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Synthesis of Purine Cyclonucleoside having 8,3′-O-Anhydro Linkage*1

Since the first purine cyclonucleoside has been reported,1) a number of purine nucleosides having 8,2′-(S- and -O)-,2~4) 8,5′-(S- and -O)-,5,6) and 8,3′-S-2) 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.3) As the first 2,3′-cyclonucleoside has been synthesized in the pyrimidine deoxyribonucleoside,7) we attempted to synthesize 8,3′-anhydro-8-oxy-9-β-D-(2-deoxy*threo*pentofuranosyl)adenine (I) starting from 2′-deoxyadenosine.

8-Bromo-2′-deoxyadenosine8) was converted to 5′-trityl derivative*2 (III) (UV : $\lambda_{max}^{pH\,1}$ 263 mμ, λ_{max}^{EtOH} 265 mμ, $\lambda_{max}^{pH\,1}$ 265 mμ. IR : ν_{max}^{KBr} cm^{-1} : 1075 (sugar C-O-C), 700 (trityl). Paper chromatography : Rf (A)*3 0.84, Rf (B) 0.91, Rf (C) 0.90) in the yield of 78%.

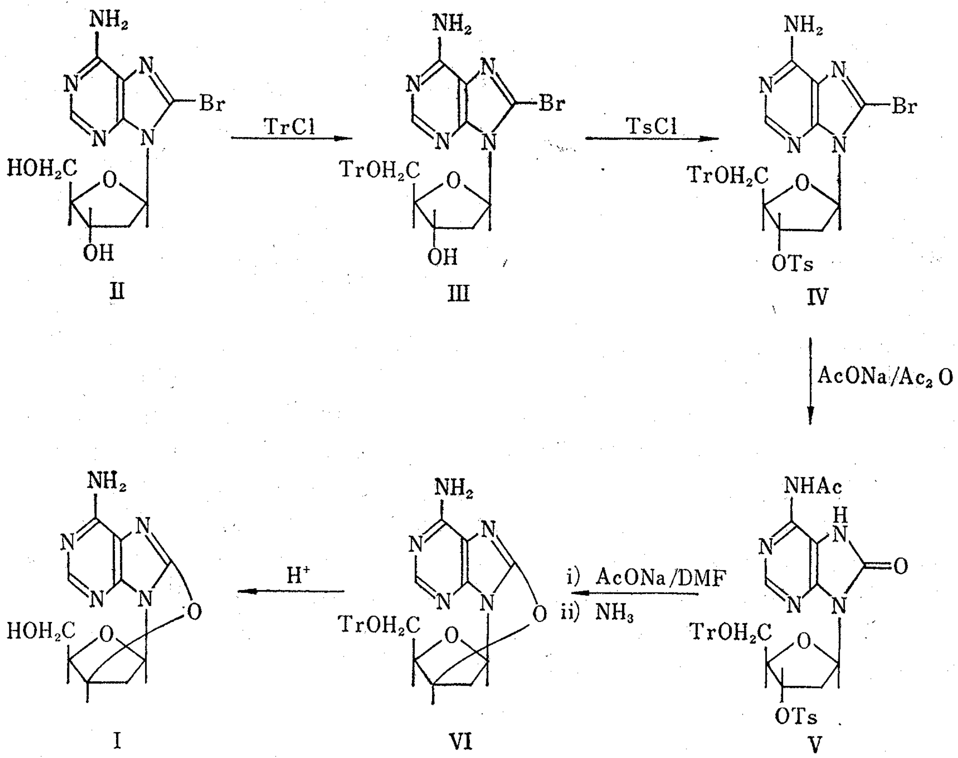

Chart 1.

[*1] A preliminary account of this study has been presented at the XXI International Congress IUPAC, 1967, Praha.

[*2] All crystalline compounds appeared in this paper had the elmental 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-ammonia-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$_4$OAc (pH 7.5), 7:3.

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Compound Ⅲ was then tosylated with 1.5 equivalents of tosyl chloride. 3′-O-Tosyl-5′-O-trityl-8-bromoadenosine (Ⅵ) (Prisms from EtOH-dioxane, m.p. 176~177°. UV : $\lambda_{\text{max}}^{\text{pH 1}}$ mμ : 264, 272 (shoulder); $\lambda_{\text{max}}^{\text{EtOH}}$ 264 mμ; $\lambda_{\text{max}}^{\text{pH 11}}$ 264 mμ. IR : $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 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 acid⁹⁾ in preventing cleavage of the glycosidic linkage in 2′-deoxynucleoside. Resulting 8-oxy compound (V) (amorphous powder. UV : $\lambda_{\text{max}}^{\text{pH 1}}$ 287 mμ; $\lambda_{\text{max}}^{\text{EtOH}}$ 283 mμ; $\lambda_{\text{max}}^{\text{pH 11}}$ 267 mμ; 301 mμ. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-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^6-acetyl group, afforded a trityl-cyclonucleoside (Ⅵ) (m.p. 266° from n-PrOH. UV : $\lambda_{\text{max}}^{\text{pH 1}}$ 264 mμ, $\lambda_{\text{max}}^{\text{EtOH}}$ 262 mμ (ε 15400), $\lambda_{\text{max}}^{\text{pH 11}}$ 262 mμ. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-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 Ⅵ 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°. UV : $\lambda_{\text{max}}^{\text{pH 1}}$ 262 mμ (ε 14200), $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 263 mμ (ε 14200), $\lambda_{\text{max}}^{\text{pH 11}}$ 263 mμ (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-methoxyadenosine¹⁰⁾ and elemental analysis data suggested the structure 8,3′-anhydro-8-oxy-9-β-D-(2-deoxy*threo*pentofuranosyl)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 mμ. This is in contrast to the natural purine nucleoside, which has negative Cotton effect in the major absorption region.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.¹²⁾

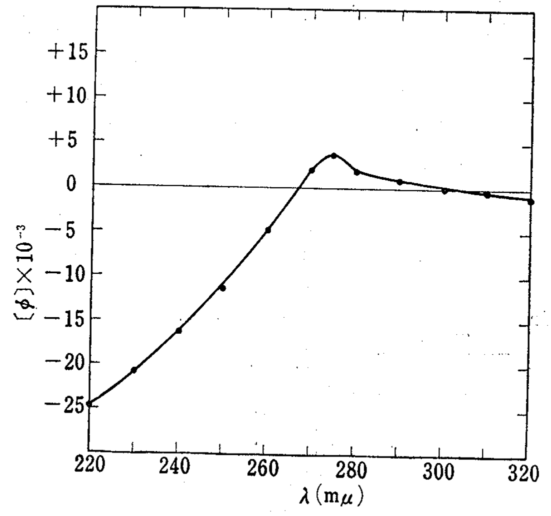

Fig. 1. Optical Dispersion Curve of 8,3′-Anhydro-8-oxy-9-β-D-(2-deoxy*threo*pentofuranosyl)adenine

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