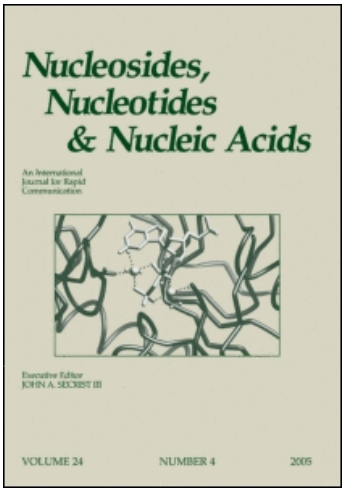

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SYNTHESIS OF 9-(2-HYDROXYETHOXYMETHYL)GUANINE (ACYCLOVIR) FROM GUANOSINE

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Abstract: A convenient synthesis of 9-(2-hydroxyethoxymethyl)guanine (acyclovir) from guanosine by chemical transpurination was developed. The isomerization of the 7-isomer to the desired 9-isomer and the purification of the 9-isomer was achieved simply by concentration, heating and further crystallization.

Introduction

The discovery of 9-(2-hydroxyethoxymethyl)guanine (acyclovir)[1a-c] (**1**) which has potent activity against herpes simplex type 1 and 2 viruses triggered a world wide effort to synthesize guanine nucleosides and acyclic nucleoside analogues.[2a-f] Several methods for the synthesis of acyclovir have been reported. Previously, Boryski and Golankiewicz reported[3] transpurination of tetraacetylguanosine[4] (**6**), leading to 9- and 7-(2-acetoxyethoxymethyl)-N^2-acetylguanine (**5**). However, many problems occur when adapting this method for large-scale production, because it requires many steps and isolation of intermediary products, and has less regioselectivity.

Here, we wish to report more convenient and economical synthesis of acyclovir (**1**) from natural guanosine (**2**) by chemical transpurination.

Results and Discussion

Reacting 1,3-dioxolane (**3**) with acetic anhydride in the presence of acid catalyst gave (2-acetoxyethoxy)methyl acetate[5] (**4**). The transpurination reaction of guanosine (**2**) with this acyclic sugar moiety **4** in the presence of acetic anhydride and catalytic amount of acid gave a mixture of 9-(2-acetoxyethoxymethyl)-N^2-acetylguanine (**5a**) and 7-(2-acetoxyethoxymethyl)-N^2-acetylguanine (**5b**) in high yield (FIG. I). Various acid catalysts were applicable to the transpurination, as summarized in TABLE 1. The reaction proceeded with or without solvent.

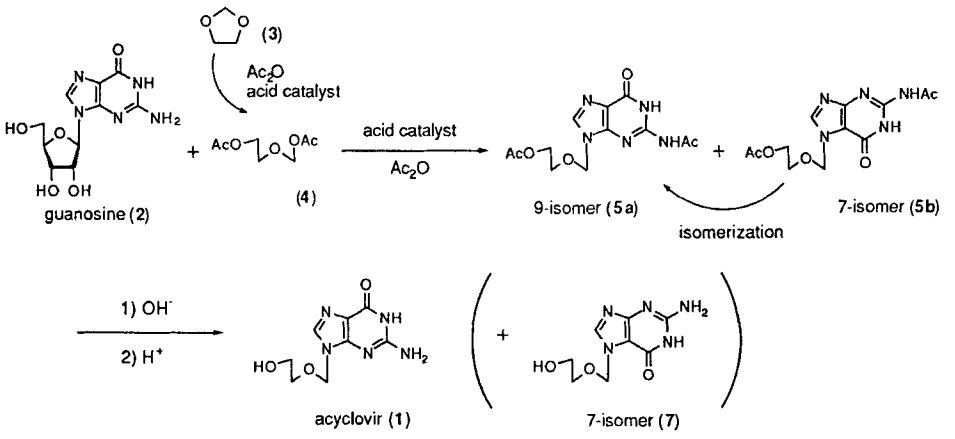

FIG. 1

TABLE 1. Transpurination reaction from guanosine.

additives (equiv.)		catalyst[a]	solvent	conditions temp. (°C)	time (h)	products (% yield) 5a	5b
4 (2)	Ac2O (8)	p-TsOH•H2O		100	24	48	38
4 (2)	Ac2O (8)	H2SO4		100	24	42	35
4 (2)	Ac2O (8)	H2NPhSO3H		100	24	40	36
4 (2)	Ac2O (8)	H3PO4		100	24	47	38
4 (2)	Ac2O (8)	p-TsOH•H2O	MeCN	82	48	30	19
4 (2)	Ac2O (8)	p-TsOH•H2O	DMF	120	24	35	21
4 (2)	Ac2O (8)	H2NPhSO3H	DMF	120	24	33	19
3 (2)	Ac2O (8)	H3PO4		100	24	45	39

[a] 0.1 equiv. of catalyst was used for the reaction.

HPLC analysis of the reaction revealed that tetraacetylguanosine (**6**) was produced first and the transformation of **6** into **5** was observed subsequently. Indeed, the reaction starting from the fully protected nucleoside **6** gave the comparable formation of **5** even in the absence of acetic anhydride, but the transpurination of guanosine (**2**) itself did not occur without acetic anhydride (FIG. II).

Since the catalyst in the synthesis of the acyclic sugar moiety **4** could be the same as that used in transpurination, the one pot reaction of guanosine with 1,3-dioxolane (**3**) and acetic anhydride in the presence of acid catalyst gave similar results (TABLE 1).

To obtain the desired, biologically active N-9 isomer **5a** exclusively, isomerization of the N-7 isomer **5b** to **5a** is required. This was realized by distilling off volatile

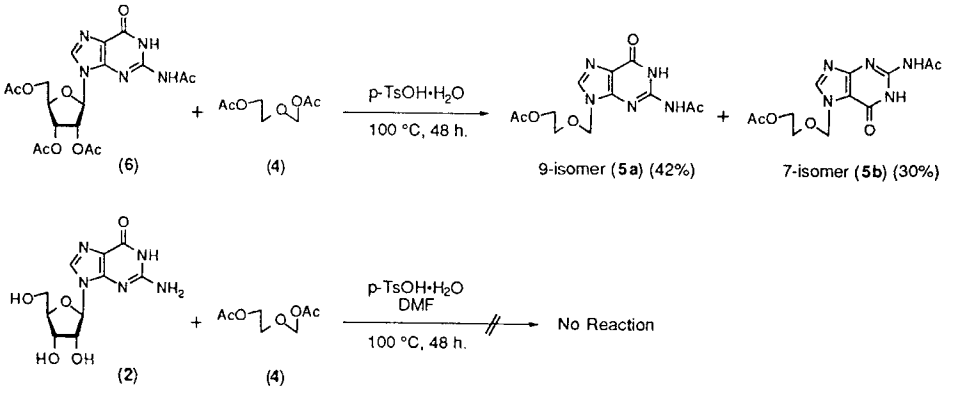

FIG. II

TABLE 2. Isomer ratios in the process.

procedure	conditions temp. (°C)	time (h)	pressure (mmHg)	9-/7- isomer ratio[a]
Transpurination[b]	90-100	19.0	760	1.45
Concentration	90-100	1.0	30-40	c.a. 2.0
Isomerization	90-100	3.0	30	6.34
	90-100	22.5	30	17.1
Crystallization	25	1.0	760	120

[a] The ratios were calculated based on HPLC peak area.

[b] Guanosine (**2**) was reacted with 1,3-dioxolane (**3**) (2 equiv.) and Ac_2O (7 equiv.) in the presence of p-TsOH•H_2O (0.1 equiv.).

components from the reaction mixture, followed by heating the residue at 100 °C under reduced pressure (FIG. I). These isomerization conditions were considerably milder than those reported previously[3] and afforded a much higher N-9/N-7 ratio. After the isomerization, by adding an appropriate solvent such as ethyl acetate, acetonitrile or water to the residue, **5a** was crystallized selectively from the concentrate (TABLE 2).

Treating **5a** with aqueous sodium hydroxide followed by neutralization with hydrochloric acid gave acyclovir (**1**) in 92% yield with high isomeric purity, which means that the overall yield of **1** from guanosine was 78%.

Experimental

9-(2-acetoxyethoxymethyl)-N^2-acetylguanine (5a)

To 50 g (176.5 mmol) of guanosine were added 62 g (353 mmol) of **4**, 180 g (1.75 mol) of acetic anhydride and 3.4 g (17.5 mmol) of p-toluenesulfonic acid

monohydrate, and the mixture was stirred at 100 °C for 20 h. The reaction mixture was concentrated under reduced pressure (10 mmHg) at 50 °C for 1 h. The resulting residue was stirred at 100 °C under reduced pressure (10 mmHg) for 20 h. The mixture was cooled to room temperature and 100 mL of ethyl acetate was added, and stirred further for 1 h. The crystals were separated by filtration, washed with ethyl acetate (20 mL), and dried under reduced pressure. The crude crystals (53 g) contained 46.9 g of **5a** (86% yield), accompanied with 270 mg (0.5%) of **5b**, which were determined by HPLC.

9-[2-(hydroxyethoxy)methyl]guanine (1) (acyclovir)

10 g of crude crystals containing **5a** were dissolved in 100 mL of 5% aqueous NaOH and the mixture was stirred at room temperature overnight. The reaction mixture was neutralized by 1M HCl and the resulting precipitate was filtered to provide 6.4 g of **1** (92% yield): m.p. 247-248 °C; $\lambda_{max}(H_2O)$ 252 nm (ε 12127); $\lambda min(H_2O)$ 221 nm (ε 2298); ^1H NMR(400MHz, Me_2SO-d_6) δ 3.47 (4H, s, H-3', 4'), 4.67 (1H, brs, OH), 5.35 (2H, s, H-1'), 6.50 (2H, brs, NH_2), 7.81 (1H, s, H-8), 10.63 (1H, brs, CONH). ^{13}C NMR (400 MHz, Me_2SO-d_6) δ 60.14 (C-4'), 70.62 (C-3'), 72.27 (C-1'), 116.73 (C-5), 138.00 (C-8), 151.67 (C-4), 154.11 (C-2), 157.05 (C-6); fast atom bombardment mass spectrum, m/z 226 (MH^+). Anal. Calcd. for $C_8H_{11}N_5O_3$: C, 42.67; H, 4.92; N, 31.10. Found: C, 42.39; H, 4.98; N, 30.95.

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