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Biologically Active Polycycloalkanes. 1. Antiviral Adamantane Derivatives

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Convenient methods for the synthesis of 1-substituted 3-adamantyl chlorides and bromides (**2**), 1-adamantylphenols and -cresols (**3**), and 1-adamantylacetic (**6**) as well as 1,3-adamantanediacetic (11) acids are described. Several novel derivatives were synthesized from these key intermediates: adamantylcyclohexanols (**4**) and -cyclohexanones (**5**) from adamantylphenols (**3**), and esters (**7**, **12**, and **22**), amides (**13** and **18**), thioamides (**9** and **16**), amidine (**10**), nitrile (**15**), and amines (14 and 17) from 1-adamantanecarboxylic (**19**) and -acetic (**6**) acids and 1,3-adamantanediacetic acid (11). Some adamantylpyrimidines (**24**) and -purines (**25** and **26**) were also prepared. Antiviral activities of the compounds obtained in this work and a series of new 1-adamantyl alkyl ketones synthesized before, together with those of some known adamantane derivatives, were tested in vitro on monolayer culture of chick embryo fibroblasts against Newcastle disease virus.

A number of examples have been documented of the use of adamantane compounds as medicines and drugs.[1] However, it seems that many of the compounds tested so far, except for some aminoadamantanes, have been limited to those derivatives which have functional groups of well-known biological activities, and which, therefore, should be regarded as adamantyl analogs of the corresponding drugs. We have prepared various new derivatives of adamantane such as halides, alcohols, ketones, carboxylic acids, esters, amides, nitriles, etc., and have found many of them active as antiviral agents. It is interesting to note that some of the compounds synthesized in this work are more active than amantadine (1-aminoadamantane);[2] although most of them have no particular functional group with established biological activity.

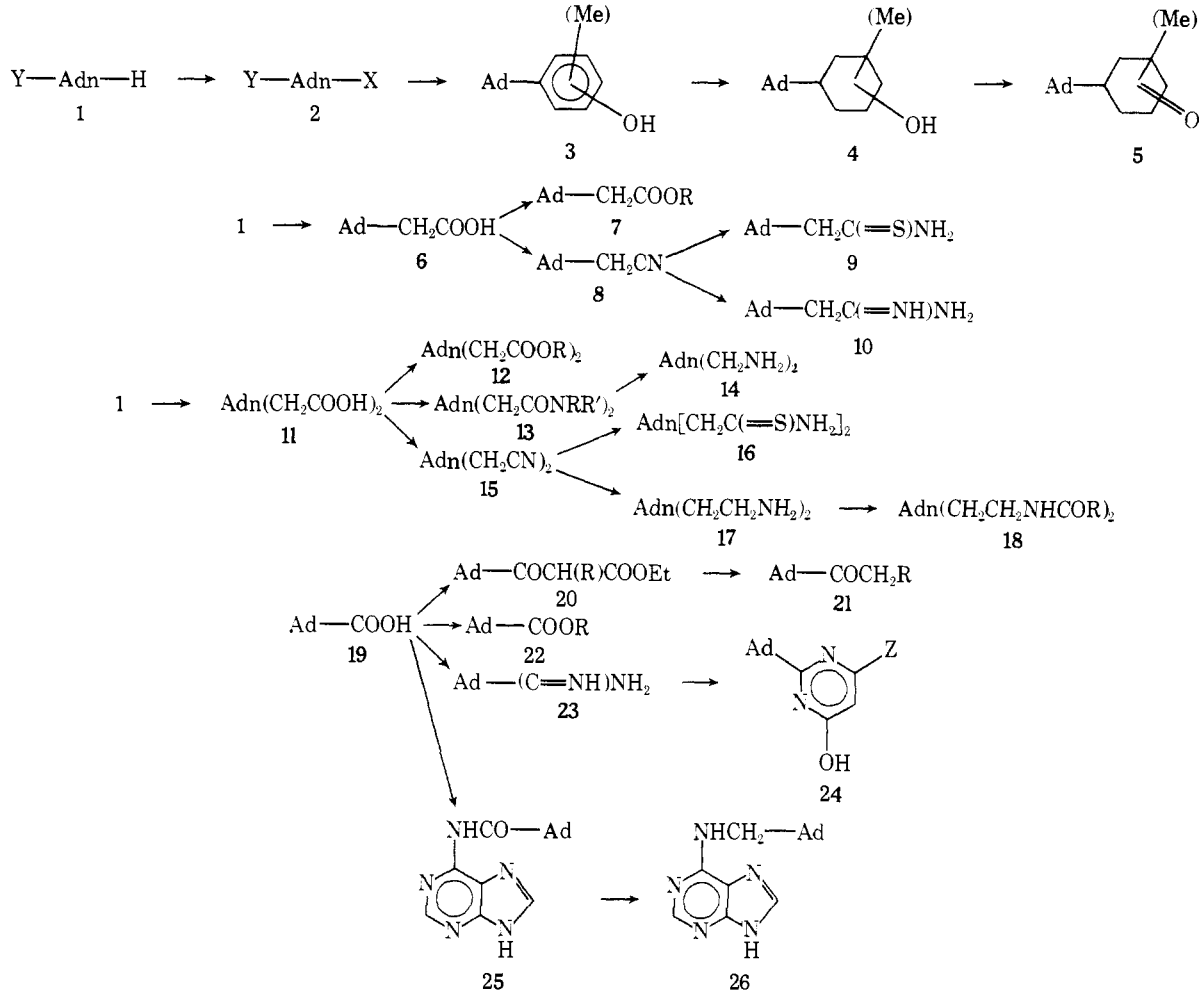
We have recently published preliminary accounts of convenient methods for the synthesis of 1-substituted 3-adamantyl halides,[3] *o*- and *p*-(1-adamantyl)phenols and -cresols,[4] 1-adamantylacetic acid,[5] and 1,3-adamantanediacetic acid.[5] A series of 1-adamantyl alkyl ketones were also prepared.[6] These compounds have served as key intermediates for the synthesis of several derivatives, as summarized in Scheme I.

Chemistry. Ionic[7a] reaction of adamantane with liquid bromine under reflux,[7b] or better at room temperature,[8] offers an excellent method for the preparation of 1-bromoadamantane (**2**, Y = H; X = Br). However, pure 1-chloroadamantane (**2**, Y = H; X = Cl) has been rather difficult to obtain, because of the contamination with 2-chloroadamantane or 1,3-dichloroadamantane (**2**, X = Y = Cl). 2-Chloroadamantane was a by-product in photochlorination[9] of **1**, while 1,3-dichloroadamantane was an impurity in chlorination of 1 by metal chlorides[10] or by *tert*-butyl chloride under aluminum chloride catalysis.[11] We found[3] that pure 1-haloadamantane (**2**, Y = H) free from any contaminating 2-halo and/or 1,3-dihalo compounds was obtained by the reaction of 1-adamantyl cation with halide anion in concentrated sulfuric acid. 1-Adamantyl cation was generated in situ from adamantane by hydride exchange with the *tert*-butyl cation which, in turn, could be formed from *tert*-butyl alcohol in sulfuric acid.[12] The source of halide anion may be alkali metal and alkaline earth metal halides, or hydrogen halides. The method was effective only for the preparation of adamantyl chloride and bromide. Alkali metal fluorides were unreactive toward 1-adamantyl cation, and iodide anion was oxidized to iodine under these reaction conditions.

The halogenation with halide anion in sulfuric acid was applicable to some 1-substituted adamantanes 1 to give the corresponding 3-halo derivatives **2**. This halogenation method was successful, however, only with those compounds which had sufficiently electropositive substituents, in accordance with the carbonium ion nature of the reaction. Taft's polar substituent constant (σ^*)[13] is a measure for the effect of the substituent Y, those having σ^* larger than +1.9 (Y = $CHCl_2$, COOH, Cl, etc.) giving no **2**. This is also consistent with the absence of any 1,3-dihalides in the reaction of unsubstituted adamantane.

1-Phenyl-, 1-methoxy-, and 1-sulfhydryladamantanes gave only 1-haloadamantanes (**2**, Y = H) on reaction with halide anion in sulfuric acid in the presence of *tert*-butyl cation. Cleavage of halo, hydroxy, acetoxy, methoxy,[14-16] and alkylthio[17] groups in the 1 position of adamantane under carbocation-forming conditions is well known, but no example of phenyl group cleavage seems to have been reported. It is interesting that substitution by the *p*-nitro

Scheme I. Synthesis of Adamantane Derivatives[a]



[a]Ad = 1-adamantyl; Adn = 1,3-adamantylene; X = Cl, Br; Y = H, Me, CH_2COOH, C_6H_4-*p*-NO_2, CH_2Cl; Z = OH, NH_2; R, R′ = H, alkyl, (poly)cycloalkyl, aralkyl, aryl, (hetero)alkylene, cycloalkylene, aralkylene.

Table I. 1-Substituted 3-Chloroadamantanes (2, X = Cl)

1-Substituent (Y)[a]	σ*	Yield, %	Mp, °C	MIC, nmol/ml	MCC, nmol/ml
$-CH_3$	0.0	98	41–42[b]	540	540
–H	+0.45	95	166–167[c]	590	2900
$-C_6H_4$-*p*-NO_2[d]		98	104–105.5	>1700	1700
$-CH_2COOH$[d]	−1.05	91	182–183.5	>4400	>4400
$-CH_2Cl$[d]	+1.05	76[e]		*f*	*f*
$-CHCl_2$[d]	+1.94	9[e]		*f*	*f*

[a]1 (Y = COOH) and 1 (Y = Cl) did not give the corresponding 2 but starting materials were recovered. [b]Lit. mp 36–38°,[18] 39–41°;[19] bp 103–105° (12 mm) [lit.[18] bp 98° (13 mm)]. [c]Lit. mp 152–156°,[11] 164.3–165.6°,[20] 165°,[7b] 168.5–169.5.[9] [d]A new compound. [e]Calculated from the peak areas of VPC. Identification of the product was made with the GC–MS. [f]Not tested because of smallness in sample size.

group in phenyl prevents the cleavage of the phenyl. The 1-substituted 3-chloroadamantanes (2) thus obtained are listed in Table I.

Alkylation of phenols by adamantyl bromide was known to afford adamantylphenols.[21–24] Substitution occurred at the para positions unless they were occupied by other groups. However, we found[4] that the reaction of 1-chloroadamantane and phenol gave a mixture of *o*- and *p*-(1-adamantyl)phenols (3). Proportion of the ortho derivatives was larger, the shorter the reaction time and the larger the ratio of adamantyl chloride to phenol. Similar results were obtained with *o*-cresol. However, 6-(1-adamantyl)-*m*-cresol was the only product of the reaction of *m*-cresol.

Heating isolated *o*-(1-adamantyl)phenol with excess phenol in the presence of hydrogen chloride led to the complete conversion of the ortho compound into the para isomer. Crossover experiments using *o*-(1-adamantyl)phenol and *m*-cresol gave 6-(1-adamantyl)-*m*-cresol as the sole product, while 6-(1-adamantyl)-*m*-cresol gave *p*-(1-adamantyl)phenol in the reaction with phenol. In contrast, *p*-(1-adamantyl)phenol did not change at all on prolonged heating with excess phenol or *m*-cresol in the presence of hydrogen chloride.

The results suggest an initial substitution of adamantyl group at an ortho position of phenols under kinetic control. Intermolecular migration of the adamantyl group, in turn,

Table II. 1-Adamantylphenols and -cresols (3)

Compound[a]	Mp, °C	Ir (KBr), cm^{-1} [b]	^1H NMR ($CDCl_3$)[c]	MIC, nmol/ml	MCC, nmol/ml
p-Ad-phenol[d]	186–187	3200, 835, 805	6.89, 7.32 (4, AB q[e])	88	88
o-Ad-phenol	145–146.5	3530, 752	6.3–7.2 (4, m)	180	260
4-Ad-*o*-cresol	138–139	3400, 870, 823, 804	6.68 (1, d[e]), 7.04 (1, d[e]), 7.10 (1, s)	83	170
6-Ad-*o*-cresol	119.5–120.5	3590, 767, 738	6.6–7.2 (3, m)	*f*	*f*
6-Ad-*m*-cresol	116–117.5	3550, 846, 798	6.23 (1, s), 6.58 (1, d[g]), 6.97 (1, d[g])	83	170
2-Ad-*p*-cresol	127.5–129	3540, 806	6.63 (1, d[g]), 6.84 (1, d[g]), 7.02 (1, s)	250	330

[a] All new compounds. Ad is 1-adamantyl. [b] Only ν_{O-H} and δ_{C-H} (aromatic, out-of-plane) are shown. [c] Only aromatic protons are shown. Ad (δ 1.6–2.2, 15 m), hydroxyl (δ 4.4–4.7, 1, s), and methyl (δ 2.23–2.26, 3, s) proton resonances are as expected. [d] Synthesized for the first time by Stepanov et al.[24] [e] J = 9 Hz. [f] Not tested because of smallness in sample size. [g] J = 8 Hz.

Table III. Adamantylcyclohexanols (4) and -cyclohexanones (5)

Compound[a]	Mp, °C	Ir (KBr), cm^{-1} [b]	MIC, nmol/ml	MCC, nmol/ml
		Cyclohexanol Derivative		
4-Ad–[c,d]	163–165	3300, 1060	*e*	*e*
2-Ad–[f]	116–121	3490, 3310, 1110	*e*	*e*
2-Ad-4-Me–[g]	82–84	3350, 1050	2000	2000
2-Ad-5-Me–[g]	113–116	3500, 1020	2000	2000
2-Me-4-Ad–[g]	111–112	3350, 1040	200	200
		Cyclohexanone Derivative		
4-Ad–[d]	79–81	1720, 1160, 1060	260	340
2-Ad–	83–84	1710, 1130, 1060	*e*	*e*
2-Ad-4-Me–	51–52	1710, 1130, 1060	410	2000
2-Ad-5-Me–	56–57	1710, 1130, 1070	200	1000
2-Ad-6-Me–	63–66	1720, 1120, 1080	200	1000

[a] All new compounds. Ad is 1-adamantyl. [b] Only those absorptions which are pertinent to the functional group are shown. Ad absorbs at 2900, 1450–1445, 1380–1360, and 970–960 in adamantylcyclohexanols, and at 2900, 1450, 1370–1340, 1100, and 990–970 in adamantylcyclohexanones. [c] Consisted of 30% cis and 70% trans isomers. [d] Synthesized for the first time by Stepanov et al.[24] [e] Not tested because of smallness in sample size. [f] 18% cis and 82% trans. [g] Isomer ratio not determined.

may be a demonstration of the thermodynamic control in determining the final product composition. Steric congestion involving bulky adamantyl group may be a major factor in determining the product stability. Thus *p*-(1-adamantyl)phenol is thermodynamically more stable than the ortho isomer, and the adamantyl group is exclusively introduced into the 6 position of *m*-cresol to avoid nonbonded interaction with the *o*-methyl group which otherwise would arise. On the other hand, there seems to be no satisfactory explanation at present for the reason why ortho substitution by the sterically unfavorable adamantyl group is kinetically favored.

Mixtures of *o*- and *p*-(1-adamantyl)phenols and -cresols were easily separable into components by extraction with aqueous sodium hydroxide. *o*-Adamantylphenols do not practically form salts on contact with sodium hydroxide solution but remain in the organic phase, whereas para isomers dissolve into the aqueous phase. The structures of the adamantylphenols and -cresols produced were determined on the basis of ir and ^1H NMR spectra. Their aromatic C–H out-of-plane deformation frequencies were well in agreement with the structure,[25a] and ^1H NMR splitting patterns of the aromatic protons in them were so closely similar to those of *tert*-butylphenols and -cresols[26] that the pertinent sections of the corresponding spectra could be almost superimposed on each other. Melting points and ir and ^1H NMR spectra of *o*- and *p*-(1-adamantyl)phenols and -cresols are listed in Table II.

Catalytic hydrogenation of *p*-(1-adamantyl)phenol over Raney nickel gave a mixture (86% yield) of *cis*- and *trans*-4-(1-adamantyl)cyclohexanols (4) in 30/70 ratio. The ratio of isomers was determined on VPC after acetylation. Assignment of the conformations to the acetate isomers was made on the basis that the ir 1240-cm^{-1} absorption of sterol acetates (ν_{C-O-C}) was a single band for the equatorial acetoxy isomers but split into multicomponents for axial conformers.[25b] With the rational assumption that the adamantyl group is always situated in the equatorial position, in view of the conformation of 4-*tert*-butylcyclohexanol,[27] the isomer showing a single absorption at the region is assigned to *trans*-4-(1-adamantyl)cyclohexanol and the other with two absorptions to the cis isomer. Other adamantylphenols and -cresols were also reduced to the corresponding cyclohexanols in 85–87% yield.

6-(1-Adamantyl)-*o*-cresol, in which dehydrogenation of the hydroxyl group occurred simultaneously with the catalytic hydrogenation of the benzene ring, gave 2-methyl-6-(1-adamantyl)cyclohexanone (5) in 88% yield. Relief of steric congestion around the hydroxyl group by the formation of a carbonyl group may be the best explanation of the result. The adamantylcyclohexanols (4) were smoothly oxidized by chromic acid in sulfuric acid[28] to the corresponding adamantylcyclohexanones (5) in 80–93% yield. The adamantylcyclohexanols and -cyclohexanones thus obtained are listed in Table III.

Bott[16] discovered that carbocations underwent addition to vinylidene chloride in concentrated sulfuric acid to form 2-substituted 1,1-dichloro-1-ethyl cations which spontaneously hydrolyzed to α-substituted acetic acids. The method is particularly useful for the preparation of *tert*-

Table IV. 1-Adamantylacetic Esters (7)

R[a]	Method[b]	Bp (mm), °C	n_D (temp, °C)	MIC, nmol/ml	MCC, nmol/ml
CH_3–	A	123–125 (7.0)	1.4959 (20)	190	290
n-C_4H_9–	A	98–100 (0.06)	1.4867 (22)	250	250
$CH_3(CH_2)_3CH(C_2H_5)CH_2$–	B	133–125 (0.09)	1.4840 (22)	3300	3300
n-$C_{12}H_{25}$–	C	182–185 (0.06)	1.4787 (22)	>2800	>2800
n-$C_{18}H_{37}$–[c]	C			>2200	>2200
c-C_6H_{11}–	B	142–143 (0.08)	1.5047 (21)	3600	3600
$C_{10}H_{15}$–[d]	B	172–173 (0.09)	1.5250 (22)	300	600
–CH_2CH_2–	A	225–230 (0.05)	1.5170 (26)	2400	2400
$O(CH_2CH_2–)_2$	A	245–250 (0.09)	1.5130 (24)	2200	2200
–$(CH_2)_{10}$–[e]	C		1.5050 (27)	1900	1900
$C(CH_2–)_4$[f]	C			>1200	>1200
–CH_2-c-C_6H_{10}-CH_2– (trans)[g]	B			>2000	2000
–$CH_2C_6H_4CH_2$–[h]	B	256–261 (0.05)		2000	>1000

[a] R in 1-adamantyl-CH_2COOR is shown. These are all new compounds. See also ref 32 and 33. [b] Esterification catalyzed by A, p-toluenesulfonic acid; B, zinc oxide; C, stannous oxide. [c] Mp 30.5–32°. [d] 5,6-*exo*-Trimethylene-2-*exo*-norbornyl.[41] [e] Not distillable. Purified with alumina column eluted by n-hexane. [f] Mp 165–167°. [g] Mp 127–128°. [h] Mp 65–67.5°.

Table V. 1,3-Adamantanediacetic Esters (12)

R[a]	Method[b]	Mp or bp (mm), °C	n_D (temp, °C)	MIC, nmol/ml	MCC, nmol/ml
n-C_4H_9–	A	163–170 (0.2)	1.4815 (25)	2700	2700
$CH_3(CH_2)_3CH(C_2H_5)CH_2$–	[c]				
	B		1.4830 (22)	[d]	[d]
n-$C_{12}H_{25}$–[e]	B		1.4760 (22)	1700	1700
n-$C_{18}H_{37}$–	C	44–44.5		1300	1300
c-C_6H_{11}–	B	200–206 (0.07)	1.5085 (20)	[d]	[d]
$C_{10}H_{15}$–[c,f]	B		1.5323 (22)	960	960

[a] R in 1,3-adamantane-$(CH_2COOR)_2$ is shown. All new compounds. See also ref 32. [b] Esterification catalyzed by A, p-toluenesulfonic acid; B, zinc oxide; C, stannous oxide. [c] Not distillable. Purified with alumina column eluted by n-hexane. [d] Not tested because representative higher alkyl esters were not active. [e] 5,6-*exo*-Trimethylene-2-*exo*-norbornyl.[41]

alkylacetic acids including 1-adamantylacetic acid (**6**). Reactant carbocations were generated from the corresponding halides, alcohols, and acetates[14–16] in his method. We modified[5a,29] the procedure so that the 1-adamantyl cation was formed directly from adamantane by hydride transfer to the *tert*-butyl cation,[12] thus avoiding the trouble of preparing 1-adamantyl halides, alcohol, or acetate beforehand.

A few percent of 1,3-adamantanediacetic acid (**11**) was an accompanying by-product in the synthesis of the monoacid **6**.[15] This is a consequence of the formation of the 1-carboxymethyl-3-adamantyl cation in the hydride transfer from the product **6** to the reactant adamantyl cation.[16] This, in turn, may be attributed to a reasonable stability of the 1-carboxymethyl-3-adamantyl cation that is also demonstrated in our successful synthesis of 1-chloro-3-adamantylacetic acid (**2**, Y = CH_2COOH; X = Cl) (Table I). Therefore, it was thought likely that increase in the amount of *tert*-butyl alcohol and vinylidene chloride in our modified synthesis[5a,29] of **6** might give rise to **11**. In actuality, however, the main product was **6**, additional reactants being converted mostly to *tert*-butylacetic acid. The reason for the failure was found to lie in the lowered concentration of sulfuric acid, which continually decreased as *tert*-butyl alcohol was transformed into the cation. It was made clear that at least 95% sulfuric acid was required for an effective hydride transfer from **6** to the *tert*-butyl cation. The addition of sulfur trioxide (in our laboratory, the most convenient form was fuming sulfuric acid) led to the solution of the problem and permitted us to establish a convenient, one-step synthesis of **11**.[5]

The acids **6** and **11** were transformed, through known methods, into esters (**7**[30,31] and **12**[32]), amides (**13**),[23] and nitriles (**8**[34] and **15**[35]). Thioamides (**9** and **16**) and the amidine (**10**) were obtained from nitriles. Amines (**14** and **17**[36]) were prepared from **13** (R = R′ = H) and **15**, respectively. Acylation of **17** led to amides **18**.[36] Similarly, 1-adamantanecarboxylic acid (**19**)[7] gave novel esters (**22**)[37] of polyhydric alcohols. The amidine (**23**)[38] from **19** via acid chloride,[15] amide,[39] and nitrile[40] reacted with malonic esters or cyanoacetic esters to give 2-(1-adamantyl)pyrimidines (**24**). Acylation of adenine with 1-adamantylcarbonyl chloride followed by lithium aluminum hydride reduction gave the adenine derivatives **25** and **26**. These preparations are summarized in Scheme I, and homologous series of compounds are listed in Tables IV–VIII. Other new compounds are shown in Table IX.

Antiviral Activity. Antiviral activity of the test compounds was determined by the tube assay method employing the Miyadera strain of Newcastle disease virus and monolayer culture of chick embryo fibroblasts as reported previously.[52] The virus solution used had a concentration of 128 hemagglutinin aggregation units. The virus solution and an aqueous solution or suspension (or emulsion) of the test compound were added simultaneously to the tissue culture. Virus multiplication was followed by measuring hemagglutinating activity, and cytotoxic effect of the test compounds was examined microscopically after 24 hr of treatment. Antiviral activities and cytotoxicities are expressed by minimum inhibitory concentration (MIC, nmol/ml) and minimum cytotoxic concentration (MCC, nmol/ml), respectively. The results for novel derivatives are

Table VI. 1,3-Adamantanebis(acetamides) (13)

RR'N–[a]	Method[b]	Mp, °C	MIC, nmol/ml	MCC, nmol/ml
H_2N–	D	181.5–183	4000	4000
CH_3NH–	E	194–196	>3600	>3600
C_2H_5NH–	E	146.5–147	c	c
n-C_4H_9NH–	E	103–104.5	c	c
n-$C_8H_{17}NH$–	D	62.5–64	c	c
n-$C_{12}H_{25}NH$–	D	74.5–76	c	c
n-$C_{18}H_{37}NH$–	D	98.5–99.5	1300	1300
c-C_6H_{11}-NH–	D	256.5–257.5	c	c
C_6H_5-CH_2NH–	D	135.5–137	>2300	>2300
C_6H_5-NH–	D	236.5–237.5	>2500	>2500
$(C_2H_5)_2N$–	E	53.5–54	c	c
$(n$-$C_4H_9)_2N$–[d]	D		c	c
C_6H_5-$N(CH_3)$–	D	124–125	c	c

[a] RR'N- in 1,3-adamantane-$(CH_2CONRR')_2$ is shown. All new compounds. See also ref 33. [b] D, reaction of amine with 1,3-adamantanebis(acetyl chloride); E, ammonolysis of dimethyl 1,3-adamantanediacetate. [c] Not tested because representative compounds in this series were not active. [d] Not crystallizable. $n^{22}D$ 1.5005.

Table VII. 1,3-Bis(2-acylaminoethyl)adamantanes (18)

R[a]	Method[b]	Mp, °C	MIC, nmol/ml	MCC, nmol/ml
CH_3–	D	187.5–188	3300	3300
n-C_3H_7–	F	141–142	>2800	>2800
n-C_7H_{15}–	D	104.5–105	>2100	>2100
n-$C_{17}H_{35}$–	F	107.5–108	>1300	>1300
C_6H_5–	D	172–172.5	>2300	>2300

[a] R in 1,3-adamantane-$(CH_2CH_2NHCOR)_2$ is shown. All new compounds. See also ref 36. [b] D, acylation by acid chloride (or anhydride in the case of acetyl); F, dehydration between amine and carboxylic acid.

shown in Tables I–IX and those for known compounds in Table X.

Although it is quite difficult to find any simple relationship between the antiviral activity and the structure or reactivity of the compounds, some apparent regularities in the activity seem to exist among closely related compounds. A maximum of the activity is sometimes seen in homologous series. The n-butyl compound has the highest activity in adamantyl alkyl ketones (**21**, Table X). Lowest members (methyl and ethyl) are the most active of all the adamantylcarboxylic and -acetic esters (**22** and **7**, Tables IV and X).

Relative positions of adamantyl and functional groups seem to be an important factor in determining the activity of isomeric compounds. For example, the adamantyl group renders activity to cyclohexanols (**4**) when substituted at the 2 position, while it does not at the 4 position (2-Ad-5-Me- and 2-Me-4-Ad-cyclohexanols, Table III). Contribution of the methyl group, however, may not be overlooked in the activity of **4**, since the activity of isomeric methyl-2-adamantylcyclohexanones (**5**) varies with the position of the methyl substituent: 5- and 6-methyl bring about higher activity than 4-methyl (Table III). Similar activity difference in adamantylphenols and -cresols (Table II) may be attributed to the same cause.

All the amides (Tables VI, VII, IX, and X) have little or no activity, while amines (and their hydrochlorides), including amantadine, are fairly active. This is in large contrast to carboxylic acids, where the acids themselves do not exhibit activities while the lower alkyl esters do.

Compounds having a functional group which is recognized as necessary for biological activity such as antibacterial, pesticidal, etc., are not always associated with the antiviral activity. Thus thiol, amines, amidines, phenols, and isothiouronium salt showed activities, while thioamides, pyrimidines, and purines were found of low activity.

It may be worth mentioning separately that lower alkyl esters [Ad-COOEt, Ad-CH_2COOMe, Ad-COCH(R)COOEt (R = H or Me), and Adn-$(CH_2COOMe)_2$] exhibit a high level of activity, whereas higher alkyl homologs are rather inactive. Interaction with cell membrane, as is suggested for the action of amantadine,[2] might also explain the change in the activities of the homologous esters with alkyl chain length.

Cytotoxicities of the compounds usually paralleled the antiviral activities, the activity and the cytotoxicity appearing at similar concentrations. However, some esters [Ad-CH_2COO-$C_{10}H_{15}$, Ad-$COCH_2COOEt$, (Ad-$COOCH_2$-$CH{=})_2$, and (Ad-$COOCH_2CH_2)_2S$; Tables IV, VIII, and X] as well as 1-adamantyl bromide (Table X) showed cytotoxicity at concentrations 1.5–2 times larger than minimum inhibitory concentrations. Many compounds (higher alkyl esters and amides, etc.) were as much nontoxic as inactive.

Experimental Section

All melting and boiling points are uncorrected. Ir spectra were taken on a Hitachi 215 spectrophotometer. ^1H NMR spectra were obtained on a Varian T-60 instrument with Me_4Si as internal standard. Mass spectra were measured on a Hitachi RMU-6D spectrometer at 75-eV ionization voltage. VPC was run on a Shimazu GC-4B-PTF chromatograph employing columns (0.25 in. $\phi \times 6$ ft) packed with 60–80 mesh Chromosorb W containing 30% silicone SE-30, Carbowax 20M, Apiezone L, or DEGS. Preparative VPC was done on a Varian Aerograph 700 instrument. The GC–MS measurements were made on a JEOL JGC-20KP gas chromatograph combined with JMS-D100 mass spectrometer. The compounds listed in Table X were prepared according to the methods of references shown in the table, except for 1-adamantyl bromide, 1-adamantylacetic acid, and 1,3-adamantanediacetic acid which were synthesized through our procedures as described in this section. All of them had the same physical properties as well as ir, ^1H NMR, and mass spectra as described in the literatures. Analyses for elements indicated by the symbols were within ±0.4% of the calculated values for all the new compounds.

1-Substituted 3-Haloadamantanes (2). To a mixture of 200 g of 96% sulfuric acid, 0.021 mol of the 1-substituted adamantane (**1**), and 75 ml of carbon tetrachloride kept between 5 and 10° was added dropwise with efficient stirring a mixture of 6.0 g (0.081 mol) of *tert*-butyl alcohol and 20 ml of carbon tetrachloride in a period of 30 min, while stream of dry hydrogen chloride was passed into the reaction mixture at a rate of 100 ml/min. The reaction was stirred at the same temperature for further 4 hr with bubbling of

Table VIII. 1-Adamantanecarboxylic Esters (22)

R[a]	Method[b]	Mp or bp (mm), C	MIC, nmol/ml	MCC, nmol/ml
$-(CH_2)_5-$	A	119.5–121.5	650	1200
$-(CH_2)_7-$	A	53–54.5, 221–225 (0.07)	250	1200
$-(CH_2)_8-$	A	127–128	2400	2400
$-(CH_2)_9-$	B	105–106.5	[c]	[c]
$-(CH_2)_{10}-$	B	59–61	[c]	[c]
$-CH(CH_3)CH_2-$	A	87–88, 211–215 (0.09)	[c]	[c]
$(CH_3)_2C(CH_2-)_2$	C	162.5–163.5	[c]	[c]
$C_2H_5C(CH_2-)_3$	B	189–191	>1600	>1600
$C(CH_2-)_4$	C	278–279	>1300	>1300
$O(CH_2CH_2-)_2$[d]	C	245–249 (0.09)	230	1200
$CH_3N(CH_2CH_2-)_2$[e]	B	219–222 (0.06)	110	450
$S(CH_2CH_2-)_2$	B	58–59.5, 242–246 (0.3)	900	1300
$-CH_2CH=CHCH_2-$ (cis)	B	59–60.5	490	970
-c-C_6H_{10}- (trans)	B	278–279	[f]	[f]
$-CH_2$-c-$C_6H_{10}CH_2-$ (trans)	B	186.5–188	>1100	>1100
2-CH_3O-4-$CH_2=CHCH_2C_6H_3-$[g]	D	97.5–98.5	>3100	>3100
2-CH_3O-4-$CH_3CH=CHC_6H_3-$[h]	D	129.5–131	[f]	[f]
$-CH_2-C_6H_4-CH_2-$	B	167.5–169	>2200	>2200

[a] R in 1-adamantyl-COOR is shown. All are new compounds. See also ref 37. [b] A, B, and C, esterification catalyzed by *p*-toluenesulfonic acid, zinc oxide, and stannous oxide, respectively; D, action of acyl chloride in pyridine. [c] Not tested because representative higher alkyl esters were not active. [d] $n^{16}D$ 1.5151. [e] $n^{26}D$ 1.5130. [f] Not tested because of smallness in sample size. [g] An eugenol ester. [h] An isoeugenol ester.

Table IX. Novel Derivatives of Adamantane

Compound	Mp or bp (mm), °C	MIC, nmol/ml	MIC, nmol/ml
9	185–186	1200	1200
10·HCl	>300	110	440
14[a]	109–111 (0.6)	310	410
15	73–74, 164–167 (0.35)	930	1900
16	187–188	890	1800
17	109–112 (0.05)	450	450
20 (R = Me)[b]	125–127 (0.4)	230	300
24 (Z = OH)	278–280	2000	4100
24 (Z = NH_2)	>300	410	410
25	265–267 dec	>3400	>3400
26	>300	>3500	>3500
N,N'-$(MeOCO)_2$-14[c]	174–175	>3200	>3200
trans-4-Ad-$C_6H_{10}OAc$[d]	97–98.5	180	900

[a] $n^{22.5}D$ 1.5290. [b] $n^{25}D$ 1.4931. [c] 1,3-Bis(methoxycarbonylaminomethyl)adamantane. [d] *O*-Acetoxy-*trans*-4-(1-adamantyl)cyclohexanol.

hydrogen chloride. The reaction mixture was poured onto 300 ml of cracked ice–water, and the crude product was separated by filtration or extraction with carbon tetrachloride and washed thoroughly with water. Recrystallization or distillation gave pure products which were listed in Table I. Anal. C, H, Cl (N).

Use of hydrogen bromide in place of hydrogen chloride in the above procedures gave 1-substituted 3-bromoadamantane (**2**, X = Br). Thus was prepared **2** (Y = H) [92% yield; mp 118.5–119° (lit. 117–117.5°,[9] 118°,[7b] 119–120°[20])] and **2** (Y = CH_2COOH) [90% yield; mp 197–199° (lit.[16] 198–199°)].

Reaction of 1-Chloroadamantane (2) with Phenol and Cresols. A mixture of 10.2 g (0.060 mol) of 1-chloroadamantane and 6.8 g (0.072 mol) of phenol was stirred at 100° for 3 hr and then at 140° for 5 hr. After being cooled, the reaction mixture was dissolved in 100 ml of ether and extracted with 100 ml of a 10% sodium hydroxide solution. White precipitates were formed in the aqueous layer, which were separated by filtration, suspended in 50 ml of water, acidified with 5% hydrochloric acid, and extracted with two 200-ml portions of ether. Combined ether extracts were washed with water, dried over anhydrous sodium sulfate, and concentrated to give 5.3 g (39% yield) of crude *p*-(1-adamantyl)phenol. Slow sublimation gave a pure sample (Table II). Anal. ($C_{16}H_{20}O$) C, H.

The residual ethereal solution from which *p*-(1-adamantyl)phenol had been separated was washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue was 4.9 g (36% yield) of crude *o*-(1-adamantyl)phenol which was sublimed to give a pure sample listed in Table II. Anal. ($C_{16}H_{20}O$) C, H.

Similar procedures using a cresol as starting material gave the products listed in Table II. Anal. C, H.

Rearrangements of *o*-(1-Adamantyl)phenols and -cresols. Crossover Experiments. A mixture of 1.0 g (0.0041 mol) of 6-(1-adamantyl)-*m*-cresol and 6.0 g (0.064 mol) of phenol was heated at 140° for 5 hr with bubbling of dry hydrogen chloride. The reaction mixture was analyzed on VPC to show all the starting material had been transformed into *p*-(1-adamantyl)phenol. Reaction of *o*-(1-adamantyl)phenol and *m*-cresol under the same conditions gave 6-(1-adamantyl)-*m*-cresol as the sole product.

1-Adamantylcyclohexanols (4). A mixture of 5.0 g (0.022 mol) of *p*-(1-adamantyl)phenol, 40 ml of ethanol, 1.0 g of Raney nickel (W-6), and 0.25 ml of triethylamine was placed in a 100-ml autoclave. The vessel was shaken at 140° for 4 hr, while the pressure was kept at about 110 kg/cm^2 with continuous supply of hydrogen. The catalyst was filtered off from the cooled reaction mixture, and the filtrate was concentrated on a steam bath. The residue was dissolved in 100 ml of ether, washed with water, and dried over anhydrous sodium sulfate. Removal of ether from the solution left 4.4 g (86% yield) of crude 4-(1-adamantyl)cyclohexanol (**4**). Sublimation gave a pure sample (Table III). The material was found to consist of 70% trans and 30% cis isomers by VPC analysis of the *O*-acetyl derivatives, as shown below. Other adamantylphenols and -cresols were similarly hydrogenated to give cyclohexanols in 85–86% yield, except that 6-(1-adamantyl)-*o*-cresol was not reduced to a cyclohexanol but converted to 2-methyl-6-(1-adamantyl)cyclohexanone (**5**) in 88% yield. Adamantylcyclohexanols thus prepared are listed in Table III. Anal. C, H.

***O*-Acetyl-*cis*- and -*trans*-4-(1-adamantyl)cyclohexanols.** A mixture of 9.4 g (0.040 mol) of 4-(1-adamantyl)cyclohexanol obtained above, 6.5 g (0.063 mol) of acetic anhydride, and 26 g of pyridine was heated at 90° for 3 hr. The cooled reaction mixture was poured onto cracked ice–water and neutralized with 10% hydro-

Table X. Antiviral Activity of Known Adamantane Derivatives

Compound[a]	Ref[b]	MIC, nmol/ml	MCC, nmol/ml
Ad-H	42	>7300	>7300
Ad-Me	7b	1300	1300
Ad-Et	14b, 43	3000	6100
Ad-Ph	7b, 43	470	2400
Ad-Br	7b, 8, *c*	470	2300
Adn-CH_3-Br	44	>4400	>4400
Ad-CH_2Cl	45	270	270
Ad-$CHCl_2$	46	230	230
Ad-OH	7b, 10, 20	3300	3300
3-HomoAd-OH	47	600	3000
Ad-CH_2OH	7b, 9	600	3000
Ad-CH_2OSO_2-C_6H_4-*p*-CH_3	7b	1600	3100
Ad-OCH_3	40	600	3000
Ad-$COCH_3$	45, 48	560	1400
Ad-$CO(CH_2)_3CH_3$	6	270	360
Ad-$CO(CH_2)_6CH_3$	6	230	300
Ad-$CO(CH_2)_{10}CH_3$	6	>3100	>3100
Ad-$CO(CH_2)_{18}CH_3$	6	>2300	>2300
Ad-$C(CH_3)$=NNH-C_6H_3-2,4-$(NO_2)_2$	45	>700	>700
Ad-COOH	7b, 12	5500	>5500
Ad-CH_2COOH	7b, 16, *c*	>5100	>5100
Adn-(CH_2COOH)	16, *c*	>4000	>4000
Adn-($CH_2COOMe)_2$	16	360	1800
Adn-Br-CH_2COOH	16, *c*	>1800	>1800
Ad-$COOC_2H_5$	7b	290	290
Ad-$COCH_2COOC_2H_5$	48	400	2000
Ad-$CONH_2$	39	2800	5600
Ad-CH_2CONH_2	49	2100	2100
Ad-C(=S)NH_2	38	2600	1300
Ad-CH_2CN	34	570	2900
Ad-C(=NH)NH_2·HCl	38	470	1200
Ad-NH_2·HCl[d]	39	1300	1300
Ad-$NHCOCH_3$	7b	2600	2600
Ad-$NHSO_2$-C_6H_4-*p*-CH_3	39	>1600	>1600
Ad-NO_2	7b, 9, 39	330	440
Ad-C_6H_4-*p*-NO_2	50	>3900	3900
Ad-SH	10b, 51	360	240
Ad-SC(=NH)NH_2·HBr	17	140	210

[a] Ad, 1-adamantyl; Adn, 1,3-adamantylene; HomoAd, homoadamantyl. [b] Reference is made to the first as well as subsequent improvements in, if any, synthesis of the compound. [c] This work. [d] Amantadine hydrochloride.

chloric acid. The mixture was extracted with two 100-ml portions of ether, and the ether solution was washed thoroughly with water and dried over anhydrous sodium sulfate. Evaporation of the ether gave 10.3 g (99% yield) of 4-(1-adamantyl)cyclohexyl acetate. The material was analyzed on VPC and found to consist of 70% trans and 30% cis isomers. The conformation of the isomers were determined by ir spectra as described before.

Recrystallization of the isomeric acetate mixture from methanol yielded 3.8 g of the pure trans compound (Table IX): mp 97.5–98.5°; ir (KBr) 2910, 1740, 1450, 1360, 1240, 1040, 894 cm^{-1}. Anal. ($C_{18}H_{28}O_2$) C, H.

The recrystallization residue was purified on preparative VPC to give the cis isomer, a liquid: ir (neat) 2900, 1740, 1450, 1360, 1240, 1210, 1180, 1110, 1010, 970, 950 cm^{-1}. Anal. ($C_{18}H_{28}O_2$) C, H.

1-Adamantylcyclohexanones (5). A solution of chromic acid in sulfuric acid was prepared according to the method of Meinwald et al.[28] A solution of 4.7 g (0.020 mol) of 4-(1-adamantyl)cyclohexanol in 200 ml of ether was kept cooled in an ice bath, and 9.4 g of the chromic acid solution prepared above was added dropwise with efficient stirring to the ether solution over a period of 15 min. The mixture was stirred at the same temperature for another 4 hr. The ether layer was separated and washed successively with water, 2% sodium bisulfite solution, water, saturated sodium bicarbonate solution, and finally with water. The ether solution was dried over anhydrous sodium sulfate and evaporated to give 4.3 g (93% yield) of crude 4-(1-adamantyl)cyclohexanone (**5**). Purification by sublimation yielded an analytical sample. Other adamantylcyclohexanols were similarly oxidized to give the corresponding cyclohexanones (Table III). Anal. C, H.

1-Adamantylacetic Acid (6).[5a,29] To a mixture of 120 ml of 95% sulfuric acid, 37 g of boron trifluoride etherate, 6.8 g (0.05 mol) of adamantane, and 50 ml of cyclohexane kept between 8 and 10° was added dropwise with efficient stirring a mixture of 15 g (0.2 mol) of *tert*-butyl alcohol and 49 g (0.5 mol) of vinylidene chloride in a period of 40 min. The reaction was stirred for a further 2 hr at the same temperature. The reaction mixture was poured onto 300 ml of ice–water and extracted with three 100-ml portions of ether. Combined ether extracts were washed once with cold water and then extracted with five 50-ml portions of 5% sodium hydroxide solution. The alkali solution was made strongly acidic by the addition of concentrated hydrochloric acid, and the resulting precipitates were filtered off and washed thoroughly with cold water. Recrystallization from 10% aqueous methanol gave 7.1 g (73% yield) of **6**, mp 137–139° (lit. mp 136°,[7b] 135–136° [16]). The melting point was not depressed on admixture with an authentic specimen prepared by the method of Bott,[16] and ir, ^1H NMR, and mass spectra were also identical with those of the authentic specimen.

1,3-Adamantanediacetic Acid (11).[5] A mixture of 80 ml of 95% sulfuric acid, 24 g of boron trifluoride etherate, 6.8 g (0.05 mol) of adamantane, and 50 ml of cyclohexane was kept between 8 and 10° in an ice bath, and a mixture of 22.2 g (0.3 mol) of *tert*-butyl alcohol and 58.2 g (0.6 mol) of vinylidene chloride in one dropping funnel and 70 g of 23% fuming sulfuric acid in the other were dropped side by side to the above mixture in a period of 2 hr. Stirring was continued for another 2 hr at the same temperature. The reaction mixture was treated in a similar way as described in the preceding paragraph to give 10.6 g (84% yield) of crude **11**, mp and mmp (with an authentic specimen[16]) 234–236° (lit.[16] 234–236°). Two recrystallizations of the crude product from 50% methanol gave 7.6 g (60% yield) of a pure product, mp 244–244.5°. A sample of the pure **11** was esterified with diazomethane,[54] and the dimethyl ester was analyzed on VPC to show that the sample contained 0.6% of 1-adamantylacetic acid as the single impurity.

1-Adamantylacetic Esters (7)[30,31] **and 1,3-Adamantanediacetic Esters (12).**[32] Esters **7** and **12** were prepared by the esterification of **6** and **11** with the corresponding alcohols in the presence of *p*-toluenesulfonic acid (method A), zinc oxide (method B), or stannous oxide (method C). Water formed in the reaction was continuously removed through a water separator,[55] and some amount of toluene was also added for azeotropic dehydration in case of alcohols with high boiling point. Esters thus prepared in 56–73% yields are listed in Tables IV and V. Anal. C, H.

1,3-Adamantanebis(acetamides) (13).[33] 1,3-Adamantanediacetyl chloride[54] was obtained by refluxing a mixture of **11** and excess thionyl chloride for 24 hr. Reaction of the acid chloride with an amine in benzene solvent in the presence of pyridine gave most of the higher alkylamines (method D). Tetrahydrofuran was used as the solvent for the reaction with 28% aqueous ammonia. Another method for preparing **13** was aminolysis of dimethyl 1,3-adamantanediacetate[16] at 250° in an autoclave (method E), which was applied to lower alkylamines. Crude products were recrystallized from tetrahydrofuran–ethanol mixtures to give pure samples in over 85% yields (Table VI). Anal. C, H, N.

1,3-Bis(aminomethyl)adamantane (14). Hoffmann reaction of 20.0 g (0.08 mol) of **13** (R = R′ = H) with 30.7 g (0.187 mol) of bromine in 350 ml of 10% sodium hydroxide solution at ambient temperature to 75° gave 10.8 g (70% yield) of **14** (Table IX). Anal. ($C_{12}H_{22}N_2$) C, H, N.

1-Adamantylacetonitrile (8) and 1,3-Adamantanebis(acetonitrile) (15).[35] 1,3-Adamantanebis(acetonitrile) (**15**) was prepared from **11** by passing ammonia at 260–300° through the molten acid containing a catalytic amount of zinc oxide and activated alumina.[35] Removal of the catalyst by filtration of a benzene solution of the crude product followed by fractional distillation of the filtrate gave an 88% yield of **15** (99.1% purity, as determined by VPC; listed in Table IX): ir (KBr) 2220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.22 (6, s, CH_2CN and bridgehead H); MS *m/e* (rel intensity) 214 (0.2, M^+), 175 (14), 174 (100, Ad − CH_2CN^+). Anal. ($C_{14}H_{18}N_2$) C, H, N.

1-Adamantylacetic acid (**6**) gave in a similar procedure the corresponding nitrile **8** in 84% yield: mp 77.5–78.5° (lit.[34] 73–74°). Ir and ^{1}H NMR spectra indicated the presence of a cyanomethyl group.

1,3-Bis(2-aminoethyl)adamantane (17). A mixture of 150 g (0.7 mol) of **15**, 7.5 g of Raney nickel (W-6), 1.5 g of sodium hydroxide, and 100 ml of 98% ethanol was heated in an autoclave to 115–120° for 2 hr with hydrogen of 120 kg/cm^2 pressure. Filtration of the catalyst and fractional distillation of the filtrate gave 129 g (83% yield) of **17** (Table IX): ir (neat) 3400, 3300, 1600 cm^{-1}; ^{1}H NMR (CCl_4) δ 2.42–2.74 (4, m, CH_2NH_2); MS *m/e* (rel intensity) 222 (3, M^+), 194 (10), 193 (55), 30 (100, CH_2CN^+). Anal. ($C_{14}H_{26}N_2$) C, H, N.

1,3-Bis(2-acylaminoethyl)adamantanes (18). Acylation of **17** by acid chlorides in benzene in the presence of pyridine (method D) gave the corresponding amides **18**. Alternatively, some **18** was obtained by azeotropic dehydration of a mixture of an acid and **17** with mixed xylene (method F). Crude products were recrystallized from the benzene–ethanol mixture to give pure compounds (83–89% yields) listed in Table VII. Anal. C, H, N.

1-Adamantanecarboxylic Esters (22).[37] Esterification of **19**[7b,12] with various mono- and polyhydroxy compounds according to either of the methods A–D as described above gave **22** in 82–91% yields, which were listed in Table VIII. Anal. C, H, (N, S).

1-Adamantylthioacetamide (9) and 1,3-Adamantanebis(thioacetamide) (16). To a solution of 1.6 g (0.009 mol) of **8** and 0.73 g of diethylamine in 40 ml of dimethylformamide kept at 60° was bubbled a stream of hydrogen sulfide at a rate of 35 ml/min for 4 hr. The reaction mixture was stirred for a further 3 hr at the same temperature. The reaction mixture was then poured onto 200 ml of cold 5% hydrochloric acid. Precipitates were filtered, and any dissolved material was recovered by ether extraction and evaporation of the ether. Combined crude products were washed with a little amount of petroleum ether and recrystallized from absolute ethanol to give 1.2 g (63% yield) of **9** (Table IX): ir (KBr) 3400, 3270, 3150, 1620, 1270, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.60 (2, s, CH_2CS). Anal. ($C_{12}H_{19}NS$) C, H, N, S.

Similarly from 5.0 g (0.023 mol) of **15** and 3.9 g of diethylamine in 50 ml of dimethylformamide at 50° was prepared 4.7 g (72% yield) of **16** (Table IX): ir (KBr) 3370, 3280, 3170, 1270, 1180 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.37 (4, s, CH_2CS). Anal. ($C_{14}H_{22}N_2S_2$) C, H, N, S.

1-Adamantylacetamidine Hydrochloride (10·HCl). Dry hydrogen chloride was bubbled for 2 hr into a solution of 2.5 g (0.014 mol) of **8** in 30 ml of absolute ethanol kept at 5°. The reaction was set aside overnight at ambient temperature. After excess hydrogen chloride was expelled from the reaction mixture by a stream of nitrogen, the reaction mixture was diluted with 20 ml of absolute ethanol and warmed to 50° while ammonia gas was passed into the mixture for 2 hr. Concentration of the reaction mixture gave precipitates of crude 1-adamantylacetamidine (**10**) hydrochloride, which was recrystallized from ethanol to give 1.5 g (46% yield) of pure material (Table IX): ir (KBr) 3320, 3130, 1680 cm^{-1}. Anal. ($C_{12}H_{21}N_2Cl$) C, H, N, Cl.

Ethyl α-(1-Adamantylcarbonyl)propionate (20, R = Me). Alkylation[6] of ethyl 1-adamantylcarbonylacetate[48] by methyl iodide gave **20** (R = Me; Table IX) in 81% yield: ir (neat) 3000, 1750, 1710, 1660, 1620, 1190, 1110, 1070 cm^{-1}; ^{1}H NMR (CCl_4) δ 3.26 (0.4, s, COCHMeCO), 4.00 and 4.20, 4.05 and 4.25 (2, two AB q, J = 7 Hz, OCH_2CH_3), 1.22, 1.25 (3, two t, J = 7 Hz, CH_2CH_3). Anal. ($C_{16}H_{24}O_3$) C, H.

2-(1-Adamantyl)-4,6-dihydroxypyrimidine (24, Z = OH) and 2-(1-Adamantyl)-4-hydroxy-6-aminopyrimidine (24, Z = NH_2). 1-Adamantylcarboxamidine (**23**) hydrochloride[38] was prepared from 1-cyanoadamantane[40] in a similar manner as for 1-adamantylacetamidine (**10**) hydrochloride. A solution of 1.1 g (0.05 mol) of **23**·HCl thus obtained in 10 ml of absolute ethanol was neutralized with 10 ml of ethanolic sodium ethoxide containing 0.35 g (0.15 g-atom) of sodium and refluxed with 0.8 g (0.05 mol) of diethyl malonate for 2 hr. After being set aside overnight at ambient temperature, the reaction mixture was concentrated, and the residue was poured onto 50 ml of cold water. The resulting mixture was adjusted to pH 2–3 by the addition of 10% hydrochloric acid. The precipitates formed were filtered off and recrystallized from ethanol–water to give 0.41 g (33% yield) of **24** (Z = OH; Table IX): ir (KBr) 3430, 1640, 1540, 1180, 820, 800 cm^{-1}. Anal. ($C_{14}H_{18}N_2O_2$) C, H, N.

Use of 0.56 g (0.05 mol) of ethyl cyanoacetate in place of diethyl malonate in the above procedure gave 0.34 g (28% yield) of **24** (Z = NH_2; Table IX): ir (KBr) 3540, 3420, 1650, 1610, 1590, 1290, 1270, 1230, 980 cm^{-1}. Anal. ($C_{14}H_{19}N_3O$) C, H, N.

N^6-(1-Adamantylcarbonyl)adenine (25) and N^6-(1-Adamantylmethyl)adenine (26). Acylation of adenine with 1-adamantylcarbonyl chloride[15] in pyridine solvent and sublimation of the crude product gave **25** (Table IX) in 89% yield: ir (Nujol) 3270, 1680, 1550, 1510, 1240, 1180, 880 cm^{-1}. Anal. ($C_{16}H_{19}N_5O$) C, H, N.

Reduction of **25** with lithium aluminum hydride in refluxing ether gave **26** (Table IX) in 78% yield: ir (Nujol) 3200, 1630, 1560, 1250, 1140, 900, 880, 860 cm^{-1}. Anal. ($C_{16}H_{21}N_5$) C, H, N.

1,3-Bis(methoxycarbonylaminomethyl)adamantane. To a solution of 5.0 g (0.02 mol) of **13** (R = R′ = H) in 50 ml of methanol containing 1.9 g (0.84 g-atom) of sodium was dropped 64 g (0.04 mol) of bromine at 0–5°, and the reaction was gradually heated until reflux. The reaction mixture was concentrated, and the residue was poured onto cold water. Precipitates formed were collected and recrystallized from benzene–ethanol to give 5.0 g (80% yield) of 1,3-bis(methoxycarbonylaminomethyl)adamantane [*N*,*N*′-bis(methoxycarbonyl)-14] (Table IX): ir (Nujol) 3320, 3100, 1720, 1690, 1560, 1530, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.95 (4, d, J = 6 Hz, CH_2NH), 3.75 (6, s, OCH_3). Anal. ($C_{16}H_{26}N_2O_4$) C, H, N.

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Synthesis and Antiviral Activity of Certain 5'-Monophosphates of 9-D-Arabinofuranosyladenine and 9-D-Arabinofuranosylhypoxanthine

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A number of 5'-phosphates of 9-D-arabinofuranosyladenine and 9-D-arabinofuranosylhypoxanthine were prepared and tested against a variety of DNA viruses in tissue culture. The syntheses of the antiviral agent 9-β-D-arabinofuranosylhypoxanthine 5'-monophosphate (**6**) and a series of related nucleotides, 9-β-D-arabinofuranosyladenine 5'-*O*-methylphosphate (**3**), 9-β-D-arabinofuranosylhypoxanthine 5'-*O*-methylphosphate (**7**), 9-β-D-arabinofuranosylhypoxanthine cyclic 3',5'-phosphate (**13**), and 9-α-D-arabinofuranosylhypoxanthine 5'-monophosphate (**17**), are described. The concepts underlying the development of these antiviral agents are discussed. Comparison of the anti-DNA viral activity is made with 9-β-D-arabinofuranosyladenine (ara-A). Reproducible antiviral activity against three DNA viruses in vitro at nontoxic dosage levels is demonstrated by **3**, **6**, and other related nucleotides.

The last decade has witnessed the recognition of nucleoside analogs as potential clinically useful antitumor and antiviral agents. Among the presently known synthetic nucleosidic antiviral agents, some of the more active analogs are 5-iodo-2'-deoxyuridine (IUDR),[1-3] 1-β-D-arabinofuranosylcytosine (ara-C),[4-10] 9-β-D-arabinofuranosyladenine (ara-A),[11-14] and the broad spectrum antiviral agent 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (ribavirin).[15,16] Of these antiviral agents, only IUDR is currently available as a prescribed drug; however, its low solubility and high toxicity make its use somewhat limited. Ara-A is presently undergoing extensive clinical evaluation against a variety of diseases primarily caused by the Herpes viruses.[17] While efficacy in humans has been established,[14,18,19] the nucleoside has certain disadvantages which may preclude its overall usefulness. These include a relative insolubility in water (0.5 mg/ml at 25°, 1.8 mg/ml at 37°) and a moderate toxicity, manifested predominantly as mild nausea, central nervous system involvement, and leucocyte chromosome breakage.[14,19] It is pertinent to note also the marked antiviral activity[20] of 9-β-D-arabinofuranosylhypoxanthine (ara-Hx), the apparent major breakdown product of ara-A.[21,22]

Numerous derivatives of ara-A have been described. Recent studies[23] with several 2-substituted ara-A derivatives (2-chloro, 2-methoxy, 2-benzyloxy, 2-methylthio) indicated 2-Cl-ara-A had antiviral efficacy in vitro, but its in vivo activity was inferior to ara-A. Replacement by N of the 8-CH moiety of α-ara-A (8-aza-α-ara-A) resulted in in vitro antiviral activity approximately equal to ara-A, although the compound was relatively ineffective and quite toxic in vivo.[24] Similar efficacy in vitro but loss of activity in vivo was also reported by Renis et al.[25] using the 5'-benzoyl and 5'-palmitoyl esters of ara-A. 9-β-D-Arabinofuranosyladenine 5'-monophosphate (ara-AMP)[26] and 9-β-D-arabinofuranosyladenine cyclic 3',5'-phosphate (cyclic ara-AMP),[27,28]