

## SYNTHESIS OF A PYRIDO[1,2-*a*]PURINE NUCLEOSIDE BY A NOVEL RING CLEAVAGE-ANNULATION REACTION OF 3- $\beta$ -D-RIBOFURANOSYLIMIDAZO-[4,5-*d*]- $\gamma$ -TRIAZIN-4-ONE

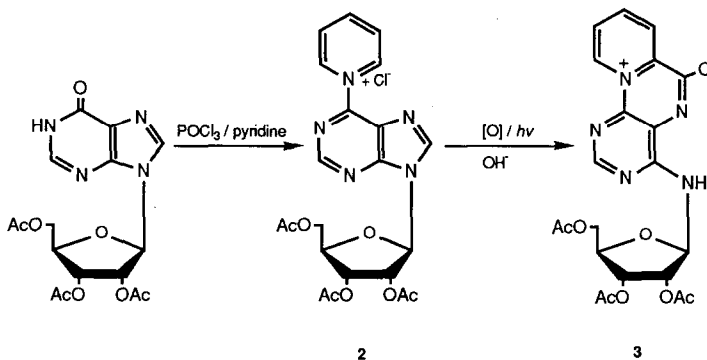
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**Abstract:** Treatment of 7-(2,3,5-tris-*O*-(*t*-butyldimethylsilyl)- $\beta$ -D-ribofuranosyl)imidazo[4,5-*d*]- $\gamma$ -triazin-4-one (**1**) with  $MnO_2$  in hot pyridine furnished 7-(2,3,5-tris-*O*-(*t*-butyldimethylsilyl)- $\beta$ -D-ribofuranosyl)pyrido[1,2-*a*]purine (**4**). Treatment of **4** with tetra-*n*-butylammonium fluoride furnished the free nucleoside **5**.

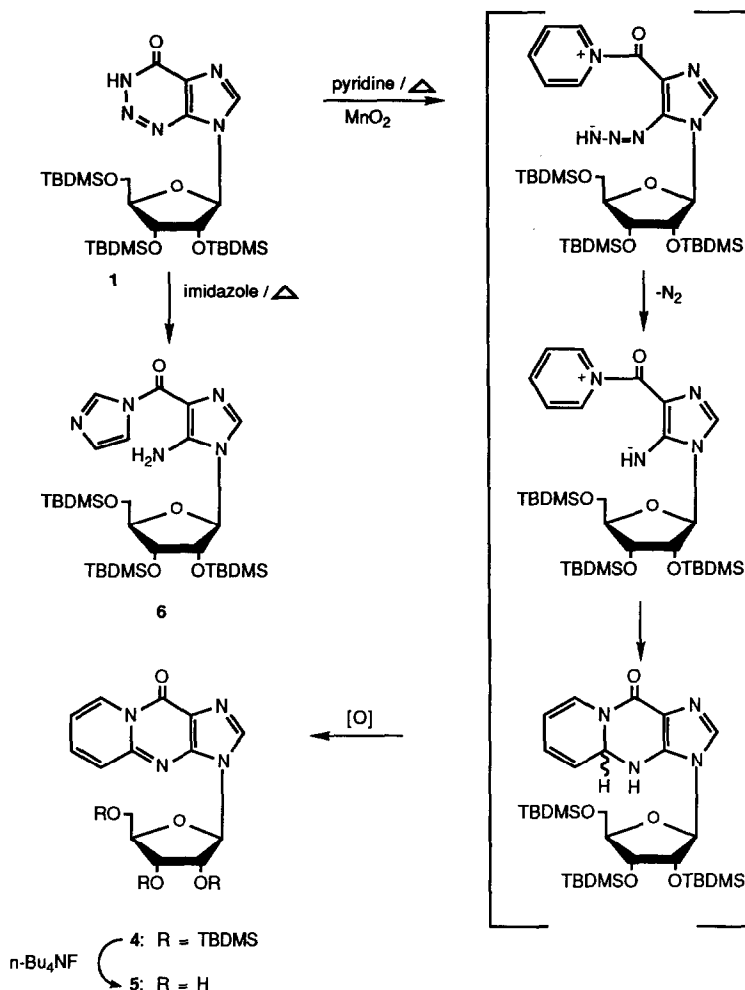
Tricyclic nucleosides are of current interest<sup>1-3</sup> not only for their biological activity, but also because many tricyclic nucleosides are fluorescent, and can serve as useful probes of biological processes. Additionally, several imidazo[1,2-*a*]purines ("Y" bases) have been found to occur in tRNA from several sources,<sup>4,5</sup> and pyrimido-[1,2-*a*]purines are thought<sup>6</sup> to be formed by the action of certain mutagens on the guanine bearing bases of DNA and RNA. This report describes the isolation and characterization of a novel pyrido[1,2-*a*]purine nucleoside.

During our attempts<sup>7</sup> to prepare 4-amino-7-( $\beta$ -D-ribofuranosyl)imidazo[4,5-*d*]- $\gamma$ -triazine (2-azaadenosine) from 7-(2,3,5-tris-*O*-(*t*-butyldimethylsilyl)- $\beta$ -D-ribofuranosyl)imidazo[4,5-*d*]- $\gamma$ -triazin-4-one (**1**), we observed the formation of a fluorescent side product (**4**). This observation was not entirely unexpected, since a reaction of



the tri-acetate of inosine with phosphorous oxychloride in pyridine had been reported<sup>8</sup> to furnish the 4-pyridinium salt **2**, and air oxidation of **2** provided the fluorescent tricyclic betaine nucleoside **3**. However, upon isolation, de-blocking and characterization, our fluorescent product (**4**) was found to be different from the previously described betaine **3**. In order to fully characterize this product, the silyl protecting groups were removed with tetra-*n*-butylammonium fluoride to obtain the deprotected nucleoside. This nucleoside was examined by  $^1H$  NMR,  $^{13}C$

NMR, IR, mass spectroscopy, and elemental analysis which allowed us to assign the structure of 3-( $\beta$ -D-ribofuranosyl)pyrido[1,2-a]purin-10-one (5) to our fluorescent nucleoside. To the best of our knowledge, this novel ring system has not been reported previously.



Our structural assignment for 5 was based on the observation of four new peaks in the aromatic region of the proton NMR spectrum which through analysis of the coupling patterns were assigned to lie contiguously on an aromatic ring. The most de-shielded proton in the  $^1\text{H}$  NMR spectrum was assigned to the C-8 position. The proximity of this proton to a carbonyl moiety was consistent with the observation of a three-bond coupling of this proton with a carbon atom having the furthest downfield absorption in the  $^{13}\text{C}$  spectrum, which in turn was

assigned as the carbonyl carbon, C-10. The other three-bond proton-carbon couplings in the  $^{13}\text{C}$  spectrum were consistent with the assigned structure, as were the proton-proton coupling patterns. Several mechanisms for the formation of this compound were considered. The one chosen to be the most likely involved a nucleophilic attack by the pyridine nitrogen lone pair at the carbonyl group of **1**, with a concomitant cleavage of the triazine ring between N-3 and C-4 to form a charged pyridinium moiety as well as a triazene moiety. Following the expulsion of molecular nitrogen from the newly formed triazene moiety, the attack of the nascent amino group on the pyridinium group would form a dihydro intermediate which could be air oxidized to afford the product. Indeed, heating **1** in pyridine at reflux, in the presence or absence of phosphorous oxychloride only afforded traces of **4**, while the reaction in the presence of manganese dioxide afforded **4** in a much improved yield. These results suggested that an oxidation step is involved in the reaction mechanism and that the presence of phosphorous oxychloride is superfluous.

Ring cleavage of the triazine ring of 3-( $\beta$ -D-ribofuranosyl)imidazo[4,5-d]- $\gamma$ -triazin-4-one has been reported<sup>10</sup> to occur upon treatment of the nucleoside with Raney nickel. However, in this case, the cleavage occurred at the 2,3-bond and not at the 3,4-bond as we propose here. The most closely related reaction, of which we are aware, is the formation of  $\gamma$ -triazolo[4,5-b]pyridines from the treatment of  $\gamma$ -triazolo[4,5-d]pyrimidines with malononitrile and or other reagents containing strongly activated methylene groups.<sup>11</sup> In this latter case, the reaction takes place with a fission of the pyrimidine ring and the subsequent annulation of the freed amino group with the attacking reagent. This is reminiscent of the mechanism which we have set forth here. To examine the scope of this reaction, **1** was heated in toluene at reflux with manganese dioxide and imidazole, but TLC analysis of this reaction did not identify any significant formation of products. In contrast, when **1** was mixed with imidazole and the mixture was heated to ca.  $130^\circ$ , evolution of a gas was noted, and the imidazoylcarbonyl-imidazole **6** was formed in good yield<sup>9</sup> (Scheme 2). Evidently ring closure was not favored when there is no positive charge formed on the attacking heterocycle. Preliminary experiments using 1,2,4-triazole instead of imidazole in this reaction would suggest that the formation of a corresponding triazoylcarbonylimidazole nucleoside is also possible, and we are exploring the applicability of this reaction to the synthesis of a variety of fused tricyclic nucleosides.

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8. **5**, mp 222-223°, <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.39 (ddd, 1H, H-8, J<sub>7,8</sub> = 7.3 Hz, J<sub>6,8</sub> = 0.8 Hz, J<sub>5,8</sub> = 0.8 Hz); 8.49 (s, 1H, H-2); 7.86 (ddd, 1H, H-6, J<sub>5,6</sub> = 9.0 Hz, J<sub>6,7</sub> = 6.3 Hz); 7.64 (ddd, 1H, H-5, J<sub>5,7</sub> = 1.4 Hz); 7.23 (ddd, 1H, H-7) 5.99 (d, 1H, H-1', J<sub>1',2'</sub> = 6.1 Hz); 5.49 (d, 1H, 2'-OH); 5.23 (d, 1H, 3'-OH); 5.18 (t, 1H, 5'-OH); 4.57 (m, 1H, H-2'); 4.16 (m, 1H, H-3'); 3.97 (dd, 1H, H-4'); 3.70-3.57(2m, 2H, H-5'ab); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>): δ 152.37 (s, C-10); 148.60 (s, C-3a); 148.31 (s, C-4a); 140.53 (d, C-2); 135.69 (d, C-6); 127.40 (d, C-8); 124.81 (d, C-5); 117.79 (s, C-10a); 113.84 (d, C-7); 87.19 (d, C-1'); 85.81 (d, m, C-4'); 74.01 (d, C-2'); 70.61 (d, C-3'); 61.53 (t, C-5'); UV λ<sub>max</sub> nm (log ε): methanol 343 (3.99), 336 (4.00), 249 (4.23); pH 1, 335 (4.11), 323 (4.12), 243 (4.27), 227 (4.33); pH 11 339 (4.05), 247 (4.25), 229 (4.32); Abs. (methanol) λ<sub>max</sub> nm. 264, 277, 365; Em. λ<sub>max</sub> nm. 422; IR(KBr) 3459, 3343, 3308, 3109, 3099, 3063, 3020, 2944, 2928, 2905, 2875, 1709, 1643, 1576, 1540, 1533, 1490, 1411, 1384, 1321, 1228, 1136, 1086, 1061, 1022, 855, 766, 635 cm<sup>-1</sup>; TLC: R<sub>f</sub> = 0.12 ethyl acetate/methanol (9:1, v:v); Anal. Calcd. for C<sub>14</sub>H<sub>14</sub>N<sub>4</sub>O<sub>5</sub>: C, 52.83; H, 4.43; N, 17.60. Found: C, 53.02; H, 4.52; N, 17.55.
9. **6**, mp 139-140 °C <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.89 (dd, 1H, H-2'', J<sub>2'',5''</sub> = 1.0 Hz, J<sub>2'',4''</sub> = 0.8 Hz); 8.05 (dd, 1H, H-4'', J<sub>4'',5''</sub> = 1.7 Hz); 7.58 (s, 1H, H-2); 7.11 (bs, 2H, NH<sub>2</sub>); 7.03 (dd, 1H, H-4''); 5.72 (d, 1H, H-1', J<sub>1',2'</sub> = 7.2 Hz); 4.47 (dd, 1H, H-2'); 4.13 (dd, 1H, H-3'); 3.02 (m, 1H, H-4'); 3.80-3.70 (2m, 1H, H-5'ab); 0.92, 0.91, 0.79 (3s, 27H, tBu); 0.11, -0.05, -0.24 (3s, 18H, Si Me); UV λ<sub>max</sub> nm (log ε): methanol 315 (4.25); pH 1 321 (4.15); pH 11 316 (4.31), 227 (4.12); IR(KBr) 3434, 3325, 2954, 2931, 2860, 1655, 1620, 1543, 1472, 1454, 1406, 1260, 1232, 1163, 1107, 1068, 964, 936, 898, 872, 837, 779, 652; TLC: R<sub>f</sub> = 0.39 chloroform/methanol (16:1, v:v); Anal. Calcd. for C<sub>30</sub>H<sub>57</sub>N<sub>5</sub>O<sub>5</sub>Si<sub>3</sub>: C, 55.26; H, 8.80; N, 10.74. Found: C, 55.15; H, 8.66; N, 10.72.
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