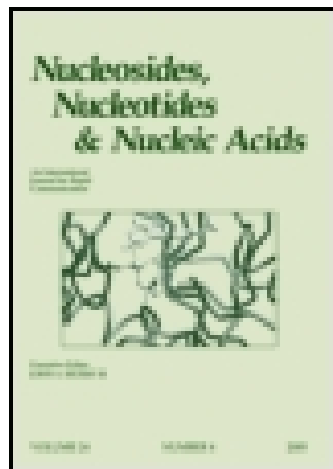


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Najim A. Al-Masoudi <sup>a</sup> & Ali A. Al-Atoom <sup>a</sup>

<sup>a</sup> Department of Chemistry , College of Science University of Basrah , Basrah, Iraq

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## SYNTHESIS AND REACTIONS OF SOME GLYCOSYLAMINE DERIVATIVES OF 6-AZAUACIL NUCLEOSIDES

Najim A. Al-Masoudi\* and Ali A. Al-Atoom

Department of Chemistry, College of Science, University of Basrah, Basrah, Iraq.

**Abstract.** Reaction of the silylated 6-azauracil (2) with 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-glucose (3) gave 1-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl)-6-azauracil (4), which gave the free nucleoside 5 on deblocking. Acetalation of 5 gave the monoacetal 6 which was oxidized into the ketone 7. Reduction of 7 gave the *allo*-nucleoside 9 which on hydrolysis afforded the free nucleoside 10. Alternatively, compound 10 was obtained from mesylation of 6 to give 8 followed by subsequent acetolysis and hydrolysis.

Several nucleoside antibiotics<sup>1</sup> containing a D-glucosamine residue exhibit a wide range of activity against gram negative and gram positive bacteria. Tunicamycin<sup>1,2</sup> is one of these antibiotics which showed remarkable activity against a number of viruses, fungi, and *Staphylococci*. Puromycin<sup>3</sup> is an analogue of such nucleosides having an amido derivative in its sugar moiety and that has antiprotozoal and antineoplastic properties<sup>4</sup>. Both D-glucosamine<sup>5-8</sup> and 6-azauracil exhibit biological interest. 6-Azauracil is known as inhibitor of RNA formation<sup>9</sup> and shows carcinostatic properties<sup>10,11</sup>. In this paper, we used both these components as starting materials in glycosylation reaction applying the Hilbert-Johnson-Birkofer procedure<sup>12</sup> to produce some glycosaminyl-6-azauracil N-1 nucleosides as potential antibacterial<sup>13</sup>, antimutagenic or antineoplastic agents.

Ribosylation of the trimethylsilylated derivative of 6-azauracil (2) with 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-glucose (3) using trimethylsilyl triflate catalyst in boiling dry 1,2-dichloroethane led to the corresponding nucleoside 4 in 71% yield. This product was purified from traces of the  $\alpha$ -anomer by chromatography. The structure of 4 was supported by its <sup>1</sup>H-nmr spectrum which showed H-1' at  $\delta$  5.87 with a large  $J_{1',2'}$  value (10 Hz), confirming the  $\beta$ -configuration. The large coupling constants

between H-2', H-3', H-4' and H-5' ( $J_{2',3'} = J_{3',4'} = J_{4',5'} = 9.5$  Hz) clearly established the  $^4C_1$  conformation of the sugar moiety. Deblocking of **4**, by treatment with sodium methoxide, proceeded smoothly to give the free nucleoside **5** in 87% yield.

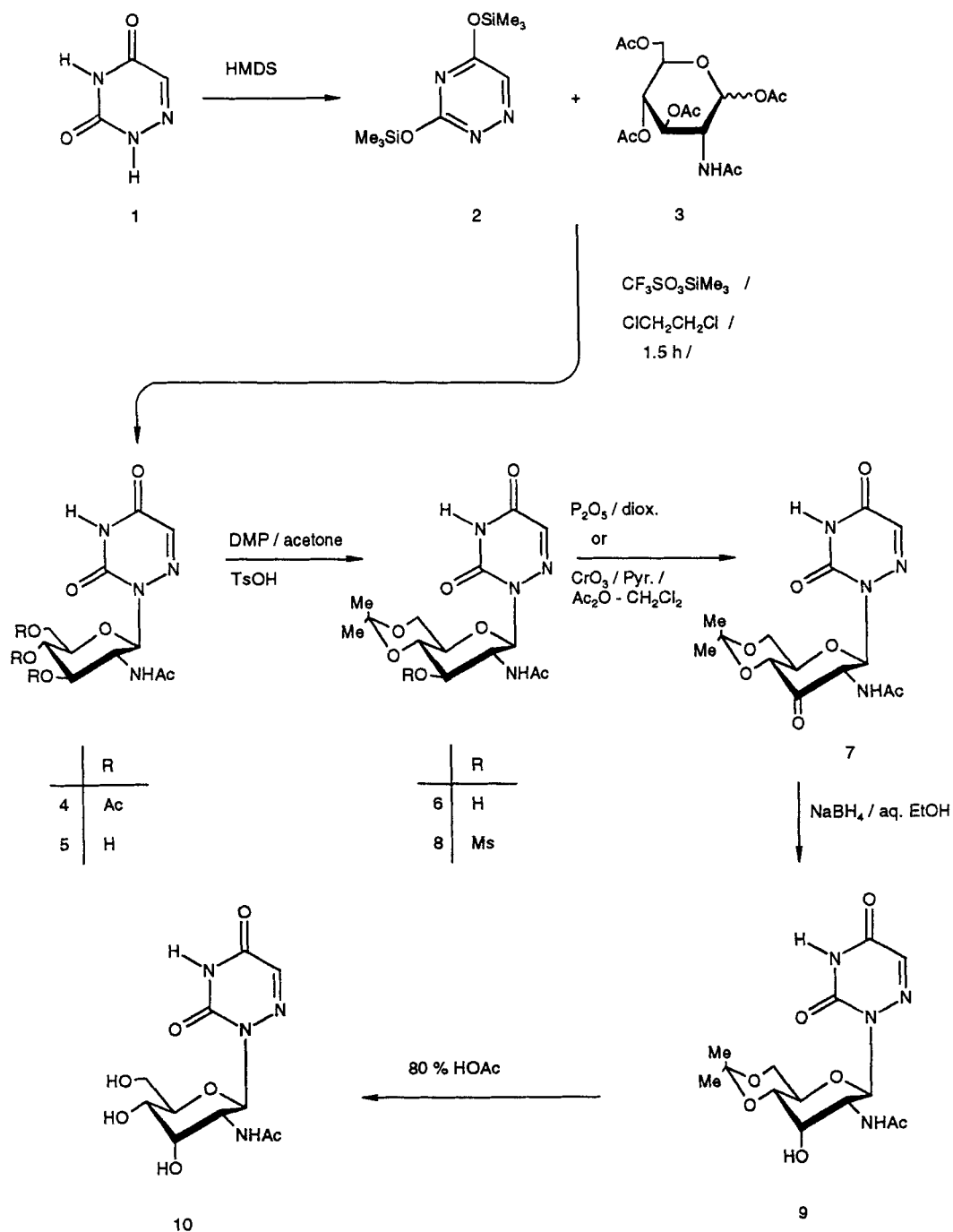
Compound **5** served as a key precursor for the preparation of other epimeric nucleosides. Thus, **5** was converted into the 4',6'-*O*-isopropylidene derivative **6** by treatment with acetone and 2,2-dimethoxypropane in the presence of toluene-*p*-sulfonic acid and isolated, chromatographically, in 68% yield. Oxidation of **6** with phosphorus pentoxide and dimethyl sulphoxide at room temperature afforded a crude ketone **7**, which was purified on a column of neutral silica gel and isolated as crystalline compound in 70% yield. On the other hand, **7** was obtained in 79% yield from oxidation of **6** by  $\text{CrO}_3/\text{pyridine}/\text{Ac}_2\text{O}$  complex (1:2:1 molar ratio) method described by Garegg *et al.*<sup>14,15</sup>. The  $^1\text{H}$ -nmr. spectra of both **6** and **7** confirmed that both products adopted the  $^4C_1$  conformation. Reduction of **7** with sodium borohydride gave, stereoselectively, the product of the *allo*-configuration, **9**, in good yield. This product was purified by chromatography from traces of the *gluco* epimer **6**. The structure of **9** was established by its  $^1\text{H}$ -nmr. spectrum which confirmed that it existed mainly in the  $^4C_1$  conformation with  $\beta$ -configuration.

Alternatively, the nucleoside **9** was prepared by a different approach. Thus, sulfonylation of **6** by treatment with methanesulfonyl chloride in dry pyridine afforded, after chromatographic purification, the crystalline mesylate **8** in 65% yield. Treatment of **8** with sodium acetate in methyl cellosolve containing traces of water for 2 h gave a higher running, unidentified product together with a compound having identical physical properties to those of the authentic sample of *allo* isomer **9**. Acid hydrolysis of the acetal group at **9** with aqueous acetic acid at room temperature led to the desired *allo* nucleoside **10**.

The attachment of the sugar moieties to the N-1 of the 6-azauracil was concluded from their U.V. spectra by comparison with known 6-azauracil analogues<sup>16,17</sup>. Thus, the spectra of all these products showed close similarity to those of the 6-azauridine.

## EXPERIMENTAL

Melting points were measured on a Gallenkamp melting apparatus and are uncorrected.  $^1\text{H}$ -nmr. spectra were measured with a JNM EX-90 FT NMR JEOL type and a Bruker WM-250 high resolution spectrometers, with (TMS) as an internal standard on a  $\delta$ -scale in ppm. U.V. spectra were recorded on SP8-100 ultraviolet spectrophotometer. T.l.c. was performed on silica gel 60 F<sub>254</sub> sheet layer (Merck).



Drying of the substances was achieved in a vacuum oven, type L.T.E. Qualivac at different temperatures.

1-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-glucopyranosyl)-6-azauracil (4). A suspension of 6-azauracil **1** (2.40 g, 21.22 mmol) and dry hexamethyldisilazane (100 ml) containing few crystals of ammonium sulfate was heated under reflux for 20 h. After cooling, the solution was evaporated to dryness under anhydrous condition to give the silylated derivative **2**. The residue was dissolved in dry 1,2-dichloroethane (100 ml) and to this was added a solution of the sugar derivative **3** (8.24 g, 21.22 mmol) dissolved in dry 1,2-dichloroethane (70 ml) followed by the addition of trimethylsilyl triflate catalyst (4.30 ml, 21.22 mmol). After heating the mixture under reflux for 1.5 h, it was cooled and evaporated to dryness and the syrupy residue was co-evaporated with ethanol (3x20 ml) to give a solid product (7.9 g). Recrystallization from ethanol afforded the desired nucleoside **4** (7.30 g, 77%), m.p. 260-262° C <sup>1</sup>H-NMR. DMSO<sub>6</sub> (δ, ppm) 12.25 (s, 1H, NH), 7.97 (d, 1H, J<sub>NH,2'</sub> = 8.9 Hz, NHAc), 7.57 (s, 1H, H-5), 5.93 (d, 1H, J<sub>1',2'</sub> = 9.5 Hz, H-1'), 4.38 (dd, 1H, J<sub>2',3'</sub> = 9.0 Hz, H-2'), 5.32 (pt, 1H, J<sub>3',4'</sub> = 10.0 Hz, H-3'), 4.89 (t, 1H, J<sub>4',5'</sub> = 9.5 Hz, H-4'), 4.19 (m, 1H, J<sub>5',6a'</sub> = 4.0 Hz, H-5), 4.05 (m, 2H, J<sub>5',6b'</sub> = 8.2 Hz, H-6a' and H-6b'), 2.00, 1.99, 1.92 (3s, 9H, OAc), 1.68 (s, 3H, NHAc). UV (nm) (MeOH) λ<sub>max</sub> = 261 (log ε 4.10), pH 12.16 (NaOH): λ<sub>max</sub> = 250 (log ε 4.06).

Anal. Calc. for C<sub>17</sub>H<sub>22</sub>N<sub>4</sub>O<sub>10</sub> (442.4): C, 46.16; H, 5.01; N, 12.67. Found: C, 46.01; H, 5.19; N, 12.51.

1-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-6-azauracil (5). A solution of **4** (1.50 g, 3.39 mmol) in sodium methoxide solution [from sodium (0.15 g, 7.80 mmol) and methanol (40 ml)] was stirred at room temperature for 17 h. The solution was neutralized with HOAc to pH 5 and evaporated to dryness to give a crude product (1.09 g). This product was dissolved in water (25 ml) and extracted with ether (20 ml). The aqueous layer was evaporated to dryness and the residue was co-evaporated with ethanol-toluene (3x). Recrystallization from ethanol-ether afforded **5** (1.04 g, 87%), m.p. 240-243° C (decomposed). <sup>1</sup>H-NMR DMSO-d<sub>6</sub> (δ, ppm): 12.45 (s, 1H, NH), 7.79 (s, 1H, J<sub>NH,2'</sub> = 8.9 Hz, NHAc), 7.57 (s, 1H, H-5), 5.59 (s, 1H, J<sub>1',2'</sub> = 9.5 Hz, H-1'), 3.96 (d, 1H, J<sub>2',3'</sub> = 9.5 Hz, H-2'), 3.72 (dt, 1H, J<sub>3',4'</sub> = 10.0 Hz, H-3'), 3.68 (m, 1H, H-4'), 3.50 (m, 1H, J<sub>5',6a'</sub> = 9.5 Hz, H-5'), 3.25 (dd, 1H, J<sub>5',6b'</sub> = 5.0 Hz, H-6a'), 3.11 (dd, 1H, J<sub>6a',6b'</sub> = 10.0 Hz, H-6b'), 5.16 (d, 1H, J = 6.2 Hz, C<sub>3'</sub>-OH), 5.12 (d, 1H, J = 5.6 Hz, C<sub>4'</sub>-OH), 4.66 (m, 1H, C<sub>6a',6b'</sub>-OH), 1.71 (s, 3H, NHAc). UV (nm) (MeOH) λ<sub>max</sub> = 255 (log ε 4.30).

Anal. Calc. for C<sub>11</sub>H<sub>16</sub>N<sub>4</sub>O<sub>7</sub> · 1/2H<sub>2</sub>O (325.27): 40.61; H, 5.26; N, 17.22. Found: 40.66; H, 4.97; N, 16.90.

1-(2-Acetamido-2-deoxy-4,6-O-isopropylidene-β-D-glucopyranosyl)-6-azauracil (6).

A solution of **5** (0.57 g, 1.75 mmol) in dry DMF (10 ml) was stirred with dry acetone (4 ml) and 2,2-dimethoxypropane (20 ml) containing toluene-p-sulfonic acid (0.1 g) for 2 h at room temperature. The solution was neutralized with anhydrous sodium carbonate, filtered and evaporated to dryness. The residue was dissolved in CHCl<sub>3</sub>-MeOH (49:1) and adsorbed on silica gel (50 g). Elution with the same eluent gave **6** (0.41 g, 62%), m.p. 221-225° C (decomposed) (recrystallized from methanol-ether). <sup>1</sup>H-NMR DMSO-d<sub>6</sub> (δ, ppm) 11.71 (s, 1H, NH), 7.56 (s, 1H, H-5), 7.85 (d, 1H, J<sub>NH,2</sub> = 8.5 Hz, NHAc), 5.69 (d, 1H, J<sub>1',2</sub> = 9.3 Hz, H-1'), 4.02 (dd, 1H, J<sub>2',3</sub> = 9.0 Hz, H-2'), 3.82 (m, 1H, J<sub>3',4</sub> = 10.0 Hz, H-3'), 3.66 (m, 1H, H-4'), 3.51-3.27 (m, 3H, H-5', H-6<sub>a</sub>' and H-6<sub>b</sub>'), 5.28 (d, 1H, J = 5.9 Hz, C<sub>3</sub>-OH), 1.45, 1.33 [2s, 6H, (CMe)<sub>2</sub>], 1.75 (s, 3H, NHAc). UV (nm) (MeOH) λ<sub>max</sub> = 250 (log ε 3.73).

**Anal.** Calc. for C<sub>14</sub>H<sub>20</sub>N<sub>4</sub>O<sub>7</sub>. (356.3): C, 47.19; H, 5.65; N, 15.72. Found: C, 46.79; H, 5.52; N, 15.89.

1-(2-Acetamido-2-deoxy-4,6-O-isopropylidene-3-O-methanesulfonyl-β-D-glucopyranosyl)-6-azauracil (8).

To a cooled, stirred solution of **6** (0.40 g, 1.12 mmol) in dry pyridine (20 ml), methanesulfonyl chloride (1.5 ml) was added. After 16 h. at room temperature, a few drops of water were added with stirring for 30 min., and the reaction mixture was partitioned between chloroform and water. The organic extract was washed successively with 5% H<sub>2</sub>SO<sub>4</sub>, 5% NaHCO<sub>3</sub> and finally with water. The organic layer was dried (MgSO<sub>4</sub>), filtered and evaporated to give a crude product. Purification of this product on column of silica gel (20 g), using CHCl<sub>3</sub>-MeOH (9:1) as eluent afforded the crystalline mesylate **8** (0.30 g, 65%), m.p. softening at 84° C and decomposed at 99-101° C. <sup>1</sup>H-NMR CDCl<sub>3</sub> (δ, ppm): 8.59 (s, 1H, NH), 7.78 (d, 1H, J<sub>NH,2</sub> = 8.5 Hz), NHAc), 7.41 (s, 1H, H-5), 6.01 (d, 1H, J<sub>1',2</sub> = 9.5 Hz, H-1'), 5.01 (dd, 1H, J<sub>2',3</sub> = 9.0 Hz, H-2'), 5.62 (t, 1H, J<sub>3',4</sub> = 9.0 Hz, H-3'), 4.32 (dd, 1H, J<sub>4',5</sub> = 10.0 Hz, H-4'), 4.21-3.72 (m, 3H, H-5', H-6' and H-6''), 3.59 [s, 3H, (OSO<sub>2</sub>Me)], 1.92, 1.88 [2s, 6H, (CMe)<sub>2</sub>], 1.89 (s, 3H, NHAc). UV (nm) (MeOH) λ<sub>max</sub> = 258 (log ε 3.96).

**Anal.** Calc. for C<sub>15</sub>H<sub>22</sub>N<sub>4</sub>O<sub>9</sub>S (434.4): C, 41.47; H, 5.10; N, 12.90. Found: C, 41.62; H, 4.92; N, 12.81.

1-(2-Acetamido-2-deoxy-4,6-O-isopropylidene-β-D-ribo-hex-3-ulopyranosyl)-6-azauracil (7).

a. A mixture of **6** (140 mg, 0.37 mmol) in *N,N*-dimethylformamide (10 ml) containing dimethyl sulfoxide (0.5 ml) and phosphorus pentoxide (140 mg, 0.98 mmol) was heated, with stirring, for 3 h., at 85° C. The reaction mixture was evaporated to give a crude product. This was adsorbed on column

of silica gel (15 g) and the appropriate fractions, which eluted with  $\text{CHCl}_3$ -MeOH (9:1), were combined and evaporated to yield the desired ketone **7** (90 mg, 70%), m.p. 180-185° C (decomposed) (recrystallized from ethanol-ether).  $^1\text{H-NMR}$  DMSO- $d_6$  ( $\delta$ , ppm): 12.33 (s, 1H, NH), 7.95 (d, 1H,  $J_{\text{NH},2} = 3.0$  Hz, NHAc), 7.39 (s, 1H, H-5), 5.60 (d, 1H,  $J_{1',2'} = 9.8$  Hz, H-1'), 5.96 (d, 1H, H-2'), 4.70 (d, 1H,  $J_{4',5'} = 10$  Hz, H-4'), 4.03 (ddd, 1H,  $J_{5',6a'} = 6.0$  Hz, H-5'), 3.94 (dd, 1H,  $J_{5',6b'} = 8.6$  Hz, H-6<sub>a</sub>'), 3.67 (dd, 1H,  $J_{6a',6b'} = 11.5$  Hz, H-6<sub>b</sub>'), 1.49, 1.36 [2s, 6H, (CMe)<sub>2</sub>], 1.77 (s, 3H, NHAc), UV (nm) (MeOH)  $\lambda_{\text{max}} = 260$  (log  $\epsilon$  3.78).

**Anal.** Calc. for  $\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_7$  (354.3): C, 47.46; H, 5.12; N, 15.81. Found: C, 47.19; H, 5.08; N, 15.72.

b. A solution of **6** (0.47 g, 1.25 mmol) in dry dichloromethane (2 ml) was added to a stirred solution of 3 molar equivalent of the pre-mixed complex of  $\text{CrO}_3$  (1)/ pyridine (2)/  $\text{Ac}_2\text{O}$  (1) (400 mg/ 0.67 ml/ 0.44 ml) in dry dichloromethane (9.5 ml). The reaction mixture was left in stirring at room temperature for 1 h. The mixture was added carefully to a supernatant layer of ethyl acetate (100 ml) of silica gel column. Elution with ethyl acetate gave the syrupy ketone **7** (0.35 g, 79%) which recrystallized from ethanol-ether to give an analytical sample, m.p. and mixed m.p. with the other physical data were identical to those of the authentic sample prepared in the experiment a.

1-(2-Acetamido-2-deoxy-4,6-O-isopropylidene- $\beta$ -D-allopyranosyl)-6-azauracil (9).

(a). A solution of **8** (0.35 g, 0.98 mmol) in a mixture of ethanol (7 ml) and water (7 ml) was stirred with sodium borohydride (0.15 g, 3.97 mmol) at room temperature for 1 h. More sodium borohydride (0.05 g) was added and the reaction mixture was stirred for another 30 min., and then evaporated to dryness. The residue was partitioned between water (20 ml) and ethyl acetate (4x30 ml). The combine organic extracts were dried ( $\text{MgSO}_4$ ), filtered and evaporated to give a crystalline product (0.37 g). Recrystallization from ethanol-ether afforded compound **9** (0.32 g, 86%), m.p. softening at 160° C and decomposed at 220° C.  $^1\text{H-NMR}$  DMSO- $d_6$  ( $\delta$ , ppm): 12.01 (s, 1H, NH), 7.83 (d,  $J_{\text{NH},2} = 9.0$  Hz, NHAc), 7.40 (s, 1H, H-5), 5.84 (d, 1H,  $J_{1',2'} = 9.9$  Hz, H-1'), 4.39 (pt, 1H,  $J_{2',3'} = 6.5$  Hz, H-2'), 4.10 (m, 1H,  $J_{3',4'} = 6.5$  Hz, H-3'), 3.93 (dd, 1H,  $J_{4',5'} = 9.0$  Hz, H-4'), 3.89-3.64 (m, 3H, H-5', H-6<sub>a</sub>' and H-6<sub>b</sub>'), 5.56 (d, 1H,  $J = 4.0$  Hz, C<sub>3</sub>-OH), 1.46, 1.33 [2s, 6H, (CMe)<sub>2</sub>], 1.73 (s, 3H, NHAc). UV (nm) do(MeOH)  $\lambda_{\text{max}} = 252$  (log  $\epsilon$  3.75).

**Anal.** Calc. for  $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_7 \cdot \text{H}_2\text{O}$  (374.3). C, 44.92; H, 5.92; N, 14.97. Found: 44.81; H, 5.30; N, 15.01.

(b). A solution of **8** (130 mg, 0.17 mmol) in methyl cellosolve (15 ml) containing sodium acetate (160 mg, 2.00 mmol) and traces of water was heated under reflux for 3

h. After cooling, the mixture was evaporated to dryness and the residue was partitioned between chloroform and water. The organic extract was dried ( $\text{MgSO}_4$ ), filtered and concentrated to 5 ml and then adsorbed on silica gel (25 g). Elution with  $\text{CHCl}_3$ -MeOH (9:1) afforded first, an unidentified product (30 mg). The second eluted product was characterized as compound **9** (120 mg, 43%) as major product, indistinguishable by t.l.c.,  $^1\text{H-NMR}$ , U.V., m.p. and mixed m.p. from sample prepared in experiment a.

1-(2-Acetamido-2-deoxy- $\beta$ -D-allopyranosyl)-6-azauracil (10).

Compound **9** (0.20 g, 0.53 mmol) was treated with 80% acetic acid (5 ml) at room temperature for 16 h. The solution was evaporated to dryness and the residue was co-evaporated with toluene-ethanol (3x30 ml). The solid product was stirred with ether for 4 h., filtered and recrystallized from methanol-ether to yield nucleoside **10** (0.16 g, 84%), m.p. softening at  $194^\circ\text{C}$ , decomposed at  $226^\circ\text{C}$ .  $^1\text{H-NMR}$  DMSO- $d_6$  ( $\delta$ , ppm): 11.66 (s, 1H, NH), 7.92 (d, 1H,  $J_{\text{NH},2'} = 8.6\text{ Hz}$ , NHAc), 7.39 (s, 1H, H-5), 5.78 (d, 1H,  $J_{1',2'} = 9.0\text{ Hz}$ , H-1'), 4.0-3.71 (m, 10H, H-2', H-3', H-4', H-5', H-6<sub>a</sub>', H-6<sub>b</sub>', C<sub>3</sub>'-OH, C<sub>4</sub>'-OH, C<sub>6a</sub>'-OH and C<sub>6b</sub>'-OH), 1.79 (s, 3H, NHAc). UV (nm) (MeOH)  $\lambda_{\text{max}} = 254$  (log  $\epsilon$  4.01).

Anal. Calc. for  $\text{C}_{11}\text{H}_{16}\text{N}_4\text{O}_7 \cdot 2\text{H}_2\text{O}$  (352.3): C, 37.50; H, 5.72; N, 15.90. Found: C, 37.63; H, 5.58; N, 15.63.

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