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GLYCOSYLATION REACTIONS OF 6-NITRO-1,3-DIDEAZAPURINE AND 6-NITRO-1-DEAZAPURINE †

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SUMMARY: In glycosylations utilizing $SnCl_4$ activation or S_N2 displacement of the α-chlorosugar, two closely related purines, namely 6-nitro-1,3-dideazapurine **1** and 6-nitro-1-deazapurine **2**, give different distributions of isomeric products.

Glycosylation of 6-nitro-1-deazapurine **2** (Figure 1) with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (TAR) **3** and 1-chloro-2-deoxy-3,5-di(p-toluyl)-D-*erythro*-pentofuranose **9** (Figure 2) are important because catalytic hydrogenation can directly yield 1-deazaadenosine and 2′-deoxy-1-deazaadenosine, respectively.[1-4] The former has been shown to be an antitumor agent,[1] an adenosine receptor antagonist,[2] an inhibitor of adenosine deaminase[3] and blood platelet aggregation.[4] In our studies of unusual DNA and RNA structures, we became interested in 1,3-dideazaadenosine and 1-deazaadenosine because they lack the nitrogens necessary to form Watson-Crick hydrogen bonds but can still participate in Hoogsteen hydrogen bonding.

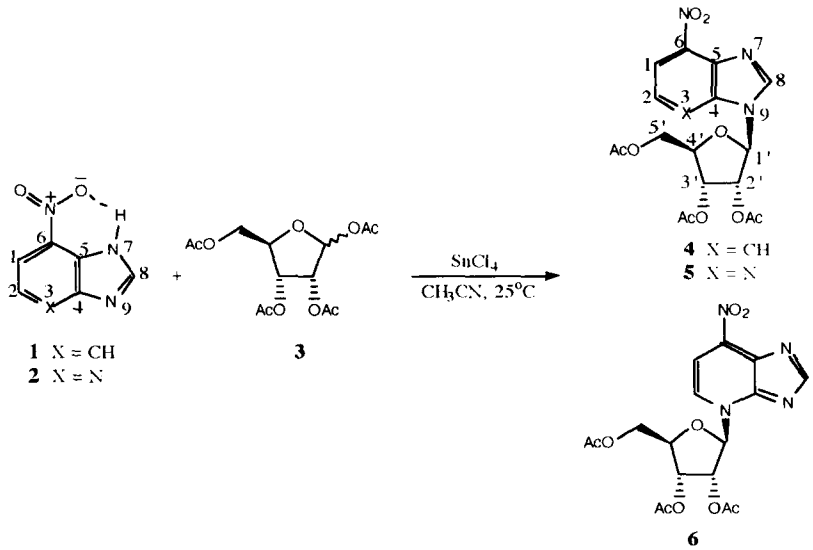

Figure 1: Glycosylation of **1** and **2** with TAR

Table 1 summarizes the results of the glycosylations of **1** and **2** with TAR, using the traditional $SnCl_4$ activation in acetonitrile (Figure 1).[5] As expected, in both glycosylations, participation by the neighboring 2′-acetyloxy group excluded the formation of α-anomers. In addition, we have argued[6] that, due to the steric and electron withdrawing effects of the 6-NO_2 group and the existence of **1** in its intramolecularly hydrogen bonded form,[7] the N-9 nitrogen will be more nucleophilic than the N-7. Thus, as predicted, glycosylation of **1** gave exclusively the N-9 β-isomer **4**.[6]

Purine	Reaction Time	% yield		
		9-β	7-β	3-β
1	16 h	86	0	---
2	2.5 h	50.6	0	39.4
2	16 h	60.1	0	26.9

Table 1: Isomeric distribution in the $SnCl_4$ catalyzed glycosylation reactions of **1** and **2** with TAR

Contrary to a previous report,[1] however, glycosylation of **2** gave a mixture of two isomers. In addition, the product distribution was also found to depend on the reaction time (Table 1). While the ^{1}H-NMR data of the major isomer was identical to that reported[1] for the N-9 β-anomer, for the reasons described below, we believe the minor product is the N-3 β-isomer **6** and not the N-7 β-isomer: (i) As with **1**,[6,7] the steric and electron withdrawing effects of the 6-NO_2 group and the existence of the intramolecularly hydrogen bonded form, should exclude the formation of the N-7 β-isomer from **2**. (ii) The H-1′ and H-8 signals of the minor isomer were not shifted downfield as compared to the corresponding proton signals of the major N-9 β-isomer.[8] In all examples reported to date,[9] this particular ^{1}H-NMR trend has been reliable in distinguishing between the N-7 and N-9 β-isomers, including the N-7 and N-9 β-isomers obtained from **1**.[6] (iii) Since the lone pair on N-3 is never involved in aromatic resonance, it should be more nucleophilic than the N-9 nitrogen. Thus, the N-3 β-isomer **6** should be the kinetic product. However, it is less stable than the N-9 β-isomer **5**, as glycosylation through N-3 disrupts aromaticity on both rings. Therefore, with time, **6** can equilibrate to the thermodynamically favored N-9 β-isomer **5**. A similar time dependent rearrangement has been reported for 1-deazapurine, the purine that lacks the 6-NO_2 group, when glycosylation was performed under the same reaction conditions.[10]

The purines **1** and **2** also behave differently in the sodium salt glycosylations (Figure 2). Whereas **1** yielded a mixture of products (Table 2), glycosylation of **2** was essentially regio- and stereo-specific giving only the N-9 β-isomer **11**.[11] The pseudo triplet nature of the H-1′ signals in ^{1}H-NMR allowed us to assign β-configuration for compounds **10**, **11**, and **12**.[9a] Furthermore, the H-1′ proton of **13** had a doublet of doublet pattern expected for the α-anomer.[9a, 12] In the reactions of purine **1**, the regioisomers were assigned based on the downfield shifts of the H-1′ and H-8 protons of **10** relative to **12**.[9a] Additional support was also obtained through NOE experiments. Whereas irradiation of the H-1′ and H-3′ protons of the sugar gave an NOE of 3.5% and 2.0%, respectively, for the H-3 of **10**, there was no detectable enhancement for H-3 upon irradiation of any of the sugar protons in **12**.

The foregoing results on the sodium salt glycosylations may be rationalized as follows. When the negative charge is on the N-7 nitrogen, it can be effectively stabilized via the mesomeric effect of the 6-NO_2 group. As a result, it will be less nucleophilic than the N-9 anion and, hence, the predominant formation of the N-9 β-isomers (**10** and **11**) in both glycosylations. The competition from the N-7 β-isomer **12** is presumably due to steric hindrance exerted by the H-3 hydrogen of **1**, which sufficiently slows down the reaction at N-9. This theory is supported by the fomation of a small amount of the N-9 α-isomer **13**; with slow reacting bases, the α-chlorosugar is known to anomerize to the more reactive β-chloro derivative, thereby leading to the formation of some α-isomers.[9a] The exclusive formation of the N-9 β-isomer **11**, during the sodium salt glycosylation of **2**, also provides further support for this rationale.

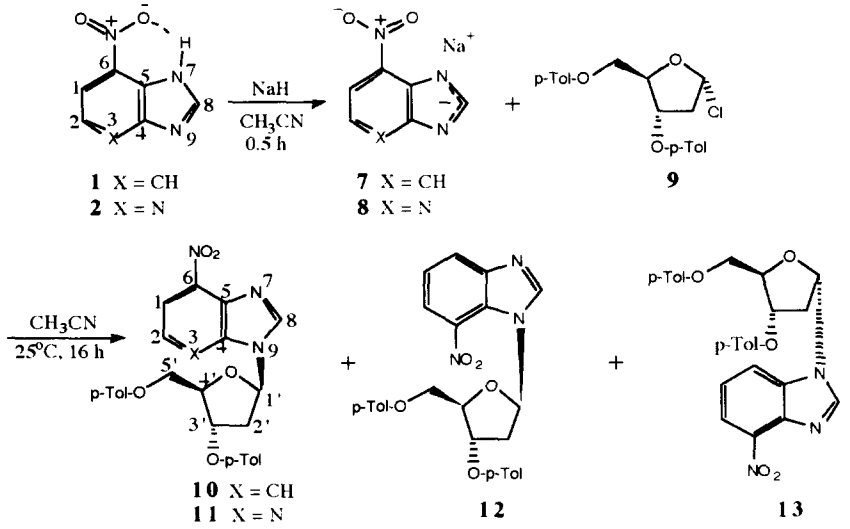

Figure 2: Sodium salt glycosylation of **1** and **2** with 1-chloro-2-deoxy-3,5-di(p-toluyl)-D-*erythro*-pentofuranose

Purine	% yield		
	9-β	7-β	9-α
1	62	10	trace
2	86	0	0

Table 2: Isomeric distribution in the sodium salt glycosylation reactions of **1** and **2**

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REFERENCES AND NOTES

† The numbering scheme of adenosine, as outlined in Figure 1 and 2, has been used throughout this manuscript.

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8. ^{1}H-NMR data for **5** (300 MHz, $CDCl_3$): δ 2.02, 2.05, 2.14 (CH_3, s), 4.24 - 4.35 (H-5′ and H-5″, m), 4.39 - 4.48 (H-4′, m), 5.67 (H-3′, pseudo t, J = 5.4 Hz), 6.08 (H-2′, pseudo t, J = 5.6 Hz), 6.46 (H-1′, d, J = 5.1 Hz), 8.08 (H-2, d, J = 5.3 Hz), 8.74 (H-1, d, J =5.4 Hz), 9.04 (H-8, s). ^{1}H-NMR data for **6** (300 MHz, $CDCl_3$): δ 2.03, 2.07, 2.10 (CH_3, s), 4.38 - 4.48 (H-5′, m), 4.88 -4.95 (H-4′, m), 5.48 (H-3′, pseudo t, J = 4.7), 5.78 (H-2′, pseudo t, J = 5.5), 6.92 (H-1′, d, J = 5.4), 8.05 (H-2, d, J = 5.4), 8.70 (H-1, d, J = 5.3), 8.99 (H-8, s).
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11. All new compounds gave consistent spectral and analytical data. Selected NMR data for new compounds:
10. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.39, 2.42 (CH_3-, s), 2.84-3.04 (H-2′ and H-2″, m), 4.60-4.70 (H-5′and H-5″, m), 4.72-4.81 (H-4′, m), 5.75 -5.81 (H-3′, m), 6.46 (H-1′, pseudo t, J = 5.69 Hz), 7.17 (H-2, pseudo t, J = 8.1 Hz), 7.20 (p-Tol, d, J = 8.07), 7.26 (p-Tol, d, J = 8.07 Hz), 7.82 (p-Tol, d, J = 8.31 Hz), 7.90 (H-3, d, J = 7.76 Hz), 7.96 (p-Tol, d, J = 8.31 Hz), 8.04 (H-1, d, J = 7.53 Hz), 8.35 (H-8, s). ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 21.44, 21.51, 37.95, 63.39, 74.17, 82.70, 85.61, 117.44, 119.55, 122.31, 125.95, 126.13, 129.11, 129.24, 129.54, 135.04, 137.35, 139.03, 143.51, 144.15, 144.44, 165.75.
11. ^{1}H-NMR (300 MHz, d_6-DMSO): δ 2.37, 2.42 (CH_3, s), 2.86 (H-2′, ddd, J = 14.1 Hz, J = 6.4 Hz, J = 2.9 Hz), 3.42 (H-2″, pseudo quintet, J = 6.8 Hz), 4.54 - 4.70 (H-4′, H-5′, H-5″, m), 5.85 - 5.87 (H-3′, m), 6.75 (H-1′, pseudo t, J = 6.9 Hz), 7.28 (p-Tol, d, J = 7.9 Hz), 7.38 (p-Tol, d, J = 7.9 Hz), 7.82 (p-Tol, d, J = 8.3 Hz), 7.96 (p-Tol, d, J = 8.3 Hz), 8.03 (H-2, d, J=5.3 Hz), 8.63 (H-1, d, J=5.3 Hz), 9.03 (H-8, s).
12. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.38, 2.43 (CH_3, s), 2.69 (H-2′, pseudo quintet, J = 6.9 Hz), 3.00 (H-2″, ddd, J = 14.08 Hz, J = 5.61 Hz, J = 3.15 Hz), 4.59-4.71 (H-4′, H-5′, H-5″, m), 5.59-5.66 (H-3′, m), 6.79 (H-1′, pseudo t, J = 5.67 Hz), 7.17 (p-Tol, d, J = 7.97 Hz), 7.28 (p-Tol, d, J = 7.97 Hz), 7.35 (H-2, pseudo t, J = 8.07 Hz), 7.81 (p-Tol, d, J = 8.25 Hz), 7.96 (p-Tol, d, J = 8.25 Hz), 8.02 (H-3, d, J = 8.58 Hz), 8.08 (H-1, d, J = 8.01 Hz), 8.52 (H-8, s). ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 21.60, 21.67, 40.32, 63.69, 74.10, 82.76, 88.24, 121.09, 121.75, 124.96, 126.16, 126.34, 127.35, 129.21, 129.48, 129.76, 136.16, 142.92, 144.12, 144.47, 147.59, 165.96.
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