Furanose–Pyranose Isomerization in a Synthesis of 8-Azapurine Nucleosides

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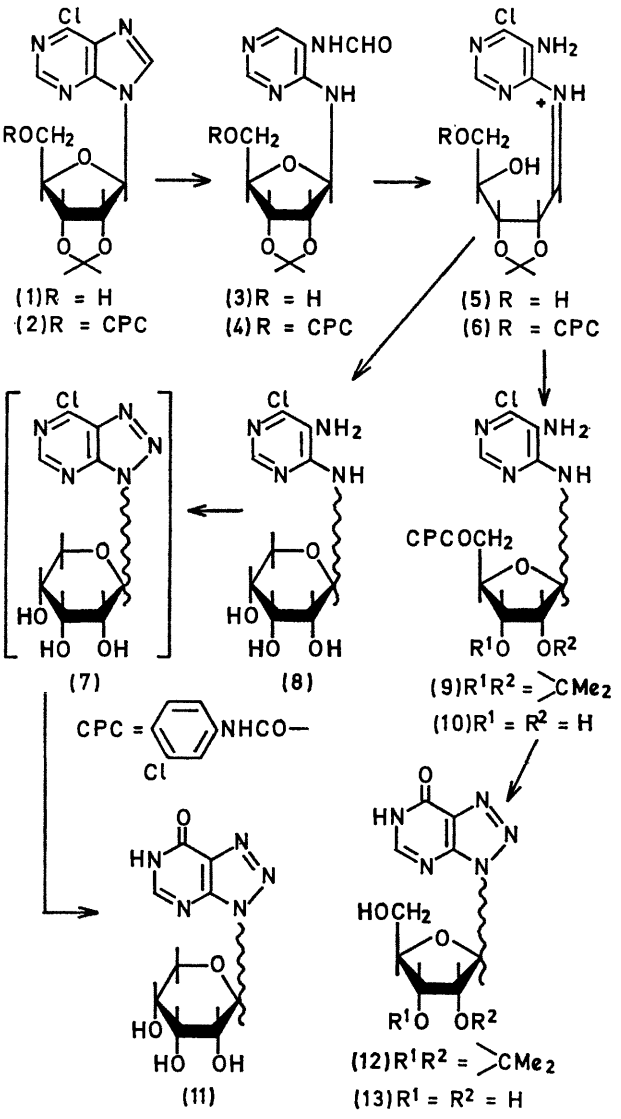
Summary The four isomeric 9-ribosyl derivatives of 8-azahypoxanthine have been prepared from 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine by ring opening and re-closure reactions.

THE synthesis of 8-azapurine (*v*-triazolo[4,5-*d*]pyrimidine) nucleosides from purine nucleosides by opening of the imidazole ring has the obvious advantage of being unambiguous with respect to the location of the sugar moiety. A solution of 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine (**1**) in 0·5 N-sodium hydroxide in dioxan–water (1 : 1) kept at room temperature for 45 min. gave a 67% yield of 4-chloro-5-formylamino-6-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)pyrimidine (**3**) and a 7·6% yield of 2′,3′-*O*-isopropylideneinosine. Selective hydrolysis of the formyl group by further treatment with base was not possible, but the amide linkage could be hydrolysed by treatment with methanolic hydrochloric acid under conditions that resulted, not in cleavage of the ribose moiety, but in isomerization of the ribofuranose to the ribopyranose ring.[1] The principal product was the β-D-ribopyranose (**8**) although a small amount of the α-anomer was also formed. The α- and β-ribopyranosylamino-pyrimidines (**8**) were not separated and identified as such but were converted, by treatment with sodium nitrite in aqueous acetic acid, into 9-D-ribopyranosyl-8-azahypoxanthine (**11**), resulting from nitrosation and ring closure to the 6-chloro-9-D-ribopyranosyl-8-azapurine (**7**), the chlorine of which is labile[2] and is hydrolysed under these conditions. The anomers of (**11**) were separated and identified on the basis of their ^{1}H n.m.r. spectra. The coupling constant of the C-1′ and C-2′ protons of the β-anomer, β-(**11**), is 9·5 Hz indicating that it exists in the N-conformation.[3,4] The coupling constant of the C-1′ and C-2′ protons of the α-anomer, α-(**11**), is 2·5 Hz. The C-1′ proton of α-(**11**) is downfield from the C-1′ proton of β-(**11**) supporting, but not establishing the N-conformation for α-(**11**).[5]

If the 5′-hydroxyl of (**1**) is blocked by a group stable to both the acid and base treatment described above, isomerization to the pyranose sugar can be prevented. Reaction of 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine (**1**) with *m*-chlorophenyl isocyanate gave 6-chloro-9-[5-*O*-(*m*-chlorophenylcarbamoyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl]purine (**2**), which on treatment with base underwent imidazole ring cleavage to give a 45% yield of 4-chloro-6-[5-*O*-(*m*-chlorophenylcarbamoyl)-2,3-*O*-isopropylidene-β-D-ribofuranosylamino]-5-formylaminopyrimidine (**4**). Treatment of (**4**) with methanolic hydrochloric acid gave four products: 5-amino-4-chloro-6-[5-*O*-(*m*-chlorophenylcarbamoyl)-α- and -β-D-ribofuranosylamino]pyrimidine (**10**) and their 2,3-*O*-isopropylidene derivatives (**9**). Treatment of (**10**) with sodium nitrite in aqueous acetic acid followed by methanolic sodium methoxide gave 8-azainosine β-(**13**) and its α-anomer, α-(**13**). In the same way (**9**) was converted into the isopropylidene derivatives (**12**) of (**13**). Acid hydrolysis of (**12**) to 8-azainosine, β-(**13**) and its α-anomer, α-(**13**) confirmed their identity. Thus, by the correct selection and use of blocking groups all four isomeric 9-ribosyl derivatives of 8-azahypoxanthine have been prepared.



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[1] This reaction is similar to the first step in the acid catalysed hydrolysis of *N*-arylglycosylamines; B. Capon, and B. E. Connett, *Tetrahedron Letters*, 1964, 1395.

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