Introduction of an Azide Group into Some Uridine Derivatives via 2',3'-Benzoxonium and 2',3'-Azidonium Intermediates

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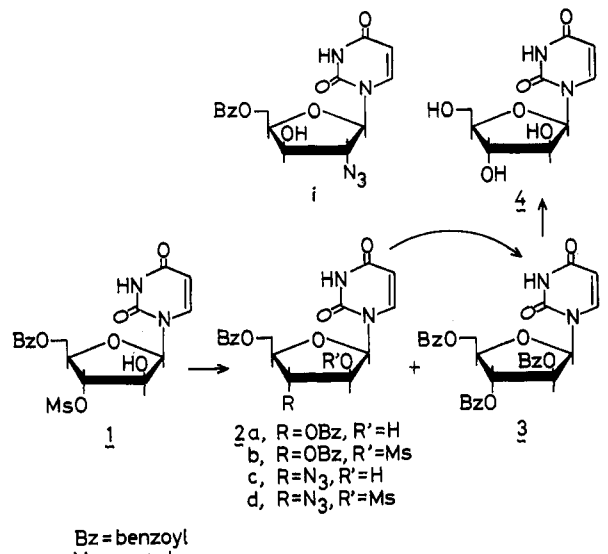
With a view to probing the reactions of supposed 2',3'-benzoxonium (**5**) and 2',3'-azidonium (**19**) intermediates with azide ion, their precursors, **2b** and **2d**, were synthesized. **2b** with azide ion gave 1-(2'-azido-2'-deoxy-3',5'-di-*O*-benzoyl-β-D-ribofuranosyl)uracil (**7**) and its 3'-debenzoylated analogue (**8**). These were converted to the known compounds, **11a,b.** Treatment of 1-(2'-azido-2'-deoxy-5'-*O*-benzoyl-3'-*O*-mesyl-β-D-ribofuranosyl)uracil (**12**), obtained from **8**, with potassium *tert*-butoxide and sodium *p*-chlorobenzoate gave 1-(2'-azido-5'-*O*-benzoyl-2',3'-dideoxy-β-D-glyceropent-2'-enofuranosyl)uracil (**14**) and 1-(5'-*O*-benzoyl-2'-*O*-*p*-chlorobenzoyl-3'-deoxy-2',3'-imino-β-D-arabinofuranosyl)uracil (**15**), respectively. **2d** with azide ion gave 5'-*O*-benzoyl-2',3'-dideoxy-2',3'-diazidouridine (**21a**), which was converted to **21b** and the corresponding diamino compound (**22c**). 5'-*O*-Benzoyl-2',3'-dideoxy-2',3'-diamino compound (**22a**) obtained from **21a** was converted to a cyclic urea (**23**) for structural assignments of **21** and **22.** Some mechanistic comments are also presented.

Among the many known routes for the synthesis of amino nucleosides or their precursors, reactions of modified nucleosides with azide ion have attracted our recent concern, largely through the multiple aspects of an azide reaction[1] which would uniquely modify natural nucleosides.[2,25] In the pyrimidine series, nucleophilic ring openings of 2,2'-,[3] 2,3'-anhydro,[4] and 2',3'-epoxy nucleosides[5] with amines and/or azide salts have been explored. However, we lack appropriate methods for introducing an "up" amino group into pyrimidine nucleosides[6] although in the adenine series up-side amination through an azide has been achieved in a few cases.[7] With respect to this point, a 2',3'-ribo benzoxonium (Scheme II, **5**) or the corresponding azidonium cation intermediate (Scheme IV, **19**) deserves investigation as a possible acceptor of azide ion, since it is established that **5** can accept external benzoate anion at $C_{2'}$[8] or $C_{3'}$[9] from the "up" side, accompanied by a intramolecular reaction leading to a 2,2'-anhydro nucleoside. On the other hand, azidonium chemistry as a logical extension remains as yet to be explored in the nucleoside area, and appeared to assure a direct route to 2',3'-diamino sugar nucleosides. Syntheses of this type of compounds were once proposed by Baker et al.[10] but have not yet been described. This paper describes the results of a synthetic study carried out using 1-(3',5'-di-*O*-benzoyl-2'-*O*-mesyl-β-D-arabinofuranosyl)uracil (**2b**) and 1-(3'-azido-3'-deoxy-5'-benzoyl-2'-*O*-mesyl-β-D-arabinofuranosyl)uracil (**2d**) as precursors for the obligatory intermediates, **5** as well as **19.**

Syntheses of the Substrates, 2b and 2d, for Azide Reactions. 1-(3',5'-Di-*O*-benzoyl-β-D-arabinofuranosyl)uracil (**2a**) was obtained from 1-(5'-*O*-benzoyl-3'-*O*-mesyl-β-D-arabinofuranosyl)uracil (**1**)[5] by the known method.[8] This time, a minor by-product, 1-(2',3',5'-tri-*O*-benzoyl-β-D-arabinofuranosyl)uracil (**3**), was isolated by chromatography. The structure of **3** was based upon analysis, spectroscopic data (see Experimental Section and Table I), and deprotection to spongouridine (**4**). Appearance of an NH resonance at 9.10 ppm in its NMR spectrum excluded N-benzoylation. This compound has proved to be formed by reaction between **2a** and sodium benzoate.[11]

Similarly, treatment of **1** with a 2:1 mixture of sodium azide and ammonium chloride gave a TLC-homogeneous foam, the NMR spectrum of which exhibited two kinds of anomeric proton signals at 6.15 (¾ H, d, J = 3.9 Hz) and 5.83 ppm (¼ H, s), a H_5 signal at 5.90 ppm (d, $J_{5,6}$ = 8.0 Hz), and a $C_{5'}$-methylene signal at 4.2 ppm as a broad singlet. The resonances of the other sugar protons merged into a complex multiplet at a range of 4.4–5.0 ppm. This product was hence concluded to be a 4:1 mixture of 1-(3'-azido-3'-deoxy-5'-*O*-benzoyl-β-D-arabinofuranosyl)uracil (**2c**) and its xylo isomer (i), and was directly used for the next step. In this reaction, intermediacy of an 2',3'-epoxy compound[5] was evidenced by TLC in a separate, time-controlled experiment. Mesylation of impure **2c** gave 1-(3'-azido-3'-deoxy-5'-*O*-benzoyl-2'-*O*-mesyl-β-D-arabinofuranosyl)uracil (**2d**) as crystals. These substrates were fully characterized spectroscopically.

Scheme I



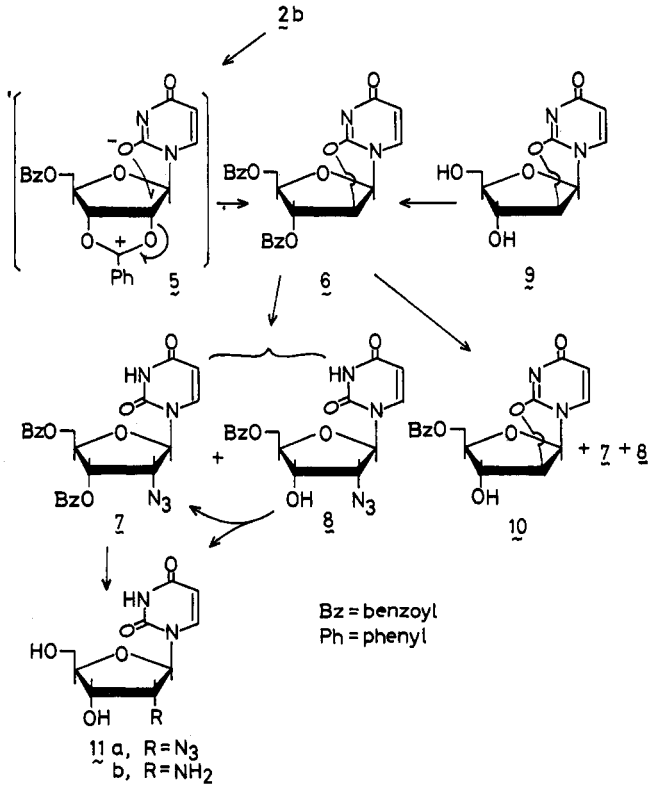
Reaction of 1-(3',5'-Di-*O*-benzoyl-2'-*O*-mesyl-β-D-arabinofuranosyl)uracil (2b) with Azide Ion. After many trial experiments using sodium azide alone, sodium azide–ammonium chloride mixture in various molar ratios, and several temperature conditions, we chose the use of a large excess of a 3:2 mixture of sodium azide and ammonium chloride, and a reaction temperature of 120 °C. In all cases two primary products were detected by thin layer chromatography, and elongation of time or raising the temperature above 120 °C frequently caused deglycosidation and formation of a couple of secondary products, presumably by thermal decomposition of the introduced azide function.[12] It is to be noted that the use of a one to one mixture of the reagents at 120 °C retarded the reaction and consequently caused considerable deglycosidation in spite of the higher solubility in DMF of ammonium azide.[2] Thus, the selected reaction conditions described in this paper gave only the two primary products, 1-(2'-azido-2'-deoxy-5'-*O*-benzoyl-β-D-ribofuranosyl)uracil (**8**) and 1-(2'-azido-2'-deoxy-3',5'-di-*O*-benzoyl-

Table I. NMR Spectra of Uridine Derivatives[a-c]

Registry no.	Compd	$C_{5'}H$	$C_{4'}H$	$C_{3'}H$	$C_{2'}H$	$C_{1'}H$	C_5H	N_3H
4348-69-0	**3**[d]	4.82 (m)	4.50 (m)	5.60 (dd) $J_{2',3'}$ = 1.8 Hz $J_{3',4'} \simeq$ 3.0 Hz	5.82 (dd) $J_{1',2'}$ = 4.2 Hz $J_{2',3'}$ = 1.8 Hz	6.45 (d) $J_{1',2'}$ = 4.2 Hz	5.52 (dd) $J_{5,6}$ = 8.0 Hz $J_{5,NH}$ = 1.6 Hz	9.10 (br s)
59686-41-8	**2d**[f]	4.47–4.75 (m)		4.16 (m)	5.31 (dd) $J_{1',2'}$ = 5.0 Hz $J_{2',3'}$ = 4.0 Hz	6.16 (d) $J_{1',2'}$ = 5.0 Hz	5.58 (d) $J_{5,6}$ = 8.0 Hz	10.86 (br s)
26889-44-1	**7**[d]	4.54–4.88 (m)		5.50 (t) $J_{2',3'} = J_{3',4'}$ = 8.0 Hz	4.38 (dd) $J_{1',2'}$ = 4.5 Hz $J_{2',3'}$ = 6.0 Hz	5.96 (d) $J_{1',2'}$ = 4.5 Hz	5.54 (d) $J_{5,6}$ = 8.0 Hz	8.91 (br s)
59686-42-9	**8**[f]	4.20–4.75 (m)				5.77 (d) $J_{1',2'}$ = 4.3 Hz	5.52 (d) $J_{5,6}$ = 8.0 Hz	9.03 (br s)
31616-01-0	**6**[e]	4.36 (m)	4.81 (m)	5.74 (m) J = 6.0 and ca. 1.5 Hz		6.46 (d) $J_{1',2'}$ = 6.0 Hz	5.87 (d) $J_{5,6}$ = 8.0 Hz	
24877-18-7	**10**[e]		4.11–4.60 (m)		5.35 (d) $J_{1',2'}$ = 6.0 Hz	6.37 (d) $J_{1',2'}$ = 6.0 Hz	5.95 (d) $J_{5,6}$ = 8.0 Hz	
59686-43-0	**12**[d]	4.40–4.72 (m) (including $H_{2'}$)		5.33 (t) $J_{2',3'} = J_{3',4'}$ = 6.2 Hz		5.68 (d) $J_{1',2'}$ = 3.7 Hz	5.55 (d) $J_{5,6}$ = 8.0 Hz	9.57 (br s)
59686-44-1	**14**[d]	4.57 (t) $J_{4',5'}$ = 3.5 Hz	5.18 (o) $J_{4',5'} = J_{3',4'}$ = 3.5 Hz $J_{1',4'}$ = 1.6 Hz	6.82 (dd) $J_{1',3'}$ = 1.6 Hz $J_{3',4'}$ = 3.5 Hz		5.83 (t) $J_{1',3'} = J_{1',4'}$ = 1.6 Hz	5.38 (d) $J_{5,6}$ = 8.0 Hz	9.42 (br s)
59686-45-2	**21a**[f]	4.20–4.28 (m)				5.67 (d) $J_{1',2'}$ = 2.1 Hz	5.50 (d) $J_{5,6}$ = 8.0 Hz	10.77 (br s)
59686-46-3	**22a**[e]	3.10–3.65 (m) (in amino envelope)	4.0 (m)	4.50 (t) J = 5.2 and 3.0 Hz		5.65 (br s)	5.44 (d) $J_{5,6}$ = 8.0 Hz	*g*
59686-47-4	**24**[e]	3.80–4.20 (m)		4.55 (d) J = 5.3 Hz		6.10 (d) $J_{1',2'}$ = 5.3 Hz	5.42 (d) $J_{5,6}$ = 8.0 Hz	*g*

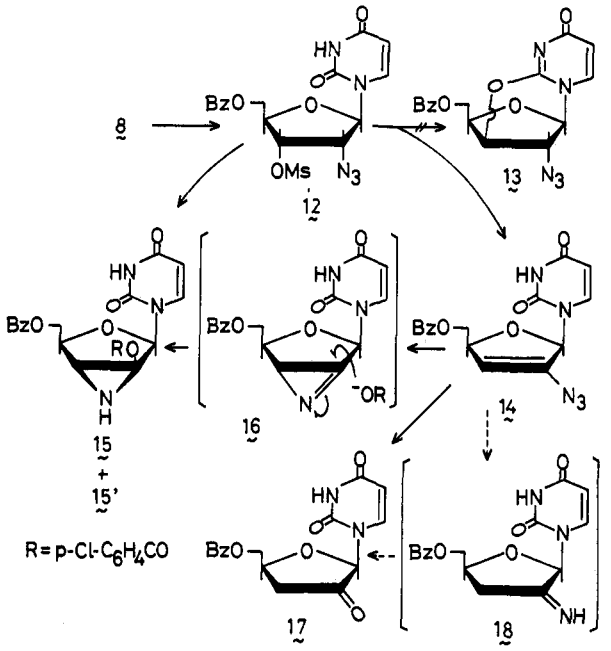
[a] The spectra of **3**, **7**, and **22a** were measured at 100 MHz, the others at 60 MHz. [b] (s) = singlet, (d) = doublet, (dd) = doublet of doublets, (t) = triplet, (o) = octet, (m) = multiplet. All these terms are used to refer to the apparent forms of splittings for the sake of visualization. Thus, for example, the t and dd for H_3, denote a similar ABX type resonance. [c] In most cases H_6 signals were overlayed on the benzoyl envelope and hence were omitted. [d] In $CDCl_3$. [e] In Me_2SO-d_6. [f] In a mixture of $CDCl_3$ and Me_2SO-d_6. [g] Did not appear clearly.

Scheme II

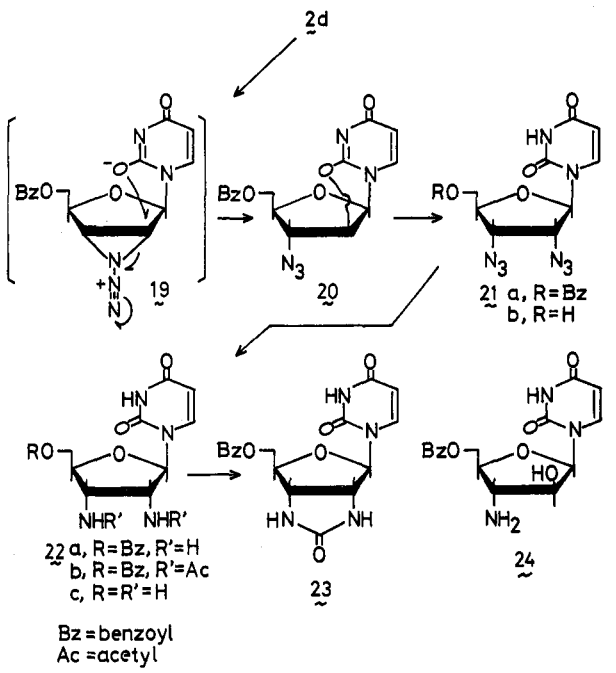


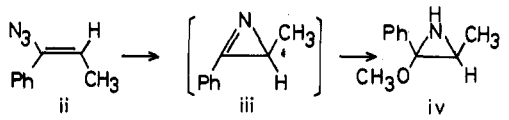
β-D-ribofuranosyl)uracil (**7**), in 53 and 16% yield, respectively, at the stage the starting material disappeared. Crystalline **7** exhibited uridine absorptions and well-resolved nuclear magnetic resonances[13] (see Table I). The resonance at 5.50 ppm was assigned to the benzoyloxy-deshielded $H_{3'}$, which interacted with 2′ and 4′ protons with the same coupling constant, 6.0 Hz, while the doublet of doublets at 4.38 ppm was reasonably assigned to the azido-shielded 2′ proton. However, these data failed to assign configurations at $C_{2'}$ and $C_{3'}$, since a survey of literature values[14] for $H_{1'}$–$H_{2'}$ coupling constants permits no definitive discrimination between ribo and arabino configurations. This situation also holds for all the compounds described in this paper. Nevertheless, the melting point, 156–157 °C, and the general resonance pattern strongly suggested its identity with a described substance,[3] and the structure was established by comparison with an authentic sample kindly provided by Dr. Moffatt.[15] The minor variations of the spectroscopic data would be explainable in terms of instrumental differences. The structure of noncrystalline **8** was confirmed by its conversion into **7** and conclusively by the experiments depicted in Scheme III. The ill-resolved NMR spectrum failed to locate the benzoyl group at this stage. Thus, the exclusive formation of the ribonucleosides, **7** and **8**, requires 2,2′-anhydro-1-(3′,5′-di-*O*-benzoyl-β-D-arabinofuranosyl)uracil (**6**), as the sole second intermediate. Since in our case no trace of **6** was detected by TLC, the molecules of **6** seem to have been intercepted as they formed and, accordingly, the major rate-determining step appears to be generation of the benzoxonium intermediate, **5**. Evidence for the intermediacy of **6** was obtained starting from an authentic preparation of **6** which was conveniently synthesized from 2,2′-anhydro-β-D-arabinofuranosyluracil (**9**).[3] Reaction of **6** with a 3:2 mixture of sodium azide and ammonium chloride under similar conditions gave **8** in a similar yield (60%) and

Scheme III



Scheme IV





a negligible amount of **7**, while the use of a 1:1 mixture afforded 2,2′-anhydro-1-(5′-*O*-benzoyl-β-D-arabinofuranosyl)uracil (**10**, 43%), **8** (18%), and **7** (15%). The structure of **10** was clear on the basis of analysis and spectroscopic data (see Experimental Section and Table I). The location of the benzoyloxy group was confirmed by the rather deshielded chemical shift of the $C_{5'}$ protons at the range of 4.11–4.60 ppm. Reasons for the formation of **10** and also of **8** are uncertain at present. It was consistently observed that **8** appeared slightly later than **7**, usually after a reaction time of 40–60 min, while **7** was detected after 20–30 min and persisted until the end of the reaction. Thus, an explanation for the genesis of **8** (**7** and/or **10**) requires another scrupulous study. Deprotection of **7** and **8** gave 2′-azido-2′-deoxyuridine (**11a**)[3] as a syrup, which was directly reduced to 2′-amino-2′-deoxyuridine (**11b**).[3] Attempted crystallization of **11b** was unsuccessful in our case.

At an earlier stage, we attempted to convert **8** into a 2,2′- or 2,3′-anhydro compound (**13**) for its structural elucidation, since it was expected that such a rigid system would give more convincing spectroscopic information, especially with respect to NMR spectroscopy. Accordingly, **8** was mesylated to 1-(2′-azido-2′-deoxy-5′-*O*-benzoyl-3′-*O*-mesyl-β-D-ribofuranosyl)uracil (**12**), the NMR spectrum of which showed the mesyl-deshielded 3′-proton signal at 5.33 ppm as a tripletlike ABX pattern (Table I). The absence of coupling of $H_{3'}$ with the anomeric proton firmly established the location of the hydroxyl in **8**. Treatment of **12** with potassium *tert*-butoxide caused no cyclization, but gave exclusively 1-(2′-azido-5′-*O*-benzoyl-2′,3′-dideoxy-β-D-glyceropent-2′-enofuranosyl)-uracil (**14**) as a syrup. Although **14** is rather unstable as is usual with common vinyl azides and therefore its repeated elemental analysis has failed to offer reasonable values, sufficient structural informations were given by NMR spectroscopy. Thus, in the spectrum of **14**, the $H_{4'}$ signal appeared at 5.18 ppm as an octetlike multiplet, $H_{1'}$ at 5.83 ppm (tripletlike long-range couplings), and $H_{3'}$ at 6.82 ppm (dd). These resonance patterns characteristic for 2′-substituted didehydro nucleosides have already been documented by us.[16] Heating **12** with sodium *p*-chlorobenzoate in DMF gave 1-(5′-*O*-benzoyl-2′-*O*-*p*-chlorobenzoyl-3′-deoxy-2′,3′-imino-β-D-arabinofuranosyl)uracil (**15**) and an unknown compound (**15′**). The structure of **15** was confirmed by 100-MHz NMR spectroscopy[13] (see Experimental Section). Thus, the broad, two-proton singlet at 3.30 ppm collapsed, on D_2O addition, to a one-proton doublet at 3.33 ppm with a small coupling constant (1.2 Hz). This should be assigned to an aziridine proton somewhat deshielded by one or both of the ester functions.[17] Appearance of the $H_{1'}$ signal as a singlet and the small $H_{3'}$–$H_{4'}$ coupling constant substantiate the proposed structure (**15**) with a "down" 2′,3′-imino function, in which the dihedral angle between $H_{3'}$ and $H_{4'}$ is quite close to 90°.[18] The formation of **15** is explainable by the reaction sequence **12** → **14** → **16** → **15**. This was also verified by a separate, tiny scale experiment using **14** and sodium *p*-chlorobenzoate.[23] In this case, **15** was detected by TLC as one of the two major products. Synthesis of analogous 2-methoxy-2-phenyl-3-methylaziridine (iv) from a vinyl azide (ii) via an azirine (iii) has been recorded by Hassner et al.[19]

Several trials of one-step reduction of **14** to a 2′-amino-2′,3′-dideoxynucleoside have been unsuccessful. Specifically, atmospheric pressure hydrogenation of **14** in the presence of palladium on charcoal gave 5′-*O*-benzoyl-3′-deoxy-2′-ketouridine (**17**),[16b] which must have resulted by hydrolysis of an intervening imine (**18**) during the reduction or the workup procedure.

Reaction of 1-(3′-Azido-3′-deoxy-5′-*O*-benzoyl-2′-*O*-mesyl-β-D-arabinofuranosyl)uracil (2d) with Azide Ion. Several trial experiments, conducted on small scales, revealed that the use of excess sodium azide at a temperature between 115 and 120 °C is preferable to the use of sodium azide–ammonium chloride mixtures to suppress deglycosidation to a minimum. Thus, reaction of **2d** with 4 molar equiv of sodium azide gave 1-(2′,3′-dideoxy-2′,3′-diazido-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil (**21a**) in 59% yield. Although a certain degree of deglycosidation was inevitable, no other notable side reactions were observed, provided purity of the starting material and the temperature condition just below 120 °C were

assured. The configurations of the azide groups could not be assigned by available spectroscopic methods but were finally established chemically. **21a** was deprotected to 1-(2′,3′-dideoxy-2′,3′-diazido-β-D-ribofuranosyl)uracil (**21b**), a syrup, which was directly hydrogenated to 1-(2′,3′-dideoxy-2′,3′-diamino-β-D-ribofuranosyl)uracil (**22c**). On the other hand, similar reduction of **21a** gave crystalline 1-(2′,3′-dideoxy-2′,3′-diamino-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil (**22a**) in a modest yield. To establish cis stereochemistry for the two amino groups, **22a** was heated with acetic anhydride merely to give 1-(2′,3′-dideoxy-2′,3′-diacetamido-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil (**22b**), but not a 2′,3′-cyclic acetamidine. However, **22a** with diphenyl carbonate provided the desired product, 1-(2′,3′-dideoxy-2′,3′-diamino-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil 2′,3′-carbonate (**23**), which was characterized by analysis, uv, and mass spectroscopy (see Experimental Section). If azide ion attacks **19** from the "up" side, there should be formed one or both of the two possible trans isomers (xylo and arabino derivatives), while there are no obvious, mechanistic reasons to support a cis lyxo configuration. In addition, a possibility of benzoyloxy rearrangement to $C_{2'}$ or $C_{3'}$ with concomitant introduction of an azide group at $C_{5'}$ is excluded, since in the NMR spectrum of **21a** the resonance of the $C_{5'}$ methylene occurred at an usually observed, ester-deshielded position, while those of the azido-shielded $H_{2'}$ and $H_{3'}$ were extensively shifted upfield to merge with $C_{4'}$ and $C_{5'}$ protons (Table I).

Circular dichroism spectra[20] of **22a** and 1-(3′-amino-3′-deoxy-5′-*O*-benzoyl-β-D-arabinofuranosyl)uracil (**24**) obtained from **2c** were measured and compared with the described values for uridine and spongouridine.[21] Although the arabino type amino nucleoside, **24**, exhibited an intense positive Cotton effect at 267 nm comparable with spongouridine, the corresponding molar ellipticity of **22a** is located between that of uridine and spongouridine, thus excluding direct configurational assignment at $C_{2'}$.

Thus, as in the case of the reaction of **2b**, a 2,2′-anhydro nucleoside, **20**, must have intervened and been immediately intercepted by azide ion. In both cases, it is highly improbable that azide ion directly attacks **2b** and **2d** from the bottom side extruding the leaving group at the secondary carbon atom.[22] This seems to be verified by the above observation that the reactions were retarded by the use of less basic ammonium azide,[2] which might have retarded production of the second intermediates (**6** and **20**). Although the desired "up" side introduction of an azide group was completely excluded, this work has introduced the new and important species, **14** and **15**, which would supply a variety of new entries into the chemistry of nucleosides. Moreover, synthesis of **21a** represents a successful synthetic use of neighboring group participation by an azide group and suggests interesting extensions to purine ribonucleoside derivatives.

Experimental Section[24]

Reaction of 1-(5′-*O*-Benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)uracil (1) with Sodium Benzoate. Synthesis of 2a, 3, and 4. A mixture of **1** (2.89 g, 6.79 mmol) and sodium benzoate (2.77 g, 19.22 mmol) in *N,N*-dimethylformamide (DMF, 48 ml) was stirred at 120–125 °C for 2 h. After cooling, the solvent was evaporated off and the residue thoroughly digested with ice–water (30 ml). The precipitate was collected by suction, dissolved in chloroform (100 ml), and dried over sodium sulfate and the solution evaporated to a gum, which was applied on a silica gel column (18 × 3 cm) and eluted with solvent B. The first, practically homogeneous fraction was recrystallized from a mixture of methanol and chloroform to give 360 mg (9.5%) of **3**: mp 203–205 °C; λ_{max} (MeOH) 235 nm (ε 48 900) and 259 (13 300).

Anal. Calcd for $C_{30}H_{24}N_2O_9$: C, 64.74; H, 4.35; N, 5.03. Found: C, 64.92; H, 4.49; N, 4.89.

A suspension of **3** (0.265 g, 0.477 mmol) in a mixture of methanol (12 ml) and concentrated ammonia (3 ml) was stirred at room temperature for 2 h, and the resulting solution left at room temperature for 38 h. The mixture was evaporated, and the residue coevaporated with ethanol several times and triturated with ethyl acetate (2 ml). The insoluble solid was collected, redissolved in ethanol (2 ml), treated with Norit, and again evaporated to give a syrup, which crystallized on scratching with ethanol. The ethyl acetate solution gave another crop. The combined product was recrystallized to give 93 mg (80%) of **4**, mp 219–222 °C (lit.[9a] 213–216 °C), identical with an authentic specimen in terms of infrared and ultraviolet spectroscopy.

The second fraction gave 2.04 g (66.5%) of **2a**, identical in all respects with an authentic sample.[8]

Reaction of 2a with Sodium Benzoate. A mixture of **2a** (0.2 g, 0.443 mmol) and sodium benzoate (159 mg, 1.12 mmol) in DMF (3 ml) was stirred at 120–125 °C for 2 h. The mixture was worked up similarly with the reaction between **1** and sodium benzoate to afford 35 mg (14%) of **3** and the starting material in unspecified yield after column chromatography using silica gel (14 × 1.5 cm) and solvent C. Increasing the amount of the basic catalyst did not significantly change the yield of **3**.

1-(3′-Azido-3′-deoxy-5′-*O*-benzoyl-β-D-arabinofuranosyl)uracil (2c). A mixture of **1** (1 g, 2.35 mmol), sodium azide (925 mg, 14.1 mmol), and ammonium chloride (380 mg, 7.1 mmol) in DMF (25 ml) was stirred at 105–110 °C for 1 h. After cooling, the inorganic materials were filtered off and the filtrate evaporated. The residue was quickly digested with a small amount of ice–water, neutralized with acetic acid, and partitioned between ethyl acetate (50 ml) and water (10 ml). The separated ethyl acetate solution was dried over sodium sulfate and evaporated to a practically homogeneous (in terms of TLC using solvent A, B, E, and F) foam (**2c** + i, total yield 0.774 g, 88%; NMR spectroscopically estimated yield of **2c** was ca. 66%), which was clearly distinguished from the starting material and intermediary 2′,3′-epoxy nucleoside[5] by TLC: ir (KBr) νN_3 2120 cm^{-1}; λ_{max} (MeOH) 226 nm (ε 15 600) and 260 (10 300).

This product excluded crystallization or separation by available techniques, and hence was directly used for the next step.

1-(3′-Azido-3′-deoxy-5′-*O*-benzoyl-2′-*O*-mesyl-β-D-arabinofuranosyl)uracil (2d). To a solution of the above obtained mixture of **2c** and i (1.1 g, 2.95 mmol) (estimated amount of **2c** was 825 mg, 2.21 mmol) in pyridine (10 ml) was added at 0 °C methanesulfonyl chloride (0.37 ml, 4.4 mmol). The mixture was left at room temperature for 18 h, treated with methanol (3 ml) for 30 min, and evaporated. The pasty residue was dissolved in methanol (10 ml) and poured into ice–water (200 ml) under vigorous stirring. The precipitate was collected by suction, dissolved in ethyl acetate, and dried over sodium sulfate. After the solvent was evaporated, the residue was triturated with a small volume of solvent B to give crystals, which were collected. The filtrate was concentrated and again treated with the same solvent mixture to give another crop. The same procedure was repeated until the filtrate gave no more crystals. The final crop was obtained by silica gel column chromatography using the same solvent mixture. The combined product was recrystallized from a mixture of methanol and acetone to afford **2d** as granules of mp 160–162 °C: yield 64–68% (based on the estimated amount of **2c**); ir (KBr) νN_3 2120 cm^{-1}; λ_{max} (MeOH) 231 nm (ε 15 700) and 259 (10 300).

Anal. Calcd for $C_{17}H_{17}N_5O_8S$: C, 45.24; H, 3.80; N, 15.52. Found: C, 45.16; H, 3.82; N, 15.30.

Reaction of 1-(3′,5′-Di-*O*-benzoyl-2′-*O*-mesyl-β-D-arabinofuranosyl)uracil (2b) with a Mixture of Sodium Azide and Ammonium Chloride (3:2, Molar Ratio). A mixture of **2b** (1.06 g, 2.0 mmol), sodium azide (390 mg, 6.0 mmol), and ammonium chloride (215 mg, 4.0 mmol) in DMF (15 ml) was stirred at 120 °C for 2 h. Further sodium azide (390 mg, 6.0 mmol) and ammonium chloride (215 mg, 4.0 mmol) were added, and the reaction was continued for another 2 h at the same temperature. After cooling, the inorganic materials were filtered off and the filtrate evaporated. The residue was taken into acetone (30 ml), neutralized with acetic acid, and filtered, and the filtrate was evaporated to a gum, which was shown by TLC (solvent E) to be a mixture of two products, the faster moving being the minor. The total was applied on a silica gel column (20 × 2 cm) and eluted with solvent B to give, from the faster moving fraction, a homogeneous syrup (**7**, 150 mg, 15.7%), which crystallized on prolonged drying at 50 °C and then at room temperature under high vacuum. A portion was recrystallized from a mixture of methanol and *n*-hexane to needles: mp 156–157 °C (lit.[3] 153–154 °C); ir (KBr) νN_3 2120 cm^{-1}; λ_{max} (MeOH) 234 nm (ε 30 200) and 258 (12 500).

Anal. Calcd for $C_{23}H_{19}N_5O_7$: C, 57.86; H, 4.01; N, 14.67. Found: C, 58.02; H, 4.12; N, 14.49.

This sample was identified with an authentic sample[3] by mixed fusion, infrared, and ultraviolet spectroscopy.

The succeeding eluents gave 395 mg (53%) of **8** as a practically pure

foam, a portion of which was further purified by TLC using silica gel and solvent A for spectroscopic measurements and analysis: ir (KBr) νN_3 2120 cm^{-1}; λ_{max} (MeOH) 231 nm (ϵ 14 200) and 261 (8800).

Anal. Calcd for $C_{16}H_{15}N_5O_6$: C, 51.47; H, 4.05; N, 18.76. Found: C, 51.73; H, 4.22; N, 18.49.

To a cooled solution of **8** (20 mg, 0.054 mmol) in pyridine (1 ml) was added benzoyl chloride (0.008 ml, 0.064 mmol). The mixture was left at 0 °C overnight, treated with 1 drop of water for 1 h at room temperature, and evaporated to a gum, which was taken into chloroform (10 ml) and dried over sodium sulfate. After evaporation of the solvent, the residue was heated in 95% pyridine (1 ml) at 95 °C for 1 h. After the solvent was evaporated off, the residue was repeatedly coevaporated with ethanol and applied on a silica gel column (1 × 13 cm). Elution with solvent B gave 20 mg (78%) of **7** as a syrup, which was brought to crystals by seeding, mp 157–159 °C, identical with the above obtained **7** in terms of mixed fusion, infrared, and ultraviolet spectroscopy.

2,2′-Anhydro-1-(3′,5′-di-*O*-benzoyl-β-D-arabinofuranosyl)-uracil (6). To a stirred suspension of **9**[3] (1.50 g, 6.63 mmol) in a mixture of DMF (25 ml) and pyridine (25 ml) was added benzoyl chloride (1.8 ml, 15.45 mmol). The mixture was stirred at room temperature overnight, treated with water (2 ml) for 30 min, and evaporated to give a solid residue, which was digested with ice–water (20 ml) and collected by suction. Recrystallization from acetonitrile gave 2.11 g (73%) of **6**: mp 275–277 °C (lit.[9a] 260–262 °C): λ_{max} (MeOH) 227 nm (ϵ 42 400) and 252 (11 000, sh).

Anal. Calcd for $C_{23}H_{18}N_2O_7$: C, 63.59; H, 4.17; N, 6.45. Found: C, 63.34; H, 4.37; N, 6.56.

Reaction of 2,2′-Anhydro-1-(3′,5′-di-*O*-benzoyl-β-D-arabinofuranosyl)uracil (6) with Azide Ion. Method A. A mixture of **6** (1.25 g, 2.88 mmol), sodium azide (565 mg, 8.64 mmol), and ammonium chloride (310 mg, 5.76 mmol) in DMF (20 ml) was stirred at 110–120 °C for 10 h. After cooling, the inorganic materials were filtered off and the filtrate evaporated to give a syrupy residue, which was partitioned between ethyl acetate (100 ml) and water (20 ml). The ethyl acetate extract was worked up as usual and applied on a silica gel column. Elution with solvent B gave 640 mg (60%) of **8** as a homogeneous foam, identified with an authentic sample of **8** by infrared and ultraviolet spectroscopy. A negligible amount of **7** was also obtained from the faster moving fractions.

Method B. A mixture of **6** (220 mg, 0.51 mmol), sodium azide (165 mg, 2.50 mmol), and ammonium chloride (135 mg, 2.50 mmol) in DMF (4 ml) was stirred at 110 °C for 26 h. TLC (silica gel and solvent F, twice developed) indicated the disappearance of the starting material and formation of three products. After cooling, the insolubles were filtered off and the filtrate evaporated to a paste, which was partitioned between chloroform (50 ml) and water (15 ml). The separated chloroform layer was worked up as usual and chromatographed on a silica gel column (2 × 15 cm) using solvent B to give 35 mg (15%) of **7** and 35 mg (18%) of **8**. These were identified with the above obtained authentic samples in all respects.

On the other hand, concentration of the aqueous layer afforded a crystalline precipitate, which was collected and recrystallized from methanol to give 75 mg (43%) of **10** as colorless needles: mp 201–202.5 °C; λ_{max} (MeOH) 227 nm (ϵ 21 700) and 251 (8500, inflection).

Anal. Calcd for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 9.25. Found: C, 58.01; H, 4.24; N, 8.97.

1-(2′-Azido-2′-deoxy-β-D-ribofuranosyl)uracil (11a). Compound **7** (350 mg, 0.94 mmol) in a mixture of methanol (6 ml) and concentrated ammonium hydroxide (2 ml) was stirred at room temperature overnight. The mixture was evaporated and the residue repeatedly coevaporated with ethanol and then chromatographed on a silica gel plate (20 × 20 cm, 2 mm thick) using solvent F. Elution of the main band with acetone gave 170 mg (67%) of a homogeneous syrup, ir (KBr) νN_3 2120 cm^{-1}. This substance, obtainable also from **8**, resisted crystallization, and was hence directly used for the next step.

1-(2′-Amino-2′-deoxy-β-D-ribofuranosyl)uracil (11b). Compound **11a** (170 mg, 0.63 mmol) with 10% palladium on charcoal (70 mg) in methanol (30 ml) was stirred under hydrogen (1 atm) at room temperature overnight. The catalyst was filtered off and the filtrate evaporated to a syrup, which resisted crystallization. The total was dissolved in ethanol (5 ml), acidified with saturated hydrogen chloride solution in dioxane (0.5 ml), and then evaporated to give a crystalline solid, which was recrystallized from methanol to afford 100 mg (57%) of the hydrochloride of **11b**: mp 245–247 °C; λ_{max} (MeOH) 260 nm (ϵ 9350); mass spectrum *m/e* 244 $(M - HCl + H)^+$, 243 $(M - HCl)^+$, 132 $(M - HCl - base)^+$, 131 $(M - HCl - uracil)^+$, 112 (uracil).

Anal. Calcd for $C_9H_{13}N_3O_5 \cdot HCl$: C, 38.65; H, 5.05; N, 15.02. Found: C, 38.82; H, 5.06; N, 14.94.

1-(2′-Azido-2′-deoxy-5′-*O*-benzoyl-3′-*O*-mesyl-β-D-ribofuranosyl)uracil (12). To a stirred ice-cold solution of **8** (640 mg, 1.72 mmol) in pyridine (8 ml) was added methanesulfonyl chloride (0.16 ml, 2.06 mmol). The mixture was left at 0 °C overnight, treated with methanol (2 ml) at room temperature for 30 min, and evaporated. The residue was partitioned between ethyl acetate (60 ml) and water (20 ml). The separated ethyl acetate layer was worked up as usual and chromatographed on a silica gel column (20 × 2.5 cm) using solvent B to give 600 mg (77%) of **12** as a homogeneous foam. A portion of this product was further purified by TLC using the same solvent mixture for analysis: ir (KBr) νN_3 2120 cm^{-1}; λ_{max} (MeOH) 229 nm (ϵ 14 500) and 257 (10 100).

Anal. Calcd for $C_{17}H_{17}N_5O_8S$: C, 45.24; H, 3.80; N, 15.52. Found: C, 45.55; H, 4.05; N, 15.24.

1-(2′-Azido-5′-*O*-benzoyl-2′,3′-dideoxy-β-D-glyceropent-2′-enofuranosyl)uracil (14). Potassium *tert*-butoxide (630 mg, 5.62 mmol) was added in portions to an ice-cold, stirred solution of **12** (1.01 g, 2.24 mmol) in dry tetrahydrofuran (THF, 15 ml). The mixture was stirred at 0 °C for 40 min, left at −20 °C overnight, and carefully neutralized with acetic acid. The mixture was evaporated below 35 °C and the residue partitioned between ethyl acetate (60 ml) and water (20 ml). The separated organic layer was dried over sodium sulfate and evaporated and the obtained paste was chromatographed on a silica gel column (2.5 × 13 cm) with use of solvent B to give 520 mg (64%) of **14** as a homogeneous foam: ir (KBr) νN_3 2130 cm^{-1}; λ_{max} (MeOH) 230 nm (ϵ 21 200) and 258 (13 600, sh).

Reaction of 12 with Sodium *p*-Chlorobenzoate. A mixture of **12** (600 mg, 1.43 mmol) and sodium *p*-chlorobenzoate (355 mg, 1.98 mmol) in DMF (10 ml) was stirred at 90 °C for 2.5 h. Additional sodium *p*-chlorobenzoate (355 mg, 1.98 mmol) was added and the reaction continued for another 2 h. TLC at this stage, using silica gel and solvent A and E, indicated two main products in approximately equal amounts and no starting material. The mixture was evaporated and the residue digested with ice–water (15 ml) to give a precipitate, which was collected by suction, dried, and chromatographed on a silica gel column (1.6 × 22 cm) using solvent D. The first, crystalline fraction gave 115 mg (16.7%) of **15** as colorless needles of mp 170–172 °C after recrystallization from methanol: λ_{max} (MeOH) 237 nm (ϵ 31 700) and 261 (15 300); NMR (Me_2SO-d_6) δ 3.30 (2 H, br s, NH and $H_{3'}$, reduced to one proton d at 3.33 ppm on D_2O addition, $J_{3',4'}$ = 1.2 Hz, $H_{3'}$), 4.44–4.58 (2 H, br d, J = 4.2 Hz, 5′-CH_2), 4.58–4.77 (1 H, broad complex multiplet, $H_{4'}$), 5.67 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), 6.44 (1 H, s, $H_{1'}$), 7.40–7.70 (5 H, m, aryl protons), 7.85–8.10 (5 H, m, H_6 and aryl protons), and 11.30 (1 H, br s, N_3H, D_2O exchangeable).

Anal. Calcd for $C_{23}H_{18}N_3O_7Cl$: C, 57.09; H, 3.75; N, 8.68. Found: C, 57.10; H, 3.97; N, 8.65.

The second fraction gave 180 mg of TLC-homogeneous syrup (**15′**), the infrared spectrum of which exhibited a weak absorption at 2130 cm^{-1} suggesting contamination by **14**. Rechromatography did not result in further purification.

Catalytic Reduction of 14. A solution of **14** (205 mg, 0.58 mmol) in methanol (25 ml) containing 10% palladium on charcoal (50 mg) was stirred under hydrogen (1 atm) for 6 h at room temperature. The catalyst was filtered off and the filtrate evaporated to a gum, which was applied on a silica gel column (1 × 15 cm) and eluted with solvent B to give 100 mg (55%) of **17** after recrystallization from methanol, mp 192–194 °C. Identity with an authentic sample[16b] was confirmed by mixed fusion, infrared, and ultraviolet spectroscopy.

1-(2′,3′-Dideoxy-2′,3′-diazido-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil (21a). A mixture of **2d** (660 mg, 1.46 mmol) and sodium azide (380 mg, 5.8 mmol) in DMF (7 ml) was stirred at 115–120 °C for 4.5 h. TLC using silica gel, solvent A and/or E revealed that almost all the starting material was consumed and a faster moving substance formed with a slight amount of uracil. The mixture was evaporated, digested with a small volume of ice–water, neutralized with acetic acid, and partitioned between ethyl acetate (70 ml) and water (20 ml). The ethyl acetate solution was dried over sodium sulfate and evaporated to give a glass, which crystallized on standing overnight with a few drops of methanol. The crystals were collected and the mother liquor evaporated to a tar, which was chromatographed on a silica gel column (1.5 × 20 cm) using solvent B to give another crop. The combined crops were recrystallized from methanol to afford 310 mg (59%) of **21a**: mp 166–167 °C; ir (KBr) νN_3 2120 cm^{-1}; λ_{max} (MeOH) 228 nm (ϵ 16 900) and 259 (11 300).

Anal. Calcd for $C_{16}H_{14}N_8O_5$: C, 48.24; H, 3.54; N, 28.13. Found: C, 48.19; H, 3.70; N, 27.97.

1-(2′,3′-Dideoxy-2′,3′-diazido-β-D-ribofuranosyl)uracil (21b). Compound **21a** (400 mg, 1.01 mmol) in a mixture (16 ml) of methanol and concentrated ammonium hydroxide (3:1) was stirred at room temperature overnight. After the solvent was evaporated, the residue

was repeatedly coevaporated with ethanol to remove residual water, charged on a silica gel plate (20 × 20 cm, 2 mm thick), and developed with solvent G. Elution of the main band gave 210 mg (71%) of **21b** as a homogeneous foam. This compound resisted crystallization and was hence directly used for the next step.

1-(2′,3′-Dideoxy-2′,3′-diamino-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil (22a). A mixture of **21a** (517 mg, 1.3 mmol) in methanol (100 ml) was stirred in a hydrogen atmosphere with 10% palladium on charcoal (150 mg) overnight. The mixture was filtered to give a glass, which crystallized from a mixture of ethanol and methanol. Recrystallization from ethanol gave 200 mg (44%) of **22a** as needles: mp 103–105 °C; λ_{max} (MeOH) 224 nm (ε 16 400) and 261 (11 000); CD (MeOH) Cotton effects θ (nm) −11 900 (240) and +14 900 (267).

Anal. Calcd for $C_{16}H_{18}N_4O_5$: C, 55.48; H, 5.24; N, 16.18. Found: C, 55.57; H, 5.32; N, 16.01.

1-(2′,3′-Dideoxy-2′,3′-diacetamido-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil (22b). A mixture of **22a** (90 mg, 0.26 mmol) and acetic anhydride (2 ml) was heated at 100 °C for 1 h and then cooled with ice–water. Methanol (2 ml) was added and the total was left at 0 °C for 1 h and then at room temperature for a couple of hours. Evaporation of the solvent gave a syrup, which crystallized on scratching with a few drops of ethyl acetate. Recrystallization from a mixture of methanol and ethanol gave 70 mg (62.5%) of **22b:** mp 160–162 °C; λ_{max} (MeOH) 224 nm (ε 16 600) and 259 (11 300).

Anal. Calcd for $C_{20}H_{22}N_4O_7 \cdot CH_3OH$: C, 54.53; H, 5.62; N, 12.11. Found: C, 54.28; H, 5.55; N, 12.36.

1-(2′,3′-Dideoxy-2′,3′-diamino-β-D-ribofuranosyl)uracil (22c). A solution of **21b** (200 mg, 0.8 mmol) in ethanol (50 ml) was stirred in a hydrogen atmosphere with 10% palladium on charcoal (100 mg) for 5 h. The mixture was filtered and evaporated to a glass, which was charged on a silica gel plate (20 × 10 cm) and developed twice with solvent E to remove small amounts of faster moving impurities. Elution of the main band with ethanol and evaporation of the solvent gave a homogeneous glass, which resisted crystallization. The total was dissolved in dry methanol (7 ml), treated with Norit, concentrated to ca. 3 ml, and precipitated into vigorously stirred dry ether (30 ml). The precipitate was collected by centrifugation and dried at 50 °C under high vacuum to give a rather hygroscopic foam, yield 66 mg (40%), λ_{max} (MeOH) 260 nm (ε 9100).

Anal. Calcd for $C_9H_{14}N_4O_4$: C, 44.62; H, 5.83; N, 23.13. Found: C, 44.62; H, 5.57; N, 22.85.

1-(2′,3′-Dideoxy-2′,3′-diamino-5′-*O*-benzoyl-β-D-ribofuranosyl)uracil 2′,3′-Carbonate (23). A mixture of **22a** (100 mg, 0.29 mmol) and diphenyl carbonate (80 mg, 0.37 mmol) in DMF (8 ml) was stirred at 125–130 °C for 4 h. An aliquot was withdrawn, evaporated, and examined by TLC (silica gel, solvent G) to show no starting material and two other faster moving spots, one of which being that of diphenyl carbonate. The mixture was evaporated, charged on a silica gel plate (20 × 20 cm, 2 mm thick), and developed with solvent G. The desired portion was eluted with ethanol and the solvent evaporated off to leave an amorphous powder, which was dissolved in methanol (2 ml) and treated with Norit. The methanol solution was concentrated to a minimum volume and left at room temperature for a couple of days to effect very slow crystallization: mp 250–252 °C; yield 20%; λ_{max} (MeOH) 226 nm (ε 14 800) and 259 (11 000); mass spectrum *m/e* 261 (M − uracilyl)$^+$, 262 (M − uracilyl + H)$^+$, 111 (uracilyl)$^+$ and 112 (uracil)$^+$.

Anal. Calcd for $C_{17}H_{16}N_4O_6$: C, 54.84; H, 4.33; N, 15.05. Found: C, 54.57; H, 4.62; N, 14.85.

1-(3′-Amino-3′-deoxy-5′-*O*-benzoyl-β-D-arabinofuranosyl)uracil (24). A mixture of the above obtained impure **2c** (0.2 g) and 10% palladium on charcoal (100 mg) in ethanol (30 ml) was stirred in a hydrogen atmosphere overnight. After the usual workup and preparative TLC (silica gel and solvent F), 0.1 g (ca. 66% based on pure **2c**) of **24** was obtained as fine needles: mp 238–239 °C (MeOH); λ_{max} (MeOH) 227 nm (ε 20 800) and 262 (14 500); CD (MeOH) Cotton effects θ (nm) −11 100 (238) and +22 400 (267).

Anal. Calcd for $C_{16}H_{17}N_3O_6$: C, 55.33; H, 4.93; N, 12.10. Found: C, 55.15; H, 5.02; N, 11.85.

Registry No.—**1,** 55263-52-0; **2a,** 55263-53-1; **2b,** 18743-34-5; **2c,** 58540-97-9; **9,** 3736-77-4; **11a,** 26929-65-7; **11b,** 26889-39-4; **15,** 59710-47-3; **17,** 38359-55-6; **21b,** 59686-48-5; **22b,** 59686-49-6; **22c,** 59686-50-9; **23,** 59686-51-0; i, 59686-52-1; sodium benzoate, 532-32-1; sodium azide, 26628-22-8; methanesulfonyl chloride, 124-63-0; benzoyl chloride, 98-88-4; sodium *p*-chlorobenzoate, 3686-66-6; acetic anhydride, 108-24-7; diphenyl carbonate, 102-09-0.

References and Notes

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(11) That compound **3** forms by a base-catalyzed disproportionation mechanism from two molecules of **2a** was evidenced in separate experiments, which will be described elsewhere.
(12) A trial experiment has shown that a sample of 5′-azido-5′-deoxy-2′,3′-*O*-isopropylideneuridine smoothly decomposes at 115–120 °C during several hours to give highly insoluble polymer-like products.
(13) The measurement was carried out at 100 MHz by Takeda Chemical Industries, Co., Ltd., for which we are grateful.
(14) $J_{1',2'}$ values shown by compounds with or without an azide group seem to vary extensively between 3 and 7 Hz, depending upon the differences of substituents or protecting groups, irrespective of the configurations. For example, see ref 3 and 7*a*.
(15) We thank Dr. Moffatt for a generous gift of authentic samples of **8** and **12b.**
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(20) We are indebted to Dr. H. Ogura and his group, Kitazato University, Tokyo, for the measurements, for which a JASCO Model J-20 recording spectropolarimeter was used.
(21) Uridine, θ −4000 (240 nm) and +9200 (267 nm); spongouridine, θ −6500 (235 nm) and +22 000 (266 nm) [D. W. Miles, W. H. Inskeep, M. J. Robins, M. W. Winkley, R. K. Robins, and H. Eyring, *J. Am. Chem. Soc.*, **92,** 3872 (1970)].
(22) Considerable efforts may have been devoted to exploration of such direct (without neighboring group participation) substitutions at $C_{2'}$ and $C_{3'}$ in nucleosides, but there seems to have been no successful case.
(23) This reagent is more soluble in DMF than sodium benzoate.
(24) The general methods used are similar to those described earlier.[2] Melting points were obtained on a Yanagimoto micromelting point apparatus and are not corrected. All evaporations were conducted in vacuo at or below 40 °C. Solvent mixtures used for column and thin layer chromatography are as follows: $CHCl_3$/EtOAc, 1:1 (v/v) (solvent A), 3:1 (B), 4:1 (C), 5:1 (D); $CHCl_3$/MeOH, 9:1 (v/v) (E); 20% EtOH/benzene, F; 30% EtOH/benzene, G. These are designated as solvent A, B, C, etc., in all cases.
(25) **Note Added in Proof.** In a very recent issue of this journal, Robins et al. corrected the mechanism for the conversion[2] of O^2→2′-anhydro-1-(5-*O*-benzoyl-3-*O*-methanesulfonyl-β-D-arabinofuranosyl)uracil to the corresponding N^3→3′-anhydro-2-amino-1-(5-*O*-benzoyl-3-deoxy-β-D-lyxofuranosyl)-4-pyrimidinone [*J. Org. Chem.*, **41,** 1886 (1976)].