Nucleoside Annelating Agents: Structures and Electrophilic Behavior of the Products Formed with *N*-Chlorocarbonyl Isocyanate

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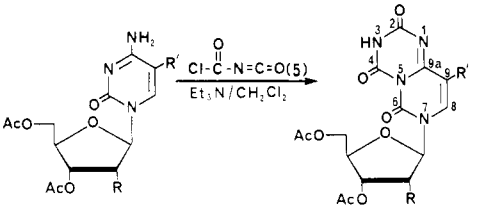
The course of reaction of O-protected cytidine, 2′-deoxycytidine, 5-methyl-2′-deoxycytidine, adenosine, guanosine, and 2-amino-6-chloro-9-β-D-ribofuranosylpurine with *N*-chlorocarbonyl isocyanate (**5**) was determined. In the pyrimidine series, reaction of 2′,3′,5′-tri-*O*-acetylcytidine with **5** afforded 2,3,4,5,6,7-hexahydro-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrimido[1,6-*a*]-1,3,5-triazine-2,4,6-trione (**6a**). The reaction of 3′,5′-di-*O*-acetyl-2′-deoxycytidine and 3′,5′-di-*O*-acetyl-2′-deoxy-5-methylcytidine with **5** gave analogous products **6b** and **6c** containing the N-bicyclic system. The *triazinedione* ring of **6** was found to be susceptible to opening in methanol and methanolic ammonia. Methylation of **6b** with methyl iodide afforded an *N*-methylated bis-nucleoside **13** along with a product **14** that resulted from opening of the triazine ring. In the purine series, reaction of 2′,3′,5′-tri-*O*-acetyladenosine with **5** yielded 7,9-dioxo-3,7,8,9-tetrahydro-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,3,5-triazino[2,1-*i*]purine (**19**). Treatment of the latter with methanolic ammonia opened the *pyrimidine* ring to give 4-amino-5-(2,4-dioxo-1,2,3,4-tetrahydro-1,3,5-triazin-6-yl)-3-β-D-ribofuranosylimidazole (**20**). Compound **20** was diazotized with $NaNO_2$/HCl to form the tricyclic azapurine derivative 7,9-dioxo-3,7,8,9-tetrahydro-3-β-D-ribofuranosyl-1,3,5-triazino[2,1-*i*]-5-azapurine (**21**). Treatment of 2′,3′,5′-tri-*O*-benzoylguanosine with **5** gave 3,5,6,7,8,10-hexahydro-6,8,10-trioxo-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,3,5-triazino[1,2-*a*]purine (**22**) which resembles an extended xanthosine. Deprotection of the benzoyl groups of **22** with methanolic ammonia proceeded with ring opening of the triazine ring to give N^2-(ureidocarbonyl)guanosine (**23**). 2-Amino-6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine reacted with **5** to afford two products: 6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-ureidopurine (**24**) and 6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-(2,4,6-trioxo-1,3,5-triazino)purine (**25**). Deprotection of **25** with methanolic ammonia gave 2-substituted adenosine derivative 2-(2,4,6-trioxo-1,3,5-triazinyl)adenosine (**26**), while dehalogenation of **25** with Pd/C followed by the same deprotection gave the analogous 2-substituted nebularine **27**. The structures of the products were established with the aid of high-field ^1H and ^{13}C NMR, IR, UV, mass spectral, and elemental analysis, and, where necessary, by X-ray crystallography. Reaction of α-aminoheterocycles with *N*-chlorocarbonyl isocyanate for protection, terminating in reaction of an intermediate triazinedione with tetrabutylammonium fluoride for deprotection, constitutes a potentially useful sequence that permits manipulation elsewhere in the molecule, but sensitivity to methanol may be a problem.

There have been many reports of the incorporation of additional unsaturated five-membered heterocyclic rings onto the original purine[1-10] and pyrimidine[1,3,5,11] nucleosides. Many of the modified nucleosides are fluorescent,[12-14] and selected modified products have been found to enter biochemical pathways.[15-18] Of particular significance is the capability of both 1,N^6-ethenoadenine (ε-adenine)[3,7,8,15-17,19-26] and 3,N^4-ethenocytosine (ε-cytosine)[17,18] nucleotides to substitute for the adenine nucleotides in a variety of biological systems.[27,28] Reports of the annelation of unsaturated six-membered rings onto the pyrimidine and purine bases and nucleosides are sparse

Scheme I



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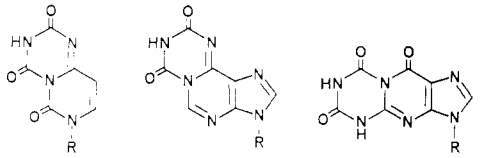
and are limited mainly to modified guanine residues.[4,29]

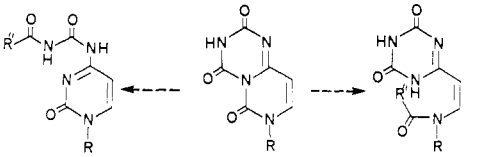
In this laboratory, we have sought compounds that would react with various nucleic acid bases and nucleosides to incorporate additional five-[30] and six-membered rings.[31-33] We have now examined the behavior of bifunctional electrophilic reagent *N*-chlorocarbonyl isocyanate (**5**), which appeared well suited for the construction of a new triazine ring incorporating the exocyclic amino group and a ring nitrogen attached to the same carbon. The synthesis and reactivity of *N*-chlorocarbonyl isocyanate have been reviewed.[34] More recently, it has been shown that this compound reacts with 2-aminopyridine, 2-aminopyrmidine, and 2-aminoquinazoline to give 2,4-dioxo-1,3,5-triazinyl-fused heterocycles.[35] By analogy, the reaction of **5** with suitably protected cytidine, adenosine, and guanosine should afford the new 2,4-dioxo-1,3,5-triazinyl-substituted ribonucleosides **1–3** (R = tri-*O*-protected-β-D-ribofuranosyl).



1 2 3

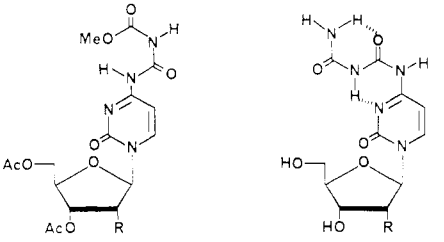
The treatment of 2′,3′,5′-tri-*O*-acetylcytidine, 3′,5′-di-*O*-acetyl-2′-deoxycytidine, and 3′,5′-di-*O*-acetyl-5-methyl-2′-deoxycytidine (**4a–c**, respectively) with *N*-chlorocarbonyl isocyanate (**5**) (Scheme I) in anhydrous methylene chloride in the presence of triethylamine at room temperature afforded in each case a major new nucleoside product. A bathochromic shift in the λ_{max} of the qualitative UV spectra of **6a–c** relative to those of **4a–c** indicated that annelation had taken place. The high-resolution proton magnetic resonance spectrum of **6a** in $(CD_3)_2SO$ revealed, in addition to two doublets at δ 7.8 and 6.1 (J = 8.1 Hz), corresponding, respectively, to the 6- and 5-protons of the original pyrimidine ring, the presence of a D_2O-exchangeable proton at δ 11.52, and the ^{13}C NMR spectrum (see Experimental Section) showed a total of 17 resonances. Eight of the nine resonances in the high field region (<103 ppm) were ascribed to the ribose moiety, while the signal at δ 102 was ascribed to C-5 of the original pyrimidine ring.[36] In the low field region (>140 ppm), the three resonances at δ 172.29, 171.35, and 171.30 were assigned to the acetyl carbonyl carbons, the four between δ 160 and 145 to the remaining carbonyl carbons and to C-4, and the signal at δ 141.8 to the C-6 of the original pyrimidine ring. In addition to these NMR data for **6a**, the low- and high-resolution FAB mass spectral and elemental analytical data were consistent with the structures assigned to **6a–c**.

Compounds **6a** and **6b** were found to undergo facile reaction in methanolic solution at room temperature, complete within 2 h, each compound to afford a product of higher R_f (by TLC analysis). The FAB mass spectrum of each product showed an MH^+ peak consistent with the addition of 1 molar equiv of methanol to **6a** and **6b**. The characteristic differences observed between the ^1H NMR spectra of the methanol addition products and those of **6a** or **6b** were downfield shifts of the C5 and C6 proton resonances of the original pyrimidine ring. Similarly, when **6a** or **6b** was treated with methanolic ammonia at room temperature, the FAB mass spectrum of the product formed indicated the addition of a molar equivalent of ammonia. In the ^1H NMR spectrum $[(CD_3)_2SO]$ of the ammonia product(s), in addition to four exchangeable protons at δ 10.60, 10.48, 7.32, and 7.18, the H-6 proton resonance appeared at δ 8.4 (~0.7 ppm downfield from that of H-8 of **6a** or **6b**), and the H-5 proton resonance appeared at 6.6 (~0.8 ppm downfield from that of H-9 of **6a** or **6b**). On the basis of spectroscopic evidence, the addition of a molecule of methanol or ammonia with subsequent ring opening could give rise to **7** or **8** as possible products.



7 6 R′ = OCH_3, NH_2 8

The addition of water, alcohol, or aqueous ammonia with subsequent ring opening has been reported for 2,4-dioxo-1,2,3,4-tetrahydro-1,3,5-triazine compounds 5-azauracil and 5-azauridine and also 5-azacytidine.[37-40] With these compounds, the addition of alcohol takes place at C-6 to produce an alcohol adduct,[37-39] and the addition of water or aqueous ammonia gives ring-opened products.[37,40] In compounds having the pyrimido[1,2-*a*]-1,3,5-triazine ring system, it is mainly the pyrimidine ring that opens upon treatment with water or amines.[41,42] Since analogy and the analytical and spectroscopic data were insufficient to distinguish between the two possible ring-opened products (**7**, **8**), we sought confirmation of the structures by X-ray crystallography. The X-ray examination of the separate products revealed the structures to be of type **7**, that is, N^4-[[(methoxycarbonyl)amino]carbonyl]-3′,5′-di-*O*-acetyl-2′-deoxycytidine (**9b**) and N^4-(ureidocarbonyl)-2′-deoxycytidine (**10b**). The analogous cytidine products were established accordingly as **9a** and **10a**.



9a, R = OAc
b, R = H

10a, R = OH
b, R = H

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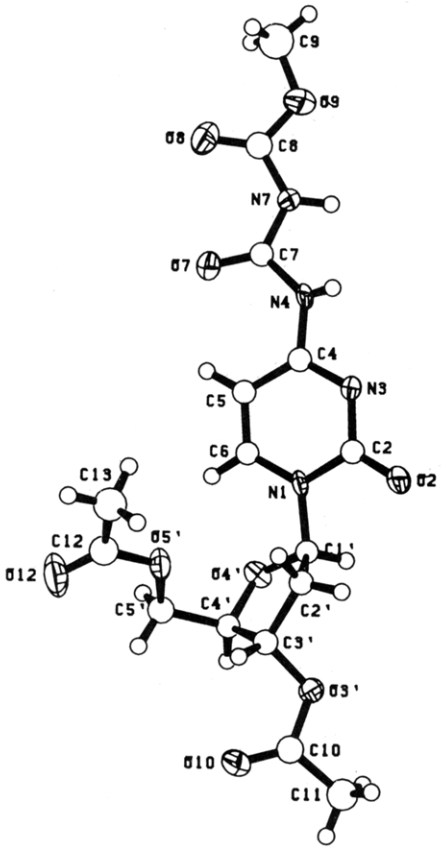

Figure 1. Single ORTEP drawing of N^4-[[(methoxycarbonyl)-amino]carbonyl]-3′,5′-di-*O*-acetyl-2′-deoxycytidine (**9b**).

Table I. Selected Bond Lengths for Crystalline $C_{16}H_{20}N_4O_9$ (9b) and $C_{11}H_{15}N_5O_6$ (10b)

bond[a]	length, Å	
	9b[b]	**10b**[b]
N1–C2	1.38 (1)	1.408 (7)
C2–O2	1.22 (1)	1.238 (6)
C2–N3	1.38 (1)	1.354 (8)
N3–C4	1.31 (1)	1.314 (7)
C4–C5	1.42 (1)	1.421 (8)
C5–C6	1.33 (1)	1.323 (9)
C6–N1	1.36 (1)	1.361 (7)
C4–N4	1.38 (2)	1.377 (8)
N4–C7	1.38 (2)	1.363 (8)
C7–O7	1.19 (1)	1.233 (8)
C7–N7	1.37 (1)	1.361 (7)
N7–C8	1.37 (1)	1.400 (7)
C8–O8	1.19 (1)	1.230 (7)
C8–O9	1.33 (1)	
O9–C9	1.43 (2)	
C8–N8		1.305 (8)

[a] Atoms are labeled in agreement with Figure 1 and Figure 2. [b] The numbers in parentheses are the estimated standard deviations in the last significant digit. Bond lengths for the β-D-ribofuranosyl moiety are not included.

The single-crystal X-ray structure determination of **9b** showed the "proximal" conformation of the compound (Figure 1), with the substituent at N4 turned toward the C5 of the pyrimidine ring. Literature NMR spectroscopic data for an N^4-alkyl compound, e.g., N^4-methylcytosine, indicate a 20:1 preference for the "distal" conformation[43,44] while an X-ray structure determination of an N^4-acyl compound, e.g., N^4-acetylcytidine, shows this type to be

Table II. Bond Angles in Crystalline $C_{16}H_{20}N_4O_9$ (9b)[a] and $C_{11}H_{15}N_5O_6$ (10b)[a]

type[b]	angle, deg	
	9b	**10b**
$N_1C_6C_5$	121.8 (8)	122.4 (5)
$C_6C_5C_4$	116.8 (9)	116.8 (5)
$N_4C_4C_5$	123.2 (9)	117.5 (5)
$N_4C_4N_3$	114.6 (7)	120.1 (5)
$C_4N_3C_2$	120.2 (7)	120.3 (5)
$N_3C_2O_2$	122.0 (8)	123.2 (5)
$N_3C_2N_1$	118.1 (9)	118.8 (5)
$O_2C_2N_1$	119.9 (9)	118.0 (5)
$C_6N_1C_2$	120.5 (9)	119.2 (5)
$C_2N_1C_{1'}$	115.3 (8)	118.1 (4)
$C_{1'}N_1C_6$	124.2 (6)	122.7 (5)
$C_4N_4C_7$	128.9 (8)	130.7 (5)
$N_4C_7O_7$	124.0 (1)	120.1 (5)
$O_7C_7N_7$	126.0 (1)	123.0 (5)
$C_7N_7C_8$,	125.4 (8)	127.5 (5)
$N_7C_8O_8$	126.0 (1)	116.5 (5)
$O_8C_8O_9$	125.0 (1)	
$N_7C_8N_8$		116.5 (5)
$N_8C_8O_8$		124.6 (5)

[a] The numbers in parentheses are the estimated standard deviations in the last significant digit. [b] Atoms arre labeled in agreement with Figure 1 and Figure 2. Angles for the β-D-ribofuranosyl moiety are not included.

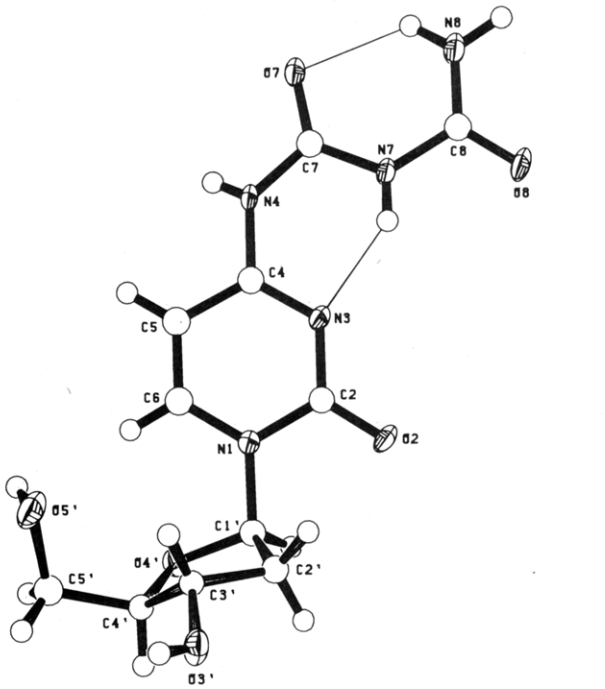

Figure 2. Single ORTEP drawing of N^4-(ureidocarbonyl)-2′-deoxycytidine (**10b**).

in the proximal conformation in the solid state.[45] For **9b**, as in N^4-acetylcytidine, there is an apparent intramolecular hydrogen bond (attraction) between H5 and O7, and the six-membered ring is planar. The ^{1}H NMR chemical shift for the proton at C5 of **9b**, while the corresponding proton had a value of δ 6.09 in **6b**, has moved downfield to δ 6.92, indicating an increasing acidity for this proton. A downfield shift of H-5 was noted previously for cytidine → N^4-acetylcytidine.[45] The bond lengths and bond angles for **9b** are provided in Tables I and II. Two intermolecular hydrogen bonds between H4–O2 and between H7–N3 link a continuous chain of molecules related by the 2_1-screw

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Table III. Hydrogen-Bonding Interactions in Crystalline $C_{16}H_{20}N_4O_9$ (9b)[a] and $C_{11}H_{15}N_5O_6$ (10b)[a]

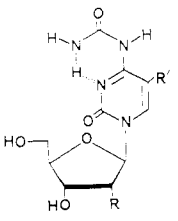
A–H···B	H···B	A···B	<A–H···B
	9b (Intermolecular)		
N_4–H_4···O_2	2.23 (8)	2.888 (9)	161 (10
N_7–H_7···N_3	2.08 (7)	2.996 (10)	171 (6)
	10b (Intramolecular)		
N_7–H_7···N_3	1.96 (5)	2.669 (7)	142 (4)
N_8–H_{8b}···O_7	2.07 (4)	2.685 (6)	129 (4)
C_6–H_6···$O_{5'}$	2.531 (8)	3.315 (8)	140 (6)
	10b (Intermolecular)		
$O_{5'}$–$H_{5'}$···O_2	2.02 (5)	2.769 (6)	167 (5)
$O_{3'}$–$HO_{3'}$···O_7	2.08 (4)	2.756 (5)	161 (5)
N_8–H_{8a}···$O_{3'}$	1.97 (4)	2.894 (7)	172 (4)
N_4–H_4···O_8	2.13 (4)	2.802 (6)	168 (6)

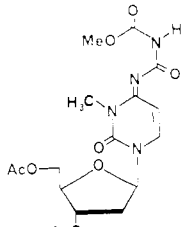
[a] The numbers in parentheses are the estimated standard deviations in the last significant digit.

along the polar axis of the crystal.

An ORTEP view of the structure **10b** provided by X-ray crystallography is shown in Figure 2. The N^4 substituent in this case has a distal conformation. It has been shown that a ureido substituent at position 6 of the purines exists mainly in the distal conformation,[46-49] which signifies away from the imidazole ring. The "distal" conformation found in **10b** allows for the intramolecular hydrogen bonding between H7···N3 and between H8b···O7. In addition to these intramolecular hydrogen bonds, there are four intermolecular hydrogen bonds (Table III). The main differences between the X-ray structures of **9b** and **10b** are the conformation of the N^4 substituent and the hydrogen-bonding pattern.

In contrast to the observed *triazinedione* ring opening of **6a** and **6b** with methanol and methanolic ammonia, compound **6c** was unaffected by methanol at room temperature and reverted to the starting material **4c** upon heating in methanol. When treated with methanolic ammonia at room temperature, **6c** afforded a new product, the ^{1}H NMR spectrum [$(CD_3)_2SO$] of which showed the presence of only three exchangeable protons, instead of the four observed for compounds **10a** and **10b**. On the basis of the ^{1}H NMR spectrum and FAB mass spectral and elemental analytical data, this compound was assigned the structure N^4-carbamoyl-5-methyl-2′-deoxycytidine (**11c**). Similar products **11a** and **11b** were obtained when **9a** and **9b**, formed on treatment of **6a** and **6b** with methanol (see above), were treated further with methanolic ammonia at room temperature. The side-chain ureido group, with three exchangeable N–H protons, is shown in the distal conformation in **11a–c**, consistent with the observed up-



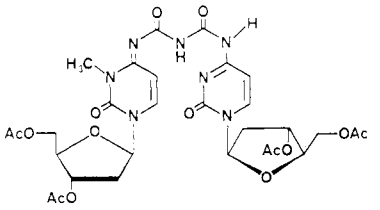


12

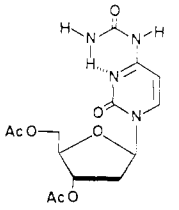
11a, R = OH, R′ = H
b, R = R′ = H
c, R = H, R′ = CH_3

field shift of the C5 proton in going from **9a** and **9b** (δ 6.92) to **11a** and **11b** (δ 6.3). The synthesis of this type of compound by the reaction of cytosine or cytidine with alkyl or aryl isocyanates[50,51] or with *N*-methyl-*N*-nitrosourea[52] has been documented. The methylation of **9b** with CH_3I/K_2CO_3 in acetone gave a monomethylated product with the most likely structure N^4-[[(methoxycarbonyl)-amino]carbonyl]-3-methyl-3′,5′-di-*O*-acetyl-2′-deoxycytidine (**12**), by analogy with the reported methylation of N^4-(methylcarbamoyl)cytosine,[50] which gave 1,3-dimethyl-N^4-(methylcarbamoyl)cytosine and 1-methyl-N^4-(methylcarbamoyl)cytosine.

When **6b** was "methylated" with CH_3I/K_2CO_3 in acetone at room temperature, two major products were isolated by column chromatography. The ^{1}H NMR spectrum of the product of higher R_f value showed the presence of two exchangeable protons, four pyrimidine ring protons (C-H=CH), one methyl group, and two sets of ribose ring protons. The low-resolution FAB mass spectrum of this product showed an MH^+ peak at 706, while elemental analysis and the high-resolution FAB mass spectrum indicated the molecular formula of the compound to be $C_{29}H_{35}N_7O_{14}$. These data were interpreted to suggest that two cytidine rings are linked together through a ureido chain and that one of these rings is methylated. Accordingly, this product was assigned structure **13**. The second reaction product showed an MH^+ peak at 355 in the mass spectrum and three exchangeable protons in the ^{1}H NMR spectrum. On the basis of comparison with compounds **11a–c**, this compound was assigned structure **14**. It is interesting to note that when **6b** was heated with acetone/K_2CO_3, the triazine ring opened to yield compound **14** only. It is apparent that adventitious water in the spectroscopic-grade acetone was sufficient for the ring opening leading to each product.



13



14

Since the pyrimido[1,6-*a*]-1,3,5-triazine ring of **6** was found to be susceptible to a ring opening during the methanolic ammonia deprotection of ribose acetyl groups, we considered that the protection of the ribose hydroxyl groups with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane[53] (TIPDS-Cl_2) would be helpful. This protecting group is easily removed by treatment with tetrabutylammonium fluoride (TBAF) in THF solution.[54] Treatment of 2′-

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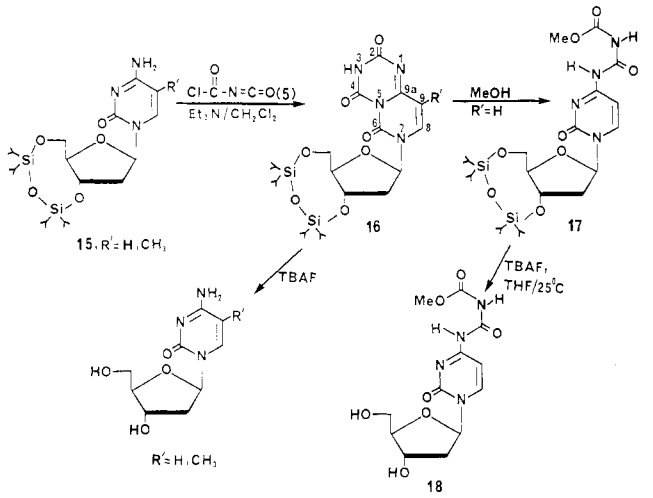
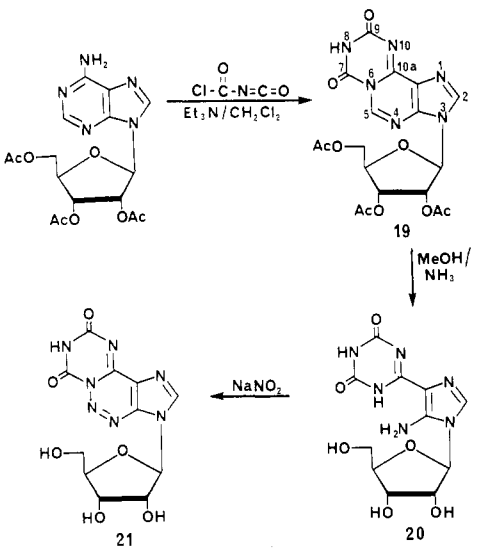
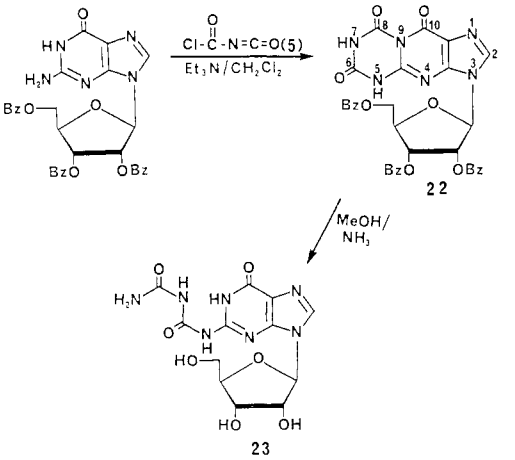
Scheme II



Scheme III



Scheme IV



deoxycytidine and 5-methyl-2′-deoxycytidine with TIPDS-Cl_2 in pyridine at room temperature afforded the corresponding 3′,5′-cyclic disiloxanyl derivatives **15** (R′ = H and R′ = CH_3). The reaction of these with **5** gave the fused 1,3,5-triazine-2,4-dione ring compounds **16** (R′ = H and R′ = CH_3) (Scheme II). Compound **16** (R′ = H) upon treatment with methanol at room temperature gave the triazine ring-opened methanol adduct, compound **17**, similar to **9a** and **9b**. Deprotection of the 3′,5′-cyclic disiloxanyl group with a 1 M solution of TBAF in dry THF afforded compound **18**. When **16** (R′ = H) and **16** (R′ = CH_3) were each subjected to the same conditions, however, a ring opening and hydrolysis occurred to give 2′-deoxycytidine and 5-methyl-2′-deoxycytidine, respectively. Since the reaction of **16** with tetrabutylammonium fluoride occurred with the removal of three ring atoms (CONHCO) of the triazinedione moiety, we tested the potential of this reagent for cleavage of other triazine-fused compounds, viz. **6a–c**, **19**, and **22** (see below). Treatment of **6a–c** with a 1 M solution of TBAF in dry THF for 45 min gave **4a–c**, respectively, while similar removal of three ring atoms (CONHCO) of the triazinedione moiety in **19** and **22** was complete in 24 h to give tri-*O*-acetyladenosine and tri-*O*-benzoylguanosine, respectively. This finding constitutes a potential new protection–deprotection sequence for α-amino heterocyclic compounds, but sensitivity to methanol may be a problem. By contrast, treatment of **25** (see below) containing a triazine*tri*one ring, with a 1 M solution of TBAF did not give any ring-opened product; compound **25** was recovered unchanged.

The reaction of *N*-chlorocarbonyl isocyanate (**5**) was examined also with representative purine nucleoside derivatives. In anhydrous dichloromethane in the presence of triethylamine at room temperature, this reagent (**5**) gave with 2′,3′,5′-tri-*O*-acetyladenosine a new product for which the ^1H NMR spectrum showed one exchangeable proton at δ 12.05. The proton at the original 2 position was shifted to δ 9.14. All the spectral data were consistent with its structure assignment as 7,9-dioxo-3,7,8,9-tetrahydro-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,3,5-triazino[2,1-*i*]-purine (**19**). When this *N*-tricyclic compound was treated with methanolic ammonia at room temperature, the product had a proton magnetic resonance spectrum which showed the presence of exchangeable protons for two NH groups (together) and one NH_2 group at δ 10.42 and 7.27, respectively. The loss of the CH signal at δ 9.14 in **19** indicated that the *pyrimidine* ring rather than the triazinedione ring had opened. This type of pyrimidine ring opening has been obsered when other ring combinations such as found in 1,N^6-ethenoadenosine,[55] 1,N^6-ethenoadenosine 3′,5′-cyclic phosphate,[56] pyrido[2,1-*i*]purines,[57] and quinazolino[2,1-*i*]purines[58] were treated with alkali or amines. On the basis of the ^1H NMR spectral and high-resolution FAB mass spectral data, the product from **19** was assigned the structure 4-amino-5-(2,4-dioxo-1,2,3,4-tetrahydro-1,3,5-triazin-6-yl)-3-β-D-ribofuranosylimidazole (**20**), which is an excellent candidate for ring closure with various reagents, for example, with $NaNO_2$ in aqueous HCl to give the azapurine derivative 7,9-dioxo-3,7,8,9-tetrahydro-3-β-D-ribofuranosyl-1,3,5-triazino[2,1-*i*]-5-azapurine (**21**).

Treatment of 2′,3′,5′-tri-*O*-benzoylguanosine with *N*-chlorocarbonyl isocyanate (**5**) in anhydrous dichloromethane (Scheme IV) afforded a sole product, the ^1H NMR [$(CD_3)_2SO$] of which showed the presence of two exchangeable proton resonances at δ 12.40 and 11.75. The low-resolution FAB mass spectrum showed an MH^+ peak at 665, and the high-resolution FAB mass spectrum was consistent with the empirical formula $C_{33}H_{24}N_6O_{10}$. On

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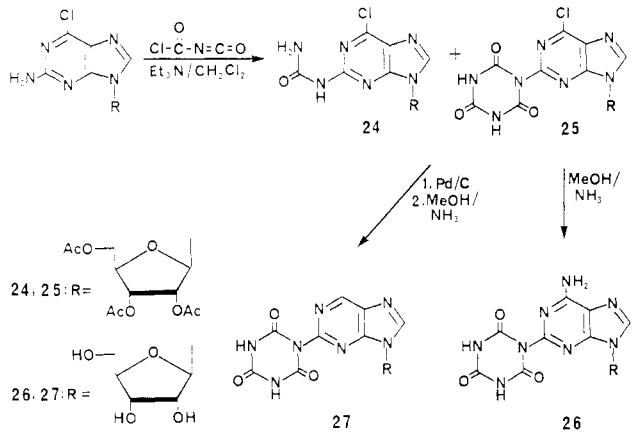
Scheme V



the basis of these data, the compound was assigned the structure 3,5,6,7,8,10-hexahydro-6,8,10-trioxo-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,3,5-triazino[1,2-*a*]purine (**22**). The terminal rings of this compound resemble those of xanthosine; therefore, **22** may be regarded as a laterally extended xanthosine analogue, and thus it bears a close resemblance to *lin*-benzoxanthosine.[59,60] Removal of the benzoyl groups from compound **22** with methanolic ammonia led to triazinedione ring opening and the addition of 1 molar equiv of ammonia to give the N^2-substituted guanosine derivative N^2-(ureidocarbonyl)guanosine (**23**).

The reaction of 2-amino-6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine with 1 equiv of **5** in dry dichloromethane afforded two products (Scheme V) which were separated by column chromatography. The product with the higher R_f value showed an MH^+ peak at 471 in the low-resolution FAB mass spectrum and the presence of one NH_2 and one NH group in the ^1H NMR spectrum. On the basis of these data, the product was identified as 6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-ureidopurine (**24**). The second eluted product showed an MH^+ peak at 541 in the low-resolution FAB mass spectrum, had a high-resolution FAB mass spectrum consistent with the empirical formula $C_{19}H_{18}ClN_7O_{10}$, and showed the presence of two exchangeable protons in the ^1H NMR spectrum. By analogy with the observation[34] that 4-chloroaniline reacts with 2 equiv of *N*-chlorocarbonyl isocyanate to afford monosubstituted isocyanurates, this product was assigned the structure 6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-(2,4,6-trioxo-1,3,5-triazinyl)purine (**25**). Compound **25** was the major product obtained when 2-amino-6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-purine was treated with 2 equiv of **5**. The removal of the acetyl protecting groups of **25** with methanolic ammonia led also to the replacement of the chloro group with an amino group to give the adenosine derivative **26** bearing an isocyanurate (2,4,6-trioxo-1,3,5-triazino) group at the 2-position. A 2-substituted nebularine derivative (9-β-D-ribofuranosyl-2-(2,4,6-trioxo-1,3,5-triazinyl)purine, **27**) was obtained by dehalogenation with H_2/Pd/C followed by deprotection with methanolic ammonia.

Compounds **10b** and **11a–c**, which were tested as representative examples, were devoid of antiviral activity against Herpes Simplex Virus Type I (HSV-1) and of cytotoxicity toward monkey kidney cells (CV-1 cells).[61]

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Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by Mr. Josef Nemeth and his staff at the University of Illinois. ^1H NMR spectra were recorded on a General Electric QE-300 or GN-500 spectrometer at 300 or 500 MHz, respectively. ^{13}C NMR spectra were recorded at 75.5 or 125.7 MHz. Tetramethylsilane was used as internal standard in all NMR spectra, and the following abbreviations are used: s, singlet; d, doublet; t, triplet; ; m, multiplet; br, broad; and ex, exchangeable with D_2O. Complete NMR spectral assignments on some of the compounds reported were based on proton–proton spin decoupling experiments, proton-coupled ^{13}C NMR data, and short-range heteronuclear correlation (HETCOR) spectroscopy. Fast-atom bombardment (FAB) mass spectra were obtained on a VG ZAB-1 HF spectrometer. Infrared (IR) spectra were recorded on a Nicolet 7199 Fourier-transform spectrophotometer and ultraviolet (UV) spectra on a Beckman Acta MVI spectrophotometer. Thin-layer chromatography (TLC) was run wither on Merck precoated silica gel F-254 plates or Analtech precoated silica gel plates with fluorescent indicator and was visualized with ultraviolet light. The following solvent systems were used: A, chloroform–methanol (19:1, v/v); B, chloroform–methanol (9:1, v/v); C, chloroform–methanol (4:1, v/v). Merck silica gel 60 was used for column chromatography. Radial preparative layer chromatography was performed on a Chromatotron instrument (Harrison Research, Inc., Palo Alto, CA).

Dichloromethane was distilled from P_2O_5 under nitrogen and stored over 4-Å molecular sieves. All anhydrous reactions were carried out under a dry nitrogen atmosphere. *N*-Chlorocarbonyl isocyanate was purchased from the Aldrich Chemical Co.

2,3,4,5,6,7-Hexahydro-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrimido[1,6-*a*]-1,3,5-triazine-2,4,6-trione (6a). A solution of *N*-chlorocarbonyl isocyanate (0.55 g, 5.2 mmol) in dry dichloromethane (5 mL) was added dropwise during 5 min to a stirred solution of 2′,3′,5′-tri-*O*-acetylcytidine (1.85 g, 5 mmol) in anhydrous dichloromethane (50 mL). The clear solution was stirred for 1 h at 25 °C, triethylamine (0.52 g, 5.2 mmol) was added, and the reaction mixture was stirred for 30 min. Water (50 mL) was added. The organic layer was washed twice with water, dried (Na_2SO_4), and evaporated to give a white solid which was triturated with ether and filtered to give (after drying) 2.0 g (91%) of pure **6a**: R_f (solvent B) 0.43; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.9 (br s, 1, NH, ex), 7.51 (d, J = 8.1 Hz, 1, 8-H), 6.09 (d, J = 8.1 Hz, 1, 9-H), 5.91 (d, J = 4.2 Hz, 1, 1′-H), 5.34 (t, J = 5.4 Hz, 1, 2′-H), 5.23 (t, J = 5.4 Hz, 1, 3′-H), 4.32 3,4′-H, 3, 4′-H, 5′-CH_2), 2.09, 2.05 (2s, 9, $COCH_3$); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 172.29, 171.35, 171.30 ($COCH_3$); 159.85, 156.02, 147.66, 146.35, 141.88, 102.35, 91.82, 81.27, 74.50, 70.89, 63.70; 20.75, 20.40 ($COCH_3$); IR (KBr) 3200 br (NH), 3000 br, 1750, 1720, 1650, 1635, 1400, 1230, 1180, 1025 cm^{-1}; low-resolution FAB mass spectrum, 439 (MH^+); high-resolution FAB mass spectrum, obsd 439.1091, $C_{17}H_{19}N_4O_{10}$ requires 439.1101; qual. UV λ_{max} (MeOH) 307, 240 mm.

2,3,4,5,6,7-Hexahydro-7-(3,5-di-*O*-acetyl-2-deoxy-β-D-ribofuranosyl)pyrimido[1,6-*a*]-1,3,5-triazine-2,4,6-trione (6b): yield 74%; R_f (solvent B) 0.43; ^1H NMR [$(CD_3)_2SO$, 300 MHz] δ 11.52 (s, 1, NH, ex), 7.73 (d, J = 8.1 Hz, 1, 8-H), 6.09 (m, 2, 9-H, 1′-H), 5.20 (m, 1, 3′-H), 4.25 (m, 3, 4′-H, 5′-CH_2), 2.44 (m, 2, 2′-CH_2), 2.06, 2.05 (2 s, 6, $COCH_3$); low-resolution FAB mass spectrum, 381 (MH^+); high-resolution FAB mass spectrum, obsd 381.1056, $C_{15}H_{17}N_4O_8$ requires 381.1046; qual. UV λ_{max} (MeOH) 307, 240 nm.

2,3,4,5,6,7-Hexahydo-7-(3,5-di-*O*-acetyl-2-deoxy-β-D-ribofuranosyl)-9-methylpyrimido[1,6-*a*]-1,3,5-triazine-2,4,6-trione (6c): yield 79%; R_f (solvent B) 0.44; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.82 (br s, 1, NH, ex), 7.50 (s, 1, 8-H), 6.24 (q, J = 6.3 Hz, 1, 1′-H), 5.23 (m, 1, 3′-H), 4.37 (m, 3, 4′-H, 5′-CH_2), 2.68 (m, 2, 2′-H), 2.13, 2.09 (2 s, 9, CH_3 and $COCH_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.40, 170.23 ($COCH_3$); 157.25, 153.70, 145.83, 144.39, 135.07, 109.39, 86.42 (C-1′), 82.57 (C-4′), 73.62 (C-3′), 63.40 (C-5′), 37.50 (C-2′), 20.67 ($COCH_3$), 14.22 (CH_3); low-resolution FAB mass spectrum, 395 (MH^+); high-resolution FAB mass spectrum, obsd

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395.1207, $C_{16}H_{19}N_4O_8$ requires 395.1202; qual. UV λ_{max} (MeOH) 314, 240 nm.

N^4-[[(Methoxycarbonyl)amino]carbonyl]-2',3',5'-tri-*O*-acetylcytidine (9a). A solution of compound **6a** (1.1 g, 2.5 mmol) in methanol (25 mL) was allowed to stand overnight at room temperature. The solid that formed was separated by filtration (0.750 g), and the mother liquor was concentrated to give additional **9a** (0.200 g (total yield: 0.950 g, 80%)): mp 110 °C; R_f (solvent B) 0.60; ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 11.16 (s, 1, NH, ex), 10.44 (s, 1, NH, ex), 8.14 (d, J = 7.4 Hz, 1, 6-H), 6.92 (d, J = 7.2 Hz, 1, 5-H), 5.93 (d, J = 4.1 Hz, 1, 1'-H), 5.48 (t, J = 6.0 Hz, 1, 2'-H), 5.36 (t, J = 6.0 Hz, 1, 3'-H), 4.33 (m, 3, 4'-H, 5'-CH_2), 3.73 (s, 3, OCH_3), 2.07, 2.05 (2 s, 9, $COCH_3$); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 172.17, 171.30, 164.48, 159.60, 155.86, 151.72, 146.93, 97.99, 92.22, 81.30, 75.06, 71.25, 63.96, 20.78, 20.44; IR (KBr) 3200 br (NH), 3010, 1800, 1745, 1725, 1650, 1610, 1495, 1430, 1400, 1330, 1245, 1225, 1200, 1120, 1100 cm^{-1}; low-resolution FAB mass spectrum, 471 (MH^+); UV λ_{max} nm (ϵ) (pH 7) 293 (9250), 244 (17 000); (MeOH) 295 (8170), 245 (17 200); (pH 1) 296 (10 400), 243 (15 800); (pH 11) 293 (16 700), 261 (16 400). Anal. Calcd for $C_{18}H_{22}N_4O_{11}$: C, 45.95; H, 4.71; N, 11.91. Found: C, 45.76; H, 4.73; N, 11.91.

N^4-[[(Methoxycarbonyl)amino]carbonyl]-3',5'-di-*O*-acetyl-2'-deoxycytidine (9b): yield 82%; mp 194–195 °C; R_f (solvent B) 0.61; ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 11.16 (s, 1, NH, ex), 10.39 (s, 1, NH, ex), 8.13 (d, J = 7.4 Hz, 1, 6-H), 6.92 (d, J = 7.4 Hz, 1, 5-H), 6.12 (t, J = 6.7 Hz, 1, 1'-H), 5.20 (m, 1, 3'-H), 4.29 (m, 3, 4'-H, 5'-CH_2), 3.73 (s, 3, OCH_3), 2.36 (m, 2, 2'-CH_2), 2.07, 2.06 (2 s, 6, $COCH_3$); ^{13}C NMR [$(CD_3)_2SO$, 75.5 MHz] δ 170.35, 170.22, 162.09, 153.57, 149.94, 145.28, 95.39, 87.02 (C-1'), 74.46 (C-4'), 74.27, 63.84, 53.07, 37.47, 20.91, 20.81; low-resolution FAB mass spectrum, 413 (MH^+); UV λ_{max} nm (ϵ) (pH 7) 293 (11 200), 242 (17 800); (MeOH) 295 (10 100), 243 (17 600); (pH 1) 299 (12 400), 241 (14 800); (pH 11) 292 (17 600), 259 (17 200). Anal. Calcd for $C_{16}H_{20}N_4O_9$: C, 46.60; H, 4.89; N, 13.59. Found: C, 46.72; H, 4.94; N, 13.65.

N^4-(Ureidocarbonyl)cytidine (10a). A suspension of **6a** (0.438 g, 1 mmol) in 40 mL of methanol previously saturated at −5 °C with ammonia was sealed in a flask and stirred at room temperature for 24 h. The resulting solution was evaporated to dryness in vacuo, and the residues was extracted with chloroform (3 × 25 mL). The solid remaining was dissolved in hot ethanol (95%, 50 mL), filtered, and allowed to stand in the refrigerator overnight to afford 0.250 g (76%) of **10a**: mp 194–195 °C; ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 10.61 (s, 1, NH, ex), 10.48 (s, 1, NH, ex), 8.41 (d, J = 7.5 Hz, 1, 6-H), 7.31 (s, 1, NH, ex), 7.18 (s, 1, NH, ex), 6.58 (d, J = 7.5 Hz, 1, 5-H), 5.76 (d, J = 2.7 Hz, 1, 1'-H), 5.51 (d, 1, OH, ex), 5.15 (t, 1, OH, ex), 5.03 (d, 1, OH, ex), 3.90 (m, 3, 2'-H, 3'-H, 4'-H), 3.77–3.55 (m, 2, 5'-CH_2); low-resolution FAB mass spectrum, 330 (MH^+); UV λ_{max} nm (ϵ) (pH 7) 292 (12 300), 243 (15 900); (pH 1) 297 (12 900), 240 (14 500); (pH 11) 298 (26 700). Anal. Calcd for $C_{11}H_{15}N_5O_7$: C, 40.13; H, 4.59; N, 21.17. Found: C, 40.28; H, 4.60; N, 20.88.

N^4-(Ureidocarbonyl)-2'-deoxycytidine (10b): yield 80%; mp 189–190 °C; ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 10.60 (s, 1, NH, ex), 10.48 (s, 1, NH, ex), 8.31 (d, J = 7.2 Hz, 1, 6-H), 7.32, 7.18 (2 s, 2, NH, ex), 6.60 (d, J = 7.2 Hz, 1, 5-H), 6.10 (t, J = 6.1 Hz, 1, 1'-H), 5.27 (d, 1, OH, ex), 5.05 (t, 1, OH, ex), 4.21 (m, 1, 3'-H), 3.85 (m, 1, 4'-H), 3.59 (m, 2, 5'-CH_2), 2.30–2.00 (m, 2, 2'-CH_2); low-resolution FAB mass spectrum, 314 (MH^+); UV λ_{max} nm (ϵ) (pH 7) 291 (11 700), 241 (14 800); (pH 1) 297 (12 300), 239 (13 200); (pH 11) 297 (22 200). Anal. Calcd for $C_{11}H_{15}N_5O_6$: C, 42.17; H, 4.83; N, 22.36. Found: C, 41.94; H, 4.88; N, 22.35.

N^4-Carbamoylcytidine (11a). A suspension of **9a** (0.500 g, 1.06 mmol) in methanol (30 mL) previously saturated with ammonia at −5 °C was sealed in a flask and stirred at room temperature for 24 h. The white solid that separated was isolated by filtration to give 170 mg of **11a**. The filtrate was concentrated in vacuo and triturated with chloroform (3 × 25 mL) to give additional **11a** (total yield 240 mg, 79%): mp 159–60 °C (methanol); ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 9.78 (s, 1, NH, ex), 8.27 (d, 2, J = 7.2 Hz, NH, 6-H), 7.26 (s, 1, NH, ex), 6.30 (d, J = 6.6 Hz, 1, 5-H), 5.76 (d, J = 2.7 Hz, 1, 1'-H), 5.47, 5.15, 5.06 (3 s, 3, OH, ex), 3.95–3.67 (m, 5, 2',3',4',5'-H); low-resolution FAB mass spectrum, 287 (MH^+), 155 (B^+ + 2); UV λ_{max} nm (ϵ) (pH 7) 285 (10 400), 239 (11 750); (pH 1) 299 (14 700); (pH 11) 287 (11 700), 239 (10 800). Anal. Calcd for $C_{10}H_{14}N_4O_6$: C, 41.95; H, 4.92; N, 19.57. Found: C, 41.92; H, 4.93; N, 19.17.

N^4-Carbamoyl-2'-deoxycytidine (11b): yield 70%; mp 179–181 °C (MeOH); ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 9.76 (s, 1, NH, ex), 8.32 (d, 1, NH, ex), 8.17 (d, J = 7.4 Hz, 1, 6-H), 7.24 (br s, 1, NH, ex), 6.29 (d, J = 7.0 Hz, 1, 5-H), 6.11 (t, J = 6.3 Hz, 1, 1'-H), 5.26 (d, J = 4.2 Hz, 1, OH, ex), 5.04 (t, J = 5.1 Hz, 1, OH, ex), 4.21 (m, 1, 3'-H), 3.83 (m, 1, 4'-H), 3.58 (m, 2, 5'-CH_2), 2.22–2.00 (m, 2, 2'-CH_2); low-resolution FAB mass spectrum, 271 (MH^+); UV λ_{max} nm (ϵ) (pH 7) 285 (11 900); (pH 11) 287 (14 200); (pH 1) 299 (16 600). Anal. Calcd for $C_{10}H_{14}N_4O_5$: C, 44.44; H, 5.22; N, 20.73. Found: C, 44.18; H, 5.22; N, 20.92.

N^4-Carbamoyl-5-methyl-2'-deoxycytidine (11c): yield 65%; mp 180–182 °C (methanol); ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 9.20 (br s, 1, NH, ex), 8.66 (br s, 1, NH, ex), 7.99 (s, 1, 6-H), 7.40 (s, 1, NH, ex), 6.12 (t, J = 6.7 Hz, 1, 1'-H), 5.25 (d, J = 3.9 Hz, 1, OH, ex), 5.08 (t, J = 4.9 Hz, 1, OH, ex), 4.23 (m, 1, 3'-H), 3.81 (m, 1, 4'-H), 3.59 (m, 2, 5'-CH_2), 2.17 (m, 2, 2'-CH_2), 1.98 (s, 3, CH_3); low-resolution FAB mass spectrum, 285 (MH^+), 169 (B^+ + 2); UV λ_{max} nm (ϵ) (pH 7) 293 (10 600); (pH 11) 294 (11 500); (pH 1) 309 (16 800). Anal. Calcd for $C_{11}H_{16}N_4O_5$: C, 46.47; H, 5.67; N, 19.71. Found: C, 46.37; H, 5.79; N, 19.57.

Crystallographic Analysis of N^4-[[(Methoxycarbonyl)amino]carbonyl]-3',5'-di-*O*-acetyl-2'-deoxycytidine (9b) and N^4-(Ureidocarbonyl)-2'-deoxycytidine (10b). Colorless crystals of **9b** were grown from methanol, and pale yellow crystals of **10b** were obtained from H_2O. The reflections were observed on a Syntex $P2_1$ automated diffractometer (**10b**) or an Enraf-Nonius CAD4 automated k-axis diffractometer (**9b**) equipped with a graphite monochromator using Mo K$\bar{\alpha}$ (λ = 0.71073 Å) radiation. The variable-scan option was used at 3–16°/min for **9b** and 3–20°/min for **10b**. Three standard reflections were monitored every 100 reflections for **10b** and per 2700-s exposure time for **9b**; an examination of these at the end of the data collection showed insignificant crystal decomposition. Anomalous dispersion and Lorentz and polarization effect[62] were applied for data correction.

The structures were solved by the direct methods program SHELXS-86.[63] Correct positions for all non-hydrogen atoms were deduced from an E-map. Subsequent least-square difference Fourier calculations revealed positions for the hydrogen atoms; however, hydrogen atoms bound to carbon were included as fixed contributors in "idealized" positions. The scattering curves were taken from the analytical expression used in the International Tables for X-ray Crystallography.[64]

For **9b**, reflections were collected on a crystal of dimensions 0.1 × 0.2 × 0.6 mm to give the following data: $C_{16}H_{20}N_4O_9$, M_r 412.36, monoclinic, $P2_1$, a = 8.706 (4) Å, b = 7.228 (3) Å, c = 15.352 (5) Å, α = 90°, β = 92.69(4), V = 965 (1) Å^3, $F(000)$ = 432, ρ_{calcd} (Z = 2) = 1.419 g/cm^3, μ = 1.10 cm^{-1}. Of 2749 reflections, 988 were considered observed at $I > 2.58\sigma(I)$.[65] Full matrix least-squares refinements on the positional and anisotropic thermal parameters of the non-hydrogen atoms converged to an agreement factor of R = 0.060, R_w = 0.062.[66] The final value of $E = [\sum\omega(|F_o| - |F_c|)^2/(m-n)]^{1/2}$ (where m is the number of observations and n is the number of variables) was 1.27. A final difference map showed no peak greater than 0.26 e/Å^3.

The crystal properties of **10b**, observed for a crystal of dimensions 0.1 × 0.3 × 0.3 mm, were as follows: $C_{11}H_{15}N_5O_6$, M_r 313.27, monoclinic, $P2_1$, a = 6.677 (2) Å, b = 20.262 (7) Å, c = 5.046 (1) Å, α = 90°, β = 105.25 (2), V = 658.7 (4) Å^3, $F(000)$ = 328, ρ_{calcd} (Z = 2) = 1.579 g/cm^3, μ = 1.219 cm^{-1}. Of 1074 reflections, 834 were considered observed at $I > 1.96\sigma(I)$.[65] The parameter of the non-hydrogen atoms converged to an agreement factor of

(62) Stout, G. H.; Jensen, L. H. *X-Ray Structure Determination, A Practical Guide*; MacMillan: New York, 1968; pp 195–199.

(63) Sheldrick, G. M. *SHELXS-86, Crystallographic Computing 3*; Sheldrick, G. M., Kruger, C., Goddard, R., Eds.; Oxford University Press: Oxford, 1985; pp 175–189.

(64) *International Tables for X-Ray Crystallography, vol.* IV; Ibers, J. A., Hamilton, W. C., Eds.; Kynoch Press: Birmingham, England, 1974; pp 71–102.

(65) Corfield, P. W. R.; Doedens, R. J.; Ibers, J. A. *Inorg. Chem.* **1967**, *6*, 197.

(66) $R = \sum||F_o| - |F_c||/\sum|F_o|$, $R_w = [\sum\omega||F_o| - |F_c||^2/\sum\omega|F_o|^2]^{1/2}$.

$R = 0.042$, $R_w = 0.044$.[66] The final value of E was 1.39, and the final difference map showed no peak greater than 0.24 e/Å^3.

N^4-[[(Methoxycarbonyl)amino]carbonyl]-3-methyl-3′,5′-di-*O*-acetyl-2′-deoxycytidine (12). A solution of **9b** (0.206 g, 0.5 mmol) in 25 mL of spectroscopic-grade acetone was treated with CH_3I (0.198 g, 1.4 mmol) and anhydrous K_2CO_3 (0.165 g, 1.2 mmol). The mixture was stirred at room temperature for 24 h, filtered, and concentrated in vacuo to give a white solid. Purification by column chromatography on silica gel (2% CH_3OH/$CHCl_3$) gave **12** (0.150 g, 70%): ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 11.24 (s, 1, NH, ex), 8.17 (d, J = 7.5 Hz, 1, 6-H), 7.22 (d, J = 7.5 Hz, 1, 5-H), 6.13 (t, J = 7.0 Hz, 1, 1′-H), 5.20 (m, 1, 3′-H), 4.26 (m, 3, 4′-H, 5′-CH_2), 3.83 (s, 3, OCH_3), 3.16 (s, 1, N-CH_3), 2.37 (m, 2, 2′-CH_2), 2.08, 2.03 (2 s, 6, $COCH_3$); low-resolution FAB mass spectrum, 427 (MH^+), 227 ($B^+ + 2$); high-resolution FAB mass spectrum, obsd 427.1455, $C_{17}H_{23}N_4O_9$ requires 427.1465; UV λ_{max} nm (ϵ) (MeOH) 297 (9680), 245 (19 800); (pH 1) 303 (11 300), 245 (13 500); (pH 11) 286 (11 100), 242 (9250).

Methylation of 6b. A solution of **6b** (0.380 g, 1 mmol) in acetone (25 mL) was treated with anhydrous K_2CO_3 (0.165 g, 1.2 mmol) and CH_3I (0.425 g, 3 mmol), and the reaction mixture was stirred at 60 °C for 6 h. The solution was filtered and evaporated to dryness in vacuo. TLC of the reaction mixture showed two major products. These were separated by radial chromatography using chloroform–methanol (90:10) as the eluent to afford **13** (0.120 g): mp 140–42 °C; R_f (solvent B) 0.63; ^{1}H NMR [$(CD_3)_2SO$, 500 MHz] δ 11.20 (s, 1, NH, ex), 10.55 (s, 1, NH, ex), 8.12 (d, J = 7.5 Hz, 1, 6a-H), 7.19 (d, J = 7.5 Hz, 1, 5a-H), 7.73 (d, J = 8.1 Hz, 1, 6b-H), 6.73 (d, J = 8.1 Hz, 1, 5b-H), 6.14 (2 t, J = 6.0Hz, 2, 1′-H), 5.20 (m, 2, 3′-H), 4.24 (m, 6, 4′-H, 5′-CH_2), 3.35 (s, 3, N-CH_3), 2.40 (m, 4, 2′-CH_2), 2.08, 2.05, 2.04 (3 s, 12, $COCH_3$); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 170.27, 170.14, 170.05 ($COCH_3$), 162.47, 160.70, 159.80, 154.99, 151.11, 149.32 (remaining CO and C-4), 142.67 (C-6), 136.44 (C-6), 136.44 (C-6), 98.41 (C-5), 96.49 (C-5), 87.10 (C-1′), 86.40 (C-1′), 82.76 (C-4′), 82.45 (C-4′), 74.09 (C-3′), 73.71 (C-3′), 63.52 (C-5′), 63.43 (C-5′), 38.73 (C-2′), 37.90 (C-2′), 30.27 (N-CH_3), 20.71, 20.64($COCH_3$); low-resolution FAB mass spectrum, 706 (MH^+); high-resolution FAB mass spectrum, obsd 706.2312, $C_{29}H_{35}N_7O_{14}$ requires 706.2320; UV λ_{max} nm (ϵ) (MeOH) 307 (31 000); 255 (17 600); (pH 1) 311 (33 000); 247 (17 000); (pH 11) 302 (31 200). Anal. Calcd for $C_{29}H_{35}N_7O_{14}$: C, 49.36; H, 5.00; N, 13.89. Found: C, 49.11; H, 5.16; N, 13.78.

Further elution afforded 0.080 g of **N^4-carbamoyl-3′,5′-di-*O*-acetyl-2′-deoxycytidine (14)**: mp 159–160 °C; R_f (solvent B) 0.40; ^{1}H NMR ($(CD_3)_2SO$, 500 MHz) δ 9.82 (s, 1, NH, ex), 8.25 (br s, 1, NH, ex), 7.93 (d, J = 7.5 Hz, 1, 6-H), 7.25 (br s, 1, NH, ex), 6.34 (d, J = 6.1 Hz, 1, 5-H), 6.13 (q, J = 6.8 Hz, 1, 1′-H), 5.19 (m, 1, 3′-H), 4.24 (br s, 3, 4′-H, 5′-CH_2), 2.37 (m, 2, 2′-CH_2), 2.07, 2.04 (2 s, 6, $COCH_3$); ^{13}C NMR ($CDCl_3$, 500 MHz) 170.38, 170.23 (*C*O and C-4), 155.25 (C-2), 141.70 (C-6), 97.55 (C-5), 87.17 (C-1′), 82.96 (C-4′), 74.18 (C-3′), 63.66 (C-5′), 38.91 (C-2′), 20.92 ($COCH_3$); low-resolution FAB mass spectrum, 355 (MH^+), 155 ($B^+ + 2$); UV λ_{max} nm (ϵ) (MeOH) 285 (9300), 240 (11 400). This compound was formed uniquely from **6b** and acetone and K_2CO_3. Anal. Calcd for $C_{14}H_{18}N_4O_7 \cdot 0.25H_2O$: C, 46.86; H, 5.20; N, 15.61. Found: C, 46.96; H, 5.20; N, 15.36.

2,3,4,5,6,7-Hexahydro-7-[2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxanediyl)-β-D-ribofuranosyl]pyrimido[1,6-*a*]-1,3,5-triazine-2,4,6-trione (16, *R′* = H). This compound was prepared in a similar manner to **6**, starting from 2′-deoxy-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxanediyl)cytidine (**15**, R′ = H), yield 89%; ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 11.51 (s, 1, NH, ex), 7.72 (d, J = 8.1 Hz, 1, 8-H), 5.96 (m, 2, 9-H, 1′-H), 4.44 (m, 1, 3′-H), 4.07 (m, 1, 4′-H), 3.97–3.79 (m, 2, 5′-CH_2), 2.43 (m, 2, 2′-CH_2), 1.08–1.05 (m, 28, 4 × CH_3CHCH_3); low-resolution FAB mass spectrum, 539 (MH^+).

2,3,4,5,6,7-Hexahydro-9-methyl-7-[2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxanediyl)-β-D-ribofuranosyl]pyrimido-[1,6-*a*]-1,3,5-triazine-2,4,6-trione (16, R′ = CH_3): yield from **15** (R′ = CH_3), 76%; mp 158–160 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.36 (br s, 1, NH, ex), 7.73 (s, 1, 8-H), 6.02 (d, J = 6.6 Hz, 1, 1′-H), 4.40 (q, 1, 3′-H), 4.20 (q, 1, 4′-H), 4.40–3.81 (m, 2, 5′-CH_2), 2.54–2.30 (m, 2, 2′-CH_2), 2.08 (s, 3, CH_3), 1.10–1.01 (m, 28, 4 CH_3CHCH_3); low-resolution FAB mass spectrum, 553 (MH^+). Anal. Calcd for $C_{20}H_{40}Si_2N_4O_7$: C, 52.15; H, 7.29; N, 10.14. Found: C, 51.76; H, 7.32; N, 9.88.

N^4-[[(Methoxycarbonyl)amino]carbonyl]-2′-deoxy-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxanediyl)cytidine (17). This was prepared by treating **16** (R′ = H) (1 g) with MeOH (25 mL) at room temperature for 3 h as reported for the preparation of **9**: yield 90%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.20 (br s, 2, NH, ex), 8.22 (d, J = 7.5 Hz, 1, 6-H), 7.46 (d, J = 6.0 Hz, 1, 5-H), 6.03 (d, J = 6.9 Hz, 1, 1′-H), 4.30 (m, 1, 3′-H), 4.17 (m, 1, 4′-H), 3.93 (m, 2, 5′-CH_2), 3.74 (s, 3, OCH_3), 2.57–2.23 (m, 2, 2′-CH_2), 1.16–0.91 (m, 28, 4 × CH_3CHCH_3).

N^4-[[(Methoxycarbonyl)amino]carbonyl]-2′-deoxycytidine (18). To a stirred solution of **17** (0.570 g, 1 mmol) in anhydrous THF (7 mL) was added tetrabutylammonium fluoride (1 M solution, 0.6 mL) dropwise during 5 min, and the reaction mixture was stirred at room temperature for 45 min. The mixture was concentrated in vacuo and purified by radial chromatography using $CHCl_3$/MeOH (4:1) as eluent to give 0.190 g (58%) of **18**: mp 163–164 °C; ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 11.18 (s, 1, NH, ex), 10.35 (s, 1, NH, ex), 8.35 (d, J = 7.4 Hz, 1, 6-H), 6.85 (d, J = 7.4 Hz, 1, 5-H), 6.09 (t, J = 6.1 Hz, 1, 1′-H), 5.28 (d, J = 4.3 Hz, 1, OH, ex), 5.06 (d, J = 5.0 Hz, 1, OH, ex), 4.21 (m, 1, 3′-H), 3.85 (m, 1, 4′-H), 3.72 (s, 3, OCH_3), 3.58 (m, 2, 5′-CH_2), 2.31–2.00 (m, 2, 2′-CH_2); ^{13}C NMR [$(CD_3)_2SO$, 75.5 MHz] δ 161.66, 153.66, 153.35, 149.79 (CO and C-4), 145.19 (C-6), 94.70 (C-5), 87.95 (C-1′), 86.27 (C-4′), 69.85 (C-3′), 60.88 (C-5′), 52.92 (C-2′), 40.85 (OCH_3); low-resolution FAB mass spectrum, 329 (MH^+); UV λ_{max} nm (ϵ) (pH 7) 293 (9500), 242 (15 000); (pH 1) 299 (11 500), 239 (12 000); (pH 11) 290 (15 000), 258 (15 700). Anal. Calcd for $C_{12}H_{16}N_4O_7$: C, 43.90; H, 4.91; N, 17.07. Found: C, 44.20; H, 5.01; N, 17.03.

7,9-Dioxo-3,7,8,9-tetrahydro-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,3,5-triazino[2,1-*i*]purine (19). A solution of **5** (0.53 g, 5 mmol) in methylene chloride (5 mL) was added dropwise over 5 min to a stirred solution of 2′,3′,5′-tri-*O*-acetyladenosine (1.97 g, 5 mmol) in dry methylene chloride (30 mL). The reaction mixture was stirred at room temperature for 30 min, Et_3N (0.50 g, 5 mmol) was added, and stirring was continued for 15 min. The solution was diluted with 50 mL of methylene chloride and extracted with water (2 × 30 mL). The organic layer was dried (Na_2SO_4) and concentrated to give a white solid which was triturated with ether and filtered to give **19** (1.85 g, 80%): mp 120 °C (softens); ^{1}H NMR ($CDCl_3$ + $(CD_3)_2SO$, 300 MHz) δ 12.05 (br s, 1, NH, ex), 9.14 (s, 1, 5-H), 8.31 (s, 1, 2-H), 6.25 (d, J = 4.8 Hz, 1, 1′-H), 5.86 (t, 1, 2′-H), 5.58 (t, 1, 3′-H), 4.43 (m, 3, 4′-H, 5′-CH_2), 2.16, 2.13, 2.09 (3 s, 9, $COCH_3$); ^{13}C NMR ($CDCl_3$ + $(CD_3)_2SO$, 75.5 MHz) δ 169.28, 168.60, 168.37, 152.39, 148.90, 146.28, 145.13, 140.69, 139.31, 122.64, 85.67, 79.49, 72.41, 69.35, 61.95, 19.80, 19.55, 19.40; low-resolution FAB mass spectrum, 463 (MH^+); UV λ_{max} nm (ϵ) (MeOH) 280 (16 000), 272 sh (15 200). Anal. Calcd for $C_{18}H_{18}N_6O_9 \cdot 0.25H_2O$: C, 46.31; H, 3.99; N, 18.00. Found: C, 46.21; H, 4.07; N, 17.62.

4-Amino-5-(2,4-dioxo-1,2,3,4-tetrahydro-1,3,5-triazin-6-yl)-3-β-D-ribofuranosylimidazole (20). A solution of **19** (0.92 g, 2 mmol) in 20 mL of methanol saturated with ammonia was stirred at room temperature in a sealed vessel for 12 h. The mixture was then concentrated in vacuo and triturated with cold methanol (20 L) to give a white solid which was filtered and dried to afford 0.49 g (75%) of **20**: ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 10.42 (br s, 2, NH, ex), 7.60 (s, 1, 2-H), 7.27 (s, 2, NH_2, ex), 5.56 (d, J = 6.7 Hz, 1, 1′-H), 5.50–5.19 (b, 3, OH, ex), 4.05 (t, 1, 2′-H), 3.94 (m, 1, 3′-H), 3.60 (m, 1, 4′-H), 3.35 (m, 2, 5′-CH_2); low-resolution FAB mass spectrum, 327 (MH^+); high-resolution FAB mass spectrum, obsd 327.1060, $C_{11}H_{15}N_6O_6$ requires 327.1053; UV λ_{max} nm (ϵ) (pH 7) 329 (16 750), 258 sh (4700), 244 sh (7100); (pH 1) 325 (16 500), 244 sh (7100); (pH 11) 309 (15 500), 261 (8700).

7,9-Dioxo-3,7,8,9-tetrahydro-3-β-D-ribofuranosyl-1,3,5-triazino[2,1-*i*]-5-azapurine (21). A mixture of **20** (0.40 g, 1.22 mmol) in 2 N hyrochloric acid (25 mL) was cooled to 0 °C to −5 °C and treated dropwise with a solution of sodium nitrite (0.40 g in 5 mL H_2O) over 5 min. The reaction mixture was stirred at this temperature for 1 h and then at room temperature for 30 min. It was cooled in a refrigerator for 2 h, and the white solid which separated was filtered, washed with ethanol and then with water, and dried to give **21** (0.21 g, 51%): ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 12.09 (s, 1, NH, ex), 9.00 (s, 1, 2-H), 6.19 (d, J = 4.8 Hz, 1, 1′-H), 4.57 (t, 1, 2′-H), 4.20 (t, 1, 3′-H), 4.05 (m, 1, 4′-H), 3.80–3.62 (m, 2, 5′-CH_2); low-resolution FAB mass spectrum, 338 (MH^+); UV λ_{max} nm (ϵ) (pH 7) 320 sh (3700), 255 (18 200); (pH

1) 320 sh (3700), 284 (15 200), 275 (15 800); (pH 11) 320 sh (3800), 285 sh (9400), 254 (19 000). Anal. Calcd for $C_{11}H_{11}N_7O_6 \cdot H_2O$: C, 37.19; H, 3.69; N, 27.60. Found: C, 37.07; H, 3.62; N, 27.29.

3,5,6,7,8,10-Hexahydro-6,8,10-trioxo-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,3,5-triazino[1,2-*a*]purine (22). A stirred solution of 2',3',5'-tri-*O*-benzoylguanosine (1.19 g, 2 mmol) in anhydrous dichloromethane (60 mL) was treated dropwise with a solution of **5** (0.21 g, 2 mmol) in dichloromethane (5 mL) over 5 min. The reaction mixture was stirred at room temperature under nitrogen for 30 min during which time a thick precipitate formed. Triethylamine (0.2 g, 2 mmol) was added, and the resulting clear yellowish solution was further stirred for 15 min. This solution was transferred to a separatory funnel containing 50 mL of chloroform and was extracted with water (25 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo, triturated with ether, and filtered to give **22** (1.2 g, 89%) as a white solid: ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 12.40 (s, 1, NH, ex), 11.75 (s, 1, NH, ex), 8.20 (s, 1, 2-H), 7.99–7.44 (m, 15, 3 × COC_6H_5), 6.43 (s, 1, 1'-H), 6.26–6.18 (m, 2, 2', 3'-H), 4.88–4.65 (m, 3, 4'-H, 5'-CH_2); low-resolution FAB mass spectrum, 665 (MH^+), 221 ($B^+ + 2$); high-resolution FAB mass spectrum, obsd 665.1627, $C_{33}H_{25}N_6O_{10}$ requires 665.1632.

N^2-(Ureidocarbonyl)guanosine (23). A solution of **22** (0.40 g, 0.6 mmol) in 20 mL of methanol saturated with ammonia was stirred in a sealed vessel for 50 h. The mixture was then concentrated in vacuo to give a white solid which was washed with chloroform (2 × 20 mL) and methanol (2 × 20 mL) and filtered to give **23** (0.21 g, 94%) as a white powder: ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 10.5 (br, 2, NH, ex), 8.07 (s, 1, 8-H), 7.20 (br s, 1, NH, ex), 6.6 (s, 1, NH, ex), 5.73 (s, 1, 1'-H), 5.41, 5.23, 5.05 (br s, 3, OH, ex), 4.50 (m, 1, 2'-H), 4.14 (m, 1, 3'-H), 3.90 (m, 1, 4'-H), 3.61–3.53 (m, 2, 5'-CH_2); low-resolution FAB mass spectrum, 370 (MH^+); high-resolution FAB mass spectrum; obsd 370.1114, $C_{12}H_{16}N_7O_7$ requires 370.1111.

Reaction of 2-Amino-6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine with 5. The reaction conditions were similar to those for the reaction of 2',3',5'-tri-*O*-acetyladenosine with **5**. The reaction mixture was purified by column chromatography using CH_2Cl_2/MeOH (9:1) as eluent.

The first product to elute was **6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-ureidopurine (24)**: yield, 30%; R_f (solvent B) 0.63; ^{1}H NMR [$(CD_3)_2$ SO, 300 MHz] δ 8.50 (br s, 2, NH, ex), 8.15 (s, 1, H-8), 8.09 (br s, 1, NH, ex), 6.09 (d, J = 4.5 Hz, 1, 1'-H), 5.83 (t, 1, 2'-H), 5.58 (t, 1, 3'-H), 4.46 (m, 3, 4'-H, 5'-CH_2), 2.17, 2.13 (2 s, 9, $COCH_3$); low-resolution FAB mass spectrum, 471 (MH^+, ^{35}Cl), 473 (MH^+, ^{37}Cl), 437 (M^+ – Cl), 213 ($B^+ + 2$).

The second product to elute was **6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-(2,4,6-trioxo-1,3,5-triazino)purine (25)**: yield, 45%; mp 140 °C (softens); R_f (solvent B) 0.44; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.50 (br s, 2, NH, ex), 8.46 (s, 1, 8-H), 6.26 (d, J = 5.7 Hz, 1, 1'-H), 5.88 (t, 1, 2'-H), 5.60 (t, 1, 3'-H), 4.50 (m, 1, 4'-H), 4.40 (m, 2, 5'-CH_2), 2.15, 2.09, 2.05 (3 s, 9, 3 × $COCH_3$); low-resolution FAB mass spectrum, 540 (MH^+, ^{35}Cl), 542 (MH^+, ^{37}Cl), 506 (M^+ – Cl), 282 ($B^+ + 2$); high-resolution FAB mass spectrum, obsd 540.0882, $C_{19}H_{19}ClN_7O_{10}$ requires 540.0882; UV (MeOH) λ_{max} nm (ε) 265 (7980). Anal. Calcd for $C_{19}H_{18}ClN_7O_{10}$: C, 42.27; H, 3.36. Found: C, 42.42; H, 3.65.

2-(2,4,6-Trioxo-1,3,5-triazinyl)adenosine (26). A solution of **25** (0.500 g, 0.92 mmol) in 20 mL of methanol saturated with ammonia was stirred in a sealed flask for 12 h. The reaction mixture was concentrated in vacuo, washed with chloroform (2 × 25 mL), and filtered to give **26** (0.330 g, 90%). Recrystallization from hot ethanol gave pure **26**: mp 228–230 °C dec; ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 11.50 (br s, 2, NH, ex), 8.50 (s, 1, 8-H), 7.78 (br s, 2, NH_2, ex), 5.84 (d, J = 6.0 Hz, 1, 1'-H), 5.52 (d, 1, OH, ex), 5.22 (m, 2, OH, ex), 4.53 (m, 1, 2'-H), 4.11 (m, 1, 3'-H), 3.93 (m, 1, 4'-H), 3.60 (m, 2, 5'-CH_2); low-resolution FAB mass spectrum, 395 (MH^+), 263 ($B^+ + 2$); high-resolution FAB mass spectrum, obsd 395.1069, $C_{13}H_{15}N_8O_7$ requires 395.1063; UV (pH 7) λ_{max} nm (ε) 259 (13 700); (pH 1) 259 (13 200); (pH 11) 261 (13 600). Anal. Calcd for $C_{13}H_{14}N_8O_7 \cdot 0.25H_2O$: C, 39.15; H, 3.66; N, 28.10. Found: C, 38.77; H, 3.66; N, 27.88.

9-β-D-Ribofuranosyl-2-(2,4,6-trioxo-1,3,5-triazinyl)purine (2-(2,4,6-Trioxo-1,3,5-triazinyl)nebularine) (27). A solution of **25** (0.540 g, 1 mmol) in ethanol (50 mL) was treated with Pd/C (10%, 0.250 g) and concentrated NH_4OH (1 mL) and was then hydrogenated in a Parr apparatus under 3 atm of hydrogen for 6 h. The suspension was filtered; the filtrate was concentrated to give a white solid. This was dissolved in 20 mL of methanol saturated with ammonia and stirred in a sealed flask for 12 h. The reaction mixture was concentrated in vacuo, washed with chloroform (2 × 25 mL), and recrystallized from ethanol to give **27** (0.260 g, 68%) as a white crystalline solid: mp 235 °C dec; ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 11.92 (s, 2, NH, ex), 9.35 (s, 1, 6-H), 9.04 (s, 1, 8-H), 6.02 (d, J = 5.1 Hz, 1, 1'-H), 5.65, 5.30, 5.10 (br s, 1 each, OH, ex), 4.60 (m, 1, 2'-H), 4.17 (m, 1, 3'-H), 3.97 (m, 1, 4'-H), 3.60 (m, 2, 5'-CH_2); low-resolution FAB mass spectrum, 380 (MH^+), 248 ($B^+ + 2$); high-resolution FAB mass spectrum, 380.0959, $C_{13}H_{14}N_7O_7$ requires 380.0954; UV λ_{max} nm (ε) (pH 7) 265 (7600); (pH 1) 264 (7500); pH (11) 267 (8200). Anal. Calcd for $C_{13}H_{13}N_7O_7$: C, 41.17; H, 3.45. Found: C, 41.49; H, 3.65.

Cleavage of the Triazinediones with TBAF. General Procedure. To a stirred solution of triazinedione (e.g., **6a–c**, **19**, **22**) (1 mmol) in anhydrous THF (15 mL) was added tetrabutylammonium fluoride (1 M solution, 1 mL) dropwise during 5 min, and the reaction mixture was stirred at room temperature for 45 min in the case of **6a–c** and 24 h for **19** and **22**. The mixture was concentrated in vacuo and purified by radial chromatography using $CHCl_3/CH_3OH$ (4:1) as eluant to give the ring-opened product in 70–85% yield.

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Supplementary Material Available: Tables of final atomic positional parameters, anisotropic thermal parameters, torsion angles, bond lengths and angles, and stereoviews from X-ray structure determination of **9b** and **10b** (11 pages). Ordering information is given on any current masthead page.