# The Synthesis of the Nucleoside from Factor G: Simultaneous Formation of Anomeric Purine Nucleosides from an Acyglycosyl Halide (1)

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*Sir:*

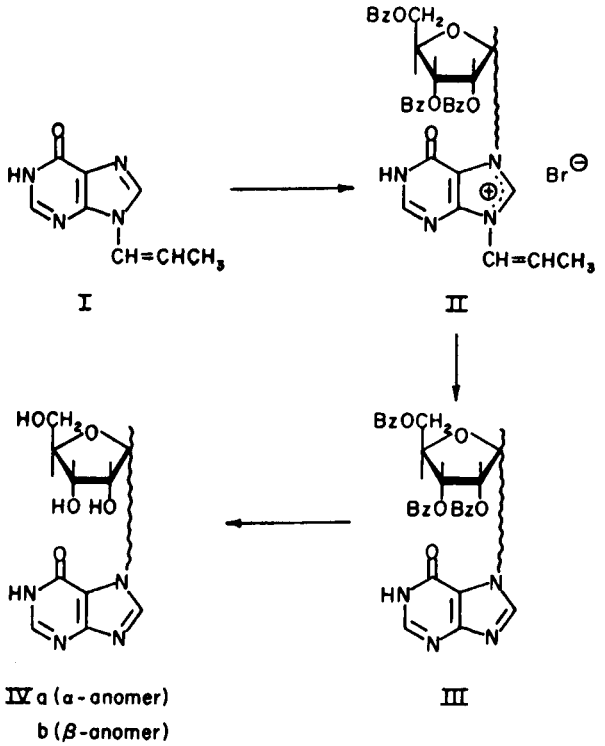
The identity of the nucleoside from pseudovitamin $B_{12}$ (2) has been established as 7-α-D-ribofuranosyladenine by synthesis (3). This synthesis involved the mercuri coupling of *N*-benzoyl-3-benzyladenine with 5-benzoyl-D-ribofuranosyl chloride 2,3-cyclic carbonate (4), followed by removal of the blocking groups. By using the 2,3-cyclic carbonate, participation of the group at C-2 (5) in the coupling reaction was avoided and both α- and β-anomers were formed. Separation of the anomers was achieved by column chromatography. Pseudovitamin $B_{12}$ has been converted to Factor G by nitrous acid deamination of its purine moiety, and Factor G has been hydrolyzed in acid to give hypoxanthine (6). These facts indicate that the nucleoside in Factor G is 7-α-D-ribofuranosylhypoxanthine (IVa). We have reported the synthesis of 7-β-D-ribofuranosylhypoxanthine (IVb) from the chloromercuri derivative of 3-benzylhypoxanthine and tri-*O*-acetylribofuranosyl chloride as described above for the adenine nucleosides (7). We now wish to report the synthesis of the nucleoside from Factor G (IVa), as well as IVb, by an entirely different, simpler route. 9-Propenylhypoxanthine (I) (8) was allowed to react with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in DMF for 4.5 days at room temperature. The propenyl group of the betaine II was removed by permanganate oxidation under neutral conditions (8) at room temperature to give 7-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)hypoxanthine (III), which was purified by chromatography on a column of SilicAR TLC-7 and then debenzoylated with methanolic sodium methoxide. The pmr spectrum of the resultant nucleoside (IV) revealed that it was an approximately 1:1 mixture of α- and β-anomers (36% yield from II). Separation of the anomers was achieved by chromatography on a cellulose column. The β-anomer (IVb) was identified by comparison with the sample previously prepared (7). The identity of the α-anomer (IVa) was confirmed by elemental analyses, optical rotation, and its pmr spectrum, since the signal due to the C-1′ proton occurs downfield from the C-1′ proton of the β-anomer (3, 9, 10): $[\alpha]_D^{25}$ -78.1 ± 0.3 (c 0.99 in water); λ max in mμ (ε x $10^{-3}$): 0.1 *N* hydrochloric acid, 252 (9.23), *p*H 7 buffer, 257 (8.47), 0.1 *N* sodium hydroxide, 263 (8.83); $\bar{\nu}$ in $cm^{-1}$: 3370 (OH); 1685 (C = O); 1590, 1535, and 1500 (C = C, C = N); δ in ppm: 3.57 m ($C_5$,H), 4.20 m ($C_2$′, $C_3$′, $C_4$′H), 5.37 m (OH, NH), 6.66 d ($C_1$′H, $J_{1'2'}$ 4.4), 8.00 and 8.39 ($C_8$H and $C_2$H).

*Anal.* Calcd. for $C_{10}H_{12}N_4O_5$: C, 44.79; H, 4.51; N, 20.90. Found: C, 45.04; H, 4.67; N, 20.98.

β-Anomer (IVb) λ max: *p*H 1, 252, *p*H 7, 257, *p*H 13, 263; δ in ppm: 3.68 m ($C_5$,H), 4.00 m and 4.38 m ($C_2$′, $C_3$′, $C_4$′H), 6.23 d ($C_1$′H, $J_{1'2'}$ 4.3), 8.03 and 8.60 ($C_8$H and $C_2$H).

This anomeric pair presents yet another exception to Hudson's rules. It is interesting that the 7-D-ribofuranosyladenines obey Hudson's rules, whereas the 7-D-ribofuranosylguanines (10), like the hypoxanthines, do not.

The formation of equal quantities of the α- and β-



anomers of a glycosylpurine from the reaction of a purine with a glycosyl halide containing a participating acyloxy group at C-2 has not been previously reported. The first step of the reaction described herein is attachment of C-1 of the sugar to a tertiary nitrogen (N-7 of I). It could be that under the conditions employed (4.5 days at room temperature) with this relatively poor nucleophile, a $C_1$-$C_5$ orthoester ion intervenes in the reaction of the α-ribosyl bromide (11) just as the $C_1$-$C_2$ orthoester ion intervenes in the reaction of the β-ribosyl bromide (5). Thus the anomeric mixture of ribosyl bromides employed in this reaction would give an anomeric mixture of nucleosides, α from α and β from β. Alternatively, the α-bromide could undergo nucleophilic attack by I to form the β-anomer IVb, and the β-bromide could form the orthoester ion as has been postulated but, instead of being attacked at C-1 of the furanose ring, it might suffer attack at C-2 of the dioxalane ring to give a transient 1,2-orthoacetyl hypoxanthinium bromide, which undergoes rearrangement to the α-anomer IVa (12). Work has been initiated to distinguish between these two possible mechanisms. This reaction is obviously closely related to the Hilbert-Johnson synthesis of pyrimidine nucleosides which is known to give under certain conditions both α- and β-ribonucleosides (13).

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