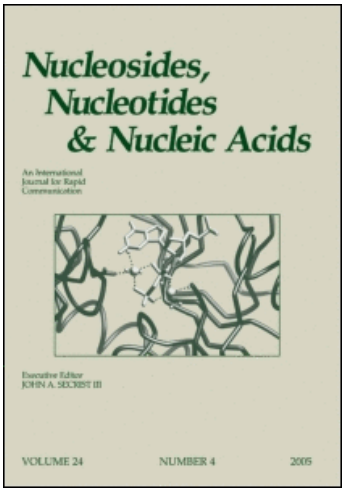

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M. Madre[a]; R. Zhuk[a]; M. Lidaks[a]
[a] Institute of Organic Synthesis, Latvian Academy of Sciences, Riga, Latvia, USSR

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NEW PRODRUGS OF ACICLOVIR WITH ANTIVIRAL ACTIVITY*

M.Madre, R.Zhuk*, M.Lidaks

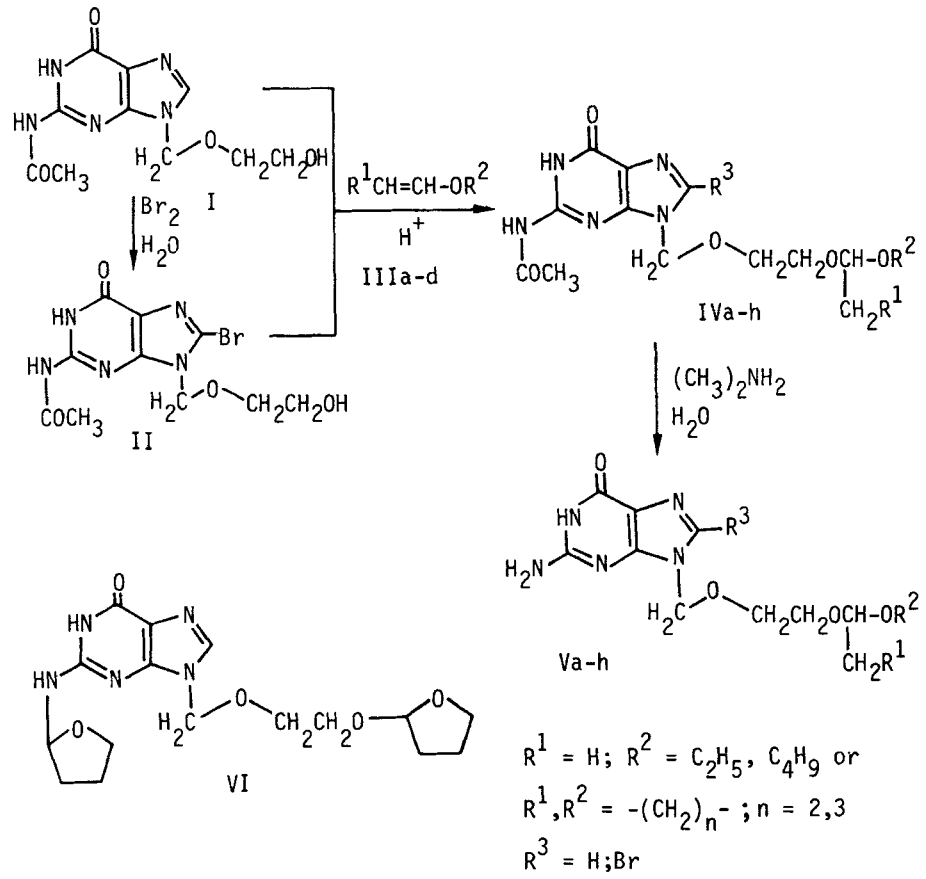
Institute of Organic Synthesis,
Latvian Academy of Sciences,
226006, Riga, Latvia, USSR

Abstract. A series of O-alkoxyalkylethers of aciclovir (ACV) have been synthesized in the reaction of 9-[2-hydroxyethoxymethyl]-N^2-acetylguanine and its 8-bromo derivative with α-vinylethers. The compounds are characterized by much higher solubility as compared with ACV and display very good antiviral activity against HSV-1 in mice.

Aciclovir is known to be a very effective antiviral drug. However it has some drawbacks caused by its low solubility in water as well as in organic solvents [1-3]. Therefore the synthesis of soluble transport forms of ACV with better pharmacokinetic properties is an urgent task. Some attempts in this direction have been undertaken, but no considerable enhancement of solubility was achieved [3-5].

With this aim in view, 9-[2-(alkoxyalkyloxy)ethoxymethyl]-N^2-acetylguanines IVa-d were prepared by etherification of the hydroxy group of guanine derivative I with acyclic and cyclic α-vinyl ethers: α-vinylethyl (IIIa), α-vinylbutyl (IIIb), 2,3-dihydrofuran (IIIc) and 2,3-dihydropyran (IIId). The reaction was carried out in dimethylformamide (DMFA) at room temperature in the presence of an acid catalyst (p-toluenesulphonic acid, trifluoroacetic acid or 6N HCl solution in dioxane). The yield of IVa-d was 60-70%. An increase in the reaction temperature or the use of HCl solution in dioxane instead p-toluenesulphonic acid reduced reaction selectivity. The main by-product isolated in the reaction of guanine derivative I with 2,3-dihydrofuran was identified as 9-[2-(2-tetrahydrofuryloxy)ethoxymethyl]-N^2-(2-tetrahydrofuryl)guanine (VI). The same compound was also obtained in the reaction of ACV with 2,3-dihydrofuran. 8-Bromo derivative II used as starting compound yielded ethers IVe-h. 8-Bromo derivative II

* This is a preliminary communication. The full paper will be published in Khimiya Geterotsikl.Soed. Part of the data were included in the patent appl. PCR 88-03.923 A, publ. 02.06.88.



reacts with α-vinylethers faster compared with compound I. Ethers IVa-h treated with aqueous methylamine at room temperature lead to ethers Va-h in quantitative yield.

The solubility of ethers IV and Va-h in water and chloroform was determined and compared with that of ACV (~2 mg/ml, [3]). The solubility of I, II and Va-h in water was similar to that of ACV. On the other hand, the solubility of IVa,c,d exceeded 100 mg/ml, being 50 times that of ACV. The solubility of butyl derivative IVb is 7.7 mg/ml. Compounds IVa-d are also highly soluble in chloroform (>200 mg/ml). 8-Bromo substituent lowers the solubility of ethers IVe-h in water (<2 mg/ml) as well as in chloroform (<20 mg/ml).

Ethers IV, Va-h have very low antiviral activity *in vitro* and probably requires *in vivo* activation. Thus, 9-[2-(2-tetrahydrofuryloxy)ethoxymethyl]-N^2-acetylguanine (IVc) given intravenously (100 mg/kg) to mice 3 h after intracerebral inoculation with HSV-1 and then daily for 7 days diminished the lethality of mice by 66% (compared with 100% lethality

in the control). The antiviral activity of this compound given by different routes of administration and its pharmacokinetics are currently under investigation.

EXPERIMENTAL

Compounds were homogeneous in TLC on Silufol UV-254 in two solvent systems ($CHCl_3$:CH_3OH 10:1 and 5:1). Silicagel L40/100 (Chemapol) was used for preparative column chromatography. Elemental analysis for C,H, N corresponds to the calculated values. ^1H NMR spectra were recorded on a Bruker WH 90+DS apparatus (90 MHz) in DMSO-d_6 with TMS as internal standard and confirmed the proposed structures.

9-[2-(Alkoxyalkyloxy)ethoxymethyl]- and 8-bromo-9-[2-(alkoxyalkyloxy)ethoxymethyl]-N^2-acetylguanines (IVa-h) (general procedure).

To a suspension of guanine derivative I or II (5 mmol) in 30 ml DMFA 0.8 mmol of p-toluenesulphonic acid and 20-25 mmol of α-vinyl ether were added with stirring. The mixture was stirred at room temperature for 24-48 h, the course of the reaction being checked by TLC. After neutralization with $NaHCO_3$ the solid precipitate was filtered off and the filtrate evaporated under vacuum. The residue was dissolved in 150 ml of chloroform, washed with 15 ml of 5% $NaHCO_3$ solution and dried over Na_2SO_4. The chloroform was evaporated and the residue was applied to a silica gel column. Ethers Va-h were eluted with chloroform-methanol (40:1). Fractions containing the title compound were pooled, evaporated and the residue recrystallized from ethanol.

The general procedure for deacetylation. A mixture containing compound IVa-h (3.5 mmol) and 20 ml of 25% methylamine solution in water was stirred at room temperature for 2 h and then evaporated in vacuum. The residue was recrystallized from ethanol (IVa-d) or ethanol-water (IVe-h).

9-[2-(2-Tetrahydrofuryloxy)ethoxymethyl]-N^2-(2-tetrahydrofuryl)-guanine (VI). Compound VI was synthesized according to the general procedure for ethers IVa-h. Starting from 1.35 g (6 mmol) ACV, 2 ml 6N HCl solution in dioxane and 2.2 g (2.4 ml, 30 mmol) of 2,3-dihydrofuran. The yield of VI was 0.48 g (22%).

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