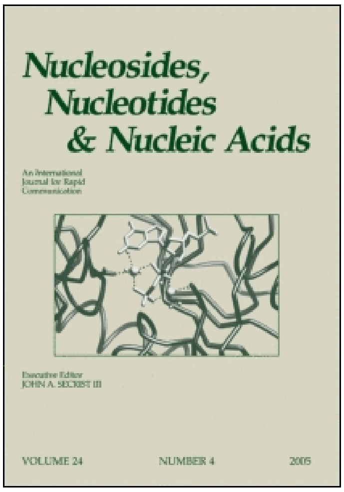

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Nucleosides. 140. Stereoselectivity of the Reaction of 1-(2,3-Anhydro-5-O-Benzoyl-β-D-Lyxofuranosyl)Uracil with Ammonium Azide. Isolation and Characterization of 2-Azido-XYLO-Nucleoside Derivatives.[1]

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NUCLEOSIDES. 140. STEREOSELECTIVITY OF THE REACTION OF 1-(2,3-ANHYDRO-5-O-BENZOYL-β-D-LYXOFURANOSYL)URACIL WITH AMMONIUM AZIDE. ISOLATION AND CHARACTERIZATION OF 2-AZIDO-XYLO-NUCLEOSIDE DERIVATIVES.[1]

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Abstract: The composition of the products of reaction of 1-(2,3-anhydro-5-O-benzoyl-β-D-lyxofuranosyl)uracil (**1**) with NH_4N_3 was studied by a reverse-phase HPLC system which was found to separate the 3-azido-arabino **2** and 2-azido-xylo **3** isomers that were formed. The use of a 10:1 ratio of NH_4N_3 to **1** in refluxing EtOH was found to minimize ring opening at C-2 (7%). The higher stereoselectivity of ring opening produced by using a large excess of NH_4N_3 was suppressed by conducting the reaction in DMF. Preventing the escape of the NH_3 by-product only resulted in debenzoylation. The isolation of pure, crystalline **3** was achieved by reverse-phase preparative HPLC. Separation from the arabino isomer was also effected by debenzoylation and selective acetonide formation with the xylo isomer, which allowed facile isolation of the latter by normal phase chromatography. Hydrolysis of the acetonide **7** provided unprotected 2-azido-xylo nucleoside **6**, which was also obtained by NaOMe treatment of **3**. The mechanistic basis for the stereoselectivity of epoxide opening is discussed.

In 1976, we reported [2] a synthesis of 1-(3-acetamido-2-O-acetyl-5-O-benzoyl-3-deoxy-β-D-arabinofuranosyl)uracil (**4b**) (see Scheme I) by treatment of 1-(2,3-anhydro-5-O-benzoyl-β-D-lyxofuranosyl)uracil (**1**) with boron trifluoride etherate in acetonitrile followed by acetylation. At that time we also described an alternative route to **4b** involving

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*This paper is being re-printed because two pages were inadvertently omitted when it was published in *Nucleosides & Nucleotides*, 6(3), 621-630 (1987).

opening of epoxide **1** by refluxing in ethanol with 1.65 equivalents of NH_4N_3 to provide pure 1-(3-azido-5-O-benzoyl-3-deoxy-β-D-arabinofuranosyl)uracil (**2**) after recrystallization of the crude product. Shortly thereafter, we reported[3] that pure **2** could be obtained in 86% yield by treatment of **1** with 10 equivalents of NH_4N_3, again after recrystallization of the reaction product.

Recently, this reaction was repeated by Hummel and Carty,[4] who reported that the use of 2.0 equivalents of NH_4N_3 provided a crude product which, based on the ^1H NMR spectrum, consisted of **2** and another uracil nucleoside in a 4:1 ratio. Upon recrystallization of the product from MeOH, they also obtained pure **2**. Subsequent debenzoylation and catalytic reduction were performed on the crude product, however. Consequently, the final product was a mixture of **4c** and another amino nucleoside which was isolated by ion-exchange chromatography and identified as the 2'-amino xylo nucleoside **8** (by conversion to the known[5] HCl salt). On this basis, it was concluded that the minor product from the reaction of NH_4N_3 with **1** was the 2'-azido xylo compound **3**. Since we utilized **2** in pure, crystalline form, for the preparation of the amino nucleosides **4a** and **4b**, **8** was not found in our reduction products.

The isolated yield of 86% for our later preparation[3] of **2** from **1** taken together with the 4:1 ratio of **2** to **3** cited for the reaction products before crystallization by Hummel and Carty seem to indicate that the differences in reaction conditions that were employed altered the stereoselectivity of the ring-opening. We therefore studied the composition of the reaction products in detail in order to better understand the control of selectivity of azide ion attack at C-3' of lyxo epoxide **1**.

The reaction of **1** (0.5 g) with a 10 molar excess of NH_4N_3 was monitored by TLC using several solvent systems and at the completion of the reaction (after 18 h), only one spot was detected as we had reported.[3] However, the formation of a small amount of by-product was suggested by the presence of a singlet at 5.83 in the ^1H NMR in $CDCl_3$ [in d_6-DMSO this resonance appeared as a doublet at 5.76 ppm (J = 2.4 Hz)]. The use of 1.65 equivalents of NH_4N_3 in the reaction caused an increase in the intensity of this peak which was assigned by Hummel and Carty[4] to the anomeric proton of the 2'-azido xylo compound **3**. We found that it was possible to readily separate **1**, **2** and the by-product by analytical reverse-phase high performance liquid chromatography (HPLC). The mobile phase found to provide optimal resolution on our system was 60:40 H_2O:MeOH (containing a trace of AcOH). Typical retention times for these components (detected by UV absorption at 254 nm) were 10.6, 17.8 and 23.5 minutes, respectively. The results of the HPLC analyses for these and other reactions of **1** with NH_4N_3 are shown in Table 1. The identity of the by-product as xylo isomer **3** was confirmed by isolation from the reaction mixture and characterization as described later in this report.

The HPLC analysis of the products of the above reaction using 10 equivalents of NH_4N_3 in EtOH showed that ring opening was complete and that 7% of the product was **3**, which was consistent with the ^1H NMR (exp. 1). In the case where only 1.65 equivalents were used, the ratio of **2** to **3** was 3.3:1 with 25% of **1** remaining unreacted (exp. 2); addition of another 1.1 equivalents of NH_4N_3 to this mixture and further refluxing for another three days to bring the reaction to completion did not significantly alter this ratio (exp. 3). It is apparent from these experiments that increasing the amount of NH_4N_3 in the reaction with **1** in refluxing EtOH increases both the selectivity for attack at C-3' and the rate of ring opening.

Since an equivalent of NH_3 is released during this reaction and its removal from the reaction medium may be altered by such factors as the scale of reaction (considerably larger in Carty's study where 7.27 g of **1** was used), unobstructed reflux condensers and vigorous stirring were employed. To determine whether the retention of NH_3 in the medium influences the direction of ring-opening, the reaction was conducted using 1.65 equivalents of NH_4N_3 in EtOH in a sealed glass tube at 95-100°C (exp. 4). HPLC analysis of the product showed that it contained, in addition to **2** (61%) and **3** (15%), 22% of a polar constituent (retention time = 3.6 min). The latter was isolated by silica gel chromatography and was determined by ^1H NMR to consist of a mixture of the 5'-de-O-benzoylated azides **5** and **6** in a ratio of 1.63:1 (appearing as a single spot on TLC) making the overall arabino to xylo ratio 75:23 (3.3:1). Thus, the presence of ammonia does not appear to exert any influence (by altering the basicity of the medium, for example) on the direction of ring opening. The high ratio of **2** to **3** and low ratio of 5 to 6 indicate that ammonolysis of the ester linkage appears to be more facile for 3 than for 2. Debenzoylation prior to ring-opening does not significantly increase the extent of azide attack[3] at C-2', and thus regiospecificity probably is not responsible for the product ratios observed.

An interesting result was obtained when DMF was used as the reaction solvent instead of EtOH. At 110°C in DMF, the reaction of 1 with both 1.65 and 10 equivalents of NH_4N_3 reached completion in less than two hours to provide almost identical ratios (3.6:1) of 2 to 3 in the product mixture (exp. 5 and 6).

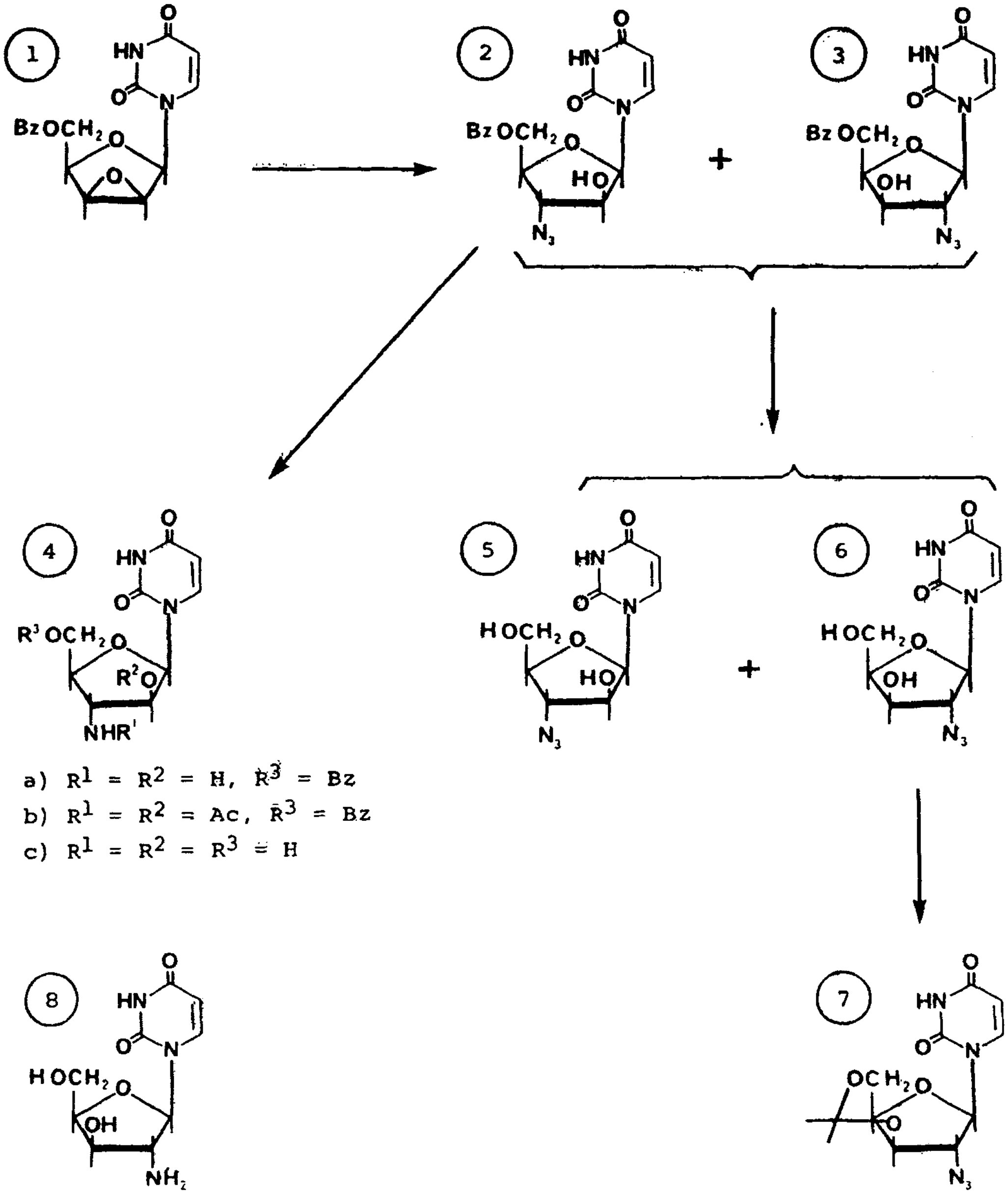
Epoxide ring-opening under neutral and basic conditions has been interpreted[6] as proceeding through a "borderline-S_N2" transition state in which C-O bond breaking is more advanced than in regular S_N2 reactions. Ring-opening of 2,3-anhydro-β-D-lyxofuranosides, with few exceptions, occurs at C-3.[7] It has been suggested [8] that, although the steric environments of the epoxide ring carbons in the β-lyxosides are very similar, the nature of the substituents at C-1 and C-4 causes greater destabilization, <u>via</u> inductive electron withdrawal, of the transition state for nucleophilic reaction at C-2 than at C-3. The results reported for the reaction of 1 with NH_4N_3 would appear to be consistent with such a "borderline-S_N2" transition state for epoxide cleavage, as all conditions employed in this and previous[2,3,4] studies have resulted in predominant attack at C-3'.

The increase in regioselectivity of epoxide cleavage observed with greater amounts of NH_4N_3 may be the result of an increase in the ionic strength of the solution, which is known[9] to accelerate S_N1 reactions (the "salt effect"). It might also be argued that the greater electron deficiency at C-2' of 1 in the ground state could enhance the affinity of nucleophiles for this position and that this effect is suppressed when a large excess of nucleophile is present.

The reduced regioselectivity observed when DMF was used as the solvent, i.e., the absence of a dependence on reagent excess, may be due to a higher nucleophilicity of N_3^- in this solvent. Such a solvent effect is well precedented.[10] For example, the reaction of 1-(2,3-anhydro-β-D-lyxofuranosyl)adenine with NaOBz has been reported[11] to occur in DMF but not in diethyleneglycol. Furthermore, superior nucleophiles are considerably less selective for C-3 attack in furanoside epoxides. Thus, reaction of $NaSCH_2Ph$ with methyl 2,3-anhydro-β-D-lyxofuranoside results in a 3:2 ratio of C-2 to C-3 attack,[12] whereas much less nucleophilic NH_3 affords predominantly the product from the expected C-3 attack.[13] Enhancement of nucleophilicity probably was a factor contributing to the reversal in regioselectivity and would also be expected to favor an S_N2 mechanism. In conclusion, this study of the reaction of **1** with NH_4N_3 has revealed that both the amount of the nucleophile and the nature of the solvent used influence the regioselectivity of ring-opening, presumably by altering the relative expressions of the S_N1 and S_N2 components of the reaction.

As the synthesis of **3** and its debenzoylated analog **6** has not been previously reported, their isolation from the reaction mixture was desirable. Thus, the crude product obtained in experiment #3 which contained 21% of the minor product, was chromatographed on a silica gel column to yield a crystalline mixture of **2** and **3**. A substantial amount of pure **2** was selectively separated by fractional crystallization. The mother liquor was subjected to preparative reverse-phase HPLC, to provide pure 2'-azido xylo nucleoside in 9.7% yield overall from **1** (47% recovery). The product was crystallized and the IR and ^1H NMR spectral data as well as elemental analyses agreed with the structure of **3** for this compound. Its ^1H NMR spectrum showed that the doublet at δ 5.76 in DMSO-d_6 observed for the product mixture resulting from ring-opening of **1** was indeed the anomeric signal for **3**. Furthermore, **3** was found to co-migrate on the analytical HPLC with the major reaction product (retention time of 23.5 minutes).

The deprotected analog **6** was most conveniently isolated by acetonide formation. Thus, combined products from the reaction of **1** with NH_4N_3, which consisted of 24% **3**, were freed of polar impurities by partitioning between $CHCl_3$ and H_2O, and then debenzoylated to yield a mixture of **5** and **6** (Scheme I). Treatment of the mixture with acetone in the presence of p-toluenesulfonic acid and 2,2-dimethoxypropane selectively formed the acetonide with the 3' and 5' hydroxyl groups of the xylo isomer **6** to give crystalline 1-(2-azido-2-deoxy-3,5-O-isopropylidene-β-D-xylofuranosyl)uracil (**7**) which was isolated in colorless crystalline form in 18% overall (77% recovery) yield from **1** after chromatographic purification. Compound **7** was deprotected with formic acid to yield 1-(2-azido-2-deoxy-β-D-xylofuranosyl)uracil (**6**)



a) $R^1 = R^2 = H$, $R^3 = Bz$
b) $R^1 = R^2 = Ac$, $R^3 = Bz$
c) $R^1 = R^2 = R^3 = H$

Scheme I

which was identical with material obtained by debenzoylation of pure **3**. In addition to aiding isolation, the ability of **6** to yield an acetonide provides further evidence for the 2'-azido-*xylo* configuration of **3** and **6**.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL PFT-100 spectrophotometer in Me_2SO-d_6 or $CDCl_3$ using Me_4Si as an internal standard. Analytical TLC was performed on silica gel Analtech Uniplates developed with 9:1 $CHCl_3$:MeOH and visualized using short wavelength UV light. Column chromatography was conducted under low pressure using flash grade silica gel (Merck #9385, 0.040-0.063 nm). Analytical HPLC was performed on a Waters C_{18}-μBondapak column (10 μ, 3.9 mm I.D. x 30 cm) using a Waters Model 6000A solvent delivery system, U6K injector and Model 440 UV detector (254 nm), and water:methanol (60:40 v/v; 1 mL HOAc added per gallon) as the mobile phase with a flow rate of 1 mL/min. Preparative HPLC was carried out on a Waters Prep LC 500A using a Prep Pak-500 C_{18} column. Elemental analyses were performed by Spang Microanalytical Laboratory.

Reactions of Ammonium Azide[14] with 1 using Different Molar Ratios.

The quantities of reactants shown in Table 1 were stirred in 25 mL refluxing ethanol, using a wide bore condenser and no drying tube (to allow ammonia to escape easily). After the specified period of time, a sample was withdrawn, diluted with H_2O/MeOH, filtered and analyzed by analytical HPLC. Typical retention times: **5** and **6** - 3.6 min; **1** - 10.6 min; **2** - 17.8 min; **3** - 23.5 min.

Reaction in Sealed Tube and Characterization of Products (exp. #4).

Epoxide **1** and NH_4N_3 in absolute EtOH (12 mL) were heated in a sealed tube in a bomb for 24 h at 95-100°C. The resulting solution, which was analyzed by HPLC, was then evaporated *in vacuo* and twice dissolved in MeOH and evaporated to afford a syrup. This was chromatographed on silica gel using 12:1 CH_2Cl_2:MeOH as the eluent to yield **2** and **3** (61:15) and a slower migrating, chromatographically homogeneous (TLC) component which, based on the ^{1}H NMR spectrum, was 62% **5**[3] and 38% **6**. ^{1}H NMR (d_6-DMSO) δ 3.66 (m, 2H, H-5',5''), 3.94-4.44 (m, 3H, H-2',3',4'), 4.85 (t, 0.4H, 5'-OH xylo, exch.), 5.26 (t, 0.6H, 5'-OH arabino, exch.), 5.59

Table 1. Composition of Products from Reaction of 1-(2,3-Anhydro-5-O-benzoyl-β-D-lyxofuranosyl)uracil and Ammonium Azide as Determined by HPLC.[a]

	Reaction Conditions					Products		
						HPLC Peak Integration as % of Total		
Experiment No.	Amount of 1 (g)	Amount of NH_4N_3[b] (g)	Molar ratio NH_4N_3/1	Solvent (mL)	Reaction time(h) (temperature °C)	2	3	5 + 6
1	0.5	0.91	10.0	EtOH(25)	18 (reflux)	92	7	1
2	1.0	0.3	1.65	EtOH(25)	22 (reflux)	56[h]	17	1
3	1.0	0.5[c]	2.75	EtOH(25)	96 (reflux)	70	21	7
4	0.5	0.15	1.65	EtOH(12)	24[d](95-100)	61(75)[e]	15(23)[f]	22[g]
5	0.25	0.075	1.65	DMF (8)	1.5 (110)	76	21	2
6	0.25	0.45	10.0	DMF (8)	0.5 (110)	72	20	4

[a] For conditions, see Experimental

[b] Reference 14

[c] Last 0.2 g added during final 2 days (0.1 g/day)

[d] In sealed tube in bomb (see Experimental)

[e] Including 5

[f] Including 6

[g] 5 14% and 6 8% based on ^{1}H NMR integration after separation from 2 and 3

[h] 25% of product is unreacted 1

(d, overlap with δ 5.67, total 1H, H-5 arabino), 5.67 (d, H-5, xylo), 5.76 (d, 0.4H, H-1' xylo and overlapping 0.4H, 3'-OH, xylo exch., $J_{1',2'}$ = 2.44 Hz), 6.03 (d, 0.6H, H-1' arabino, $J_{1',2'}$ = 6.10 Hz), 6.11 (d, 0.6H, 2'-OH arabino, exch.), 7.70 (d, overlap with δ 7.74, total 1H, H-6 arabino, $J_{5,6}$ = 8.24 Hz), 7.74 (d, H-6 xylo, $J_{5,6}$ = 7.93 Hz), 11.3 (m, 1H, NH exch.).

1-(2-Azido-5-O-benzoyl-2-deoxy-β-D-xylofuranosyl)uracil (3). The mixture obtained in experiment #3 as an ethanolic solution was evaporated to dryness, dissolved in $CHCl_3$ (35 mL) and extracted with water (2 x 25 mL), dried (Na_2SO_4) and evaporated to an oil. Chromatography on silica gel using CH_2Cl_2:MeOH (20:1) as eluent yielded a mixture of **2** and **3** (4:1 by HPLC analysis; one spot on TLC) as a crystalline solid. This was dissolved in methanol, water added until slightly turbid and the solution allowed to stand to permit crystallization of pure **2** (0.36 g). Another crop of **2** was collected on cooling of the mother liquor. The filtrate was evaporated, dissolved in MeOH (14 mL) and water was then added (21 mL). This slightly turbid solution was filtered through a Millipore filter and then injected onto a preparative HPLC column using H_2O:MeOH (3:2) as the mobile phase. The band representing **3** was eluted with MeOH:H_2O (4:3), with considerable band broadening leading to overlap with **2**. The elution was monitored by analytical HPLC and the fractions containing pure **3** were evaporated to yield a yellow syrup. The colored contaminants were removed by silica gel chromatography (20:1 CH_2Cl_2:MeOH) to provide **3** as a colorless, chromatographically homogeneous syrup (0.11 g, 9.7%). This was triturated repeatedly with ether and the supernatants were treated with EtOH, concentrated in vacuo and cooled to yield white needles (18 mg): mp = 103-105°C. ^{1}H NMR (d_6-DMSO) δ 4.35-4.59 (m, 5H, H-2',3',4',5',5''), 5.64, (d, 1H, H-5, $J_{5,6}$ = 7.9 Hz), 5.83 (d, 1H, H-1', $J_{1',2'}$ = 1.8 Hz), 6.06 (d, 1H, 3'-OH, $J_{3',OH}$ = 3.3 Hz), 7.52-8.02 (m, 6H, H-6 and benzoyl); IR (KBr) 3500 (OH), 2120 (N_3) cm^{-1}.

Anal. Calcd. for $C_{16}H_{15}N_5O_6$: C, 51.48; H, 4.05; N, 18.76. Found: C, 51.40; H, 4.08; N, 18.60.

1-(2-Azido-2-deoxy-3,5-O-isopropylidene-β-D-xylofuranosyl)uracil (7). The product mixtures from a few reactions of **1** (total 1.9 g, 5.75 mmol) with NH_4N_3 were combined. HPLC analysis showed this mixture to consist of 23.75% of **3**, 68.0% of **2** and 6.5% of **5** and **6**. It was dissolved in $CHCl_3$ (50 mL) and the solution extracted with H_2O (4 x 30 mL), dried (Na_2SO_4) and evaporated to yield a foam that was free of the polar material (including **5** and **6**) by TLC. This was dissolved in dry MeOH (50 mL) and treated with NaOMe (6 mmol). After stirring for 5 h at room temperature, the reaction was neutralized with IR-50 resin (H+), the resin washed with MeOH and the solutions evaporated, co-evaporated twice with water and then with absolute EtOH and MeOH/PhMe to yield a mixture of **5** and **6**.

This was dissolved in anhydrous Me_2CO (300 mL), 2,2-dimethoxypropane (2 mL) and pTsOH (50 mg) were added and then the solution was stirred at room temperature for 16 h. After stirring for 3 h with anhydrous potassium carbonate, the mixture was filtered, evaporated to dryness and partitioned between $CHCl_3$ (300 mL) and H_2O (300 mL). The aqueous layer was extracted with $CHCl_3$ (2 x 200 mL) and the combined $CHCl_3$ solutions dried (Na_2SO_4) and concentrated. Chromatography on silica gel using 2% EtOH in $CHCl_3$ as the eluent provided after evaporation and trituration with ether 0.33 g of acetonide **7** as white crystals (18.3% yield from **1**, 77% from **3**): mp 211-212°C (slow dec. from 180°C): ^1H NMR ($CDCl_3$) δ 1.32 and 1.45 (2s, 6H, iPr), 4.09-4.24 (m, 5H, H-2',3',4',5',5''), 5.73 (d, 1H, H-5, $J_{5,6}$ = 8.24 Hz), 5.84 (s, 1H, H-1'), 8.02 (d, 1H, H-6), 8.31 (br, s, 1H, NH, exch.); IR (KBr) 2120 (N_3) cm^{-1}.

Anal. Calcd. for $C_{12}H_{15}N_5O_5$: C, 46.60; H, 4.89; N, 22.64. Found: C, 46.64; H, 4.86; N, 22.74.

A compound isolated as a foam that eluted later from the column appeared according to the ^1H NMR in $CDCl_3$ to be an acetal. The spectrum was altered by addition of D_2O and, after evaporation of the solvent, the material was redissolved in d_6-DMSO and the NMR indicated that conversion to nearly pure **5** had occurred.

1-(2-Azido-2-deoxy-β-D-xylofuranosyl)uracil (6).

A. The acetonide **7** (40 mg, 0.13 mmol) was dissolved in conc. HCOOH (4 mL) and the solution stirred at room temperature for 2.5 h. After evaporation <u>in vacuo</u> and three co-evaporations with EtOH, the oil was treated with saturated NH_3/MeOH for 5 min. The solution was evaporated, the residue dissolved in water, re-evaporated and then twice dissolved in water (20 mL) and lyophilized to provide **6** as a hygroscopic white powder (32 mg, 91%): mp <100°C. ^{1}H NMR (d_6-DMSO) δ 3.69 (m, 2H, H-5',5''), 3.94-4.28 (m, 3H, H-2',3',4'), 4.85 (m, 1H, 5'-OH), 5.66 (d, 1H, H-5, $J_{5,6}$ = 7.6 Hz), 5.76 (d, 2H, H-1' and overlapping 3'-OH exch.), $J_{1',2'}$ = 2.44 Hz), 7.74 (d, 1H, H-6), 11.3 (br, s, 1H, NH); IR (KBr) 3450 (OH), 2120 (N_3) cm^{-1}.

Anal. Calcd. for $C_9H_{11}N_5O_5 \cdot 1/4\ H_2O$: C, 39.49; H, 4.23; N, 25.58. Found: C, 39.62; H, 4.22; N, 25.64.

B. Pure **3** (15 mg, 0.040 mmol) was dissolved in dry MeOH (1 mL) and 0.1 mmol NaOMe was added. After stirring for 5 h, the solution was neutralized with IRC-50 resin, which was washed with MeOH and the solutions filtered and evaporated. After co-evaporation with water and then EtOH, trituration with ether yielded resinous solid with ^{1}H NMR and R_f on TLC (8:1 CH_2Cl_2:MeOH) identical with that of **6** obtained by Method A.

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