g) were decapitated and injected ip with 10 mL of Hank's balanced salt solution (HBSS) containing 0.1% human albumin and 5 mM potassium phosphate. The peritoneum was massaged for 1 min and the lavage fluid aspirated and centrifuged at 350*g*. The supernatant was discarded and the cell pellets were suspended in 2 mL of rat antisera (prepared as in the PCA test) containing 0.1 mg of heparin. After sensitization by shaking the suspension at 37 °C for 2 h, the cells were centrifuged. The resulting cell pellets were resuspended and diluted to the final working volume in buffered HBSS. Aliquots (1.5 mL) of the sensitized cell suspension were challenged with 0.5 mL of EA (80 mg/mL). Drugs were tested at several different concentrations by adding them simultaneously with the antigen challenge. After antigen and drug additions, the cells were incubated for 10 min and histamine was assayed fluorimetrically. Percent inhibition was determined by comparison with histamine release in the absence of drug.

Inhibition of Allergic Bronchospasm in Sensitized Rats. The methods employed were similar to those previously described for this model.[8,9] Male Harlan–Wistar rats (225–275 g) were sensitized by treatment with egg albumin intramuscularly (1 mg/rat) and β pertussis vaccine ip (2×10^{10} organisms/rat). This procedure generates an immediate hypersensitivity reaction with maximum IgE antibody.[7]

Thirteen to fifteen days after sensitization, the rats were anesthesized with urethane (1.5 g/kg, ip) and the duodenum was exposed through a small abdominal incision. For id administration, drugs in solution or suspension were injected directly into the lumen of the duodenum. A cannulated jugular vein was used for iv drug or EA administration. A cannulated carotid artery was connected to a Statham P23D6 pressure transducer for blood-pressure measurements. The trachea was cannulated and connected to a Statham P23-BB pressure transducer to obtain measurements of pulmonary ventilation.

Rats were challenged with a 2 mg/rat dose of EA (iv), and the changes in pulmonary ventilation pressure and mean arterial blood pressure arising from the ensuing anaphylactic syndrome were measured. Drugs were administered (iv or id) at various time intervals prior to antigen challenge. Drug effects on the antigen-induced syndrome were derived by comparison of responses in individual drug-treated animals to a mean response obtained in a separate group of non-drug-treated (control) animals.

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Antiviral Activity of Aliphatic Nucleoside Analogues: Structure–Function Relationship

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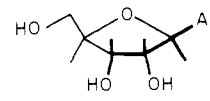
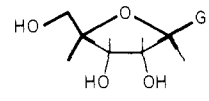
Of a series of 58 aliphatic nucleoside analogues, (*S*)-9-(2,3-dihydroxypropyl)adenine [(*S*)-DHPA] proved to be the most active congener, when assayed for antiviral activity in primary rabbit kidney cell cultures challenged with either vaccinia or vesicular stomatitis virus. Whereas most analogues derived from substituted purine and pyrimidine bases and bearing various hydroxy- or amino-substituted alkyl chains did not show evidence of antiviral activity at a concentration of 2 mM, (*S*)-DHPA inhibited both vaccinia and vesicular stomatitis virus replication at 0.05–0.1 mM. For 9-[(*RS*)-2,3-diazidopropyl]adenine and some di- and trihydroxybutyl analogues of DHPA, viz., 9-[(2*RS*,3*SR*)-2,3-dihydroxybutyl]adenine, 9-[(*RS*)- or 9-[(*S*)-3,4-dihydroxybutyl]adenine, 9-[(2*S*,3*R*)-2,3,4-trihydroxybutyl]adenine, and 3-(adenin-9-yl)-(*RS*)-alanine, an antiviral effect was noted at a concentration of 0.5–1 mM.

Two nucleoside analogues, in which the cyclic carbohydrate moiety was replaced by an acyclic side chain, have recently been reported to possess marked antiviral activity in both cell culture systems and animal models. (*S*)-DHPA, the *S* enantiomer of 9-(2,3-dihydroxypropyl)-adenine, was found to inhibit the replication of a number of DNA and RNA viruses (vaccinia, herpes simplex, vesicular stomatitis, and measles).[1] The related compound 9-[(2-hydroxyethoxy)methyl]guanine (acycloguanosine) proved selectively inhibitory to herpes viruses; acycloguanosine would owe its antiherpes activity to the fact that it is specifically phosphorylated to the monophosphate derivative in herpes-infected cells and that, upon further conversion to the triphosphate, it would inhibit herpes virus DNA polymerization more effectively than cellular DNA synthesis.[2,3]

Both compounds are derived from the natural nucleosides, of which DHPA has preserved the base-C(1)-



(*S*)-DHPA



acycloguanosine

C(2)-C(3) portion, whereas acycloguanosine retained the base-C(1)-O-C(4)-C(5) fragment.

In studies aimed at delineating the structural requirements that underlie the broad-spectrum antiviral activity of (*S*)-DHPA, various aliphatic nucleoside analogues of nucleic acid bases were synthesized and their antiviral potentials were assessed in primary rabbit kidney cell cultures challenged with either an RNA virus (vesicular

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Table I. Antiviral Activity of 2,3-Dihydroxypropyl Derivatives of Heterocyclic Bases

compd	config	base residue	MID, μg/mL: vesicular stomatitis virus	MID, μg/mL: vaccinia virus
1a	9-(*S*)	adenine	7-20	10-40
1a	9-(*R*)	adenine	300	⩾400
1a	9-(*RS*)	adenine	20-40	40-70
1b	9-(*RS*)	2-amino-adenine	>400	>400
1c	9-(*RS*)	2-methylthio-adenine	>400	400
1d	9-(*RS*)	8-bromo-adenine	>200	>200
1e	9-(*RS*)	8-hydroxy-adenine	>400	>400
1f	9-(*RS*)	8-mercapto-adenine	>400	>400
2	9-(*RS*)	N^6-methyl-adenine	⩾400	⩾400
3	9-(*RS*)	N^6-dimethyl-adenine	>400	>400
4	9-(*RS*)	6-mercapto-purine	>400	>400
5	9-(*S*)	hypoxanthine	>400	>400
6	9-(*RS*)	guanine	>400	>400
7	7-(*RS*)	guanine	⩾400	>400
8	3-(*RS*)	adenine	>400	>400
9	9-(*RS*)	adenine *N*-oxide	>400	>400
10a	1-(*S*)	uracil	400	>400
10b	1-(*S*)	thymine	>400	>400
10b	1-(*R*)	thymine	>400	>400
11	3-(*S*)	thymine	>400	>400
12	1-(*RS*)	cytosine	400	>400
13	1-(*RS*)	6-azauracil	>400	>400

stomatitis) or a DNA virus (vaccinia).

Compounds. The preparation of the compounds listed in Table I has been described earlier; the compounds **1a**, **6–8**, and **10–13** were prepared by the condensation of the sodium salts of the appropriate bases with 1-*O*-*p*-toluenesulfonyl-2,3-*O*-isopropylidene-D- or -DL-glycerol,[4] DL-glycerol 1,2-cyclic carbonate,[5] or 2,2-dimethyl-4-(chloromethyl)-1,3-dioxolane[6] (compounds **1b,c**). The 8-substituted adenine derivatives **1e,f** were obtained by the appropriate reactions of the 8-bromo derivative **1d** prepared by bromination of **1a** or its triacetate **18a**.[6] From the diacetate of the hypoxanthine derivative **5** obtained by deamination of **18a**,[6] the mercaptopurine derivative **4** was prepared by thiation and methanolysis, whereas the 6-(methylamino)- and 6-(dimethylamino)purine derivatives **2** and **3** were obtained by treatment of the intermediary chloro compound with the appropriate amine.[6]

Of the derivatives modified at the aliphatic chain (Table II), compounds **14**,[7] **15**,[8] **16**, **27**,[4] **29**,[4] and **35**[9] were prepared by modification of the known procedures and the acyl derivatives of DHPA by treatment of DHPA with an acid anhydride (**18a,b**)[6] or an acid chloride (**18c–e**). The methoxy derivatives of DHPA (**19–21**) were obtained by the condensation of the suitably substituted DL-glycerol derivatives with adenine;[5,10] the amino analogues of DHPA (**24–26**) were obtained by treatment of DHPA with tosyl chloride, conversion of the tosyl derivatives to the azido compounds (**22** and **23**), and hydrogenolysis of the latter on Pd/C catalyst.[10] The preparation of *erythro*- and *threo*-2,3,4-trihydroxybutyl derivatives of adenine and uracil (**28** and **30**) has been published elsewhere.[11,12] Compounds **17** and **34** were prepared by sodium borohydride reduction of the corresponding carboxylic acid esters,[10] whereas the derivatives **31–33** were obtained by condensation of the sodium salt of adenine or uracil with the *p*-toluenesulfonyl derivatives of the appropriate partially protected polyols.[10] The 3-substituted propionic acid derivatives **37** and **38** were isolated from the deamination of compound **35** by nitrous acid and compound **36** resulted from ruthenium-catalyzed oxidation of DHPA.[10]

All compounds were characterized by elemental analysis, ultraviolet spectra, and ^{1}H NMR spectra, as described in the original papers, and were all homogeneous chromatographically.

Antiviral Activity. The antiviral effects of the compounds were determined in primary rabbit kidney cell cultures infected with either vaccinia or vesicular stomatitis virus. Therefore, primary rabbit kidney cells grown to confluency in cell culture tubes were inoculated with 100 $CCID_{50}$ of vaccinia virus or vesicular stomatitis virus, 1 $CCID_{50}$ being the virus dose required to infect 50% of the cell cultures. After 1 h of virus adsorption, residual virus was removed and the cell cultures were incubated with maintenance medium (Eagle's minimal essential medium supplemented with 3% calf serum) containing varying concentrations of the test compounds (400, 200, 100, ... μg/mL). Viral cytopathogenicity (CPE, cytopathic effect) was recorded as soon as it reached completion in the control virus-infected cell cultures (usually 2 days after vesicular stomatitis virus infection and 3 days after vaccinia virus infection). Antiviral activity is expressed as the minimum inhibitory dose (MID) of compound required to reduce viral CPE by 50%.

Results and Discussion

The results of the antiviral tests are presented in Tables I and II. The indicated values represent data obtained for three to six separate determinations; where appropriate, the range of values is also indicated.

Three reference compounds [5-iodo-2′-deoxyuridine (5-I-dUrd), 1-(β-D-arabinofuranosyl)cytosine (*ara*-C), and 9-(β-D-arabinofuranosyl)adenine (*ara*-A)] were included in all assays. The MID values recorded for these compounds were as follows: with vesicular stomatitis virus as challenge virus, >400 μg/mL for 5-I-dUrd, 10–20 μg/mL for *ara*-C, and 20–40 μg/mL for *ara*-A; with vaccinia virus as challenge virus, 0.1–0.2 μg/mL for 5-I-dUrd, 0.02–0.04 μg/mL for *ara*-C, and 0.3–0.6 μg/mL for *ara*-A.

Unlike (*S*)-DHPA, which inhibited vaccinia and vesicular stomatitis virus replication at a concentration of about 20 μg/mL (0.1 mM), the *R* enantiomer of **1a** showed no antiviral activity unless the concentration was increased to 1.5–2 mM. As noted before,[1] the racemic mixture (*RS*)-DHPA (**1a**) was almost as active as (*S*)-DHPA, suggesting that the *R* enantiomer does not compete with the *S* enantiomer for the same action site(s). The differential activity of both enantiomers also indicates that to be effective as antiviral agents the side chain of chiral acyclic nucleoside analogues should resemble the conformation of the sugar moiety of natural nucleosides and possess the same absolute configuration. (*S*)-DHPA and its phosphate esters have indeed been shown to resemble the natural ribonucleosides both in chiroptical properties[4] and response to some nucleases.[13] Alternatively, the specificity of the antiviral effect of (*S*)-DHPA may reflect the involvement of a chiral partner molecule at the target cells. Evidently, this partner molecule should be an enzyme or an enzymatic system.

Modifications of the purine moiety of (*RS*)-DHPA (Table I), e.g., methylation of the 6-amino group (**2** and **3**), introduction of an amino (**1b**) or methylthio group (**1c**) at C(2), or substitution of hydrogen by a bromine, hydroxy, or mercapto group (**1d–f**) at C(8), invariably led to inactive

Table II. Antiviral Activity of Substituted Adenine and Uracil Derivatives Modified at the Aliphatic Chain

compd	structure	MID, μg/mL: vesicular stomatitis virus	MID, μg/mL: vaccinia virus
14	9-(2-hydroxyethyl)adenine	>400	>400
15	9-(2-aminoethyl)adenine	>400	>400
16	9-[(*RS*)-2-hydroxypropyl]adenine	>400	>400
17	9-(3-hydroxypropyl)adenine	200	300-400
18a	9-[(*S*)-2,3-diacetoxypropyl]adenine	300-400	>400
18b	9-[(*RS*)-2,3-dipropionoxypropyl]adenine	300-400	>400
18c	9-[(*RS*)-3-(palmitoyloxy)-2-hydroxypropyl]adenine	>400	100[c]
18d	9-[(*RS*)-3-(pivaloyloxy)-2-hydroxypropyl]adenine	>400	300
18e	9-[(*RS*)-2,3-bis(pivaloyloxy)propyl]adenine	>400	300
19	9-[(*RS*)-2-methoxy-3-hydroxypropyl]adenine	300-400	>400
20	9-[(*RS*)-2-hydroxy-3-methoxypropyl]adenine	≥400	≥400
21	9-[(*RS*)-2,3-dimethoxypropyl]adenine	300-400	≥400
22	9-[(*RS*)-3-azido-2-hydroxypropyl]adenine	200	>400
23	9-[(*RS*)-2,3-diazidopropyl]adenine	400	150
24	9-[(*RS*)-2-amino-3-hydroxypropyl]adenine	100-400	≥400
25	9-[(*RS*)-2-hydroxy-3-aminopropyl]adenine	200	400
26	9-[(*RS*)-2,3-diaminopropyl]adenine	≥400	>400
27	9-[(*S*)-3,4-dihydroxybutyl]adenine	100-200	200-400
27	9-[(*RS*)-3,4-dihydroxybutyl]adenine	200	100-300
28a[a]	9-[(2*R*,3*S*)-2,3,4-trihydroxybutyl]adenine	300	>400
	9-[(2*S*,3*R*)-2,3,4-trihydroxybutyl]adenine	100	200
28b[b]	9-[(2*R*,3*R*)-2,3,4-trihydroxybutyl]adenine	300	>400
	9-[(2*S*,3*S*)-2,3,4-trihydroxybutyl]adenine	≥400	>400
	9-[(2*RS*,3*RS*)-2,3,4-trihydroxybutyl]adenine	200	400
29	1-[(*S*)-3,4-dihydroxybutyl]uracil	>400	>400
30a[b]	1-[(2*R*,3*R*)-2,3,4-trihydroxybutyl]uracil	400	>400
	1-[(2*RS*,3*RS*)-2,3,4-trihydroxybutyl]uracil	>400	>400
30b[a]	1-[(2*RS*,3*SR*)-2,3,4-trihydroxybutyl]uracil	>400	>400
31	1-[(*RS*)-3,5-dihydroxypentyl]uracil	>400	>400
32	9-[(*RS*)-3,5-dihydroxypentyl]adenine	>400	>400
33[a]	9-[(2*RS*,3*SR*)-2,3-dihydroxybutyl]adenine	100-200	150-300
34	2-(adenin-9-yl)propane-1,3-diol	300-400	>400
35	3-(adenin-9-yl)-(*RS*)-alanine	100	200
36	3-(adenin-9-yl)-(*R*)-lactic acid	300-400	≥400
37	3-(hypoxanthin-9-yl)-(*RS*)-lactic acid	>400	>400
38	3-(hypoxanthin-9-yl)-(*RS*)-2-chloropropionic acid	>400	>400

[a] Erythro isomer. [b] Threo isomer. [c] Toxic.

compounds. Particularly noteworthy is the inactivity of 9-[(*RS*)-2,3-dihydroxypropyl]guanine (**6**) and the hypoxanthine derivative **5**. The latter compound can be considered as the deaminated derivative of (*S*)-DHPA. It was detected in minor quantities in liver and urine after intraperitoneal administration of (*S*)-DHPA to mice.[14] It was also detected in cell-free extracts of rat liver which had been incubated with (*S*)-DHPA.[14] Furthermore, the inactivity of compound **5** relative to (*S*)-DHPA would seem reminiscent of the decrease in antiviral activity that parallels the deamination of *ara*-A [9-(β-D-arabinofuranosyl)adenine] to *ara*-Hx [9-(β-D-arabinofuranosyl)-hypoxanthine]. As demonstrated in several cell culture systems with either herpes simplex, herpes zoster, or vaccinia as the challenge virus, *ara*-Hx is only $^1/_{10}$ to $^1/_{50}$ as active as its parent compound *ara*-A.[15-20]

None of the pyrimidine counterparts of (*S*)-DHPA, whether a uracil (**10a**), thymine (**10b**), or cytosine (**12**) derivative, *S* or *R* enantiomer, exhibited any antiviral activity. Similarly, neither of the 2,3-dihydroxypropyl analogues of the biologically active nucleosides containing 6-mercaptopurine (**4**) or 6-azauracil (**13**) possessed any activity against either of the two viruses tested. Thus, the nature of the heterocyclic base (adenine) may be critical for activity.

Similarly, substitution of one or both hydroxyl groups of the 2,3-dihydroxypropyl moiety by an amino group (**24–26**) reduced the antiviral activity of (*RS*)-DHPA. Its effect was also annihilated if either or both of the hydroxyl groups were O-methylated (**19–21**). The deleterious effect of this O-methylation is parallel to the drastic decrease in antiviral activity that has been observed previously upon 2′-, 3′-, or 5′-O-methylation of *ara*-C [1-(β-D-arabinofuranosyl)cytosine], formycin A, *ara*-A, and ribavirin [1-(β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide].[21-24] Similarly, the activity of DHPA was lost by acetylation (**18a**), propionylation (**18b**), or pivaloylation (**18d,e**) of the molecule. Although substitution of the primary 3-hydroxyl group in DHPA by the lipophilic palmitoyl group resulted in a compound (**18c**) that did exhibit a distinct activity against vaccinia virus, the cytotoxicity of the compound at the active antiviral concentration excludes this compound from the group of potentially interesting antiviral compounds.

If the aliphatic side chain at C(9) of adenine was shortened to a two-carbon unit (**14** and **15**), no antiviral activity was noted. A marked reduction of the antiviral potential was also encountered upon replacement of the hydroxyl groups in DHPA by azido functions (**22** and **23**). It should be pointed out, however, that 9-[(*RS*)-2,3-diazidopropyl]adenine (**23**) possessed a distinct activity against vaccinia virus, in which respect it appears to be the second-best inhibitor after (*RS*)-DHPA itself.

Of the two homologous 9-hydroxypropyladenines, only the 3-hydroxypropyl derivative **17** (which can be regarded as the 2-deoxy derivative of DHPA) displayed a moderate antiviral activity. The 2-hydroxypropyl compound **16** was totally devoid of activity. Compound **33** [9-[(2*RS*,3*SR*)-2,3-dihydroxybutyl]adenine] can be considered as a DHPA derivative in which the 3-methylene function is substituted

by a methyl group. The latter compound did exhibit a significant antiviral activity (MID: 0.5–1 mM).

The homologue of DHPA, 9-[(*S*)-3,4-dihydroxybutyl]-adenine (**27**), and its racemate were slightly active in the assay systems employed. Although these compounds could theoretically be regarded as analogues of 2′-deoxyribonucleosides, it is unlikely that they assume a conformation analogous to that of the natural nucleosides.[4] Whether there is a relation between the absolute configuration of these compounds and their virus-inhibitory properties remains to be determined. For the more distantly related 3,5-dihydroxypentyl derivative **32**, no trace of antiviral activity could be detected.

The 2,3,4-trihydroxylbutyl derivatives possess two asymmetric carbon atoms and, therefore, gave rise to both an *erythro* and *threo* series of compounds. These compounds demonstrate a strong specificity both in terms of stereochemistry and absolute configuration, as far as their response to some nucleases is concerned: e.g., ribonuclease T2 cleaves only the D-*threo* series of cyclic phosphodiesters.[25] Accordingly, differences were noted in the antiviral activities of this class of compounds: both D- and L-*threo* derivatives **28b** showed little, if any, antiviral activity, whereas the L-*erythro*-(2*S*,3*R*) compound **28a** proved rather effective. The above-mentioned (2*RS*,-3*SR*)-2,3-dihydroxybutyl derivative **33**, which also exhibited an antiviral activity, can be regarded as the 4-deoxy analogue of **28a**. It is also noteworthy that the absolute configuration at the C(2) atom of 9-[(2*S*,3*R*)-2,3,4-trihydroxybutyl]adenine (**28a**) corresponds to that of (*S*)-DHPA.

In neither the *threo*- or *erythro*-2,3,4-trihydroxybutyl series, nor the 3,4-dihydroxybutyl series, did the uracil derivatives **29–31** exhibit any appreciable antiviral activity.

The last group of aliphatic nucleoside analogues examined comprised the 3-substituted propionic acid derivatives, which might be regarded as oxidation products of DHPA and its congeners. The most active congener of this group was the alanine derivative **35** which showed an MID of 0.5–1 mM. As expected, neither of the hypoxanthine derivatives **37** or **38** exhibited an appreciable antiviral effect.

Conclusion. The antiviral activity of aliphatic nucleoside analogues seems to depend on rather specific structural requirements. The unique activity of (*S*)-DHPA results from the combination of at least three factors: the adenine base, the 2,3-dihydroxypropyl substituent at the 9 position, and the absolute configuration of the molecule. In this combination, the substitutions of the adenine base or various alterations of the side chain result generally in a decrease or complete loss of antiviral activity. With regard to increasing antiviral activity, the order of the side chains would be as follows: $CH_3CH(OH)CH_2$ < $HOCH_2CH_2CH_2$ < $CH_3CH(OH)CH(OH)CH_2$ (*erythro*) = $HOCH_2CH(OH)CH_2CH_2$ < (2*S*,3*R*)-$HOCH_2CH(OH)CH(OH)CH_2$ << (*S*)-$HOCH_2CH(OH)CH_2$.

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