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A Convenient Synthesis of 9-(2-Hydroxyethoxymethyl)guanine (Acyclovir) and Related Compounds[1)]

HIROATSU MATSUMOTO,* CHISATO KANEKO, KEIKO YAMADA, TADAO TAKEUCHI, TAKEO MORI, and YOSHIHISA MIZUNO

Research Laboratory, Minophagen Pharmaceutical Co., 2–5233, Komatsubara, Zama, Kanagawa 228, Japan

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A convenient and economical synthesis of 9-(2-hydroxyethoxymethyl)guanine (**1**, acyclovir, Zovirax, or acyclic guanosine: an antiherpetic agent) from guanine was developed *via* N^2,*O*-diacetylacyclovir. Two closely related compounds, N^2-acetylacyclovir (**7**) and *O*-acetylacyclovir (**8**), were also prepared by selective deacetylation.

Keywords——acyclovir; N^2-acetylacyclovir; *O*-acetylacyclovir; alkylation; *p*-toluenesulfonic acid; antiherpetic agent

Schaeffer and coworkers[2)] first reported that 9-(2-hydroxyethoxymethyl)guanine (**1**, acyclovir) may be highly specific inhibitor of herpes viruses proliferation. Since then, a large number of nucleoside analogs in which the carbohydrate moiety is replaced by an acyclic substituent (*viz.*, 2-hydroxyethoxymethyl or 1,3-dihydroxy-2-propoxymethyl) have been prepared.

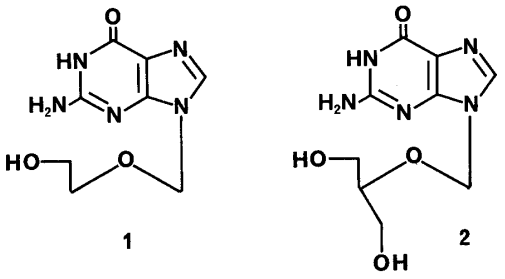

Chart 1

Several methods for the introduction of a 2-hydroxyethoxymethyl group into purines for the synthesis of acyclovir or acyclic nucleosides have been tried,[3–10)] with limited success. Schaeffer and colleagues have carried out the base-promoted alkylation of 2,6-dichloropurine with 2-benzoxyethoxymethyl chloride to obtain the *N*-9 substituted product in 41% yield.[2)] Acyclovir was prepared in 13% overall yield from the *N*-9 derivative in four steps including ammonolysis and hydrogenolytic debenzylation. Barrio and coworkers[11)] have studied the reaction at −63 °C of chloro- or methylthio-substituted purine with 2-trimethylsilyloxyethoxymethyl chloride to afford the *N*-9 substituted products in 50—80% yields. Robins and Hatfield[12)] started from 2,6-dichloropurine or 2-amino-6-chloropurine which was reacted with 2-acetoxyethoxymethyl bromide to obtain the *N*-9 substituted derivative in 89% or 84% yield, respectively.

Problems associated with these procedures were that the reagents employed were quite expensive and that the amination of the 2-chloro group was tedious. Therefore, the yield of **1**

was usually not satisfactory. According to the patent literature[13] on the synthesis of acyclovir, the drug was prepared in 24% yield by debenzylation of the product obtained by the reaction of trimethylsilylated guanine and 2-benzoxyethoxymethyl chloride. As a closely related example, it is worthy of note that Martin *et al.*[14] employed alkylation of *N*, 9-diacetylguanine with 2-*O*-(acetoxymethyl)-1,3-di-*O*-benzylglycerol in the presence of a catalytic amount of *p*-toluenesulfonic acid in sulfolane (95 °C, 72 h), and the subsequent debenzylation and deacetylation gave rise to 9-(1,3-dihydroxy-2-propoxymethyl)guanine (**2**, DHPG) in 27% overall yield. This procedure involves the use of a solvent (solvent method), which may permit a homogeneous reaction and contribute to the improvement of the yield.

We adopted the solvent method and examined the effect of several parameters (solvent, catalyst, and reaction temperature) upon the yield of protected acyclovir.

It was found the N^2,*O*-diacetylacyclovir (**5**) could be synthesized in fair or good yield by the condensation of *N*,*N'*-diacetylguanine(s) (**3**) and 2-oxa-1,4-butanediol diacetate in the presence of *p*-toluenesulfonic acid or sulfanilic acid in organic solvents.

The present paper deals with a convenient synthesis of the 9-(2-hydroxyethoxymethyl)guanine and closely related compounds.

Results and Discussion

Effects of Catalysts and Reaction Temperature

Sato and coworkers[15] have developed a fusion method for the nucleoside synthesis. They have examined the catalytic activities of a number of protic acids as well as Lewis acids.

We evaluated the effect of catalysts such as *p*-toluenesulfonic acid, sulfanilic acid, *o*-, *m*-, and *p*-, nitrobenzenesulfonic acid, zinc chloride, and iron(II) sulfate upon the yields in acyclovir synthesis.

We also examined the effect of reaction temperature, in the range from 60 to 120 °C. Concerning reaction temperature, the best yield of **5** was obtained at 100 °C (with the exception of zinc chloride and 2,4-dinitrobenzenesulfonic acid). In connection with the catalysts, *p*-toluenesulfonic acid and sulfanilic acid were found to be the best in terms of the catalytic activity. On the other hand, large differences in reactivity were observed when aprotic acids were used as catalysts. When *o*-, *m*-, or *p*-, nitrobenzenesulfonic acid was utilized, the yield of **5** was 55%, 50%, and 59%, respectively. Therefore, it may be concluded that the use of isomeric nitrobenzenesulfonic acid does not result in much difference in the yield of **5**. The use of 2,4-dinitrobenzenesulfonic acid as the catalyst at 100 °C reduced the yield to a considerable extent, indicating that the acid is too strong to act as an effective

TABLE I. Effect of Catalysts and Temperature on Yield of N^2,*O*-Diacetylacyclovir[a]

Catalyst	Reaction temperature and product yield (%) 80 °C		100 °C	
	5	**6**	**5**	**6**
p-Toluenesulfonic acid	31	53	66	26
Sulfanilic acid	51	27	66	28
p-Nitrobenzenesulfonic acid	56	33	59	24
2,4-Dinitrobenzene sulonic acid	50	19	38	20
Iron(II) sulfate	12	7	38	21
Zinc chloride	—[b]	—	—	—

a) Compound (**3**) (1 eq) was reacted with **4** (2 eq) in the presence of the indicated catalyst (0.025 eq) in DMSO. *b*) The symbol (—) indicates that one (**3**) of the starting materials was recovered unchanged.

catalyst.

Selective Deprotection of N^2,*O*-Diacetylacyclovir

Treatment of **5** with methanol saturated with ammonia gave rise to **1** in 86% yield, which means that overall yield of **1** from guanine was 43%. *O*-Acetylacyclovir (**8**) could be isolated in 81% yield on reaction of **5** with methanolic methoxide at room temperature. On the other hand, treatment of **5** with aqueous ammonium hydroxide (pH 11.6) gave rise to N^2-acetylacyclovir (**7**) in 55% yield (50 °C, 1 h). Compound (**7**) would be a suitable starting material for the preparation of acyclovir phosphate, which might be anticipated to be active against a line of herpes simplex lacking thymidine kinase.

Finally, it is worthy of note that among the solvents we examined, dimethyl sulfoxide (DMSO) was found to be the solvent of choice in terms of the solubility of substrates and the yield of **1**.

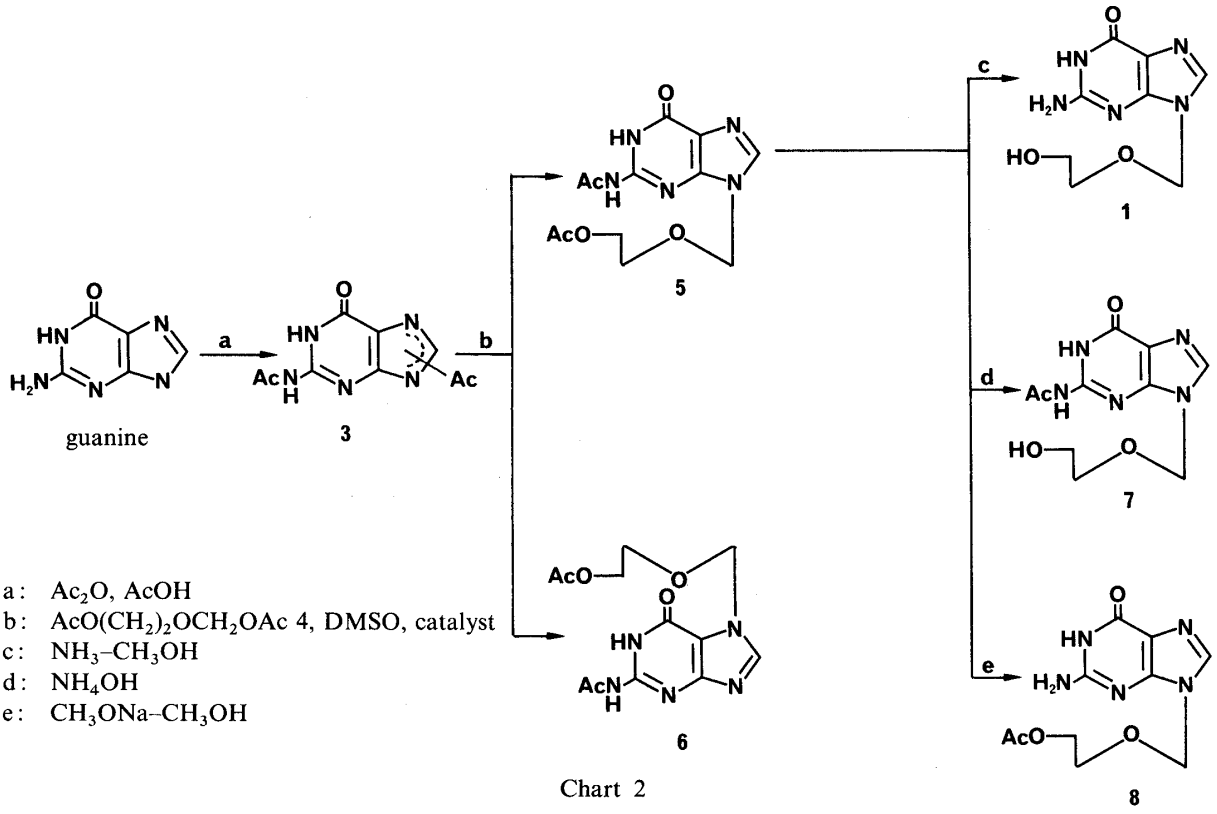

Chart 2

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus, and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained on a JEOL-270 spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, m = multiplet. Ultraviolet (UV) spectra were measured on a Hitachi 200-20 spectrophotometer. Column chromatography was performed with Kieselgel 60 (E. Merck, 70—230 mesh ASTM).

2-Oxa-1,4-butanediol Diacetate (4)——Acetyl bromide (50 g, 0.4 mol) was added dropwise to 1,3-dioxolane (26.6 g 0.36 mol) with cooling in an ice bath, the reaction temperature being maintained below 5 °C. The reaction mixture was allowed to warm to room temperature, and then a solution of sodium acetate (50 g) in acetic acid (200 ml) was added at 110 °C. The reaction mixture was stirred for 1 h. Insoluble material (NaBr) was filtered off and the filtrate was distilled *in vacuo* initially to remove acetic acid and then fractionated *in vacuo*. The fraction boiling at 114—118 °C/10 mmHg[16] was collected. The yield of **4** was 38 g (60%).

***N*,*N'*-Diacetylguanine(s) (3)**——Diacetylguanine was prepared, with reference to the procedure of Beauchamp and coworkers.[17] A mixture of guanine (15.1 g, 0.1 mol), acetic anhydride (200 ml) and acetic acid (300 ml) was

heated with stirring at 140 °C for 18 h. The resulting solution was then cooled to room temperature and 50 ml of water was added dropwise and the resulting mixture was cooled to 0 °C. The crystalline precipitate was collected by filtration and washed with water until the washings were neutral, then and dried *in vacuo* at 80 °C. The yield was 17.8 g (76%). UV λ_{max} nm: [50% (v/v) CH_3OH–H_2O] 280, 260; (0.1 N HCl) 260; (0.1 N NaOH) 279. ^{1}H-NMR (DMSO-d_6) δ: 2.2 (3H, s, CH_3CO), 2.8 (3H, s, CH_3CO), 8.4 (1H, s, H-8), 11.7 (1H, s, H-1). *Anal.* Calcd for $C_9H_9N_5O_3$: C, 45.96; H, 3.86; N, 29.78. Found: C, 45.91; H, 3.72; N, 29.76.

Combustion values were consistent with the diacetylguanine structure, and the ^{1}H-NMR spectra of the diacetyl derivative indicated the presence of a pair of three-proton signals which are due to N^2- and N^7- (or N^9-)acetyl groups.

N^2-Acetyl-9-(2-acetoxyethoxymethyl)guanine (Diacetylacyclovir) (5) and N^2-acetyl-7-(2-acetoxyethoxymethyl)-guanine (6)——A mixture of 2-oxa-1,4-butanediol diacetate (6 g, 34 mmol), diacetylguanine (4 g, 17 mmol), *p*-toluenesulfonic acid monohydrate (80 mg, 0.42 mmol) and DMSO (50 ml) was heated with stirring at 100 °C for 16 h, then concentrated to dryness. The resulting oil was chromatographed on a column of silica gel using CH_2Cl_2–CH_3OH–H_2O (60 : 39.2 : 0.8, v/v) as an eluting system. From the early fractions, **6** (1.4 g, 26% yield) was obtained. From the later fractions, **5** (3.5 g, 66% yield) was obtained. Compound (**5**): mp 189—190 °C. UV λ_{max} nm (ε): [50% (v/v) CH_3OH–H_2O] 277 sh (5100), 259 (7200); (0.1 N HCl) 274 sh (8500), 262 (10100); (0.1 N NaOH) 262 (4800). ^{1}H-NMR (DMSO-d_6) δ: 1.96 (3H, s, CH_3CO); 2.19 (3H, s, CH_3CO), 3.68 (2H, m, H-3′), 4.07 (2H, m, H-4′), 5.48 (2H, s, H-1′), 8.14 (1H, s, H-8). ^{13}C-NMR (DMSO-d_6) δ: 20.43 (CH_3CO), 23.65 (CH_3CO), 62.55 (C-3′), 66.57 (C-4′), 72.30 (C-1′), 120.08 (C-8), 148.75 (C-4), 157.80 (C-6), 170.10 (C=O), 170.90 (C=O). *Anal.* Calcd for $C_{12}H_{15}N_5O_5$: C, 46.60; H, 4.89; N, 22.65. Found: C, 46.58; H, 4.90; N, 22.57. Compound (**6**): mp 184—185 °C. UV λ_{max} nm (ε): [50% (v/v) CH_3OH–H_2O] 282 sh, 262 (5000); (0.1 N HCl) 263 (22700); (0.1 N NaOH) 268 (5200), 224 (10800). ^{1}H-NMR (DMSO-d_6) δ: 1.96 (3H, s, CH_3CO), 2.18 (3H, s, CH_3CO), 3.72 (2H, m, H-3′), 4.08 (2H, m, H-4′), 5.70 (2H, s, H-1′), 11.63 (1H, s, NH), 12.72 (1H, s, HN-$COCH_3$). ^{13}C-NMR (DMSO-d_6) δ: 20.62 (CH_3CO), 23.79 (CH_3CO), 62.83 (C-3′), 66.48 (C-4′), 75.03 (C-1′), 111.23 (C-5), 145.19 (C-9), 152.58 (C-6), 157.50 (C-4), 170.30 (C=0), 174.38 (C=0).

9-(2-Hydroxyethoxymethyl)-N^2-acetylguanine (7)——A mixture of **5** (2 g, 6.47 mmol) and 200 ml of 1 N NH_4OH (pH 11.6) was stirred at 50 °C for 1 h. The resulting solution was neutralized with Amberlite IR-120B (H^+) and the solvent was removed *in vacuo*. The starting material was recovered by eluting initially with 4% (v/v) CH_3OH–CH_2Cl_2 and further elution with 8% (v/v) CH_3OH–CH_2Cl_2 gave **7**. Yield: 955 mg (55%), mp 248—250 °C. UV λ_{max} nm (ε): [50% (v/v) CH_3OH–H_2O] 275 (9600), 258 (11900); (0.1 N HCl) 275 sh, 264 (10800); (0.1 N NaOH) 264 (7300). ^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s, N-$COCH_3$), 5.47 (2H, s, H-1′), 8.13 (1H, s, H-8), 11.75 (1H, s, NH), 12.05 (1H, s, HN-$COCH_3$). ^{13}C-NMR (DMSO-d_6) δ: 59.9 (C-3′), 70.50 (C-4′), 72.6 (C-1′), 120.1 (C-5), 140.0 (C-8), 148.0 (C-2). *Anal.* Calcd for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found: C, 45.16; H, 5.21; N, 26.16.

9-(2-Acetoxyethoxymethyl)guanine (8)——Compound (**5**) (100 mg, 0.32 mmol) was dissolved in 20 ml of methanol containing 5.7 l of sodium methylate (28% in methanol). The mixture was stirred at room temperature for 16 h. The solvent was then removed on a flash evaporator and the residue was triturated with 20 ml of acetone. The product was collected by filtration to give 70.1 mg (81% yield) of **8**, mp 210—215 °C. UV $_{max}$ nm (ε): [50% (v/v) CH_3OH–H_2O] 274 sh (5300), 250 (8300); (0.1 N HCl) 277 sh (6600), 256 (10000); (0.1 N NaOH) 264 (3100), 257 (3100). ^{1}H-NMR (DMSO-d_6): 1.93 (3H, s, CH_3CO), 3.67 (2H, m, H-3′), 4.08 (2H, m, H-4′), 5.35 (2H, s, H-1′), 6.41 (1H, s, NH_2), 7.76 (1H, s, H-8), 10.59 (1H, s, NH).

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References and Notes

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