Reactions of the Derivatives of 5-Bromopyrimidine Nucleosides with Sodium Azide

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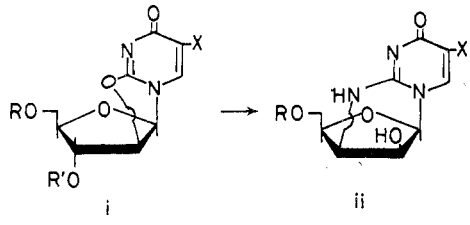
To exploit azide chemistry in the nucleoside field, protected 5-bromopyrimidine nucleosides were synthesized as substrates for the reaction of azide ion. These include 2′,3′-*O*-isopropylidene-5′-*O*-benzoyl- and -5′-*O*-tosyl-5-bromouridine (**2a** and **2b**), 2′,3′-*O*-anisylidene-5′-*O*-benzoyl-5-bromouridine (**2c**), and 2′,3′-*O*-isopropylidene-5′-*O*-mesyl-5-bromocytidine (**11**). **2a,b** with sodium azide yielded the same compound, 9,5′-cyclo-3-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-8-azaxanthine (**3a**), while a similar reaction with **2c** gave the corresponding 2′,3′-*O*-anisylidene analogue (**3b**). Acidic hydrolysis of **3a,b** gave 9,5′-cyclo-3-β-D-ribofuranosyl-8-azaxanthine (**4**). **11** with sodium azide gave 5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene-5-bromocytidine (**12**) and 9,5′-cyclo-3-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-8-azaisoguanine (**13**). **3a** and **13** were also obtained merely by heating 5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene-5-bromouridine (**6**) and **12**, respectively, suggesting an intramolecular addition–elimination mechanism for the formations of **3a,b** and **13**. Hydrazinolysis of **3a** gave N^1,5′-anhydro-N^5-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-4-carboxyhydrazino-5-amino-υ-triazole (**9**).

Azides exhibit many aspects of reactivity which can lead to amines, imines, nitrenes, and triazoles depending upon reaction conditions and the character of the substrate,[1] although their principal use in the nucleoside area has been limited to the syntheses of amino sugar nucleosides more or less related to natural products.[2,3] Recently we reported a selective, one-step synthesis of derivatives (ii) of 2,3′-imino-1-(β-D-lyxofuranosyl)uracil from readily available 2,2′-anhydro uracil arabinosides (i) and azide ion.[4] This reaction involves the leaving group directed, selective attack of azide ion at C-2 followed by intramolecular nucleophilic displacement at C-3′ with release of a nitrogen molecule.



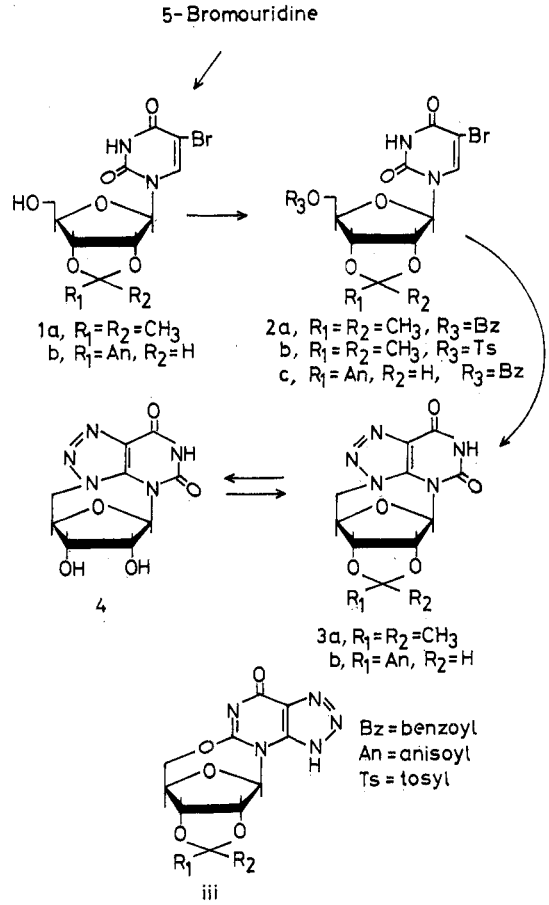
i ii

R = H, benzoyl or trityl
R′ = tosyl or mesyl
X = H or Br

Our attention was directed next to the possible interaction between 5′ carbon and an azide group introduced at C-6 when an appropriate leaving group is present at C-5′. The readily available 5-bromopyrimidine nucleoside derivatives seemed to be convenient substrates for such an investigation; some of the 5-halopyrimidine nucleosides are known to be chemicals of biological interest and vulnerable to the attack of some nucleophiles at the 5,6 double bond in the sense of nucleophilic addition reactions.[5] A few complex and hence interesting situations were foreseen for the present investigation: (a) the initial attack of azide ion could occur either at C-5′ or C-6, (b) the introduced azide group could induce intramolecular reactions with or without decomposition of the nitrogen chain, and (c) the possible interaction between the C-6 azide and 5′ carbon could take a concerted or limited course since the formation of a 5,6-fused triazole is highly possible. This paper describes the results of a synthetic study carried out on the basis of the above considerations.

2′,3′-*O*-Isopropylidene-5-bromouridine (**1a**)[6] and 2′,3′-*O*-anisylidene-5-bromouridine (**1b**)[7] were prepared by known methods. In the first experiment, **1a** was treated with excess sodium azide to observe the reactivity of the base moiety, but gave an intractable complex mixture. Hence, 5′-*O*-benzoyl-2′,3′-*O*-isopropylidene-5-bromouridine (**2a**) was used to preclude possible participation by the 5′-hydroxyl group, in the expectation that a 5,6-υ-triazolopyrimidine nucleoside retaining the protecting group at C-5′ would be formed exclusively since similar reactions of 5-nitropyrimidines as well as their nucleoside derivatives with sodium azide have been documented.[8,9]

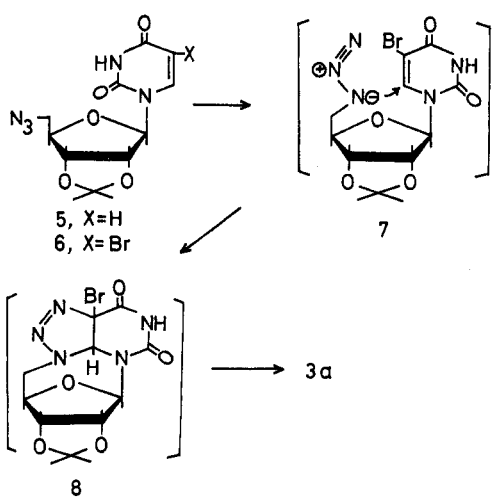
Reaction of **2a** with excess sodium azide in *N*,*N*-dimethylformamide (DMF) at 110 °C gave, unexpectedly, 9,5′-cyclo-3-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-8-azaxanthine (**3a**) as the only product in 70% yield. The same compound was also formed in a similar but shorter time reaction from 2′,3′-*O*-isopropylidene-5′-*O*-tosyl-5-bromouri-



dine (**2b**). Its analysis (empirical formula $C_{12}H_{13}N_5O_5$) and mass spectroscopic data (M^+ *m/e* 307) showed the incorporation of an azide unit as such and the elimination of the 5′-benzoyloxy or tosyloxy group. This substance showed no azide absorption in the ir spectrum and no NMR signals for pyrimidine 5 and 6 protons and hence must be a triazole derivative fused at the 5 and 6 positions of the base. Nuclear magnetic resonance spectroscopy (vide infra) gave no conclusive structural informations at this stage.

Since compound **3a** tended to be partially hydrated during crystallization and rendered the analysis rather cumbersome, 5′-*O*-benzoyl-2′,3′-*O*-anisylidene-5-bromouridine (**2c**) was also prepared and submitted to a similar azide reaction, yielding highly characterizable crystals of 9,5′-cyclo-3-(2′,3′-*O*-anisylidene-β-D-ribofuranosyl)-8-azaxanthine (**3b**). Compounds **3a** and **3b** gave similar uv absorption patterns with maxima at around 230 and 255 nm except that intensity order of the two maxima in **3b** was reversed owing to the presence of the anisoyl and were deprotected to the same, single product, 9,5′-cyclo-3-β-D-ribofuranosyl-8-azaxanthine (**4**), which was obtained both in the form of its methanol solvate and as solvent-free crystals. Compound **4** absorbed at 240 and 257 nm and could be reconverted to **3a**. However, the above data were not sufficient to rule out another possible structure, iii, in which the 2 oxygen is bound to the 5′ methylene, as long as no literature analogue was available for direct uv spectral comparison.

Accordingly, an unambiguous synthesis of **3a** was attempted. 5′-Azido-5′-deoxy-2′,3′-*O*-isopropylideneuridine (**5**)[10] was treated with *N*-bromoacetamide to give 5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene-5-bromouridine (**6**), which on heating in DMF at 110–120 °C afforded **3a** in a high yield (crude yield: quantitative). This intramolecular ther-



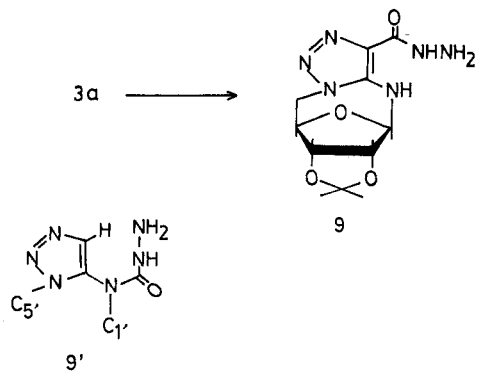
mal reaction must have proceeded via nucleophilic addition of the azide group followed by elimination of the elements of hydrogen bromide as in the formation of 5,6-anhydro-2′,3′-*O*-isopropylidene-6-hydroxyuridine[5a] or of a 6-cyanouridine derivative[5b] from **1a** by the action of alkali or cyanide ion.

At this point, some comments on the unusual features of the NMR spectra of **3a** and **4** are in order[11] (see Experimental Section). In the 100-MHz spectrum of **3a** there appeared widely separated, well-resolved $H_{5'a}$ (doublet, J_{gem} = 12 Hz) and $H_{5'b}$ signals (doublet of doublets, J_{gem} = 12 Hz, $J_{4',5'b}$ = 4.5 Hz) at 5.16 and 4.60 ppm, respectively. We are not aware of values as low as 5.16 ppm for the chemical shifts of the 5′-methylene protons of a nucleoside derivative. O^2-5′-[12] and 6,5′-cycloprimidine nucleosides[13] are known to show highly nonequivalent 5′ protons between 3.88 and 4.73 ppm. As an example of *N*,5′-cyclonucleosides, 2′,3′-*O*-isopropylidene-N^2,5′-cycloisocytidine[14] shows 5′-proton signals at 3.17 and 3.40 ppm as a set of doublets with J_{gem} = 13.8 Hz.[14] N substitution at a heterocyclic ring would, admittedly, be expected to shift the 5′-proton signals to lower field as compared with an imino bridged 5′-cyclonucleoside. Inspection of a molecular model of **3a** in the endo conformation (with the N^9 lone pair lying over the furanose ring and the N^3 lone pair over the $C_{1'}$–$C_{2'}$ bond) has shown that one of the 5′-methylene protons with a dihedral angle of approximately 90° can take a position coplanar with the triazole ring (deshielding zone), while the other lies in the vicinity of its shielding zone. Thus, the influence of the triazole ring current seems to be responsible for the unusually low, widely separated chemical shifts of the 5′ protons. On the other hand, an exo conformer requires dihedral angles of 0 and 120° between $H_{4'}$ and $H_{5'}$ and hence is improbable.[15] Overlap of $H_{2'}$ and $H_{3'}$ signals is also found in 2′,3′-*O*-isopropylidene-O^2,5′-cyclouridine.[12]

The deprotected analogue, **4**, also showed similar patterns for the 5′ protons (see Experimental Section). A notable difference from **3a** is the separation of the resonances of $H_{2'}$, $H_{3'}$, and $H_{4'}$, the last being significantly shifted upfield. The reason for the apparition of $H_{2'}$ and $H_{3'}$ signals as a rather ill-defined quartet and quintet is uncertain at present.[16] However, the homogeneity of **4** and the skeletal identity with **3a** are evident from the appearance of the signals of the other sugar protons and the reconversion into **3a** (vide supra).

Thus, while some uncertainty attended the interpretations of the irregular resonances of **4**, the structures of **3** and **4** were firmly established by the thermal conversion of **6** into **3a**.

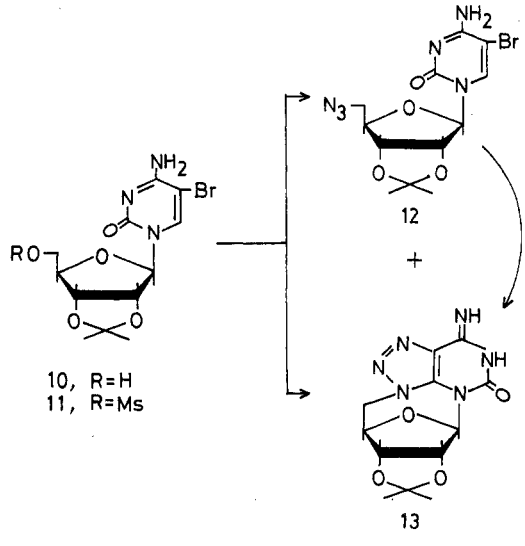
Prior to this cyclization experiment, a few degradation reactions were carried out to obtain some structural information. Heating **4** in 3 N hydrochloric acid at 95–100 °C for 12 h resulted in complete recovery of **4**, while heating **3a** in 1 N sodium hydroxide at 60–70 °C for 24 h revealed a slow and complex degradation, but no products were isolated. On the other hand, brief treatment of **3a** with 85% hydrazine allowed isolation of a homogeneous crystalline product which absorbed at 238 and 259 nm (sh). Analysis and mass spectroscopic data (see Experimental Section) indicated the incorporation of a molecule of hydrazine with expulsion of a –NHC=O unit (probably as carbamic acid). These data seem to be sufficient to assign to this compound the structure of N^1,5′-anhydro-N^5-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-4-carboxyhydrazino-5-amino-*v*-triazole (**9**) since genesis of another partial structure, **9′**, arising by fission of the triazole-conjugated carbonyl, is highly improbable under the mild reaction conditions. This hydra-



zide also presented some unusual features in the NMR spectrum[11] (see Experimental Section). Resonances of the 5′ methylene appeared at 4.12 and 4.94 ppm as a set of

clear-cut doublets of doublets with J_{gem} = 14 and $J_{4',5'a}$ = $J_{4',5'b}$ = 2.3 Hz. These chemical shifts are comparable with those of **3a** and **4** and suggest that the triazole ring and N^1,5′ bonding are present intact. The signal of the anomeric proton appeared at 5.30 ppm as a triplet (J = 1.8 Hz) which collapsed to a sharp singlet on D_2O addition. This indicated the presence of an imino group bonded with $C_{1'}$ and absence of interaction between $H_{1'}$ and $H_{2'}$. The reason for the appearance of the anomeric proton signal as a triplet, not as a doublet, is uncertain at present.[17] In addition, no signal corresponding to an isolated heteroaromatic proton was observed. Thus, in spite of the ambiguous resonance of $H_{1'}$, there is no obvious reason to support the alternative structure, **9′**.[18,19]

The azide reactions were then applied to a few cytidine analogues. 2′,3′-*O*-Isopropylidene-5-bromocytidine (**10**)[20] was treated with methanesulfonyl chloride to give a good yield of 2′,3′-*O*-isopropylidene-5′-*O*-mesyl-5-bromocytidine (**11**) as crystals. A TLC controlled reaction of **11** with sodium azide revealed two main products at the stage of disappearance of the starting material (see Experimental Section). In this case, extensive resinification was inevitable but preparative TLC permitted isolation of these products, the faster moving of which was a foam (14%) presenting an azide absorption at 2120 cm^{-1} (KBr) and uv absorption at 284 nm. These spectral data immediately permitted the conclusion that its structure was 5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene-5-bromocytidine (**12**), also supported by the following description. The slower moving crystalline product (8%) was 9,5′-cyclo-3-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-8-azaisoguanine (**13**) on the basis of analysis and spectral data.[21] For comparison, the uv spectra of **3a** and **13**



are represented in Figure 1, which also includes the CD spectrum of **3a**.[22] Compound **12** was formed in much higher yield (73%) in neutral medium[23] using ammonium azide generated in situ. Thermal conversion of **12** into **13** was, however, accompanied by resinification, giving merely 15% of **13**.

The formation of 9,5′-cyclized nucleosides **3a,b** and **13** from **2a–c** and **11** was unexpected and posed the question whether the actual intermediates were exclusively 5′-azido-5′-deoxy compounds like **6** and **12** or not. Although **13** was isolated as a by-product in the reaction of **11**, this did not preclude 8-azaxanthine or 8-azaisoguanine nucleosides with a leaving group of C-5′ as intermediates, in which ionized 9-NH could easily substitute at the 5′ methylene (the same chance would be open also for 2-keto oxygen in such a case). In a separate experiment, we synthesized 5′-*O*-trityl-2′,3′-*O*-isopropylidene-5-bromouridine (**14**) and submitted

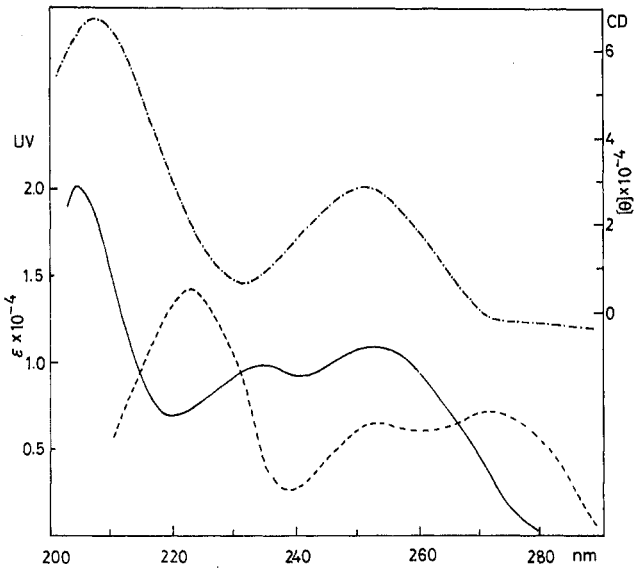
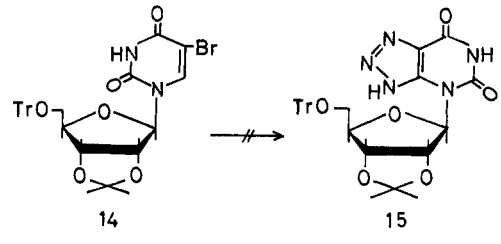


Figure 1. Uv [—, 9,5′-cyclo-3-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-8-azaxanthine (**3a**); - - -, 9,5′-cyclo-3-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-8-azaisoguanine (**13**)] and CD spectra (**3a**) in methanol.

it to a similar azide reaction, but starting material only was recovered after 50-h reaction at 110 °C with 5.5-fold excess sodium azide. This suggests that 5-bromopyrimidine bases



are unexpectedly inert toward external azide ion and that 5′-azido-5′-deoxy compounds are the only intermediates in our reactions. The persistence of **12** and extensive degradation in the case of the cytidine analogue (**11**) are in contrast to the behavior of uracil analogues (**2a–c**). This would imply that the 6 position in 5-bromocytidine analogues is far less electrophilic and hence complex reactions initiated by thermal decomposition of the 5′-azide group preceded its nucleophilic attack on the base moiety.[24]

In conclusion, this work presents the possibility of a one-step synthesis of other types of 6,5′-cyclized nucleosides using proper nucleophiles.

Experimental Section

All the melting points are uncorrected. The ultraviolet spectra were measured on a Jasco Model ORD/UV spectrophotometer. The nuclear magnetic resonance spectra were determined using a JNM C-60 HL spectrometer and tetramethylsilane as a internal standard, while the 100-MHz spectra were recorded with a Varian HA-100 spectrometer.[11] The circular dichroism spectrum was recorded with a Jasco Model J-20 recording spectropolarimeter in the laboratory of Professor H. Ogura, Kitazato University, Tokyo, for which we are grateful. Elemental analyses were carried out by Miss Y. Kawai using a Perkin-Elmer 240 elemental analyzer in this laboratory. Wakogel B-5 silica gel and Mallinkrodt silicic acid (100 mesh) were used for thin layer and column chromatography, respectively.

2′,3′-*O*-Anisylidene-5-bromouridine (1b). To a mixture of 5-bromouridine (2.68 g), anisaldehyde (1.5 ml), and ethyl orthoformate (3 ml) in DMF (8.3 ml) was added saturated hydrogen chloride solution in dioxane (2.5 ml). After standing overnight, the mixture was neutralized with solid sodium bicarbonate and the inorganic material was filtered off. The filtrate was evaporated in vacuo to a gum, which was partitioned between ethyl acetate (200

ml) and water (50 ml). The separated ethyl acetate solution was dried over sodium sulfate and evaporated to a paste, which was triturated with a small volume of ether. The ethereal solution was decanted off, and the residue was digested with a small amount of methanol to effect crystallization. Repeated crystallization from a mixture of ethanol and acetone gave colorless needles, mp 224–226 °C (2.16 g, 59%).

Anal. Calcd for $C_{17}H_{17}N_2O_7Br$: C, 46.27; H, 3.88; N, 6.35. Found: C, 46.34; H, 3.87; N, 6.29.

5′-*O*-Benzoyl-2′,3′-*O*-isopropylidene-5-bromouridine (2a). Benzoyl chloride (0.5 ml, 4.6 mmol) was slowly added to a stirred, ice-cold solution of 2′,3′-*O*-isopropylidene-5-bromouridine (**1a**, 1.39 g, 3.83 mmol) in pyridine (8 ml). After stirring under ice cooling for 1 h, the mixture was left at room temperature for several hours and evaporated in vacuo to a syrup. This was dissolved in methanol (20 ml) and poured into ice–water (200 ml) under vigorous stirring. The precipitate was collected by suction, dried on a porous plate, and recrystallized from methanol to give colorless needles (1.50 g, 84%): mp 206–208 °C; λ_{max} (MeOH) 225 nm (ϵ 13 500) and 274 (8300).

Anal. Calcd for $C_{19}H_{19}N_2O_7Br$: C, 48.88; H, 4.10; N, 5.99. Found: C, 49.07; H, 4.22; N, 5.99.

2′,3′-*O*-Isopropylidene-5′-*O*-tosyl-5-bromouridine (2b). Tosyl chloride (0.3 g, 1.56 mmol) was added to an ice-cold stirred solution of **1a** (0.5 g, 1.3 mmol) in pyridine (3 ml) and the mixture was left at room temperature overnight. After addition of further tosyl chloride (0.1 g), the mixture was stirred at room temperature for 3 h, treated with a small amount of water, and then evaporated in vacuo. The residue was taken into chloroform (30 ml), washed with water (10 ml), dried over sodium sulfate, and evaporated. Crystallization from benzene gave **2b** as prisms containing a molecule of benzene: mp 125–127 °C; yield 80–85%; λ_{max} (MeOH) 220 nm (ϵ 18 600) and 270 (10 200).

Anal. Calcd for $C_{19}H_{21}N_2O_8SBr \cdot C_6H_6$: C, 50.42; H, 4.53; N, 4.71. Found: C, 50.70; H, 4.67; N, 4.95.

2′,3′-*O*-Anisylidene-5′-*O*-benzoyl-5-bromouridine (2c). To a stirred ice-cold solution of **1b** (1.05 g, 2.4 mmol) in pyridine (6 ml) was added benzoyl chloride (0.32 ml, 2.88 mmol), and the mixture was stirred at room temperature for several hours. After the reaction was quenched with a small amount of water, the mixture was evaporated, redissolved in acetone (10 ml), and precipitated into ice–water (150 ml). The separated solid was air dried and recrystallized from a mixture of methanol and ethyl acetate to give 1.08 g (83%) of **2c** as needles: mp 221–223 °C; λ_{max} (MeOH) 224 nm (ϵ 34 800) and 272 (13 500).

Anal. Calcd for $C_{24}H_{21}N_2O_8Br$: C, 52.86; H, 3.88; N, 5.14. Found: C, 52.77; H, 3.97; N, 5.14.

9,5′-Cyclo-3-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-8-azaxanthine (3a). Method A. A mixture of **2a** (1.88 g, 4.0 mmol) and sodium azide (480 mg, 7.4 mmol) in DMF (16 ml) was stirred at 110 °C for 30 h. During the reaction, an aliquot was taken every 2 or 3 h, thoroughly evaporated, and examined by TLC using solvent systems ethyl acetate–chloroform (3:1 v/v), 20% ethanol in benzene, 10% methanol in chloroform, etc., to show only one product with the starting material. After further addition of sodium azide (240 mg, 3.7 mmol), the reaction was continued for an additional 10 h, until the starting material disappeared. The mixture was cooled, the insoluble material filtered off, and the filtrate evaporated in vacuo to a paste, which was extracted with ethyl acetate (3 × 50 ml) in the presence of water (50 ml). The ethyl acetate solution was back-washed with water (10 ml), dried over sodium sulfate, and evaporated to give a crystalline residue. Recrystallization from a mixture of methanol and ethyl acetate gave 844 mg (70%) of **3a** as colorless plates: mp above 300°; λ_{max} (MeOH) 235 nm (ϵ 9800) and 255 (10 500); MS *m/e* 307 (M^+), 292 ($M^+ - CH_3$); NMR (Me_2SO-d_6 + D_2O) δ 1.27 (3 H, s, Me), 1.48 (3 H, s, Me), 4.60 (1 H, dd, J_{gem} = 12, $J_{4',5'b}$ = 4.5 Hz, $H_{5'b}$), 4.84 (1 H, d, $J_{4',5'b}$ = 4.5 Hz, $H_{4'}$, partially overlapped on the signals of $H_{2'}$ and $H_{3'}$), 4.88 (2 H, br s, $H_{2'}$ and $H_{3'}$), 5.16 (1 H, d, J_{gem} = 12 Hz, $H_{5'a}$), and 6.32 (1 H, s, $H_{1'}$).

Anal. Calcd for $C_{12}H_{13}N_5O_5$: C, 46.90; H, 4.26; N, 22.80. Found: C, 47.09; H, 4.32; N, 22.53.

Method B. A mixture of **2b** (521 mg, 0.88 mmol) and sodium azide (57 mg, 0.88 mmol) in DMF (5 ml) was stirred at 110 °C for 5 h. After another addition of sodium azide (57 mg, 0.88 mmol), heating was continued for a further 10 h, during which most of the starting material was consumed. The mixture was evaporated to a gum and worked up as in procedure A to give 100 mg (37%) of **3a**, identified with the product in procedure A by ir and uv spectra.

9,5′-Cyclo-3-(2′,3′-*O*-anisylidene-β-D-ribofuranosyl)-8-azaxanthine (3b). A mixture of **2c** (992 mg, 1.87 mmol) and sodium azide (240 mg, 3.7 mmol) in DMF (8 ml) was stirred at 110 °C for 20 h. Additional sodium azide (120 mg, 1.85 mmol) was added and the mixture was held under the same conditions for another 10 h. The reaction was worked up essentially as for compound 3a. Crystallization from acetonitrile gave **3b** as fine needles (650 mg, 65%): mp above 280°; λ_{max} (MeOH) 225 nm (ϵ 24 600) and 255 (13 300).

Anal. Calcd for $C_{17}H_{15}N_5O_6$: C, 52.99; H, 3.90; N, 18.18. Found: C, 53.01; H, 3.99; N, 18.11.

9,5′-Cyclo-3-β-D-ribofuranosyl-8-azaxanthine (4). A mixture of **3a** (0.1 g) and IRA-120 (H^+ form, 8 ml) in 90% methanol (40 ml) was heated to reflux for 15 h. TLC using silica gel and 20% ethanol in benzene showed the presence of a single product and no starting material. The resin was filtered and washed with 90% methanol (50 ml) and the total was evaporated to give a solid residue. Recrystallization from methanol gave 70 mg (72%) of needles (**4**), which gradually decomposed between 270 and 280 °C.

Anal. Calcd for $C_9H_9N_5O_5 \cdot CH_3OH$: C, 40.14; H, 4.38; N, 23.14. Found: C, 39.97; H, 4.15; N, 23.14.

This methanolate, on crystallization from hot water, gave the solvent-free product as massive columns which also began to decompose at around 270 °C and did not melt at below 300 °C: λ_{max} (MeOH) 240 nm (ϵ 8050) and 257 (10 800); MS *m/e* 267 (M^+); NMR (Me_2SO-d_6 + D_2O) δ 4.22 (1 H, dd, J_{gem} = 12, $J_{4',5'b}$ = 4.5 Hz, $H_{5'b}$), 4.22 (1 H, d, $J_{4',5'b}$ = 4.5 Hz, $H_{4'}$, partially overlapped on the signal of $H_{5'b}$), 4.68 (1 H, quintet, J = 3.6 Hz, $H_{2'}$ or $H_{3'}$), 4.91 (1 H, d-like quartet, J = 3.6 Hz, $H_{3'}$ or $H_{2'}$), 5.06 (1 H, d, J_{gem} = 12 Hz, $H_{5'a}$), and 6.09 (1 H, s, $H_{1'}$).

Anal. Calcd for $C_9H_9N_5O_5$: C, 40.45; H, 3.37; N, 26.21. Found: C, 40.71; H, 3.61; N, 26.40.

Compound **4** can be more conveniently prepared by heating **3a** (50 mg) in 1 N hydrochloric acid (6 ml) at 95–100 °C for 5–6 h. **3b** was analogously hydrolyzed to **4**.

Reconversion of 4 into 3a. A mixture of the methanolate of **4** (20 mg, 0.067 mmol), acetone (0.2 ml), ethyl orthoformate (0.05 ml), DMF (0.4 ml), and saturated hydrogen chloride solution in dioxane (3 drops) was left at room temperature for 18 h, neutralized with solid sodium bicarbonate, and filtered by suction after adding DMF (2 ml). The filtrate was evaporated in vacuo and the residue partitioned between ethyl acetate (30 ml) and water (10 ml). The separated ethyl acetate layer was worked up as usual to give 13 mg of homogeneous crystals, which was identified with **3a** by ir and uv spectra.

5′-Azido-5′-deoxy-2′,3′-*O*-isopropylidene-5-bromouridine (6). *N*-Bromoacetamide (320 mg, 2.3 mmol) was added to a solution of 5′-azido-5′-deoxy-2′,3′-*O*-isopropylideneuridine (**5**, 642 mg, 2.1 mmol) in anhydrous tetrahydrofuran (9 ml) and the mixture was stirred at room temperature for 3 h. TLC using chloroform–ethyl acetate (1:1 v/v) as developer indicated quantitative conversion of **5** into a faster moving substance. The solvent was evaporated off below 40 °C and the residue was partitioned between ethyl acetate (15 ml) and ice–water (5 ml). The separated organic phase was dried over sodium sulfate and evaporated to a gum, which crystallized from ethanol to afford 640 mg (79%) of **6** as granules of mp 165–167°: λ_{max} (MeOH) 272 nm (ϵ 10 200); ir (KBr) ν_{N_3} 2100 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}BrN_5O_5$: C, 37.11; H, 3.61; N, 18.04. Found: C, 37.24; H, 3.64; N, 17.88.

Thermal Conversion of 6 into 3a. A solution of 6 (300 mg, 0.775 mmol) in DMF (20 ml) was heated at 110–120 °C for 20 h. TLC at this stage revealed only one product corresponding to **3a** and no starting material. The solvent was evaporated off in vacuo, and the residue was thoroughly digested with ice–water (3 ml). The solid was collected by suction, dried on a porous plate, and crystallized from methanol to give 210 mg (70%) of **3a**, identical with the above authentic sample in terms of ir and uv spectra.

***N*^{1},5′-Anhydro-*N*^{5}-(2′-3′-*O*-isopropylidene-β-D-ribofuranosyl)-4-carboxyhydrazino-5-amino-*v*-triazole (9).** **3a** (138 mg, 0.45 mmol) was dissolved in 85% hydrazine (2.3 ml) by shaking and the solution was left at room temperature. After 30 min, crystals began to deposit. TLC after 2 h reaction indicated no starting material. After a total of 3 h, the mixture was evaporated in vacuo below room temperature and the residue repeatedly coevaporated with ethanol to remove residual water and hydrazine. Crystallization of the residual solid from methanol gave 78 mg (59%) of **9** as colorless needles: mp 233–235 °C; λ_{max} (MeOH) 238 nm (ϵ 14 000) and 259 (10 000, sh); MS *m/e* 296 (M^+), 239 ($M^+ - CH_3COCH_3$ + H^+); NMR (Me_2SO-d_6) δ 1.19 (3 H, s, Me), 1.39 (3 H, s, Me), 3.00–3.70 (~3 H, br s, NH_2 of the hydrazino group and 5-NH), 4.12 (1 H, dd, J_{gem} = 14.0, $J_{4',5'a}$ = 2.3 Hz, $H_{5'a}$), 4.28 (1 H, d, $J_{2',3'}$ = 6.0

Hz, $H_{2'}$ or $H_{3'}$), 4.54 (1 H, d, $J_{2',3'}$ = 6.0 Hz, $H_{3'}$ or $H_{2'}$), 4.55 (1 H, t, $J_{4',5'b}$ = 2.3 Hz, $H_{4'}$), 4.94 (1 H, dd, J_{gem} = 14.0, $J_{4',5'b}$ = 2.3 Hz, $H_{5'b}$), 5.30 (1 H, t, J = 1.8 Hz, $H_{1'}$, collapsed to a singlet on D_2O addition), 7.50 (1 H, d, J = 4.0 Hz, O=CNH–, D_2O exchangeable).

Anal. Calcd for $C_{11}H_{16}N_6O_4$: C, 44.59; H, 5.44; N, 28.37. Found: C, 44.79; H, 5.42; N, 28.39.

2',3'-*O*-Isopropylidene-5'-*O*-methanesulfonyl-5-bromocytidine (11). Methanesulfonyl chloride (0.3 ml, 3.87 mmol) was gradually added to a stirred solution of **10** (1.16 g, 3.2 mmol) in pyridine (8 ml) which had been precooled up to −20 °C. After standing at this temperature overnight, the mixture was left at room temperature for 1 h and treated with methanol (1 ml) for another 1 h. The solvent was evaporated in vacuo below room temperature and the residue was partitioned between ethyl acetate (90 ml) and ice–water (30 ml). The separated organic phase was dried over sodium sulfate and evaporated to a paste, which crystallized on standing with a small amount of ethanol. Recrystallization from ethanol at room temperature gave 990 mg (70%) of needles (**11**), mp 202–204 °C dec, λ_{max} (MeOH) 284 nm (ϵ 6800).

Anal. Calcd for $C_{13}H_{18}N_3O_7SBr$: C, 35.46; H, 4.12; N, 9.54. Found: C, 35.73; H, 4.31; N, 9.38.

Reaction of Sodium Azide with 2',3'-*O*-Isopropylidene-5'-*O*-methanesulfonyl-5-bromocytidine (11). A mixture of **11** (440 mg, 1 mmol) and sodium azide (120 mg, 1.85 mmol) in DMF (5 ml) was stirred at 110 °C. After 24 h, further sodium azide (65 mg, 1 mmol) was added and heating continued for an additional 9 h. During the reaction, an aliquot was withdrawn every 2 or 3 h and examined by TLC using the solvent systems, 10% methanol in chloroform and/or 30% ethanol in benzene, to show the formations of two main products with slight amounts of by-products. A considerable degree of resinification was observed. The dark mixture was filtered to remove inorganic materials and the filtrate was evaporated in vacuo. The residue was triturated with ice–water (10 ml) and the solid precipitate was collected. The aqueous filtrate was extracted with ethyl acetate (60 ml) and the extract was combined with the above obtained precipitate. The solution of the product was then dried over sodium sulfate and evaporated to a gum, which was then charged on a silica gel plate (20 × 20 cm, 2 mm thick) and developed twice using 10% methanol in chloroform. Elution of the faster moving main band with acetone and ethanol gave 70 mg (14%) of 5'-azido-5'-deoxy-2',3'-*O*-isopropylidene-5-bromocytidine (**12**) as a homogeneous foam, which resisted crystallization, ir (Kbr) ν_{N_3} 2120 cm^{-1}, λ_{max} (MeOH) 284 nm (ϵ ~7000).

On the other hand, the slower moving band gave 50 mg (8%) of 9,5'-cyclo-3-(2',3'-*O*-isopropylidene-β-D-ribofuranosyl)-8-azaisoguanine (**13**) as powderlike crystals after recrystallization from ethanol: mp 197–199 °C; λ_{max} (MeOH) 223 nm (ϵ 14 200), 253 (6400), and 271 (7000); NMR ($CDCl_3$) δ 1.30 (3 H, s, Me), 1.52 (3 H, s, Me), 4.40–5.40 (5 H, br s, $H_{2'}$, $H_{3'}$, $H_{4'}$, and 5'-CH_2), 6.70 (1 H, s, $H_{1'}$), 7.35 (1 H, br s, NH, D_2O exchangeable), and 9.20 (1 H, br s, NH, D_2O exchangeable).

Alternative Synthesis of 5'-Azido-5'-deoxy-2'-3'-*O*-isopropylidene-5-bromouridine (12) from 11 and Ammonium Azide. A mixture of **11** (765 mg, 1.74 mmol), sodium azide (210 mg, 3.23 mmol), and ammonium chloride (175 mg, 3.27 mmol) in DMF (8 ml) was stirred at 90 °C for 10 h. After cooling, inorganic materials were filtered off and the filtrate was evaporated in vacuo. The red-brown residue was triturated with ice–water (10 ml) to give a precipitate, which was filtered by suction. The filtrate was extracted with ethyl acetate (100 ml) and the separated organic phase was combined with the above obtained precipitate. The solution was dried and evaporated to a foam, which was chromatographed on a silica gel plate (20 × 20 cm, 2 mm thick) using 10% methanol in chloroform (twice developed). The main band gave 490 mg (73%) of **12** as a homogeneous foam, identified with the above obtained product by ir and uv spectra. A slight amount of **13** was also detected by TLC but was neglected.

***Thermal Conversion of* 12 into 13.** The above obtained **12** (490 mg, 1.26 mmol) in DMF (10 ml) was heated at 120 °C for 12 h. TLC showed one main, movable product corresponding to **13** and no starting material. The mixture was evaporated to a dark residue, which was dissolved in methanol (20 ml), adjusted to pH 7–8 with concentrated ammonium hydroxide–methanol (1:3 v/v), and again evaporated to a tar. This was extracted with hot acetone (4 × 30 ml) and the combined extract was submitted to preparative TLC (20 × 20 cm, 2 mm thick; $CHCl_3$–MeOH, 9:1). Elution of the main band with acetone gave 60 mg (15%) of practically pure powder, which was fully identified with an authentic specimen of **13**.

Registry No.—**1a**, 54503-61-6; **1b**, 57901-58-3; **2a**, 57901-59-4; **2b**, 57901-61-8; **2c**, 57901-62-9; **3a**, 57901-63-0; **3b**, 57901-64-1; **4**, 57901-65-2; **4** CH_3OH, 57968-00-0; **5**, 15083-05-3; **6**, 57901-66-3; **9**, 57901-67-4; **10**, 57901-68-5; **11**, 57901-69-6; **12**, 57901-70-9; **13**, 57901-71-0; 5-bromouridine, 957-75-5; anisaldehyde, 123-11-5; benzoyl chloride, 98-88-4; sodium azide, 26628-22-8; *N*-bromoacetamide, 79-15-2; methanesulfonyl chloride, 124-63-0.

References and Notes

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(16) Measurement in Me_2SO-d_6 without D_2O revealed two hydroxyl proton signals at 5.31 (J = ~6.2 Hz) and 5.63 ppm (J = ~3.9 Hz) and also a signal for a lactam NH at 11.35 ppm (br s) besides rather more complicated signals for the other furanose protons.
(17) A close inspection of the NMR spectrum of **9** in Me_2SO-d_6 without D_2O revealed, besides the broad resonance at 3.0–3.7 ppm, a very broad, shallow signal envelope (~0.5 H) at 8.8–9.5 ppm, which was D_2O exchangeable. This might suggest possibilities for a variety of partial hydrogen bondings between the 4-carboxyhydrazino and 5-imino groups. Actually, it is possible to write down variously six-membered rings hydrogen bonded between the 5-NH and the carbonyl oxygen or hydrazino NH with or without concomitant five-membered hydrogen bonding within the carboxyhydrazino group. However, no conclusion can be drawn regarding the well-resolved, sharp triplet.
(18) A short treatment of **9** with acetone at room temperature gave a faster moving (on a silica gel plate) syrup (probably acetone hydrazone), whose complete purification was, however, unsuccessful.
(19) It is interesting to note that hydrazine attacked C-6 of the 8-azaxanthine ring. This observation is parallel with the hydrazinolysis of thymidylic acid, which occurs at C-4 of the pyrimidine base: A. Temperli, H. Türler, P. Rüst, A. Danon, and E. Chargaff, *Biochim. Biophys. Acta*, **91**, 462 (1964).
(20) A good yield synthesis of this compound was learned from Dr. T. Ueda through private communication, for which we are grateful.
(21) The NMR spectrum measured at 60 MHz using a very limited amount of **13** failed to give clear-cut resonances for most of the sugar protons. Our tentative assignment of the structure with a 6-imino group is based on the separate apparitions of the two NH signals.
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(24) A trial experiment has shown that pyrolysis of **7** in DMF smoothly proceeds at 115–120 °C to give a highly insoluble polymeric compound, the structure of which is unknown at present.