TABLE VII

Amine precursor	Product (AdNR1R2) No.	R1	R2	Bp, °C (mm)	% yield
CH_3NH_2	2	H	CH_3	[a]	80
$(CH_3)_2CHNH_2$	5	H	$(CH_3)_2CH$	130–132 (16)	64
$(CH_3)_2CHCH_2NH_2$	7	H	$(CH_3)_2CHCH_2$	147–150 (16)	19
$Et_2CH(CH_3)NH_2$	8	H	$Et_2CH(CH_3)$	138–140 (14)	45
$HOCH_2CH_2CH_2NH_2$	14	H	$HOCH_2CH_2CH_2$	[a]	[b]
$C_5H_{11}NH_2$	18	H	C_5H_{11}	92–96 (0.1)	62
$C_6H_5CH_2CH_2NH_2$	21	H	$C_6H_5CH_2CH_2$	[a]	[b]
$(n\text{-}Pr)_2NH$	28	Pr	Pr	100–102 (0.65)	9
	38	$CH_2CH_2NHCH_2CH_2$		[c]	[b]

[a] Isolated as HCl salt. [b] Not determined. [c] Mp 86–87°.

Method D.—A soln of 0.10 mole of 1-bromoadamantane in 0.4–0.5 mole of the appropriate nitrile was treated dropwise with 10 ml (18 g, 0.18 mole) of concd H_2SO_4. The mixt was warmed at 50° for 2 hr, then was poured into 200 ml of ice–water, and was extd with CH_2Cl_2. The ext was washed with H_2O, dried ($MgSO_4$), and evapd. The residue was recrystd. Compds prepd by this method are listed in Table VIII.

1-(Hydroxyethylamino)adamantane (13). 1-[Bis(hydroxyethyl)amino]adamantane (32).—A mixt of 15.1 g (0.1 mole) of 1, 5 g (0.1 mole) of ethylene oxide, 10 ml of H_2O, and 40 ml of THF was heated at 70° for 12 hr in a 140-ml stainless steel bomb. The product was evapd and distd to give 0.44 g of **13**, bp 122–124° (0.04 mm), and 9.0 g of **33**, bp 152° (0.04 mm). Due to inaccuracies in determining the small net weight of $(CH_2)_2O$ from the heavy cylinder, the proportion of products varied widely from run to run. On occasion, practically no yield of monoadduct was found, but on other occasions the yield was high. Recrystn (PhMe) of the lower-boiling fraction gave **13**, mp 97–99°. Recrystn (MeCN) of the higher-boiling fraction gave **32**.

***N*-(2-Aminoethyl)-1-adamantanamine·2HCl (15).**—A soln of 2.14 g (0.05 mole) of ethylenimine in 5 ml of tetralin was dropped into a mixt of 15.1 g (0.10 mole) of 1 (free base) and 10 g (0.075 mole) of $AlCl_3$ in 10 ml of Tetralin at 180°. After 1 hr at 180°, the mixt was cooled and poured into 50 ml of ice–H_2O. The mixt was made strongly alkaline with KOH and then was extd (C_6H_6). The C_6H_6 layer was in turn extd with 1 *N* HCl. The aq layer was made strongly alk with 50% aq NaOH and was extd with Et_2O. The Et_2O layer was evapd. The residue was steam distd to remove 1 (free base). The distn residue was extd with Et_2O. The Et_2O ext was dried (KOH), evapd, dissolved in EtOH, and treated with HCl gas with cooling until the salt crystd to give 2.5 g (19%) of **15**.

***N*-(1-Adamantyl)aniline·HCl (19). *p*-1-Adamantyl)aniline·HCl (69).**—A mixt of 43 g (0.2 mole) of 1-bromoadamantane and 93 g (1.0 mole) of $PhNH_2$ was refluxed for 8 hr. The mixt was cooled, dild with 1 l. of 1 *N* NaOH soln, and steam distd to remove excess $PhNH_2$. The residue was extd with Et_2O. The ext was dried (K_2CO_3) and evapd to give 42 g of residue. This residue was chromatographed on Woelm basic alumina (activity grade I) with C_6H_6 as the eluent. The initial fraction was distd to give *N*-(1-adamantyl)aniline, a colorless liquid, bp 204.7° (25 mm), which crystd on cooling to a white solid: mp 75–82°; nmr (CCl_4), δ 1.6–2.1 (15 H, complex, aliph), 3.15 (1 H, broad, NH), 6.5–7.2 (5 H, complex, arom). Treatment with dil HCl gave **19**.

A later chromatographic fraction, recrystd from heptane,

(24) A more detailed description of the testing procedure was provided in paper I.[1]

(25) W. E. Bleidner, W. E. Hewes, T. E. Lynes, and E. C. Hermann, *J. Pharmacol. Exp. Ther.* **150**, 484 (1965).

(26) V. G. Vernier, J. B. Harmon, J. M. Stump, and T. E. Lynes, *Toxicol. Appl. Pharmacol.*, **15**, 642 (1969).

(27) (a) E. M. Neumayer, R. F. Haff, and C. E. Hoffmann, *Proc. Soc. Exp. Biol. Med.*, **119**, 393 (1965); (b) C. E. Hoffmann, E. M. Neumayer, R. F. Haff, and R. A. Goldsby, *J. Bacteriol.*, **90**, 623 (1965); (c) N. Kato, and H. J. Eggers, *Virology*, **37**, 632 (1969).

(28) For method B, see J. C. Kauer, U. S. Patent 3,256,329, June 14, 1966.

TABLE VIII

Nitrile precursor	Product No.	Product Structure	Mp, °C	Recrystn solvent
CH_3CH_2CN	88	$AdNHCOCH_2CH_3$	102.5–104.5	MeCN
$CH_3(CH_2)_2CN$	89	$AdNHCO(CH_2)CH_3$	119.1–120.0	EtOAc
$CH_3(CH_2)_4CN$	90	$AdNHCO(CH_2)_4CH_3$	86.3–87.2	MeCN
$CH_3(CH_2)_{10}CN$	91	$AdNHCO(CH_2)_{10}CH_3$	72–73[b]	10% HOAc–MeCN

[a] All amides gave correct C, H anal. [b] A fraction distg at 175–200° (0.08 mm) was taken for recrystn.

corresponded to the previously reported *p*-(1-adamantyl)aniline:[29] mp 99–105° (reported, 107–108°); nmr (CCl_4), δ 1.7–2.2 (15 H, complex, aliphatic), 3.30 (1 H, singlet, NH) 6.75 (4 H, doublet of doublets, J = 34.5 Hz, 8.5 Hz, arom); HCl salt (**69**), mp 260–263° (reported,[29b] 262°).

1-Adamantylbenzaldimine (**40**).—A soln of 15.1 g (0.10 mole) of 1 and 15.4 g (0.10 mole) of freshly distd PhCHO in 50 ml of PhMe was refluxed for 45 hr in a flask equipped with a water separator. PhMe was evapd, and the residue was recrystd (MeOH) to give 20.1 g (84%) of crystals; ir, 6.09 μ (C=N).

***N*-Benzyl-1-adamantanamine** (**20**).—The reduction was performed as in method C using equimolar amts of LAH and **40**. The product was obtd as a colorless liquid in 74% yield after distn: bp 91° (0.13 mm); $n^{25}D$ 1.5548; ir, 3.02 μ (NH), 3.25 and 3.30 (arom CH), 3.45 and 3.52 (satd CH), 6.20 and 6.67 (arom C=C).

***N*-Bromo-1-adamantanamine·HBr** (**23**).—A mixt of 5 g of 1 and 2.7 ml of Br_2 in 100 ml of H_2O was stirred for 15 min at 25° to afford 8.0 g of ppt. Recrystn ($CHCl_3$) gave 3.4 g of **23** as golden crystals.

***N*-(1-Adamantyl)hydroxylamine·HCl** (**24**).—A soln of AcO_2H was prepd by dropping 6.72 g (0.066 mole) of Ac_2O into a mixt of 1.5 ml (0.055 mole) of 90% H_2O_2, 5 ml of CH_2Cl_2, and 1 drop of concd H_2SO_4 at 0°. After 15 min at 0° and 30 min at 25°, this soln was added dropwise to a soln of 12 g (0.05 mole) of **47** in 10 ml of CH_2Cl_2 at 0°, and the mixt was allowed to warm to 25° during 16 hr. After a soln of 3 ml of H_2SO_4, 5 ml of H_2O, and 50 ml of MeOH was added at 0°, the mixt was stirred at 25° for 16 hr. It was evapd and the residue was distributed between 1 *N* HCl and Et_2O. The aq ext was treated with excess 10% NaOH soln. The ppt was filtered off, washed, and dried to give 3.53 g (38%) of colorless crystals, mp 166–169°. The product was dried at 100° for 16 hr for analysis. *Anal.* ($C_{10}H_{17}NO·H_2O$): H, N; C, calcd, 64.83; found, 65.83. Treatment with HCl in Et_2O gave **24**.

***N*,*N*-Dimethyl-1-adamantanamine *N*-Oxide** (**25**).—A soln of 17.9 g (0.10 mole) of *N*,*N*-dimethyl-1-adamantanamine (**28** (free base)) and 18 g (0.16 mole) of 30% H_2O_2 in 20 ml of MeOH was allowed to stand at 25° for 2 days. After the addn of a small amt of Pd black to decomp excess peroxide, the mixt was filtered and evapd (after a negative peroxide test). Recrystn (PhMe) of the residue gave 14.2 g (73%) of **25** hydrate: mp 130.0–132.0°; nmr (D_2O), δ 1.72 (6 H, γ-methylene), 2.12 (6 H, α-methylene), 2.78 (3 H, broad, methine), 3.12 (6 H, s, *N*-methyl), 4.87 (H_2O). *Anal.* ($C_{12}H_{21}NO·2\ H_2O$) C, H, N; picrate, mp 240° dec. *Anal.* ($C_{12}H_{21}NO·C_6H_3N_3O$) C, H.

***N*,*N*-Dimethyl-1-adamantanamine·HCl** (**26**).—A mixt of 6.90 g (0.15 mole) of 98% formic acid, 12.1 g (0.15 mole) of 37% aq CH_2O, and 7.56 g (0.05 mole) of 1 was heated at 90° for 16 hr in a hood. After cooling, the mixt was poured into 75 ml of 15% NaOH soln. The mixt was extd with Et_2O. The ether ext was washed with 12% aq NaOH, dried (KOH), and evapd to give 8.17 g of *N*,*N*-dimethyl-1-adamantanamine, bp 80° (2 mm); perchlorate, mp 180–184°. *Anal.* ($C_{12}H_{21}N·HClO_4$) C, H. Treatment of the base with HCl in Et_2O gave **26**.

***N*-(2-Hydroxyethyl)-*N*-methyl-1-adamantanamine·HCl** (**31**).—A mixt of 16.5 g (0.10 mole) of **2**, 10 ml of H_2O, and 6.6 g (0.15 mole) of $(CH_2)_2O$, and 40 ml of THF was heated in an autoclave at 70° for 12 hr. After evapn of the volatile constituents, the residue was dissolved in dil HCl and extd with Et_2O. The aq layer was evapd to give 26.4 g of crude **31**. Recrystn (MeCN) yielded 16.2 g (66%) of colorless crystals.

***N*-(2-Aminoethyl)-*N*-methyl-1-adamantanamine·HCl** (**33**).—The reaction was performed as described for **15** by using *N*-methyl-1-adamantanamine (**2** (free base)) in place of 1 and heating at 80° rather than 180°. The resulting base was pptd with dry HCl from Et_2O to give the monohydrochloride **33**.

***N*,*N*-Bis(2-chloroethyl)-1-adamantanamine·HCl** (**35**).—$SOCl_2$ (5 ml, 8.2 g, 0.069 mole) was added dropwise to a soln of 1.20 g (0.0050 mole) of **32** in 5 ml of THF at 0°. The mixt was stirred for 16 hr at 25° and then was evapd. The residue was recrystd (EtOH) to give 1.02 g (65%) of **35**.

***N*-(1-Adamantyl)aziridine** (**36**).—$ClSO_3H$ (3.84 g, 0.033 mole) was added to a suspension of 2.3 g (0.010 mole) of **14** in Et_2O. The mixt was refluxed with stirring for 2 hr and then poured onto 150 g of ice. After the addn of 9.0 g (0.16 mole) of KOH and warming until homogeneous, the mixt was steam distd. The dist was satd with K_2CO_3 and extd with Et_2O. The extract was dried (K_2CO_3) and evapd. The residue was distd to give 0.45 g (25%) of **36**, bp 60.5° (0.09 mm).

1-Methyleneazoadamantane (**39**).—To a soln of 15 g (0.1 mole) of 1 in 100 ml of PhH was added dropwise 8.5 g (0.1 mole) of 37% aq CH_2O. The temp rose to 28°. After stirring for 30 min, the mixt was treated with 1 g of powdered KOH to aid in sepg the layers. The PhH soln was sepd and evapd to give 15 g of residue. Sublimation at 125° (bath, 0.5 mm) gave 9.5 g (58%) of **39**.

1-Adamantyltrimethylammonium Perchlorate (**41**).—A mixt of 15.1 g (0.1 mole) of 1, 40 ml (91 g, 0.64 mole) of MeI, 25.2 g (0.3 mole) of $NaHCO_3$, and 150 ml of MeOH was refluxed with stirring for 16 hr. The insol material was filtered off, and the filtrate was evapd. The residue was extd repeatedly with hot $CHCl_3$. The $CHCl_3$ ext was filtered and evapd to give 31.1 g (97%) of crude 1-adamantyltrimethylammonium iodide. Recrystn (H_2O) of a portion gave crystals, mp 313° (sealed evacuated capillary). *Anal.* ($C_{13}H_{24}IN$): Calcd C, 48.60; H, 7.53; found C, 49.15; H, 8.14. Excess $HClO_4$ was added to a soln of the iodide in H_2O to give crystals of **41**, recrystallizable from H_2O.

3,3′-Diamino-1,1′-biadamantane·2HCl (**46**).—A sample of 3,3′-dibromo-1,1′-biadamantane[30] was converted into **46** by method B. The salt, which was recrystd (H_2O), did not melt below 420°.

(±)-α-Methyl-1-adamantanemethylamine·HCl (**58**).—A mixt of 14.0 g (0.235 mole) of $HONH_2·HCl$, 65 ml of pyridine, and 65 ml of EtOH was heated at 100° until homogeneous. Then 13.4 g (0.074 mole) of 1-adamantyl methyl ketone[31] was added, and the mixt was refluxed for 2 hr. After cooling, the mixt was evapd. The solid residue was stirred in H_2O, filtered off, and dried to give 14.2 g (98%) of 1-adamantyl methyl ketoxime: mp 180.5–182°; ir (Nujol), 3400–3700 (OH), 1650 cm^{-1} (C=N).

The oxime (8.3 g, 0.043 mole) was reduced with 3.3 g (0.086 mole) of LAH in refluxing THF. The reaction product was worked up as described in method C to give 5.6 g (60%) of **58**.

(−)-α-Methyl-1-adamantanemethylamine·HCl (**59**).—A mixt of 20.7 g (0.10 mole) of (+)-tartranil and 17.9 g (0.10 mole) of (±)-α-methyl-1-adamantanemethylamine in 200 ml of pyridine was refluxed for 15 hr. The pyridine was then evapd, and the syrupy residue was poured into 500 ml of 6 *N* HCl. The resulting solid was filtered off, washed, and dried to give 29 g of crude product. Then the solid was digested in 200 ml of refluxing MeCN and allowed to cool. The crystals were filtered off and dried, mp 160–170°. Recrystn from EtOH to constant mp gave 5.1 g of (+)-*N*-(α-methyl-1-adamantanemethyl)-*N*′-phenyl tartaric acid diamide; mp 200–200.5°, $[\alpha]^{23}_{546}$ + 146° (pyridine).

The diamide (5.0 g) was refluxed with 200 ml of 50% NaOH soln for 5 hr. The aniline and α-methyl-1-adamantane-

(29) (a) H. Stetter, J. Weber, and K. Wulff, *Chem. Ber.*, **97**, 3488 (1964); (b) F. N. Stepanow, E. I. Dikolenko, and G. I. Damlenko, *Zh. Org. Khim.*, **2**, 640 (1966).

(30) H. F. Reinhardt, *J. Org. Chem.*, **27**, 3258 (1962). A sample of this compound was kindly given to us by Dr. Reinhardt.

(31) S. Hala and S. Landa, *Collect. Czech. Chem. Commun.*, **25**, 2692 (1960); H. Stetter and E. Rauscher, *Chem. Ber.*, **93**, 2054 (1960); H. Stetter and P. Goebel, *ibid.*, **95**, 1039 (1962).

methylamine were removed by steam distn. The dist was extd with Et_2O. After the Et_2O soln was dried (KOH), CO_2 was bubbled through the soln. The resulting carbonate was filtered off and washed (Et_2O). The carbonate was shaken with a mixt of 10% NaOH soln and Et_2O. The ext was dried (KOH) and treated with HCl gas to give 1.4 g of **59**: $[\alpha]^{23}_{578}$ −6.56°, $[\alpha]^{23}_{546}$ −7.48°, $[\alpha]^{23}_{436}$ −13.11°, $[\alpha]^{23}_{405}$ −15.41°, $[\alpha]^{23}_{365}$ −20.26° (*c* 3.05, $CHCl_3$).

(+)-α-Methyl-1-adamantanemethylamine·HCl (60).—Substitution of (−)-tartranil for (+)-tartranil in the preceding procedure gave 5.4 g of (−)-*N*-(α-methyl-1-adamantanemethyl)-*N'*-phenyl tartaric acid diamide: $[\alpha]^{23}_{436}$ − 147.6° (pyridine). Saponification gave 5.1 g of **60**: $[\alpha]^{23}_{578}$ + 6.46°, $[\alpha]^{23}_{546}$ + 7.10°, $[\alpha]^{23}_{436}$ + 12.59°, $[\alpha]^{23}_{405}$ + 15.49°, $[\alpha]^{23}_{365}$ + 20.66° (*c* 3.10, $CHCl_3$).

α-Ethyl-1-adamantanemethylamine·HCl (61).—A soln of $CdEt_2$ in PhH was prepd by adding 19.6 g of powdered, anhyd $CdCl_2$ to 0.2 mole of EtMgBr in 100 ml of Et_2O at 0°, distg off the Et_2O, and dissolving the residue in 100 ml of hot PhH. Then a soln of 19.8 g of 1-adamantanecarboxylic acid chloride in PhH was added with vigorous stirring as rapidly as the exothermic reaction would allow. The mixt was cooled to 0° and 200 ml of ice water was added, followed by 150 ml of 20% H_2SO_4. The PhH layer, after washing, drying (Na_2CO_3), and evapn, yielded 21.6 g of crude 1-adamantyl ethyl ketone: mp 30.5–32.5°; ir (liq), 1690 cm^{-1} (C=O). The ketone was converted into its oxime [mp 177–179°; ir (Nujol), 3100–3400 (OH), 1640 cm^{-1} (C=N)], which was reduced with LAH (*cf.* the prepn of **58**) to give **61**.

***N,N*-Dimethyl-α-methyl-1-adamantanemethylamine·HCl (63).**—The Eschweiler–Clarke procedure (as in the prepn of **26**) was applied to *N*-methyl-α-methyl-1-adamantanemethylamine (**62**) to give **63**.

α,α-Dimethyl-1-adamantanemethylamine·HCl (64).—α,α-Dimethyl-1-adamantanemethanol[32] (mp 77–80°; reported,[30a] 66–70°) was prepd in good yield by the addn of 1-adamantanecarboxylic acid chloride or Me ester to MeMgBr in Et_2O. The Ritter reaction of α,α-dimethyl-1-adamantanemethanol with MeCN was performed as described in method D to give *N*-acetyl-α,α-dimethyl-1-adamantanemethylamine, mp 141–143° (MeOH–H_2O). The *N*-Ac compd was saponified with KOH in MeOH in a sealed tube at 225° for 18 hr to give α,α-dimethyl-1-adamantanemethylamine, which was converted into the hydrochloride **64**.

N-Methyl-α,α-dimethyl-1-adamantanemethylamine·HCl (65).—A soln of 12 ml of concd H_2SO_4 in 12 ml of HOAc was added dropwise to a mixt of 9.5 g of α,α-dimethyl-1-adamantanemethanol,[32b] 10 ml of HOAc, and 4.0 g of NaCN at 50–60°. After 1 hr at 50–60°, the mixt was poured onto 300 g of ice. The solid was collected by filtration to give 9.4 g of crude product, mp 158–159°. Recrystn (EtOH–H_2O) gave 6.2 g (57%) of *N*-(α,α-dimethyl-1-adamantanemethyl)formamide, mp 161.5–162°; ir (Nujol), 3200, 3090, 1670 cm^{-1} (C=O). Redn of the formamide with LAH by method C afforded **65**.

N-Ethyl-α,α-dimethyl-1-adamantanemethylamine·HCl (66).—*N*-(α,α-Dimethyl-1-adamantanemethyl)acetamide was reduced with LAH according to method C to give **66**.

***N,N*-Dimethyl-α,α-dimethyl-1-adamantanemethylamine·HCl (67).**—The Eschweiler–Clarke procedure (as in the prepn of **26**) was applied to *N*-methyl-α,α-dimethyl-1-adamantanemethylamine (**68** (free base)) to give **67** in 15% yield.

1-(2-Aminoethyl)adamantane (68).—A mixt of 5.0 g (0.077 mole) of NaN_3, 15 ml of H_2O, 15 ml of EtOH, and 5.0 g (0.0205 mole) of 1-(2-bromoethyl)adamantane[24a] was refluxed for 20 hr. The mixt was cooled and distributed between Et_2O and H_2O. The Et_2O layer was dried ($MgSO_4$) and evapd. The residue was distd (shield) to give 4.14 g (49%) of 1-(2-azidoethyl)adamantane: bp 74–77° (0.025 mm); $n^{22}D$ 1.5160. *Anal.* ($C_{12}H_{19}N_3$) C, H, N.

The azide (15.0 g, 0.0635 mole) in 100 ml of HOAc was hydrogenated at 3 atm in a Parr apparatus for 90 min with 0.5 g of PtO_2 as catalyst. The mixt residue was distributed between Et_2O and 10% aq NaOH. The Et_2O layer was extd with 2 *N* HCl. The aq ext was made strongly alk and was extd with Et_2O. The Et_2O ext was dried (K_2CO_3) and evapd. The residue was distd to give 3.38 g (30%) of **68**, bp 119° (6 mm), which formed a solid carbonate on exposure to air.

Tricyclo[4.3.1.1^{3,8}]undecan-3-amine·HCl (70).—Methyl chlorocarbonate (16 g, 0.17 mole) was dropped into a soln of 30 g (0.155 mole) of tricyclo[4.3.1.1^{3,8}]undecane-3-carboxylic acid[22] and 12.7 g (0.16 mole) of pyridine in 200 ml of Me_2CO at 5–10°, and the mixt was stirred for 90 min. A soln of 11.8 g (0.18 mole) of NaN_3 in 30 ml of H_2O was added slowly at 5–10°. After standing 17 hr at 25°, the mixt was dild with 300 ml of H_2O and extd with PhMe. The ext was washed, dried ($CaCl_2$), and heated at 100° until all N_2 had evolved. PhMe was evapd, and the residue was dissolved in 300 ml of MeOH and refluxed for 16 hr. Evapn of the solvent gave 26 g of residue, which was recrystd (Me_2CO–H_2O) to give tricyclo[4.3.1.1^{3,8}]undecane-3-carbamic acid Me ester, mp 104–106°. Sapon of the carbamic acid ester with NaOH in refluxing diethylene glycol gave the free base of **70** in 97% yield. Treatment with HCl in Et_2O gave **70**.

***N,N*-Dimethyltricyclo[4.3.1.1^{3,8}]undecan-3-amine·HCl (73).**—The Eschweiler–Clarke procedure (as in the prepn of **26**) was applied to *N*-methyltricyclo[4.3.1.1^{3,8}]undecan-3-amine (**71** (free base)) to give **73** in 74% yield.

***N,N*-Diethyltricyclo[4.3.1.1^{3,8}]undecan-3-amine·HCl (74).**—A mixt of 4.5 g (0.0233 mole) of **70**, 20 ml (39.0 g, 0.26 mole) of EtI, 6.0 g (0.0715 mole) of $NaHCO_3$, and 80 ml of MeOH was refluxed for 16 hr. After cooling, the mixt was filtered, and the filtrate was evapd. The residue was refluxed in 50 ml of 2-aminoethanol for 30 min. After cooling, the mixt was distributed between Et_2O and 200 ml of H_2O. The Et_2O ext was washed, dried (K_2CO_3), and evapd to give an oil. Since gas chromatography indicated some unchanged **70**, this impurity was removed by heating the mixt with 10 ml of Ac_2O at 100° for 4 hr. Then 5 ml of H_2O was added and heating was contd for 1 hr. The HOAc was evapd, and the residue was dissolved in C_6H_6. The C_6H_6 soln was washed with aq $NaHCO_3$ and then extd with two 50-ml portions of 1 *N* HCl. The aq ext was made alk and was extd with Et_2O. The ext was dried (K_2CO_3) and treated with HCl to give a ppt (2.1 g, 35%) of **74**.

α-Methyltricyclo[4.3.1.1^{3,8}]undecane-3-methylamine·HCl (76).—MeLi (0.1 mole) in 50 ml of Et_2O was added to 8 g (0.041 mole) of tricyclo[4.3.1.1^{3,8}]undecane-3-carboxylic acid[23] in 75 ml of Et_2O under N_2. The mixt was refluxed for 4 hr and then was hydrolyzed with 80 ml of H_2O. The Et_2O layer was sepd, washed, dried ($MgSO_4$), and evapd to give the oily 3-acetyltricyclo[4.3.1.1^{3,8}]undecane, ir, 1690 cm^{-1} (C=O).

A mixt of the crude ketone, 8 g of $HONH_2$·HCl, 50 ml of pyridine, and 50 ml of EtOH was refluxed for 2 hr. The mixt was evapd, and the residue was recrystd (EtOH–H_2O) to give 5.6 g (65%) of 3-acetyltricyclo[4.3.1.1^{3,8}]undecane oxime: mp 155.6°; ir, 1640 cm^{-1} (C=N), 3250 cm^{-1} (broad; OH). The oxime was reduced in THF soln with LAH according to method C to give α-methyltricyclo[4.3.1.1^{3,8}]undecane-3-methylamine. Treatment with HCl gave **76**.

α,α-Dimethyltricyclo[4.3.1.1^{3,8}]undecane-3-methylamine·HCl (77).—A soln of 25 g (0.105 mole) of tricyclo[4.3.1.1^{3,8}]undecane-3-carboxylic acid Me ester in 250 ml of Et_2O was refluxed for 4 hr under N_2 with 140 ml of 3 *M* MeMgBr in Et_2O. The mixt was hydrolyzed with satd NH_4Cl soln. The Et_2O layer was evapd, and the residue was steam distd to give 21 g (96%) of α,α-dimethyltricyclo[4.3.1.1^{3,8}]undecane-3-methanol, mp 83–86°.

A mixt of 20 g (0.096 mole) of the carbinol in 20 ml of HOAc and 8.0 g (0.16 mole) of NaCN was warmed to 45°, and a soln of 24 ml of H_2SO_4 in 24 ml of HOAc was added dropwise. The temp was maintained between 50 and 60° for 1 hr. The mixt was cooled and poured onto ice. The resulting solid was collected, washed, and dried. Recrystn (EtOH) gave 17 g (75%) of *N*-(α,α-dimethyltricyclo[4.3.1.1^{3,8}]undecane-3-methyl)formamide, mp 149–151°.

A mixt of 10 g (0.0043 mole) of the formamide, 15 g of KOH, and 100 ml of EtOH was refluxed for 8 hr, cooled, and poured into 500 ml of H_2O. The mixt was extd with Et_2O. The Et_2O layer was extd with dil HCl. The aq layer was made strongly alk with 50% NaOH soln. Extn with Et_2O and treatment of the dried ext with HCl gave **77** (44% yield).

***N*-Methyl-α,α-dimethyltricyclo[4.3.1.1^{3,8}]undecane-3-methylamine·HCl (78).**—*N*-(α,α-Dimethyltricyclo[4.3.1.1^{3,8}]undecane-3-methyl)formamide (see preceding prepn) was reduced with LAH by method C to give **78** (55% yield).

***N*-Glycyl-1-aminoadamantane·HCl (81).**—*N*-Chloroacetyl-1-aminoadamantane [mp 120–121°; ir (Nujol), 1650 cm^{-1} (amide

(32) (a) C. A. Grob, W. Schwarz, H. P. Fischer, *Helv. Chim. Acta*, **47**, 1385 (1964); (b) R. C. Fort, Jr., and P. v. Schleyer, *J. Org. Chem.*, **30**, 789 (1965).

C=O), 3100 and 3250 cm^{-1} (NH)] was prepd from 1, $ClCH_2COCl$, and NEt_3 in PhH.

A mixt of 25 g (0.135 mole) of potassium phthalimide and 25 g (0.11 mole) of *N*-chloroacetyl-1-aminoadamantane in 100 ml of DMF was stirred at 80° for 5 hr. The mixt was distributed between $CHCl_3$ and H_2O. The $CHCl_3$ ext was washed with 0.2 *N* NaOH soln, dried (Na_2SO_4), and evapd. The residue was triturated with Et_2O to give crystals. These were filtered off to give 36.5 g (98%) of *N*-(phthalylglycyl)-1-aminoadamantane: mp 233–235°; ir (Nujol), 1655 cm^{-1} (amide C=O), 1720 and 1770 cm^{-1} (phthalimide carbonyls), 3300 cm^{-1} (NH). Recrystn (MeOH) raised the mp, 237.9–239.5°.

A mixt of 29.0 g (0.092 mole) of *N*-(phthalylglycyl)-1-aminoadamantane and 10 ml of 100% hydrazine hydrate in 200 ml of EtOH was refluxed for 2 hr. The mixt was evapd to dryness, and the residue was digested in 1200 ml of 2 *N* HCl at 50° for 10 min. The solid was removed by filtration, and the filtrate was treated with 10% NaOH soln until pptn was complete. The solid was extd with Et_2O. The Et_2O was evapd to give 18 g of residue. A 3-g portion of residue was recrystd (H_2O) to give *N*-glycyl-1-aminoadamantane, mp 131–133°. Treatment with HCl in Et_2O gave **81**.

4-(1-Adamantyl)semicarbazide (82).—A mixt of 3.54 g (0.020 mole) of 1-adamantane isocyanate[33] and 10 ml (10 g, 0.31 mole) of anhyd hydrazine in 15 ml of DMF was allowed to stand for 30 min. The mixt was poured into 100 ml of H_2O. The ppt was filtered off, washed with H_2O, and dried. Recrystn (MeCN) gave 5 g (60%) of **86**.

1-(1-Adamantyl)-3-*p*-chlorophenylurea (84).—A soln of 7.68 g (0.050 mole) of *p*-chlorophenyl isocyanate in 100 ml of Et_2O was added to a soln of 7.56 g (0.050 mole) of 1 (free base) in 300 ml of Et_2O. The mixt was stirred for 1 hr. The crystals were filtered off and recrystd (EtOH) to give 8.48 g (55%) of **84**.

***N*-(Phenylacetyl)-1-aminoadamantane (85).**—A mixt of 40 g (0.265 mole) of 1 (free base) and 150 ml (210 g, 1.28 mole) of ethyl phenylacetate was heated in a still so that the EtOH formed distd off. When the still head temp reached 98° and the pot 227°, the mixt was cooled and PhMe was added. Crystals of **85** (53 g, 74%) formed.

1-(1-Adamantyl)-2-pyrrolidinone (87).—A mixt of 43 g (0.20 mole) of 1-bromoadamantane, 62 g (0.20 mole) of Ag_2SO_4, and 60 g (0.7 mole) of pyrrolidin-2-one was stirred and heated slowly to 60°, when a rapid temp rise to 110° occurred despite water-bath cooling. After the exothermic reaction subsided, the mixt was heated at 95° for 2 hr and filtered hot, and 50 ml of H_2O was added to the filtrate. The cooled filtrate was extd with Et_2O. The ext was dried ($MgSO_4$) and evapd to give 36.0 g of crude product. Recrystn (H_2O) gave 16.3 g (37%) of **87**.

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(33) H. Stetter and C. Wulff, *Chem. Ber.*, **95**, 2302 (1962).

Notes

8-Azatheophylline and Its Derivatives as Coronary Vasodilators[1]

D. S. BARIANA

Research Department, Abbott Laboratories Limited, Montreal, Canada

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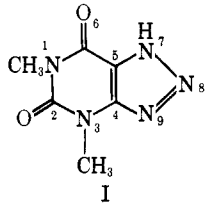
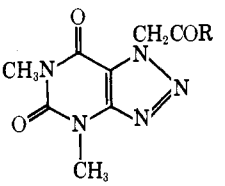
Although there is an extensive literature on theophylline, its derivatives, and water-soluble amine salts as medicinal agents, little attention has been paid to the chemistry and pharmacological effects of the 8-aza analog[2] of theophylline and its derivatives.



I

The synthesis of various derivatives and water-soluble amine salts of I for biological evaluation as coronary vasodilators was, therefore, undertaken.

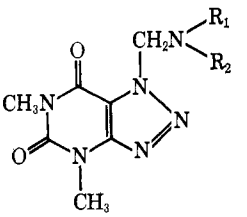
Chemistry.—The 7-acetic acid ethyl ester (II) of I was synthesized by refluxing $ClCH_2COOC_2H_5$ and I in the presence of $NaOCH_3$ according to the procedure described by Klosa[3] for the theophylline analog.



II–VIII

	R
II	OC_2H_5
III	NH_2
IV	NHC_4H_9
V	NHC_3H_7
VI	$NHCH_2CH_2OC_2H_5$
VII	$NH(CH_2)_2N(CH_3)_2$
VIII	$NH(CH_2)_3N$

Compound III was synthesized by treating $ClCH_2CONH_2$ with I in the presence of NaOH and NaI. The acid amides IV–VIII were prepared by refluxing an equimolar amount of ester II and the respective primary amines in EtOH soln for 4–6 hr. Secondary amines such as Et_2NH and *N*-phenylpiperazine did not react under these conditions. Compounds IX–XIII were obtained by treating I, a secondary amine, and 37% HCHO in EtOH soln as described previously.[4]



IX–XIII

IX	piperidine
X	morpholihe
XI	2-methylpiperidine
XII	3-methylpiperidine
XIII	4-*N*-phenylpiperazine

(1) Previous papers in this series: (a) D. S. Bariana, *Can. J. Chem.*, **46**, 3411, 3413 (1968); (b) D. S. Bariana, *J. Med. Chem.*, **12**, 927 (1969); (c) D. S. Bariana, *ibid.*, **13**, 544 (1970).

(2) F. F. Blicke and H. C. Godt, *J. Amer. Chem. Soc.*, **76**, 2798 (1954).

(3) J. Klosa, *Arch. Pharm. (Weinheim)*, **288**, 114 (1955).

(4) D. S. Bariana and C. Groundwater, *J. Heterocycl. Chem.*, **6**, 583 (1969).