Synthesis of Purine Cyclonucleoside having 8,3'-O-Anhydro Linkage

Since the first purine cyclonucleoside has been reported, a number of purine nucleosides having 8,2''-(S- and O)-, 2''+ 8,5''-(S- and O)-, and 8,3''-S-O anhydro linkage were synthesized. However, the synthesis of a cyclonucleoside having 8,3'-O-anhydro linkage could not be performed, mainly because of the difficulty in the cyclization of 3'-tosylated 8-oxyadenosine presumably due to a large steric distortion. As the first 2,3'-cyclonucleoside has been synthesized in the pyrimidine deoxyribonucleoside, we attempted to synthesize 8,3'-anhydro-8-oxy-9-β-D-(2-deoxythreopentofuranosyl)adenine (I) starting from 2'-deoxyadenosine.

8-Bromo-2'-deoxyadenosine was converted to 5'-trityl derivative (III) (UV: $\lambda_{\text{max}}^{\text{UV}}$, 263 mμ, $\lambda_{\text{max}}^{\text{IR}}$, 265 mμ. IR: $\nu_{\text{max}}$ cm$^{-1}$: 1075 (sugar C-O-C), 700 (trityl). Paper chromatography: Rf (A) 0.84, Rf (B) 0.91, Rf (C) 0.90 in the yield of 78%.

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\begin{align*}
\text{NH}_2 & \quad \text{II} \quad \text{Br} \quad \text{TrCl} \quad \text{III} \quad \text{TsCl} \quad \text{IV} \\
\text{HOH}_2 & \quad \text{Br} \quad \text{III} \quad \text{TsOH}_2 \quad \text{IV} \\
\text{NH}_2 & \quad \text{I} \quad \text{H}^+ \quad \text{VI} \quad \text{AcONa/Ac}_2 \text{O} \\
\text{NH}_2 & \quad \text{V} \quad \text{AcONa/DMF} \quad \text{ii) NH}_3 \\
\end{align*}
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Chart 1.

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*1 A preliminary account of this study has been presented at the XXI International Congress IUPAC, 1967, Prague.
*2 All crystalline compounds appeared in this paper had the elemental analysis value satisfactorily in agreement with the theoretical one.
*3 Rf (A) stands for the Rf value in the solvent A. Solvent used were: A, n-BuOH-H$_2$O, 86:14; B, iso-PrOH-ammonium-H$_2$O, 7:1:2; C, n-BuOH-AcOH-H$_2$O, 5:2:3; D, n-PrOH-H$_2$O (pH 6.5), 3:1; E, EtOH-M NH$_2$OAc (pH 7.5), 7:3.

2) *Idem*: This Bulletin, 15, 94 (1967).
Compound III was then tosylated with 1.5 equivalents of tosyl chloride. 3'-O-Tosyl-5'-O-trityl-8-bromoadenosine (V) (Prisms from EtOH-dioxane, m.p. 176~177°C. UV: λ\text{max} 264, 272 (shoulder); λ\text{max}\text{H} 264 m\mu; λ\text{max}\text{H} 264 m\mu. IR: ν\text{max} 1570 (covalent tosylate), 1070 (sugar C-O-C), 700 (trityl). Paper chromatography: Rf (A) 0.87, Rf (B) 0.82, Rf (C) 0.89, thus obtained, was converted to 8-oxy derivative by the treatment with anhydrous sodium acetate in acetic anhydride, which was superior to acetic acid in preventing cleavage of the glycosidic linkage in 2'-deoxynucleoside. Resulting 8-oxy compound (V) (amorphous powder. UV: λ\text{max} 287 m\mu; λ\text{max}\text{H} 283 m\mu; λ\text{max}\text{H} 267 m\mu; 301 m\mu. IR ν\text{max} cm\text{⁻¹}: 1740~1745 (8-CO), 1700~1710 (acetamide), 1170 (covalent tosylate). Paper chromatography: Rf (A) 0.89, Rf (B) 0.83, Rf (C) 0.90 was finally subjected to cyclization by the treatment with sodium acetate in DMF. Heating for 1 hour, followed by the ammoniacal removal of N'-acetyl group, afforded a trityl-cyclonucleoside (V) (m.p. 266° from n-ProOH. UV: λ\text{max} 262 m\mu, λ\text{max}\text{H} 262 m\mu (ε 15400), λ\text{max}\text{H} 262 m\mu. IR ν\text{max} cm\text{⁻¹}: 700 (trityl), no covalent tosylate. Paper chromatography: Rf (A) 0.76, Rf (B) 0.70, Rf (C) 0.80, Rf (E) 0.63. Compound V was refluxed in 80% acetic acid for 15 min. and purified by cellulose column chromatography. Elution with solvent B gave crystalline cyclonucleoside (I) (m.p. 266.5~267°C. UV: λ\text{max} 262 m\mu (ε 14200), λ\text{max}\text{H} 263 m\mu (ε 14200), λ\text{max}\text{H} 263 m\mu (ε 14600). IR: no trityl was found. Paper chromatography: Rf (A) 0.25, Rf (B) 0.54, Rf (D) 0.62, Rf (E) 0.63. The ultraviolet absorption properties shifted slightly toward bathochromic region from those of 8-methoxyadenosine\textsuperscript{9} and elemental analysis data suggested the structure 8,3'-anhydro-8-oxy-9-β-d-(2-deoxythreopentofuranosyl)adenine for compound I. This structure was further supported by the optical rotatory dispersion study of I. As shown in Fig. 1, the optical rotatory dispersion (ORD) curve of I has a positive Cotton effect around 260 m\mu. This is in contrast to the natural purine nucleoside, which has negative Cotton effect in the major absorption region.\textsuperscript{11} The inversion of the Cotton effect could be ascribed to the rotation of base around the nucleosidic linkage and the fixation at certain angle by the anhydro linkage.\textsuperscript{12}

Fig. 1. Optical Dispersion Curve of 8,3'-Anhydro-8-oxy-9-β-d-(2-deoxythreopentofuranosyl)adenine

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