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Hiroshi Shiragami ^a, Yoshihito Koguchi ^a, Yasuhiro Tanaka ^a, Satoshi Takamatsu ^a, Yumiko Uchida ^a, Takashi Ineyama ^a & Kunisuke Izawa ^a

^a Central Research Laboratories, Ajinomoto Co., Inc, 1-1 Suzuki-cho, Kawasaki-ku, Kawasaki, 210, Japan

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

Hiroshi Shiragami, Yoshihito Koguchi, Yasuhiro Tanaka, Satoshi Takamatsu,
Yumiko Uchida, Takashi Ineyama and Kunisuke Izawa*
Central Research Laboratories, Ajinomoto Co., Inc.
1-1 Suzuki-cho, Kawasaki-ku, Kawasaki 210, Japan

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 reported³ transpurination of tetraacetylguanosine⁴ (**6**), leading to 9- and 7-(2-acetoxyethoxymethyl)-N²-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 acetate⁵ (**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)-N²-acetylguanine (**5a**) and 7-(2-acetoxyethoxymethyl)-N²-acetylguanine (**5b**) in high yield (FIG. 1). Various acid catalysts were applicable to the transpurination, as summarized in TABLE 1. The reaction proceeded with or without solvent.

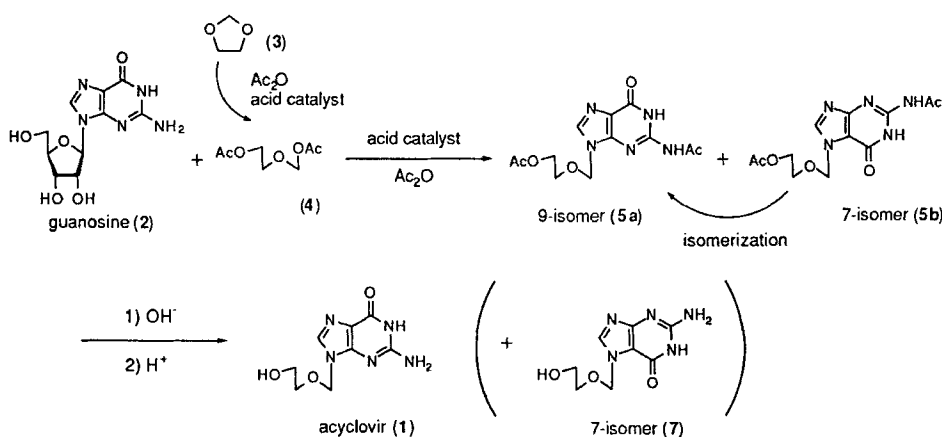


FIG. 1

TABLE 1. Transpurination reaction from guanosine.

| additives (equiv.) | catalyst ^a | solvent | conditions | | products (% yield) | |
|-----------------------|---------------------------|-------------------------------------|---------------|-------------|-----------------------|----|
| | | | temp. (°C) | time (h) | 5a | 5b |
| 4 (2) | Ac_2O (8) | p-TsOH·H ₂ O | 100 | 24 | 48 | 38 |
| 4 (2) | Ac_2O (8) | H ₂ SO ₄ | 100 | 24 | 42 | 35 |
| 4 (2) | Ac_2O (8) | H ₂ NPhSO ₃ H | 100 | 24 | 40 | 36 |
| 4 (2) | Ac_2O (8) | H ₃ PO ₄ | 100 | 24 | 47 | 38 |
| 4 (2) | Ac_2O (8) | p-TsOH·H ₂ O | MeCN | 82 | 48 | 30 |
| 4 (2) | Ac_2O (8) | p-TsOH·H ₂ O | DMF | 120 | 24 | 35 |
| 4 (2) | Ac_2O (8) | H ₂ NPhSO ₃ H | DMF | 120 | 24 | 33 |
| 3 (2) | Ac_2O (8) | H ₃ PO ₄ | 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

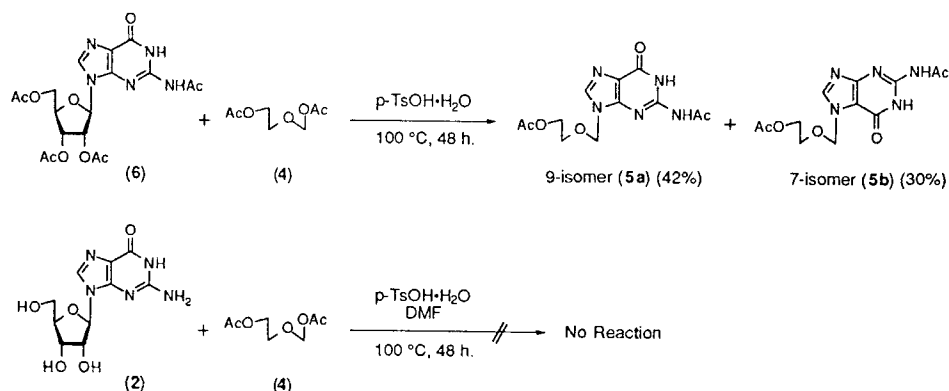


FIG. II

TABLE 2. Isomer ratios in the process.

| procedure | conditions | | | 9-/7- isomer ratio ^a |
|------------------------------|------------|----------|-----------------|---------------------------------|
| | temp. (°C) | time (h) | pressure (mmHg) | |
| 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 Ac₂O (7 equiv.) in the presence of p-TsOH·H₂O (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 previously³ 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)-N²-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; $\lambda_{\text{max}}(\text{H}_2\text{O})$ 252 nm (ϵ 12127); $\lambda_{\text{min}}(\text{H}_2\text{O})$ 221 nm (ϵ 2298); ^1H NMR(400MHz, $\text{Me}_2\text{SO}-d_6$) 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, $\text{Me}_2\text{SO}-d_6$) 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 $\text{C}_8\text{H}_{11}\text{N}_5\text{O}_3$: C, 42.67; H, 4.92; N, 31.10. Found: C, 42.39; H, 4.98; N, 30.95.

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