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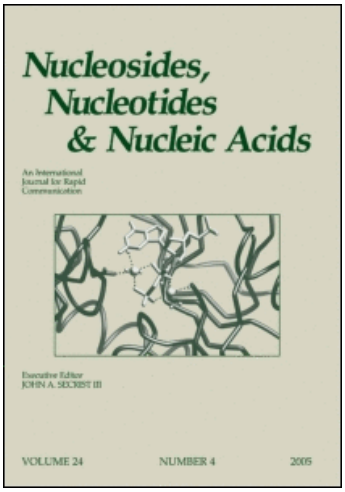

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New Analogs of Acyclovir Substituted at the Side Chain

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NEW ANALOGS OF ACYCLOVIR SUBSTITUTED AT THE SIDE CHAIN

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□ *A series of novel analogs of acyclovir, substituted with an alkyl (methyl, ethyl, n-butyl) or phenyl group at the positions 1′, 4′, and/or 5′, has been obtained in a direct one-pot coupling reaction of guanosine and the respective 1,3-dioxolanes. The new acyclonucleosides were essentially inactive in antiviral (HSV, VV, VSV, HBV) evaluation in vitro.*

Keywords Nucleoside analogs; acyclonucleosides; transpurination; 1,3-dioxolane

INTRODUCTION

It has been shown that 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir, **1a**),[1] a selective and potent antiviral drug, may be effectively synthesized via transpurination of guanosine (**2**).[2,3] Thus, reaction of O2′,O3′,O5′,N^2-tetraacetylguanosine with 2-acetoxyethyl acetoxy-methyl ether (2-oxabutane-1,4-diol diacetate)[4] leads to the formation of O5′,N^2-diacetylacyclovir (**4a**) along with its 7-regioisomer (**5a**). More recently, the approach has been simplified considerably by applying a one-pot reaction of unprotected guanosine (**2**) and 1,3-dioxolane (**3a**) instead of 2-acetoxyethyl acetoxymethyl ether, and using acetic anhydride as a solvent and reagent.[5] Because the 1,3-dioxolane system can be synthesized easily from a variety of 1,2-diols and aldehydes, we have adopted the latter procedure for the synthesis of novel analogs of acyclovir, substituted with an alkyl (methyl, ethyl, *n*-butyl) or phenyl group at the positions 1′, 4′, and/or 5′ of the side chain.

In this way, the application of 2-substituted dioxolanes should lead to the formation of 1′-substituted analogs of acyclovir (Scheme 1). Indeed, the

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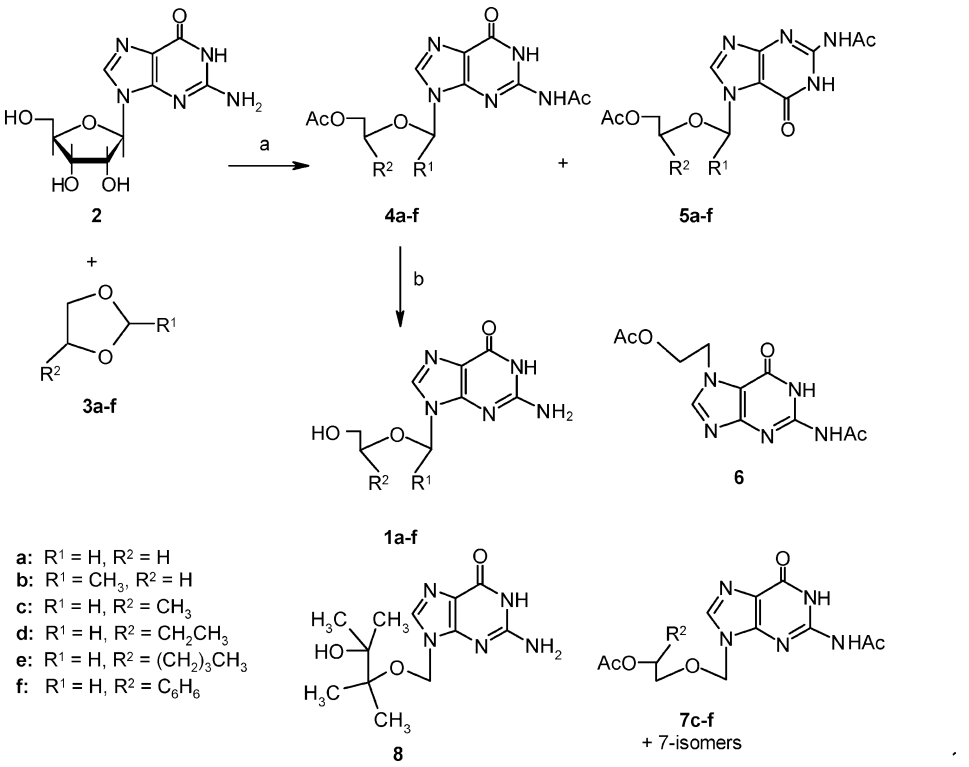

SCHEME 1 Reagents and conditions: (a) Ac_2O, *p*-TsOH, 100°C, 48 hours; (b) NH_4OH, MeOH, r.t., 24 hours.

reaction of unprotected guanosine (**2**) with 2-methyl dioxolane (**3b**), performed in acetic anhydride in the presence of *p*-toluenesulfonic acid as a catalyst, was quite similar to that of unsubstituted 1,3-dioxolane, giving the 9-isomer **4b** as the main product. However, in the case of larger substituents, the yield of 9-isomeres decreased and another product appeared in the reaction mixture. Its structure was determined as 7-(2-acetoxyethyl)-N^2-acetylguanine (**6**). The larger substituent in the position 2 of dioxolane, the higher yield of **6**. In the condensation of guanosine (**2**) with 2-phenyldioxolane compound **6** was the only reaction product. Its formation can be rationalized in the following way: in the absence of substituents, the nucleophilic attack of a heterocyclic base is directed toward C-1 of the respective oxacarbenium cation (route A in Scheme 2). However, when the center C-1 is crowded, the heterocyclic base attacks an alternative position, that is C-4 of the oxacarbenium cation (route B). This leads to the cleavage of the acyclosugar chain and to the formation of **6**, which is very stable (does not undergo the 7–9 isomerization). On the other hand, the structure of **6** may be viewed as excellent evidence that the atom N7 of guanosine is a nucleophilic center, which reacts directly with sugar cations.[3]

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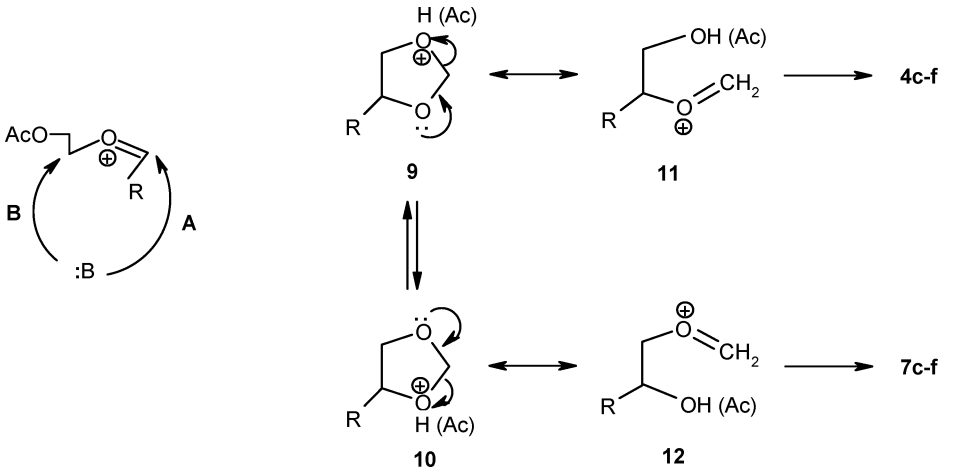

SCHEME 2 Mechanism of the side-product formation in transpurination of guanosine with substituted dioxolanes.

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In turn, the use of 4-substituted dioxolanes (**3c–f**) allowed us to obtain 4′-substituted analogs of acyclovir (Scheme 1): compounds (**4c–f**), together with the respective 7-regioisomers (**5c–f**). In fact, the reaction mixture was even more complicated due to the formation of 5′-substituted acyclonucleosides (**7c–f**) and the corresponding 7-isomers. This can be explained in the following way: the protonation of 4-alkyl(aryl)dioxolane may lead to the two protonated structures: HO1 (**9**) and HO3 (**10**) (Scheme 2). Therefore, the dioxolane ring can be opened in two possible ways, giving the oxacarbenium cations **11** and **12**, respectively. The cation **11** should be more stable because of an electron-donating effect of the neighbouring alkyl (aryl) group and, in fact, the formation of 4′-substituted acyclonucleosides (**4c–f**) prevails, while the 5′-substituted ones (**7c–f**) are formed as minor products (ca. 10%). Nevertheless, the synthesis of compounds **4c–f** required careful purification by chromatography and crystallization. The diacetyl 9-regioisomers **4b–f** were then deprotected to acyclovir analogs **1b–f**. However, the use of monoalkylated derivatives of 1,3-dioxolane created new asymmetric centers, and this apparently resulted in a racemic mixture of *R* and *S* acyclonucleosides. A further analog with no center of chirality, 4′,4′,5′,5′-tetramethylacyclovir (**8**), was obtained in a similar way.

The newly synthesized compounds **1b–f** and **8** were examined for their inhibitory effect on the replication of herpes simplex virus type 1 [HSV-1 (KOS, F, McIntyre)], type 2 [HSV-2 (G, 196, Lyons)], vaccinia virus (VV), vesicular stomatitis virus (VSV), thymidine kinase-deficient HSV-1 TK^- (KOS ACV^r) and hepatitis B virus (HBV) in cell cultures. The compounds demonstrated low cytotoxicity (minimum cytotoxic concentration >100 μM), but despite the improved solubility and enhanced lipophilicity, the new acyclonucleosides were essentially inactive against the viruses

tested. Only the 4′-methyl derivative (**1c**), which could be considered as a 3′-deoxy analog of ganciclovir, showed some moderate activity against HSV-1 and HSV-2 (minimum inhibitory concentration in the range of 4–20 μM).

EXPERIMENTAL

General Procedure for Synthesis of 1′, 4′, and/or 5′-Alkyl(aryl) Analogs of Acyclovir (1b–f, 8)

A suspension of guanosine (**2**; 2.0 mmol), an appropriate dioxolane (**3b–f** or 4′,4′,5′,5′-tetramethyl derivative; 5.0 mmol) and p-toluenesulfonic acid monohydrate (0.2 mmol) was stirred in acetic anhydride (5 mL) at room temperature for 30 minutes, and then at 100°C for 24 hours. The reaction mixture was concentrated under reduced pressure (10–15 mm Hg) at 50°C, in order to remove acetic acid and residual acetic anhydride. The residue after evaporation was stirred at 100°C, 10 mmHg, for the next 24 hours. The products were isolated by column chromatography in a chloroform—methanol or toluene—ethanol gradient. The 4′-substituted products (**4c–f**), usually contaminated with **7c–f**, were additionally purified by rechromatography in order to get analytically pure samples. The diacetyl 9-isomers were then crystallized from toluene, except for the methyl derivatives **4b** and **4c**, which were crystallized from methanol. Yield: 18–41% (**4b–f**), 15% (diacetyl **8**), 11–24% (**5b–f**). The products **4b–f** were deacetylated with 25% aqueous ammonia in methanol (1:1 v/v) at room temperature for 24 hours, to give acyclovir analogs **1b–f** in a quantitative yield. The diacetyl derivative **8** was deprotected by using 40% methylamine in water for 4 days. All acyclonucleosides were crystallized from water, and were characterized by the ^{1}H and ^{13}C NMR spectra and elemental analysis.

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