Chemistry and Antiviral Activities of Acyclonucleosides

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Introduction.

Recently, significant progress has been made in the development of antiviral chemotherapy [1-12] due to the discovery of nucleoside analogues with potent antiviral activities such as acyclovir [13], DHPG [14-18], FIAC [19,20], FMAU [19,20], BVDU [21,22], cyclaridine [23], ribavirin [24,24a], *etc.* The forerunner, acyclovir, has been marketed as an antiherpes drug (herpes type −2) since 1982 in the form of an ointment (5%) or an intravenous injectable solution. In 1985, an oral form of the drug was also approved by the FDA. The remaining compounds in the list are candidates for potential clinically useful antiviral agents in the future.

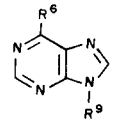
Since its inception acyclovir has played an important role as a lead compound. Thus, major efforts have been directed by the nucleoside chemists toward the synthesis of analogues of acyclovir and other acyclonucleosides with various side chains and aglycons. In this review the authors have attempted to summarize major events related to the chemistry and biology of acyclonucleosides with particular emphasis placed on the recent developments among the biologically active compounds. However, the authors did not attempt to include exhaustively all the biological literature. For more biological information, readers may consult a recent bibliographical review of acyclonucleosides by Remy and Secrist [25] and the proceedings of a symposium on acyclovir [35]. Since the term "acyclonucleosides" is rather broad and ambiguous, this review was restricted to those compounds which contain heterocycles with one or more hydroxyl groups on the alkyl side chains.

I. Purine and Purine Type Acyclonucleosides.

A. Acyclovir Analogues.

In an effort to study the binding characteristics of adenosine deaminase, Schaeffer and coworkers [26,27] reported the synthesis and adenosine deaminase inhibition activity of a number of N_9-alkyl substituted purine analogues (Table 1).

Table 1



Inhibition of Adenosine Deaminase

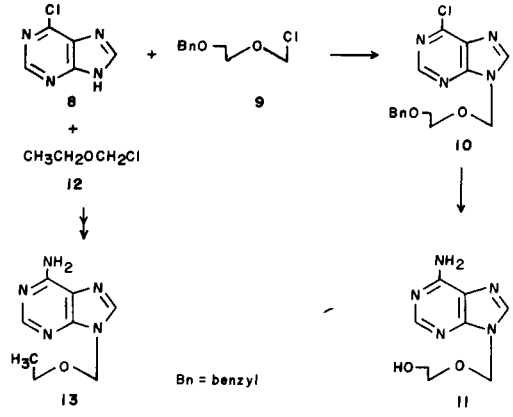
Compound	R_6	R_9	Ki × 10^{-5} *M*
1	NH_2	HO-$(CH_2)_2$-	3.8
2	$NHCH_3$	HO-$(CH_2)_2$-	34.0
3	NH_2	HO-$(CH_2)_3$-	3.0
4	$NHCH_3$	HO-$(CH_2)_3$-	9.8
5	NH_2	HO-$(CH_2)_4$-	10.0
6	$NHCH_3$	HO-$(CH_2)_4$-	12.0
7	Adenosine		7.3 [a]

[a] Km instead of Ki.

Compounds **1** and **3** were the most effective inhibitors and bound to the enzyme twice as tight as adenosine. The results indicated that 2′- or 3′-hydroxy groups of adenosine do not interact with adenosine deaminase.

It was known that 5′-deoxynucleosides of adenine do not undergo deamination with adenosine deaminase unless a properly positioned hydroxyl group is present at C-3′ as in 9-(5-deoxy-β-D-xylofuranosyl)adenine such that the 3′-hydroxyl group can assume the function of the 5′-hydroxyl group of adenosine [28-30]. This indicated that the 5′-hydroxyl group plays a special role in the deamination reaction. Based on this information Schaeffer and coworkers [31] prepared 9-(2-hydroxyethoxymethyl)adenine (**11**), which contains the 5′-hydroxyl portion of adenosine, in order to study the substrate inhibitor activity of adenosine deaminase (Scheme 1).

Scheme I

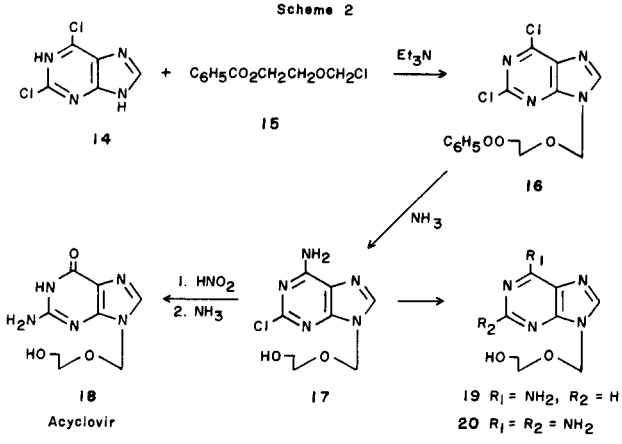


Enzymic evaluation of **11** with adenosine deaminase indicated it was a substrate with a Km of 1.3 × 10^{-4} *M* whereas the Vmax was 1.4% that of adenosine. However, the deoxy compound **13** did not exhibit any substrate activity and was a relativley weak reversible inhibitor. Based

on these results they assumed that compound **11** could be superimposable with the conformation of adenosine with respect to the adenine moiety, C-1′, ether oxygen, C-4′, C-5′, and 5′-hydroxyl group.

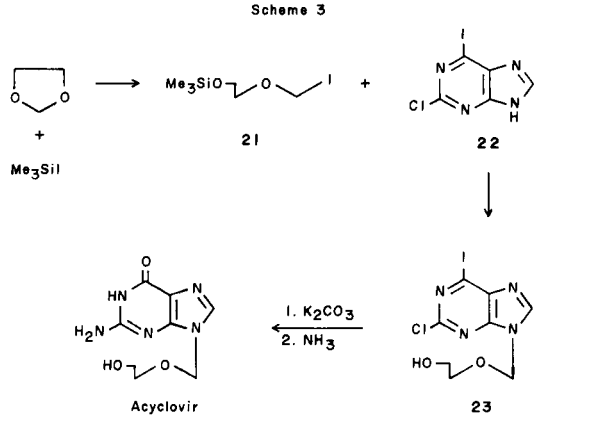
As an extention of this work, Schaeffer *et al.* [13] subsequently reported the synthesis and antiherpes activities of 9-(2-hydroxyethoxymethyl)guanine **18** (acyclovir) (Scheme 2).

Scheme 2



A more efficient method of synthesis of acyclovir was reported by Barrio and coworkers [32,33]. The synthesis involved the reaction of 1,3-dioxolane with trimethylsilyl iodide to give the desired side chain **21**, which was condensed with the purine **22**, followed by hydrolysis and ammonolysis to yield acyclovir (Scheme 3).

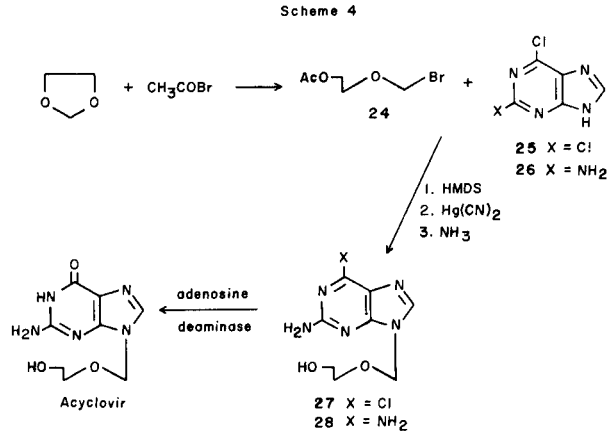
Scheme 3



Robins and Hatfield [34] also reported an efficient method for the preparation of acyclovir. They used a silylation/mercuric cyanide procedure, which effectively eliminated N-7 isomers normally found in alkylations of purine sodium salts. In the final step, an enzymic conversion of **27** or **28** afforded acyclovir (Scheme 4).

The proceedings of a symposium on acyclovir has been published [35], in which comprehensive biological information can be found. Acyclovir is a very potent inhibitor

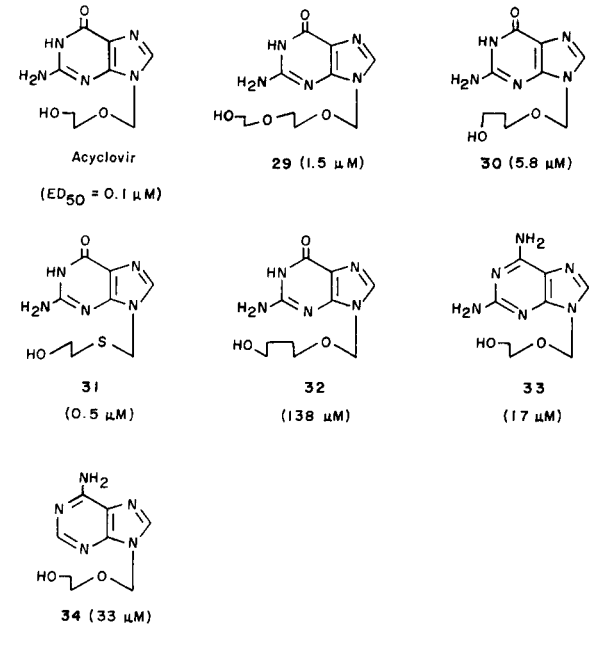
Scheme 4



of herpes simplex virus type-1 (HSV-1), type-2 (HSV-2), *varicella zoster* and cytomegalovirus replication, and it produces little cytotoxicity in uninfected cells [13,36]. It is highly specific because it is phosphorylated by herpes virus thymidine kinase, but not by cellular thymidine kinase [36,37]. Furthermore, acyclovir triphosphate, which is synthesized by cellular kinases from acyclovir monophosphate, is a significantly more potent inhibitor of the virus induced DNA polymerase than it is of the host α-DNA polymerase. These combined effects seem to be responsible for the selective antiviral effect of acyclovir [18]. The recently approved oral form markedly reduces recurrence rate while the patient is receiving medication. However, the drug does not influence the long-term natural history of the disease [38,39].

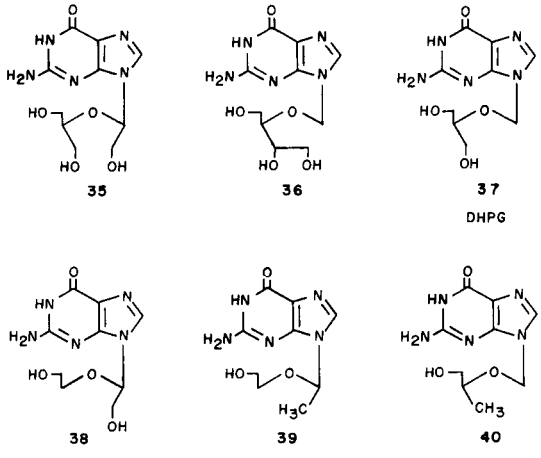
Owing to the significant antiviral activities exhibited by acyclovir, analogues **29-34** with other aglycons and side chains at N_9 were synthesized [18,40] (Fig. 1).

Fig. 1



Since compounds with a guanine moiety **29-32** are more active than the compounds with adenine **34** or 2,6-diaminopurine moieties **33**, acyclonucleosides with a guanine moiety **35-40** were synthesized for biological tests [18] (Fig. 2). Although these compounds have been mentioned

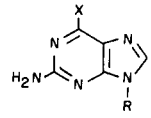
Fig. 2



as possessing some antiviral activity, the detailed biological results have not appeared, with the exception of DHPG. Keller *et al.* [40] studied the enzymatic phosphorylation and correlations with antiherpetic activities of various acyclovir analogues, including some of the compounds in Fig. 2. They found that many of the compounds that were phosphorylated by HSV thymidine kinase were inhibitors of HSV replication. They also found that several compounds not phosphorylated by the enzyme did not inhibit replication. However, some acyclic nucleosides that were phosphorylated were not good antivirals, indicating that phosphorylation catalyzed by the HSV thymidine kinase was not sufficient for inhibition of viral replication. These results emphasize not only the importance of the substrate specificity for HSV thymidine kinase but also the inhibition of HSV DNA polymerase for the antiviral activity. Also important is substrate activity towards GMP kinase and enzymes taking diphosphate to triphosphate [40].

Kelley *et al.* [41] reported nitrogen isosters of acyclovir (Table 2). When tested against HSV-1, only **41** was active with an $IC_{50} = 8\ \mu M$. In order to overcome the relative insolubility of acyclovir for eye drops or intramuscular injections, Vanderhaeghe and co-workers [42] synthesized and evaluated for antiviral activity of **46-53** (Table 3). When assayed in primary rabbit kidney cell culture against various HSV-1 and HSV-2 strains, **46-49** proved almost active as acyclovir itself, suggesting that they were readily hydrolyzed to release the parent compound. Compound **46**

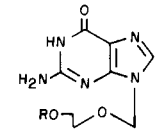
Table 2



	X	R
41	OH	$CH_2OCH_2CH_2NH_2$
42	NH_2	$CH_2OCH_2CH_2NH_2$
43	OH	$CH_2OCH_2CH_2OCH_2CH_2NH_2$
44	OH	$CH_2OCH_2CH_2NHCH_2CH_2OH$
45	OH	$CH_2OCH_2CH_2NHCOCH_3$

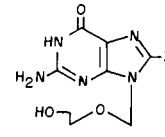
was further evaluated for its antiviral efficacy in HSV-1 keratitis in rabbits. When administered as eye drops at a concentration of 1% (at which acyclovir itself could not be dissolved) in isotonic borate buffer (*p*H 5.7), **46** effectively suppressed the development of both epithelial and stromal keratitis, and iritis therewith associated [42].

Table 3



	R
46	$COCH_2NH_2.HCl$
47	$COCH(CH_3)NH_2.HCl$
48	$COCH_2CH_2NH_2.HCl$
49	$COCH_2CH_2COONa$
50	$COCH_2N_3$
51	$COCH(CH_3)NHCOOCH_2C_6H_5$
52	$COCH_2CH_2NHCOOCH_2C_6H_5$
53	$COCH_2CH_2COOH$

Table 4

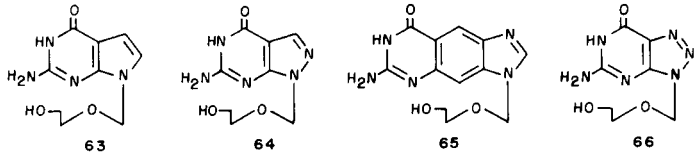


	Z
54	CH_3
55	Cl
56	Br
57	I
58	OH
59	NH_2
60	$NHCH_3$
61	$N(CH_3)_2$
62	$N(CH_2)_5$

Robins *et al* [43] also prepared and evaluated a number of 8-substituted purine acyclonucleosides for antiviral, antimetabolic and cytotoxic properties. Among these, the 8-methyl-**54**, 8-bromo-**56**, 8-iodo-**57**, and 8-amino-**59** analogues exhibited significant activities although they were less active than acyclovir (Table 4).

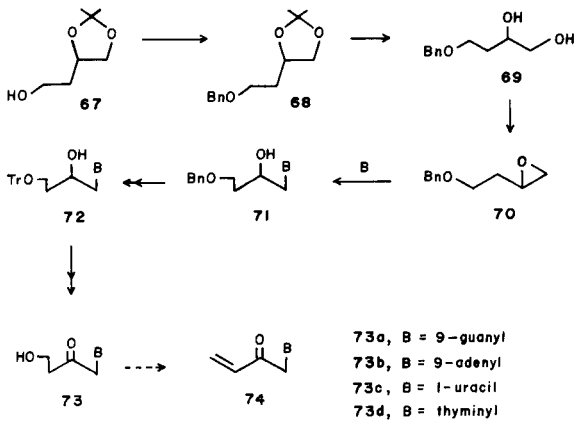
Beauchamp *et al.* [44] recently reported the acyclovir analogues **63-66** with various heterocyclic moieties such as pyrrolo[2,3-*d*]pyrimidine **63**, pyrazolo[3,4-*d*]pyrimidine **64**, benzoguanine **65**, 8-azapurine **66**, imidazole, triazole and isocytosine (Fig. 3). Compound **63** was previously reported by Seela and coworkers [45]. The analogues were evaluated against HSV-1, but only the 8-azapurine analogue **60** showed some activity (IC_{50} = 129 μM). In a test measuring the ability of these compounds to inhibit the HSV-1 thymidine kinase, **65** and **66** exhibited competition with acyclovir for binding to the enzyme.

Fig. 3



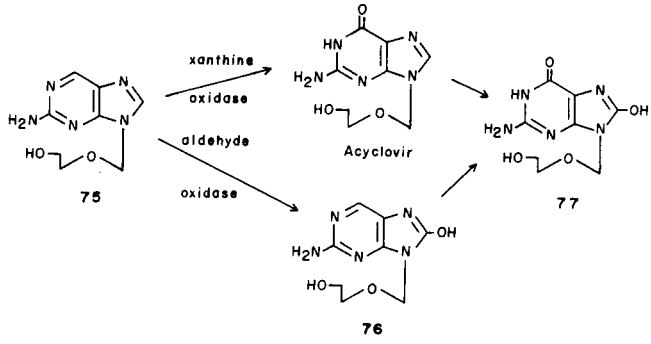
Martin *et al.* [46] prepared compounds of general structural type **73** based on the assumption that the monophosphates of these analogues would undergo β-elimination at the catalytic site of the virus kinase to give enone **74**. This enone in turn could alkylate the active site of the enzyme in the suicide destruction of the kinase (Scheme 5). Compound **73a** showed marginal activity (ID_{50} = 400 μM) against HSV-1 in Vero cells, and it was a substrate for the viral specific thymidine kinase.

Scheme 5



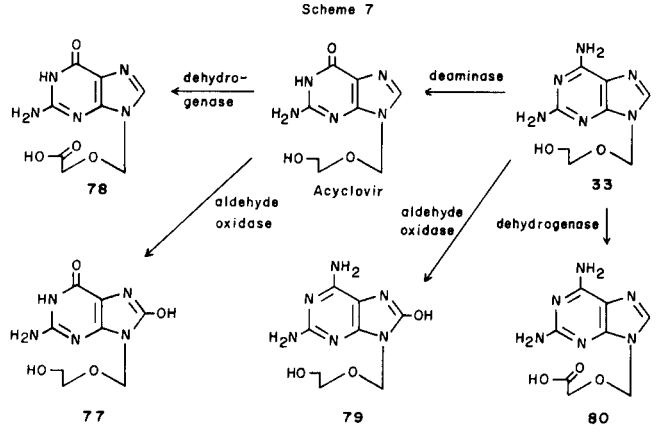
Since only 15-20 percent of the dose of acyclovir is typically absorbed in humans after oral administration, considerable effort has been devoted to find prodrug that is well absorbed after oral administration. In connection with this effort, Krenitsky *et al.* [47] reported the synthesis and biological activity of 6-deoxyacyclovir **75** (Scheme 6). 6-Deoxyacyclovir was found to be 18 times more water soluble than acyclovir. Furthermore, the prodrug was readily oxidized to acyclovir by xanthine oxidase. It was oxidized by aldehyde oxidase primarily to 8-hydroxy-6-deoxyacyclovir **76** and then to 8-hydroxyacyclovir **77**. In clinical studies of **75**, the plasma concentration of acyclovir was 5-6 times higher than that of acyclovir itself. These results suggested that 6-deoxyacyclovir might have clinical usefulness as a prodrug of acyclovir suitable for oral administration [47].

Scheme 6



Another acyclovir derivative studied as a prodrug was 2,6-diamino-9-(2-hydroxyethoxymethyl)purine (A134U) **33** [48-50]. Good *et al.* [48] and Spector *et al.* [50] found that A134U **33** was converted to acyclovir by adenosine deaminase and four other minor metabolites **77-80** (Scheme 7). Oral dosing of dogs and rats with **33** resulted in peak plasma concentrations and total urinary recoveries of acyclovir greater than those observed after equivalent oral doses of acyclovir, suggesting that **33** might be an effective prodrug of acyclovir for the use in oral therapy [48]. Maudgal

Scheme 7

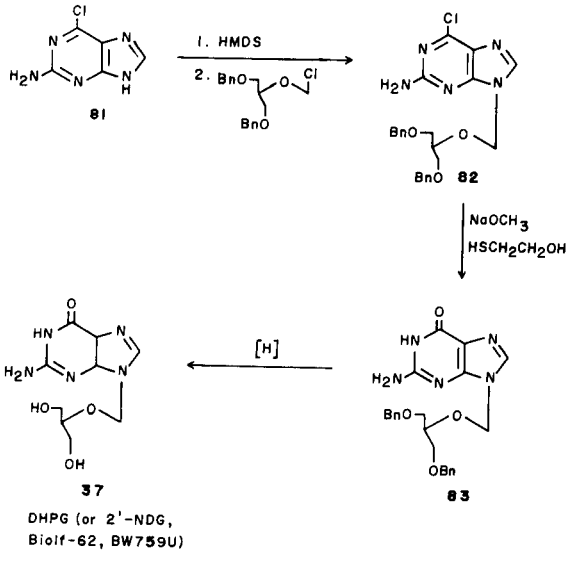


et al. [51] also studied 2'-*O*-glycylacyclovir **46** as a prodrug for the treatment of experimental herpes simplex keratouveitis.

9-[(1,3-Dihydroxy-2-propoxy)methyl]guanine (DHPG) Analogues.

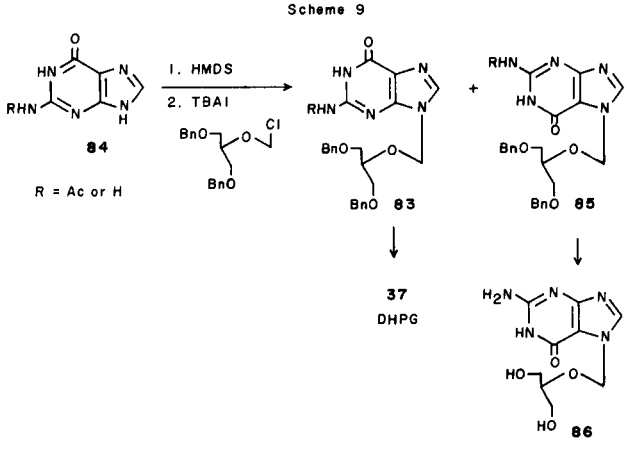
Encouraged by the useful clinical efficacy of acyclovir, much attention has been directed toward synthesis of analogues of acyclovir in order to find a more potent drug. 9-[(1,3-Dihydroxy-2-propoxy)methyl]guanine (DHPG; 2'-NDG; Biolf-62; BW759U) **37** is the result of such efforts. Four laboratories reported the synthesis and antiviral activities of compound **37** [14-38, 52-59] (Scheme 8-11). Thus

Scheme 8



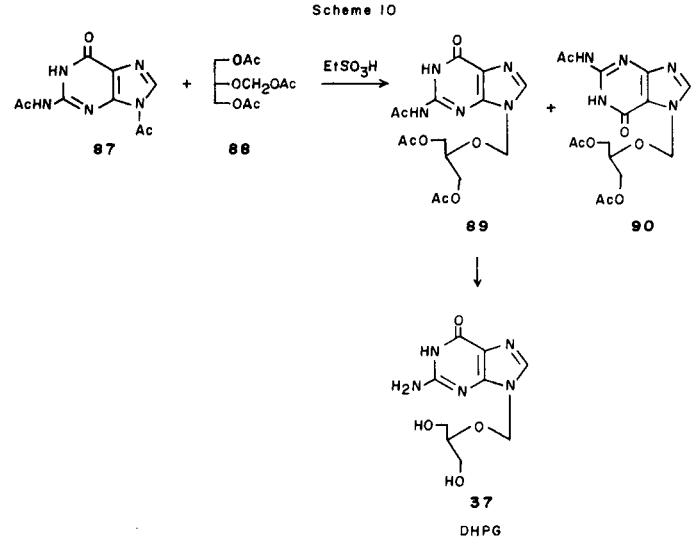
alternate routes to **37** were devised using *n*-tetrabutylammonium iodide (TBAI). The synthesis gave two products **83** and **85** in a ratio of 7 to 3. However, the mixture could be separated by fractional crystallization from ethanol [16] (Scheme 9).

Scheme 9

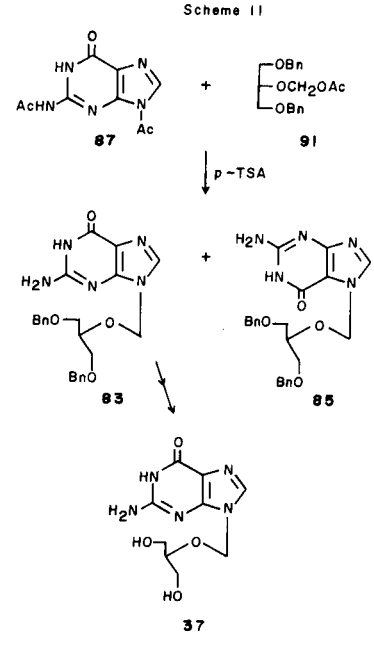


Tolman and coworkers [17,52] prepared DHPG (**37**) by a fusion method in which diacetylguanine **87** was reacted with **88** at 155-160° in the presence of ethane sulfonic acid to give a mixture of **89** and **90** (Scheme 10). They also used silylated guanine with **88** without catalyst under similar fusion conditions. Martin *et al.* [14] also reported the synthesis of DHPG (**37**) using *p*-toluenesulfonic acid as a condensing agent (Scheme 11).

Scheme 10



Scheme 11



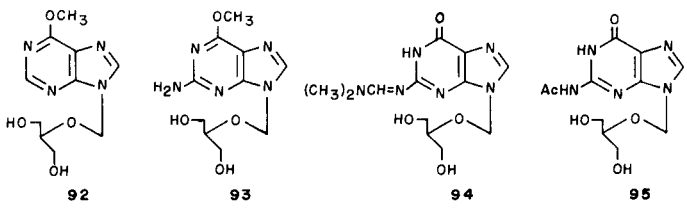
9-(1,3-Dihydrox-2-propoxymethyl)guanine (DHPG, 2'-NDG, Biol-62, BW759U) **37** has similar activity to acyclovir against HSV-1 and HSV-2 *in vitro*. DHPG also inhibits cytomegalovirus and Epstein-Barr virus [52-60]. Although the two compounds have similar activity against HSV *in vitro*, a striking difference was the superior *in vivo* activity of DHPG against herpes encephalitis and vaginitis [52-55]. DHPG is highly effective in reducing the severity of both primary and recrudescent lesions of HSV-2. The drug appears to have no effect on the latent form of the

virus [54]. However, virus variants that induced altered virus thymidine kinase and became resistant to acyclovir were still as sensitive to DHPG as the parent virus. DHPG was reported to be active against five different HSV variants with altered DNA polymerase and resistance to acyclovir [61]. The mode of action of DHPG and acyclovir are similar in that both compounds are phosphorylated by the viral induced thymidine kinase and selectively inhibit viral over host cell DNA synthesis [51,61,62]. Cheng and coworkers [62] studied the metabolism of DHPG in HeLa cells infected with HSV-1. They found that the uptake of DHPG was enhanced in the infected cells and the major metabolites were the mono-, di- and triphosphate derivatives. Virus-induced thymidine kinase was capable of phosphorylating DHPG to its monophosphate, which could be further phosphorylated to the di- and triphosphate derivatives by host cellular enzymes. Incorporation of DHPG into DNA was observed in virus-infected cells. Thus, in contrast with acyclovir, DHPG seemed not to serve as a chain terminator, but to be incorporated into DNA strands [62]. The position of DHPG incorporation was analyzed, and it was found to enter both internal and terminal linkages. DNA containing DHPG at termini was found to competitively inhibit utlization of activated DNA as primer [63]. DHPG and natural alpha [57] and beta [56] mouse interferon were evaluated for their efficacy in combination against HSV-2 infections in mice. It was found that the combination chemotherapy significantly lowered the effective dose of DHPG.

Tolman *et al.* [64] reported the synthesis and biological activities of DHPG-cyclic phosphate. The DHPG-cyclic phosphate strongly inhibited the replication of herpes simplex viruses, human cytomegalo, vaccinia, SV40, Adeno- and Varicella-zoster virus, but it did not inhibit RNA viruses. Unlike DHPG, the activity was not dependent upon the action of virus-induced thymidine kinase. Intracellular metabolism of DHPG-cyclic phosphate produced small amounts of its triphosphate which were insufficient to account for the potent antiviral activity observed. Thus, it was postulated that the mechanism of DHPG-cyclic phosphate may be different from that of DHPG or other acyclonucleosides.

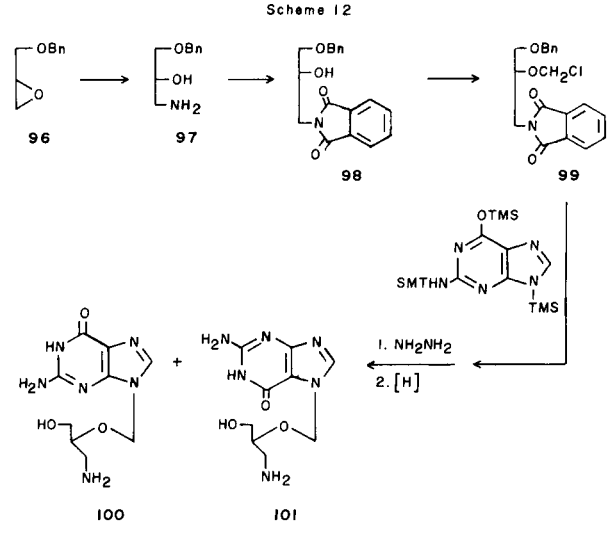
Recently, Ogilvie and Hanna [65] prepared 6-methoxypurine **92** and 2-amino-6-methoxypurine **93** from 6-chloropurines by similar reactions (Fig. 4). They reported that **93** was active (ED_{50} = 2.8 μg/ml) against equine herpes virus. Ogilvie *et al.* [66] also prepared **94** and **95** and found to be active having ED_{50} values of 2.7 and 1.4 μg/ml, respectively, against HSV-1 and 1.3 and 7.0 μg/ml respectively, against HSV-2.

Fig. 4



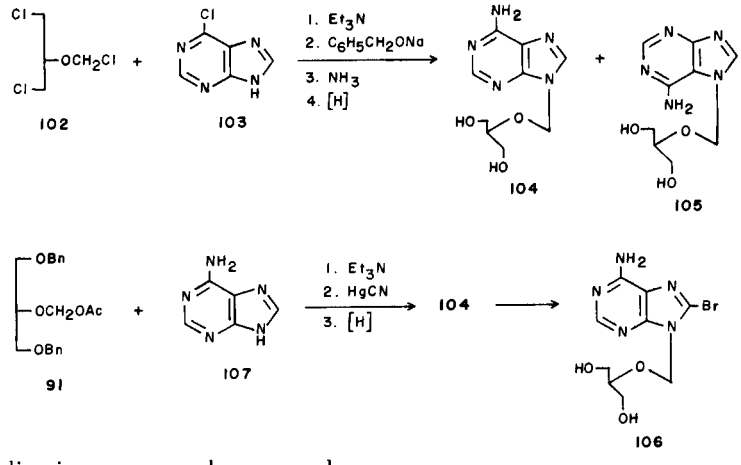
Because of the significant *in vivo* antiviral activities of DHPG, various analogues have been synthesized. Lin and coworkers [67] reported the synthesis of the aminoanalogue **100** (Scheme 12). The rationale for the synthesis of **100** was that the amino function is sterically and electronically similar to that of the hydroxyl group, which may lead to a compund with high antiviral activities and low host cytotoxicity. Such a compound also should markedly increase the water solubility, a factor critical for formulation which often limits the usefulness of antiviral agents. The detailed accounts of antiviral activity for **100** has not been published, however, it exhibited moderate antiviral activity [68]. The compound was also briefly reported by Martin *et al.* [69].

Scheme 12



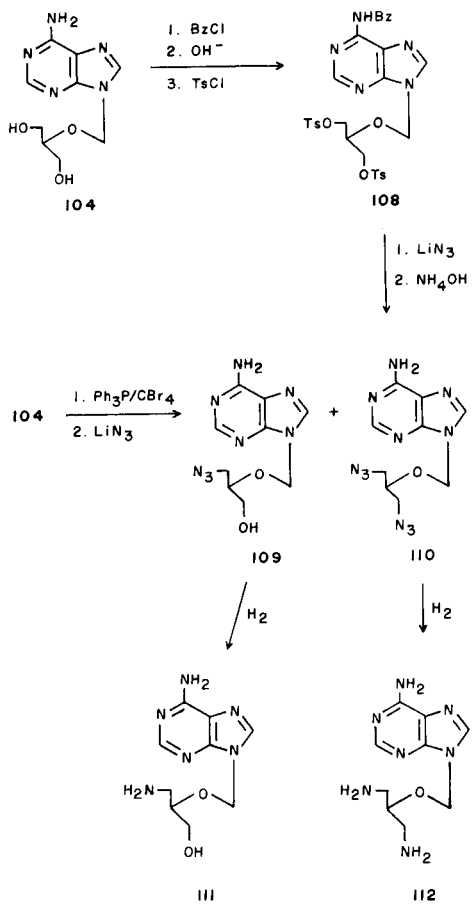
Ogilvie *et al.* [59,70] reported the synthesis and ^{13}C nmr data of a series of purine analogues of DHPG (Scheme 13-16). The adenine **104** and 8-bromoadenine **106** analogues were tested on the adenosine deaminase system. It was found that the rate of deamination of **104** (ν max = 2.55×10^{-2}) was slower than that of adenosine (ν max = 1.0), and the 8-bromo-derivative **106** was a weak competitive deaminase inhibitor (Ki = 2.04×10^{-4} *M*) [59]. All new compounds shown in Scheme 13-16 were tested against HSV-1 and HSV-2. DHPG (**37**) (Scheme 15) and **121a** (Scheme 16) were found to be most active. DHPG (**37**), **121a** and **121b** are also active against cytomegalovirus with ED_{50} values of 20, 60 and 32 μg/ml, respectively [59]. Martin *et al.* [71] also reported the synthesis and antiviral acitivity of **117** and the related compounds. They found that the 2,6-diamino derivative **117** gave ID_{50} of 3.3

Scheme I 3

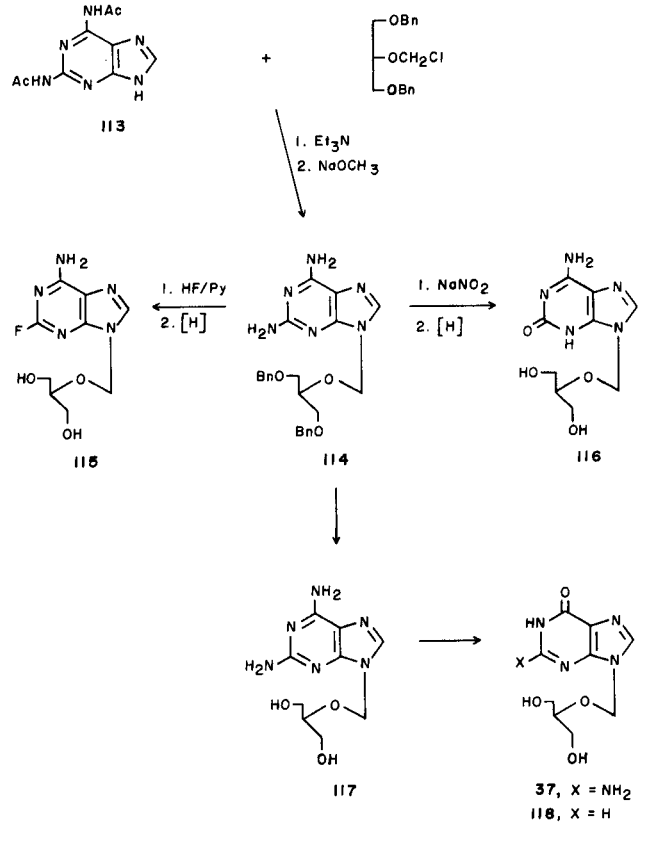


μM against HSV-1. The diamino compound was a substrate for calf intestinal mucosa adenosine deaminase, being converted to DHPG.

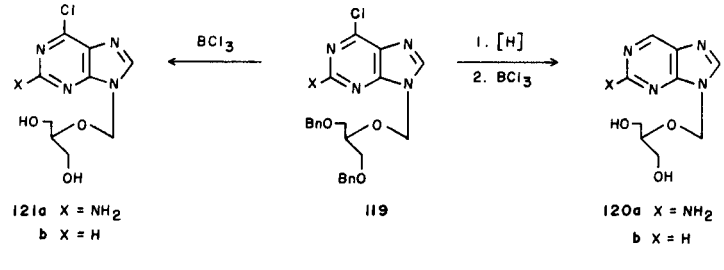
Scheme 14



Scheme 15

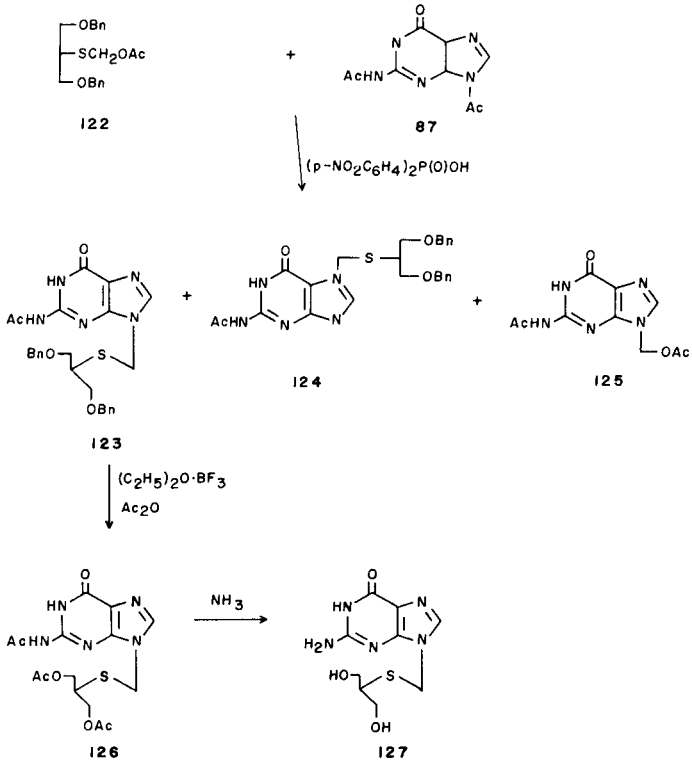


Scheme 16



McGee *et al.* [72] synthesized the thio analogue **127** of DHPG (Scheme 17). Preliminary *in vitro* screening indicated that **127** exhibited comparable activity to DHPG against HSV-1 and human cytomegalovirus. In a mouse encephalitis model (HSV-2), subcutaneous treatment with **127** lead to a 53% reduction in motality at a dose of 100 mg/kg per day.

Scheme 17

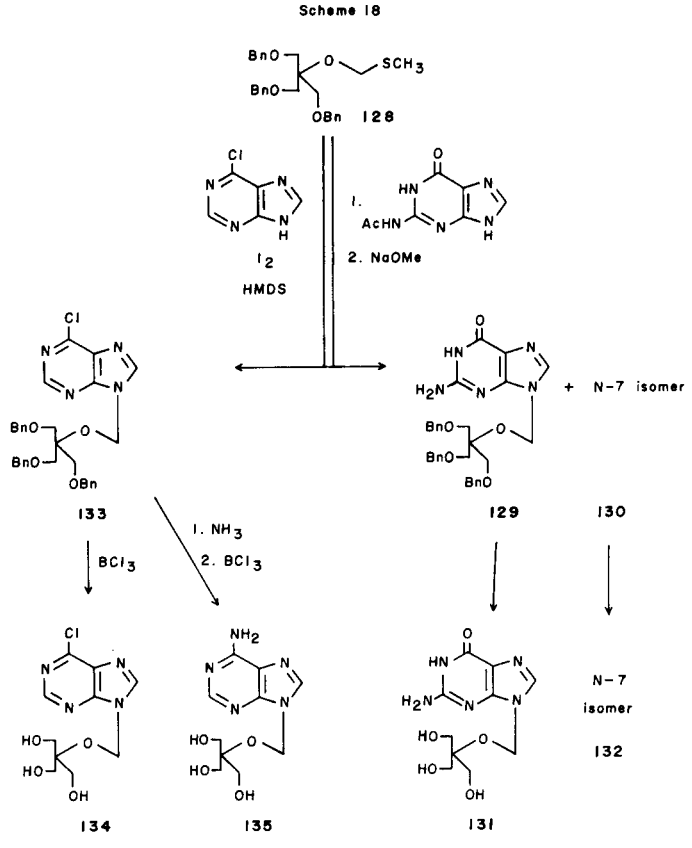


Ogilvie *et al.* [73] recently synthesized DHPG analogues **131-135** with an additional hydroxymethyl group on the acyclic side chain. However, they found that the change significantly decreased the antiherpetic activity (ED_{50} = 54 μg/ml against HSV-1 for **131**) from that of DHPG (ED_{50} = 0.2 μg/ml) (Scheme 18).

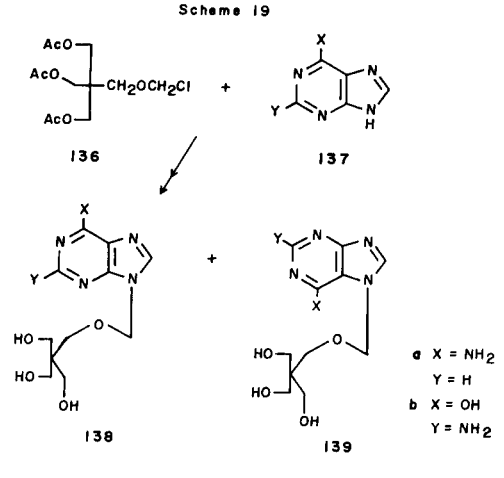
Ogilvie and Proba [74] also reported that chain extended analogues **138** had significantly reduced antiviral activity (ED_{50} >100 μg/ml) against HSV-1, HSV-2, and cytomegalovirus (Scheme 19).

Another DHPG analogue, (RS)-9-(2,3-dihydroxy-1-propoxymethyl)guanine **142** has been reported by both Lin and Lin [75] (Scheme 20) and Ashton *et al.* [76,77], (Scheme 21). Ashton *et al.* [77] also reported a stereospecific synthesis of (*R*)- and (*S*)-enantiomers from 1,2-di-*O*-benzyl-D-and-L-glycerol **147** & **150** (Scheme 22). The (*S*)-Isomer **152** was found to be 10- to 25-fold more active than the (*R*)-isomer **149** against HSV-1 and HSV-2 in cell

Scheme 18



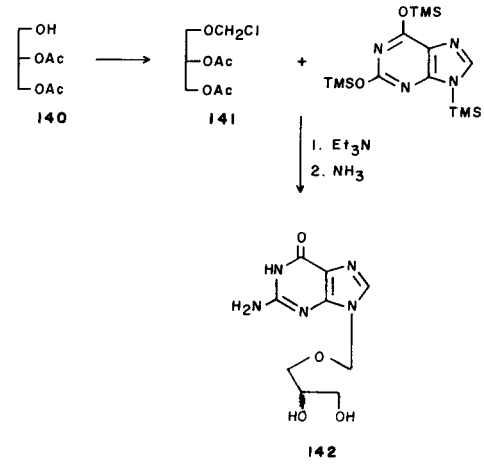
Scheme 19



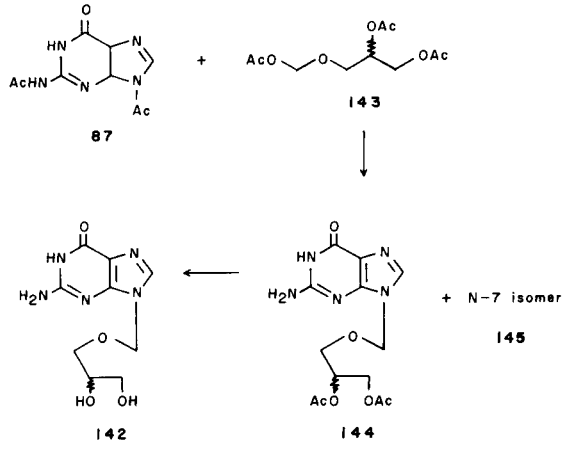
culture and had an ED_{50} comparable to those for acyclovir and DHPG. The inferior activity of the (*R*)-isomer was correlated with inhibition of viral DNA polymerase by its phosphorylated products. In mice infected intraperitoneally or orofacially with HSV-1 or intravaginally with HSV-2, the (*S*)-isomer was less efficacious than DHPG but comparable to or more active than acyclovir [77].

Since the (*S*)-isomer was more active than the (*R*)-isomer, MacCoss *et al.* [78] developed an improved stereospecific synthesis of (*S*)-9-(2,3-dihydroxy-1-propoxymethyl)-

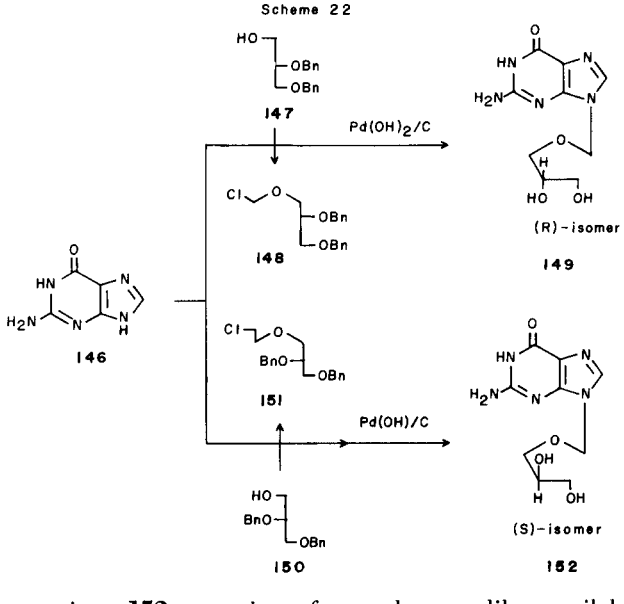
Scheme 20



Scheme 21

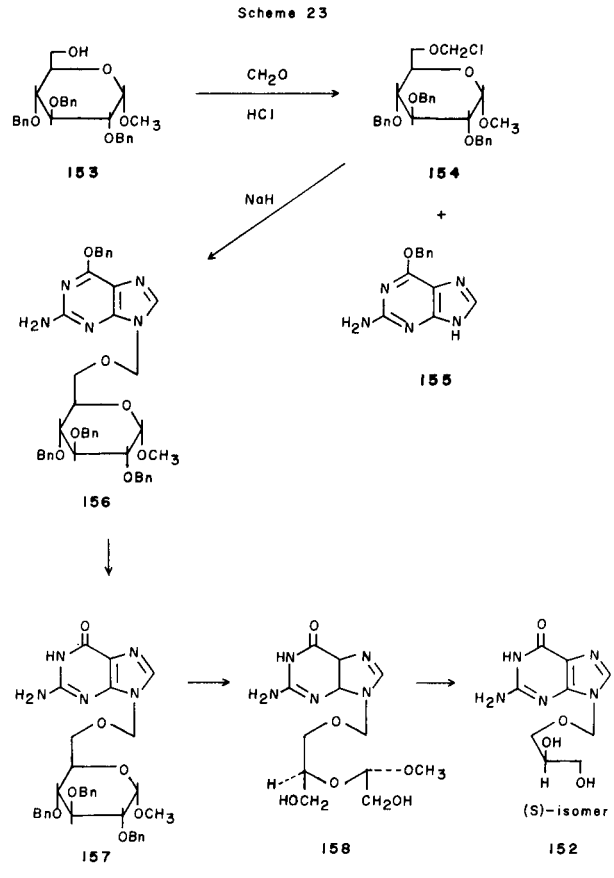


Scheme 22



guanine **152**, starting from the readily available methyl-2,3,4-tri-*O*-benzyl-D-glucopyranoside **153**. The synthesis utilized the absolute configuration defined by carbons 4, 5 and 6 of glucose (Scheme 23).

Scheme 23



Since **142** showed lower *in vivo* antiviral activity than that of DHPG [77], it was of interest to prepare **166**, **168**, **170** and **172**, which possess the acyclo side-chains of both **142** and DHPG. MacCoss *et al.* [79] prepared all four possible diastereomers from protected xylose **167** and **169** and arabinose **159** and **171**. The structure of 9-(1,3,4-trihydroxy-2-butoxymethyl)guanine has been previously described, but no stereochemistry or experimental details were given [18]. From the related reaction for the preparation of acyclovir [32] Barrio and coworkers [80] reported deoxyriboside analogues lacking the C(3')-C(4') bond **173** (Fig. 5). McCormick and McElhinney [81] briefly reported on acyclonucleosides **174** related to **173** (Fig. 5). Another interesting analogue of DHPG is its carbon isoster **179** and the diamino purine **178**. Both were originally reported without experimental details or biological data by Pandit *et al.* [82]. The N_7-isomer **179a** was also prepared (Scheme 25).

Scheme 24

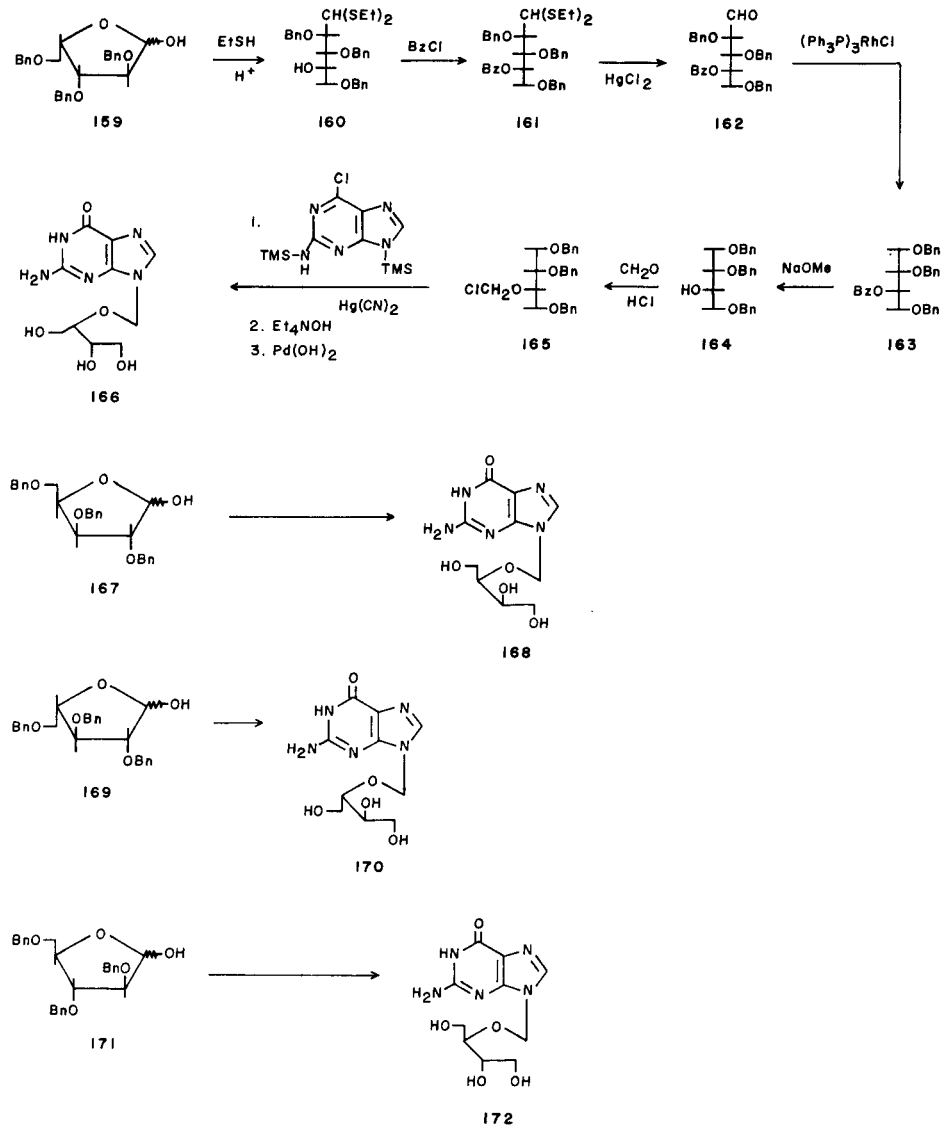
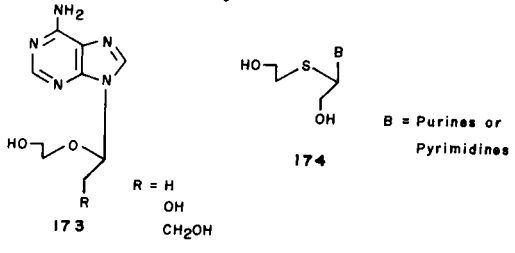
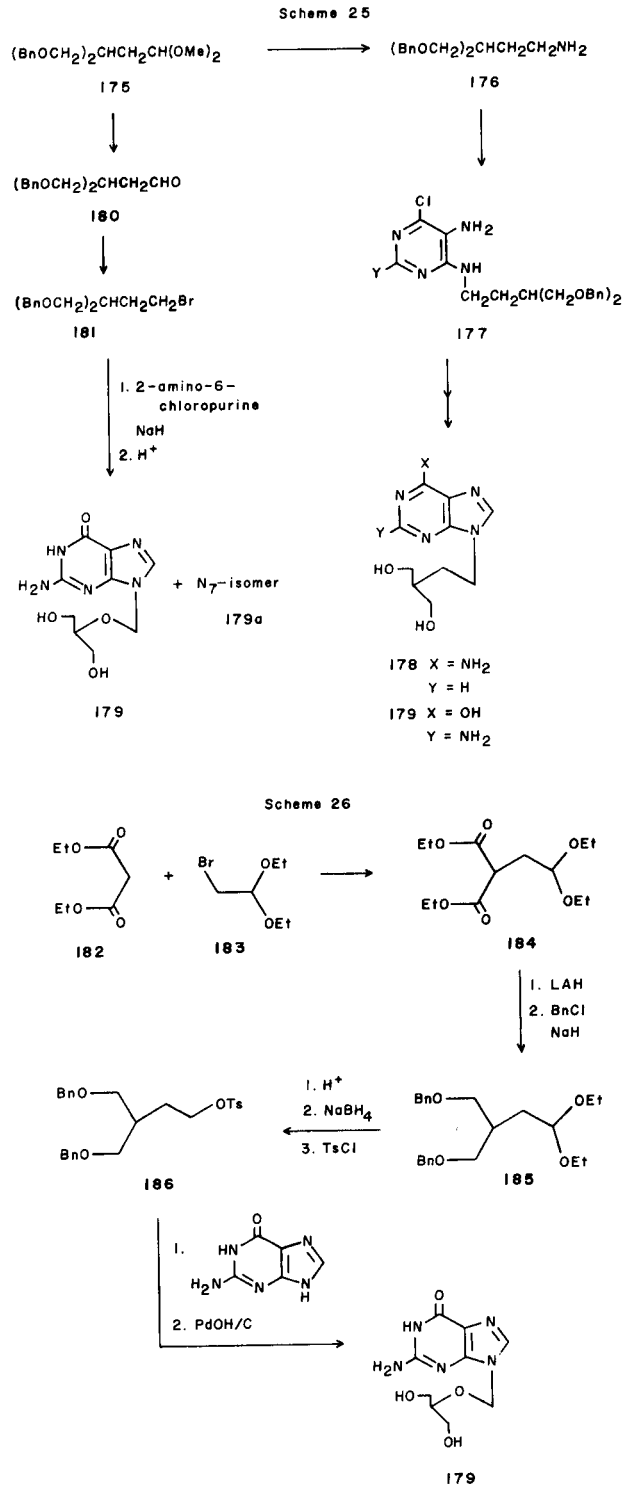
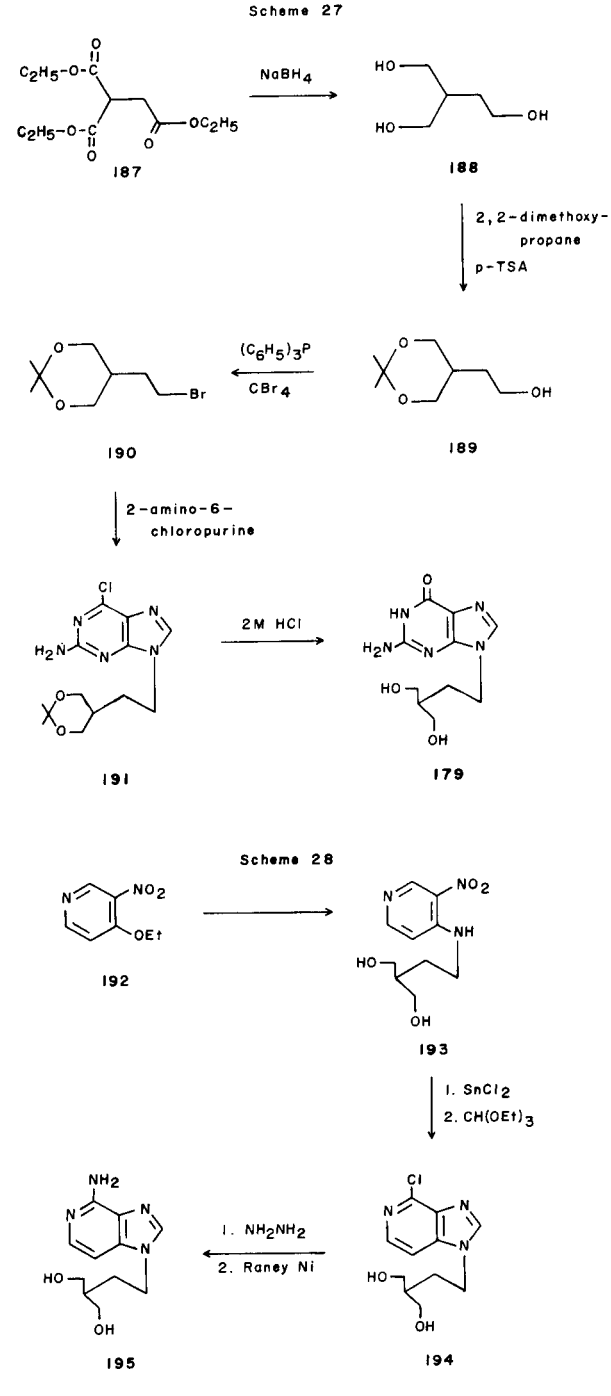


Fig. 5



Recently Tippie *et al.* [83] synthesized **179** in low yield by direct condensation of **186** with guanine (Scheme 26). They also reported the antiviral activity of **179**. Although **179** (ID_{50} = 0.5 μM) was nearly as potent *in vitro* as DHPG (ID_{50} = 0.2 μM) against HSV-1, it was less effective (ID_{50} = 4.0 μM) against HSV-2 than DHPG (ID_{50} = 0.5 μM). *In vivo* study confirmed the *in vitro* data showing **179** to be less effective than DHPG against HSV-2 (**83**). Harnden and Jarvest [84] reported an improved synthesis of **179** (Scheme 27).





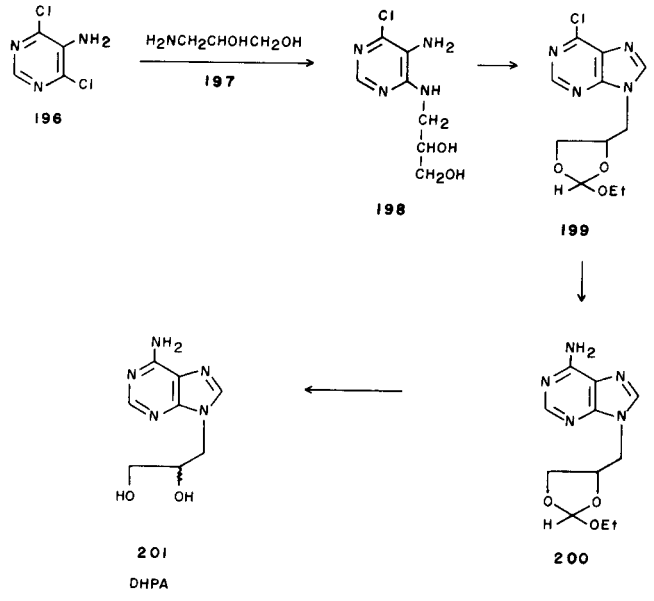
The 3-deazaadenine derivative **195** was reported by Borchardt and coworkers [85] (Scheme 28). However, **195** did not significantly inhibit the replication of vaccina virus or *S*-adenosylhomocysteine hydrolase.

C. 9-(2,3-Dihydroxypropyl)adenine (DHPA) Analogues.

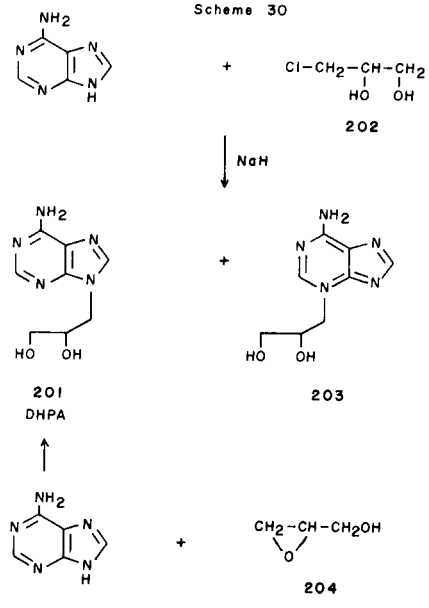
De Cercq *et al.* [86,87] reported the antiviral activity of (*S*)-9-(2,3-dihydroxypropyl)adenine (*S*-DHPA). Several viruses including vaccinia, HSV-1 and HSV-2, measles, and vesicular stomatitis were inhibited by (*S*)-DHPA. The racemic mixture (*RS*)-DHPA was almost as active as the (*S*)-enantiomer. However, the (*R*)-isomer of DHPA was inactive.

The potential antiviral activity of (*S*)-DHPA *in vivo* was assessed in mice inoculated intranasally with vesicular stomatitis virus; (*S*)-DHPA significantly increased the survival from the infection. Unlike other antiviral agents, (*S*)-DHPA did not significantly reduce DNA, RNA or protein synthesis. (*S*)-DHPA is not a substrate for adenosine deaminase of either bacterial or mammalian origin. However, (*S*)-DHPA, strongly inhibits deamination of adenosine and ara-A by adenosine deaminase. Its mode of action may be inhibition of *S*-adenosyl-L-homocysteine hydrolase [88]. (*S*)-DHPA was reported to be embryotoxic to chicks [89]. Holy and Cihak [90] studied the metabolism of (*S*)-DHPA from which they detected the deaminated product, a hypoxanthine derivative, as the only metabolite in mice.

Scheme 29



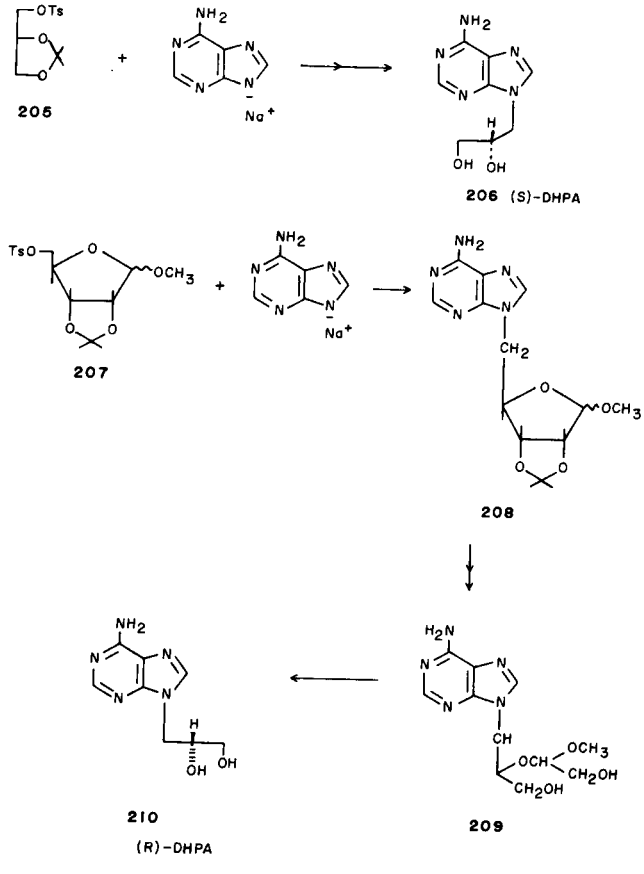
Scheme 30



The first synthesis of racemic DHPA (**201**) was reported by Schaeffer and coworkers [27] (Scheme 29). It was reported to be a weak inhibitor of adenosine deaminase.

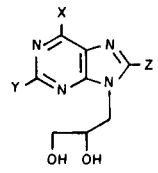
Ueda *et al.* [91] and Seita *et al.* [92] modified the synthesis, in which they used a direct condensation method (Scheme 30). However, these authors did not report the antiviral activity of DHPA.

Later, the synthesis of the (*R*)- and (*S*)-enantiomers were reported by Holy [93] in which 1-*O*-*p*-toluenesulfonyl-2,3-*O*-isopropylidene-D-glycerol **205** and 5-*O*-*p*-toluenesulfonyl-2,3-isopropylidene-D-ribofuranoside **207** were used as the starting materials for (*S*)- and (*R*)-enantiomers, respectively (Scheme 31). Various other purine derivatives were prepared [27, 87, 94-96]. Some representative compounds are listed (Table 5). None of the compouds (**211-223**) showed any significant antiviral activity.



More recently, Holy *et al.* [97] examined various alkyl derivatives of DHPA related purine bases for inhibitory effects toward rat liver *S*-adenosylhomocysteine hydrolase and antiviral activity. They found that an intact adenine moiety, and alkyl chain bound at the 9-position and bearing a vicinal diol at the 2'-3'-position with (2S) configuration are necessary. They also found that antiviral activity

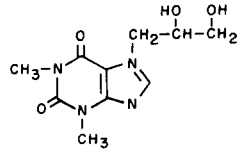
Table 5



	X	Y	Z
211	NH_2	H	NH_2
212	NH_2	H	SH
213	NH_2	H	OH
214	NH_2	H	Br
215	$NHCH_3$	H	H
216	$N(CH_3)_2$	H	H
217	OH	H	H
218	SH	H	H
219	NH_2	H	H
220	NH_2	NH_2	H
221	SCH_3	H	H
222	OH	NH_2	H
223	NH_2OH	H	H

of DHPA analogues correlated with the inhibitory activity on *S*-adenosyl-L-homocysteine hydrolase.

Holy and Vanecek [98] synthesized the (*R*)- and (*S*)-enantiomers (Fig. 6) of 7-(2,3-dihydroxypropyl)theophylline **224** in order to determine the effect of inhibition of 3,5'-cyclic-AMP phosphodiesterase and vasodilatory activity on the isolated guinea pig aorta, or the effect on blood pressure of dogs. However, the two enantiomers did not significantly differ in activity.

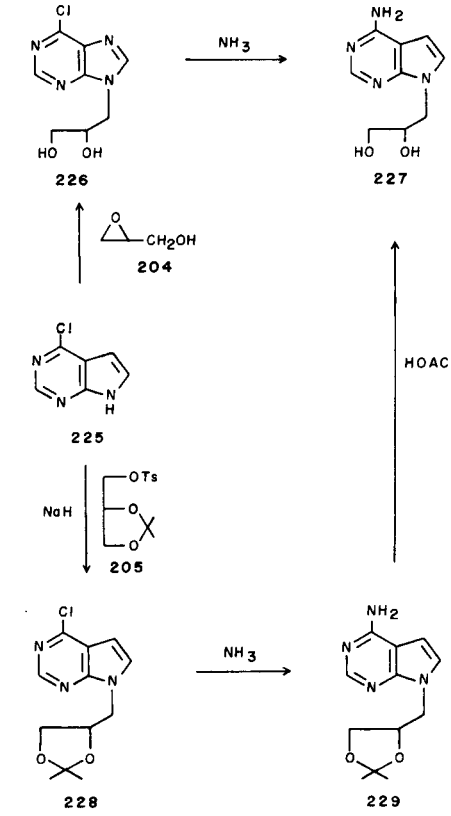


(R) or (S)

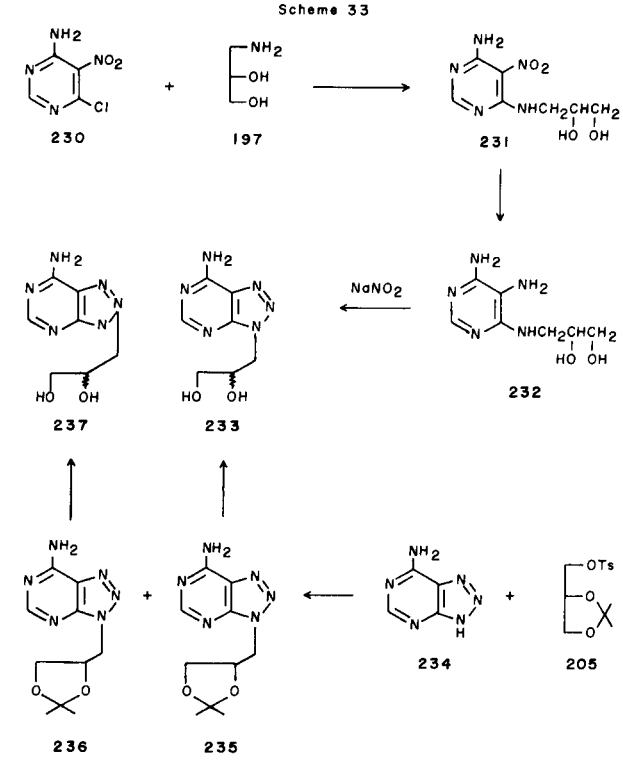
224

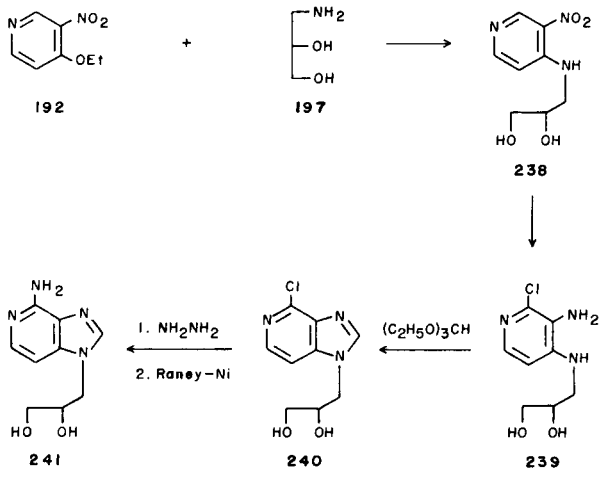
Various DHPA analogues possessing different aglycons such as pyrrolo[2,3-*d*]pyrimidine **227** (Scheme 32) [95,99], triazolo[4,5-*d*]pyrimidine **233** (Scheme 33) [100], and imidazo[4,5-*c*]pyridine **241** (Scheme 34) [85] were prepared for biological testing. The pyrrolo[2,3-*d*]pyrimidine [95,99] and triazolo[4,5-*d*]pyrimidine [100] derivatives did not show any significant biological activity. However, imidazo-[4,5-*c*]pyridine derivative **241** (Scheme 34) exhibited some antiviral activity against vaccina virus and inhibited *S*-adenosylhomocysteine hydrolase, which suggested that its antiviral activity may be related to the viral maturation [85].

Scheme 32



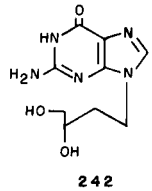
Scheme 33





Another purine acyclonucleoside, 9-(3,4-dihydroxybutyl)guanine (DHBG) **242** (Fig. 7) exhibiting significant antiherpes activity was reported [101,102]. DHBG was selectively phosphorylated by HSV thymidine kinase and had a moderate affinity for the enzyme (ID_{50} = 4-18 μM). The (*R*)-enanatiomer **242a** was more inhibitory than the (*S*)-enantiomer **242b**. Herpes virus DNA synthesis was selectively inhibited by (RS)-DHBG **242c** in infected cells, and a low cellular toxicity was observed. (RS)-DHBG had a therapeutic effect when applied topically to guinea pigs with cutaneous HSV-1 infections and to rabbits with herpes keratitis. Oral treatment of a HSV-2 infection in mice had a therapeutic effect [101].

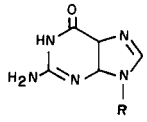
Fig. 7



Recently the antiviral activity of DHBG was compared with other related acyclonucleosides [2,103] (Table 6).

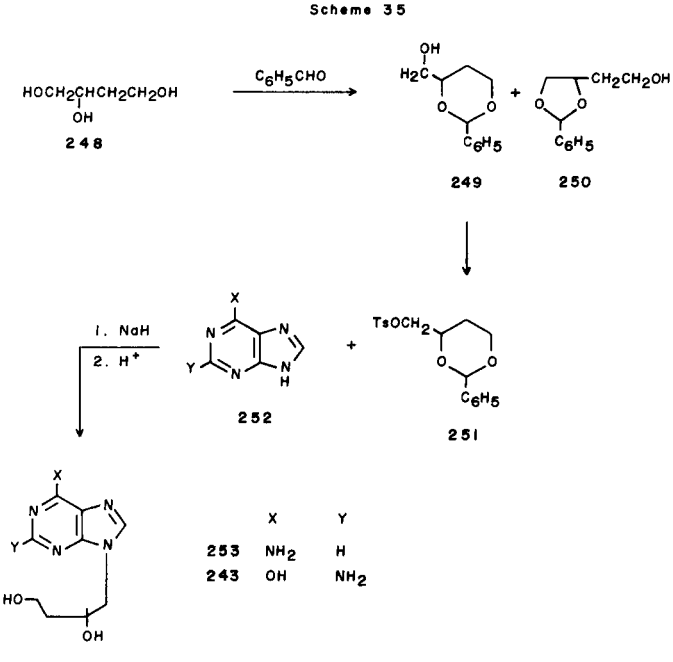
9-(4-Hydroxybutyl)guanine **247** was originally reported by Larsson *et al.* [15]. The compound inhibits different strains of HSV-1 (ID_{50} = 2-5 μM) and HSV-2 (ID_{50} = 8-13 μM), but a HSV-1 mutant lacking thymidine kinase was resistant. A selective inhibition of HSV-1 DNA synthesis by **247** was observed in infected Vero cells. The compound had a low cellular toxicity. A weak therapeutic effect on herpes keratitis in rabbits was observed whereas cutaneous HSV-1 infection in guinea pigs and systemic HSV-2 infection in mice were not affected by this compound. Zemlicka [106] reported the isomers of DHBG **253** and found little or no antiviral activity. However, the (*S*)-enantiomer was deaminated with adenosine deaminase (Scheme 35).

Table 6



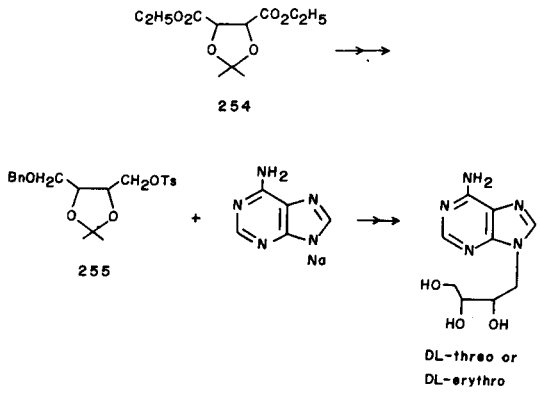
		HSV-1 plaque formation ED_{50} (μM)
242a	(R)-DHBG	2
242b	(S)-DHBG	13
242c	(RS)-DHBG	6
243	(RS)	64
244	(RS)	140
245	(RS)	43 [102]
246	(RS)	82
247		3 [105]
Acyclovir		0.3

Scheme 35



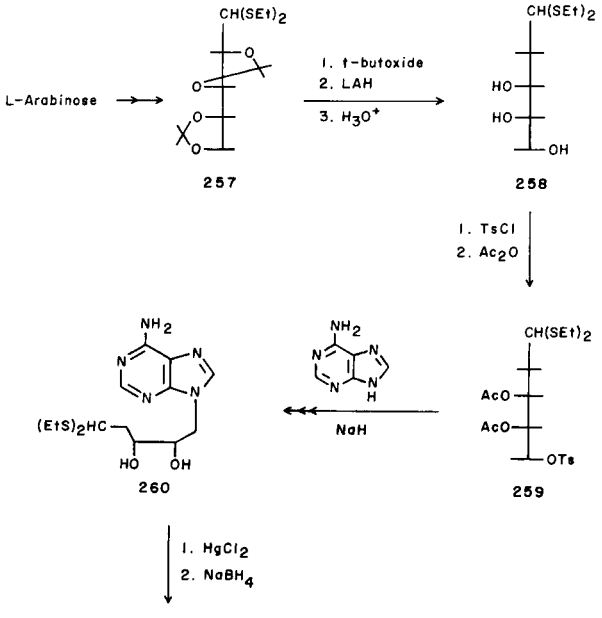
In related work, Holy [107] reported the synthesis of racemic and optically active erythro and threo 9-(2,3,4-trihydroxybutyl)adenines **256**. From the reaction of DL-tartarate and *meso*-tartarate **254** he prepared DL-threo- and DL-erythro-9-(2,3,4-trihydroxybutyl)adenine **256** (Scheme 36). D-Threo- and L-threo-isomers were prepared from 1,3-*O*-benzylidene-D-threitol and 1,3-*O*-benzylidene-L-threitol, respectively. D-Erythro- and L-erythro-isomers were also prepared from 2,3-*O*-isopropylidene-6-benzoyl-6-tosyl-D-mannofuranoside and *O*-*p*-toluenesulfonyl-5-deoxy-1,2-*O*-isopropylidene-L-arabinofuranose, respectively. Baker and Carr [108] also synthesized the L-erythro-isomer **256** from L-arabinose which stereochemically

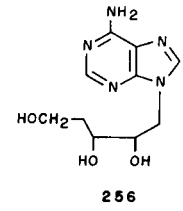
Scheme 36



represents the "bottom half" of the D-ribofuranose moiety. However, this compound was found to be inactive against herpes and polio viruses (Scheme 37).

Scheme 37

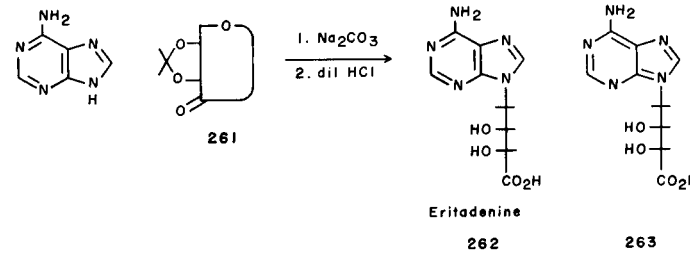




D. Eritadenine Analogues.

Eritadenine **262** is a hypolipidemic agent isolated from Japanese edible mushroom shiitake (Lentinus edodes) and its chemical structure was identified as 2(*R*),3(*R*)-dihydroxy-4-(9-adenyl)butyric acid. Deoxyeritadenine and 9-carboxypropyladenine have also been isolated from the same organism [109-113]. In the original synthesis by Chibata *et al.* [109] 4-amino-6-chloro-5-nitropyrimidine was condensed with 4-amino-2,3-dihydroxybutyric acid. Reduction of the nitro-group followed by the ring closure with triethylorthoformate afforded eritadenine. Kamiya *et al.* [112] utilized D-erythrono lactone **261** as the starting material to obtain the N_9 (eritadenine) **262** and N_3-isomer **263** (Scheme 38).

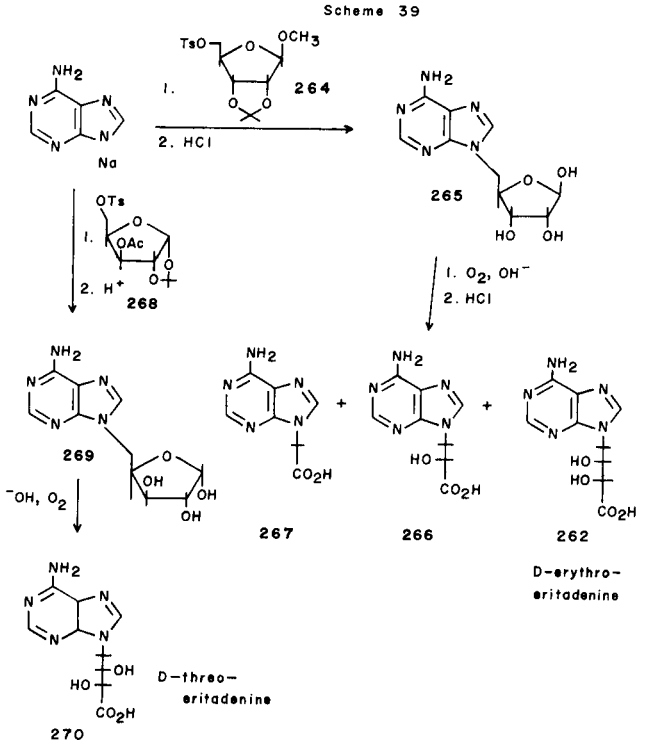
Scheme 38



Okumura *et al.* [114] also synthesized eritadenine and its derivatives with various purine moieties from similar condensations. Kawazu *et al.* [115] developed a method utilizing 5-*O*-tosylribose derivative **264**, which was condensed with sodium adenine followed by oxidation to yield eritadenine **262** and the related compounds **266** and **267** (Scheme 39). Takamura *et al.* [116] also synthesized D-threo-eritadenine **270** by a similar condensation [Scheme 39].

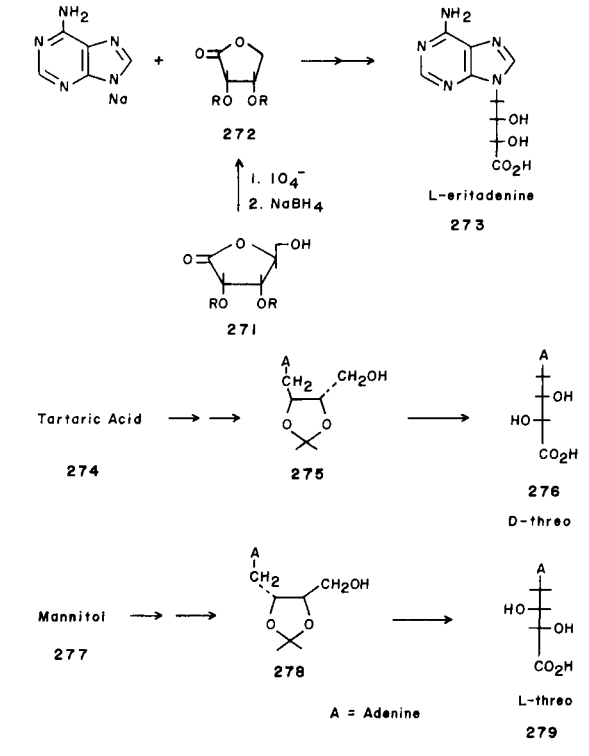
Later, Takeyama and coworkers [117] synthesized more than 100 derivatives of eritadenine, and their hypocholesterolemic activities were evaluated. From a study of the structure-activity relationships they found that the most active derivatives were the carboxylic acid derivatives with short-chain monohydroxy alcohols. These were 50 times more active than eritadenine and effective in lowering serum cholesterol in rats at the dose of 0.0001% in the diet. The carboxyl function and at least one hydroxyl

Scheme 39



group appear to be essential for activity. The intact adenine structure seems to be required for the activity, except for the N_1 position where an oxygen of alkoxy group could be attached without loss of activity.

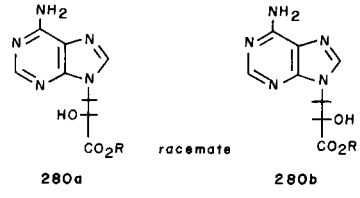
Eritadenine has hypocholesterolemic activity in that eritadenine increases the excretion of cholesterol into the feces. Eritadenine has no effect on the endogenous synthesis of cholesterol from [1-^{14}C] acetate. The isoamyl ester of eritadenine inhibits protein kinase by acting as a competitive inhibitor of ATP, which indicates that these esters act at the receptor site [113].



Recently Holy and coworkers rekindled interest in eritadine and its analogues as *S*-adenosyl-L-homocysteine hydrolase inhibitors and as antiviral agents [118-125]. They found that eritadenine and its derivatives strongly inhibit *S*-adenoxyl-L-homocysteine hydrolase (eritadenine $IC_{50} = 1.2 \times 10^{-8}$ mol/l). The enzyme was irreversibly inhibited. As an extenstion of this work they synthesized stereoisomers of eritadenine **273**, **276** and **279** [120] (Scheme 40). From the structure-activity study, they found that to be an inhibitor of *S*-adenosyl-L-homocysteine hydrolase, the analogue must contain an adenine base substituted at position 9 by an ω-carboxyalkyl (C_3-C_5) chain bearing at least one hydroxy function. The absolute configuration at the side-chain is decisive for the dihydroxy and trihydroxy compounds, but less important for the monohydroxyalkanoic acids. D-Eritadenine and 3-(adenin-9-yl)-2-hydroxypropionic acids are the most potent *S*-adenosyl-L-homocysteine hydrolase inhibitors and the only compounds possessing an antiviral activity against vesicular stomatitis, parainfluenza type 3, renovirus type 1, and vaccina virus.

Since the methyl ester of D-eritadenine is more potent as an antiviral agent than the parent compounds, De Clercq and Holy [126] examined various alkyl esters of adenyl-9-yl-2-hydroxypropanoic acid **280** (Figure 8). From the study they found that these esters showed broad inhibitory activity against vesicular stomatitis, vaccina, reo, parainfluenza, and measles viruses, and they are nontoxic to the host cell (except the furylmethyl ester) at antivirally active concentrations. They postulated that alkyl esters serve as a prodrug of 3-adenin-9-yl-2-hydroxy propanoic acid.

Fig. 8

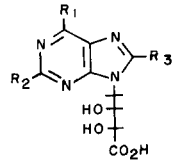


Eritadenines (D- and L-erythro) were active against vaccina, measles and vescular stomatitis virus. Eritadenine (D-erythro) was also effective against reo- and parainfluenza virus. In general, the antiviral activity of the eritadenines decreased in order D-erythro > L-erythro ≫ D-and L-threo isomer [120]. They also examined these compounds as inhibitors of *S*-adenosyl-L-homocysteine hydrolase. The inhibitory activity decreases in the order

D-erythro > L-erythro ≫ D-threo > L-threo [118]. Holy *et al.* have reported there is a correlation between the antiviral activity and inhibition of *S*-adenosyl-L-homocysteine hydrolase [97].

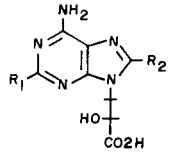
More recently, Holy *et al.* [125] examined a number of ω-carboxylalkyl derivatives of adenine and other purine bases **281-288** for their inhibitory effects on rat liver *S*-adenosyl-L-homocysteine hydrolase and their antiviral activity (Table 7-9), and including eight stereoisomeric 5-(adenyl-9-yl)-2,3,4-trihydroxypentanoic acids **297-304** [125] (Table 10).

Table 7



	R_1	R_2	R_3
281	NH_2	H	H
282	NH_2	NH_2	H
283	NH_2	SCH_3	H
284	NH_2	H	Br
285	NHC_2H_5	H	H
286	$N(CH_3)_2$	H	H
287	OH	H	H
288	SCH_3	H	H

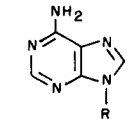
Table 8



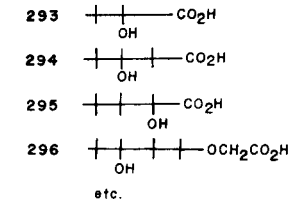
	R_1	R_2
289	H	H
290	CH_3	H
291	NH_2	H
292	H	Br

There is another class of acyclonucleosides, nucleoside triols **305**, which can be prepared from ribonucleosides by periodate oxidation followed by reduction with sodium borohydride (Fig. 9). Although nucleoside triols have been known for at least two decades [128,129], their biological evaluation has been limited except for the studies of Lerner and coworkers' [130,131]. Due to the recent discovery of antiviral agents such as acyclovir, DHPG, DHPA, DHBG, *etc.*, there is a renewed interest in this class of compound.

Table 9

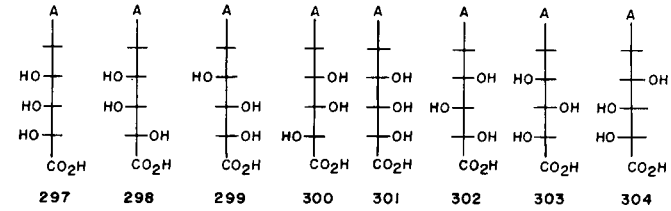


R



etc.

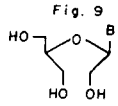
Table 10



Lerner [132] systematically studied the triol class of compounds. He purified and chemically characterized the triols derived from adenosine, cytidine, uridine. Lerner and Rossi [130] also prepared various triols from 9-β-D-xylopyranosyladenine, 9-α-D-arabinopyranosyladenine, 9-α-D-mannopyranosyladenine, 9-α-L-rhamnopyranosyladenine, 9-β-D-fucopyranosyladenine, and 9-α-L-fucopyranosyladenine for the study with adenosine deaminase. It was found that none of the triols were substrates for the enzyme. With the exception of the triol from 9-α-D-mannopyranosyladenine, all of these alcohols were competitive inhibitors. The best inhibitor was the alcohol from 9-α-L-rhamnopyransoyladenine. From a study of the triols from inosine, 6-mercapto-9-β-D-ribofuranosylpurine and 2-amino-9-β-D-ribofuranosylpurine and 2-amino-9-β-D-ribofuranosylpurine, Rossi and Lerner [131] found that the 6-amino group is necessary for inhibitory activity against adenine deaminase.

Recently, noncyclic triol derivative of guanosine was unequivocally prepared by Lerner [133]. Bessodes and Antonakis [134] also reported a convenient one pot solid phase cleavage of ribonucleosides to the triols from ribonucleosides including guanosine.

Fig. 9



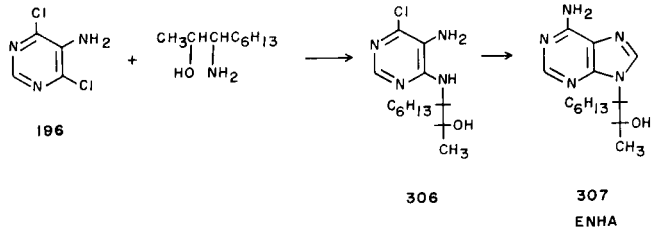
305

B = adenine
guanine
uracil
cytosine

E. Erythro-9-(2-hydroxy-3-nonyl)adenine (EHNA) Analogues.

Schaeffer and coworkers extensively studied the substrate binding characteristics of adenosine deaminase and found that the binding area for the 9-substituents is a large hydrophobic region [135], a hydroxyl binding site [27], and a specific methyl binding region [136]. Furthermore, they demonstrated that with some 9-substituted adenines containing a chiral center, there is stereoselectivity in the formation of the enzyme-inhibitor complex. For example, with some 9-(1-hydroxy-2-alkyl)adenines, the preferred chiral center for enzyme-inhibitor complex formation has the (*R*)-configuration [137] whereas with 9-(2-hydroxypropyl)adenine, the chiral center with the (*S*)-configuration is bound more tightly to the enzyme [136]. With this information Schaeffer and Schwender [138] synthesized various 9-(2-hydroxy-3-alkyl)-adenine derivatives in order to find a more potent adenosine deaminase inhibitor (Scheme 41). Erythro-9-(2-hydroxy-3-nonyl)adenine (EHNA) **307** was the most potent inhibitor (Ki = 1.6 × 10^{-9} *M*) [139]. The erythro-diastereoisomer was more active than the threo-isomer supporting the above observation that adenosine deaminase possesses a single binding site for inhibitors.

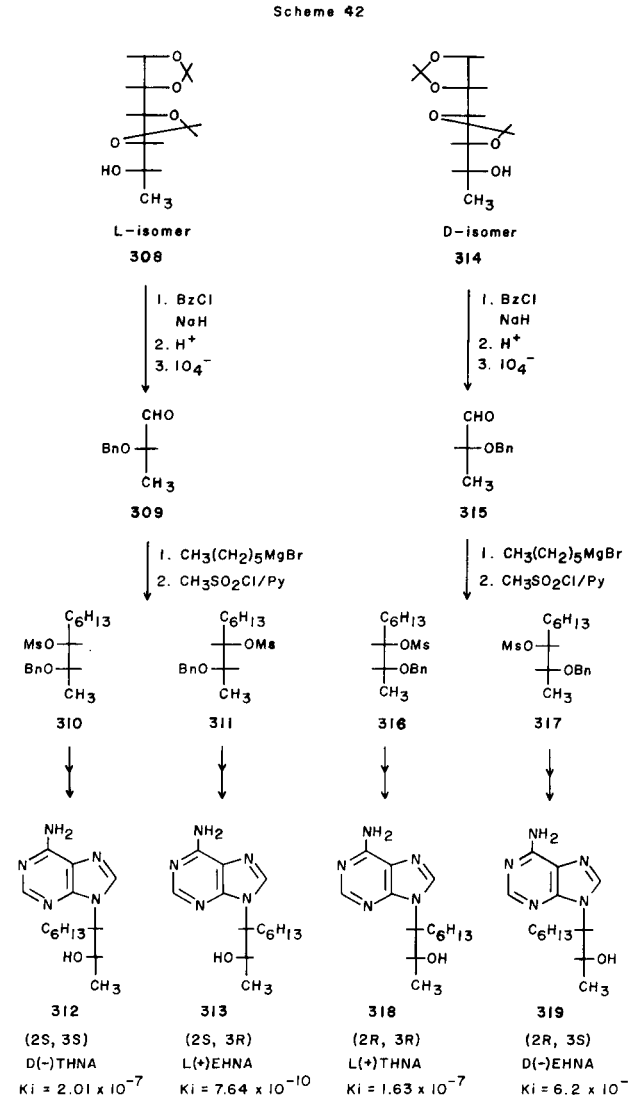
Scheme 41



Subsequently, Plunkett and Cohn [140] demonstrated that EHNA greatly potentiates the cytotoxicity of adenine nucleosides. North and Cohn [141] showed that EHNA significantly inhibits replication of HSV and markedly potentiates the cytotoxicity of ara-A and cordycepin against Hela cells and against the production of HSV in those cells. As a result of much faster reactivation of inhibited adenosine deaminase observed in the case of inhibition by EHNA than that by pentostatin and coformycin, EHNA was considered as the inhibitor of choice for use in viral chemotherapy [142,143]. EHNA inhibits HSV production by 30% while EHNA in combination with ara-A inhibits HSV production by more than 90%.

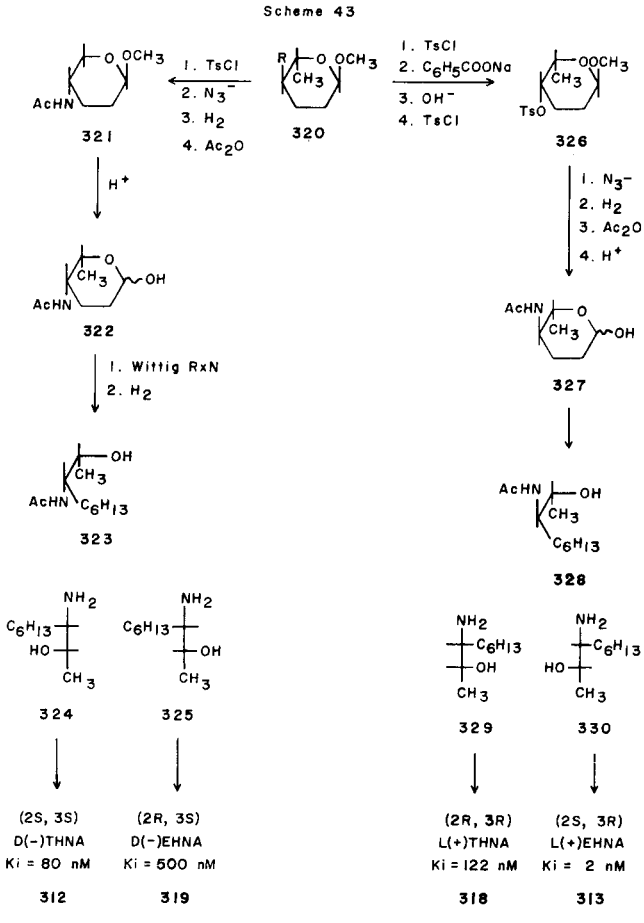
Baker *et al.* [144,145] recently reported a synthesis of D-and L-EHNA from D- and L-rhamnitol derivatives **308** and **314** (Scheme 42). They found that the L-erythor isomer **313** (Ki = 7.64 × 10^{-10} *M*) bound 80-fold more tightly to calf mucosal adenosine deaminase than the D-erythro isomer **319** (Ki = 6.23 × 10^{-8} *M*). Abushanab and coworkers [146,147] independently reported the synthesis of

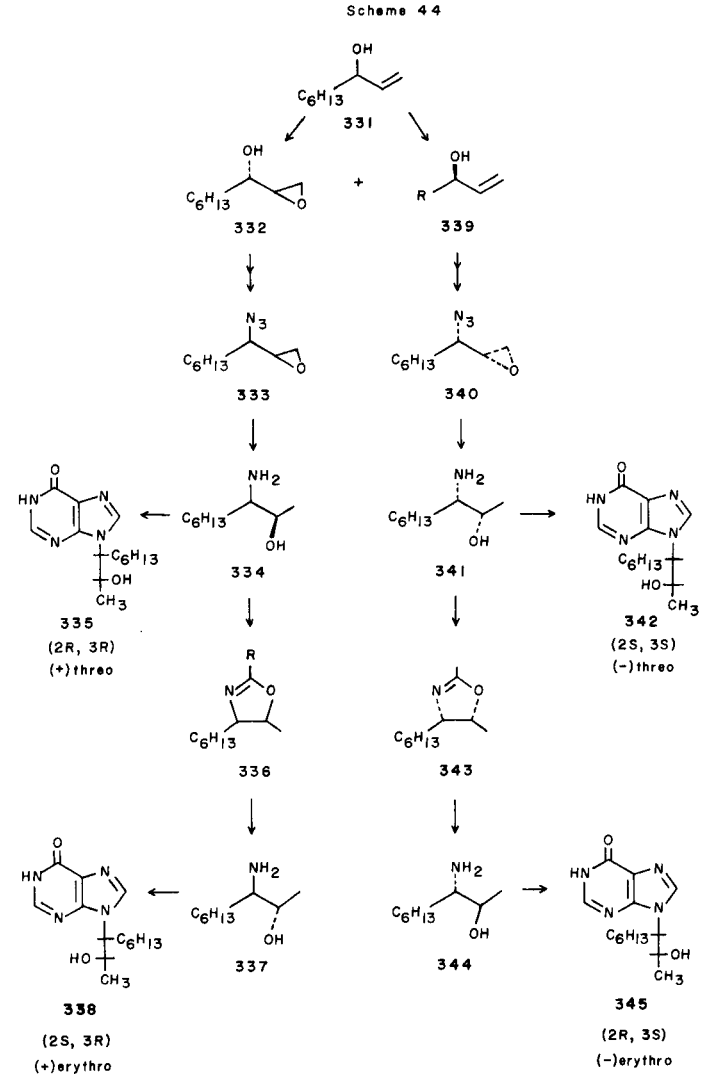
Scheme 42



erythro- and threo-EHNA. In the synthesis the key intermediates were four amino alkohols **324**, **325**, **329**, and **330** (Scheme 43). Inhibition of human erythrocyte adenosine deaminase was performed with the four isomers, and the Ki values obtained wer (+)2*S*,3*R*-EHNA **313** (2 n*M*), and (−)-2*S*,3*S*-THNA **312** (80 n*M*). Since (+)-ENHA is the most active stereoisomer, Abushanab *et al.* [148] recently reported a practical synthesis of the (+)-isomer from the key intermediate, (benzyloxethyl)oxirane.

Structurally related to EHNA, erythro-9-(2-hydroxy-3-nonyl)hypoxanthine (NPT 15392) (a mixture of **338** and **345**) has been reported to have immunopotentiating activity [149,150]. This compound enhances T-cell dependent immune response [151]. NPT 15392 does not augment *in vitro* natural killer cells or antibody-dependent cellular cytotoxicity of human blood mononuclear cells. The ef-

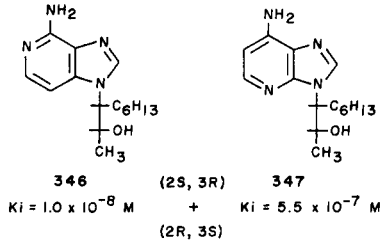




fects of NPT 15392 do not appear to be mediated by prostaglandin or interferon induction; preliminary studies indicate that cyclic 3',5'-guanosine monophosphate may be involved in the mechanism by which NPT 15392 modulates immune function [149]. Recently Abushanab and coworkers [151] reported a stereospecific synthesis of erythro- and threo-diastereomers of NPT 15392, **335**, **338**, **342** and **345** starting from 1-nonene-3-ol **331** (Scheme 44).

Due to the interesting biological activity of EHNA and its hypoxantine analogue (NPT 15392), Grifantini and coworkers [152] synthesized deaza-analogues of EHNA in order to study the structural requirement of EHNA as an inhibitor of adenosine deaminase. They found that isosteric substitution of pyrimidine nitrogens by carbons could be tolerated at the enzymic binding site. 3-Deaza-EHNA **346** was found to have an inhibitory activity comparable (Ki = 1.0×10^{-8} *M*) to EHNA (Ki = 1.6×10^{-9} *M*) [139] and 1-deaza-ENHA **347** (Ki = 5.5×10^{-7} *M*), though less potent, is a good inhibitor (Fig. 10).

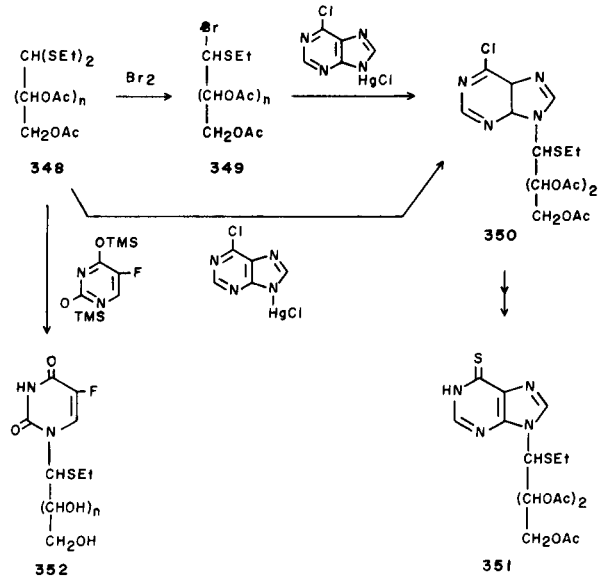
Fig. 10



F. Polyhydroxyacyclonucleosides.

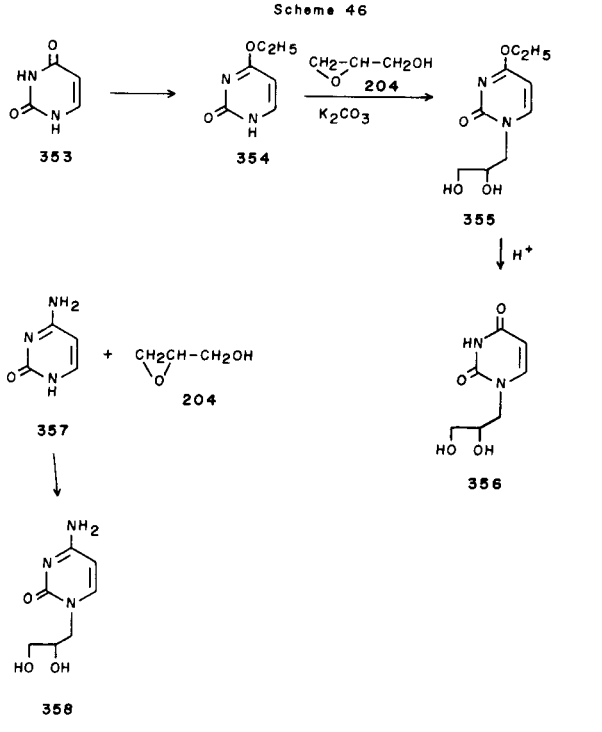
Horton, Wolfrom, and co-workers have reported a number of polyhydroxylated acyclonucleosides derived from various carbohydrates containing uracil [153,163], thymine [154, 155, 163], cytosine [153, 163, 164], 5-fluorouracil [156] adenine [153, 154, 157-160, 163], 6-chloropurine [156, 161, 163-170], and 6-mercaptapurine [160-170]. A general method of synthesis is shown (Scheme 45).

Scheme 45



The 6-mercaptopurine derivative derived from D-glucose showed *in vivo* activity in the murine L1210 leukemia cell lines. It is interesting to note that the 6-mercaptopurine derivative from D-glucose was markedly more active than the 6-mercaptopurine derivative from D-galactose [170]. Shaw and coworkers [171] reported imidazole and purine acyclic nucleoside derivatives of arabinose. Holy [172] also reported 1-(adenin-9-yl)-1-deoxy-DL-ribitol, -D-arabitol, and other pyrimidine trihydroxy pyrimidine derivatives.

Scheme 46



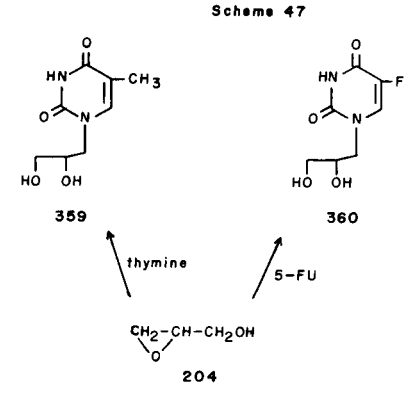
II. Pyrimidineacyclonucleosides.

In contrast to the purine acyclonucleosides pyrimidineacyclonucleosides have not shown any significant antiviral or anticancer activities. Despite this disappointment there have been continuing efforts to synthesize various pyrimidineacyclonucleosides in search of new, useful antiviral and anticancer agents. Although the original synthesis of pyrimidineacyclonucleosides were reported by Wolfrom, Horton, and co-workers, this section will exclude those compounds because of the previous brief general discussion (Scheme 45).

In their synthesis of DHPA **201** Ueda *et al.* [91] also prepared uracil **356** and cytosine derivatives **358** (Scheme 46).

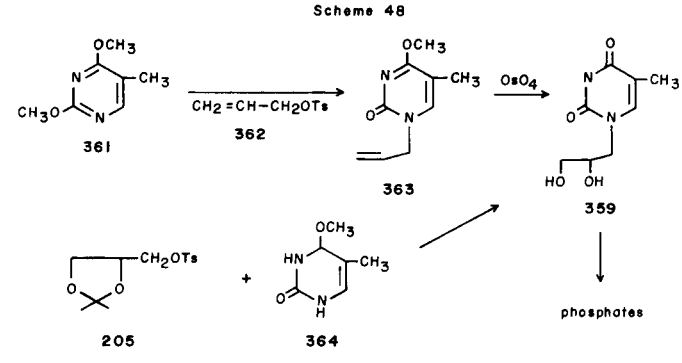
Imoto and coworkers [173] reported the synthesis of 5-substituted pyrimidineacyclonucleosides **359** and **360** by similar reactions as previously reported by Ueda *et al.* [91] and Seita *et al.* [92] (Scheme 47). They also prepared 5-bromo- and 5-iodouracil derivatives by halogenation of the uracil derivative.

Scheme 47



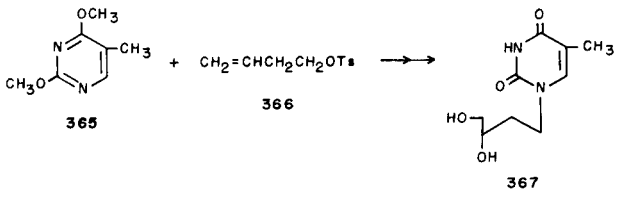
Holy and Ivanova [174] modified the above synthesis (Scheme 48). They prepared phosphates of **359** and studied the substrate characteristics of nucleolytic enzymes [174, 175].

Scheme 48



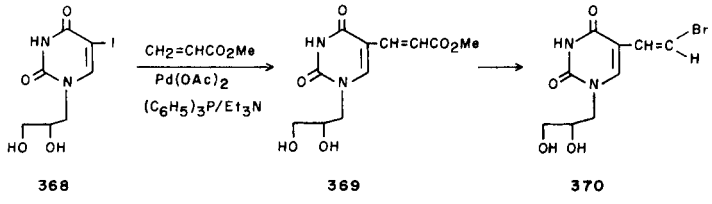
Holy [93] prepared a homo-analogue **367** in a similar condensation reaction (Scheme 49).

Scheme 49



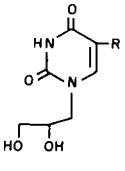
Recently, Vanderhaeghe and co-workers [100] prepared acyclonucleoside analogue **370** of *E*-5-(2-bromovinyl)-2′-deoxyuridine [21,22] (Scheme 50), but the compound did not exhibit significant antiviral activity. Robins and coworkers [43] also later reported **370** as an inactive compound.

Scheme 50



Harnden and co-workers [176] briefly reported a number of compounds **371-381** related to the above compounds (Table 11). None of the compounds were significantly active when tested against HSV-1 or influenza A virus in cell culture.

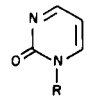
Table 11



	R		R
371	H	**379**	NO_2
372	CH_3	**380**	$CH=CH_2$
373	F	**381**	$C\equiv CH$
374	Cl		
375	Br		
376	I		
377	CF_3		
378	CN		

Based on the fact that 1-(β-D-ribofuranosyl)-2-pyrimidone exhibited antibacterial activity, Holy and coworkers [177] prepared 2-pyrimidone acyclonucleosides related to eritadenine and studied the inhibition of bacterial cytidine deaminase (Table 12).

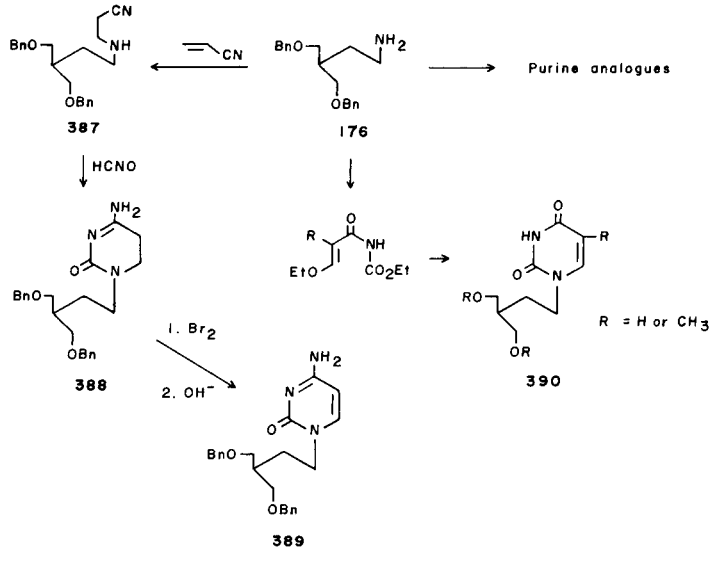
Table 12



		deamination rate
382	R = ribose	1.00
383	R = $-CH_2CH(OH)-CH_2(OH)$	1.16
384	R = $CH_2CH(OH)-COOH$	0.76
385	R = $CH_2(OH)-CH(OH)-COOH$	0.95
386	R = $CH_2CH_2(OH)-CH_2(OH)$	1.16

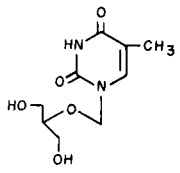
In many cases synthetic intermediates for purineacyclonucleosides were used for the pyrimidineacyclonucleosides. Pandit and coworkers [82] utilized the same intermediate **176** for the preparation of pyrimidineacyclonucleosides **389** and **390** (Scheme 51) and purineacyclonucleosides.

Scheme 51



In their synthesis of adenineacyclonucleosides, Ogilvie and Gillen [70] also reported **391** (Fig. 11) from which they prepared dinucleotides for study of substrate specificity of phosphodiesterases.

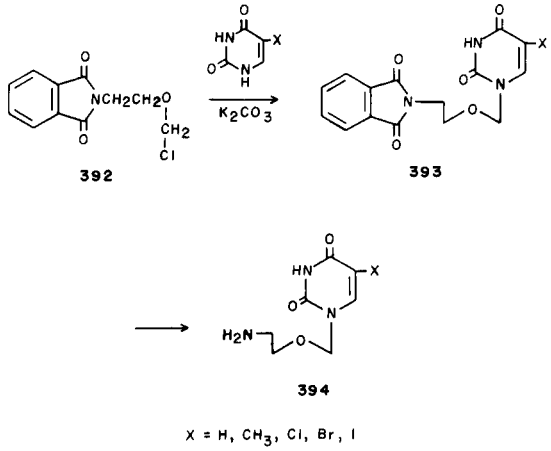
Fig. 11



391

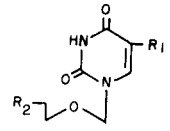
Kelley *et al.* [178] prepared 5-substituted analogues of the acyclic aminonucleoside 1-[(2-aminoethoxy)methyl]uracil **394** for antiviral evaluation (Scheme 52). However, these acyclic nucleosides exhibited neither cytotoxicity nor antiviral activity.

Scheme 52

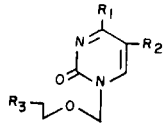


X = H, CH_3, Cl, Br, I

Table 13



	R_1	R_2
395	H	H
396	H	OH
397	H	OSO_2NH_2
398	CF_3	OH
399	F	OH
400	I	OH
401	Br	OH

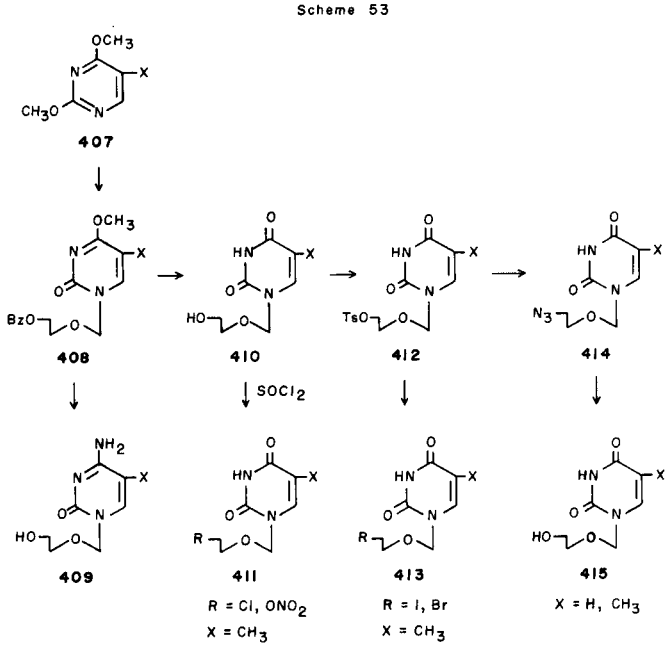


	R_1	R_2	R_3
402	NH_2	H	H
403	NH_2	H	OH
404	NH_2	Br	OH
405	$N(CH_3)_2$	H	OH
406	SH	H	OH

Kelley *et al.* [179] also reported a number of related compounds (Table 13) for antiviral screening. Again, none of the compounds exhibited any activity against HSV-1 or other DNA or RNA viruses. They also showed no significant substrate properties for HSV-1 encoded thymidine kinase. Barrio and coworkers [32] previously reported the preparation of the cytosine derivative **403** as part of their general synthetic method for acyclonucleosides including acyclovir.

Chu and coworkers [180] synthesized various 5-substituted uracil and cytosine acyclonucleosides (Scheme 53). Cha and coworkers [181] subsequently studied them as inhibitors of uridine phosphorylase. These acyclonucleosides were found to be competitive inhibitors of uridine phosphorylase but had no effect on thymidine phosphorylase, uridine kinase or thymidine kinase. The most potent compound was the thymidine derivatie **410** (X = CH_3) (Ki = 3 μM)

Scheme 53



R = Cl, ONO_2
X = CH_3

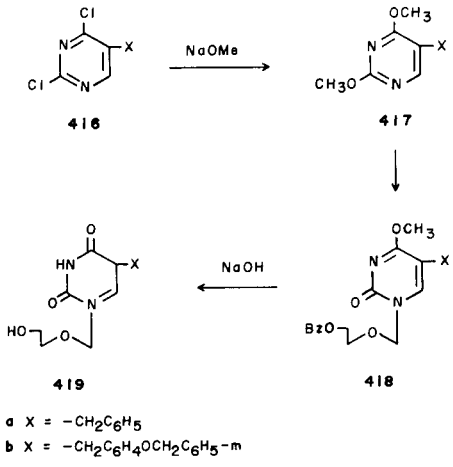
R = I, Br
X = CH_3

X = H, CH_3

Chu and coworkers [182] synthesized 5-benzylacyclouridine **419a** 5-benzyloxybenzylacyclouridine **419b** (Scheme 54) and found them to be potent inhibitors of uridine phosphorylase (Ki = 98 and 32 nM, respectively). Cha and coworkers [183] studied the structure-activity relationship of pyrimidine analogues including the acyclonucleosides.

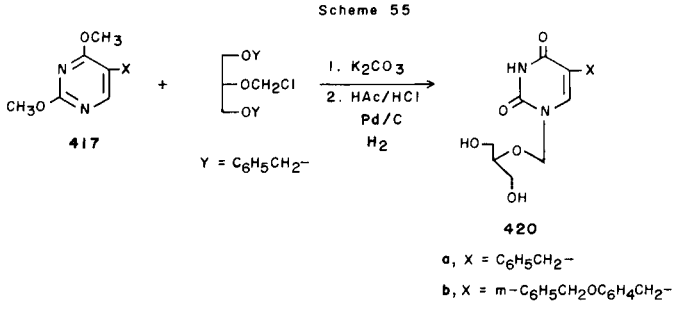
Subsequently Chu and coworkers [184] reported the synthesis and biological activity of hydroxymethyl analogues **420a** and **420b** of 5-benzylacyclouridine **419a** and 5-benzyloxybenzylacyclouridine **419b** (Scheme 55). They were reported as potent inhibitors of uridine phosphorylase with Ki values of 1.6 and 0.32 μM, respectively for the en-

Scheme 54



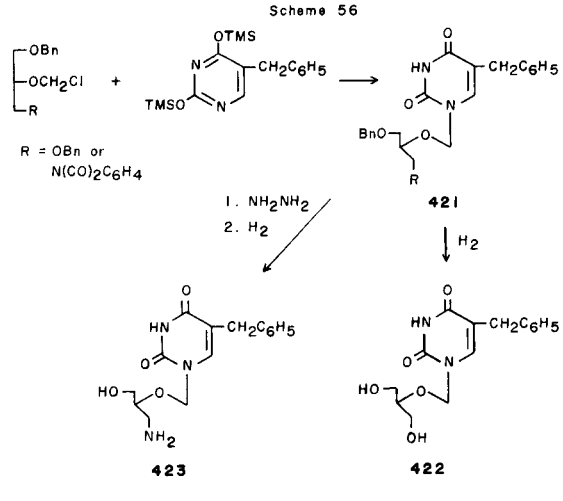
zyme from mouse liver. In addition, the compounds potentiate significantly the growth-inhibiting action of 5-fluorodeoxyuridine in cell culture.

Scheme 55



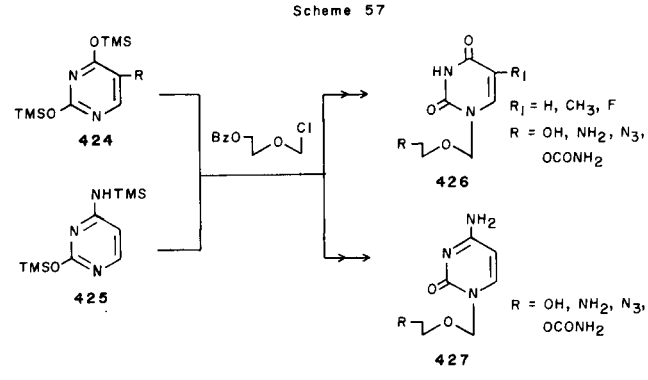
More recently Lin and coworkers [185,186] reported more soluble isomers of 5-benzylacyclouridine (Scheme 56). It was found that **420** and **423** are potent inhibitors of uridine phosphorylase isolated from Sarcoma 180 cells with a Ki value of 0.098 and 0.020 μM, respectively, and exhibited no apparent cytotoxicity against Sarcoma 180 host cells.

Scheme 56



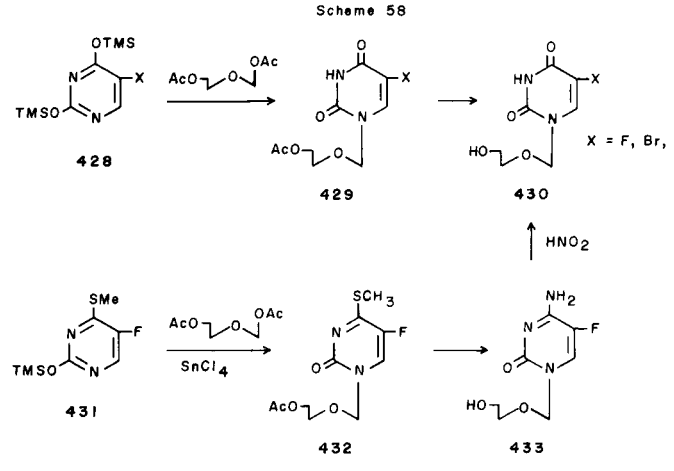
Schroeder *et al.* [187] prepaed a series of acyclonucleosides **426** and **427** for biological testing (Scheme 53). At 10^{-4} M concentrations, the compounds were inactive against L-1210 cell line in culture. However, a number of the acyclonucleosides inhibited the *in vitro* growth of *E. coli.* The most potent among these, 1-[(2-hydroxyethoxy)-methyl]-5-fluorouracil **426** (R = OH, R_1 = F), was active at an IC_{50} of 1.2 μM. It was reported that some of the analogues were also found to selectively interfere with herpes virus replication *in vitro.*

Scheme 57



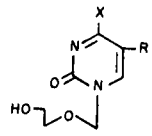
Rosowsky and coworkers [188] independently prepared uracil **430** and cytosine acyclonucleosides **433** (Scheme 58). The reported ID_{50} of **430** (X = F) against L1210 mouse leukemia cells in culture was 1.7×10^{-5} M.

Scheme 58



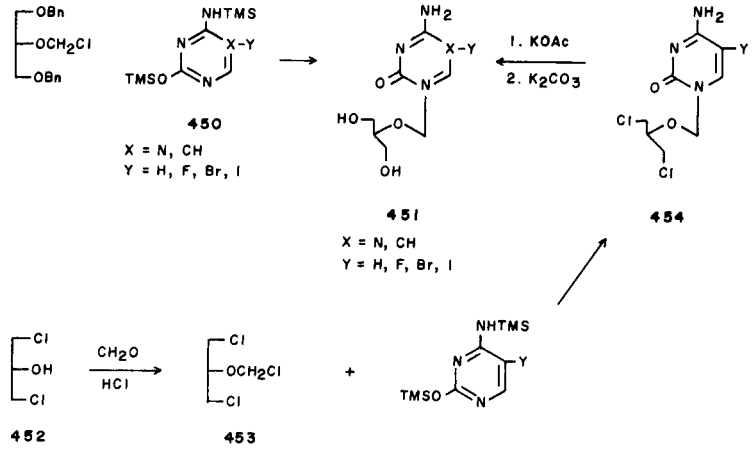
As a part of a generl synthetic scheme for acyclonucleosides, Robins and coworkers [34,43] prepared various known, as well as unreported, pyrimidine acyclonucleosides for biological evaluation. However all of these analogues **434-443** were devoid of antiviral, cytotoxic and antimetabolic activities (Table 14).

Table 14



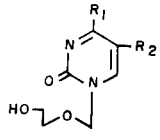
	X	R
434	OH	H
435	OH	CH_3
436	OH	F
437	OH	Cl
438	OH	Br
439	OH	I
440	OH	NO_2
441	NH_2	H
442	NH_2	NO_2
443	OH	CH=CHBr

Scheme 59



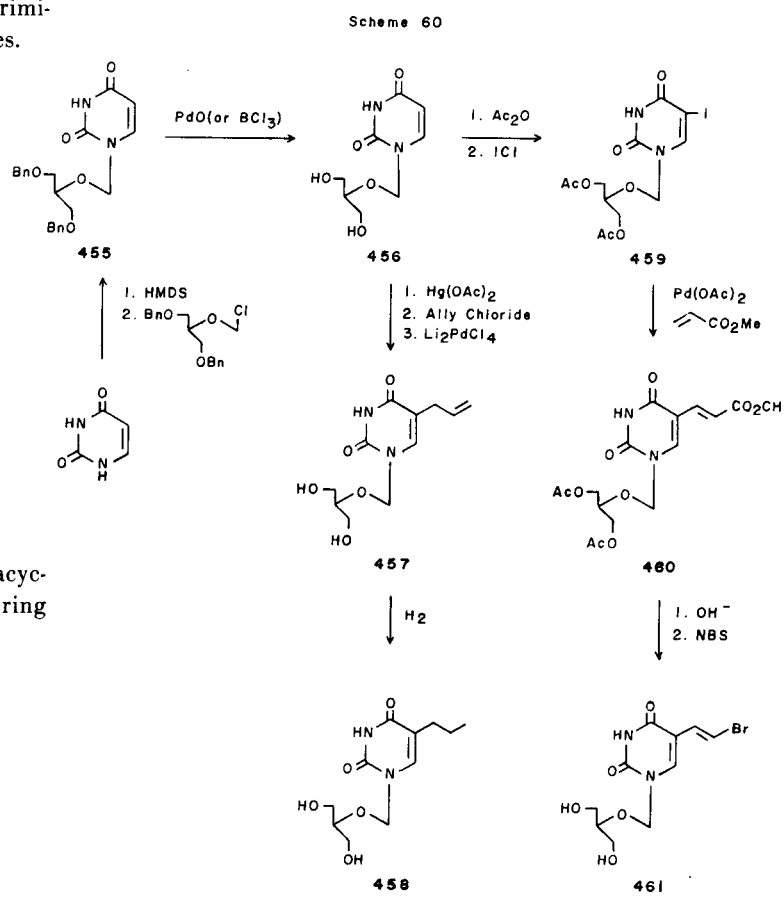
Gringel and coworkers [189] prepared various pyrimidine **444-448** (Table 15) and purine acyclonucleosides.

Table 15



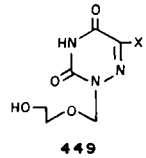
	R_1	R_2
444	OH	H
445	OH	F
446	OH	I
447	OH	CH_2OH
448	NH_2	H

Scheme 60



Lazrek and Panzica [190] briefly reported certain acyclonucleoside analogues of the *as*-triazine-3,5-dione ring system (Fig. 12).

Fig. 12



449

X = H, Br, NH_2, $NHCH_2C_6H_5$, $SCH_2C_6H_5$

The potent and broad spectrum of activity of DHPG (**37**) against herpes viruses prompted the synthesis of pyrimidine analogues containing the same side chain [71,191,-192] (Schemes 59-61). However, none of these compounds was reported to exhibit any significant antiviral activity.

As a part of efforts to determine the limits on structural changes in the side chain with respect to the optimal biological activity, Ogilvie and coworkers [70] prepared pyrimidine acyclonucleosides **467** with an additional hydroxymethyl group at the 3'-position (the 4'-carbon of natural nucleosides). None of the compounds gave any significant antiviral activity (Fig. 13).

Scheme 61

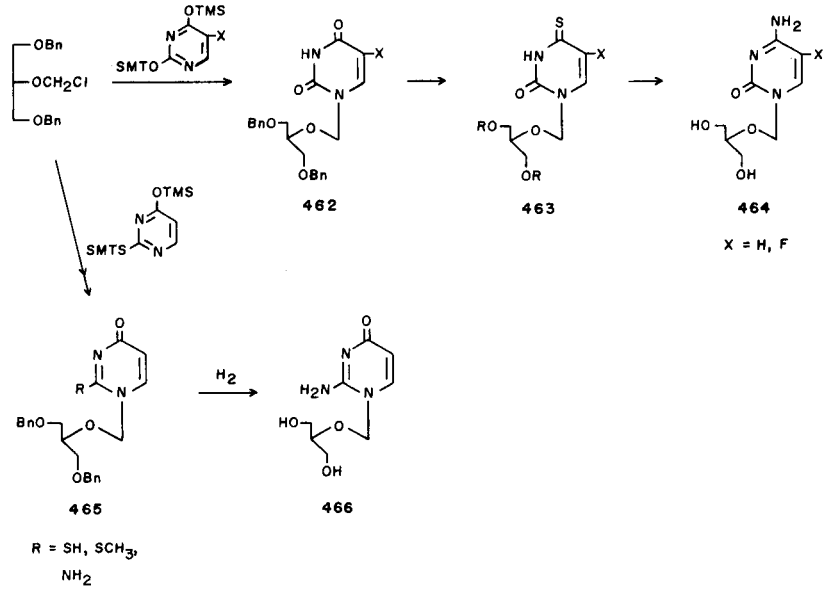
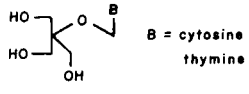


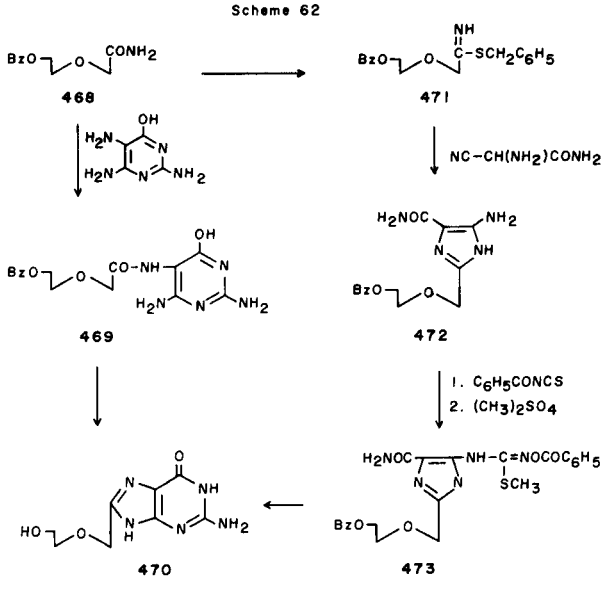
Fig. 13



III. Acyclo-*C*-Nucleosides.

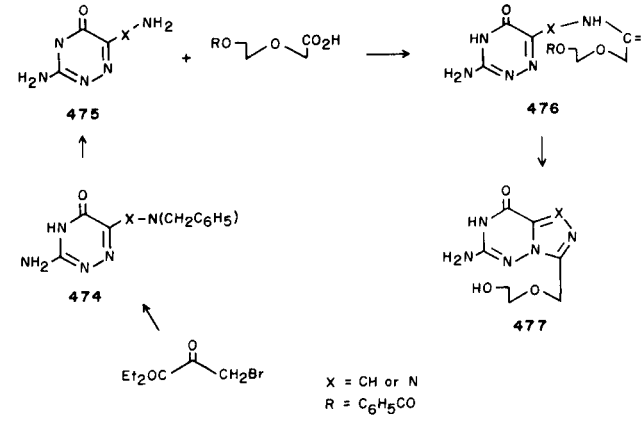
The first synthesis of acyclo-*C*-nucleosides was reported by Igolen and coworkers [193] (Scheme 62). They utilized similar synthetic strategies which were previously used for the synthesis of other types of *C*-nucleosides [194].

Scheme 62



Scopes and coworkers [195] reported the *C*-nucleoside isosters of acyclovir **477** (Scheme 63). None of the compounds exhibited any biological activity against HSV-1 and HSV-2 in cell culture.

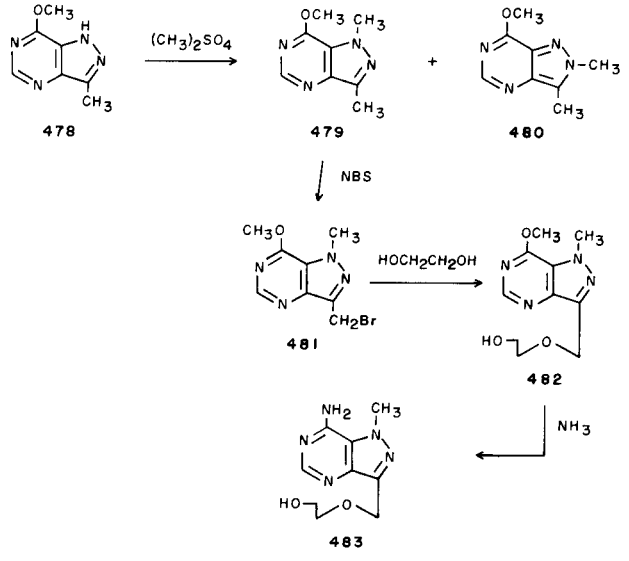
Scheme 63



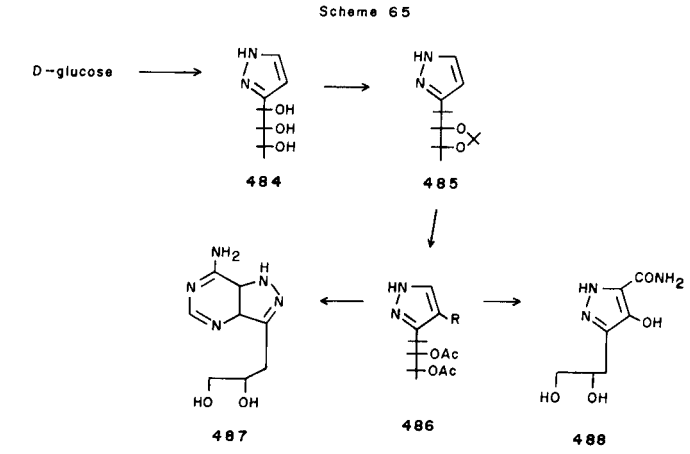
Griengl and Gunzl [196] reported an acycloanalogue of formycin **483** (Scheme 64). The compound has been tested against influenza A/Texas, influenza B/Hong, HSV-1, HSV-2, and L1210 cells, but no activity was detected.

Starting from glucose, Buchanan [197] has mentioned in some related work the synthesis of the formycin **487** and pyrazomycin **488** analogues of DHPA (Scheme 65).

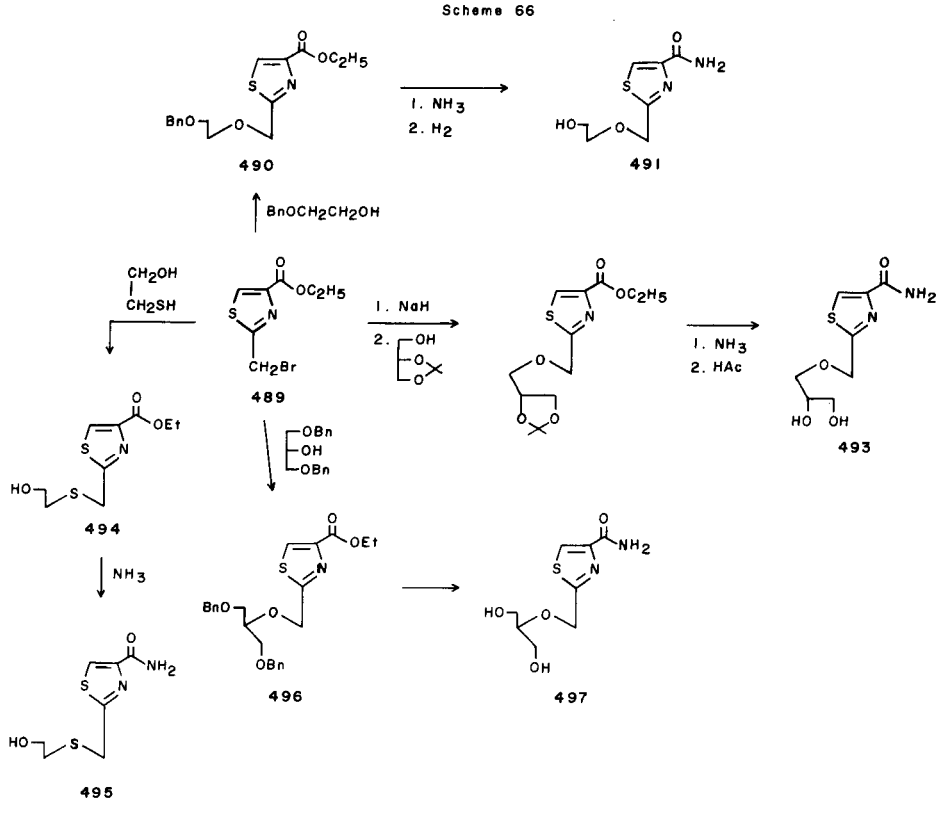
Scheme 64



Scheme 65



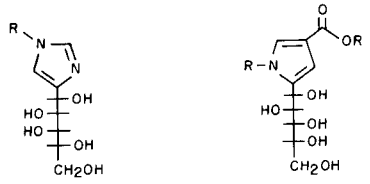
Scheme 66



Baker and Kumar [198] prepared a series of acyclo-*C*-nucleosides analogues **491**, **493**, **495** and **496** of thiazofurin [199] for anticancer and antiviral screening (Scheme 66). None of these compounds showed any significant antiviral activity.

Recently, Perez and coworkers [200-202] reported acyclo-*C*-nucleosides **498** and **499** with five-membered ring heterocycles (Fig. 14).

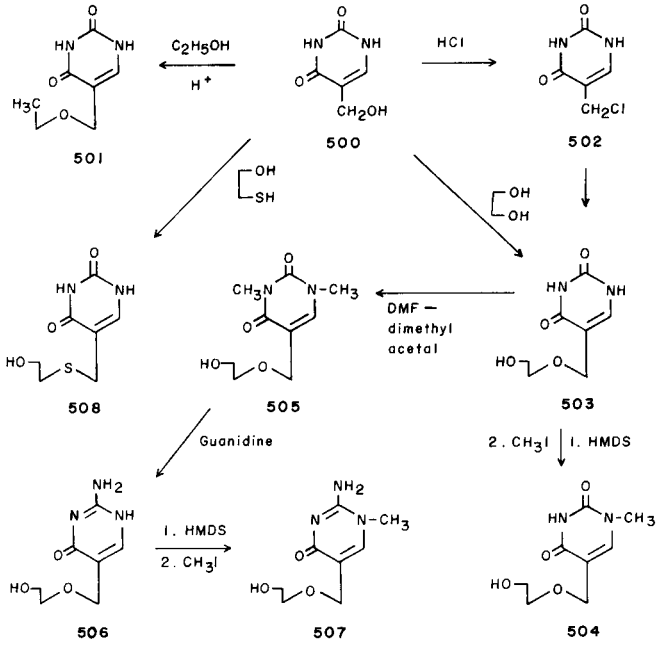
Fig. 14



498 499

Pyrimidine type acyclo-*C*-nucleosides also have been reported by Chu [203], in which pseudouridine **503**, N_1-methylpseudouridine **504** [204], pseudoisocytidine **506** [205], and N_1-methylpseudoisocytosine **107** analogues have been prepared (Scheme 67). Melbnik *et al.* [206] independently prepared **504**, **505**, and **506** by similar reactions. In a preliminary test, 1-methylacyclopseudouridine **504** (thymidine analogue) exhibited some antiviral activity [207] against HSV-1 (50% PFU reduction at 50μM). Melbnik *et al.* [206] also reported the HSV-1 and thymidine phosphorylase inhibitory activity.

Scheme 67

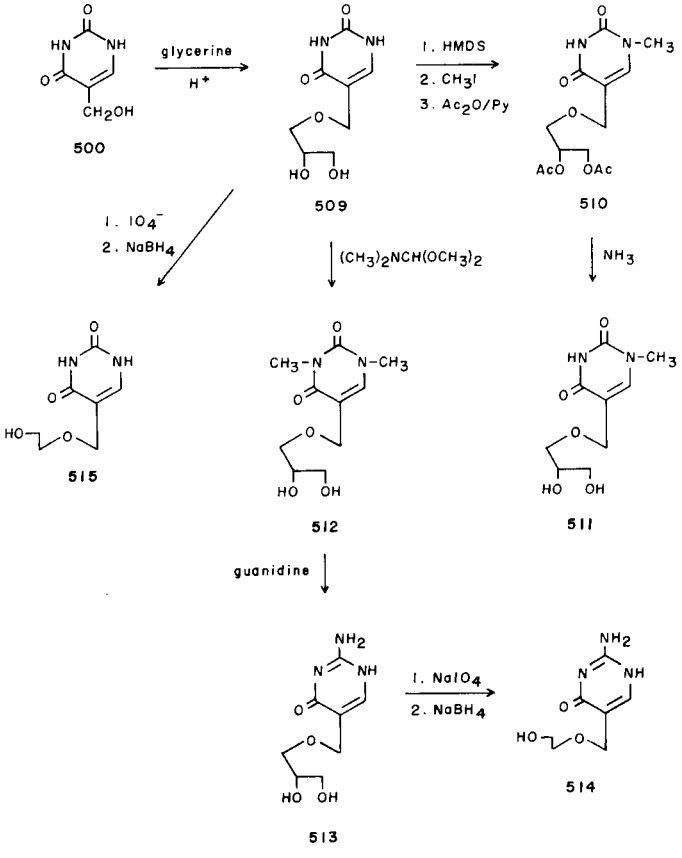


From similar reactions, Chu and coworkers [208] also prepared pyrimidine acyclonucleosides **509**-515 with iso-DHPG (**142**) type side chain (Scheme 68).

IV. Miscellaneous Acyclonucleosides.

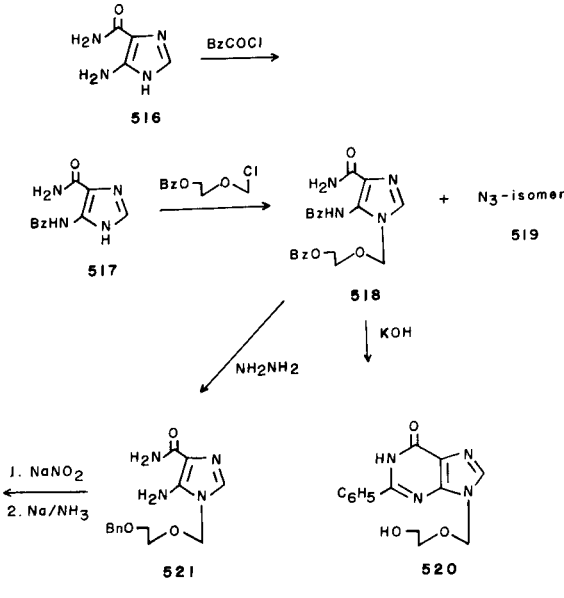
Because of the structural relationship of 5-amino-4-carbamoyl-1-β-D-ribofuranosylimidazole (AICA-riboside) to

Scheme 68

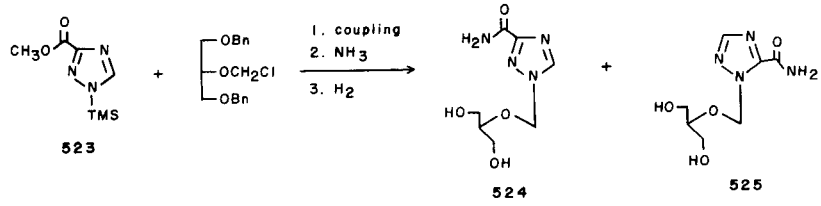


purines, Parkins and Harnden [209] prepared imidazole-acyclonucleosides **518** and **521**, which were subsequently cyclized to purine-type acyclonucleosides **520** and **522** (Scheme 69). None of the compounds showed any significant antiviral activity against HSV-1 and influenza A viruses *in vitro*.

Scheme 69



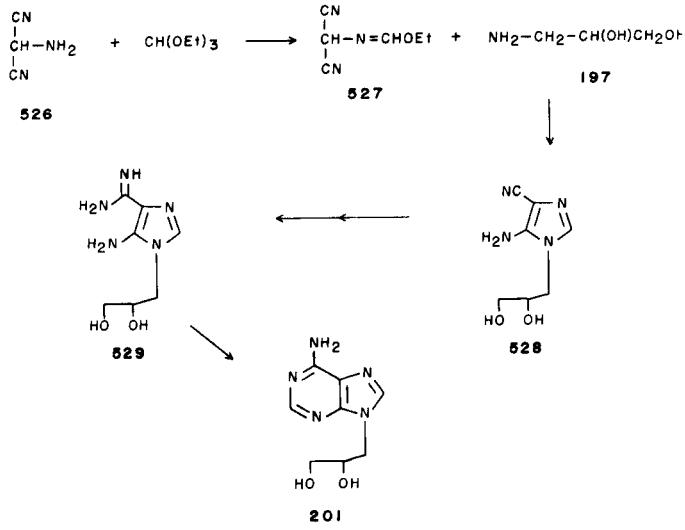
Scheme 70



Based on broad antiviral and anticancer activities exhibited by ribavirin [24], Lin and Lin [210] synthesized an acyclonucleosides analogue **524** of ribavirin containing DHPG-type (**37**) side chain as potential antiviral agents (Scheme 70).

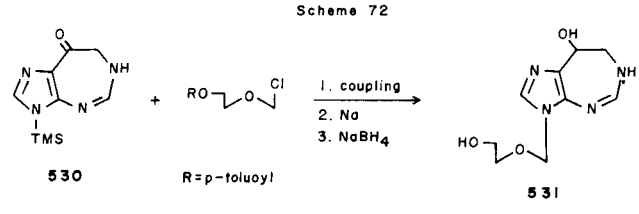
Shaw and coworkers [211] also reported the imidazole acyclonucleosides and their subsequent cyclization to DHPA **201** (Scheme 71).

Scheme 71



In order to evaluate the substrate specificity specifics of adenosine deaminase in comparison with pentostatin, Showalter and coworkers [212] prepared an acyclonucleoside analogue **531** of pentostatin (Scheme 72). The Ki value for the *in vitro* adenosine inhibitory activity of **531** was 9.8×10^{-8} *M*. The compound also potentiated the antiviral activity of ara-A.

Scheme 72



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REFERENCES AND NOTES

[1] R. Dolin, *Science,* **227**, 1296 (1985) (Review).

[2] B. Oberg and N.-G. Johansson, *J. Antimicrob. Chemother.,* **14**, Suppl. A, 5 (1984) (Review).

[3] D. L. Swallow, *Prog. Drug Res.,* **28**, 127 (1984) (Review).

[4] E. De Clercq, *Biochem Pharmacol.,* **33**, 2159 (1984) (Review).

[5] D. O. White, "Antiviral Chemotherapy, Interferons, and Vaccines" in Monographs in Virology, Vol **16**, J. L. Melnick, ed, Karger, Basel, 1984.

[6] "Antiviral Agents and Viral Diseases of Man", G. J. Galasso, T. C. Merigun and R. A. Buchanan, eds, Raven Press, New York, 1984.

[7] "Antiviral Drugs and Interferon: The Molecular Basis of Their Activity ", Y. Becker, ed, Martinus Nijhoff Publishing, Boston, 1984.

[8] P. G. Canonico, M. Kende, B. J. Luscri, and J. W. Higgins, *J. Antimicrob. Chemother.,* **14**, Suppl. A, 27 (1984) (Review).

[9] R. T. Walker, *ibid.,* **14**, Suppl. A, 119 (1984) (Review).

[10] E. De Clercq, *Biochem. J.,* **205**, 1 (1982) (Review).

[11] "Antiviral Agents: Design of Inhibitors of Viral Functions", K. K. Gauri, ed, Academic Press, New York, 1981.

[12] E. De Clercq and P. T. Torrence, *J. Carbohydr. Nucleosides, Nucleotides,* **5**, 187 (1978) (Review).

[13] H. J. Schaeffer, L. Beauchamp, P. de Miranda, G. Elion, D. J. Bauer, and P. Collins, *Nature* (London), **272**, 583 (1978).

[14] J. C. Martin, C. A. Dvorak, D. F. Smee, T. R. Matthews, and J. P. H. Verheyden, *J. Med. Chem.,* **26**, 759 (1983).

[15] J. P. H. Verheyden and J. C. Martin, U. S. Patent 4355032, October 19, 1982.

[16] K. K. Ogilvie, U. O. Cheriyan, B. K. Radatus, K. O. Smith, K. S. Galloway, and W. L. Kennell, *Can. J. Chem.,* **60**, 3005 (1982).

[17] A. K. Field, M. E. Davies, C. DeWitt, H. C. Perry, R. Liou, J. I. Germershausen, J. D. Karkas, W. T. Ashton, D. B. R. Johnson, and R. L. Tolman, *Proc. Nat. Acad. Sci.* (USA), **80**, 4139 (1983).

[18] H. J. Schaeffer, in "Nucleosides, Nucleotides and Their Biological Applications", J. L. Rideout, D. W. Henry and L. M. Beacham, eds, Academic Press, New York, 1983, pp 1-17.

[19] K. A. Watanabe, U. Reichman, K. Hirota, and J. J. Fox, *J. Med. Chem.,* **22**, 21 (1979).

[20] J. J. Fox, C. Lopez and K. A. Watanabe, in "Medicinal Chemis-

try Advances", F. G. Las Heras and S. Vega, eds, Pergamon Press: Oxford & New York, 1981, pp 27-40.

[21] E. De Clercq, J. Descamps, P. de Somer, P. J. Barr, A. S. Jones, and R. T. Walker, *Proc. Natl. Acad. Sci.*, USA, **76**, 2947 (1979).

[22] E. De Clercq, *Trends Pharmacol. Sci.*, **3**, 492 (1982).

[23] R. Vince, S. Daluge, H. Lee, W. M. Shannon, G. Arnett, T. W. Schafer, T. L. Nagabhushan, P. Reichert, and H. Tsai, *Science*, **221**, 1405 (1983).

[24] "Ribavirin: A Broad Spectrum Antiviral Agent", R. A. Smith and W. Kirkpatrick, eds, Academic Press, New York, 1980.

[24a] In January 1986, the FDA approved ribavirin for use in children for respiratory syncytial virus infections.

[25] R. J. Remy and J. A. Secrist III, *Nucleosides Nucleotides*, **4**, 411 (1985).

[26] H. J. Schaeffer and P. S. Bhargava, *Biochemistry*, **4**, 71 (1965).

[27] H. J. Schaeffer, D. Vogel and R. Vince, *J. Med. Chem.*, **8**, 502 (1965).

[28] R. H. Shah, H. J. Schaeffer and D. H. Murray, *J. Pharm. Sci.*, **54**, 15 (1965).

[29] J. L. York and G. A. Page, *Can. J. Biochem.*, **44**, 331 (1966).

[30] A. Block, M. J. Robins and J. R. McCarthy, Jr., *J. Med. Chem.*, **10**, 908 (1967).

[31] H. J. Schaeffer, S. Gurwara, R. Vince, and S. Bittner, *J. Med. Chem.*, **14**, 367 (1971).

[32] J. R. Barrio, J. D. Bryant and G. E. Keyser, *J. Med. Chem.*, **23**, 572 (1980).

[33] G. E. Keyser, J. D. Bryant and J. R. Barrio, *Tetrahedron Letters*, 3263 (1979).

[34] M. J. Robins and P. W. Hatfield, *Can. J. Chem.*, **60**, 547 (1982).

[35] *Am. J. Med.*, **73**, (1A) (1982).

[36] G. B. Elion, P. A. Furman, J. A. Fyfe, P. de Miranda, L. Beauchamp, and H. J. Schaeffer, *Proc. Natl. Acad. Sci.*, USA, **74**, 5716 (1977).

[37] P. A. Furman, M. H. St. Clair, J. A. Fyfe, J. L. Rideout, P. M. Keller, and G. B. Elion, *J. Virol.*, **32**, 72 (1979).

[38] S. E. Straus, H. E. Takiff, M. Seidlin, S. Bachrach, L. Lininger, J. J. DeGiovanna, K. A. Western, H. A. Smith, S. N. Lehrman, J. Creagh-Kirk, and D. W. Alling, *N. Engl. J. Med.*, **310**, 1545 (1984).

[39] J. M. Douglas, C. Critchlow, J. Bennetti, G. J. Mertz, J. D. Connor, M. A. Hintz, A. Fahnlander, M. Remington, C. Winter, and L. Corey, *N. Engl. J. Med.*, **310**, 1551 (1984).

[40] P. M. Keller, J. A. Fyfe, L. Beauchamp, C. M. Lubbers, P. A. Furman, H. J. Schaeffer, and G. B. Elion, *Biochem. Pharmacol.*, **30**, 3071 (1981).

[41] J. L. Kelley, M. P. Krochmal and H. J. Schaeffer, *J. Med. Chem.*, **24**, 1528 (1981).

[42] L. Colla, E. De Clercq, R. Busson, and H. Vanderhaeghe, *J. Med. Chem.*, **26**, 602 (1983).

[43] M. J. Robins, P. W. Hatfield, J. Balzarini, and E. De Clercq, *J. Med. Chem.*, **27**, 1486 (1984).

[44] L. M. Beauchamp, B. L. Dolmatch, H. J. Schaeffer, P. Collins, D. J. Bauer, P. M. Keller, and J. A. Fyfe, *J. Med. Chem.*, **28**, 982 (1985).

[45] F. Seela, A. Kehne and H.-D. Winkler, *Ann. Chem.*, 137 (1983).

[46] J. C. Martin, D. F. Smee and J. P. H. Verheyden, *J. Org. Chem.*, **50**, 755 (1985).

[47] T. A. Krenitsky, W. W. Hall, P. de Miranda, L. M. Beauchamp, H. J. Schaeffer,, and P. D. Whiteman, *Proc. Natl. Acad, Sci.*, USA, **81**, 3209 (1984).

[48] S. S. Good, H. C. Krasny, G. B. Elion, and P. De Miranda, *J. Pharmacol. Exp. Ther.*, **227**, 644 (1983).

[49] R. P. Quinn, S. S. Good, L. Gerald, and J. J. Sabatka, *Anal. Biochem.*, **134**, 16 (1983).

[50] T. Spector, T. E. Jones and L. M. Beacham III, *Biochem. Pharmacol.*, **32**, 2505 (1983).

[51] P. C. Maudgal, E. De Clercq, J. Descamps, and J. Missotten, *Arch. Ophthalmol.*, **102**, 140 (1984).

[52] W. T. Ashton, J. D. Karkas, A. K. Field, and R. L. Tolman, *Biochem. Biophys. Res. Commun.*, **108**, 1716 (1982).

[53] K. O. Smith, K. S. Galloway, W. K. Kennell, K. K. Ogilvie, and B. K. Radatus, *Antimicrob. Agents Chemother.*, **22**, 55 (1982).

[54] E. B. Fraser-Smith, D. F. Smee and T. R. Matthews, *ibid.*, **24**, 883 (1983).

[55] D. F. Smee, J. C. Martin, J. P. H. Verheyden, and T. R. Matthews, *ibid.*, **23**, 676 (1983).

[56] E. B. Fraser-Smith, D. A. Eppstein, Y. V. Marsh, and T. R. Matthews, *Antiviral Res.*, **5**, 137 (1985).

[57] E. B. Fraser-Smith, D. A. Eppstein, Y. V. Marsh, and T. R. Matthews, *Antimicrob. Agents Chemother.*, **26**, 937 (1984).

[58] M. H. St. Clair, W. H. Miller, R. L. Miller, C. U. Lambe, and P. A. Furman, *Antimicrob. Agents Chemother.*, **25**, 191 (1984).

[59] K. K. Ogilvie, N. Nguyen-Ba, M. F. Gillen, B. K. Radatus, U. O. Cheriyan, H. R. Hanna, K. O. Smith, and K. S. Galloway, *Can. J. Chem.*, **62**, 241 (1984).

[60] E. C. Mar, Y.-C. Cheng and E.-S. Huang, *Antimicrob. Agents, Chemother.*, **24**, 518 (1983).

[61] Y.-C. Cheng, E.-S. Huang Lin, J.-C. Mar, J. S. Pagano, G. E. Dutchman, and S. P. Grill, *Proc. Nat'l. Acad. Sci.*, USA, **80**, 2767 (1983).

[62] Y.-C. Cheng. S. P. Grill, G. E. Dutschman, K. B. Frank, J.-F. Chiou, K. F. Bastow, and K. Nakayama, *Antimicrob. Agents Chemother.*, **26**, 283 (1984).

[63] K. B. Frank, J.-F. Chiou and Y.-C. Cheng, *J. Biol. Chem.*, **259**, 1566 (1984).

[64] R. L. Tolman, A. K. Field, J. D. Karkas, A. W. Wagner, J. Germershausen, C. Crumpacker, and G. M. Scolnick, *Biochem. Biophys. Res. Commun.*, **128**, 1329 (1985).

[65] K. K. Ogilvie and H. R. Hanna, *Can. J. Chem.*, **62**, 2702 (1984).

[66] K. K. Ogilvie, H. R. Hanna, N. Nguyen-ba, and K. O. Smith, *Nucleosides Nucleotides*, **4**, 507 (1985).

[67] M.-C. Lin, S. K. Kuzmich and T.-S. Lin, *Tetrahedron Letters*, **25**, 613 (1984).

[68] Personal communication with Dr. Tai-Shun Lin of Yale University.

[69] J. C. Martin, G. A. Jeffrey, D. P. C. McGee, M. A. Tippie, D. F. Smee, T. R. Matthews, and J. P. H. Verheyden, presented at the 185th American Chemical Society National Meeting, Seattle, Washingon, March, 1983, CARB 43.

[70] K. K. Ogilvie and M. F. Gillen, *Tetrahedron Letters*, **21**, 327 (1980).

[71] J. C. Martin, G. A. Jeffrey, D. P. C. McGee, M. A. Tippie, D. F. Smee, T. R. Matthews, and J. P. H. Verheyden, *J. Med. Chem.*, **28**, 358 (1985).

[72] D. P. C. McGee, J. C. Martin, D. F. Smee, T. R. Matthews, and J. P. H. Verheyden, *J. Med. Chem.*, **28**, 1242 (1985).

[73] K. K. Ogilvie, N. Nguyen-Ba and R. G. Hamilton, *Can. J. Chem.*, **62**, 1622 (1984).

[74] K. K. Ogilvie and A. Z. Proba, *Nucleosides Nucleotides*, **3**, 537 (1984).

[75] T.-S. Lin and M.-C. Lin, *Tetrahedron Letters*, **25**, 905 (1984).

[76] W. T. Ashton, L. F. Canning, R. L. Tolman, J. D. Karkas, R. Liou, and A. K. Field, *Abstr.*, 146, 23rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Las Vegas, NV, October, 1983, p 106.

[77] W. T. Ashton, L. F. Canning, G. F. Reynolds, R. L. Tolman, J. D. Karkas, R. Liou, M.-E. M. Davies, C. M. DeWitt, H. C. Perry, and A. K. Field, *J. Med. Chem.*, **28**, 926 (1985).

[78] M. MacCoss, A. Chen and R. L. Tolman, *Tetrahedron Letters*, **26**, 1815 (1985).

[79] M. MacCoss, A. Chen and R. L. Tolman, *Tetrahedron Letters.*, **26**, 4287 (1985).

[80] J. D. Bryant, G. E. Keyser and J. R. Barrio, *J. Org. Chem.*, **44**, 3733 (1979).

[81] J. E. McCormick and R. S. McElhinney, *J. Chem. Res.*, 12 (1981).

[82] U. K. Pandit, W. F. A. Grose and T. A. Eggelte, *Synth. Commun.*, **2**, 345 (1972).

[83] M. A. Tippie, J. C. Martin, D. F. Smee, T. R. Matthews, and J. P.

H. Verheyden, *Nucleosides Nucleotides*, **3**, 525 (1984).
[84] M. R. Harnden and R. L. Jarvest, *Tetrahedron Letters.*, **26**, 4265 (1985).
[85] D. M. Houston, E. K. Dolence, B. T. Keller, U. Patel-Thombre, and R. T. Borchardt, *J. Med. Chem.*, **28**, 467 (1985).
[86] E. De Clerq, J. Descamps, P. De Somer, and A. Holy, *Science*, **200**, 563 (1978).
[87] E. De Clercq and A. Holy, *J. Med. Chem.*, **22**, 510 (1979).
[88] I. Votruba and A. Holy, *Collect. Czech. Chem. Commun.*, **45**, 3039 (1980).
[89] R. J. Jelink, A. Holy and I. Vortruba, *Tetratology*, **24**, 267 (1981).
[90] A. Holy and A. Cihak, *Biochem. Pharmacol.*, **30**, 2359 (1981).
[91] N. Ueda, T. Kawabata and K. Takemoto, *J. Heterocyclic Chem.*, **8**, 827 (1971).
[92] T. Seita, K. Yamauchi, M. Kinoshita, and Minoru Imoto, *Bull. Chem. Soc.* (Japan), **45**, 926 (1972).
[93] A. Holy, *Collect. Czech. Chem. Commun.*, **40**, 187 (1975).
[94] A. Holy, *ibid.*, **43**, 3103 (1978).
[95] F. Seela and A. Kehne, *Ann. Chem.*, 1940 (1982).
[96] A. Holy, *Collect. Czech. Chem. Commun.*, **48**, 1910 (1983).
[97] A. Holy, I. Votraba and E. De Clercq, *Collect. Czech. Chem. Commmun.*, **50**, 245 (1985).
[98] A. Holy and M. Vanecek, *ibid.*, **44**, 2550 (1979).
[99] M. P. La Montagne, D. C. Smith and G.-S. Wu, *J. Heterocyclic Chem.*, **20**, 295 (1983).
[100] L. Colla, R. Busson, E. De Clercq, and H. Vanderhaeghe, *Eur. J. Med. Chem.*, **17**, 569 (1982).
[101] A. Larsson, B. Oberg, S. Alenius, C.-E. Hagberg, N.-G. Johansson, B. Lindorg, and G. Stening, *Antimicrob. Agents Chemother.*, **23**, 664 (1983).
[102] K. Eklind, R. Datema, A.-C. Ericson, C.-E. Hagberg, N.-G. Johansson, S. Kovacs, A. Larsson, B. Lindborg, G. Steneng, and B. Oberg, *Nucleosides Nucleotides*, **4**, 303 (1985).
[103] A. Larsson and P.-Z. Tao, *Antimicrob. Agents, Chemother.*, **25**, 524 (1984).
[104] A. Holy, *Collect. Czech. Chem. Commun.*, **43**, 3444 (1978).
[105] A. Larsson, S. Alenius, N.-G. Johansson, and B. Oberg, *Antiviral Res.*, **3**, 77 (1983).
[106] J. Zemlicka, *Nucleosides Nucleotides*, **3**, 245 (1984).
[107] A. Holy, *Collect. Czech. Chem. Commun.*, **44**, 593 (1979).
[108] D. C. Baker, T. U. Carr III, 184th Am. Chem. Soc. Meeting, Kansas City, Missouri, Sept. 12-17, 1982, CARB 37; T. U. Carr III, M.S. Thesis, The University of Alabama, 1982.
[109] I. Chibata, K. Okumura, S. Takeyama, and K. Kodera, *Experientia*, **25**, 1237 (1969).
[110] T. Rokujo, H. Kikuchi, A. Tensho, Y. Tsukitani, T. Takenawa, K. Yoshida, and T. Kamiya, *Life. Sci.*, Part II, **9**, 379 (1970).
[111] T. Kamiya, Y. Saito, M. Hashimoto, and H. Seki, *Tetrahedron Letters*, 4729 (1969).
[112] T. Kamiya, Y. Saito, M. Hashimoto, and H. Seki, *Chem. Ind.* (London), 652 (1970).
[113] R. Suhadolnik, "Nucleosides as Biological Probes", Academic Press, New York, 1979, p 298.
[114] K. Okumura, T. Oine, Y. Yamada, M. Tomie, T. Adachi, T. Nagura, M. Kawazu, T. Mizoguchi, and I. Inoue, *J. Org. Chem.*, **36**, 1573 (1971).
[115] M. Kawazu, T. Kanno, S. Yamamura, T. Mizoguchi, and S. Saito, *J. Org. Chem.*, **38**, 2887 (1973).
[116] N. Takamura, N. Taga, T. Kanno, and M. Kawazu, *J. Org. Chem.*, **38**, 2891 (1973).
[117] K. Okumura, K. Matsumoto, M. Fukamizu, Y. Yasuo, Y. Taguchi, Y. Sugihara, I. Inoue, M. Seto, Y. Sato, N. Takamura, T. Kanno, M. Kawazu, T. Mizoguchi, S. Saito, K. Takashima, and S. Takeyama, *J. Med. Chem.*, **17**, 846 (1974).
[118] I. Votruba and A. Holy, *Collect. Czech. Chem. Commun.*, **47**, 167 (1982).
[119] A. Holy, *ibid.*, **47**, 173 (1982).
[120] A. Holy, I. Votruba and E. De Clercq, *ibid.*, **47**, 1392 (1982).
[121] A. Holy, I. Votruba and E. De Clercq, *ibid.*, **50**, 262 (1985).
[122] E. De Clercq and A. Holy, *J. Med. Chem.*, **28**, 282 (1985).
[123] E. De Clercq, *Nucleosides Nucleotides*, **4**, 3 (1985).
[124] A. Merta, I. Votruba, J. Vesely, and A. Holy, *Collect. Czech. Chem. Commun.*, **48**, 2701 (1983).
[125] A. Holy, I. Votruba and E. De Clercq, *Collect. Czech. Chem. Commun.*, **50**, 262 (1985).
[126] E. De Clercq and A. Holy, *J. Med. Chem.*, **28**, 282 (1985).
[127] A. Holy, *Collect. Czech. Chem. Commun.*, **47**, 2969 (1982).
[128] J. X. Khym and W. E. Cohn, *J. Am. Chem. Soc.*, **82**, 6380 (1960).
[129] M. Viscontini, D. Hock and P. Karrer, *Helv. Chim. Acta*, **38**, 642 (1955).
[130] L. M. Lerner and R. R. Rossi, *Biochemistry*, **11**, 2772 (1972).
[131] R. R. Rossi and L. M. Lerner, *J. Med. Chem.*, **16**, 457 (1973).
[132] L. M. Lerner, *Carbohydr. Res.*, **13**, 465 (1970).
[133] L. M. Lerner, *ibid.*, **127**, 141 (1984).
[134] M. Bessodes and K. Antonakis, *Tetrahedron Letters*, **26**, 1305 (1985).
[135] H. J. Schaeffer and D. Vogel, *J. Med. Chem.*, **8**, 507 (1965).
[136] H. J. Schaeffer and R. Vince, *ibid.*, **10**, 689 (1967).
[137] H. J. Schaeffer, R. N. Johnson, M. A. Schwartz, and C. F. Schwender, *ibid.*, **15**, 456 (1972).
[138] H. J. Schaeffer and C. F. Schwender, *ibid.*, **17**, 6 (1974).
[139] R. P. Agarwal, T. Spector and R. E. Parks, Jr., *Biochem. Pharmacol.*, **26**, 359 (1977).
[140] W. Plunkett and S. S. Cohen, *Cancer Res.*, **35**, 1547 (1975).
[141] T. W. North and S. S. Cohen, *Proc. Natl. Acad. Sci.*, USA, **75**, 4684 (1978).
[142] T. W. North and S. S. Cohen, *Pharmacol. Ther.*, **4**, 81 (1979).
[143] W. M. Shannon and F. W. Schabel, Jr., *Pharmacol. Ther.*, **11**, 263 (1980).
[144] D. C. Baker, J. C. Hanvey, L. D. Hawkins, and J. Murphy, *Biochem. Pharmacol.*, **30**, 1159 (1981).
[145] D. C. Baker and L. D. Hawkins, *J. Org. Chem.*, **47**, 2179 (1982).
[146] G. Bastian, M. Bessodes, R. P. Panzica, E. Abushanab, S.-F. Chen, J. D. Stoeckler, and R. E. Parks, Jr., *J. Med. Chem.*, **24**, 1383 (1981).
[147] M. Bessodes, G. Bastian, E. Abushanab, R. P. Panzica, S. F. Berman, E. J. Marcaccio, Jr., S.-F. Chen, J. D. Stoeckler, and R. E. Parks, Jr., *Biochem. Pharmacol.*, **31**, 879 (1982).
[148] E. Abushanab, M. Bessodes and K. Antonakis, *Tetrahedron Letters.*, **25**, 3841 (1984).
[149] J. W. Hadden, E. M. Hadden, T. Spira, and A. Ginger-Sorolla, *Int. J. Immunopharmacol.*, **2**, 198 (1980).
[150] V. J. Merluzzi, M. M. Walker, N. Williams, B. Susskind, J. W. Hadden, and R. B. Faanes, *Int. J. Immunopharmacol.*, **4**, 219 (1982).
[151] M. Bessodes, E. Abushanab and K. Antonakis, *Tetrahedron Letters.*, **25**, 5899 (1984).
[152] I. Antonini, G. Cristalli, P. Franchetti, M. Grifantini, S. Martelli, G. Lupidi, and F. Riva, *J. Med. Chem.*, **27**, 274 (1984).
[153] D. Horton and S. S. Kokrady, *Carbohydr. Res.*, **24**, 333 (1972).
[154] M. L. Wolfrom, W. von Bebenberg, R. Pagnucco, and P. McWain, *J. Org. Chem.*, **36**, 2732 (1965).
[155] M. L. Wolfrom, H. B. Bhat, P. McWain, and D. Horton, *Carbohydr. Res.*, **23**, 289 (1972).
[156] R. A. Markovs, Ph. D. Dissertation, The Ohio State University, 1975; *Diss. Abstr. Int. B*, **36**, 3964-B (1976).
[157] M. L. Wolfrom, A. B. Foster, P. McWain, W. Von Bebenburg, and A. Thompson, *J. Org. Chem.*, **26**, 3095 (1961).
[158] M. L. Wolfrom, P. McWain and A. Thompson, *ibid.*, **27**, 3549 (1962).
[159] M. L. Wolfrom, H. G. Garg and D. Horton, *ibid.*, **29**, 3280 (1964).
[160] M. L. Wolfrom, H. G. Garg and D. Horton, *ibid.*, **30**, 1096 (1965).
[161] M. L. Wolfrom, P. McWain, H. B. Bhat, and D. Horton, *Carbohydr. Res.*, **23**, 296 (1972).
[162] D. C. Baker, Ph.D. Dissertation, The Ohio State University

(1973); *Diss. Abstr. Int. B*, **34**, 5377-B (1974).

[163] D. Horton, D. C. Baker and S. S. Kokrady, *Ann. N.Y. Acad. Sci.*, **255**, 131 (1977).

[164] D. Horton and S. S. Kokrady, *Carbohydr. Res.*, **80**, 364 (1980).

[165] D. C. Baker, K. Blieszner and D. Horton, in L. B. Townsend and R. S. Tipson, eds, "Nucleic Acid Chemistry: Improved and New Synthetic Procedures, Methods, and Techniques", Vol 1, Part 2, Wiley, NY 1978, pp 627-637.

[166] D. C. Baker and D. Horton, *Carbohydr. Res.*, **69**, 117 (1979).

[167] D. Horton and R. A. Markovs, *ibid.*, **80**, 356 (1980).

[168] K. C. Blieszner, D. Horton and R. A. Markovs, *ibid.*, **80**, 241 (1980).

[169] D. Horton and C.-M. Liu, *ibid.*, **107**, 55 (1982).

[170] D. Horton, *Pure Appl. Chem.*, **42**, 301 (1975).

[171] G. Mackenzie, G. Shaw and D. H. Robinson, *J. Chem. Soc. Perkin Trans. I*, 1094 (1977).

[172] A. Holy, *Collect. Czech. Chem. Commun.*, **47**, 2786 (1982).

[173] T. Seita, M. Kinoshita and M. Imoto, *Bull. Chem. Soc.* (Japan), **46**, 1572 (1973).

[174] A. Holy and G. S. Ivanova, *Nucleic Acid Res.*, **1**, 19 (1974).

[175] A. Holy and I. Rosenberg, *Collect. Czech, Chem. Commun.*, **44**, 957 (1979).

[176] S. Bailey, C. T. Shanks and M. R. Harnden, *Nucleosides Nucleotides*, **4**, 235 (1985).

[177] A. Holy, A. Ludzisa, I. Votruba and K. Sodiva, *Collect. Czech, Chem. Commun.*, **50**, 395 (1985).

[178] J. L. Kelley, M. P. Krochmal and H. J. Schaeffer, *J. Med. Chem.*, **24**, 472 (1981).

[179] J. L. Kelley, J. E. Kelsey, W. R. Hall, M. P. Krochmal, and H. J. Schaeffer, *J. Med. Chem.*, **24**, 753 (1981).

[180] H. M. Abrams, L. Ho and S. H. Chu, *J. Heterocyclic Chem.*, **18**, 947 (1981).

[181] J. G. Niedzwicki, M. H. El Kouni, S. H. Chu, and S. Cha, *Biochem. Pharmacol.*, **30**, 2097 (1981).

[182] J. G. Niedzwicki, S. H. Chu, M. H. El Kouni, E. C. Rowe, and S. Cha, *Biochem. Pharmacol.*, **31**, 1857 (1982).

[183] J. G. Niedzwicki, M. H. El Kouni, S. H. Chu, and S. Cha, *ibid.*, **32**, 399 (1983).

[184] S. H. Chu, Z. H. Chen, E. C. Rowe, F. N. M. Naguib, M. H. El Kouni, and M. Y. Chu, *Nucleosides Nucleotides*, **3**, 303 (1984).

[185] S. A. Siegel and T.-S. Lin, *Biochem. Pharmacol.*, **34**, 1121 (1985).

[186] T.-S. Lin and M.-L. Liu, *J. Med. Chem.*, **28**, 971 (1985).

[187] A. C. Schroeder, R. G. Hughes, Jr., and A. Block, *ibid.*, **24**, 1078 (1981).

[188] A. Rosowsky, S.-H. Kim and M. Wick, *J. Med. Chem.*, **24**, 1177 (1981).

[189] H. Gringel, W. Hayden, E. Schindler, and E. Wanek, *Arch. Pharm.* (Weinheim), **316**, 146 (1983).

[190] B. H. Lazrek and R. P. Panzica, *Nucleosides Nucleotides*, **4**, 279 (1985).

[191] K. K. Ogilvie, D. M. Dixit, B. K. Radutus, K. O. Smith, and K. S. Galloway, *ibid.*, **2**, 147 (1983).

[192] K. K. Ogilvie, R. G. Hamilton, M. F. Gillen, B. K. Radatus, K. O. Smith, and K. S. Galloway, *Can. J. Chem.*, **62**, 16 (1984).

[193] F. Babin, T. Huynh-Dinh and J. Igolen, *J. Heterocyclic Chem.*, **20**, 1169 (1983).

[194] T. Huynh-Dinh, A. Kolb, C. Gouyette, and J. Igolen, *ibid.*, **12**, 111 (1975).

[195] W. L. Mitchell, M. L. Hill, R. F. Newton, P. Ravenscroft, and D. I. C. Scopes, *ibid.*, **21**, 697 (1984).

[196] H. Griengl and G. Gunzl, *ibid.*, **21**, 505 (1984).

[197] J. G. Buchanan, *Nucleosides Nucleotides*, **4**, 13 (1985).

[198] Personal communication with Dr. D. C. Baker of the University of Alabama.

[199] R. K. Robins, P. C. Srivastava, V. L. Narayanan, J. Plowman, and K. D. Paull, *J. Med. Chem.*, **25**, 107 (1982).

[200] J. F. Mota, P. A. Bravo, F. R. Vicente, J. I. F. Garcia-Hierro, and J. A. G. Perez, *ibid.*, **3**, 115 (1984).

[201] J. A. G. Perez, P. A. Bravo, F. R. Vicente, J. I. F. Garcia-Hierro, and J. F. Mota, *Carbohydr. Res.*, **126**, 91 (1984).

[202] J. A. G. Perez, J. C. P. Albarran, J. L. J. Reque, and M. A. Gonzalez, *ibid.*, **132**, 153 (1984).

[203] C. K. Chu, *J. Heterocyclic Chem.*, **21**, 9 (1984).

[204] U. Reichman, K. Hirota, C. K. Chu, K. A. Watanabe, and J. J. Fox, *J. Antibiot.*, **30**, 129 (1977).

[205] C. K. Chu, I. Wempen, K. A. Wattanabe, and J. J. Fox, *J. Org. Chem.*, **41**, 2793 (1976).

[206] S. Ya Melbnik, T. D. Miniker, I. V. Yartseva, T. P. Nedoresova, G. I. Potapova, and M. N. Preobrazhenskaya, *Bioorg. Khim.*, **9**, 1395 (1983).

[207] Results by Prof. Y.-C. Cheng. University of North Carolina School of Medicine.

[208] C. K. Chu, J. J. Suh and S. J. Cutler, unpublished work.

[209] A. Parkin and M. R. Harnden, *J. Heterocyclic Chem.*, **19**, 33 (1982).

[210] T.-S. Lin and M.-C. Lin, *Tetrahedron Letters*, **25**, 611 (1984).

[211] K. Kamaliah, G. Shaw and D. Wright, *J. Chem. Soc., Perkin Trans. I.*, 2728 (1980).

[212] H. D. H. Showalter, S. R. Putt, P. E. Borondy, and J. L Shillis, *J. Med. Chem.*, **26**, 1478 (1983).