Synthesis of v-Triazolo[4,5-c]pyridine Nucleosides and 4-(β-D-Ribofuranosyl)amino-1,2,3-thiadiazolo[5,4-b]pyridine via a Rearrangement[1]

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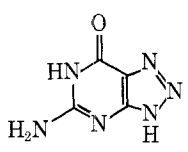
Received September 23, 1975

Nucleoside products isolated from the ribosylation of 4-chloro-v-triazolo[4,5-c]pyridine have been identified as 4-chloro-1-(β-D-ribofuranosyl)-v-triazolo[4,5-c]pyridine (major), 4-chloro-2-(β-D-ribofuranosyl)-v-triazolo[4,5-c]pyridine (minor), and 4-chloro-3-(β-D-ribofuranosyl)-v-triazolo[4,5-c]pyridine (minor). The isomer ratio was found to be dependent on the ribosylation conditions employed. Reaction of 4-chloro-1-(β-D-ribofuranosyl)-v-triazolo[4,5-c]pyridine with the appropriate nucleophile has provided 4-amino-1-(β-D-ribofuranosyl)-v-triazolo[4,5-c]pyridine (3-deaza-8-azaadenosine) and 4-methylthio-1-(β-D-ribofuranosyl)-v-triazolo[4,5-c]pyridine. However, thiation of 4-chloro-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-v-triazolo[4,5-c]pyridine, followed by deprotection, gave 4-(β-D-ribofuranosyl)amino-1,2,3-thiadiazolo[5,4-b]pyridine via a v-triazole–1,2,3-thiadiazole rearrangement. A comparison of the uv spectral data for 1-(β-D-ribofuranosyl)-v-triazolo[4,5-c]pyridine (**25**) with that of 1-methyl-v-triazolo[4,5-c]pyridine (**23**) has indicated that the site of ribosylation for **25** cannot be established by the empirical model methyl rule. Other procedures were used to establish the site of ribosylation for **25**.

The isolation[2] and characterization of the antibiotic pathocidin as 8-azaguanine (**1**) created considerable interest in the biochemical and chemotherapeutic properties of a variety of 8-azapurine derivatives. Certain 8-azapurine (v-triazolo[4,5-d]pyrimidine) derivatives have been reported[3] to act as purine antimetabolites. Some recent reports[4-7] of interesting biological and chemotherapeutic activity for 8-azapurine nucleosides, specifically 8-azainosine, prompted us to initiate research designed to furnish the 3-deaza analogues of these nucleosides. A perusal of the literature during the initiation of this study revealed that only one 3-deaza-8-azapurine (v-triazolo[4,5-c]pyridine) nucleoside had been reported[8] [**2**, 2-(β-D-ribofuranosyl)-v-triazolo[4,5-c]pyridine]. In fact, at the time there had been only a very limited amount of research conducted on the parent ring system, although there have been some recent reports[9,10] on a number of v-triazolo[4,5-c]pyridine derivatives.



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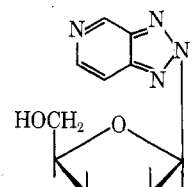

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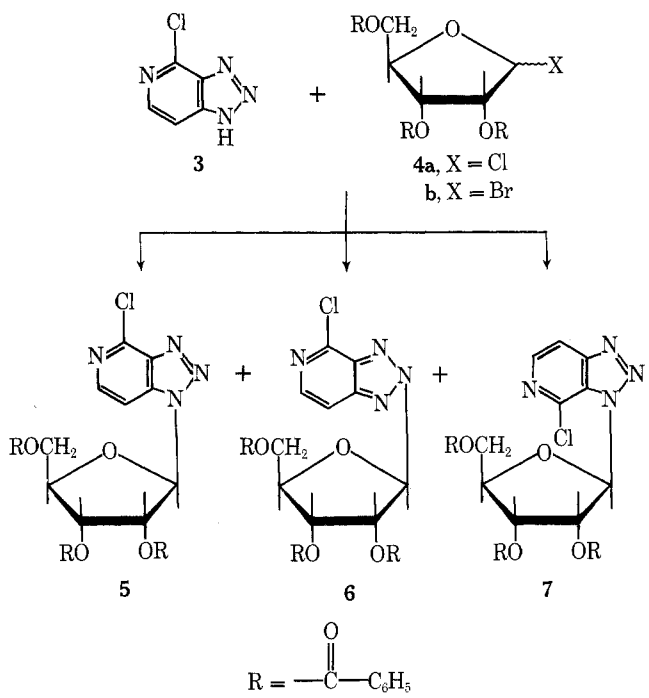
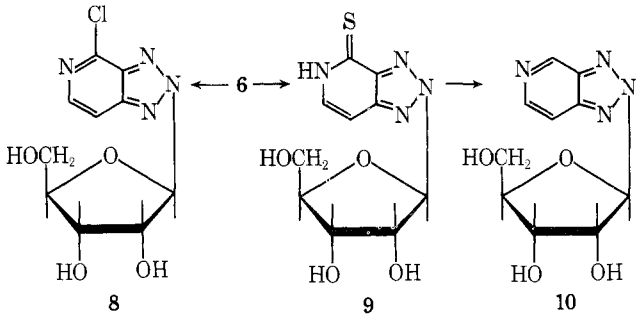
We elected to use 4-chloro-v-triazolo[4,5-c]pyridine[11] (**3**) as our starting heterocycle in the glycosylation procedure[12,13] in an effort to obtain the 1-ribosyl derivative. The condensation of 4-chloro-v-triazolo[4,5-c]pyridine (**3**) with 2,3,5-tri-O-benzoyl-D-ribofuranosyl chloride (**4a**) gave a mixture of nucleosides. This isomeric mixture was resolved by extensive column chromatography to give three nucleoside products, the structures of which were subsequently established as 4-chloro-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-v-triazolo[4,5-c]pyridine (**5**), 4-chloro-2-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-v-triazolo[4,5-c]pyridine (**6**), and 4-chloro-3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-v-triazolo[4,5-c]pyridine (**7**) in 11, 15, and 8% yield, respectively, for a total nucleoside yield of 34% (Scheme I). However, since the desired isomer (**5**) was obtained in only minor quantities, this emphasized the need for a more suitable glycosylation procedure. A variety of standard glycosylation procedures (e.g., Wittenberg, silyl fusion, and acid-catalyzed fusion)[14] and modifications were investigated; however, no significant change in the product distribution or yield was observed. A nitrogen to nitrogen glycosyl migration has been recently reported[15] for the conversion of 7-methylthio-2-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-v-triazolo[4,5-d]pyrimidine to the desired 3-glycosyl derivative. Unfortunately, attempts to obtain a similar glycosyl migration with 7-amino-2-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-v-triazolo[4,5-d]pyrimidine were unsuccessful,[15] indicating that such migrations may not be very general in scope. Iodine has been reported to be an effective catalyst in promoting glycosyl migrations with certain indazole[16] and pyrazolo[3,4-b]pyrazine[17] glycosides. These observations prompted us to try this approach with a mixture of **5**, **6**, and **7**. When this mixture was heated in toluene at reflux temperature in the presence of molecular sieve, no change in the isomeric content was observed. A variety of other

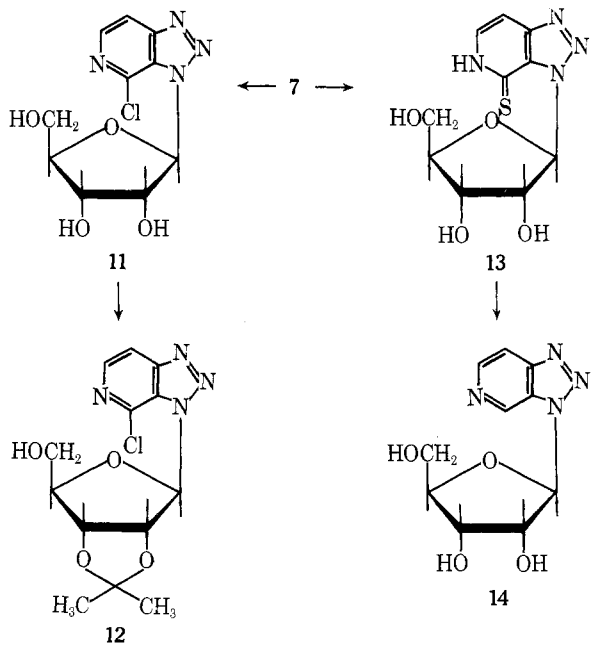
Scheme I



Scheme II



Scheme III



solvents were investigated with no glycosyl migration being observed. Treatment of a melt of the isomeric mixture with iodine resulted in extensive decomposition with no apparent glycosyl migration.

It was assumed that the monosilyl product used for glycosylation was actually a mixture of the 1-, 2-, and 3-trimethylsilyl derivatives of **3**. It was further assumed, based on proposed glycosylation mechanisms,[18] that if a trimethylsilyl derivative of higher integrity could be obtained, the isomer ratio of the nucleoside products could possibly be altered to provide **5** as the major nucleoside product.

A suspension of **3** in xylene was silylated with *N,O*-bis(trimethylsilyl)acetamide at 40 °C. The resulting solution was then heated (110 °C) with the solvent and excess silylating agent being removed at this temperature to provide a crystalline silyl derivative. This silyl derivative was glycosylated with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**4b**) in acetonitrile in the presence of mercuric cyanide at reflux temperature to give the three isomeric nucleosides, **5, 6,** and **7,** in a distribution which was much more favorable for our specific interests (**5,** 25%; **6,** 12%; and **7,** 4%). When this procedure was followed without heating the silylation mixture at an elevated temperature, the yield and isomeric distribution of the nucleoside products was similar to previous results (vide supra). This would indicate that the thermodynamically more stable monosilyl derivative of **3** was formed and that this species favored the formation of **5.** The structure of this monosilyl derivative and the dependence of the increased yield of **5** on the solvent and glycosylation procedure used is currently under investigation.

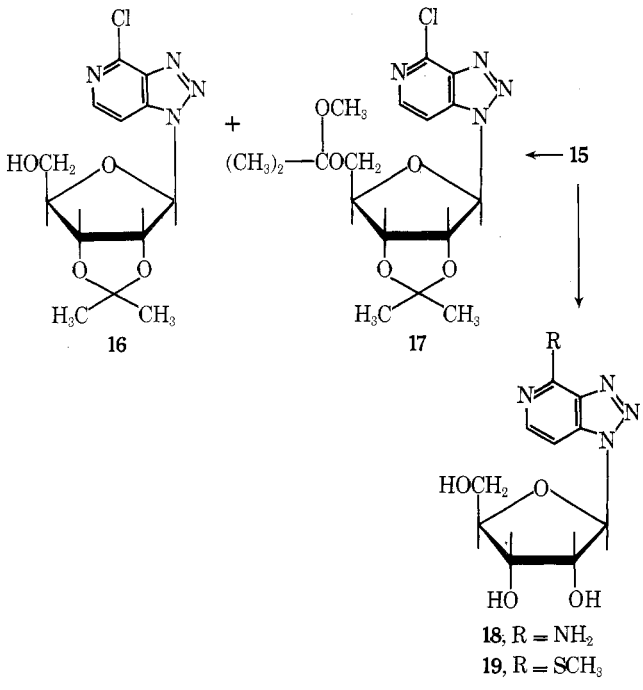
We then initiated studies designed to provide unequivocal assignments for the anomeric configuration and site of ribosylation for **5, 6,** and **7.** The nucleoside **6** was assigned the β configuration on the basis of a $J_{H1',H2'} = 0$ Hz, at δ 6.86 for the anomeric proton. Treatment of **6** with methanolic sodium methoxide provided 4-chloro-2-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (**8**) (Scheme II). Thiation and deprotection of **6** with sodium hydrogen sulfide gave 2-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine-4-thione (**9**). Dethiation of **9** with Raney nickel provided 2-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (**10**) [λ_{max} (pH 1) 296 nm (ϵ 6400), 263 (9100); λ_{max} (pH 11) 279 nm (ϵ 6600), 263 (7900); $[\alpha]^{33}D$ −83.5° (*c* 1.0, CH_3OH)] which compared favorably with the data reported previously[8] for **10** [λ_{max} (pH 1) 298 nm (ϵ 4300), 265 (6300); λ_{max} (pH 11) 280 nm (ϵ 5700), 268 (5800); $[\alpha]^{22}D$ −70° (*c* 1, CH_3OH)]. This established the actual site of ribosylation for **6** as N-2 and the anomeric configuration as β.

The coupling constant for the anomeric proton resonance of **7** was 1.0 Hz, which established the anomeric configuration of **7** as β. The nucleoside **7** was deprotected with methanolic sodium methoxide to give 4-chloro-3-β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (**11**) (Scheme III). To further substantiate the configurational assignment for **7,** the nucleoside **11** was converted to 4-chloro-3-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (**12**).[19] The difference between the chemical shifts observed for the isopropylidene methyl groups of **12** was 0.23 ($\Delta\delta$) which is in agreement with the reported values for β-ribonucleosides.[20]

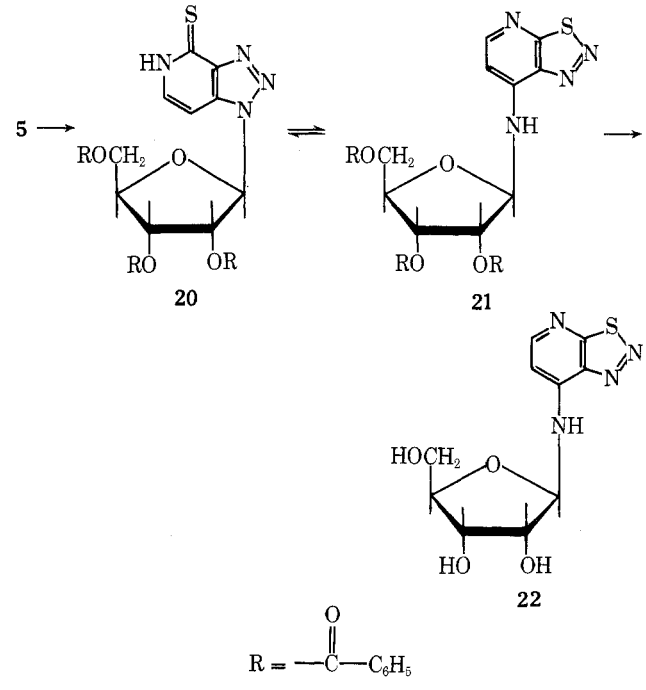
Thiation of **7** with sodium hydrogen sulfide effected a concomitant deblocking to give 3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine-4-thione (**13**). The chemical shift for the anomeric proton of **13** appeared at δ 7.83, a significant downfield shift from the normal range. A downfield chemical shift of the anomeric proton resonance peak of a number of thionucleosides has been observed[21] when the ribosyl moiety was on a ring nitrogen atom adjacent to or in very close proximity to the carbon atom bearing the thione group. These observations would indicate that the site of glycosylation of **13** was at either position 3 or 5. Dethiation of **13** with Raney nickel provided 3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (**14**). The uv spectral data for **14** [λ_{max} (pH 1) 300 nm (ϵ 6700), 224 (3000); λ_{max} (pH 11) 290 nm (ϵ 5300), 240 (4100)] and 3-methyl-*v*-triazolo[4,5-*c*]pyridine[8] [λ_{max} (pH 1) 302 nm (ϵ 4500), 250 (1900); λ_{max} (pH 11) 290 nm (ϵ 4800), 248 (2400)] were comparable. This established the actual site of glycosylation for **7** as N-3 and the anomeric configuration as β.

The coupling constant observed for the anomeric proton resonance of **5** ($J_{1',2'} = 2.8$ Hz) was not sufficiently small to permit an unequivocal assignment of anomeric configuration. Treatment of **5** with methanolic sodium methoxide furnished 4-chloro-1-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (**15**) which was converted to 4-chloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (**16**) (Scheme IV). The difference between the chemical shifts for the isopropylidene methyl groups of **16** was 0.23 ($\Delta\delta$) which is in agreement with the reported values for β-ribonucleosides.[20] This established the anomeric configuration of **16** and **5** as β. A second nucleoside product was obtained from the isopropylidenation of **15.** This product was shown to be 4-chloro-1-(2,3-*O*-isopropylidene-5-*O*-1′-methoxyisopropyl-β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (**17**), based primarily on ^1H NMR data [δ 0.99 and 1.02 (2 s, 6, isopropyl methyls), 1.45 and 1.63 (2 s, 6, isopropylidene methyls), 2.91 (s, 3, OCH_3)]. As expected **17** was readily hydrolyzed to **16** by methanol at room temperature. To

Scheme IV



Scheme V



our knowledge this type of isopropylidenation intermediate has not been documented, most likely owing to its ease of hydrolysis, though surely encountered by others. A report[22] of the selective blocking of the 5′-hydroxyl of uridine by 2,2-dimethoxypropane has appeared. Although these authors report limited isopropylidene formation they did not observe an intermediate such as **17.** Treatment of **15** with liquid ammonia provided 4-amino-1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (**18,** 3-deaza-8-azaadenosine). It is interesting to note that **18** showed a fluorescent emission maxima at 430 nm in water and may also be considered a deaza analogue of 8-azaadenosine which has shown some interesting biological properties. The reaction of **15** with the sodium salt of methanethiol provided 4-methylthio-1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (**19**). Compound **19** is of interest since it can be considered an azadeaza analogue of 6-methylthiopurine riboside which has shown some very interesting biological activity.[23]

Reaction of **5** with anhydrous dimethylformamide–sodium hydrogen sulfide resulted in thiation without concomitant deblocking to provide 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine-4-thione (**20**) (Scheme V). The chemical shift for the anomeric proton of **20** was observed at δ 7.17 while the resonance peak for the anomeric proton of **5** was observed at δ 7.28. The absence of any significant deshielding of the anomeric proton of **20** due to the magnetic anistropic effect of an adjacent thione group would indicate that the ribosyl moiety was residing at either N-1 or N-2. However, a complete dissimilarity between the uv spectral data for **20** and the uv spectral data for 2-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine-4-thione (**9**) eliminated N-2 which established the actual site of glycosylation for **20** and **5** as N-1.

An equilibrium was established between **20** and 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)amino-1,2,3-thiadiazolo-[5,4-b]pyridine (**21**) when a solution of **20,** in a variety of solvents ranging in polarity from methanol to chloroform, was allowed to stand at room temperature. It was possible to shift the equilibrium in favor of **21** by heating the solution. Although this type of υ-triazole/1,2,3-thiadiazole rearrangement is well documented,[24,25] it appeared desirable to substantiate its occurrence in this situation.

A resonance for the anomeric proton of **20** appears as a doublet centered at δ 7.17 and a partially hidden doublet at δ 7.42 was assigned to the proton at C-7. Although a more complex and less well resolved spectrum was obtained after heating the ^{1}H NMR sample for a short time, the appearance of two well-resolved doublets at δ 7.24 and 8.61 was quite obvious. The Δδ (1.37) for these two doublets was indicative of the thiadiazolo[5,4-b]pyridine ring system. It became apparent during the course of this investigation, based on our findings and data from the literature,[9] that a difference in the chemical shifts between the doublets of the A:B pattern (H-6 and H-7) for the υ-triazolo[4,5-c]pyridine ring system is approximately 0.9 (Δδ) or less. By contrast, when the heteroatom resides in a position adjacent to the five-membered ring, e.g., the υ-triazolo[4,5-b]pyridine or thiadiazolo[5,4-b]pyridine ring systems, this difference is greater than 1.0 (Δδ).

Other studies designed to provide additional substantiation for the structure of **21** included treatment of **21** with sodium methoxide to give 4-(β-D-ribofuranosyl)amino-1,2,3-thiadiazolo[5,4-b]pyridine (**22**). The ^{1}H NMR spectrum of **22** revealed a signal for the anomeric proton as a quartet centered at δ 5.81, somewhat upfield from the normal range observed for υ-triazolo[4,5-c]pyridine nucleosides. The collapse of this quartet to a doublet centered at δ 5.81 upon the addition of deuterium oxide and the concomitant disappearance of the doublet centered at δ 8.00 upon deuterium exchange suggested that the anomeric proton was spin coupled with an exchangeable hydrogen. This relationship was established by spin decoupling of the doublet centered at δ 8.00 which caused the quartet at δ 5.81 to collapse to a doublet centered at δ 5.81. These data provide unequivocal proof for the structure of **22.**

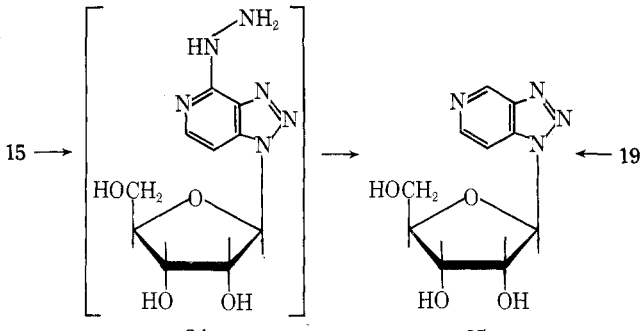
One technique generally employed for the determination of the site of glycosylation is to compare the ultraviolet spectra of the nucleoside product with that of the appropriate *N*-alkyl derivative of the aglycon. Since the uv spectral data for 1-methyl-υ-triazolo[4,5-c]pyridine (**23**) had been reported,[8] this prompted us to obtain additional corroboration for the actual site of ribosylation for **5** by dehalogenation of **15** to provide 1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine. Treatment of **15** with anhydrous hydrazine pro-

Table I. Ultraviolet Absorption Spectral Data for 23 and 25

	λ_{max} (pH 1), nm	λ_{max} (H_2O), nm	λ_{max} (pH 11), nm
25	274.5	265.5	264
23	265.5		
	257	259	258
Δ, nm	9.0	6.5	6.0

vided what we have assumed to be 4-hydrazino-1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (**24**) which was treated (without purification) with silver oxide to give 1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (**25**) (Scheme VI). A comparison of the uv spectral data obtained for **25**

Scheme VI



24 **25**

and the uv spectral data reported[8] for 1-methyl-υ-triazolo-[4,5-c]pyridine (**23**) revealed a significant discrepancy. The authenticity of the published data[8] for **23** was established by the synthesis of **23** in our laboratory and the magnitude of the difference (see Table I) between the ultraviolet absorption spectral data of **25** and **23** was of concern since this difference between a nucleoside and the model methyl compound has been generally reported to be less than 5 nm.

We assumed that the observed discrepancy in the uv spectral data might arise from a structural modification of **15** during dehalogenation. However, the synthesis of **25** by an unrelated procedure, dethiation of **19** with Raney nickel, provided a product which was identical with **25** prepared via **24**. This established that **25** was not the product of a rearrangement involving the hydrazino group. An infrared spectrum showed that **25** was not a ring-opened stabilized diazo compound[26] as established by the absence of a peak for a diazo band. The ^1H NMR spectrum and elemental analysis for **25** supported the structure indicated; however, these data could not unequivocally differentiate between **25** and 5-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine, or the possibility of a dimeric structure. The formation of a dimer during dehalogenation was refuted by the mass spectral data which showed a molecular ion of *m/e* 252. However, the possibility remained that the ribosyl moiety was attached to position 5 of the aglycon rather than position 1. The lack of any deshielding of the anomeric proton of **20** and the data substantiating the υ-triazole–1,2,3-thiadiazole rearrangement observed for **20** and **21** established that the ribosyl moiety was at N-1 for **15** and **5**. In view of the reaction conditions employed for the conversion of **15** to **25**, it is reasonable to assume that the ribosyl group would be at N-1 of **25**; however, an N-1–N-5 glycosyl migration or intermolecular transfer cannot be discounted, though both are very highly improbable.

An NMR technique which has been recently used to establish the glycosylation site of nucleosides[27,28] involves the use of ^{13}C nuclear magnetic resonance (^{13}C NMR). It has been shown for a number of heterocyclic systems that pro-

Table II. Carbon-13 Chemical Shift Data for Certain υ-Triazolo[4,5-c]pyridine Derivatives[a,b]

No.	3a, 7a	4, 6	7
27	139.28	141.79	107.64
	140.11	142.48	
23	136.73	143.67	105.42
	142.49	144.16	
25	135.94	143.98	106.31
	142.99	144.57	

[a] Chemical shifts are in parts per million from Me_4Si. *p*-Dioxane was used as internal reference and converted to the Me_4Si scale using the relationship Me_4Si = dioxane − 17.5×10^{-4} *T* (°C) − 66.32. [b] All samples were dissolved in Me_2SO-d_6.

tonation of the anionic species resulted in an upfield chemical shift for the α carbons and a downfield chemical shift for the β carbons. It was further established that for N-methylation and N-glycosylation[27] these effects are qualitatively preserved. Furthermore, it was demonstrated[27] that the ^{13}C NMR shift data of the free base and the N-alkylated species were sufficient to establish the position of alkylation by a qualitative interpretation of the α and β substituent effects, not requiring a comparison with the corresponding anionic species.

Inspection of the ^{13}C NMR spectrum of υ-triazolo[4,5-c]pyridine (**27**) showed a near degeneracy for the chemical shifts of C-3a and C-7a (see Table II) which precluded an unequivocal assignment of these two resonances. Although it was apparent from the ^{13}C NMR spectrum of **23** that one of these resonances shifted downfield while the other shifted upfield upon N-1 alkylation, it could not be readily determined which of the resonances of **27** shifted in which direction owing to the possibility of a crossover of resonance lines. It was obvious, however, that the C-4, C-6, and C-7 resonances of **27** showed no significant shift on N-1 methylation as expected. The spectrum of **25** was essentially identical with that of **23** (see Table II) and although it was not possible to unequivocally assign the ribosyl moiety of **25** to N-1 by this procedure owing to the inability to assign the C-3a and C-7a resonances, it was clearly evident that **25** was not the N-5 substituted compound. If the substituent were at N-5, an upfield shift would have been apparent for the C-4 and C-6 (α carbons) chemical shifts. Since these resonances for **25** occur at the same location as for **23** and **27** the possibility of N-5 substitution for **25** can be eliminated. This ^{13}C NMR procedure cannot differentiate between N-1, N-2, or N-3 substitution in this particular situation owing to the inability to assign the chemical shifts of the bridgehead carbons; however, previous data (vide supra) clearly indicate that **25** is not the N-2 or N-3 substituted compound.

Additional corroboration for the structure of **25** was pursued using the nuclear Overhauser effect (NOE). The conformational distribution (syn–anti) of various purine nucleosides in solution[29] as well as the determination of anomeric configuration for certain purine and pyrimidine nucleosides[30] has been investigated through the use of intramolecular nuclear Overhauser effect measurements.

Molecular models indicated that if the ribosyl moiety of **25** were to reside at N-1, the anomeric proton and H(7) would be in very close proximity. Hence, irradiation of the H(1′) proton would be expected to result in an enhancement in the integrated intensity of the H(7) signal. The H(6) and H(4) protons would show no enhancement on irradiation of the H(1′) proton since they are not in close proximity to the anomeric proton. Molecular models further indicated that if the ribosyl moiety were to reside at N-5, the anomeric proton would be in very close proximity

Table III. Nuclear Overhauser Effects Observed for 19 and 25

Compd	Proton irradiated	Proton observed	Enhancement
19	H(1′)	H(7)	0.22
	H(1′)	H(6)	0.0
25	H(1′)	H(7)	0.12
	H(1′)	H(6)	0.0
	H(1′)	H(4)	0.0

to both the H(6) and the H(4) protons. Therefore, irradiation of H(1′) in this situation would result in an enhancement in the intensity of both the H(6) and H(4) protons with no effect being observed on the H(7) proton. Irradiation of the anomeric proton signal of **19** and **25** produced the enhancements shown in Table III. These results clearly established that for **25** and **19**, the ribosyl moiety resides at N-1. Therefore, the identity of **25** as 1-(β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine has been substantiated by chemical studies as well as ^{13}C NMR, NOE, and ^{1}H NMR spectroscopy.

To our knowledge this is the first report of an exception to the time-honored empirical model methyl procedure (uv) for assigning the glycosylation site of nucleosides. The reasons for this discrepancy between **25** and **23** are not readily apparent, and we are not prepared at this time to offer any explanation for this observation. However, it does serve to indicate that corroborative evidence may be beneficial when using model methyl compounds to establish the site of glycosylation. Furthermore, the use of ^{13}C NMR α and β substituent shifts may prove to be not only less time consuming but also more reliable, especially for those ring systems amenable toward this technique.

Experimental Section

Proton magnetic resonance (^{1}H NMR) spectra were obtained with Jeol C60H, Varian A56/60, and Varian XL-100/15 spectrometers (solutions in dimethyl sulfoxide-d_6 or deuteriochloroform with sodium 2,2-dimethyl-2-silapentane-5-sulfonate or tetramethylsilane, respectively, as internal standard), with chemical shift values reported in δ, parts per million, relative to the internal standard. Nuclear Overhauser experiments were performed at 100 MHz on ca. 0.50 M samples in dimethyl sulfoxide-d_6 alone or in combination with deuterium oxide where applicable to remove resonance peaks in close proximity to those of interest. The samples were prepared in coaxial tubes with hexamethyldisilizane in the annular space as external standard. Each resonance was integrated ten times with and without the saturating field present and the NOE was then calculated from the average areas. Carbon-13 magnetic resonance spectra were obtained with a Varian XL-100/15 spectrometer equipped with a 620-F computer. Ultraviolet spectra were recorded on Beckman DK-2 and Acta CIII spectrophotometers. Fluorescence spectra were determined with an Aminco-Bowman spectrophotofluorometer. Infrared spectra were recorded on a Beckman IR8 spectrophotometer. Optical rotations were determined with a Perkin-Elmer Model 141 automatic digital read-out polarimeter. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Mass spectra were recorded on a Hewlett-Packard 5930A instrument; ion source and direct inlet temperatures, 190 °C, ionizing energy 60 eV, samples were introduced by direct probe. Thin layer chromatography was run on glass plates coated (0.25 mm) with silica gel (SilicAR 7GF, Mallinckrodt) or aluminium oxide (HF_{254}, basic, type E, Merck). Compounds of interest were detected by either ultraviolet lamp (Mineralight, 254 nm), iodine vapors, or treatment with sulfuric acid followed by heating. Evaporations were performed under reduced pressure at 40 °C with a rotary evaporator unless otherwise stated.

4-Chloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (5), 4-Chloro-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (6), and 4-Chloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-υ-triazolo[4,5-c]pyridine (7). Method A. A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride (prepared from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, 17.3 g, 33.0 mmol) in nitromethane (35 ml) was added to a suspension of 4-chloro-υ-triazolo[4,5-c]pyridine[11] (**3**, 4.7 g, 30 mmol) and potassium cyanide (2.14 g, 33 mmol) in nitromethane (300 ml), and the resulting mixture was heated at reflux temperature for 3 hr. The reaction mixture was cooled to room temperature, and the insoluble material was removed by filtration. The filtrate was evaporated to a dark syrup which was dissolved in chloroform (350 ml) and filtered. The filtrate was extracted with a saturated aqueous sodium bicarbonate solution (3 × 50 ml) and then with water (3 × 50 ml). The solution was dried over anhydrous sodium sulfate and concentrated to a syrup which was dissolved in a minimal amount of benzene and applied to the top of an aluminum oxide column (Merck, neutral, 4.5 × 50 cm) packed in benzene. The column was washed with benzene (2 l.) followed by elution with a mixture of benzene–ethyl acetate (9:1 v/v) to furnish partially resolved mixtures of the three isomeric nucleosides. The partially resolved isomers were combined into three fractions: (1) containing **6** and **7**; (2) containing **5, 6,** and **7** [R_f 0.39, 0.63, and 0.57, respectively, on Merck aluminum oxide developed with benzene–ethyl acetate (9:1 v/v)]; (3) containing **5** and **7**. The second fraction containing the three unresolved isomers was rechromatographed on a second aluminium oxide column (Merck, 3.5 × 35 cm) and eluted as above. The resulting partially resolved isomeric mixtures were combined with the similar mixture (fraction 1 or 3) from the initial column. Fraction 1 (containing **6** and **7**) was evaporated to an amber syrup which was dissolved in benzene (10 ml) and applied to an alumina column (Woelm, neutral, activity III, 3.5 × 20 cm) packed in benzene. The column was eluted with a mixture of benzene–ethyl acetate (19:1 v/v) to afford the resolved isomers. The first nucleoside to be eluted (**6**, R_f 0.63) was isolated as a light amber syrup after removal of eluent. Crystallization of this syrup from ethanol gave 2.7 g (15%) of **6** as white crystals: mp 114–116 °C; uv λ_{max} (pH 1) 246 nm (ε 33 600), 283 (sh) (19 100); λ_{max} (MeOH) 228 nm (ε 49 100), 265 (9900), 275 (9500), 282 (9600); ^{1}H NMR ($CDCl_3$) δ 6.86 (s, 1, $J_{1',2'}$ = 0.0 Hz, $H_{1'}$).

Anal. Calcd for $C_{31}H_{23}ClN_4O_7$: C, 62.15; H, 3.84; N, 9.36. Found: C, 62.20; H, 3.81; N, 9.20.

The second nucleoside to be eluted (**7**, R_f 0.57) was isolated as an amber syrup after removal of eluent. Crystallization of this syrup (after combination with **7** from fraction 3) from ethanol gave 1.4 g (8%) of **7** as thick needles: mp 147–149 °C; uv λ_{max} (pH 1) 248 nm (ε 28 200), 285 (sh) (17 100), 304 (sh) (15 300); λ_{max} (MeOH) 230 nm (ε 44 900), 277 (sh) (6900), 283 (7500), 294 (6900); ^{1}H NMR ($CDCl_3$) δ 7.19 (d, 1, $J_{1',2'}$ = 1.0 Hz, $H_{1'}$).

Anal. Calcd for $C_{31}H_{23}ClN_4O_7$: C, 62.15; H, 3.84; N, 9.36. Found: C, 62.25; H, 3.86; N, 9.25.

Fraction 3, containing **5** and **7**, was evaporated to an amber syrup which was dissolved in benzene (8 ml) and applied to an alumina column (Woelm, neutral, activity III, 3.5 × 20 cm) packed in benzene. The column was eluted with a mixture of benzene–ethyl acetate (9:1 v/v) to afford the resolved isomers. The first nucleoside to be eluted (**7**, R_f 0.57) was combined with that obtained from fraction 1 (vide supra). The second nucleoside to be eluted (**5**, R_f 0.39) was isolated as an amber syrup after removal of eluent. Crystallization of this syrup from methanol gave 2.0 g (11%) of **5** as white crystals: mp 135–136 °C; uv λ_{max} (pH 1) 245 nm (ε 35 400), 275 (sh) (23 900); λ_{max} (pH 11) 241 nm (ε 40 200), 274 (sh) (21 600); λ_{max} (MeOH) 230 nm (ε 44 300), 266 nm (ε 9900); ^{1}H NMR ($CDCl_3$) δ 7.31 (d, 1, $J_{1',2'}$ = 2.8 Hz, $H_{1'}$), 8.19 (d, 1, $J_{7,8}$ = 6.0 Hz, H_7), 8.48 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6).

Anal. Calcd for $C_{31}H_{23}ClN_4O_7$: C, 62.15; H, 3.84; N, 9.36. Found: C, 62.09; H, 3.89; N, 9.53.

Method B. *N,O*-Bis(trimethylsilyl)acetamide (12 ml) was added to a suspension of **3** (5.0 g, 32 mmol) in xylene (50 ml) and the solution was heated at 40 °C for 1 h. The solvent and excess silylating agent were removed under reduced pressure at 110 °C to give a dark amber syrup. This syrup was heated at 110 °C for 1 h and then allowed to cool to room temperature, giving a dark solid. Mercuric cyanide (8.8 g, 39 mmol) was added to the silylation product and after acetonitrile (100 ml) was added, the mixture was brought to reflux temperature under a nitrogen atmosphere. A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (prepared from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, 16.4 g, 32 mmol) in acetonitrile (35 ml) was added to the reaction mixture and this was followed by an additional quantity of acetonitrile (30 ml). The resulting mixture was heated at reflux temperature for 1 h, cooled, and filtered and the filtrate was evaporated to a residue. The residue was then extracted with chloroform (4 × 100 ml) and filtered, and the filtrate was evaporated to a residue. The residue was ex-

tracted with chloroform (4 × 100 ml), filtered, and evaporated to a syrup. This syrup was dissolved in chloroform (300 ml) and extracted sequentially with a saturated aqueous sodium bicarbonate solution (3 × 50 ml), a 30% aqueous potassium iodide solution (3 × 50 ml), and water (3 × 60 ml). The chloroform solution was dried over anhydrous sodium sulfate and concentrated to a syrup (27 g). This syrup was dissolved in benzene (25 ml) and applied to an alumina column (J. T. Baker, 6.5 × 40 cm) which had been packed in benzene. The column was washed with 2.0 l. of benzene followed by elution with a mixture of benzene–ethyl acetate (9.25:0.75 v/v). The first nucleoside to be eluted was **6** (2.5 g of syrup) which was followed by an unresolved mixture (2.7 g of syrup) and then **5** (5.5 g of syrup). The mixture of unresolved nucleosides was rechromatographed as above to provide additional **5** and **6** as well as resolved **7**. The individual nucleosides were obtained in crystalline form as described in method A. The yields of each of the isomers obtained by this procedure follow: **6**, 2.0 g (12%); **7**, 0.9 g (4%); and **5**, 4.6 g (25%). The physical and spectral properties for **5**, **6**, and **7** prepared by this method was identical with those given in method A (melting point and ^{1}H NMR).

4-Chloro-2-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (8). A solution of **6** (250 mg, 0.42 mmol) in methanol (35 ml) was cooled to 15 °C and sufficient sodium methoxide was added to adjust the pH of the solution to 10. The solution was stirred at 15 °C for 1 h and then at room temperature for 2.5 h. The reaction mixture was neutralized with Amberlite IRC-120 resin (H^+ form prewashed with methanol) and the resin removed by filtration. The filtrate was evaporated to afford a solid which was coevaporated with benzene and then triturated with benzene (25 ml). Recrystallization from a minimal amount of water provided 95 mg (79%) of **8**: mp 151–153 °C dec; uv λ_{max} (pH 1) 261 nm (ϵ 6500), 292 (6800); λ_{max} (pH 11) 260 nm (ϵ 6100), 292 (6300); λ_{max} (H_2O) 262 nm (ϵ 4600), 292 (5300); ^{1}H NMR (Me_2SO-d_6) δ 6.37 (d, 1, $J_{1',2'}$ = 3.0 Hz, $H_{1'}$), 8.16 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 8.34 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6).

Anal. Calcd for $C_{10}H_{11}ClN_4O_4 \cdot 0.5H_2O$ (verified by ^{1}H NMR): C, 40.61; H, 4.06; N, 18.95. Found: C, 40.77; H, 4.04; N, 18.86.

2-(β-D-Ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine-4-thione (9). A solution of **6** (1.5 g, 2.5 mmol) and sodium hydrogen sulfide (700 mg, 12.5 mmol) in methanol (100 ml) was heated at reflux temperature for 1.5 h. The solution was cooled to room temperature and neutralized with Amberlite IRC-120 resin (H^+ form, prewashed with methanol) and the resin was then removed by filtration. The filtrate was evaporated to a yellow residue which upon coevaporation with benzene gave a solid. The solid was then triturated at room temperature with benzene (45 ml). The resulting solid was dissolved in methanol and evaporated in the presence of silica gel (SilicAR CC7, 1 g) at reduced pressure. The resulting mixture was placed on top of a silica gel column (SilicAR CC7, 2.5 × 20 cm, dry packed), and the column was eluted with a chloroform–methanol mixture (5:1 v/v) to provide 570 mg (80%) of **9**. An analytical sample was prepared by recrystallization from ethyl acetate–methanol: mp 173–175 °C; uv λ_{max} (pH 1) 237 nm (ϵ 19 300), 365 (12 800); λ_{max} (pH 11) 236 nm (ϵ 22 700), 362 (9400); λ_{max} (MeOH) 240 nm (ϵ 17 900), 369 (13 400); ^{1}H NMR (Me_2SO-d_6) δ 6.27 (d, 1, $J_{1',2'}$ = 3.0 Hz, $H_{1'}$), 7.27 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 7.57 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6), 13.28 (broad singlet, 1, H_5).

Anal. Calcd for $C_{10}H_{12}N_4O_4S$: C, 42.25; H, 4.23; N, 19.71. Found: C, 42.08; H, 4.17; N, 19.56.

2-(β-D-Ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (10). To a solution of **9** (200 mg, 0.7 mmol) in ethanol (20 ml) was added W2 Raney nickel (300 mg, prewashed with water until the pH of the aqueous suspension remained at 7 and this was followed by slurrying the catalyst in ethanol several times). This mixture was stirred vigorously at room temperature for 15 min, additional Raney nickel (200 mg) was added, and then stirring was continued for an additional 15 min. The catalyst was removed by filtration and the filtrate was evaporated at reduced pressure in the presence of silica gel (SilicAR CC7, 250 mg). The resulting mixture was placed on top of a silica gel column (SilicAR CC7, 2.5 × 15 cm) and elution with a mixture of chloroform–methanol (5:1 v/v) provided 105 mg (60%) of **10**. Recrystallization from ethanol gave fine yellow crystals: mp 183–184 °C (lit.[8] 167–168 °C); $[\alpha]^{33}D$ −83.5° (*c* 1, CH_3OH) [lit.[8] $[\alpha]^{22}D$ −70° (*c* 1, CH_3OH)]; uv λ_{max} (pH 1) 263 nm (ϵ 9100), 296 (6400); λ_{max} (pH 11) 263 nm (ϵ 7900), 279 (6600); λ_{max} (H_2O) 262 nm (ϵ 8100), 279 (sh) (6600) [lit.[8] λ_{max} (pH 1) 265 nm (ϵ 6300), 298 (4300); λ_{max} (pH 11) 268 nm (ϵ 5800), 280 (5700)]; ^{1}H NMR (Me_2SO-d_6) δ 6.37 (d, 1, $J_{1',2'}$ = 3.5 Hz, $H_{1'}$), 8.00 (dd, 1, $J_{7,6}$ = 6.0, $J_{7,4}$ = 1.5 Hz, H_7), 8.55 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6), 9.58 (wide singlet, 1, H_4).

4-Chloro-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (11). A solution of **7** (450 mg, 0.75 mmol) in methanol (50 ml) was adjusted to pH 9 by the addition of sodium methoxide. This solution was stirred at room temperature for 4 h and then neutralized to pH 7 with Amberlite IRC-120 resin (H^+ form, prewashed with methanol). The resin was removed by filtration. The filtrate was evaporated to a residue which was coevaporated with benzene to provide a solid. This solid was triturated with benzene (50 ml) and recrystallized from a minimal amount of water with charcoal treatment to give 150 mg (70%) of **11**: mp 158–160 °C dec; uv λ_{max} (pH 1) 232 nm (ϵ 4400), 295 (7200); λ_{max} (pH 11) 236 nm (ϵ 4300), 295 (7300); ^{1}H NMR (Me_2SO-d_6) δ 6.74 (d, 1, $J_{1',2'}$ = 3.4 Hz, $H_{1'}$), 8.20 (d, 1, $J_{7,6}$ = 5.5 Hz, H_7), 8.42 (d, 1, $J_{6,7}$ = 5.5 Hz, H_6).

Anal. Calcd for $C_{10}H_{11}ClN_4O_4$: C, 41.88; H, 3.84; N, 19.55. Found: C, 41.79; H, 3.98; N, 19.32.

4-Chloro-3-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (12). To a suspension of **11** (240 mg, 0.8 mmol) in acetone (15 ml) and 2,2-dimethoxypropane (2.5 ml) was added a 0.01% solution of sulfuric acid in acetone (24 ml). After stirring at room temperature for 1 h, a solution of saturated aqueous sodium bicarbonate (5 ml) was added. The resulting mixture was evaporated and the residual solid was extracted with chloroform (3 × 20 ml). The chloroform solution was concentrated to a small volume and applied to a silica gel column (SilicAR CC7, 2.5 × 20 cm, dry packed) and the column was eluted with chloroform–ethyl acetate (2:1 v/v). The fractions containing **12**, as indicated by TLC [R_f 0.28 on silica gel developed with chloroform–ethyl acetate (2:1 v/v)], were combined and evaporated to give a syrup. Coevaporation of the syrup three times with diethyl ether at 5 °C gave a white foam which readily reverted to a syrup (330 mg) upon warming to room temperature. Thin layer chromatography showed the presence of only one compound: ^{1}H NMR (C_6D_6–Me_2SO-d_6) δ 1.35 and 1.58 (2 s, 6, isopropylidene methyls), 6.86 (s, 1, $J_{1',2'}$ = 0.0 Hz, $H_{1'}$), 7.52 (d, 1, $J_{7,6}$ = 5.5 Hz, H_7), 7.89 (d, 1, $J_{6,7}$ = 5.5 Hz, H_6).

3-(β-D-Ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine-4-thione (13). To a solution of **7** (1.5 g, 2.5 mmol) in methanol (100 ml) was added 20 ml of a methanolic solution of sodium hydrogen sulfide (prepared by dissoloving 500 mg of sodium in 55 ml of methanol and then saturating this solution with hydrogen sulfide). This solution was heated at reflux temperature for 5 h. The reaction mixture was processed by the same procedure as that used for the synthesis of **9** and furnished 410 mg (58%) of **13**: mp 177–178°C; uv λ_{max} (pH 1) 266 nm (ϵ 17 400), 366 (13 200); λ_{max} (pH 11) 351 nm (ϵ 10 800); λ_{max} (H_2O) 226 nm (ϵ 15 400), 367 (11 800); ^{1}H NMR (Me_2SO-d_6) δ 7.44 (d, 1, $J_{7,6}$ = 7.0 Hz, H_7), 7.63 (d, 1, $J_{6,7}$ = 7.0 Hz, H_6), 7.84 (d, 1, $J_{1',2'}$ = 3.5 Hz, $H_{1'}$).

Anal. Calcd for $C_{10}H_{12}N_4O_4S \cdot 0.5H_2O$ (verified by ^{1}H NMR): C, 40.96; H, 4.44; N, 19.11. Found: C, 40.90; H, 4.55; N, 19.27.

3-(β-D-Ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (14). To a solution of **13** (110 mg, 0.38 mmol) in ethanol (20 ml) was added W2 Raney nickel (200 mg, prewashed with water until the pH of the aqueous slurry remained at 7 and this was followed by slurrying several times in ethanol). This mixture was stirred vigorously at room temperature for 15 min, additional catalyst (100 mg) was then added, and the stirring was continued for an additional 15 min. The mixture was filtered through a Celite pad which was then washed with ethanol. The filtrate was evaporated to a syrup which upon coevaporation with ethyl acetate gave a pale yellow solid. Recrystallization from ethanol with charcoal treatment gave 65 mg (67%) of **14** as pale yellow crystals: mp 166–168 °C; uv λ_{max} (pH 1) 224 nm (ϵ 3000), 300 (6700); λ_{max} (pH 11) 240 nm (ϵ 4100), 290 (5300); λ_{max} (H_2O) 240 nm (ϵ 4400), 289 (5600) ^{1}H NMR (Me_2SO-d_6) δ 6.53 (d, 1, $J_{1',2'}$ = 5.5 Hz, $H_{1'}$), 8.18 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 8.62 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6), 9.68 (s, 1, H_4).

Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.76; N, 22.22. Found: C, 47.84; H, 4.82; N, 22.20.

4-Chloro-1-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (15). A solution of **5** (1.0 g, 1.67 mmol) in methanol (60 ml) was treated by the same procedure as that used for the synthesis of **11** to furnish 450 mg (94%) of **15**: mp 171–172 °C; uv λ_{max} (pH 1) 268 nm (ϵ 7400); λ_{max} (pH 11) 268 nm (ϵ 8000); λ_{max} (H_2O) 267 nm (ϵ 7200); ^{1}H NMR (Me_2SO-d_6) δ 6.50 (d, 1, $J_{1',2'}$ = 5.0 Hz, $H_{1'}$), 8.31 (d, 1, $J_{7,8}$ = 5.5 Hz, H_7), 8.52 (d, 1, $J_{6,7}$ = 5.5 Hz, H_6).

Anal. Calcd for $C_{10}H_{11}ClN_4O_4 \cdot 1.0H_2O$ (verified by ^{1}H NMR): C, 39.41; H, 4.27; N, 18.39. Found: C, 39.68; H, 3.95; N, 18.02.

4-Chloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridine (16). To a suspension of **15** (240 mg, 0.8 mmol) in acetone (25 ml) and 2,2-dimethoxypropane (4.0 ml) was added a 0.05% solution of sulfuric acid in acetone (20 ml). After stirring at room temperature for 1 h, a solution of saturated aqueous sodium bicarbonate (8 ml) was added. The resulting mixture

was evaporated to dryness and the residual solid was extracted with chloroform (3 × 25 ml). Thin layer chromatography showed the presence of two nucleoside products [R_f 0.62 and 0.24 on SilicAR 7GF developed with chloroform–ethyl acetate (2:1 v/v)]. The chloroform solution was evaporated to a small volume and applied to the top of a silica gel column (SilicAR CC7, 2.5 × 20 cm, dry packed) and eluted with chloroform–ethyl acetate (2:1 v/v) to resolve the nucleoside mixture. The first nucleoside to be eluted, 4-chloro-1-(2,3-*O*-isopropylidene-5-*O*-1′-methoxyisopropyl-β-D-ribofuranosyl)-v-triazolo[4,5-c]pyridine (**17**), resisted crystallization and remained a syrup: ^{1}H NMR ($CDCl_3$) δ 0.99 and 1.02 (2 s, 6, isopropyl methyls), 1.45 and 1.63 (2 s, 6, isopropylidene methyls), 2.91 (s, 3, OCH_3), 3.32 (d, 2, $H_{5'}$), 6.40 (d, 1, $J_{1',2'}$ = 1.5 Hz, $H_{1'}$), 7.68 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 8.32 (d, 1, $J_{6,7}$ = 6.0 Hz, $H_{1'}$). Evaporation of the fractions containing **16** gave a syrup which crystallized to furnish 175 mg (67%) of the desired product: mp 120–121 °C; uv λ_{max} (pH 1) 270 nm (ε 9500); λ_{max} (pH 11) 268 nm (ε 9200); λ_{max} (MeOH) 267 nm (ε 9100); ^{1}H NMR (Me_2SO-d_6) δ 1.44 and 1.66 (2 s, 6, isopropylidene methyl), 6.87 (d, 1, $J_{1',2'}$ = 1.5 Hz, $H_{1'}$), 8.24 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 8.53 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6).

Anal. Calcd for $C_{13}H_{15}ClN_4O_4$: C, 47.74; H, 4.59; N, 17.15. Found: C, 47.82; H, 4.61; N, 17.02.

4-Amino-1-(β-D-ribofuranosyl)-v-triazolo[4,5-c]pyridine (3-Deaza-8-azaadenosine, 18). A solution of **15** (1.0 g, 3.48 mmol) in liquid ammonia (40 ml) was heated in a steel reaction vessel at 85 °C for 6 h. The excess ammonia was removed to afford a solid which was dissolved in methanol (35 ml) and evaporated at reduced pressure in the presence of silica gel. This residue was applied to the top of a silica gel column (SilicAR CC7, 3.5 × 20 cm, dry packed) and eluted with a chloroform–methanol mixture (4:1 v/v). The fractions containing **18**, as indicated by TLC [R_f 0.45 on silica gel (SilicAR 7GF) developed with chloroform–ethanol (2:1 v/v)], were combined and evaporated to afford a white solid. Recrystallization from a minimal amount of water provided 475 mg (51%) of **18**: mp 212–215 °C dec; $[\alpha]^{26}$D −84.0° (*c* 1, H_2O); uv λ_{max} (pH 1) 274 nm (ε 12 100); λ_{max} (pH 11) 295 nm (ε 7500); λ_{max} (H_2O) 290 nm (ε 7800); ^{1}H NMR (Me_2SO-d_6) δ 3.65 (m, 2, $H_{5'}$), 4.10 (q, 1, $J_{3',4'}$ = 4.5, $J_{4',5'}$ = 7.5 Hz, $H_{4'}$), 4.32 (q, 1, $J_{3',2'}$ = 10.0, $J_{3',4'}$ = 4.5 Hz, $H_{3'}$), 4.75 (q, 1, $J_{2',1'}$ = 5.0, $J_{2',3'}$ = 10.0 Hz, $H_{2'}$), 5.05 (t, 1, $J_{5',O5'}$ = 5.0 Hz, 5′ OH), 5.40 (d, 1, $J_{3',O3'}$ = 6.0 Hz, 3′ OH), 5.67 (d, 1, $J_{2',O2'}$ = 6.0 Hz, 2′ OH), 6.13 (d, 1, $J_{1',2'}$ = 5.0 Hz, $H_{1'}$), 7.13 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 7.24 (s, 2, 4-NH_2), 7.90 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6).

Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.78; N, 26.22. Found: C, 44.99; H, 5.06; N, 26.35.

Thin layer chromatography indicated the presence of a small quantity of a faster moving nucleoside which was not isolated [R_f 0.85 on SilicAR 7GF developed with chloroform–methanol (4:1 v/v)].

4-Methylthio-1-(β-D-ribofuranosyl)-v-triazolo[4,5-c]pyridine (19). A solution of **15** (286 mg, 1.0 mmol) in ethanol (30 ml) containing sodium (50 mg) and methanethiol (0.2 ml) was heated at reflux temperature for 1 h. The reaction mixture was neutralized with Amberlite IRC-120 resin (H^+ form, prewashed with ethanol) and filtered and the filtrate evaporated to a solid which was triturated with chloroform (25 ml). This crude solid was dissolved in methanol and evaporated to dryness in the presence of silica gel (SilicAR CC7, 1 g). This mixture was then placed on top of a silica gel column (SilicAR CC7, 3.5 × 10 cm, dry packed). The column was eluted with chloroform–methanol (4.25:0.75 v/v) and the fractions containing **19**, as indicated by TLC [R_f 0.58 on silica gel (SilicAR 7GF) developed with chloroform–methanol (4:1 v/v)], were combined and allowed to slowly evaporate at room temperature to provide 205 mg (68%) of **19**: mp 174–175 °C; uv λ_{max} (pH 1) 312 nm (ε 20 700); λ_{max} (pH 11) 303 nm (ε 14 000); λ_{max} (MeOH) 299 nm (ε 15 700); ^{1}H NMR (Me_2SO-d_6) δ 2.78 (s, 3, SCH_3), 6.43 (d, 1, $J_{1',2'}$ = 5.0 Hz, $H_{1'}$), 7.92 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 8.50 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6); $[\alpha]^{25}$D −85.0° (*c* 0.96, CH_3OH).

Anal. Calcd for $C_{11}H_{14}N_4O_4S$: C, 44.29; H, 4.70; N, 18.79. Found: C, 44.16; H, 4.86; N, 18.36.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-v-triazolo[4,5-c]pyridine-4-thione (20). Hydrogen sulfide (25 ml) was condensed into a reaction flask containing sodium (75 mg) which had been cooled to −75 °C in a dry ice–isopropyl alcohol bath and protected from moisture. Dimethylformamide (25 ml) was added in 5-ml portions over 1.5 h during which time the temperature was maintained at −75 °C. Following dimethylformamide addition the solution was stirred at −75 °C for 1 h and then allowed to slowly approach room temperature by a gradual warming of the dry ice–isopropyl alcohol bath. The dark blue dimethylformamide–sodium hydrogen sulfide solution was stirred at room temperature for 1.5 h. To this solution was added **5** (1.8 g, 3.0 mmol) and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was filtered through a Celite pad. The filtrate was cooled to 0 °C and poured into cold water (125 ml at 5 °C) and a cream-colored precipitate formed. The pH of the aqueous suspension was adjusted to 7 with a solution of 1 N sodium hydroxide and then cooled to 0 °C. The solid was collected by filtration, washed with cold water (50 ml), and then dissolved in chloroform (350 ml). The aqueous layer was separated and washed with chloroform (3 × 25 ml). The combined chloroform solutions were dried over sodium sulfate at 10 °C for 12 h. The drying agent was removed and the filtrate evaporated at 0–5 °C in vacuo to furnish a yellowish syrup which was coevaporated with carbon tetrachloride (2 × 30 ml). The resulting solid was suspended in carbon tetrachloride (50 ml) and placed in a freezer at −25 °C for 24 h. The solid was collected by filtration, washed with carbon tetrachloride (50 ml), and air dried to furnish 1.55 g (86%) of **20**: mp 174–177 °C; uv λ_{max} ($CHCl_3$) 276 nm (ε 4800), 284 (4200), 334 (17 600); ^{1}H NMR (Me_2SO-d_6) δ 4.74 (s, 2, $H_{5'}$), 5.13 (m, 1, $H_{4'}$), 6.31 (t, 1, $H_{3'}$), 6.59 (q, 1, $H_{2'}$), 7.17 (d, 1, $J_{1',2'}$ = 2.2 Hz, $H_{1'}$), 7.42 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7).

Anal. Calcd for $C_{31}H_{24}N_4O_7S$: C, 62.42; H, 4.03; N, 9.39. Found: C, 62.31; H, 4.16; N, 9.13.

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)amino-1,2,3-thiadiazolo[5,4-b]pyridine (21). A solution of **20** (1.25 g, 2.1 mmol) in ethanol (200 ml) was heated at reflux temperature for 2.5 h. The reaction mixture was evaporated to a syrup which resisted crystallization. The syrup was dissolved in ethanol (50 ml) and treated with charcoal and the filtrate was evaporated to provide **21** as a foam (1.05 g, 84%): uv λ_{max} (pH 1) 236 nm (ε 44 300), 275 (sh) (17 700), 327 (10 700); λ_{max} (pH 11) 237 nm (ε 44 900), 275 (sh) (17 600), 341 (10 400); λ_{max} (MeOH) 232 nm (ε 5300), 275 (10 600), 338 nm (ε 8400); ^{1}H NMR (Me_2SO-d_6) δ 6.25 (m, 2, $H_{1'}$, $H_{2'}$), 7.20 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 8.59 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6), 9.74 (d, 1, NH).

Anal. Calcd for $C_{31}H_{24}N_4O_7S$: C, 62.42; H, 4.03; N, 9.39. Found: C, 62.24; H, 4.24; N, 9.33.

4-(β-D-Ribofuranosyl)amino-1,2,3-thiadiazolo[5,4-b]pyridine (22). A solution of **21** (750 mg, 1.25 mmol) in methanol (50 ml) was adjusted to pH 9 by the addition of sodium methoxide. This solution was stirred at 15 °C for 1 h and then at room temperature for 5 h. The reaction mixture was allowed to stand at 4 °C for 2 days. The crystalline solid which had formed was collected by filtration and washed with methanol (10 ml) to furnish 190 mg of **22**. Treatment of the filtrate by the same procedure as that used for the isolation of **11** gave an additional 80 mg of **22** to provide a total of 270 mg (69%) of **22**. Recrystallization from a minimal amount of methanol provided an analytical sample: mp 202–204°; uv λ_{max} (pH 1) 252 nm (ε 11 900), 275 (8300), 322 (8700); λ_{max} (pH 11) 243 nm (ε 13 100), 272 (5600), 338 (5900); λ_{max} (MeOH) 234 nm (ε 13 900), 270 (5300), 339 (5700); ^{1}H NMR (Me_2SO-d_6) δ 4.83 (t, 1, $C_{5'}OH$), 5.80 (q, 1, $J_{1',2'}$ = 5.0, $J_{1',4}$ = 8.0 Hz, $H_{1'}$), 7.09 (d, 1, $J_{5,6}$ = 5.5 Hz, H_5), 7.99 (d, 1, $J_{4,1'}$ = 8.0 Hz, 4-NH), 8.57 (d, 1, $J_{6,5}$ = 5.5 Hz, H_6).

Anal. Calcd for $C_{10}H_{12}N_4O_4S$·0.5H_2O: C, 40.96; H, 4.10; N, 19.11. Found: C, 41.09, H, 4.41; N, 19.12.

1-Methyl-v-triazolo[4,5-c]pyridine (23). A solution of 3-amino-4-methylaminopyridine dihydrochloride[31] (250 mg, 1.25 mmol) in water (5 ml) containing 1.5 mequiv of hydrochloric acid was cooled to 3 °C. A precooled sodium nitrite solution (115 mg in 1 ml of H_2O) was added rapidly and the mixture was stirred at 3–5 °C for 1 h and then at room temperature for 1.5 h. The pH of the reaction mixture was adjusted to 7 with a 1 N aqueous sodium hydroxide solution and then evaporated to a solid which was coevaporated with ethanol. This solid was extracted with diethyl ether (5 × 15 ml) and the ether evaporated to give a solid which was vacuum sublimed (102 °C, 0.05 mmHg) to furnish 150 mg (90%) of **23**: mp 118–120 °C (lit.[32] 120 °C); uv λ_{max} (pH 1) 275 nm (ε 4600); λ_{max} (pH 11) 264 nm (ε 6000); λ_{max} (MeOH) 265 nm (ε 5800); ^{1}H NMR (Me_2SO-d_6) δ 4.45 (s, 3, NCH_3), 7.98 (dd, 1, $J_{7,6}$ = 6.0, $J_{7,4}$ = 1.0 Hz, H_7), 8.66 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6), 9.54 (d, 1, $J_{4,7}$ = 1.0 Hz, H_4).

1-(β-D-Ribofuranosyl)-v-triazolo[4,5-c]pyridine (25). A solution of **15** (500 mg, 1.75 mmol) in anhydrous hydrazine (10 ml) was heated at reflux temperature for 1 h. The reaction mixture was evaporated to afford an amber syrup which was coevaporated twice with ethanol. The resulting solid was dissolved in water (10 ml), treated with charcoal, and filtered and the filtrate was diluted with 10 ml of ethanol. Silver oxide (2.5 g) was added and the suspension was stirred with no external heating for 20 min. The solution was then heated on a steam bath for 1 h. The mixture was fil-

tered, the filtrate treated with charcoal and filtered, and the filtrate was evaporated to a dark syrup. This syrup was dissolved in methanol and evaporated in the presence of silica gel (SilicAR CC7, 1 g). This mixture was placed on the top of a silica gel column (SilicAR CC7, 2.5 × 10 cm, dry packed) and eluted with chloroform–methanol (4:1 v/v). The fractions containing **25,** as indicated by TLC [R_f 0.75 on silica gel (SilicAR 7GF) developed with chloroform–ethanol (2:3 v/v)], were combined and evaporated to an amber syrup which crystallized to provide 165 mg (38%) of **25:** mp 161–163 °C; uv λ_{max} (pH 1) 266 nm (ϵ 5400); λ_{max} (pH 11) 259 nm (ϵ 6600); λ_{max} (MeOH) 256 nm (ϵ 6700); ^{1}H NMR (Me_2SO-d_6) δ 6.48 (d, 1, $J_{1',2'}$ = 5.0 Hz, $H_{1'}$), 8.25 (d, 1, $J_{7,6}$ = 6.0 Hz, H_7), 8.70 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6), 9.62 (s, 1, H_4).

Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.76; N, 22.22. Found: C, 47.44; H, 4.58; N, 22.37.

3,4-Diaminopyridine (26). To a solution of 4-amino-2-chloro-3-nitropyridine[33] (1.74 g, 10 mmol) in ethanol containing 1 N sodium hydroxide (10 ml, 10 mequiv) was added 5% palladium on carbon (250 mg) and this mixture was hydrogenated at atmospheric pressure until hydrogen uptake had ceased. The resulting mixture was filtered and the filtrate evaporated to a residue which was dried in vacuo at 75 °C. The resulting solid was triturated briefly with cold water (5 ml) and the solid was collected by filtration. Recrystallization from water provided 725 mg (72%) of **26:** mp 217–219 °C (lit.[34] 218–219 °C); uv λ_{max} (pH 1) 285 nm (ϵ 7400); λ_{max} (pH 11) 246 nm (ϵ 5800), 283 (3500); λ_{max} (MeOH) 253 nm (ϵ 4100), 295 (5800); ^{1}H NMR (Me_2SO-d_6) δ 4.55 (s, 2, 3-NH_2), 5.38 (s, 2, 4-NH_2), 6.49 (d, 1, $J_{5,6}$ = 5 Hz, H_5), 7.56 (d, 1, $J_{6,5}$ = 5 Hz, H_6), 7.73 (s, 1, H_2).

v-Triazolo[4,5-*c*]pyridine (27). A solution of 3,4-diaminopyridine (**26**, 725 mg, 6.6 mmol) in water (7 ml) containing hydrochloric acid (12 mequiv) was cooled to 3 °C. A solution of soium nitrite (530 mg in 1.5 ml of water) was added rapidly to this solution which was stirred at 5 °C for 1 h and then at 20 °C for an additional 1 h. The solution was filtered, neutralized with 6 N sodium hydroxide to pH 7, and then evaporated to dryness to afford a solid. This solid was triturated with cold water (3 ml), and the solid collected by filtration and recrystallized from water to give 595 mg (75%) of **27**: mp 243–245 °C (lit.[32] 240 °C); uv λ_{max} (pH 1) 261 nm (ϵ 4600); λ_{max} (pH 11) 264 nm (ϵ 4400), 279 (4600); λ_{max} (MeOH) 258 nm (ϵ 4300); ^{1}H NMR (Me_2SO-d_6) δ 7.96 (dd, 1, $J_{7,4}$ = 1.0, $J_{7,6}$ = 6.0 Hz, H_7), 8.57 (d, 1, $J_{6,7}$ = 6.0 Hz, H_6), 9.55 (d, 1, $J_{4,7}$ = 1.0 Hz, H_4), 15.00 (s, 1, H_1).

Acknowledgments. This investigation was supported by Research Contract NIH-N01-CM-43806 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Public Health Service. The authors are indebted to Steven J. Manning and Suzanne Mason for technical assistance.

Registry No.—**3,** 36258-82-9; **4a,** 5991-01-5; **4b,** 22860-91-9; **5,** 57680-35-0; **6,** 57680-36-1; **7,** 57680-37-2; **8,** 57680-38-3; **9,** 57680-39-4; **10,** 3969-28-6; **11,** 57680-40-7; **12,** 57680-41-8; **13,** 57680-42-9; **14,** 57680-43-0; **15,** 57680-44-1; **16,** 57680-45-2; **17,** 57680-46-3; **18,** 57680-47-4; **19,** 57680-48-5; **20,** 57680-49-6; **21,** 57680-50-9; **22,** 57680-51-0; **23,** 57680-52-1; **25,** 57680-53-2; **26,** 54-96-6; **27,** 273-05-2; 4-chloro-*v*-triazolo[4,5-*c*]pyridine, 36258-82-9; 2,2-dimethoxypropane, 77-76-9; methanethiol, 74-93-1; 3-amino-4-methylaminopyridine 2HCl, 57680-54-3; 4-amino-2-chloro-3-nitropyridine, 2789-25-5.

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