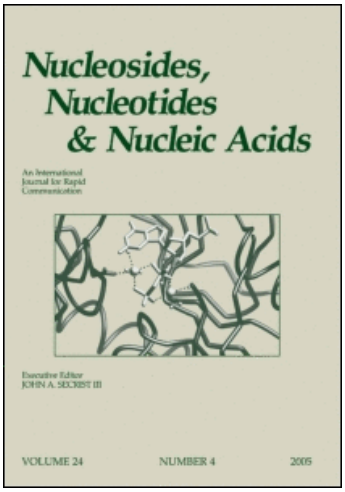

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UNSATURATED ANALOGUES OF ACYCLIC NUCLEOSIDE PHOSPHONATES: AN UNUSUAL ARBUZOV REACTION WITH UNACTIVATED TRIPLE BOND

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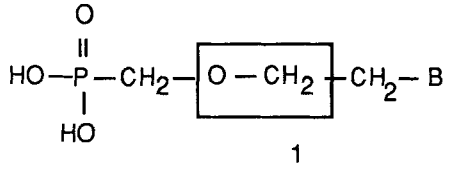
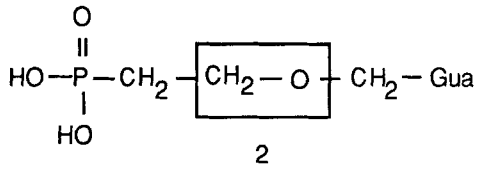
ABSTRACT: Phosphonates 6 and 8 were prepared by reaction of the corresponding chloroalkenes 5 and 7 with triethyl phosphite. Dealkylation of 6 and 8, combined with acid hydrolysis in case of 8, gave phosphonic acids 3a and 4b. By contrast, chloroalkyne 9 and triethyl phosphite afforded only 2-amino-6-chloro-N^9-ethylpurine (10). The same reaction performed in the presence of tetrabutylammonium iodide led to diphosphonate 11. Compound 4b inhibited the growth of murine leukemia L 1210 in culture (IC_{50} 10 μM).

Phosphonate analogues of nucleotides exhibiting antiviral activity have been a subject of several recent studies[1-4]. Thus, compound 1a is an effective anti-HIV agent whereas the guanine derivative 1b is a powerful inhibitor of herpes simplex and cytomegalovirus[1,5,6]. By contrast, a regioisomer of

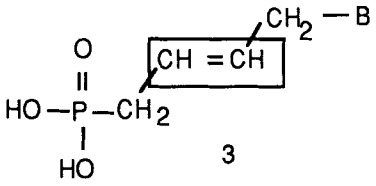


1



2

1a: B = Ade (PMEA) 1b: B = Gua (PMEG)



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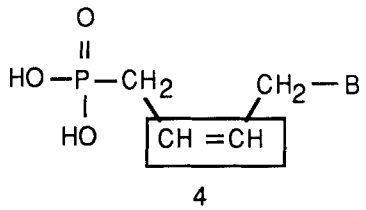
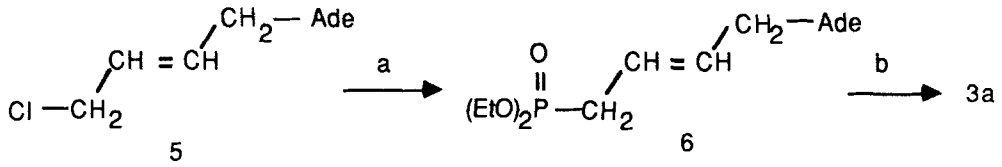


4

B = Nucleic acid base (series a: B = Ade, series b: B = Gua)

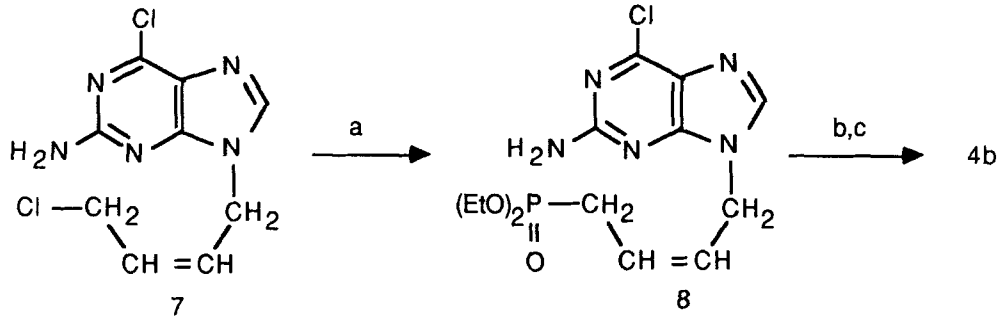
1b, compound 2, is ineffective as an antiviral agent[6]. Bioisosteric[7] analogues of 1 or 2 are therefore of interest as potential antiviral or antitumor agents. Replacement of CH_2O of 1 or 2 with CH=CH leads to two series of phosphonate analogues - E- and Z-derivatives 3 and 4. We have now prepared the first two members of this new type of nucleotide analogues - phosphonates 3a and 4b.

E-Alkene[8] 5 was refluxed with triethyl phosphite for 3.5 h to give diethyl phosphonate 6 in 61 % yield (Scheme 1). Dealkylation[9] of 6 with Me_3SiI in $CHCl_3$ at -40° for 30 min. and at room temperature for 2 h led to phosphonic acid 3a isolated in 69 % yield. Similarly, Z-alkene[10] 7 was heated with triethyl phosphite at 110° for 4 h to afford diethyl phosphonate 8 (68 %, Scheme 2). Dealkyla-



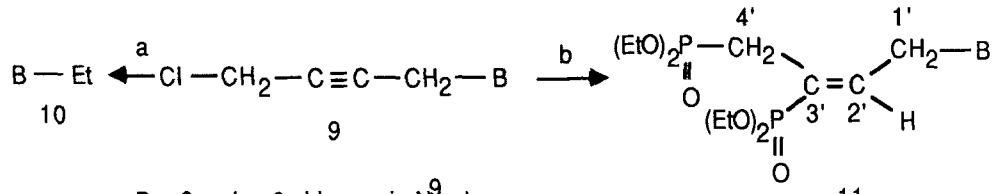
a. $(EtO)_3P$, reflux. b. Me_3SiI, $CHCl_3$.

Scheme 1



a. $(EtO)_3P$, 110°. b. Me_3SiI, $CHCl_3$. c. 0.1 M HCl, reflux.

Scheme 2



B = 2-amino-6-chloropurin-N^9-yl

a. $(EtO)_3P$, 110°. b. $(EtO)_3P$, NBu_4I, 110°.

Scheme 3

tion followed by a 14-h reflux in 0.1 M HCl gave phosphonic acid 4b which was purified by a charcoal adsorption - desorption procedure[11] and isolated as a sodium salt in 65 % yield.

Surprisingly, the reaction of chlorobutyne[12] 9 with triethyl phosphite took an unexpected turn. Simple heating at 110° for 3 h afforded 2-amino-6-chloro-N^9-ethylpurine in 39 % yield (10, Scheme 3) as the only product. It is likely that the butyne moiety of 9 or the respective 4'-phosphonylated intermediate suffered elimination under the reaction conditions. The released 2-amino-6-chloropurine was then alkylated by a phosphonylated fragment formed during the reaction. Because chloride anion is a poor nucleophile, it was anticipated that introduction of a stronger nucleophilic agent (e. g., iodide) could suppress the elimination by favoring the dealkylation step in the Arbuzov reaction. This was

confirmed by heating 9 with triethyl phosphite in the presence of a four-fold molar excess of tetrabutylammonium iodide at 110° for 1 h. Diphosphonate 11 was isolated as the only product in 58 % yield. It is obvious that Arbuzov reaction at the carbon 4' of 9 was accompanied by an interaction with the triethyl phosphite at the triple bond. Although the reaction mechanism of this " double Arbuzov reaction " has not been completely clarified, it is possible that intermediary 4'-phosphonate undergoes an isomerization to the corresponding allene. This transformation is then followed by addition of triethyl phosphite (formation of an ylid intermediate) and Arbuzov-type of dealkylation. The source of protons, necessary for conversion of ylid to alkene 11, has not been identified with certainty. Reaction with hydrogen iodide formed via a phosphite-induced elimination from ethyl iodide (see ref.[13] for an analogy) or water during the work up procedure may provide effective protonation of the intermediary ylid. Some similarity to the proposed reaction course may be seen in an interaction of alkynoic acids or esters with triethyl phosphite[14] or triethylphosphine[15]. However, in the latter transformations, free starting or external acids (e. g., HCl) provided the source of protons. Formally, the reaction may be viewed as an addition of diethyl phosphite $(EtO)_2P(O)H$ to the triple bond of the respective 4'-phosphonate intermediate resulting from chloroalkene 9.

The structure assignment of 11 was supported by ^1H and ^{31}P NMR spectroscopy as well as by UV and electron-impact mass spectra. The ^1H NMR showed that compound 11 is ca. 90 % pure E-isomer. The Arbuzov reaction with a multiple bond system of the presumed intermediate(s) resulting from 9 exhibits then a high degree of regio- and stereoselectivity. The most characteristic signal of the ^1H NMR spectrum of 11 is the 2' vinylic proton which appears at δ 6.69 as a doublet of quartets with a width of 41 Hz. The $J_{H,P}$ is 22 Hz, in accord with the range of ca.10 - 20 Hz, associated with a cis arrangement of hydrogen and phosphonyl group[16] of unsaturated phosphonates. As expected, this signal is coupled with $H_{1'}$ (δ 5.02, doublet of triplets). No allylic coupling with $H_{4'}$ (δ 4.02, quartet) was detected. Studies of nuclear Overhauser effect (NOE) showed the strongest interaction between the $H_{2'}$ and $H_{1'}$ (5.7 %) followed by that of $H_{1'}$ and H_8 (purine, 3 %). The $H_{1'}$ - $H_{4'}$ NOE is relatively weak (2.1 - 2.5 %) but it is in accord with the cis configuration of both methylene groups. The ^{31}P NMR spectrum of 11 exhibited two multiplets, at δ 17.41 and 25.13, which were transformed, upon proton decoupling, to two doublets of $^3J_{P,P}$ 13.2 Hz.

Compound 4b inhibited the growth of murine leukemia L 1210 in culture as determined by a clonogenic assay[17] (IC_{50} 10 μM). This result has shown that biologically active unsaturated analogues of acyclic nucleoside phosphonates can be obtained. Analogues 3a and 6 were inactive (IC_{50} > 300 μM).

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