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(44) In separate experiments **22** could not be obtained in analytically pure form. The crude product had λ_{max} (MeOH) 228, 269, and 330 nm and its NMR spectrum showed C_1'H to be strongly deshielded and appearing under the benzoate protons.

5-Aza-7-deazapurine Nucleosides. 2.[1] Synthesis of Some 8-(D-Ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine Derivatives

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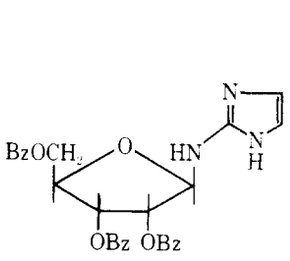
Syntheses of a number of differently ring-substituted 5-aza-7-deazapurine nucleosides are described. Stannic chloride catalyzed condensation of 2-nitroimidazole with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose surprisingly gives the α nucleosides as the predominant product. The desired β-D-ribofuranosyl derivative can, however, be obtained using 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide and mercuric cyanide. Reduction of the nitro groups in the above compounds gives the α and β anomers of 2-amino-1-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)imidazole (**9a, 10a**). The latter compounds can be converted into the α and β anomers of 8-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*,8*H*)-dione (**13**$^{\alpha,\beta}$) and their 2(8*H*)-one-4(3*H*)-thione counterparts (**16**$^{\alpha,\beta}$) through cyclization with phenoxycarbonyl isocyanate and phenoxycarbonyl isothiocyanate, respectively. Further functional group modifications of **13**$^{\alpha,\beta}$ and **16**$^{\alpha,\beta}$ then allow the preparation of the anomeric 8-(D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*,8*H*)-dithiones (**17**$^{\alpha,\beta}$) and the corresponding 4-amino-2-oxonucleosides (**19**$^{\alpha,\beta}$). The orientation of ring substituents in certain of these compounds is confirmed by hydrolysis studies. Preparation of the anomers of 4(8*H*)-imino-8-(D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine hydrochloride (**29**$^{\alpha,\beta}$) is also achieved via cyclization of **9a** and **10a** with ethyl *N*-cyanoformimidate. ^{1}H and ^{13}C NMR data is provided for the various compounds prepared.

In a recent paper[1] we outlined our interest in the synthesis of 8-(β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazines which can be looked upon as 5-aza-7-deazapurine nucleosides. In view of the paucity of information concerning the parent heterocyclic ring system, we preferred to approach this problem via elaboration of a triazine ring from a suitable 2-amino-1-(β-D-ribofuranosyl)imidazole. Our initial effort in this direction was, however, foiled since stannic chloride catalyzed condensation of 2-aminoimidazole with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose led predominantly to ribosylation of the exocyclic amine (giving **1**) rather than of the expected ring nitrogen. Nevertheless, **1** was a useful synthetic intermediate which was converted into a variety of 2,4-disubstituted 1-(β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazines (**2**) via cyclizations with aryloxycarbonyl isocyanates and their sulfur analogues.[1]



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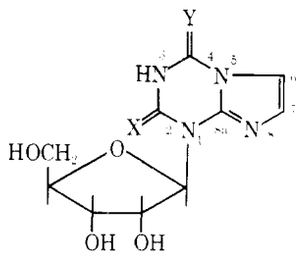

2

In the present paper we explore an alternate approach for the preparation of 2-amino-1-(β-D-ribofuranosyl)imidazole via reduction of the corresponding 2-nitroimidazole nucleoside. 2-Nitroimidazole (**3**) itself has been of some interest since this simple structure has been assigned to the antibiotic azomycin.[2] Its synthesis has been achieved by Beaman et al.[3] via diazotization of the readily available 2-aminoimidazole.[4] The synthesis is, nevertheless, tedious since it involves evaporation of large amounts of water (in our case, 100 L for the preparation of 20 g of **3**) and lengthy continuous extraction.

The preparation of 1-(β-D-ribofuranosyl)-2-nitroimidazole (**5b**) has been briefly reported by Rousseau et al.[5] via acid-catalyzed fusion of **3** with tetra-*O*-acetyl-β-D-ribofuranose followed by ester hydrolysis. Since the reported yield was only 17.5%, we felt that alternate routes should be explored. Accordingly, **3** was condensed with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of stannic chloride and mercuric cyanide. Following chromatography on silicic acid, a homogeneous nucleoside was isolated in 61% yield and subsequently obtained in crystalline form. The identical crystalline compound was obtained from the condensation of the unstable trimethylsilyl derivative of **3** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of stannic chloride according to the general method of Niedballa and Vorbrüggen[6] as also applied to purines.[7]

Based upon sound mechanistic reasoning and extensive experimental precedent,[8] one would anticipate that the predominant product in the reactions above would have the β-anomeric configuration (**5a**) due to participation by the 2′-*O*-benzoyl group. Hence it came as a great surprise when we were ultimately able to show, as will be seen in the subsequent discussion, that the isolated product was, in fact, 1-(2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl)-2-nitroimidazole (**4a**) rather than the expected β anomer (**5a**).

Fortunately, we subsequently found that the desired β anomer (**5a**) could be obtained in 68% yield by condensation of **3** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide[9] in acetonitrile at 60 °C in the presence of mercuric cyanide.

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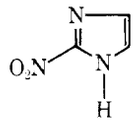
Table I. ^{1}H NMR Chemical Shifts (ppm) at 100 MHz

compd	solvent[a]	$C_{1'}$-H	$C_{2'}$-H	$C_{3'}$-H	$C_{4'}$-H	$C_{5'a}$-H	$C_{5'b}$-H	imidazole protons		other
4a	C	7.16 (d)	6.30 (dd)	5.91 (dd)	5.07 (ddd)	4.62 (dd)	4.81 (dd)	c		7.2–8.2 (m, 17, Ar, C_4-H, C_5-H)
4b	D	6.52 (d)	4.41 (dd)	4.00 (dd)	4.18 (dd)	3.43 (dd)	3.60 (dd)	7.10 (d)	7.56 (d)	
4c	C	6.88 (d)	5.83 (dd)	5.38 (dd)	4.69 (dt)	4.22 (dd)	4.37 (dd)	7.16 (d)	7.37 (d)	1.84, 1.91, 2.13 (s, 3, OAc)
5a	C	6.95 (m)[b]	5.82 (m)	5.82 (m)	4.80 (m)	4.80 (m)	4.80 (m)	7.09 (d)	7.55 (d)	7.2–8.2 (m, 15, Ar)
5b	D	6.21 (d)	3.9–4.2 (m)	3.9–4.2 (m)	3.9–4.2 (m)	3.61 (dd)	3.82 (dd)	7.17 (d)	8.16 (d)	
6a	D	6.17 (d)	5.46 (dd)	4.00 (m)	3.5 (m)	3.5 (m)	3.5 (m)	6.51 (d)	6.83 (d)	
6b	C	6.19 (d)	5.61 (dd)	4.81 (dd)	4–4.5 (m)	4–4.5 (m)	4–4.5 (m)	6.64 (d)	6.69 (d)	2.04, 2.12 (s, 3, OAc)
9a	D	6.35 (d)	6.01 (dd)	5.85 (dd)	5.05 (m)	4.57 (dd)	4.69 (dd)	6.41 (d)	6.91 (d)	7.3–8.2 (m, 15, Ar)
9b	D	5.67 (d)	4.14 (dd)	3.99 (dd)	4.0 (m)	3.40 (dd)	3.59 (dd)	6.30 (d)	6.80 (d)	
10a	D	6.20 (m)[b]	5.85 (m)	5.85 (m)	4.70 (m)	4.70 (m)	4.70 (m)	6.42 (d)	6.79 (d)	7.3–8.2 (m, 15, Ar)
10b	D	5.38 (d)	4.12 (dd)	4.00 (dd)	3.82 (dt)	3.52 (d)		6.35 (d)	6.69 (d)	
11b	D	5.93 (d)	4.92 (dd)	4.78 (dd)	4.38 (m)	3.28 (dd)	3.43 (dd)	6.55 (d)	6.78 (d)	1.25, 1.36 (s, 3, CMe_2)
13$^\alpha$a	C	6.72 (d)	6.12 (dd)	5.91 (dd)	4.99 (m)	4.59 (dd)	4.73 (dd)	c		7.2–8.2 (m, 17, Ar, C_6-H, C_7-H)
13$^\beta$a	C	6.47 (d)	5.85 (m)	5.85 (m)	4.64 (dd)	4.13 (dd)	4.79 (dd)	7.12 (d)	c	7.2–8.2 (m, 15, Ar)
13$^\alpha$b	D	6.00 (d)	4.32 (dd)	4.08 (m)	4.08 (m)	3.38 (dd)	3.53 (dd)	7.29 (d)	7.42 (d)	
13$^\beta$b	D	5.65 (d)	4.22 (dd)	4.05 (dd)	3.89 (m)	3.50 (dd)	3.67 (dd)	7.39 (d)	7.47 (d)	
14a	D	6.17 (d)	4.85 (m)	4.85 (m)	4.29 (m)	3.51 (dd)	3.62 (dd)	7.16 (d)	7.36 (d)	1.25, 1.38 (s, 3, CMe_2)
14b	D	6.17 (d)	4.92 (dd)	4.77 (dd)	4.40 (ddd)	3.39 (dd)	3.50 (dd)	7.18 (d)	7.38 (d)	1.23, 1.40 (s, 3, CMe_2)
16$^\alpha$a	C	6.70 (d)	6.12 (dd)	5.90 (dd)	4.96 (m)	4.58 (dd)	4.73 (dd)	7.18 (d)	c	7.1–8.1 (m, 16, Ar, $C_{6(7)}$-H)
16$^\beta$a	C	6.49 (d)	5.90 (m)	5.90 (m)	4.85 (m)	4.69 (dd)	4.83 (dd)	7.02 (d)	7.48 (d)	7.2–8.2 (m, 15, Ar)
16$^\alpha$b	D	6.05 (d)	4.38 (dd)	4.12 (m)	4.12 (m)	3.5 (m)		7.53 (d)	7.58 (d)	
16$^\beta$b	D	5.66 (d)	4.23 (dd)	4.06 (dd)	3.91 (m)	3.51 (dd)	3.66 (dd)	7.59 (s)	7.59 (s)	
17$^\alpha$a	C	6.87 (d)	6.17 (dd)	5.94 (dd)	5.03 (m)	4.61 (dd)	4.78 (dd)	c		7.2–8.2 (m, 17, Ar, C_6-H, C_7-H)
17$^\beta$a	C	6.06 (d)	5.80 (dd)	5.89 (dd)	4.7 (m)	4.7 (m)		7.06 (d)	c	7.2–8.2 (m, 16, Ar, $C_{6(7)}$-H)
17$^\alpha$b	D	6.13 (d)	4.39 (dd)	4.1 (m)	4.1 (m)	3.4 (dd)	3.60 (dd)	7.63 (d)	7.68 (d)	
17$^\beta$b	D	5.85 (d)	4.32 (dd)	4.19 (dd)	4.05 (m)	3.67 (m)		7.79 (d)	7.83 (d)	
18$^\alpha$	C	6.80 (d)	6.11 (dd)	5.90 (dd)	4.98 (m)	4.56 (dd)	4.73 (dd)	6.90 (d)	7.20 (d)	2.63 (s, 3, SMe), 7.2–8.2 (m, 15, Ar)
18$^\beta$	C	6.58 (d)	5.82 (dd)	5.89 (dd)	4.8 (m)	4.62 (dd)	4.79 (dd)	6.82 (d)	6.97 (d)	2.61 (s, 3, SMe), 7.2–8.2 (m, 15, Ar)
19$^\alpha$	D	6.02 (d)	4.29 (dd)	4.05 (dd)	4.00 (m)	3.35 (dd)	3.52 (dd)	7.38 (d)	7.44 (d)	
19$^\beta$	D	5.76 (d)	4.34 (dd)	4.14 (dd)	3.97 (m)	3.60 (m)		7.49 (d)	7.60 (d)	
21	C	6.76 (d)	6.10 (dd)	5.90 (dd)	4.91 (m)	4.55 (dd)	4.74 (dd)	6.62 (d)	6.93 (d)	1.25 (t, 3, CH_3CH_2), 4.11 (q, 2, CH_3CH_2), 7.2–8.2 (m, 15, Ar)
26$^\alpha$	C	6.96 (d)	6.29 (dd)	5.99 (dd)	5.16 (m)	4.15 (dd)	4.82 (dd)	c		8.24 and 8.87 (NCH=NCN), 7.2–8.2 (m, 17, Ar, C_4-H, C_5-H)
26$^\beta$	C	6.51 (d)	5.13 (dd)	6.03 (dd)	4.9 (m)	4.9 (m)		c		8.21 and 8.83 (NCH=NCN), 7.2–8.1 (m, 17, Ar, C_4-H, C_5-H)
29$^\alpha$	D	6.41 (d)	4.48 (dd)	4.12 (dd)	4.26 (m)	3.43 (dd)	3.59 (dd)	8.15 (d)	8.72 (d)	8.51 (s, 1, C_2-H)
29$^\beta$	D	6.09 (d)	4.37 (dd)	4.19 (dd)	4.04 (m)	3.62 (dd)	3.77 (dd)	8.38 (d)	8.79 (d)	8.55 (s, 1, C_2-H)

[a] Solvents are C, $CDCl_3$, and D, Me_2SO-d_6. Spectra of carbinol protons are reported after addition of D_2O. [b] Virtual coupling. [c] With aromatics.



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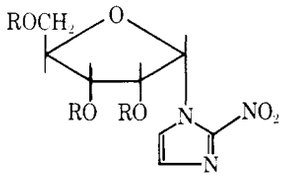
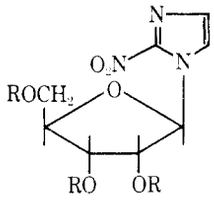
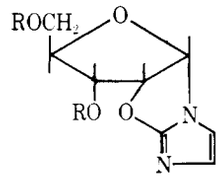


4a, R = Bz
b, R = H
c, R = Ac



5a, R = Bz
b, R = H
c, R = Ac



6a, R = H
b, R = Ac

While the ^{1}H NMR spectra of **4a** and **5a** were very different (Tables I and II), they were not particularly revealing with regard to structural assignments. The α anomer (**4a**) showed well-resolved sugar protons amenable to first-order analysis, while in the β anomer (**5a**) the 2′ and 3′ protons were superimposed, as were the 4′ and 5′ protons. As would be expected,[10] $C_{1'}$-H of the α anomer was deshielded by 0.21 ppm relative to the same proton in **5a**. While $J_{1',2'}$ in the α anomer was 5.5 Hz, the superimposition of $C_{2'}$-H and $C_{3'}$-H in **5a** led to virtual coupling and obscured the value of $J_{1',2'}$. More definitive proof of anomeric configurations for **4a** and **5a** came from further transformations to be described shortly.

The totally unexpected selective formation of the α anomer during ribosidation of **3** or its trimethylsilyl derivative under the conditions described above is difficult to rationalize. It is recognized that minor amounts of "1′,2′-*cis*" nucleosides can often be isolated from various types of condensation reactions.[11] In certain cases this would appear to be the result of partial anomerization brought about by strong Lewis acids such as titanium tetrachloride,[12] but almost inevitably the "1′,2′-*trans*" product predominates. An apparent exception was the reported formation of up to 2:1 mixtures of α and β nucleosides from condensation of chloromercuripurines with 2,3-di-*O*-acetyl-5,6-dideoxy-6-(di-*O*-ethylphosphono)-D-*ribo*-hexofuranosyl chloride.[13a] Transanular participation by the bulky phosphonate moiety was invoked to explain this anomaly, but subsequent work suggests that the purported α-D-ribo product was, in fact, the trans oriented α-D-arabino isomer arising by prior epimerization at $C_{2'}$.[13b] We are aware of no precedent for the formation of a furanosyl "1′,2′-*cis*" nucleoside as the major reaction product, as was the case with **4a**. Once the authentic β anomer, **5a**, was available, it was possible to reexamine photographs of the TLC patterns and NMR spectra of the crude reaction mixtures leading to **4a** and to conclude that only very low yields of the β anomer were present.

It is our tentative feeling that the selective formation of the α nucleoside, **4a**, involves participation by the 2-nitro function. Loosely based upon a proposal by Lemieux and Morgan[14] to explain the selective formation of 2-pyridyl-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside, we suggest the possible intermediacy of a nitronate ester such as **8** arising by addition of the nitronic acid tautomer of **3** (**7**) to the 1,2-benzoxonium ion derived from the 2-*O*-benzoyl sugar. Generation of a cat-

Table II. First-Order Coupling Constants (Hz)

compd	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	$J_{6,7}$
4a	5.5	5.5	3	3.5	3.5	12	
4b	4.5	4.5	5	4	3.5	12	1
4c	5.5	5	3.5	4	4	12	1.5
5a	*a*[b]	*a*	*a*	*a*	*a*	*a*	1
5b	1	*a*	*a*	2.5	2	12	1
6a	5	5	*a*	*a*	*a*	*a*	1.5
6b	5	5.5	9	*a*	*a*	*a*	1.5
9a	5	5	5	4	4	11	1.5
9b	4	4	4	4	2.5	12	1
10a	*a*[b]	*a*	*a*	*a*	*a*	*a*	1.5
10b	5	5	3	3.5	3.5	0	2
11b	4	6	1.5	6.5	6.5	11	1.5
13$^\alpha$a	5	5	4.5	3.5	3.5	11	*a*
13$^\beta$a	5.5	5.5	*a*	2.5	1	13	3
13$^\alpha$b	5.5	5.5	*a*	3	3	12	3
13$^\beta$b	4.5	4.5	4.5	3	3	12	3
14a	3.5	*a*	*a*	3.5	4	12	3
14b	4	5.5	1.5	7.5	6.5	13	3
16$^\alpha$a	5	5	4	3	3	12	3
16$^\beta$a	5.5	*a*	*a*	2	*a*	12	3
16$^\alpha$b	5.5	4	*a*	*a*	*a*	*a*	3
16$^\beta$b	4.5	4	4	3	2.5	12	0
17$^\alpha$a	5	5	5	4	4	11.5	*a*
17$^\beta$a	6	6	6	*a*	*a*	*a*	3
17$^\alpha$b	5.5	4.5	*a*	4	4	12	3
17$^\beta$b	4.5	4.5	4.5	*a*	*a*	*a*	4
18$^\alpha$	5	5	4.5	4	2.5	12	3
18$^\beta$	5.5	5.5	5.5	2	1.5	12	3
19$^\alpha$	5	4	*a*	4	2	12	3
19$^\beta$	5.5	5	3.5	*a*	*a*	*a*	3
21	5	5	5	4	3.5	12	2.5
26$^\alpha$	5.5	5	3	4	3	12	*a*
26$^\beta$	4.5	5	5	*a*	*a*	*a*	*a*
29$^\alpha$	5.5	5	4	3.5	*a*	12	2.5
29$^\beta$	4	4	5	2	2	12	2.5

[a] Unresolved. [b] Virtual coupling.

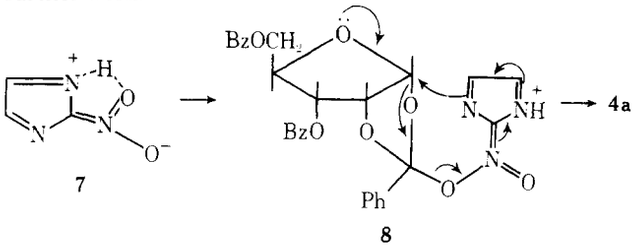
Table III. ^{13}C NMR Chemical Shifts (ppm)

compd	solvent[a]	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	C_2	C_4	C_6	C_7	C_{8a}	other
4b	D	89.79	70.97	70.54	85.69	61.15	144.47					124.35, 126.95, (C_4, C_5)
5b	D	92.03	75.85	67.85	84.04	59.26	144.31					123.44, 127.76 (C_4, C_5)
6a	D	89.69	80.56	69.89	85.34	59.72	159.72					110.04, 129.71 (C_4, C_5)
9a	D	83.13	70.97	71.62	78.77	64.17	148.89					112.45, 125.25 (C_4, C_5) + benzoate
9b	D	84.20	70.97	70.41	83.16	61.25	148.76					114.27 (C_5), 122.59 (C_4)
10b	D	87.48	73.66	70.09	84.65	61.28	149.05					112.22 (C_5), 123.66 (C_4)
13$^{\alpha}$b	D	84.04	70.64	70.38	85.37	61.47	145.87	155.10	106.40 or 118.79		150.39	
13$^{\beta}$b	D	87.22	73.60	69.89	85.30	60.86	145.77	155.13	107.93	115.93	150.42	
16$^{\alpha}$b	D	84.06	70.64	70.29	85.53	61.38	153.31	171.68	108.91	119.60	148.08	
16$^{\beta}$b	D	87.39	73.80	69.80	85.30	60.76	152.11	171.58	110.21	116.94	148.05	
17$^{\alpha}$b	D	84.62	70.74	70.22	85.95	61.31	178.96	167.72	109.85	120.77	142.98	
17$^{\beta}$b	D	87.65	74.09	69.72	85.32	60.60	178.96	167.72	111.34	117.81	143.14	
19$^{\alpha}$	D	83.52	70.55	70.42	85.04	61.47	150.42 or 162.47		105.49	118.46	149.61	
19$^{\beta}$	D	87.03	70.09	73.31	85.34	61.12	150.42 or 162.45		106.92	115.90	149.22	
22	D						150.68	171.84	111.02	120.97	146.75	
24	D						150.25	153.05	108.32	125.19	146.19	
26$^{\alpha}$	C	84.49	71.10 or 71.94		82.74	63.91			109.94	118.76		109.72 (CN), 161.31 (=NCH=NCN), 169.18 (=N-CH=NCN)
29$^{\alpha}$	D	85.69	71.16	70.25	86.77	61.28	160.99	151.46	108.78	122.33	146.19	
29$^{\beta}$	D	88.72	74.74	69.57	85.89	60.37	161.25	151.53	109.88	119.54	146.32	

[a] Solvents are C, $CDCl_3$, D, Me_2SO-d_6.

ionic center at $C_{1'}$ would then permit concerted attack by the imidazole ring nitrogen already held in an α configuration. It should be noted that several papers have described the ribosylation of 4-nitroimidazoles using both iodine-catalyzed fusion of the 1-*O*-acetyl sugar[16] or mercury salt catalyzed reaction with the glycosyl halide.[17] The former route gave excellent yields of 1-(D-ribofuranosyl)-4-nitroimidazoles with a 9:1 ratio of β and α anomers, while the latter only reports low yields of the β isomers. Perhaps the possibility of forming several hydrogen-bond stabilized nitronic acid tautomers (**7**) of **3**, as opposed to a single such form with the 4-nitroimidazoles, plays a role in the unique results reported. The precise function of the stannic chloride remains obscure.

The phenomenon above seems to be unique to the furanose system since condensation of **3** with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose in the presence of stannic chloride and mercuric cyanide led to the isolation of a 61% yield of 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-nitroimidazole. The β configuration of this compound was assured by the typical trans diaxial coupling constant of 8.5 Hz between $C_{1'}$-H and $C_{2'}$-H. A fuller understanding of the factors controlling the stereochemistry of glycosidation of **3** will clearly require further work.



7 8

Debenzoylation of **4a** and **5a** followed rather different patterns. Thus, treatment of the β isomer, **5a,** with sodium methoxide was straightforward and gave crystalline 1-(β-D-ribofuranosyl)-2-nitroimidazole (**5b**) in 81% yield. This compound was identical with a sample of **5b** obtained through the kindness of Professor L. B. Townsend.[5] Similar treatment of **4a,** however, led to an essentially TLC homogeneous product that was a mixture of two substances by NMR analysis. A similar result was observed using methanolic ammonia rather than sodium methoxide. In either case one product was initially formed and was subsequently slowly transformed into the second. By working up two reactions, one after a short reaction time and one after prolonged treatment, it was possible to isolate samples that were greatly enriched in one or the other product. Following acetylation of a roughly 1:1 mixture, it was possible to separate the two compounds, the initial product forming a triacetate while the other gave only a diacetate. Of particular significance was the fact that the triacetate analyzed correctly for the expected **4c** while the diacetate contained no nitro group. The latter fact was confirmed by the substantial upfield shift of the imidazole ring protons from 7.16 and 7.37 ppm (in **4c**) to 6.64 and 6.69 ppm. Based upon analytical and NMR data we conclude that the second product is the O^2,2′-anhydronucleoside, **6a,** formed by displacement of the 2-nitro function on the imidazole ring by the cis oriented 2′-hydroxyl group.

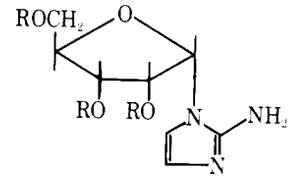
The above conclusion is supported by the ^1H and ^{13}C NMR spectra of highly enriched samples of **4b** and **6a** as compared with those of pure **5b.** As would be expected,[10] the α anomer, **4b,** showed $C_{1'}$-H at lower field (6.52 ppm) and with a larger value of $J_{1',2'}$ (4.5 Hz) than that of **5b** (6.21 ppm, $J_{1',2'}$ = 1 Hz). The ^1H NMR spectra of O^2,2′-anhydronucleosides have been investigated in some detail.[18] Typically the conversion of a pyrimidine nucleoside to the corresponding O^2,2′-anhydro derivative is accompanied by substantial downfield shifts of both $C_{1'}$-H and $C_{2'}$-H. The transformation of **4b** to **6a** leads to a similar deshielding of $C_{2'}$-H by 1.05 ppm. The $C_{1'}$ proton, however, undergoes a 0.35 ppm upfield shift that can be explained by a general increase in the electronegativity of the imidazole ring upon displacement of the nitro function. The somewhat unusual nucleophilic displacement of the nitro group[19] is confirmed by elemental analyses, by the upfield shift of the imidazole protons (see above), and by ^{13}C NMR spectroscopy, which shows a shift of C_2 from 144.47 ppm in **4b** to 159.72 ppm in **6a.** This deshielding is similar to that observed for C_1 in going from nitrobenzene (148.3 ppm) to anisole (158.9 ppm).[20] As would be expected,[21] the α and β nucleosides, **4b** and **5b,** showed positive and negative Cotton effects, respectively, in their ORD spectra.

Reduction of the nitro groups in **4a** and **5a** was readily achieved in the presence of Raney nickel, giving 2-amino-1-(2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl)imidazole (**9a**) and

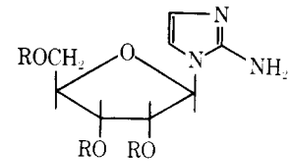
its β anomer (**10a**), respectively. Each of these anomers could then be debenzoylated with methanolic ammonia to give the crystalline triols **9b** and **10b** without difficulty. Once again, while the values of $J_{1',2'}$ (4 Hz for **9b** and 5 Hz for **10b**) are not diagnostic of anomeric configuration, $C_{1'}$-H in the α anomer is, as expected,[10] deshielded by 0.29 ppm relative to its β counterpart. In addition, the ^{13}C NMR spectra of **9b** and **10b**, as was the case with the nitroimidazoles **4b** and **5b**, showed the expected 2–5 ppm shielding of $C_{1'}$ and $C_{2'}$ in the α anomers due to steric crowding.[22,23]

In our preceding paper[1] we reported that condensation of 2-aminoimidazole with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of stannic chloride and mercuric cyanide led to glycosylation of the exocyclic amino group rather than the expected ring nitrogen. Subsequently we observed that treatment of 2-aminoimidazolium sulfate with hexamethyldisilazane led to the formation of crystalline, but unstable, bis(trimethylsilyl) derivative (NMR analysis). Condensation of this material with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide[9] in the presence of mercuric cyanide led to only one significant product with the mobility expected for a protected nucleoside. This substance was chromatographically isolated in 26% yield and proved to be identical with **10a** obtained via reduction of **5a**.

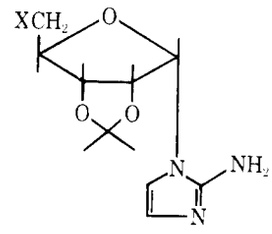
Before clarification of the totally unexpected stereochemistry of **4a** discussed above, we attempted to show that this



9a, R = Bz
b, R = H



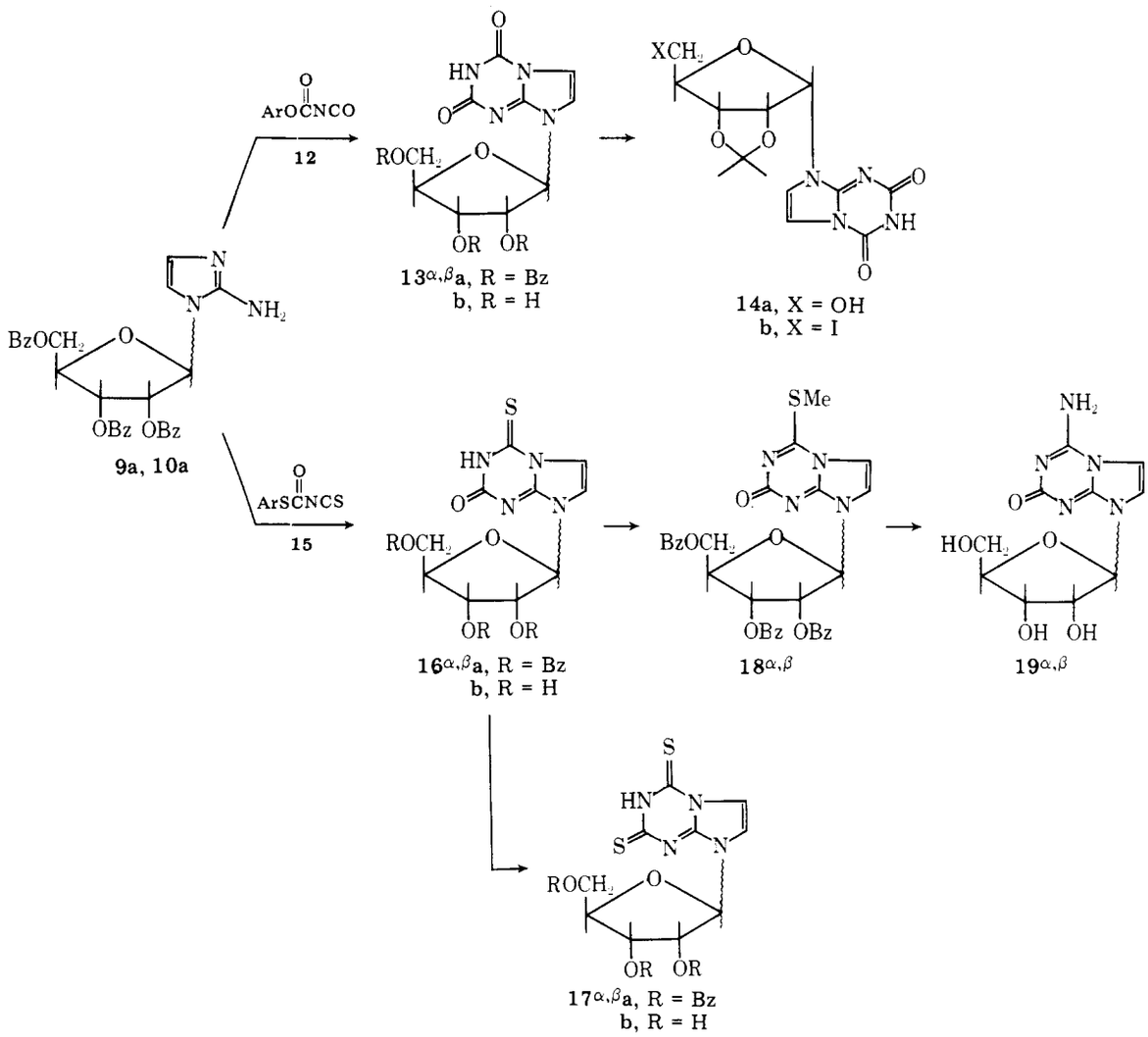
10a, R = Bz
b, R = H



11a, X = OH
b, X = I

substance was indeed the β anomer, **5a**, via formation of a cyclonucleoside. Thus, the reduced and debenzoylated nucleoside, **9b**, was converted into the 2',3'-acetonide (**11a**) and then treated with methyltriphenoxyphosphonium iodide.[24] In this way 2-amino-1-(5-deoxy-5-iodo-2,3-*O*-isopropylidene-α-D-ribofuranosyl)imidazole (**11b**) was isolated in an overall yield of 79% from **9b**. As would be expected in view of

Scheme I[a]



[a] Compounds **13** and **16–19** have been prepared in both the α- and β-anomeric series and are designated by superscripts. Thus, **16**$^{\alpha}$**a** refers to the pure α anomer of **16a**.

the actual α configuration, **9b** showed no tendency to form a cyclonucleoside upon heating in inert solvents. This sequence has not been repeated with the β isomer **10b.**

Since both anomers (**9a** and **10a**) of the 2-aminoimidazole nucleosides were available, we have investigated their annulation to variously functionalized 5-aza-7-deazapurine nucleosides through reactions with aryloxycarbonyl isocyanates and related compounds[25] as outlined in Scheme I.

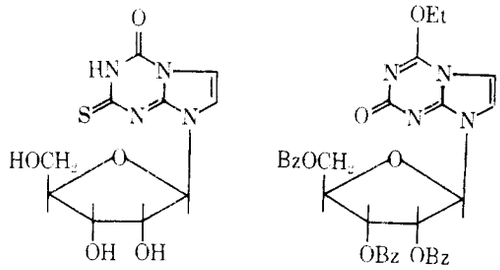
Treatment of **9a** and **10a** with phenoxycarbonyl isocyanate (**12**)[26] in dioxane at room temperature readily led, respectively, to the α and β anomers of 8-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*,8*H*)-dione (**13$^{\alpha}$a** and **13$^{\beta}$a**), which were isolated by chromatography on silicic acid. Much precedent exists for the conversion of aminoazoles to functionalized triazine derivatives through the use of reagents related to **12**,[25] and the homogeneity of the products is assured by analytical, spectroscopic, and chromatographic data. Debenzoylation of **13$^{\alpha}$a** and **13$^{\beta}$a** was effected with methanolic ammonia and led to the crystalline triols, **13$^{\alpha}$b** and **13$^{\beta}$b**, in yields of 73 and 85%, respectively. Once again, before the α-anomeric configuration of **4a** (and hence **9a**) had been established, **13$^{\alpha}$b** was converted into the crystalline 2′,3′-acetonide, **14a**, and then treated with methyltriphenoxyphosphonium iodide to give the 5′-iodo derivative **14b.** As would be expected from its α configuration, **14b** showed no tendency to be transformed into a cyclonucleoside upon heating at 100 °C in dimethylformamide, dimethyl sulfoxide, or hexamethylphosphoramide.

In order to obtain analogues of **13$^{\alpha,\beta}$** in which the heterocyclic ring bears different substituents at C_2 and C_4, **9a** and **10a** were reacted with *S*-phenylthiocarbonyl isothiocyanate (**15**) prepared in situ from *S*-phenyl chlorothioformate and potassium thiocyanate.[1] We have previously found **15** to give higher yields of heterocycles than the more common phenoxycarbonyl isothiocyanate.[1] The reactions above took place readily in ethyl acetate at room temperature and gave, after chromatographic isolation, the α and β anomers of 8-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2(8*H*)-one-4(3*H*)-thione (**16$^{\alpha}$a** and **16$^{\beta}$a**) in yields of 33 and 36%, respectively. The decreased yields of **16$^{\alpha,\beta}$a** relative to those of the dioxo compounds, **13$^{\alpha,\beta}$a**, are consistent with our previous observations in the isomeric 1-(β-D-ribofuranosyl) series[1] and are presumably a consequence of the tendency of the intermediate thiourea to lose thiocyanic acid with formation of a carbamate.[27] Debenzoylation of **16$^{\alpha}$a** and **16$^{\beta}$a** with methanolic ammonia at room temperature gave the crystalline free nucleosides **16$^{\alpha}$b** and **16$^{\beta}$b** in yields of 68 and 76%, respectively.

The reaction between, e.g., **10a** and **15** can clearly lead to two possible nucleosides, namely, the 2-oxo-4-thiono compound, **16$^{\beta}$a**, and the isomeric 2-thiono-4-oxo compound, **20.** Which of these compounds is formed will depend upon the relative nucleophilicities of the exocyclic amine and the ring nitrogen of **10a** and the initial point of attack of the nitrogen function on **15.** In our preceding work[1] we were faced with a similar problem of distinguishing between the 2-oxo-4-thiono (2; X = O, Y = S) and the 2-thiono-4-oxo (2; X = S, Y = O) isomers in the related 1-(β-D-ribofuranosyl) compounds. In that case a definitive answer in favor of the 2-oxo-4-thiono structure could be reached through the use of ^{13}C NMR spectroscopy. This was possible since the higher field carbonyl function (C_2) showed a small (~4 Hz) three-bond coupling to the anomeric proton.[28] In addition, the anomeric proton in **2** (X = O, Y = S) did not show the marked deshielding shown by other nucleosides bearing a thione function adjacent to the site of glycosidation.[1,29]

Unfortunately, neither of the above approaches is applicable for distinguishing between **16$^{\beta}$** and **20** since the site of glycosidation is not adjacent to a readily assignable carbonyl or thiocarbonyl group. In an effort to resolve this problem, we attempted to desulfurize **16$^{\alpha}$a** and the related *S*-methyl derivative **18$^{\alpha}$** under a variety of conditions. Treatment of these compounds with Raney nickel in dioxane gave no new products, but similar treatment of **16$^{\alpha}$a** in ethanol led to replacement of the sulfur by an ethoxyl group, giving **21** that was characterized by ^1H NMR. Treatment of **16$^{\beta}$a** with hydrogen peroxide in dilute methanolic hydrochloric acid led to the clean formation of the dioxo compound, **13$^{\beta}$a**, rather than to the expected reduction product.[30]

In view of the problems above, we turned to a degradative method to distinguish between **16$^{\beta}$b** and **20.** To this end, small samples of **16$^{\beta}$b** and the well-characterized 1-(β-D-ribofuranosyl) isomer **2** (X = O, Y = S) were hydrolyzed using 1 N hydrochloric acid at 60 °C. Both compounds gave the same crystalline imidazo[1,2-*a*]-1,3,5-triazine-2(1*H*)-one-4(3*H*)-thione (**22**) as judged by TLC behavior, UV spectra under both acidic and basic conditions, and high-resolution mass spectroscopy. Thus, the product from condensation of **10a** and **15** has the 4-oxo-4-thiono structure **16$^{\beta}$a**, the heterocyclic base being identical with that derived from **2** (X = O, Y = S). It should be noted that there is a marked difference in the rates of hydrolysis of the 1-(β-D-ribofuranoside) (**2**; X = O, Y = S) and its 8-(β-D-ribofuranosyl) isomer, **16$^{\beta}$b.** The former is completely hydrolyzed in 1 N hydrochloric acid at 60 °C within 2 h, while the latter requires roughly 28 h. A similar rapid acidic hydrolysis of the structurally related 3-(β-D-ribofuranosyl)adenine relative to that of adenosine has been reported by Leonard and Laursen.[31] Since the UV spectra of **16$^{\alpha}$b** and **16$^{\beta}$b** were essentially identical in both acidic and basic solutions, it seems safe to conclude that the same heterocyclic moiety is present in both anomers. Confirmation of this point came from acidic hydrolysis of the α anomer **16$^{\alpha}$b** as above, which once again gave **22** as judged by TLC and UV spectroscopy under a variety of conditions.



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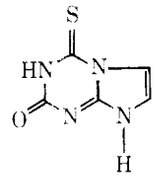
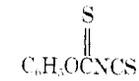
21



22



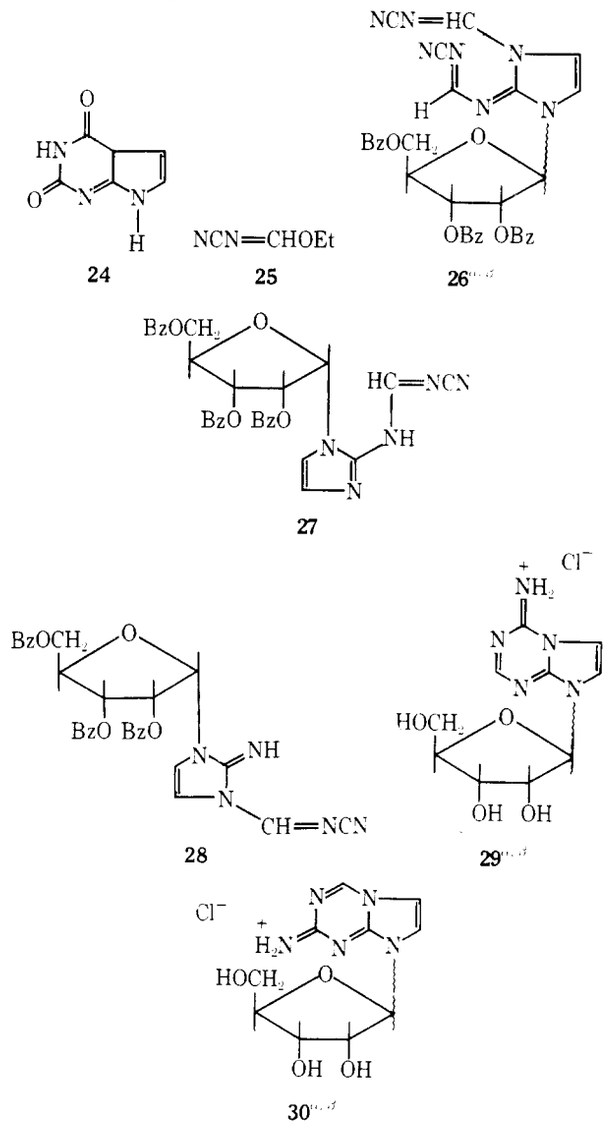
23

In our previous work[1] we showed that the reaction of **1** with *O*-phenylthiocarbonyl isothiocyanate (**23**) led to the formation of the 2,4-dithione (**2**; X, Y = S) in 30–35% yield. In contrast, the reaction of **9a** with **23** rapidly led to a plethora of products with no major component having the TLC mobility expected for the desired **17$^{\alpha}$a.** The dithiones **17$^{\alpha}$a** and **17$^{\beta}$a** could, however, be obtained in yields of 62 and 67% by treatment of the 2-oxo-4-thiono compounds **16$^{\alpha}$a** and **16$^{\beta}$a** with phosphorus pentasulfide in dioxane.[32] Debenzoylation was effected with methanolic ammonia at room temperature without any apparent displacement of the thione functions, giving the crystalline α and β anomers of 8-(D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*,8*H*)-dithione (**17$^{\alpha}$b** and **17$^{\beta}$b**) in satisfactory yields. As might be expected, replacement of the 2-oxo functions by sulfur was accompanied by a substantial

bathochromic shift in the UV spectra and a downfield shift of C_2 in the ^{13}C NMR spectrum to a position compatible with a thiourea carbon.[33] Treatment of **17** with ammonia under more forcing conditions has not been investigated.

In order to activate the 4-thiono function on the heterocyclic ring for nucleophilic displacement, **16$^{\alpha}$a** and **16$^{\beta}$a** were treated with methyl iodide in the presence of sodium bicarbonate. Following chromatography on silicic acid, the 4-methylthio derivatives, **18$^{\alpha}$** and **18$^{\beta}$**, were isolated in 51–53% yields. That alkylation had indeed occurred on sulfur was confirmed by the ^1H NMR spectra, which showed methyl singlets at 2.63 and 2.61 ppm, respectively, whereas *N*-methyl derivatives would be expected to appear at substantially lower field. Treatment of these methylthio derivatives with methanolic ammonia at room temperature led to debenzoylation and displacement of the sulfur function, giving the crystalline α and β anomers of 4-amino-8-(D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2(8*H*)-one (**19$^{\alpha}$**, **19$^{\beta}$**), both in yields of 78%. These compounds can be looked upon as 5-aza-7-deaza analogues of isoguanosine and its α anomer. Once again, the N^1-(β-D-ribofuranosyl) isomer of **19$^{\beta}$** was available from our previous work,[1] and it was of interest to examine the acidic hydrolysis of the two compounds. As was the case with the thio nucleosides **16$^{\beta}$b** and **2** (X = O, Y = S), the N^1-riboside was markedly more labile, being roughly 50% hydrolyzed after 15 h in 1 N hydrochloric acid at room temperature, while **19$^{\beta}$** remained largely unchanged. Both were completely hydrolyzed in 15 h at 60 °C in 1 N hydrochloric acid. Both isomers led to the isolation of modest yields of the same crystalline heterocycle, but elemental analyses and mass spectrometry showed this product to be imidazo[1,2-*a*]-1,3,5-triazine-2,4(1*H*,3*H*)-dione (**24**) resulting from hydrolysis of both the glycosidic bond and the 4-amino function. The modest yields of **24** are a reflection of some difficulty in the separation of the base from other reaction byproducts, but there was no clear indication of the initial formation of the desired 4-aminoimidazo[1,2-*a*]-1,3,5-triazin-2(8*H*)-one. An authentic sample of **24** could be prepared by treatment of 2-aminoimidazolium sulfate with phenoxycarbonyl isocyanate in pyridine.

A further objective of the present work was the preparation of the 5-aza-7-deaza analogue of adenosine. To this end, **9a** and **10a** were reacted at room temperature in either dioxane or ethanol with an excess of ethyl *N*-cyanoformimidate (**25**), a reagent known to convert amidines and 2-aminoazoles to aminotriazines.[34] Depending upon the conditions, these reactions normally give the aminotriazine directly or provide intermediate *N*-cyanoamidines that can be thermally cyclized. In our hands, the reactions of **9a** or **10a** with **25** led to the formation of several less polar products. The major components were isolated by chromatography and appear to be the bis adducts **26$^{\alpha}$** and **26$^{\beta}$**. While these compounds could not be isolated in analytically pure form, their ^1H NMR spectra each show the presence of two *N*-cyanoformamidine proton signals as one-proton singlets at roughtly 8.2 and 8.8 ppm, and the presence of two amidine carbons is confirmed by ^{13}C signals at 161.31 and 169.19 ppm for **26$^{\alpha}$**. Reaction with the second equivalent of **25** appears to be very rapid since a reaction between equimolar amounts of **9a** and **25** leads mainly to the bis adduct **26$^{\alpha}$** and unreacted **9a** with only traces of a mono adduct with a TLC mobility very similar to that of **9a**. Upon heating **26$^{\alpha}$** in ethanol at 45 °C for 16 h, one of the cyanoformamidine groups appears to be lost, giving a mono adduct, probably **27**, showing a single formamidine proton at 7.80 ppm. Structure **27** is preferred over the isomer **28** since the formamidine proton in the latter would be expected to have a chemical shift similar to that of the comparable proton in the bis adduct **26$^{\alpha}$**. On the other hand, the formamidine proton in **27** has a rather different environment than either of those in **26$^{\alpha}$** (assuming that **27** does not acquire an imino form). This product has not been further investigated since cyclization of **26$^{\alpha}$** or **26$^{\beta}$** could be directly achieved through mild treatment with sodium methoxide. From these reactions crystalline iminonucleoside hydrochlorides were isolated and found to have mobilities just slightly greater than that of adenosine upon borate electrophoresis in 1 M acetic acid. We consider these products to be the α and β anomers of 4(8*H*)-imino-8-(D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine hydrochloride (**29$^{\alpha}$** and **29$^{\beta}$**), although we can provide no positive evidence to exclude the isomeric 2-imino structures (**30**). We base this conclusion upon prior precedent showing that treatment of aminoazoles with **25** proceeds via initial displacement of the ethoxyl group by the exocyclic amine followed by cyclization.[34] Cyclization of the bis adducts, **26$^{\alpha,\beta}$**, presumably requires initial loss of one group, and if, as discussed above, this loss proceeds so as to give **27** and its β anomer, the 4-imino structures **29$^{\alpha,\beta}$** will result.



While the ^1H and ^{13}C NMR spectra of both anomers of **29** are completely interpretable, they unfortunately provide no unequivocal support for this structure rather than the isomer **30**. Assignments for the ^{13}C signals of all of the sugar carbons have been confirmed by single frequency proton decoupling. The heterocyclic ring carbons are specifically assigned by consideration of the proton-coupled spectrum of **29$^{\alpha}$**. Thus, a distinction between C_7 and C_6 can be made since in addition to the normal couplings to C_7-H (J = 207.5 Hz) and C_6-H (7.5 Hz), C_7 shows an additional three-bond coupling to $C_{1'}$-H (J = 4 Hz). As would be expected, the latter coupling is not ob-

served for C_6-H, which only shows one- and two-bond couplings of 210 and 11.7 Hz. The bridgehead carbon, C_{8a}, appears as a complex signal showing three-bond couplings to a number of protons. Since C_2 bears a hydrogen it appears as a doublet with J = 206 Hz at 160.99 ppm, while the C_4 imino carbon is a narrow doublet (J = 12.2 Hz) typical of meta proton coupling in heterocycles.[35] Since both C_2 and C_4 are flanked by two ring nitrogens, the assignments for these two carbons could easily be reversed as in structure **30**[α].

In general, the use of ^{13}C NMR spectroscopy has been of great value in the course of the work described in this and the preceding paper.[1] Throughout the present work the expected upfield shifts of $C_{1'}$ and $C_{2'}$ are evident in each of the β anomers relative to their α counterparts. The chemical shifts of the C_2 and C_4 carbons are in general diagnostic of the functional modifications introduced and are closely paralleled in both the α and β series. Definitive assignments of the imidazole carbons C_6 and C_7 are made on the basis of the 3–5 Hz three-bond couplings of C_7 to the anomeric proton in the proton-coupled spectra, while C_{8a} is characteristically of low amplitude and exhibits a number of proton couplings.

The various final products in this work have been subjected to a general biological screen through the cooperation of Shionogi Research Laboratories, Osaka, Japan.[36] With the exception of **29**[β] (but not the α anomer), which showed cytotoxicity against HeLa and L-1210 cells in culture (ED_{50} 2.6 and 0.5 μg/mL), none of the compounds showed significant activities in vitro against a variety of bacteria, viruses, and fungi or against L-1210 leukemia in mice.

The general procedures developed in this and the preceding paper[1] make functionalized imidazo[1,2-*a*]-1,3,5-triazine nucleosides readily available and suggest a number of interesting possibilities for further work.

Experimental Section

General Methods. The general methods used were described in a preceding paper.[1]

1-(2,3,5-Tri-*O*-benzoyl-α-D-ribofuranosyl)-2-nitroimidazole (4a). (a) Stannic chloride (1.0 mL, 8 mmol) was added to a stirred solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (2.02 g, 4 mmol) in acetonitrile (80 mL) in the presence of 2-nitroimidazole (540 mg, 4.8 mmol) and mercuric cyanide (2.0 g, 8 mmol) at 60 °C. After 75 min, the clear solution was cooled and evaporated, leaving a foam that was dissolved in chloroform and filtered. The filtrate was washed with saturated aqueous sodium bicarbonate, 40% potassium iodide, and water (two times), dried ($MgSO_4$), and evaporated. The residue was chromatographed on a column of silica gel G (100 g) using benzene–ethyl acetate (9:1) to give 1.36 g (61%) of pure **4a** as a foam. Subsequently this material was crystallized from dichloromethane–methanol with mp 138.5–140 °C: λ_{max} (MeOH) 230 nm (ε 40 500), 275 (4900), 283 (5300), 317 (7300).

Anal. Calcd for $C_{29}H_{23}N_3O_9$ (557.50): C, 62.47; H, 4.16; N, 7.54. Found: C, 62.20; H, 4.27; N, 7.63.

(b) A mixture of 2-nitroimidazole (41 mg, 0.36 mmol),[3] hexamethyldisilazane (2 mL), and ammonium sulfate (5 mg) was heated under reflux in pyridine (0.5 mL) for 1 h. The solvents were then removed in vacuo at room temperature leaving a solid residue of crude trimethylsilyl derivative. This was dissolved in anhydrous acetonitrile (5 mL)[37] together with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (150 mg, 0.3 mmol), and stannic chloride (0.07 mL, 0.6 mmol) was added. The mixture was heated at 60 °C for 1 h and then evaporated to dryness. A solution of the residue in chloroform was washed with aqueous sodium bicarbonate and water and then purified by preparative TLC using three developments with benzene–ethyl acetate (9:1), giving 64 mg (38%) of **4a** that was identical with that from method a by melting point and NMR. By TLC the presence of a minor amount of the β isomer could also be detected in the crude reaction.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-2-nitroimidazole. Stannic chloride (0.060 mL, 0.52 mmol) was added in a drybox to a solution of penta-*O*-acetyl-α-D-glucopyranose (100 mg, 0.26 mmol) and mercuric cyanide (131 mg, 0.52 mmol) in acetonitrile (8 mL) containing a suspension of **3** (35 mg, 0.31 mmol). The resulting solution was heated at 60 °C for 1.5 h and then evaporated to dryness. A filtered solution of the residue in methylene chloride (20 mL) was shaken with saturated aqueous sodium bicarbonate, and after filtration the organic phase was washed with 30% aqueous potassium iodide and water. The organic phase was dried and evaporated, leaving 110 mg of a syrup containing predominantly one product. This substance was purified by preparative TLC using toluene–ethyl acetate (3:2), giving 70 mg (61%) of the title compound as a homogeneous foam: ^1H NMR ($CDCl_3$) 1.87, 1.98, 2.03, 2.05 (s, 3, OAc), 3.9–4.2 (m, 2, $C_{5'}$-H, $C_{6'a}$-H), 4.30 (dd, 1 $J_{6'a,6'b}$ = 12 Hz, $J_{5',6'b}$ = 5 Hz, $C_{6'b}$-H), 5.1–5.5 (m, 3, $C_{2'}$-H, $C_{3'}$-H, $C_{4'}$-H), 6.41 (s, 1, $J_{1',2'}$ = 8.5 Hz, $C_{1'}$-H), 7.15, 7.34 (d, 1, J = 1.5 Hz, C_4-H, C_5-H) ppm; ^{13}C NMR ($CDCl_3$)[38] 20.19, 20.51, 20.64 (CH_3CO), 61.54 ($C_{6'}$), 67.81 ($C_{4'}$), 71.03 ($C_{3'}$), 72.95 ($C_{5'}$), 75.42 ($C_{2'}$), 83.22 ($C_{1'}$), 121.84 (C_5), 129.92 (C_4), 144.79 (C_2), 169.18, 169.54, 169.93, 170.58 (CH_3CO) ppm; λ_{max} (MeOH) 219 nm (ε 4400), 309 (6400); ORD (MeOH) $[\Phi]^{pk}_{365}$ 6800°, $[\Phi]_{325}$ 0°, $[\Phi]^{tr}_{260}$ −24 200°.

Anal. Calcd for $C_{17}H_{21}N_3O_{11}$ (443.36): C, 46.05; H, 4.77; N, 9.48. Found: C, 45.80; H, 4.81; N, 9.22.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2-nitroimidazole (5a). 2-Nitroimidazole (14.9 g, 132 mmol)[3] was added to a stirred solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide [from 60.5 g (120 mmol) of the β-1-*O*-acetate according to Stevens et al.[9]] and mercuric cyanide (91 g, 350 mmol) in anhydrous acetonitrile (2.4 L) and heated at 60 °C for 2.5 h. The solvent was then evaporated, and the residue was dissolved in dichloromethane (1 L) and filtered. The filtrate was washed with saturated aqueous sodium bicarbonate, 30% potassium iodide, and water. The dried ($MgSO_4$) phase was evaporated, leaving a syrup which was chromatographed on a column of silica gel G (3 kg) using benzene–ethyl acetate (9:1) to give 45.4 g (68%) of **5a** contaminated with a trace of 2,3,5-tri-*O*-benzoyl-D-ribofuranose. This material could not be induced to crystallize and was used as such in the next steps. An analytical sample was prepared by preparative TLC using three developments with benzene–ethyl acetate (9:1): λ_{max} (MeOH) 231 nm (ε 43 700), 275 (5300), 283 (5700), 305 (6800).

Anal. Calcd for $C_{29}H_{23}N_3O_9$ (557.50): C, 62.47; H, 4.16; N, 7.54. Found: C, 62.44; H, 4.36; N, 7.13.

1-(β-D-Ribofuranosyl)-2-nitroimidazole (5b). A solution of **5a** (280 mg, 0.4 mmol) in methanolic sodium methoxide (2.0 mL, 0.05 M) was kept at room temperature for 2.5 h, leading to direct crystallization of 75 mg of **5b**. Preparative TLC of the filtrates using chloroform–methanol (4:1) gave a further 4 mg (total yield 81%) of crystalline **5b** with mp 188–190 °C dec. This material was identical (NMR) with a sample of **5b** provided by Professor L. B. Townsend:[5] λ_{max} (MeOH, H^+) 222 nm (ε 3300), 325 (7500); λ_{max} (MeOH, OH^-) 220 nm (ε 4000), 325 (7400); ORD (H_2O) $[\Phi]^{pk}_{331}$ 17 500°, $[\Phi]_{300}$ 0°, $[\Phi]^{tr}_{273}$ −22 600°.

1-(α-D-Ribofuranosyl)-2-nitroimidazole (4b) and the 2,2′-Anhydronucleoside (6a). A solution of **4a** (557 mg, 1 mmol) in methanolic sodium methoxide (2 mL, 0.22 M) was stored at room temperature for 4 h and then neutralized and evaporated. The residue was partitioned between water and ethyl acetate, and the aqueous phase was evaporated and triturated with ethanol, giving 104 mg (43%) of TLC homogeneous **4b** that was predominantly one product (**4b**) by NMR analysis: λ_{max} (0.1 N HCl and 0.1 N NaOH) 327 nm; ORD (H_2O) $[\Phi]^{tr}_{335}$ −11 100°, $[\Phi]_{303}$ 0°, $[\Phi]^{pk}_{274}$ 17 000°.

Acetylation, as below, gave the triacetate **4c.**

Continued treatment as above, or treatment of **4b** with saturated methanolic ammonia at room temperature for 16 h, led to formation of the 2,2′-anhydronucleoside **6a,** which is chromatographically identical with **4b.** A preparation containing roughly equal amounts of **4b** and **6a** was prepared using the ammonia treatment. A sample of this mixture (25 mg, ~0.1 mmol) was treated for 4 h at room temperature with acetic anhydride (0.1 mL) in pyridine (0.5 mL) and then evaporated to dryness. Preparative TLC using chloroform–acetone (4:1) gave two well-resolved bands detected with iodine or a hot wire. Elution of the faster band gave 10 mg (~27%) of the pure triacetate (**4c**) as a syrup.

Anal. Calcd for $C_{14}H_{17}N_3O_9$ (371.30): C, 45.28; H, 4.62; N, 11.32. Found: C, 45.27; H, 4.87; N, 10.80.

Elution of the slower band gave 9 mg (~32%) of pure **6b,** which spontaneously crystallized with mp 91–93 °C.

Anal. Calcd for $C_{12}H_{14}N_2O_6$ (282.25); C, 51.06; H, 5.00; N, 9.93. Found: C, 50.61; H, 5.21; N, 9.56.

2-Amino-1-(2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl)imidazole (9a). A solution of **4a** (18.0 g, 32.3 mmol) in ethyl acetate (1.7 L) was reduced under 1 atmosphere of hydrogen at room temperature for 1.5 h in the presence of Raney nickel (85 g). The mixture was filtered through Celite, and the filtrate was evaporated to a syrup that was chromatographed on a column of silica gel (1.6 kg) using chloroform–methanol (19:1) to give 12.1 g (71%) of **9a** as a homogeneous

white foam: λ_{max} (MeOH) 229 nm (ε 42 000), 269 (2900), 275 (3200), 282 (2700).

Anal. Calcd for $C_{29}H_{25}N_3O_7$ (527.50): C, 66.03; H, 4.78; N, 7.97. Found: C, 66.20; H, 4.82; N, 8.08.

2-Amino-1-(α-D-ribofuranosyl)imidazole (9b). A solution of **9a** (1.06 g, 2 mmol) in methanolic ammonia (25 mL) was stored at room temperature for 20 h and then evaporated. A methanolic solution of the residue was treated with charcoal (400 mg), evaporated, and crystallized from ethanol, to give 360 mg (83%) of **9b** with mp 198–200 °C: λ_{max} (0.1 N HCl) 213 nm (ε 8000).

Anal. Calcd for $C_8H_{13}N_3O_4$ (215.20): C, 44.65; H, 6.09; N, 19.53. Found: C, 44.67; H, 6.25; N, 19.49.

2-Amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole (10a). (a) Reduction of **5a** (20.0 g, 36 mmol) in the presence of Raney nickel at room temperature for 90 min was conducted as described for **4a.** Chromatography on a column of silica gel (3 kg) using chloroform–methanol (9:1) gave 25.8 g (68%) of **10a** as a foam: λ_{max} (MeOH) 229 nm (ε 42 000), 274 (3000), 281 (2400).

Anal. Calcd for $C_{29}H_{25}N_3O_7$ (527.50): C, 66.03; H, 4.78; N, 7.97. Found: C, 66.16; H, 4.97; N, 8.12.

(b) Finely powdered 2-aminoimidazolium sulfate (530 mg, 4 mmol)[4] was suspended in hexamethyldisilazane (7 mL) and heated under reflux for 1.5 h. Excess reagent was evaporated in vacuo, and the residue was distilled at 0.4 mm pressure in a Kugelrohr apparatus[39] with an oven temperature of 60–70 °C, giving 0.55 g (60%) of crystalline bis(trimethylsily) derivative which was unstable and became yellow upon storage. This material was directly reacted with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (from 1.08 g (2 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose[9]) and finely powdered mercuric cyanide (1.52 g, 6 mmol) in benzene (40 mL) under reflux for 2 h. After evaporation of the solvent, a filtered solution of the residue in chloroform was washed with 30% aqueous potassium iodide and water. The dried solution was evaporated, leaving a foam that was chromatographed on a column containing 120 g of silica gel using chloroform–methanol (39:1) to give 278 mg (26%) of **10a** as a foam, identical with that from method a by TLC and NMR.

2-Amino-1-(β-D-ribofuranosyl)imidazole (10b). Debenzoylation of **10a** (528 mg, 1 mmol) with methanolic ammonia (12 mL) was done as above for **9a.** Preparative TLC of the crude product using chloroform–methanol (7:3) followed by crystallization from aqueous ethanol gave 129 mg (60%) of **10b** with mp 136–137 °C.

Anal. Calcd for $C_8H_{13}N_3O_4 \cdot 0.5H_2O$ (224.21): C, 42.85; H, 6.29; N, 18.74. Found: C, 42.95; H, 6.22; N, 18.83.

2-Amino-1-(5-deoxy-5-iodo-2,3-*O*-isopropylidene-α-D-ribofuranosyl)imidazole (11b). Perchloric acid (40 μL of 70%) was added to a stirred suspension of **9b** (65 mg, 0.3 mmol) in acetone (15 mL) and 2,2-dimethoxypropane (0.3 mL). After 15 min the clear solution was neutralized with ammonia and evaporated to dryness. The residue was purified by preparative TLC using chloroform–methanol (4:1); elution of the major band gave 91 mg of the acetonide **11a** as an extremely hygroscopic foam. This material (25 mg, ~0.1 mmol) was reacted with methyltriphenoxyphosphonium iodide (91 mg, 0.2 mmol) in dimethylformamide (1.7 mL) containing pyridine (17 μL, 0.2 mmol) at room temperature for 1 h. The solution was evaporated, and the residue was purified by preparative TLC using chloroform–methanol (4:1) to give 24 mg (79% from **9b**) of **11b** as a foam that was homogeneous by NMR and was not further characterized.

8-(2,3,5-Tri-*O*-benzoyl-α-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*,8*H*)-dione (13$^{\alpha}$a). A solution of phenoxycarbonyl isocyanate (0.40 mL, 3 mmol)[26] in dioxane (4 mL) was added dropwise over 30 min at room temperature to a stirred solution of **9a** (1.06 g, 2 mmol) in dioxane. After a further 3 h, methanol (1 mL) was added and the solvent was evaporated. The residue was purified by preparative TLC using chloroform–methanol (9:1) to give 1.10 g (92%) of almost completely pure **13$^{\alpha}$a** as a foam that was suitable for direct use. An analytical sample was prepared by preparative TLC using chloroform–methanol (19:1) λ_{max} (MeOH) 230 nm (ε 46 300), 256 sh (12 400), 281 sh (3800).

Anal. Calcd for $C_{31}H_{24}N_4O_9$ (596.50): C, 62.41; H, 4.06; N, 9.39. Found: C, 62.31; H, 4.27; N, 9.31.

8-(α-D-Ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*,8*H*)-dione (13$^{\alpha}$b). A solution of **13$^{\alpha}$a** (131 mg, 0.22 mmol) in saturated methanolic ammonia (3 mL) was kept at room temperature for 48 h and then evaporated to dryness. The residue was purified by preparative TLC using chloroform–methanol (4:1), and the major product was crystallized from water, giving 45 mg (73%) of **13$^{\alpha}$b** with mp 182–183 °C: λ_{max} (0.1 N HCl) 235 nm (ε 10 800), 256 (10 800).

Anal. Calcd for $C_{10}H_{12}N_4O_6$ (284.20): C, 42.25; H, 4.26; N, 19.71. Found: C, 42.24; H, 4.37; N, 19.89.

If the hydrolysis was run using unpurified **13$^{\alpha}$a** and **13$^{\alpha}$b** was isolated by direct crystallization from methanol without chromatography, the product crystallized together with a mole of urea arising from excess **12.** This form had mp 191–192 °C and was identical with the free compound by NMR.

Anal. Calcd for $C_{10}H_{12}N_4O_6 \cdot CO(NH_2)_2$ (344.26): C, 38.37; H, 4.68; N, 24.41. Found: C, 38.34; H, 4.50; N. 24.24.

8-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*,8*H*)-dione (13$^{\beta}$a). A reaction between **10a** (1.06 g, 2 mmol) and phenoxycarbonyl isocyanate (0.4 mL, 3 mmol) was carried out as for **9a.** Chromatography of the crude product on a column of silica gel G (100 g) using chloroform–acetone (9:1) gave 800 mg (67%) of pure **13$^{\beta}$a** as a white foam: λ_{max} (MeOH) 231 nm (ε 49 500), 255 sh (11 900), 281 sh (3000).

Anal. Calcd for $C_{31}H_{24}N_4O_9$ (596.50): C, 62.41; H, 4.06; N, 9.39. Found: C, 62.31; H, 4.27; N, 9.31.

8-(β-D-Ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4-(3*H*,8*H*)-dione (13$^{\beta}$b). A solution of **13$^{\beta}$a** (700 mg, 1.17 mmol) in saturated methanolic ammonia (20 mL) was kept at room temperature for 16 h and then evaporated to dryness. The residue was partitioned between ethyl acetate and water, and the aqueous phase was evaporated and crystallized from aqueous ethanol, giving 256 mg of **13$^{\beta}$b** as a hemihydrate with mp 175–177 °C. Preparative TLC of the mother liquors using chloroform–methanol (7:3) gave a further 26 mg (total yield 85%) of **13$^{\beta}$b.** An analytical sample had mp 177–178 °C: λ_{max} (0.1 N HCl) 234 nm (ε 10 700), 256 (10 300); λ_{max} (0.1 N NaOH) 239 nm (ε 11 400), 249 (12 500).

Anal. Calcd for $C_{10}H_{12}N_4O_6 \cdot 0.5H_2O$ (293.20): C, 40.96; H, 4.47; N, 19.11. Found: C, 41.13; H, 4.47; N, 19.22.

8-(2,3-*O*-Isopropylidene-α-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*,8*H*)-dione (14a). Perchloric acid (20 μL, 70%) was added to a stirred suspension of **13$^{\alpha}$b** (60 mg, 0.2 mmol) in acetone (10 mL) and 2,2-dimethoxypropane (0.2 mL). After 1.5 h the clear solution was neutralized with 1 N ammonium hydroxide and evaporated. The residue was purified by preparative TLC using chloroform–methanol (4:1) and crystallized from acetone–methanol (2:1), giving 59 mg (87%) of **14a** with mp 217–219 °C: λ_{max} (0.1 N HCl) 234 nm (ε 10 900), 256 (10 800).

Anal. Calcd for $C_{13}H_{16}N_4O_6$ (324.29): C, 48.15; H, 4.97; N, 17.28. Found: C, 47.98; H, 4.91; N, 17.12.

8-(5-Deoxy-5-iodo-2,3-*O*-isopropylidene-α-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*,8*H*)-dione (14b). A solution of **14a** (32 mg, 0.1 mmol) and methyltriphenoxyphosphonium iodide (65 mg, 0.14 mmol) in dimethylformamide (1.2 mL) containing pyridine (10 μL, 0.14 mmol) was kept at room temperature for 1 h and at 60 °C for 1 h. After evaporation, the residue was purified by preparative TLC using chloroform–methanol (9:1), giving 41 mg (95%) of **14b** as a pure, white foam with a UV spectrum identical with that of **14a.** This compound was characterized only by NMR. It remained unchanged after heating at 100 °C for 4 h in dimethylformamide, dimethyl sulfoxide, or hexamethylphosphoramide.

8-(2,3,5-Tri-*O*-benzoyl-α-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-2(8*H*)-one-4(3*H*)-thione (16$^{\alpha}$a). A mixture of *S*-phenyl chlorothioformate (2.5 mL, 20 mmol) and potassium thiocyanate (2.06 g, 21 mmol) was stirred at room temperature for 75 min in ethyl acetate (50 mL). A solution of **9a** (5.28 g, 10 mmol) in ethyl acetate (50 mL) was then added to the yellow solution, and the mixture was stirred at room temperature for 2.5 h. Following the addition of methanol (5 mL) and evaporation of the solvent, the residue was chromatographed on a column of silica gel G (500 g) using chloroform–acetone (19:1 and 9:1) to give 2.04 g (33%) of **16$^{\alpha}$a** as a white foam: λ_{max} (MeOH) 230 nm (ε 40 800), 270 (14 400), 300 (11 200).

Anal. Calcd for $C_{31}H_{24}N_4O_8S$ (612.60): C, 60.78; H, 3.95; N, 9.15. Found: C, 60.46; H, 3.94; N, 9.11.

9-(α-D-Ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-2(8*H*)-one-4(3*H*)-thione (16$^{\alpha}$b). A solution of **16$^{\alpha}$a** (860 mg, 1.4 mmol) in saturated methanolic ammonia (20 mL) was stored at room temperature for 48 h and then evaporated. The residue was purified by preparative TLC using chloroform–methanol (4:1), and the eluted major band was decolorized with charcoal and crystallized from water, giving 284 mg (68%) of **16$^{\alpha}$b** with mp 138–140 °C: λ_{max} (0.1 N HCl) 252 nm (ε 13 500), 268 (15 000), 299 (11 500); λ_{max} (0.1 N NaOH) 248 nm (ε 18 000), 280 (16 000); ORD (H_2O) $[\Phi]^{pk}_{279}$ 8600°, $[\Phi]_{271}$ 0°, $[\Phi]^{tr}_{258}$ −18 700°.

Anal. Calcd for $C_{10}H_{12}N_4O_5S \cdot H_2O$ (318.30): C, 37.73; H, 4.43; N, 17.60. Found: C, 37.87; H, 4.61; N, 17.60.

8-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-2(8*H*)-one-4(3*H*)-thione (16$^{\beta}$a). The reaction of **10a** (5.28 g, 10 mmol) with **15** (prepared in situ as above for **9a**) in ethyl acetate at room temperature for 2.5 h was carried out as above for

16$^{\alpha}$a. Chromatography on a column of silica gel (500 g) using benzene–ethyl acetate (4:1) gave 2.2 g (36%) of **16$^{\beta}$a** as a white foam that resisted crystallization: λ_{max} (MeOH) 230 nm (ϵ 41 800), 271 (15 600), 299 (13 000).

Anal. Calcd for $C_{31}H_{24}N_4O_8S$ (612.60): C, 60.78; H, 3.95; N, 9.15. Found: C, 60.46; H, 3.94; N, 9.11.

8-(β-D-Ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-2(8*H*)-one-4(3*H*)-thione (16$^{\beta}$b). A solution of **16$^{\beta}$a** (660 mg, 1.07 mmol) in saturated methanolic ammonia (20 mL) was stored at room temperature for 17 h and then evaporated. An aqueous solution of the residue (2 mL) was washed three times with ethyl acetate (1 mL) and evaporated. The crystalline residue was crystallized from aqueous ethanol, giving 246 mg (76%) of **16$^{\beta}$b** with mp 181.5–182.5 °C: λ_{max} (0.1 N HCl) 251 nm (ϵ 12 600), 269 (13 900), 299 (11 400); λ_{max} (0.1 N NaOH) 248 nm (ϵ 16 600), 280 (15 500).

Anal. Calcd for $C_{10}H_{12}N_4O_5S$ (300.30): C, 39.99; H, 4.03; N, 18.66. Found: C, 39.82; H, 4.13; N, 18.82.

8-(2,3,5-Tri-*O*-benzoyl-α-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*,8*H*)-dithione (17$^{\alpha}$a). A solution of **16$^{\alpha}$a** (920 mg, 1.5 mmol) and phosphorus pentasulfide (1.5 g, 6.75 mmol) in dioxane (75 mL) was heated at 80 °C for 1.5 h and then evaporated. A filtered solution of the residue in chloroform was evaporated, and the residue was purified by chromatography on a column of silicic acid (80 g) using benzene–ethyl acetate (9:1), giving 588 mg (62%) of **17$^{\alpha}$a** as a homgeneous foam. An analytical sample was prepared by preparative TLC using benzene–ethyl acetate (4:1): λ_{max} (MeOH) 230 nm (ϵ 38 300), 297 (30 500), 312 sh (27 700).

Anal. Calcd for $C_{31}H_{24}N_4O_7S_2$ (628.70): C, 59.22; H, 3.85; N, 8.91. Found: C, 59.21; H, 4.01; N, 8.86.

8-(2,3,5-Tri-*O*-benzoyl-α-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*,8*H*)-dithione (17$^{\beta}$a). Thiation of **16$^{\beta}$a** (1.84 g, 3 mmol) with phosphorus pentasulfide (3.3 g, 15 mmol) in dioxane (150 mL) at 80 °C for 2 h was conducted as described for **16$^{\alpha}$a.** Chromatography on a column of silica gel Grade 81 (165–300 mesh) from R. J. Schoop and Assoc., Moraga, Calif., (200 g) using benzene containing 5% and then 7% ethyl acetate gave 1.26 g (67%) of **17$^{\beta}$a** as a homogeneous, pale yellow foam: λ_{max} (MeOH) 230 nm (ϵ 40 500), 296 (31 200), 315 sh (26 400).

Anal. Calcd for $C_{31}H_{24}N_4O_7S_2$ (628.70): C, 59.22; H, 3.85; N, 8.91. Found: C, 58.98; H, 4.13; N, 8.70.

8-(α-D-Ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4-(3*H*,8*H*)-dithione (17$^{\alpha}$b). A solution of **17$^{\alpha}$a** (670 mg, 1.07 mmol) in saturated methanolic ammonia (10 mL) was kept at room temperature for 21 h and then evaporated. The residue was purified by preparative TLC using chloroform–methanol (4:1) followed by crystallization from water to give 191 mg (57%) of **17$^{\alpha}$b** with mp 151–152 °C: λ_{max} (0.1 N HCl) 293 nm (ϵ 34 900), 310 sh (25 000); λ_{max} (0.1 N NaOH) 289 nm (ϵ 27 000), 306 (29 200).

Anal. Calcd for $C_{10}H_{12}N_4O_4S_2$ (316.40): C, 37.96; H, 3.82; N, 17.71. Found: C, 37.75; H, 3.82; N, 17.59.

8-(β-D-Ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4-(3*H*,8*H*)-dithione (17$^{\beta}$b). A solution of **17$^{\beta}$a** (1.0 g, 1.59 mmol) in methanolic ammonia (25 mL) was stored at room temperature for 18 h and then evaporated. A solution of the residue in aqueous methanol was rapidly treated with Dowex 50 (H^+) resin, filtered, and evaporated. The residue was crystallized from water, giving 310 mg (62%) of **17$^{\beta}$b** with mp 168–169 °C: λ_{max} (0.1 N HCl) 294 nm (ϵ 35 300), 310 sh (25 600); λ_{max} (0.1 N NaOH) 291 nm sh (ϵ 25 400), 306 (27 900).

Anal. Calcd for $C_{10}H_{12}N_4O_4S_2$ (316.40): C, 37.96; H, 3.82; N, 17.71. Found: C, 38.00; H, 3.84; N, 17.65.

8-(2,3,5-Tri-*O*-benzoyl-α-D-ribofuranosyl)-4-methylthioimidazo[1,2-*a*]-1,3,5-triazin-2(8*H*)-one (18$^{\alpha}$). Methyl iodide (0.43 mL, 6.9 mmol) was added to a solution of **16$^{\alpha}$a** (1.41 g, 2.3 mmol) in a mixture of dioxane (5 mL) and methanol (10 mL) in the presence of sodium bicarbonate (232 mg, 2.76 mmol). After stirring at room temperature for 32 h, the mixture was evaporated and the residue was chromatographed on a column of silica gel (150 g) using chloroform containing 30% and 40% acetone to give 757 mg (53%) of pure **18$^{\alpha}$** as a foam. An analytical sample was prepared by preparative TLC using chloroform–methanol (19:1): λ_{max} (MeOH) 233 nm (ϵ 53 200), 257 sh (15 400), 272 sh (7500), 282 sh (6100), 298 sh (2900).

Anal. Calcd for $C_{32}H_{26}N_4O_8S$ (626.63): C, 61.33; H, 4.18; N, 8.94. Found: C, 61.37; H, 4.33; N, 9.25.

8-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4-methylthioimidazo[1,2-*a*]-1,3,5-triazin-2(8*H*)-one (18$^{\beta}$). A reaction between **16$^{\beta}$a** (1.53 g, 2.5 mmol) and methyl iodide (0.47 mL, 7.5 mmol) in the presence of sodium bicarbonate (315 mg, 3.75 mmol) was conducted as described for **16$^{\alpha}$a** and gave 792 mg (51%) of **18$^{\beta}$** as a homogeneous, white foam: λ_{max} (MeOH) 233 nm (ϵ 54 900), 255 sh (17 100), 274 sh (7800), 283 sh (6800), 300 sh(3300).

Anal. Calcd for $C_{32}H_{26}N_4O_8S$ (626.63): C, 61.33; H, 4.18; N, 8.94. Found: C, 61.37; H, 4.33; N, 9.25.

4-Amino-8-(α-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-2(8*H*)-one (19$^{\alpha}$). A solution of **18$^{\alpha}$** (752 mg, 1.2 mmol) in saturated methanolic ammonia (12 mL) was stored at room temperature for 24 h and then evaporated. The residue was triturated three times with acetone (1 mL), and the resulting solid was crystallized from water, giving 282 mg (78%) of **19$^{\alpha}$** as a hydrate with mp 192–193 °C: λ_{max} (0.1 N HCl) 243 nm (ϵ 12 200), 265 sh (6700); λ_{max} (0.1 N NaOH) 247 nm (ϵ 12 700); $[\alpha]^{20}_D$ −6.2° (*c* 0.6, 0.1 N HCl).

Anal. Calcd for $C_{10}H_{13}N_5O_5 \cdot H_2O$ (301.30): C, 39.87; H, 5.02; N, 23.30. Found: C, 40.15; H, 5.00; N, 23.26.

4-Amino-8-(β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-2(8*H*)-one (19$^{\beta}$). A solution of **18$^{\beta}$** (700 mg, 1.1 mmol) in saturated methanolic ammonia (20 mL) was stored at room temperature for 24 h and then evaporated, leaving a residue that was dissolved in water (5 mL) and washed three times with ethyl acetate (3 mL). Concentration of the aqueous phase gave 245 mg (78%) of **19$^{\beta}$** with mp 240–300 °C dec depending upon the rate of heating: λ_{max} (0.1 N HCl) 242 nm (ϵ 12 400), 265 sh (6800); λ_{max} (0.1 N NaOH) 247 nm (ϵ 15 000).

Anal. Calcd for $C_{10}H_{13}N_5O_5$ (283.30): C, 42.40; H, 4.63; N, 24.73. Found: C, 42.39; H, 4.55; N, 24.94.

8-(2,3,5-Tri-*O*-benzoyl-α-D-ribofuranosyl)-4-ethoxyimidazo[1,2-*a*]-1,3,5-triazin-2(8*H*)-one (21). A solution of **16$^{\alpha}$a** (61 mg, 0.1 mmol) was stirred in ethanol at 75 °C for 2 h in the presence of Raney nickel (600 mg net weight). The mixture was filtered through Celite, and the filtrate was evaporated and purified by preparative TLC using chloroform–methanol (19:1), which separated one major band less polar than **16$^{\alpha}$a** from a mixture of polar products. Elution of this band gave 7 mg of **21** that was characterized only by NMR. Attempted desulfurization of **16$^{\alpha}$a** or **18$^{\alpha}$** in dioxane was unsuccessful.

Imidazo[1,2-*a*]-1,3,5-triazin-2(1*H*)-one-4(3*H*)-thione (22). (a) By Hydrolysis of 16$^{\beta}$b. A solution of **16$^{\beta}$b** (40 mg, 0.13 mmol) in 1 N hydrochloric acid (1.5 mL) was heated at 60 °C for 28 h, during which time a crystalline material separated. After storage at 4 °C for 2 h, the crystals were separated and washed with water, giving 15 mg (67%) of **22** which begins to discolor at 223 °C but does not melt below 300 °C: λ_{max} (0.1 N HCl) 247 nm (ϵ 10 600), 266 (10 100), 298 (9500); λ_{max} (0.1 N NaOH) 247 nm (ϵ 10 500), 271 (8000), 300 sh (3300); mass spectrum (70 eV), *m/e* 168.0101 (M^+, calcd 168.0105), 109.0279 (M^+ − NHCS, calcd 109.0275); ^1H NMR (Me_2SO) 7.20 (d, 1, $J_{6,7}$ = 2.5 Hz, C_6-H or C_7-H), 7.51 (d, 1, C_7-H or C_6-H) ppm.

(b) By Hydrolysis of 2 (X = O, Y = S). A solution of **2** (9 mg) in 1 N hydrochloric acid (0.4 mL) was heated at 60 °C for 2 h, which led to complete hydrolysis of **2** as judged by TLC using chloroform–methanol (4:1). Storage at 4 °C led to crystallization of 1 mg (20%) of **22,** identical with that above by UV, TLC, and mass spectral analysis. Isolation of further **22** by preparative TLC of the mother liquors was not attempted.

(c) By Hydrolysis of 16$^{\alpha}$b. Treatment of **16$^{\alpha}$b** (5 mg) in 200 μL of 1 N hydrochloric acid at 60 °C for 4 h did not lead to complete hydrolysis. Isolation of the base by preparative TLC gave a major band that was identical with **22** above by TLC and by UV analysis under both acidic and basic conditions.

Imidazo[1,2-*a*]-1,3,5-triazine-2,4(1*H*,3*H*)-dione (24). A mixture of phenoxycarbonyl isocyanate (0.50 mL, 3.7 mmol) and 2-aminoimidazolium sulfate (320 mg, 2.4 mmol)[4] in pyridine (45 mL) was stirred at room temperature for 3 h and then evaporated. The residue was purified by preparative TLC using chloroform–methanol (85:15), and the major slow-moving component crystallized from methanol, giving 90 mg (24%) of **24** which slowly turned brown above 230 °C but did not melt: λ_{max} (0.1 N HCl) 232 nm (ϵ 8500), 253 (7600); λ_{max} (0.1 N NaOH) 249 nm (ϵ 10 000); ^1H NMR (Me_2SO) 6.99 (d, 1, $J_{6,7}$ = 2 Hz, $C_{6(7)}$-H), 7.29 (d, 1, $C_{7(6)}$-H) ppm.

Anal. Calcd for $C_5H_4N_4O_2$ (152.11): C, 39.48; H, 2.65; N, 36.84. Found: C, 39.20; H, 2.77; N, 36.50.

Acidic Hydrolysis of 19$^{\alpha}$ and Its 1-(β-D-Ribofuranosyl) Isomer. (a) A solution of **19$^{\alpha}$** (85 mg) in 1 N hydrochloric acid was heated at 60 °C for 15 h and then evaporated to dryness. The residue was neutralized with ammonia and purified by preparative TLC using three developments with chloroform–methanol (4:1). Elution of the major band and crystallization from water gave 12 mg (27%) of **24** that was identical with that above by melting point, TLC, UV, and NMR analysis: mass spectrum (70 eV), *m/e* 152 (M^+).

(b) Hydrolysis of **2** (X = O, Y = NH) (20 mg) was carried out as in method a above and gave 4 mg (37%) of **24** that was identical with that from method a by melting point, TLC, and UV analysis.

4(8*H*)-Imino-8-(α-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-tria-

zine Hydrochloride (29$^{\alpha}$). A solution of **9a** (2.64 g, 5 mmol) and ethyl *N*-cyanoformimidate (1.3 mL, 15 mmol)[34a] in anhydrous dioxane (12 mL) was stirred at room temperature for 5 h and then evaporated. The resulting oil was chromatographed on a column of silicic acid (250 g) using benzene–ethyl acetate (2:1) to give 1.43 g (45%) of the almost pure bis adduct, **26**$^{\alpha}$, that did not give elemental analyses within acceptable limits and was used directly.

A solution of **26**$^{\alpha}$ (254 mg, 0.4 mmol) in methanolic sodium methoxide (7 mL of 0.11 M) was stirred at room temperature for 2 h and then acidified to pH 1 with 1 N hydrochloric acid. The solution was then adjusted to pH 7 with 1 N ammonium hydroxide and evaporated to a small volume. An aqueous solution (7 mL) of the residue was extracted three times with ethyl acetate (1 mL) and then evaporated. The residue was purified by preparative TLC using chloroform–methanol (7:3), and the major polar component crystallized from aqueous ethanol, giving 75 mg (58%) of **29**$^{\alpha}$ as a monohydrate that darkens above 160 °C but does not melt below 300 °C: λ_{max} (H_2O) 210 nm (ϵ 16 000), 248 (5400), 253 (5200), 288 (10 300); λ_{max} (0.1 N NaOH) 240 nm sh (ϵ 8900), 247 (10 600), 254 sh (8600), 300 (9100); ORD (H_2O) $[\Phi]^{pk}_{310}$ 2700°, $[\Phi]_{289}$ 0°, $[\Phi]^{tr}_{255}$ −5500°.

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot HCl \cdot H_2O$ (321.70): C, 37.33; H, 5.01; N, 21.77. Found: C, 37.64; H, 4.75; N, 22.03.

4(8*H*)-Imino-8-(β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine Hydrochloride (29$^{\beta}$). A solution of **10a** (5.28 g, 10 mmol) and ethyl *N*-cyanoformimidate (2.6 mL, 30 mmol) in anhydrous ethanol (25 mL) was stirred at room temperature for 2.25 h and then evaporated. The residue was chromatographed on a column of silica gel using benzene–ethyl acetate (2:1), giving 1.51 g (24%) of slightly impure and rather unstable **26**$^{\beta}$ as a pale yellow solid that was used directly.

A solution of **26**$^{\beta}$ (1.26 g, 2 mmol) in methanolic sodium methoxide (34 mL, 0.12 M) was stirred at room temperature for 2 h and worked up as described for **29**$^{\alpha}$. Evaporation of the aqueous phase followed by crystallization from water gave 227 mg of pure **29**$^{\beta}$ which darkened above 170 °C but did not melt below 300 °C. Preparative TLC of the mother liquors using chloroform–methanol (7:3) gave a further 39 mg (total yield 44%) of **29**$^{\beta}$: λ_{max} (H_2O) 210 nm (ϵ 15 400), 248 (5300), 288 (10300); λ_{max} (0.1 N NaOH) 241 nm sh (ϵ 8300), 247 (9700), 253 sh (8200), 299 (10 200); ORD (H_2O) $[\Phi]^{tr}_{310}$ −4400°, $[\Phi]_{287}$ 0°, $[\Phi]^{pk}_{270}$ 3300°.

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot HCl$ (303.70): C, 39.54; H, 4.65; N, 23.06. Found: C, 39.60; H, 4.60; N, 23.17.

Registry No.—**3**, 527-73-1; **4a**, 67773-76-6; **4b**, 67773-77-7; **4c**, 67773-78-8; **5a**, 67773-79-9; **5b**, 17306-43-3; **6a**, 67773-80-2; **6b**, 67773-81-3; **9a**, 67773-83-4; **9b**, 67773-83-5; **10a**, 67773-84-6; **10b**, 67773-85-7; **11a**, 67774-09-8; **11b**, 67773-86-8; **13**$^{\alpha}$**a**, 67773-89-9; **13**$^{\beta}$**a**, 67773-88-0; **13**$^{\alpha}$**b**, 67773-89-1; **13**$^{\beta}$**b**, 67410-61-1; **14a**, 67773-90-4; **14b**, 67773-91-5; **15** (Ar = Ph), 67464-17-9; **16**$^{\alpha}$**a**, 67773-92-6; **16**$^{\beta}$**a**, 67773-93-7; **16**$^{\alpha}$**b**, 67773-94-8; **16**$^{\beta}$**b**, 67773-95-9; **17**$^{\alpha}$**a**, 67773-96-0; **17**$^{\beta}$**a**, 67773-97-1; **17**$^{\alpha}$**b**, 67773-98-2; **17**$^{\beta}$**b**, 67773-99-3; **18**$^{\alpha}$, 67774-00-9; **18**$^{\beta}$, 67774-01-0; **19**$^{\alpha}$, 67774-02-1; **19**$^{\beta}$, 67774-03-2; **21**, 67774-04-3; **22**, 67774-10-1; **24**, 67410-57-5; **26**$^{\alpha}$, 67774-05-4; **26**$^{\beta}$, 67774-06-5; **29**$^{\alpha}$, 67774-07-6; **29**$^{\beta}$, 67774-08-7; 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-nitroimidazole, 67774-11-2; 1-*O*-acetyl-2,3,5-tri-*O*-,benzoyl-β-D-ribofuranose, 6974-32-9; penta-*O*-acetyl-α-D-glucopyranose, 604-68-2; 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide, 22860-91-9; 2-aminoimidazolium sulfate, 42383-61-9; methyltriphenoxyphosphonium iodide, 17579-99-6; iodomethyltriphenoxyphosphorane, 4167-97-3; phenoxycarbonyl isocyanate, 5843-43-6.

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