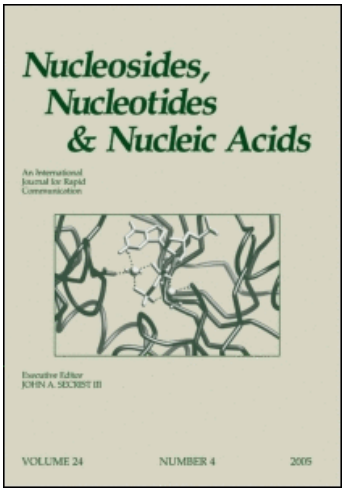

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Synthesis of Phosphonic Acid Analogs of Acyclovir (ACV) and Canciclovir (DHPG)

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SYNTHESIS OF PHOSPHONIC ACID ANALOGS OF ACYCLOVIR (ACV) AND GANCICLOVIR (DHPG)

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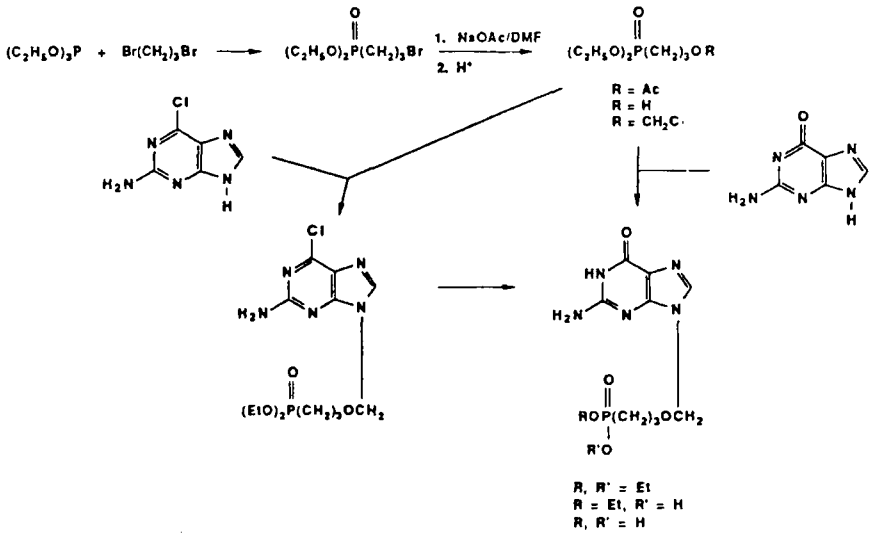
Abstract: Isosteric Phosphonic acid analogs of acyclovir and ganciclovir have been synthesized for evaluation for antiviral activity.

Acyclovir, 9-(2-hydroxyethoxylmethyl) guanine is one from a total of 7 drugs that have been licensed by the FDA for use in the treatment of viral infections. ACV shows excellent activity against herpes simplex 1, herpes simplex 2 and varicella zoster, all members of the herpes family of DNA viruses. DHPG, a structural close relative of ACV, is also active against the above herpes viruses. In addition, DHPG is the only drug to date to show activity against human cytomegalovirus, (HCMV). The mechanism by which ACV expresses its activity is of interest. The herpes virus has a number of unique enzyme systems, among them a viral thymidine kinase. The function of thymidine kinase (T.K.) is to phosphorylate thymidine to thymidine monophosphate (thymidylic acid) and this is further phosphorylated by other kinases to the triphosphate which is now a substrate for the synthesis of DNA by DNA polymerase. Surprisingly, herpes simplex thymidine kinase is able to phosphorylate the guanine analog ACV to the monophosphate which is then further phosphorylated to the triphosphate where it serves as a substrate for viral DNA polymerase. Since ACV triphosphate is monofunctional, it cannot propagate the DNA chain thus becomes a chain terminator. DHPG probably acts in a similar fashion against herpes, however, HCMV does not have a viral specific thymidine kinase, but uses the cellular kinases for its

nucleotide phosphates, so DHPG must have a different mechanism for its HCMV activity. DHPG is not monofunctional, as is ACV, so it does not behave as a chain terminator in DNA synthesis. DHPG exhibits significant cellular toxicity, probably due to incorporation into host DNA.

The preparation of isosteric phosphonic acid analogs of ACV was undertaken in order to prepare compounds that may not need a viral T.K. to be activated to the triphosphate, e.g., HCMV. The possibility of obtaining a less toxic analog of DHPG was also a consideration. Phosphonic acid analogs of ACV and DHPG were prepared and evaluated for antiviral activity. The synthesis is described in this paper. The antiviral effects are described in an accompanying paper.

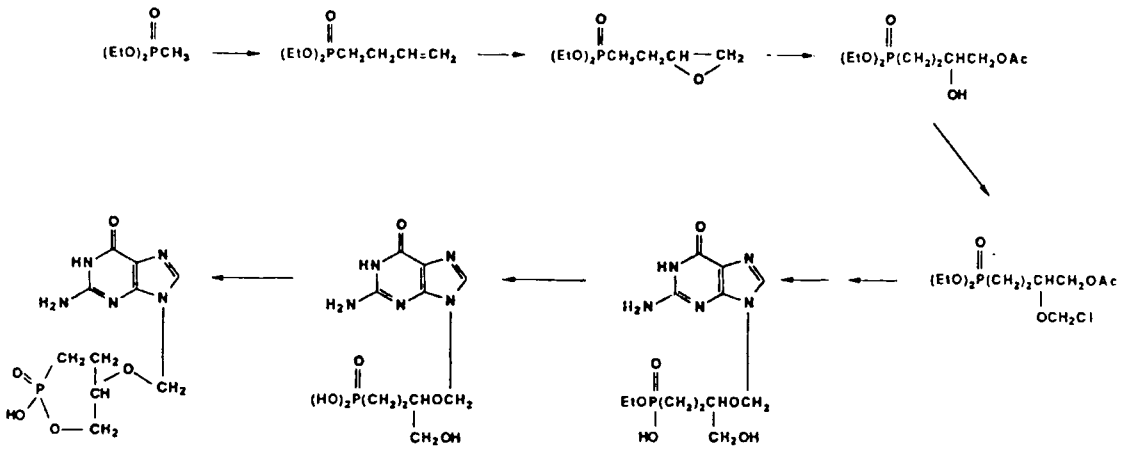
The synthesis started with the reaction of triethylphosphite with 1,3-dibromopropane to give diethyl 3-bromopropyl phosphonate in 71% yield. Replacement of the bromide by acetate was accomplished using sodium acetate in DMF. Acid calatyzed hydrolysis of the O-acetate using Dowex 50 (H^+) gave the 3-hydroxypropyl phosphonate in 50% overall yield from the bromide. Chloromethylation was accomplished using paraformaldehyde and hydrogen chloride to give the 3-chloromethoxy propyl phosphonate, suitable for coupling with an appropriate purine. A number of approaches have been used to couple the chloromethyl sugar to a guanine analog. The most convenient from the standpoint of ease of handling, solubility characteristics, etc. utilized 2-amino-6-chloropurine as starting material. Treatment of this purine with hexamethyldisilazane gave a di-trimethylsilyl derivative which was condensed with the chloromethyl either to give a 47% yield of crystalline 2-amino-6-chloropurine nucleoside phosphonate as the diethyl ester. Treatment of the blocked acyclonucleoside with tetraethylammonium hydroxide and trimethylamine hydrolized the 6-chloro group and gave a 72% yield of crystalline guanine nucleoside phosphonate as the diethyl ester. Heating the diethyl ester with conc. ammonium hydroxide gave a 65% yield of the monoethyl ester that was homogeneous on TLC and HPLC with satisfactory UV spectrum for a 9-substituted guanine.



An alternative synthesis was developed, starting from guanine. Silation of guanine was accomplished by standard procedures to yield a very labile disilyl guanine derivative that was alkylated directly with the chloromethyl ether described previously. When 1 mole of mercuric cyanide was present,a yield of 35% of 9-substituted guanine was obtained with small amounts (≈2%) of 7-substituted isomer. If mercuric cyanide was omitted during the condensation, yields up to 55% were obtained, however the product obtained contained 10% of 7-subtituted isomer which could be separated by reverse phase chromatography of the monoesters.

Complete de-sterification of the phosphonate was readily accomplished by treatment of the mono ethyl ester with bromotrimethylsilane to yield the diacid in good yield after purification.

Phosphonate derivatives of ganciclovir were prepared by a sequence of reactions starting from diethyl methylphosphonate. Preparation of the lithium salt, using butyl lithium/cuprous iodide, followed by reaction with allyl bromide gave an 80% yield of diethyl 3-butenyl phosphonate. Epoxidation of the olefin with meta chloroperbenzoic acid gave a 75% yield of the epoxide. Acid catalyzed cleavage of the epoxide with glacial acetic acid gave a 50% yield of



the 4-acetoxy-3-hydroxybutyl phosphonate. M/S indicated that the right isomer was formed. Chloromethylation gave the desired chloromethyl ether which was condensed with the di-TMS derivative of 2-amino-6-chloropurine to give the blocked nucleoside. Treatment with aqueous 1N NaOH gave the monoethyl phosphonate in 21% overall yield. The mono ester was also completely deblocked by treatment with bromotrimethyl silane followed by water to give the phosphonic diacid. Cyclization of the diacid using DCC in pyridine gave the cyclic phosphonate in reasonable yield. (Supported in part by NIAID, Contract NO1-A1-72643).

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