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 N¹ 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-methylisothioureia 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 (acyclovir¹⁾, **3**) is a highly specific inhibitor of herpes virus proliferation with minimal cytotoxicity 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 N¹ is displaced by O, S, or sp² carbon. In this report we describe the first synthesis of the oxygen analog (**4**) (Fig. 1) of acyclovir.

It is interesting to note that the antibiotic oxanosine⁵⁾ (**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%CH₃OH-CHCl₃), 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%. ¹H-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 δ 7.25 and δ 7.69, respectively. 2-H signal of compound (**6b**) should be more deshielded because of electron-withdrawing effect of 5-ethoxycarbonyl group. Therefore, the isomer having 2-H signal at δ 7.25 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%CH₃OH-H₂O) 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

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REFERENCES AND NOTES

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- 7) The structural assignment rests upon UV, MS and $^1\text{H-NMR}$ in addition to elemental analysis. UV λ_{max} nm (ϵ): **6a**- 269 (10900), 238sh (4300) [$\text{H}_2\text{O}:\text{CH}_3\text{OH}$ (1:1)]; 268 (9900), 247 (7700) [0.1N $\text{HCl}:\text{CH}_3\text{OH}$ (1:1)], 269 (10900) [0.1N $\text{NaOH}:\text{CH}_3\text{OH}$ (1:1)]. **6b**- 280 (14600), 233 (5530) [$\text{H}_2\text{O}:\text{CH}_3\text{OH}$ (1:1)]; 274 (12100), 240 (7970) [0.1N $\text{HCl}:\text{CH}_3\text{OH}$ (1:1)]; 280 (13400) [0.1N $\text{NaOH}:\text{CH}_3\text{OH}$ (1:1)]. $^1\text{H-NMR}$ (DMSO-d_6 , TMS as a standard) δ : **6a**- 1.25 (t, 3H, CH_3CH_2), 1.99 (s, 3H, $\text{CH}_3\text{C=O}$), 3.61 (t, 2H, H-3'), 4.14 (m, 4H, H-4' and CH_3CH_2), 5.28 (s, 2H, H-1'), 6.12 (s, 3H, NH_2), 7.25 (s, 1H, H-2). **6b**- 1.27 (t, 2H, CH_3CH_2), 1.98 (s, 3H, $\text{CH}_3\text{C=O}$), 3.57 (t, 2H, H-3'), 4.17 (m, 4H, H-4' and CH_3CH_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 $^1\text{H-NMR}$. $^1\text{H-NMR}$ (DMSO-d_6 , vide supra) δ : 1.27 (m, 6H, CH_3CH_2), 3.63 (t, 2H, H-3'), 4.05 (t, 2H, H-4'), 4.21 (m, 4H, CH_3CH_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, $^1\text{H-NMR}$ and MS in addition to elemental analysis. $^1\text{H-NMR}$ (DMSO-d_6 , vide supra) δ : 1.18 (m, 6H, CH_3CH_2), 2.36 (s, 3H, SCH_3), 3.24 (m, 4H, CH_3CH_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^+). $^1\text{H-NMR}$ (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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