A SERIES OF NOVEL ACYCLIC NUCLEOSIDES I SYNTHESIS OF 5-AMINO-3-[(2-HYDROXYETHOXY)METHYL]-3H-IMIDAZO[4,5-d][1,3]OXAZIN-7-ONE

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A novel acyclic nucleoside (**4**) that N^1 of acyclovir (**3**) is replaced by oxygen atom was prepared. 5-Amino-1-[(2-acetoxyethoxy) methyl]-4-ethoxycarbonylimidazole (**6a**) was treated with ethoxycarbonyl isothiocyanate to give compound (**7**). Methylation of **7** with MeI afforded S-methylisothiourea derivative (**8**). Treatment of the latter with alkali followed by neutralization afforded 5-amino-3-[(2-hydroxyethoxy)methyl]-3H-imidazo[4,5-d][1,3]oxazin-7-one (**4**).

KEYWORDS —— 3-substituted-3H-imidazo[4,5-d][1,3]oxazin-7-one; acyclic nucleoside; ethoxycarbonyl isothiocyanate; oxanosine; fusion method; antiviral agent

It is well documented that 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir[1], **3**) is a highly specific inhibitor of herpes virus proliferation with minimal cytotoxity and thus one of excellent antiviral agents in terms of chemotherapeutic index.[2] Numerous attempts aiming at modification of the heterocyclic base or the acyclic side chain of **3** have been done in order to examine the relationship between structure and function.[3,4]

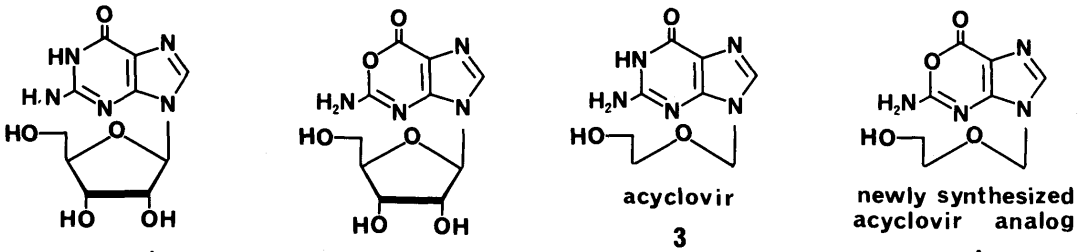

Fig.1

In order to define the function of position 1 in the interaction of the drug with the viral encoded enzymes to exert antiviral activity, we planned to synthesize analogs in which N^1 is displaced by O, S, or sp^2 carbon. In this report we describe the first synthesis of the oxgen analog (**4**) (Fig. 1) of acyclovir.

It is interesting to note that the antibiotic oxanosine[5] (**2**), isolated in 1981[6a,b] and the structure confirmed by chemical synthesis in 1983,[6c] bears the identical heterocyclic aglycon with **4**.

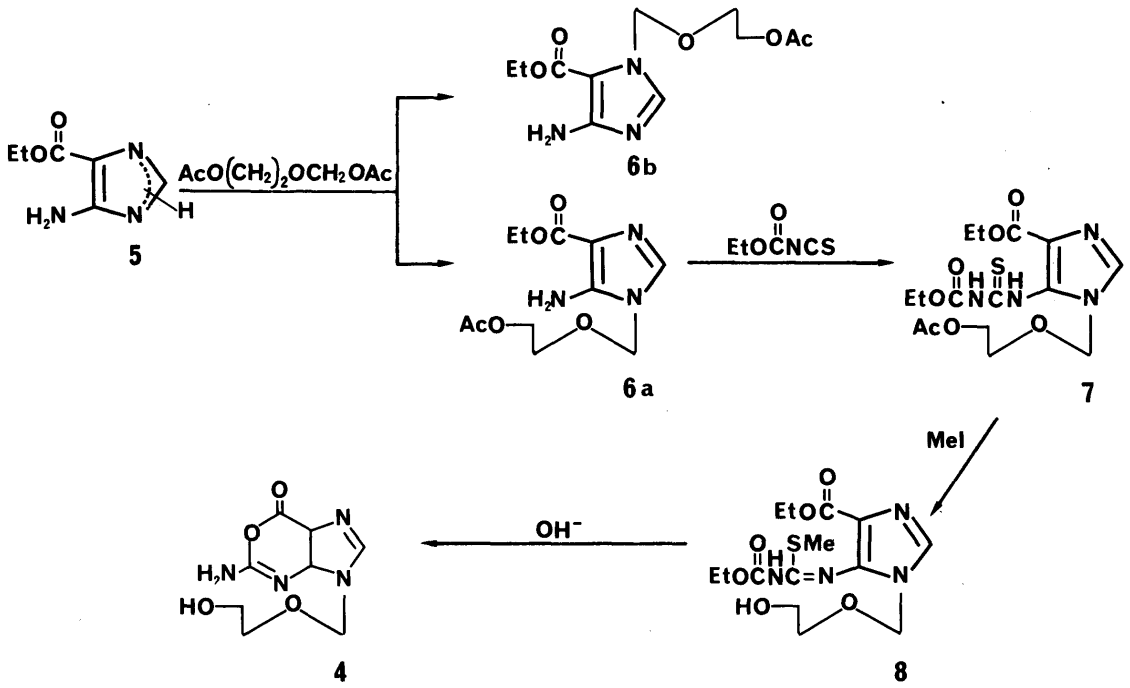

Chart 1

As shown in Chart 1, the synthesis of **4** started with 1-[(2-acetoxyethoxy)methyl]-5-amino-4-ethoxycarbonylimidazole (**6a**) which in turn was prepared from 4(5)-amino-5(4)-ethoxycarbonylimidazole (**5**) and 2-oxa-1,4-butanediol diacetate at 140°C for 2 h. After work-up including column chromatography (silica gel, 1%CH_3OH-$CHCl_3$), a pair of positional isomers (**6a**) and (**6b**) were isolated : pure **6a** (mp 86-87°C)[7] was obtained in 19% yield and **6b**[7] in 27%. ^{1}H-NMR spectra were particularly helpful for differentiation of two positional isomers. The signal due to 2-H of two positional isomers (**6a** and **6b**) appeared at δ7.25 and δ7.69, respectively. 2-H signal of compound (**6b**) should be more deshielded because of electon-withdrawing effect of 5-ethoxycarbonyl group. Therefore, the isomer having 2-H signal at δ7.25 was assigned the 1-[(2-acetoxyethoxy)methyl]imidazole structure and it was found that observed values are in agreement with values reported in other related system.[8]

A stirred suspension of **6a** in acetonitrile was treated with ethoxycarbonyl isothiocyanate at 50°C for 16 h to give compound (**7**)[9] (76% yield). Reaction of **7** with methyl iodide afforded methylthio derivative (**8**)[10] in 75% yield, mp 100-101°C. For the ring closure, an alkaline solution of **8** was heated at 95-100°C for 30 min.

Cooled and neutralized solution was subjected to HPLC using reverse phase system (the solvent, 18%CH_3OH-H_2O) and desired product (**4**)[11] was obtained in 18.4% yield, mp 190-192°C. It is worthy of note that the UV spectra of **4** (acyclic oxanosine) was found to be completely superimposable with reported UV spectrum of oxanosine,[6b] confirming that the product is indeed 3H-(2-hydroxyethoxy)methyl derivative (**4**) (Fig. 2).

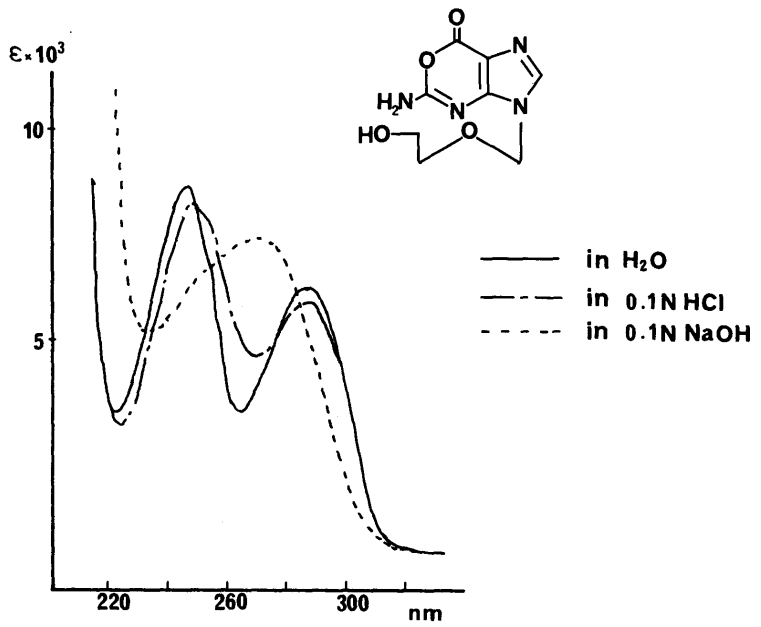

Fig. 2. UV Spectra of Acyclic Oxanosine

ACKNOWLEDGEMENT The authors are indebted to the staff of the Center for Instrumental Analysis of Hokkaido University for measurements of MS, NMR spectra and elemental analysis.

REFERENCES AND NOTES

1) 9-[(2-Hydroxyethoxy)methyl]guanine (**3**) is termed as Zovirax or acyclic guanosine besides Acyclovir. However in this paper acyclovir is employed.
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7) The structural assignment rests upon UV, MS and ^{1}H-NMR in addition to elemental analysis. UV λ_{max}^{nm} (ε): **6a**- 269 (10900), 238sh (4300) [H_2O:CH_3OH (1:1)]; 268 (9900), 247 (7700) [0.1N HCl:CH_3OH (1:1)], 269 (10900) [0.1N NaOH:CH_3OH (1:1)]. **6b**- 280 (14600), 233 (5530) [H_2O:CH_3OH (1:1)]; 274 (12100), 240 (7970) [0.1N HCl:CH_3OH (1:1)]; 280 (13400) [0.1N NaOH:CH_3OH (1:1)]. ^{1}H-NMR (DMSO-d_6, TMS as a standard)δ: **6a**- 1.25 (t, 3H, $C\underline{H}_3CH_2$), 1.99 (s, 3H, $C\underline{H}_3C$=O), 3.61 (t, 2H, H-3′), 4.14 (m, 4H, H-4′ and $CH_3C\underline{H}_2$), 5.28 (s, 2H, H-1′), 6.12 (s, 3H, NH_2), 7.25 (s, 1H, H-2). **6b**- 1.27 (t, 2H, $C\underline{H}_3CH_2$), 1.98 (s, 3H, CH_3C=O), 3.57 (t, 2H, H-3′), 4.17 (m, 4H, H-4′ and $CH_3C\underline{H}_2$), 5.47 (s, 2H, H-1′), 5.74 (s, 2H, NH_2), 7.69 (s, 1H, H-2).

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9) The structure was confirmed by UV, MS and ^{1}H-NMR. ^{1}H-NMR (DMSO-d_6, vide supra) δ: 1.27 (m, 6H, $C\underline{H}_3CH_2$), 3.63 (t, 2H, H-3′), 4.05 (t, 2H, H-4′), 4.21 (m, 4H, $CH_3C\underline{H}_2$), 5.31 (s, 2H, H-1′), 7.89 (s, 1H, H-2), 11.13 (s, 1H, S=C-NH), 11.69 (s, 1H, O=C-NH-C=S). MS m/z: 402 (M^+).

10) This structure was supported by the data of UV, ^{1}H-NMR and MS in addition to elemental analysis. ^{1}H-NMR (DMSO-d_6, vide supra)δ: 1.18 (m, 6H, $C\underline{H}_3CH_2$), 2.36 (s, 3H, SCH_3), 3.24 (m, 4H, $CH_3C\underline{H}_2$), 4.01 (m, 4H, H-3′ and H-4′), 5.12 (s, 2H, H-1′), 7.62 (s, 1H, H-2), 10.05 (s, 1H, NH). MS m/z: 374 (M^+).

11) UV λ_{max} nm (ε): 287 (6730), 246 (9240), 205 (16700) (H_2O); 286 (6410), 248 (8810) (0.1N HCl); 273 (7980) (0.1N NaOH). MS m/z: 226 (M^+), 152 (BH^+). ^{1}H-NMR (DMSO-d_6, vide supra)δ: 3.47 (4H, H-3′ and H-4′), 5.33 (s, 2H, H-1′), 7.85 (s, 1H, H-2), 7.88 (s, 1H, NH).

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