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A NEW METHOD FOR THE SYNTHESIS OF 2'-SUBSTITUTED PURINE NUCLEOSIDES TOTAL SYNTHESIS OF AN ANTIBIOTIC 2'-AMINO-2'-DEOXYGUANOSINE

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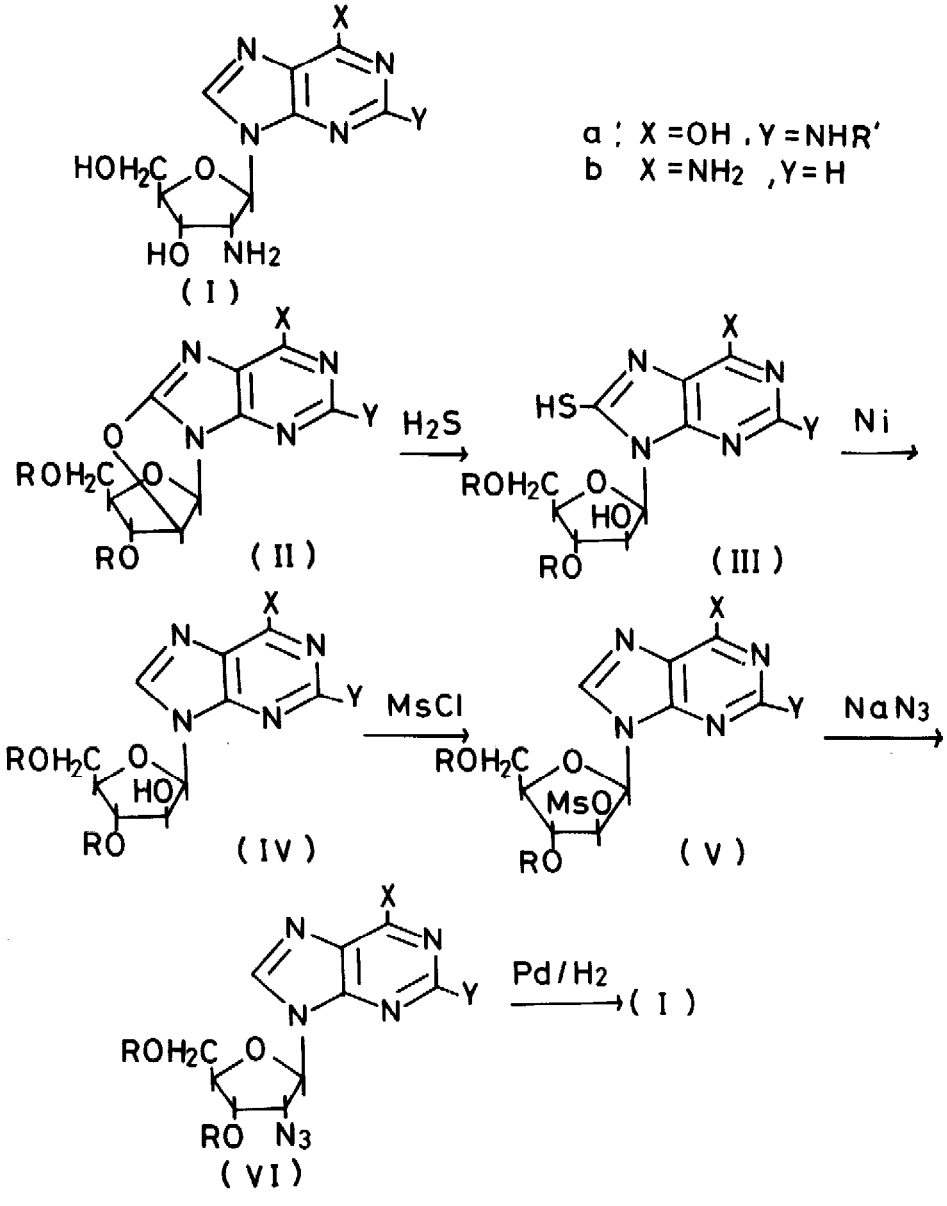
It is of considerable interest to synthesize aminonucleosides in relation to antibiotics such as puromycin.[1] Recently Nakanishi et al.[2] found an antibiotic (Ia, R'=H) having antibacterial and anticancer activities from the culture broth of Aerobacter sp. KY 3071 and elucidated its structure as 2'-amino-2'-deoxyguanosine, which is the first natural nucleoside having the 2'-amino-ribose structure. We attempted, therefore, to synthesize 2'-aminonucleosides starting from the naturally occurring adenosine and guanosine via cyclonucleosides.[3]

We first investigated the reaction of 2'-O-methanesulfonyl-9-β-D-arabinofuranosyladenine, which could be obtained from 8,2'-anhydro-8-oxy-9-β-D-arabinofuranosyladenine[4], with sodium azide in DMF. However, the reaction proceeded through 2',3'-riboepoxide as Robins et al.[5] reported and gave a xylosyl type compound. We then introduced non-participating tetrahydropyranyl groups to 8,2'-O-cycloadenosine (IIb, R=H) by the reaction with 2,3-dihydropyrane in the presence of p-tpluenesulfonic acid at 4° overnight. The compound IIb (R= tetrahydropyranyl) was obtained as crystals[6] of m.p. 184-186° in a yield of 59 %. IIb (R=Thp) was then heated with hydrogen sulfide in pyridine at 110° for 10 hrs as reported earlier.[7] 3',5'-D-O-tetrahydropyranyl-8-mercapto-9-β-D-arabinofuranosyladenine (IIIb, R=Thp) was obtained as amorphous powder, which was subjected to dethiolation reaction using Raney nickel as catalyst. After refluxing for 2 hrs UV absorption changed from λ_{max}^{EtOH} 305 nm to 260 nm. Di-O-

Tetrahydropyranyl-arabinosyladenine (IVb, R=Thp) was obtained as a caramel in an overall yield of 95% from IIb (R=Thp). The compound IVb (R=Thp) was then mesylated as usual to give 3',5'-di-O-tetrahydropyranyl-2'-O-mesylarabinosyl-adenine (Vb, R=Thp) in a yield of 71%. The structure of this compound was confirmed by UV ($\lambda_{max}^{50\%EtOH}$ 259 nm, λ_{max}^{pH2} 256 nm, λ_{max}^{pH12} 258 nm), IR (ν_{max}^{KBr} 1180 cm^{-1}) and mass spectrometry (M^+ =513). The compound Vb was then heated with sodium azide in DMF at 150° for 7.5 hrs. A compound (VIb, R=Thp) having UV ($\lambda_{max}^{50\%EtOH}$ 259 nm) and IR spectra (ν_{max}^{KBr} 2100 cm^{-1}) was obtained in a yield of 47%. Deprotection of this compound with acetic acid gave 2'-azido-2'-deoxyadenosine (VIb, R=H) having m.p. 221-222.5°[8] in a yield of 57%. The compound VIb (R=H) ahowed UV[$\lambda_{max}^{50\%EtOH}$ 259 nm (ε15,100), λ_{max}^{pH2} 257 (15,100), λ_{max}^{pH12} 259 (15,200)], IR (ν_{max}^{KBr} 2110 cm^{-1}) and PMR spectrum [δ 8.33 (s, 1H, h-8), 8.11 (s, 1H, H-2), 7.28 (br, 2H, N^6-H), 6.04 (d, 1H, H-1', $J_{1'-2'H}$=5.5 Hz), 5.97 (d, 1H, 3'-OH), 5.24 (t, 1H, 5'-OH), 4.60 (m, 2H, H-5', $J_{5'H-5'-OH}$=6.0 Hz)]. C^{13}-NMR spectroscopy showed that 2'-C signal shifted as large as 9 ppm relative to that of adenosine due to magnetic anisotropy of 2'-azido group. This sample showed the same Rf values [Rf(A)[9] 0.68, Rf(B) 0.83] with those reported by Mengel et al.[10] Finally, the compound VIb (R=H) was hydrogenated over palladium charcoal as catalyst to give 2'-amino-2'-deoxyadenosine (Ib), m.p. 197-198°, in a yield of 76%. Although this m.p. was higher by 6-7° than that of Mengel,[10] it was the same with that reported by Wolfrom[11]. The compound (Ib) showed UV absorption spectra [λ_{max}^{H2O} 259.5 nm (ε 14,800), λ_{max}^{pH2} 256.5 (14,900), λ_{max}^{pH12} 259.5 (14,600)] and Rf values [Rf(B) 0.57, Rf(C) 0.42], which were the same with a sample of Mengel.[10]

In order to synthesize 2'-amino-2'-deoxyguanosine, the same type of reactions were applied to 8,2'-anhydro-8-oxy-9-β-D-arabinofuranosylguanine[4](IIa, R=H). Thus the compound IIa(R=H) was transformed to 3',5',N^2-triacetyl-arabinofuanosylguanine (IVa, R=Ac) in an overall yield of 55%. This compound had m.p. 147-149° and the structure was elucidated from its UV ($\lambda_{max}^{50\%EtOH}$ 257, 294 nm) and NMR spectra. The compound IVa (R=Ac) was then mesylated to give compound Va (R=Ac) and the protecting groups were altered to the non-participating Thp group by a series of reactions. N^2,3',5'-Di-O-tetrahydropyranyl-2'-O-mesyl-

arabinofuranosylguanine (Va, R=Thp) was obtained in an overall yield of 36% and showed UV [$\lambda_{max}^{50\%EtOH}$ 255, 275(sh) nm] and IR bands (ν_{max}^{KBr} 1180 cm^{-1}) as expected. When the compound Va (R=Thp) was heated with sodium azide in acetamide at 210° for 10 min, a compound (VIa, R=Thp) having UV spectrum [$\lambda_{max}^{50\%EtOH}$ 252, 275(sh) nm; λ_{max}^{pH2} 256, 280(sh); λ_{max}^{pH12} 264] and IR bands (ν_{max}^{KBr} 2100 cm^{-1}) was obtained in a yield of 18%.



The compound VIa (R=Thp) was treated with acetic acid to remove Thp groups and 2'-azido-2'-deoxyguanosine (VIa, R=H) , m.p. 185-192° (decomp. at 230°), was obtained in ayield of 40%. The compound VIa (R=H) was then hydrogenated over palladium charcoal to give 2'-amino-2'-deoxyguanosine (Ia) as a crystalline compound having m.p. 250-252° in a yield of 65%. This sample showed UV spectrum [$\lambda_{max}^{H_2O}$ 252, 275(sh) nm; λ_{max}^{pH2} 256, 280(sh); λ_{max}^{pH12} 256, 268] and Rf values [Rf(B) 0.25, Rf(C) 0.28, Rf(D) 0.51], which were identical with an authentic sample of 2'-amino-2'-deoxyguanosine of Nakanishi et al.[2] Thus the structure of the antibiotic 2'-amino-2'-deoxyguanosine was synthetically confirmed.

The present method provides a new route to synthesize 2'-substituted purine nucleosides and a variety of their phosphates as well as polynucleotides are being synthesized in our laboratory.

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