s-Triazolo[1,5-a]pyrimidine Nucleosides. Site of N-Glycosylation Studies and the Synthesis of an N-Bridgehead Guanosine Analog[1]

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Direct glycosylation of *O*-trimethylsilyl-5-chloro-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**1**) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in acetonitrile at room temperature gave 5-chloro-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**3**) in good yield, which on aminolysis with methanolic ammonia furnished 5-chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**5**). Treatment of **5** with nucleophilic reagents gave 5-substituted 3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-ones, including 5-mercapto- (**8e**), 5-methylamino- (**8c**), 5-dimethylamino- (**8d**), and 5-amino-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**8b**), an analog of guanosine possessing a bridgehead nitrogen atom. Treatment of **5** with hydrazine gave a rearrangement product (**7**) identified as 3-[pyrazolin-5(1*H*,2*H*)-on-3-ylamino]-4-β-D-ribofuranosyl-*s*-triazole. Treatment of **5** with liquid ammonia gave a ring-opened product which was tentatively identified as 6-amino-2-[*N*-(β-D-ribofuranosyl)cyanamido]pyrimidin-4-one (**9**). A similar product tentatively identified as 4-amino-6-chloro-2-[*N*-(β-D-ribofuranosyl)cyanamido]pyrimidine (**17**) was formed under the glycosylation conditions with *N*-trimethylsilyl-7-amino-5-chloro-*s*-triazolo[1,5-*a*]pyrimidine (**14**). Glycosylation of *O*-trimethylsilyl-5-methyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**2**) and *N,O*-bis(trimethylsilyl)-7-amino-*s*-triazolo[1,5-*a*]pyrimidin-5-one (**16**) gave the 3-β-D-ribofuranosyl derivatives (**4** and **18**, respectively), whereas glycosylation of *N*-trimethylsilyl-7-amino-*s*-triazolo[1,5-*a*]pyrimidine (**15**) gave *only* the 4-β-D-ribofuranosyl derivative (**19**). The sites of glycosylation have been determined unequivocally by chemical conversion to compounds of known structure and by pmr spectral comparisons of the H-2 chemical shifts. The anomeric configuration of **5** has been determined unequivocally as β by cyclonucleoside formation.

In recent years many unnatural nucleosides have been described which resemble at first glance the natural purine nucleosides, adenosine and guanosine, but which actually differ in some minor aspect. The number of these "counterfeits" which could be prepared and identified employing alternative heterocyclic systems has been limited by the capability of the organic chemist to unequivocally assign the site of glycosylation and anomeric configuration. In many cases the efficiency of a particular nucleoside preparation has been decreased by the lack of specificity of the glycosylation reaction and the formation of two or more isomeric glycosyl derivatives,[2,3] requiring tedious separation and characterization.

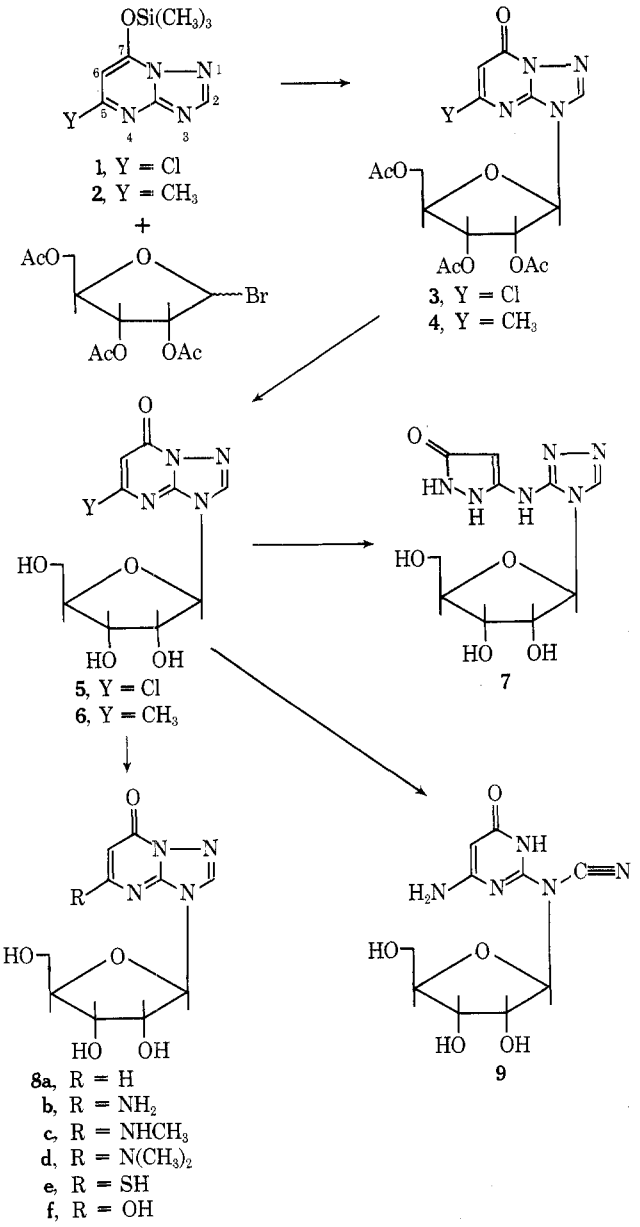
It was the initial objective of our investigation to prepare the guanosine analog in the *s*-triazolo[1,5-*a*]pyrimidine system, a bridgehead nitrogen system easily pictured as purine with N-1 and C-5 interchanged. This heterocyclic system is of particular interest since the corresponding nucleosides lack an N(H) function at position 1 of purine; hydrogen bonding of the Watson–Crick type, therefore, would not be possible.

Winkley, *et al.*,[3] have described the glycosylation of *s*-triazolo[1,5-*a*]pyrimidin-7-one, but the procedure gave a mixture of the 3- and 4-ribofuranosyl isomers and no evidence was presented for the assignment of the β configuration at the anomeric center. Recently, Tindall, *et al.*,[4] and Schmidt and Townsend[5] have demonstrated the directive effect of certain 8-halogen derivatives upon the site of purine glycosylation. For this reason 5-chloro-*s*-triazolo[1,5-*a*]pyrimidin-7-one[6] was chosen as the starting material for the nucleoside synthesis. The halogen at the position adjacent to N-4 could be predicted to deactivate that nitrogen in the glycosylation reaction. Treatment of 5-chloro-*s*-triazolo[1,5-*a*]pyrimidin-7-one with hexamethyldisilazane according to the general procedure described by Wittenberg[7] gave the trimethylsilyl derivative (**1**, Scheme I) which was treated with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in acetonitrile at room temperature to furnish a good yield of a single crystalline triacetylated nucleoside (**3**). Nucleoside **3** was the only nucleoside which could be detected by tlc or column chromatography procedures (some heterocyclic starting material could be isolated from the reaction product). Similarly, in other glycosylation reactions reported in this study, no other nucleosides were detected by tlc other than those isolated and characterized in the Experimental Section. Treatment of **3** with methanolic ammonia at ambient temperature gave the deacetylated nucleoside **5**, which was shown by elemental analysis to have retained the 5-chloro group. Dehalogenation of **5** with 10% palladium on carbon in a hydrogen atmosphere gave 3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**8a**) identical with an authentic sample,[3,8] confirming the directive affect of the 5-chloro group to give exclusively the N-3 glycosyl derivative.

Our first attempt to prepare the guanosine analog **8b** from **5** by treatment with liquid ammonia in a sealed vessel gave a product (**9**) in excellent yield, which lacked the strong ultraviolet absorption (near 270 nm) characteristic of other *s*-triazolo[1,5-*a*]pyrimidin-7-ones. In the case of **9** a strong absorption in the infrared spectrum at 2230 cm^{-1} was also observed. Since **9**[9] possessed a pyrimidine-like ultraviolet spectrum and cleavage of the triazole between the adjacent nitrogens would give an *N*-cyanopyrimidine derivative, the structure of **9** was tentatively assigned as 6-amino-2-[*N*-(β-D-ribofuranosyl)cyanamido]pyrimidin-4-one. The tentative structure assignment was supported by elemental analysis and by pmr spectral analysis, which showed only one aromatic proton, corresponding to H-5 of pyrimidine (or H-6 of *s*-triazolo[1,5-*a*]pyrimidine). A similar product showing an absorption in the infrared spectrum at 2235 cm^{-1} was isolated[10] in 1963 from a Hilbert–Johnson type alkylation reaction, but a structure was not proposed.

Treatment of **5** with *methanolic* ammonia at room temperature for several days gave 5-amino-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**8b**),[11] the guanosine analog. The 5-chloro moiety was further demonstrated to be reactive toward other nucleophilic agents under mild conditions by treatment with methylamine and dimethylamine to furnish the corresponding 5-methylamino (**8c**) and 5-dimethylamino (**8d**) derivatives. Treatment of **5** with thiourea in ethanol gave, instead of the expected 5-mercapto nucleoside (**8e**), the glycosyl-cleavage product,

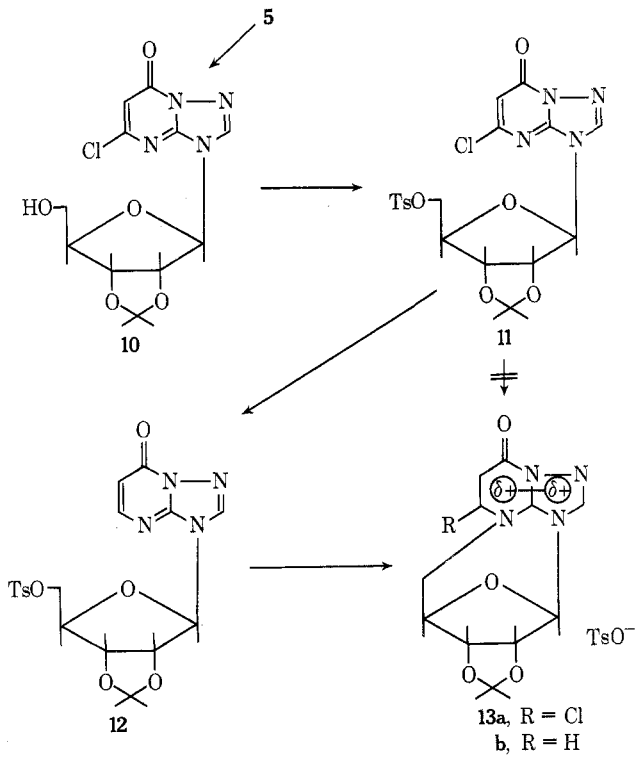
Scheme I



5-chloro-s-triazolo[1,5-a]pyrimidin-7-one. When **5** was stirred at ambient temperature for 2 hr with methanolic hydrogen sulfide–ammonium carbonate, however, the 5-mercapto nucleoside (**8e**) could be isolated in good yield. 5-Hydroxy-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (**8f**, the xanthosine analog) was prepared from **5** by the method of Goodman, *et al.*,[12] using alkaline 2-mercaptoethanol.

Treatment of **5** with methanolic hydrazine gave a derivative (**7**) which was presumed on the basis of elemental analysis to be the 5-hydrazino derivative. However, there was a conspicuous absence of an absorption in the 270-nm region of the ultraviolet spectrum characteristic of s-triazolo[1,5-a]pyrimidine derivatives. Theorizing that ring opening and reclosure had occurred as well as the nucleophilic displacement of chloride, the structure **7** (see Scheme I) was tentatively assigned to the compound. Ultraviolet spectral comparisons of the hydrazine-treated product (**7**) with 3-aminopyrazolin-5(1*H*,2*H*)-one showed them to be very similar and therefore supported the structure of **7** as 3-[pyrazolin-5(1*H*,2*H*)-on-3-ylamino]-4-β-D-ribofuranosyl-s-triazole, since 3-amino-s-triazole and the carbohydrate moiety have no significant absorption in the ultraviolet spectral region.

Scheme II



Although the anomeric configuration of **5** could tentatively be assigned β on the basis of several empirical rules (see ref 1 for a brief discussion of those rules), a more rigorous proof was in order for this unusual heterocyclic nucleoside series. Isopropylidenation of the 5-chloro nucleoside (**5**) gave **10** (Scheme II), which was treated with *p*-toluenesulfonyl chloride in pyridine to furnish the 5′-*O*-*p*-toluenesulfonyl-2′,3′-*O*-isopropylidene derivative (**11**). Treatment of **11** with DMSO or acetonylacetone at 100–110° for 2–4 hr did *not* produce the cyclonucleoside (**13a**). This result would indicate either that **5** has the α configuration[13] or that N-4 (because of the adjacent electron-withdrawing chloro group) is not nucleophilic enough to displace the 5′-tosylate. Treatment of the 5-chloro-2′,3′-*O*-isopropylidene-5′-*O*-*p*-toluenesulfonyl nucleoside (**11**) with 10% palladium on carbon in a hydrogen atmosphere gave the corresponding dehalogenated derivative (**12**). A solution of **12** in DMSO was heated at 100° for 4 hr to effect cyclonucleoside formation (**13b**), allowing the anomeric configuration of **5** (and hence **8a–f**) to be unequivocally assigned β. The identity of **13b** as the cyclonucleoside was confirmed by the presence of an ionic sulfonate absorption in the infrared spectrum at 1200 cm^{-1} and the drastic decrease in chromatographic mobility in nonpolar solvents of **13b** compared to **12.** Instead of the 10-nm bathochromic shift observed with cyclonucleoside formation in the purine series,[14] a small (3 nm) hypsochromic shift was observed with the formation of **13b.**

Since the ability of aromatic halogens to influence the site of glycosylation has now been firmly established, several other heterocyclic derivatives were utilized in the glycosylation reaction in order to assess the directive effects of other substituents at C-5.

Glycosylation of *O*-trimethylsilyl-5-methyl-s-triazolo[1,5-a]pyrimidin-7-one (**2**) under the same alkylation conditions used for **1** gave a single nucleoside product (**4**) which was deacetylated with methanolic ammonia. The site of glycosylation of the deacetylated nucleoside product (**6**) was not easily assigned since **6** could not be converted to a nucleoside of known structure. The ultraviolet maxima of

Table I
H-2 Chemical Shifts in the Pmr Spectra of Some 3- and 4-Substituted *s*-Triazolo[1,5-*a*]pyrimidine Derivatives

Substituted *s*-triazolo-[1,5-*a*]pyrimidine	3 or 4 substituent	H-2 chemical shift,[a] ppm	
7-One	3-Methyl[3]	8.91	
7-One	4-Methyl[3]		8.31
7-One	3-β-D-Ribofuranosyl (**8a**)[3]	9.19	
7-One	4-β-D-Ribofuranosyl (**20**)[3]		8.33
5-Chloro-7-one	3-β-D-Ribofuranosyl (**5**)	9.22	
5-Methyl-7-one	3-β-D-Ribofuranosyl (**6**)	9.10	
5-Amino-7-one	3-β-D-Ribofuranosyl (**8b**)	9.20	
5-Methylamino-7-one	3-β-D-Ribofuranosyl (**8c**)	8.88	
5-Dimethylamino-7-one	3-β-D-Ribofuranosyl (**8d**)	8.85	
5-Mercapto-7-one	3-β-D-Ribofuranosyl (**8e**)	8.80	
5-Hydroxy-7-one	3-β-D-Ribofuranosyl (**8f**)	9.09	
7-Amino-5-one	3-β-D-Ribofuranosyl (**18**)	8.98	
7-Amino	4-β-D-Ribofuranosyl (**19**)		8.18

[a] Pmr spectra were determined on a Hitachi R20A instrument using DMSO-d_6 as a solvent and DSS as an internal reference.

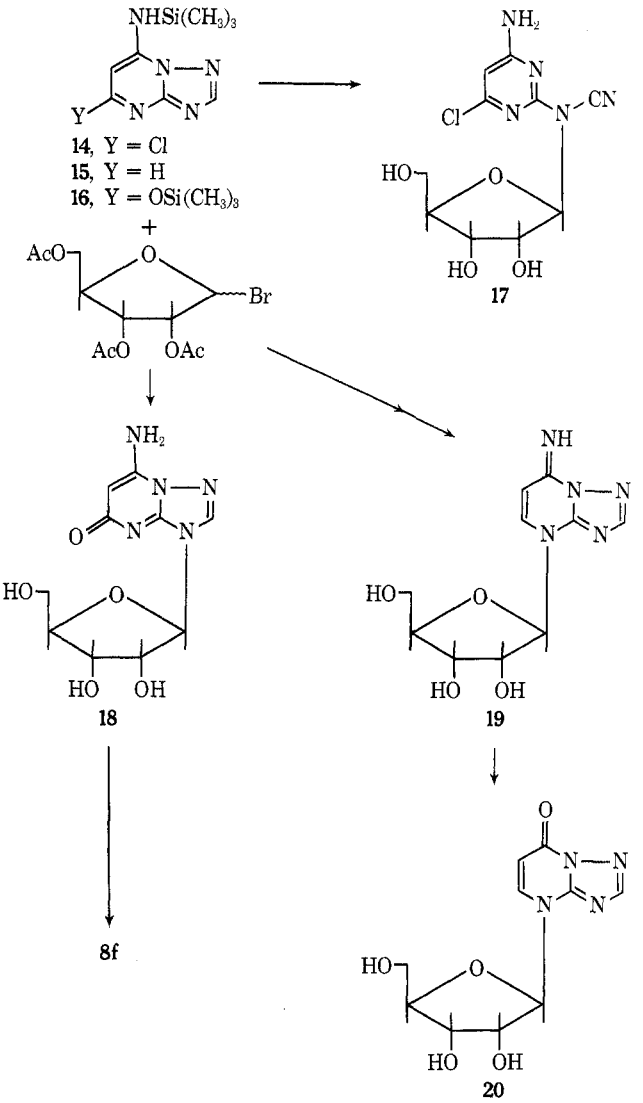
the 3- and 4-methyl-*s*-triazolo[1,5-*a*]pyrimidine derivatives were not sufficiently different to permit assignment of the site of glycosylation of **6**. Pmr spectral comparison of the H-2 chemical shift of **6** with the corresponding shifts in DMSO-d_6 (see Table I) of the 3- and 4-methyl derivatives as well as the H-2 chemical shifts of the 3-β-D-ribofuranosyl (**8a**) and 4-β-D-ribofuranosyl (**20**) derivatives indicated **6** to be a 3-D-ribofuranosyl derivative. A summary of the pmr chemical shifts in Table I shows that glycosylation or alkylation on N-3 causes the H-2 chemical shift to be in the region 8.9–9.2 ppm, while the H-2 chemical shift of the corresponding N-4 isomers appears in the region 8.1–8.3 ppm.

The structure establishment of **6** as 5-methyl-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one made it evident that the 5-methyl group adjacent to N-4 prevented glycosylation at N-4.

Glycosylation of *N*-trimethylsilyl-7-amino-5-chloro-*s*-triazolo[1,5-*a*]pyrimidine (**14**, Scheme III) would be predicted to yield the N-3 glycosyl product on the basis of previous studies. In fact, only one nucleoside product could be isolated from the reaction and this material possessed an infrared absorption at 2230 cm^{-1} and a pyrimidine-like ultraviolet spectrum similar to that of **9**. Deacetylation in the usual manner gave a nucleoside (**17**)[9] whose tentative structure was assigned as 4-amino-6-chloro-2-[*N*-(β-D-ribofuranosyl)cyanamido]pyrimidine and was supported by the elemental analysis.

Glycosylation of the *N*-trimethylsilyl derivative of 7-amino-*s*-triazolo[1,5-*a*]pyrimidine (**15**) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in a fusion reaction using aluminum chloride as a catalyst gave a single nucleoside product, which after treatment with methanolic ammonia in the usual manner gave an amino nucleoside (**19**). The structure of **19** was assigned as 7-imino-4-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidine on the basis of pmr data (see Table I). The site of glycosylation was established as N-4 by acidic hydrolysis of the imino function in **19** to the corresponding 7-oxo derivative (**20**) which was identical with an authentic sample[3] by ultraviolet and infrared spectral comparisons as well as chromatographic mobility comparisons. The formation of a single nucleoside product is surprising, since in the glycosylation of the corresponding 7-oxo analog,[3] *both* N-3 and N-4 isomers were isolated in near-equal amounts. It may be therefore inferred that the remote 7-amino (imino) group may also have some directive effect upon the determination of the site of glycosylation.

Scheme III



Glycosylation of the same system plus a bulky but electron-donating trimethylsilyloxy group at C-5 (**16**) gave again only one nucleoside product, which was deacetylated in the same manner to give 7-amino-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-5-one (**18**) in good yield. The site of glycosylation as N-3 was determined on the basis of spectroscopic data (see Table I) and the deamination of **18** to **8f** (whose structure has been unequivocally determined).

Thus it appears that the determination of the site of glycosylation is influenced not only by the presence of electron-withdrawing groups but also the presence of bulky substituents adjacent to potential glycosylation sites.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Specific rotations were measured in a 1-dm tube with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Proton magnetic resonance (pmr) spectra were obtained on a Varian A-60 spectrophotometer and a Hitachi R-20A spectrophotometer in DMSO-d_6 using DSS as an internal reference. Ultraviolet spectra were recorded on a Cary Model 15 spectrometer and infrared spectra on a Perkin-Elmer 257 spectrophotometer (KBr pellets). Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich. Evaporations were carried out under reduced pressure with bath temperature below 30°. Detection of components on silica gel

F-254 (EM Reagents) was by ultraviolet light and with 10% sulfuric acid in methanol spray followed by heating. Chromatography solvent mixtures were by volume and the silica gel for column chromatography was purchased from E. Merck (7734).

Trimethylsilyl derivatives of various s-triazolo[1,5-a]pyrimidines were prepared by heating the heterocyclic derivatives under reflux in an excess of freshly distilled hexamethyldisilazane with a catalytic amount of ammonium sulfate under anhydrous conditions until complete solution was achieved and evolution of ammonia ceased (20–25 hr). The excess hexamethyldisilazane was removed by distillation under reduced pressure and the residue (oil or crystalline solid) was used directly without further purification. Glycosylation reaction mixtures were analyzed by tlc; all spots possessing ultraviolet absorption and a carbohydrate moiety (detected by spraying with 10% H_2SO_4 in MeOH and heating) were isolated and characterized.

5-Chloro-3(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-s-triazolo[1,5-a]pyrimidin-7-one (3). To tetra-O-acetyl-β-D-ribofuranose (10.5 g, 0.033 mol) in dry dichloromethane (50 ml) at −20° was added a solution of dry dichloromethane (originally 50 ml) which had been saturated at −20° with dry hydrogen bromide gas. The mixture was protected from moisture with a drying tube and allowed to warm to 0°. The solvent was evaporated and the resulting syrup was coevaporated twice with dry toluene (50 ml). The residual syrup was dissolved in "Nanograde" acetonitrile (100 ml) and was added to the trimethylsilyl derivative [**1**, prepared from 5.2 g (0.030 mol) of 5-chloro-s-triazolo[1,5-a]pyrimidin-7-one[6] in dry acetonitrile (50 ml). The reaction vessel was sealed and the mixture was stirred at room temperature. After 48 hr the reaction mixture was filtered to remove some solid material (heterocyclic starting material, 0.6 g) and the dark filtrate was evaporated to a syrup. Sodium bicarbonate (5.0 g), water (20 ml), and ethanol (50 ml) were added. The mixture was evaporated to dryness. Coevaporation with absolute ethanol several times afforded a dry residue which was extracted with chloroform (3 × 100 ml). The combined extracts were washed with cold saturated aqueous sodium bicarbonate solution (2 × 100 ml) followed by water (3 × 100 ml). The chloroform phase was dried over anhydrous sodium sulfate and then evaporated to dryness to a foam which was triturated with absolute ethanol (75 ml) at 0°. The solid that separated was collected, washed with ethanol, and crystallized from aqueous ethanol with charcoal treatment to yield 7.5 g of product (58%), mp 202°. A small sample was recrystallized from aqueous ethanol to obtain analytically pure sample: mp 203°; $[\alpha]^{25}D$ −10.3° (c 1.0, DMSO); uv λ_{max} (pH 1) 284 nm (ε 11,200), λ_{max} (pH 7) 284 nm (ε 12,900), and λ_{max} (pH 11) 284 nm (ε 11,600).

Anal. Calcd for $C_{16}H_{17}N_4O_8Cl$: C, 44.81; H, 3.97; N, 13.07. Found: C, 44.80; H, 4.03; N, 12.90.

5-Methyl-3-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-s-triazolo[1,5-a]pyrimidin-7-one (4). A solution of 2,3,5-tri-O-acetyl-D-ribofuranosyl bromide from 5.5 g (0.017 mol) of tetra-O-acetyl-β-D-ribofuranose in dry acetonitrile (80 ml) was added to the trimethylsilyl derivative [**2**, prepared from 2.30 g (0.0153 mol) of 5-methyl-7-hydroxy-s-triazolo[1,5-a]pyrimidine[15] and the resulting solution was stirred at room temperature for 45 hr in a sealed reaction vessel. After 5 hr some solid had begun to form, and, upon termination of the reaction, the mixture was nearly solid. The solid was collected and washed with acetonitrile. The combined filtrate and washings were evaporated to dryness. The resulting foam was triturated with cold ethanol (25 ml) and the solid that separated was collected. The combined solids were crystallized from aqueous ethanol to provide pure material to yield 4.0 g (64%): mp 224°; $[\alpha]^{25}D$ −25.4° (c 1.0, DMSO); uv λ_{max} (pH 1) 240 nm (sh, ε 5700), 280 (14,300), λ_{max} (pH 7) 240 nm (ε 5700), 280 (13,900), and λ_{max} (pH 11) 240 nm (sh, ε 5700), 280 (14,100).

Anal. Calcd for $C_{17}H_{20}N_4O_8$: C, 50.00; H, 4.94; N, 13.72. Found: C, 50.09; H, 4.92; N, 13.80.

5-Chloro-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (5). 5-Chloro-3-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-s-triazolo[1,5-a]pyrimidin-7-one (**3**, 5.0 g, 0.0116 mol) was dissolved in methanolic ammonia (100 ml, saturated at 0°). The container was sealed and left at room temperature overnight. The solution was then filtered and the filtrate was evaporated to dryness. The residue was triturated with anhydrous ether (4 × 75 ml) and the ether-insoluble gum was dissolved in a minimum volume of ethanol. It was applied to a silica gel column (3.5 × 50 cm) prepacked in ethyl acetate–water–isopropyl alcohol (4:2:1, upper phase). The column was eluted with the same solvent system and 15-ml fractions were collected. The fractionation was monitored by tlc on silica gel using the eluting solvent as the developer. The fractions 60–100 were pooled and the solvent was evaporated; the residual syrup was triturated with ethanol (20 ml) whereupon the compound crystallized out as white needles to yield 3.0 g (85%), mp 168–169°. Recrystallization from aqueous ethanol gave analytically pure crystals: mp 169–170°; $[\alpha]^{25}D$ −14.1° (c 1.0, DMSO); uv λ_{max} (pH 1) 283 nm (ε 13,600), λ_{max} (pH 7) 283 nm (ε 10,800), and λ_{max} (pH 11) 242 nm (sh, ε 5500), 283 (13,600).

Anal. Calcd for $C_{10}H_{11}N_4O_5Cl$: C, 39.68; H, 3.64; N, 18.51. Found: C, 39.67; H, 3.83; N, 18.53.

5-Methyl-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (6). 5-Methyl-3-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-s-triazolo[1,5-a]pyrimidin-7-one (**4**, 3.0 g, 0.0073 mol) was dissolved in methanolic ammonia (60 ml, saturated at 0°). The container was sealed and left at room temperature overnight. The solution was filtered and the filtrate was evaporated to dryness. The residue was collected, washed thoroughly with cold ethanol, and recrystallized from ethanol containing a few drops of water to yield 1.9 g (92%): mp 240° dec; $[\alpha]^{25}D$ −37.2° (c 1.0, DMSO); uv λ_{max} (pH 1) 242 nm (sh, ε 6200), 280 (13,800); λ_{max} (pH 7) 242 nm (sh, ε 6000), 280 (13,800); and λ_{max} (pH 11) 242 nm (sh, ε 6200), 280 (13,800).

Anal. Calcd for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 46.88; H, 4.85; N, 19.88.

3-[Pyrazolin-5(1*H*,2*H*)-on-3-ylamino]-4-β-D-ribofuranosyl-s-triazole (7). 5-Chloro-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (**5**, 1.0 g, 0.0033 mol) was suspended in anhydrous methanol (30 ml), and hydrazine (10 ml, 95%) was added with stirring at room temperature. Immediately a clear solution was obtained which began to turn brown. The mixture was refrigerated overnight and the solvent was evaporated. The residual syrup was coevaporated several times with methanol and finally triturated with ethanol (25 ml). The solid that separated was collected, washed with cold ethanol (2 × 5 ml), and crystallized from aqueous ethanol to yield 0.65 g (66%) of **7**: mp 225° dec; $[\alpha]^{25}D$ −45. 4° (c 1.0, DMSO); uv λ_{max} (pH 1) 240 nm (ε 8700); λ_{max} (pH 7) 240 nm (ε 7500); and λ_{max} (pH 11) 233 nm (ε 10,200).

Anal. Calcd for $C_{10}H_{14}N_6O_5$: C, 40.27; H, 4.73; N, 28.18. Found: C, 40.43; H, 4.84; N, 28.45.

3-β-D-Ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (8a). 5-Chloro-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (**5**, 0.5 g, 0.00165 mol) was dissolved in 50% aqueous ethanol (25 ml) containing a few drops of concentrated ammonium hydroxide. To this solution was added 150 mg of palladium on carbon (10%) and the mixture was hydrogenated at 40 psi at room temperature for 3 hr, after which the catalyst was removed by filtration on a Celite pad and washed with hot ethanol (2 × 10 ml). The combined filtrates and washings were evaporated to dryness. Coevaporation with absolute ethanol several times afforded white solid which was recrystallized from aqueous ethanol as colorless needles to yield 0.25 g (57%): mp 245–246° dec; mmp with authentic sample[3] 245–247° dec; $[\alpha]^{26}D$ −39.5° (c 1.0, H_2O) [lit.[3] mp 243–248° dec; $[\alpha]^{30}D$ −39.3° (c 1.0, H_2O)]; uv λ_{max} (pH 1, 7, 11) 242 nm (ε 5900) and 285 (12,600).

Anal. Calcd for $C_{10}H_{12}N_4O_5$: C, 44.78; H, 4.51; N, 20.89. Found: C, 44.70; H, 4.52; N, 20.90.

5-Amino-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (8b). 5-Chloro-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (**5**, 0.50 g, 0.00165 mol) was dissolved in methanolic ammonia (25 ml, saturated at room temperature) and the solution was allowed to stand at room temperature in a stoppered pressure bottle for several days. The solution was evaporated to dryness and the residue was coevaporated several times with methanol to a foam. The dry foam was dissolved in anhydrous methanol (10 ml), filtered, and cooled and an excess of anhydrous ether was added. The copious precipitate that separated was collected, washed with ether, and dried to yield 250 mg, no definite melting point: $[\alpha]^{25}D$ −14.8° (c 1.0, H_2O); uv λ_{max} (pH 1) 238 nm (sh, ε 6300), 280 (9030); λ_{max} (pH 7) 245 nm (sh, ε 5700), 281 (9780); and λ_{max} (pH 11) 245 nm (sh, ε 4700), 281 (9780).

Anal. Calcd for $C_{10}H_{13}N_5O_5 \cdot H_2O$: C, 39.87; H, 5.02; N, 23.25. Found: C, 39.96; H, 4.90; N, 23.40.

5-Methylamino-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (8c). 5-Chloro-3-β-D-ribofuranosyl-s-triazolo[1,5-a]pyrimidin-7-one (**5**, 1.0 g, 0.0033 mol) was dissolved in methanolic monomethylamine (50 ml, saturated with anhydrous monomethylamine at 0°) and the solution was allowed to stand at room temperature in a stoppered pressure bottle. After 24 hr, the solution was filtered and the filtrate was evaporated to dryness. The syrup was coevaporated several times with absolute ethanol to remove last traces of monomethylamine. The residual foam was triturat-

ed with cold methanol and the solid that separated was collected and washed with methanol (2 × 5 ml). It was crystallized from aqueous methanol as needles to yield 0.30 g (31%): mp 192° dec; $[\alpha]^{25}D$ −5.7° (*c* 1.0, DMSO); uv λ_{max} (pH 1) 225 nm (ε 29,700), 268 (12,800); λ_{max} (pH 7) 226 nm (ε 29,700), 268 (12,800); and λ_{max} (pH 11) 227 nm (ε 29,700), 267 (13,100).

Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56. Found: C, 44.33; H, 5.00; N, 23.46.

5-Dimethylamino-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (8d). 5-Chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**5**, 1.0 g, 0.0033 mol) was dissolved in methanolic dimethylamine (50 ml, saturated with anhydrous dimethylamine at 0°) and the solution was allowed to stand at room temperature in a stoppered pressure bottle. After 65 hr the crystalline needles that separated were collected and washed with methanol. The combined filtrate and washings were evaporated to dryness. The syrup was coevaporated several times with absolute ethanol to remove last traces of dimethylamine. The crystalline residue was collected and washed with ethanol. The combined solids were recrystallized from aqueous methanol to yield 0.90 g (88%): mp 220–221° dec; $[\alpha]^{25}D$ −2.4° (*c* 1.0 g, DMSO); uv λ_{max} (pH 1) 228 nm (ε 31,100), 274 (14,000); λ_{max} (pH 7) 230 nm (ε 31,100), 273 (14,300); and λ_{max} (pH 11) 232 nm (ε 31,100), 273 (14,300).

Anal. Calcd for $C_{12}H_{17}N_5O_5$: C, 46.30; H, 5.50; N, 22.50. Found: C, 46.22; H, 5.31; N, 22.27.

5-Mercapto-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (8e). Dry ammonium carbonate (1.2 g, 0.0105 mol) in absolute methanol (10 ml) was saturated with anhydrous hydrogen sulfide gas at −5°. 5-Chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**5**, 0.5 g, 0.00165 mol) was added and the mixture was stirred at room temperature for 2 hr. The exothermic reaction was accompanied by gas evolution. Water (10 ml) containing concentrated ammonium hydroxide (1.0 ml) was added. The reaction mixture was heated at 60° for 30 min, cooled, and filtered and the filtrate was carefully neutralized with glacial acetic acid. The mixture was again filtered and the filtrate was evaporated to dryness. The residue was collected, washed with ethanol (3 × 5 ml), and crystallized from water–ethanol with charcoal treatment to yield 0.15 g (31%): mp 218° dec; $[\alpha]^{25}D$ +8.3° (*c* 1.0, DMSO); uv λ_{max} (pH 1) 236 nm (ε 18,900), 287 (12,000); λ_{max} (pH 7) 236 nm (ε 18,900), 287 (12,000); and λ_{max} (pH 11) 237 nm (ε 15,300), 276 (sh, 11,600), 298 (12,300).

Anal. Calcd for $C_{10}H_{12}N_4O_5S$: C, 40.00; H, 4.03; N, 18.66. Found: C, 39.86; H, 3.77; N, 18.84.

5-Hydroxy-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (8f). Method 1. A solution of 5-chloro-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**3**, 1.1 g, 0.00256 mol) and mercaptoethanol (0.65 ml, 0.009 mol) in methanol (20 ml) was treated with 1 *N* sodium methoxide (8.8 ml) and water (0.08 ml) and heated at reflux temperature for 4 hr. The reaction mixture was cooled and filtered and the filtrate was evaporated to dryness. The residue was dissolved in methanol (10 ml) containing glacial acetic acid (0.8 ml) and concentrated to about 5 ml. The solution was then applied to a silica gel column [2.5 × 45 cm, prepacked in ethyl acetate–water–isopropyl alcohol (4:2:1, upper phase)]. The column was eluted with the same solvent system and 10-ml fractions were collected. The fractionation was monitored by tlc, the appropriate fractions were pooled, and the solvent was evaporated. The residual syrup was dissolved in ethanol (4–5 ml) and excess anhydrous ether was added. The copious white precipitate that separated was collected, washed with ether, and dried to obtain amorphous powder, yield 0.20 g (28%): $[\alpha]^{25}D$ +12.5° (*c* 1.0, H_2O); uv λ_{max} (pH 1) 230 nm (sh, ε 7100), 315 (3300); λ_{max} (pH 7) 230 nm (sh, ε 6800), 315 (3300); λ_{max} (pH 11) 232 nm (sh, ε 5000), 287 (5900).

Anal. Calcd for $C_{10}H_{12}N_4O_6 \cdot \frac{1}{2}H_2O$: C, 40.96; H, 4.44. Found: C, 41.00; H, 4.50.

Method 2. Deamination of Isoguanosine Analog (18). To an ice-cold solution of 7-amino-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-5-one (**18**, 0.9 g, 0.00317 mol) in water (10 ml) and glacial acetic acid (1.5 ml) was added sodium nitrite (1.5 g, 0.0217 mol). The flask was loosely stoppered and stirred overnight at 0–5°. The solution was evaporated to dryness, and the residue was dissolved in water (20 ml) and neutralized with sodium bicarbonate. The neutral solution was taken to dryness, dissolved in ethyl acetate containing a few drops of methanol, and applied to a silica gel column (2.5 × 40 cm) prepacked in ethyl acetate–water–isopropyl alcohol (4:2:1, upper phase). The column was eluted with the above solvent system and 15-ml fractions were collected. The fractionation was monitored by tlc on silica gel and the fractions containing the major product were pooled. The solvent was evaporated and the residue was dissolved in ethanol (2–3 ml). Excess anhydrous ether (50 ml) was added. The white precipitate was collected and dried over methanol under vacuum to furnish a white, hygroscopic solid. Uv, ir, and chromatographic behavior were identical with those of the compound prepared by method 1.

6-Amino-2-[*N*-(β-D-ribofuranosyl)cyanamido]pyrimidin-4-one (9). 5-Chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**5**, 1.0 g, 0.0033 mol) was dissolved in liquid ammonia (20 ml) and the solution was allowed to stand at room temperature in a sealed steel reaction vessel for 24 hr. After cooling the vessel was opened and the solution was evaporated to dryness. The residue was coevaporated several times with methanol to a foam. The foam was triturated with anhydrous ether (150 ml), and the white solid that separated was collected, washed thoroughly with anhydrous ether, and dissolved in water (50 ml). The aqueous solution was freeze dried to obtain white powder, yield 0.60 g: $[\alpha]^{25}D$ −5.1° (*c* 1.0, DMSO); uv λ_{max} (pH 1) 231 nm (ε 10,900), 265 nm (sh, 6600); λ_{max} (pH 7) 236 nm (ε 7700), 273 (6000); and λ_{max} (pH 11) 236 nm (ε 8000); ir 2230 cm^{-1}; pmr (DMSO-d_6) δ 5.89 (1 H, doublet, $J_{1',2'}$ = 5.5 Hz, H-1'), 5.69 (1 H, singlet, H-6).

Anal. Calcd for $C_{10}H_{13}N_5O_5$: C, 42.40; H, 4.63; N, 24.73. Found: C, 42.39; H, 4.53; N, 24.69.

5-Chloro-3-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one (10). 2,2-Dimethoxypropane (1.0 ml) and 70% perchloric acid (1.0 ml) were added to dry acetone (250 ml);[16] the mixture was protected from moisture and stirred at room temperature for 5 min before 5-chloro-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**5**, 0.80 g, 0.00265 mol) was added in one portion. The mixture was stirred for 45 min and pyridine (1.0 ml) was added. The volume was reduced to 25 ml, 10% aqueous sodium bicarbonate (30 ml) was added, and the remaining acetone was removed. Cold water (20 ml) was added to the aqueous solution, which was then left at 5° overnight. The white, crystalline material that separated was collected, washed with cold water (2 × 5 ml), and recrystallized from ethanol–water as needles to yield 0.60 g (67%): mp 190°; pmr (DMSO-d_6) δ 1.38, 1.57 (6 H, two singlets, 2',3'-isopropylidene).

Anal. Calcd for $C_{13}H_{15}N_4O_5Cl$: C, 45.55; H, 4.38; N, 16.35. Found: C, 45.48; H, 4.40; N, 16.40.

5-Chloro-3-(2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one (11). Compound **10** (0.50 g, 0.00146 mol) was dissolved in dry pyridine (5 ml), and *p*-toluenesulfonyl chloride (0.30 g, 0.00157 mol) was added. The solution was left in the dark at 5° for 36 hr with occasional shaking. The solution was poured into ice–water (200 ml) and the mixture was extracted with chloroform (3 × 50 ml). The combined organic layers were washed with cold 1 *M* sulfuric acid (2 × 50 ml) followed by cold water until the washings were neutral. The chloroform solution was dried over anhydrous sodium sulfate and evaporated to 10 ml, and methanol (25 ml) was added before the remaining chloroform was removed. Dry ether was added, and the white solid that separated was collected and crystallized from methanol to yield 0.48 g (67%): mp 176°; pmr (DMSO-d_6) δ 7.47 (4 H, quartet, benzenoid H of tosyl), 1.34, 1.54 (6 H, two singlets, 2',3'-isopropylidene).

Anal. Calcd for $C_{20}H_{21}N_4O_7SCl$: C, 48.33; H, 4.23; N, 11.28. Found: C, 48.21; H, 4.37; N, 11.15.

3-(2,3-*O*-Isopropylidene-5-*O*-*p*-toluenesulfonyl-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one (12). 5-Chloro-3-(2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**11**, 0.5 g, 0.001 mol) was dissolved in 50% aqueous ethanol (25 ml) containing a few drops of concentrated ammonium hydroxide. To this solution was added 120 mg of palladium on carbon (10%) and the mixture was hydrogenated at 40 psi at room temperature for 3 hr, after which the catalyst was removed by filtration on a Celite pad. The catalyst was washed with hot ethanol (2 × 10 ml). The combined filtrate and washings were evaporated. The residual white solid was crystallized from aqueous ethanol as needles to yield 0.30 g (65%): mp 190° dec; uv λ_{max} (pH 1) 270 nm (ε 10,500); λ_{max} (pH 7) 270 nm (ε 11,000); λ_{max} (pH 11) 275 nm (ε 11,900); pmr (DMSO-d_6) δ 8.96 (1 H, singlet, H-2), 7.92 (1 H, doublet, H-5), 7.46 (4 H, quartet, benzenoid H of tosyl), 6.17 (1 H, doublet, H-6), 1.34, 1.54 (6 H, two singlets, 2',3'-isopropylidene).

Anal. Calcd for $C_{20}H_{22}N_4O_7S$: C, 51.95; H, 4.79; N, 12.12. Found: C, 51.96; H, 4.57; N, 12.10.

3-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one 5',4-Cyclonucleoside *p*-Toluenesulfonate (13b). 3-(2,3-*O*-Isopropylidene-5-*O*-*p*-toluenesulfonyl-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidin-7-one (**12**, 0.10 g) was added to dry dimethyl sulfoxide (5 ml) and the mixture was heated, with

stirring, at 100–110° for 4 hr. After chilling overnight the solution was filtered and the filtrate was evaporated to dryness. The residue was taken in ethanol, decolorized by charcoal treatment, and triturated with anhydrous ether (25 ml). The white solid that separated was collected, washed with ether (2 × 10 ml), and crystallized from aqueous ethanol to yield 50 mg: mp >240° dec; uv λ_{max} (pH 1) 267 nm (ϵ 8600); λ_{max} (pH 7) 267 nm (ϵ 8600); and λ_{max} (pH 11) 273 nm (ϵ 10,600); ir 1200 cm^{-1}.

4-Amino-6-chloro-2-[*N*-(β-D-ribofuranosyl)cyanamido]pyrimidine (17). To the trimethylsilyl derivative (14) from 3.4 g (0.020 mol) of 5-chloro-7-amino-*s*-triazolo[1,5-*a*]pyrimidine[6] was added 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide [from 7.0 g (0.022 mol) of tetra-*O*-acetyl-β-D-ribofuranose] in anhydrous acetonitrile (100 ml). The reaction vessel was sealed and stirred at room temperature for 27 hr. The reaction mixture was filtered and the filtrate was evaporated to a syrup. Sodium bicarbonate (3.0 g), water (10 ml), and ethanol (25 ml) were added. The mixture ws evaporated to dryness. Coevaporation with absolute ethanol several times afforded dry residue which was extracted with chloroform (3 × 100 ml). The combined extracts were washed with cold saturated aqueous sodium bicarbonate solution (2 × 100 ml) followed by water (3 × 100 ml) and dried over anhydrous sodium sulfate. The chloroform was evaporated to dryness to a foam which was dissolved in a minimum volume of chloroform and applied to a silica gel column (4.5 × 35 cm) prepacked in chloroform. The column was eluted with chloroform–acetone (8:2) and each 25-ml fraction was collected. The fractionation was monitored by tlc and appropriate fractions were pooled and solvent evaporated to yield cream-colored foam, 1.5 g: uv λ_{max} (pH 1) 235, 275 nm; λ_{max} (pH 7) 235, 275 nm; and λ_{max} (pH 11) 235, 275 nm; ir 2230 cm^{-1}.

The above blocked nucleoside (1.4 g) was dissolved in methanolic ammonia (50 ml, methanol presaturated with ammonia at 0°) and the solution was allowed to stand at room temperature overnight. The solution was filtered and the filtrate was evaporated to dryness. The residue was triturated with anhydrous ether (5 (5 × 25 ml) and filtered. The semisolid was dissolved in a minimum volume of water and chromatographed on a silica gel column (2.5 × 35 cm) eluting with isopropyl alcohol–water–ethyl acetate (1:2:4, upper phase). The appropriate fractions were pooled and solvent was evaporated. The residual solid was crystallized from aqueous ethanol to yield 0.5 g: mp 128–130°; uv λ_{max} (pH 1) 235 nm (ϵ 9050), 275 (6050); λ_{max} (pH 7) 235 nm (ϵ 9050), 275 (6050); and λ_{max} (pH 11) 235 nm (ϵ 9050), 275 (6050); ir 2230 cm^{-1}; pmr (DMSO-d_6) δ 5.95 (1 H, doublet, $J_{1',2'}$ = 6.0 Hz, H-1′), 6.31 (1 H, singlet, H-6).

Anal. Calcd for $C_{10}H_{12}N_5O_4Cl$: C, 39.81; H, 4.00; N, 23.21. Found: C, 39.57; H, 4.15; N, 23.11.

7-Amino-3-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-5-one (18, Isoguanosine Analog). To the bis(trimethylsilyl) derivative (16), prepared from 4.53 g (0.033 mol) of 7-amino-*s*-triazolo-[1,5-*a*]pyrimidin-7-one,[6] was added 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide [prepared from 10.5 g (0.033 mol) of tetra-*O*-acetyl-β-D-ribofuranose] in dry acetonitrile (100 ml). The reaction vessel was sealed and stirred at room temperature for 75 hr. The clear brown solution was evaporated to a syrup. Sodium bicarbonate (5.0 g), water (20 ml), and ethanol (50 ml) were added. The mixture was evaporated to dryness. Coevaporation with absolute ethanol several times afforded a dry residue which was extracted with chloroform (3 × 100 ml) and dried over anhydrous sodium sulfate. The chloroform solution was decolorized with charcoal and evaporated to yield a foam which was highly soluble in water. The foam was dissolved in a minimum volume of water and applied to a silica gel column (5 × 75 cm) prepacked in ethyl acetate–water–isopropyl alcohol (4:2:1, upper phase). The column was eluted with the same solvent system and 30-ml fractions were collected. The fractionation was monitored by tlc on silica gel with the eluting solvent as the developer. Fractions 120–160 were pooled and the solvent was evaporated to yield a cream-colored foam, 9.5 g (78%): $[\alpha]^{25}D$ +41.6° (*c* 0.5, H_2O); uv λ_{max} (pH 1) 267 nm (ϵ 15,600); λ_{max} (pH 7) 265 nm (ϵ 10,700); and λ_{max} (pH 11) 265 nm (ϵ 10,700).

The above acetylated nucleoside (8.0 g) was dissolved in methanolic ammonia (200 ml, saturated at 0°) and was allowed to stand at room temperature overnight. The solution was filtered, the solvent was evaporated, and the residue was triturated with absolute ethanol. The solid material was filtered, dissolved in a minimum volume of water, and chromatographed on a silica gel column (3.5 × 50 cm) eluting with isopropyl alcohol–ammonium hydroxide–water (7:1:2). The fractions containing the major uv-absorbing component were pooled and the solvent was evaporated. The resulting foam was dissolved in water and freeze dried (3.50 g, 64%) to yield a hygroscopic solid: $[\alpha]^{25}D$ −3.2° (*c* 1.0, H_2O); uv λ_{max} (pH 1) 266 nm (ϵ 13,300); λ_{max} (pH 7) 264 nm (ϵ 9100); and λ_{max} (pH 11) 264 nm (ϵ 9100).

Anal. Calcd for $C_{10}H_{13}N_5O_5$: C, 42.40; H, 4.63; N, 24.73. Found: C, 42.22; H, 4.41; N, 24.92.

7-Imino-4-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidine (19). To the syrupy trimethylsilyl derivative (15) from 5.4 g (0.040 mol) of 7-amino-*s*-triazolo[1,5-*a*]pyrimidine[17] was added 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide [prepared from 14.0 g (0.044 mol) of tetraacetyl ribofuranose] and a catalytic amount of $AlCl_3$ (about 50 mg). The mixture was thoroughly mixed and heated at 100° (oil-bath temperature) for 10 min with oil pump vacuum applied and good stirring. Within 2–3 min the mixture began to solidify, accompanied by frothing. The reaction mixture was cooled, $AlCl_3$ was decomposed by the addition of cold water, and the reaction mixture was extracted with chloroform (250 ml). The chloroform solution was washed with aqueous sodium bicarbonate solution (2 × 100 ml) followed by water (3 × 75 ml) and then dried over anhydrous sodium sulfate. After removal of the drying agent, the chloroform was evaporated and the residual foam (12.0 g) was dissolved in enough benzene–ethyl acetate (1:1) to facilitate pouring and applied to a silica gel column (4.5 × 50 cm, 70–230 mesh) prepacked in benzene–ethyl acetate (1:1). The column was eluted with benzene–ethyl acetate–ethanol (5:5:1) and 20-ml fractions were collected. The fractionation was monitored by tlc on silica gel with the eluting solvent as the developer. The fractions containing the major uv-absorbing component were pooled and the solvent was evaporated to afford 4.0 g of cream-colored amorphous 7-amino-4-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-*s*-triazolo[1,5-*a*]pyrimidine.

The blocked nucleoside (4.0 g) was dissolved in methanolic ammonia (100 ml, saturated at 0°) and was allowed to stand at room temperature overnight. The solution was filtered and the solvent was evaporated. The solid that separated was collected, washed with cold methanol (2 × 10 ml), and recrystallized from ethanol as needles to yield 2.0 g (19%): mp 177° dec; $[\alpha]^{25}D$ −55.4° (*c* 1.0, H_2O); uv λ_{max} (pH 1) 291 nm (ϵ 17,800); λ_{max} (pH 7) 289 nm (ϵ 15,100); and λ_{max} (pH 11) 274 nm (ϵ 15,100).

Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found: C, 44.78; H, 5.00; N, 26.33.

4-β-D-Ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidin-7-one (20). To an ice-cold solution of 7-imino-4-β-D-ribofuranosyl-*s*-triazolo[1,5-*a*]pyrimidine (19, 0.10 g) in water (1 ml) and glacial acetic acid (0.15 ml) was added sodium nitrite (0.15 g). The flask was loosely stoppered and stirred overnight at 0–5°. The clear solution was evaporated *in vacuo* to dryness. The residue was dissolved in water (5 ml) and carefully neutralized with solid sodium bicarbonate. The neutral solution was taken to dryness, dissolved in a minimum volume of ethyl acetate containing a few drops of methanol, and applied to a silica gel column (1.5 × 30 cm) prepacked in ethyl acetate–water–isopropyl alcohol (4:2:1, upper phase). The column was eluted with the same solvent system and 10-ml fractions were collected. The fractionation was monitored by tlc on silica gel and the appropriate fractions were pooled. The solvent was evaporated and the residue was triturated with ethanol (5 ml). The solid was collected and crystallized from water–ethanol to yield 30 mg, mp 220–222°, mmp with authentic sample 218–221°; uv, ir, and chromatographic behavior were identical with those reported for an authentic sample.[3]

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Registry No.—**1**, 50805-14-6; **2**, 50805-15-7; **3**, 50805-19-1; **4**, 50805-20-4; **5**, 50805-21-5; **6**, 50805-22-6; **7**, 50805-23-7; **8a**, 32817-07-5; **8b**, 50805-24-8; **8c**, 50805-25-9; **8d**, 50805-26-0; **8e**, 50805-27-1; **8f**, 50805-28-2; **9**, 50805-29-3; **10**, 50805-30-6; **11**, 50805-31-7; **12**, 50805-32-8; **13b**, 50805-34-0; **14**, 50805-16-8; **15**, 50805-17-9; **16**, 50805-18-0; **17**, 50805-35-1; **18**, 50805-36-2; **19**, 50805-37-3; **20**, 33037-54-6; tetra-*O*-acetyl-β-D-ribofuranose, 13035-61-5; 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide, 39110-68-4.

References and Notes

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Micellar Effects upon the Reaction of the Tri-*p*-anisylmethyl Cation with Aliphatic Amines[1]

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Anionic micelles of sodium lauryl sulfate, NaLS, catalyze the reaction of the tri-*p*-anisylmethyl cation, R^+, with butyl- and hexylamines and with 2-methylpyrrolidine. The catalysis increases with increasing length of the alkyl group of the amine, but is decreased by its branching. Cationic micelles of cetyltrimethylammonium bromide, CTABr, have little effect on the reaction rate, but nonionic micelles of Igepal are feebly catalytic.

Micellar effects upon the reaction of nucleophilic anions with stable triphenylmethyl dye cations have been extensively studied.[3,4] For example, cationic micelles catalyzed, and anionic micelles inhibited, attack of hydroxide ion. Micellar effects upon the attack of water on the more reactive tri-*p*-anisylmethyl cation (R^+) have also been examined. Anionic micelles increase, but cationic and nonionic micelles decrease, k_b, but these micelles have no effect on k_f.[9] The reactions with hydroxide and azide ions were strongly inhibited by anionic micelles.

$$R^+ + H_2O \underset{k_b}{\overset{k_f}{\rightleftharpoons}} ROH + H^+$$

The present work covers micellar effects on the reaction of R^+ with aliphatic amines,[10] using cetyltrimethylammonium bromide (CTABr), sodium lauryl sulfate (NaLS), and Igepal (nonylphenyl polyethylene oxide, mol wt 1403).

Experimental Section

Materials and Rate Measurements. The purification of the surfactants has been described.[9] The tri-*p*-anisylmethyl cation was introduced as its chloride in dilute HCl. All solutions were made up using redistilled, deionized water, and were degassed.

The reactions were followed at 25.0° using a Durrum-Gibson stopped-flow spectrophotometer.[9] A solution of R^+ in dilute HCl, usually 0.1 *M*, was in one drive syringe, and the amine in NaOH was in the other (NaOH was in slight excess over HCl). The surfactant was in both syringes.

The first-order rate constants, k_ψ, in reciprocal seconds, were calculated using a Hewlett-Packard desk computer.

Results and Discussion

Effect of Micellar Charge. The effects of cationic and nonionic micelles upon the reaction of amines with R^+ are summarized in Table I, in which the values of k_ψ in the absence of surfactant are compared with those in the presence of CTABr and Igepal (Ig). Cationic micelles of CTABr have almost no effect on the rate of reaction, probably because R^+ is not taken up by the cationic micelles,[9] but these micelles markedly affect the equilibrium between R^+ and ROH in dilute acid.[11,12]

Nonionic micelles of Igepal catalyze the reaction of R^+ with *n*-hexylamine, which is the most hydrophobic amine used (Table I), suggesting that the rate enhancement is at least in part a proximity effect due to incorporation of the reagents in the micelle. This incorporation is almost certainly incomplete, and there is no rate maximum or plateau as is often observed in micellar catalysis.[4-8]

Anionic micelles of NaLS catalyze the reaction (Figures 1-3). At a constant amine concentration, the variation of rate constant with surfactant concentration is typical of micellar catalysis. There is little or no effect at very low concentrations of surfactant, but once micelles begin to form, the rate increases as reagents are incorporated into the micelle. The simple kinetic treatment predicts that the rate will not increase until the critical micelle concentration (cmc) of the surfactant is reached,[5-8,13] but the rate increase at NaLS concentrations well below the cmc[14] (Figures 1 and 2) is very common, especially with hydrophobic solutes, and arises because the reagents promote micellization, or there is some catalysis by submicellar aggregates.[5-8] The former explanation seems the more probable because the lowest surfactant concentrations necessary for catalysis are observed with the most hydrophobic amine.

The rate enhancements in the plateau region are given in Table II. They increase with increasing length of the amine chain, and decrease with chain branching.

One unusual feature of the micellar catalysis is that, with increasing surfactant concentration, the rates increase to plateau values, rather than to the maxima which are exhibited by most micellar-catalyzed bimolecular reactions.[16,17] These rate maxima have been ascribed to a dilution of the reagents in the micellar pseudophase once there are sufficient micelles to remove the reagents from the aqueous to the micellar phase;[16] *cf.* ref 7 for an alternative explanation.

The absence of rate maxima (Figures 1 and 2) may be due to the low surfactant concentrations required for catalysis, but formation of a reactive complex between R^+ and the amine should also give plateaux rather than rate maxima.

The rate of the water reaction of R^+ was unaffected by micelles, irrespective of their charge, and reactions of R^+