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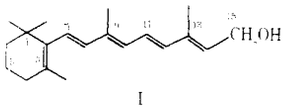

I

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

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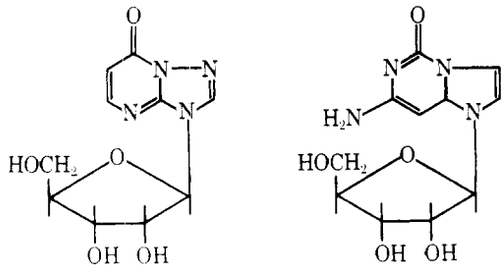
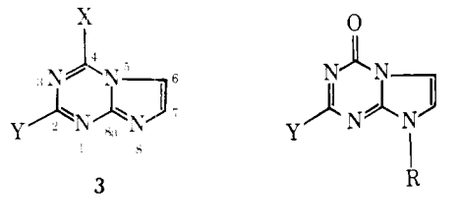
Stannic chloride catalyzed condensation of 2-aminoimidazole with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose somewhat surprisingly gives 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylamino)imidazole (**10**) rather than the expected glycosylation of a ring nitrogen. Reaction of **10** with a number of different aryloxycarbonyl isocyanates and their sulfur analogues afforded 1-(β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazines bearing oxo and thiono substituents at the 2 and 4 positions. Certain amino-substituted compounds were also prepared via aminolysis of the thiones or their *S*-methyl derivatives. The orientation of substituents was generally deduced through the use of ^{13}C NMR spectroscopy with particular reference to the existence of small three-bond couplings involving the anomeric proton.

During the past few decades, innumerable analogues of purine nucleosides modified in either the heterocyclic base or the sugar moiety have been described.[1] In spite of this plethora of base analogues, relatively few compounds have been prepared in which a nitrogen atom is located at one of the ring junctions. The most noticeable exception to this generality has been a quite detailed study on the synthesis of nucleosides derived from *s*-triazolo[2,3-*a*]pyrimidin-7-one (e.g., **1**)[2] and imidazo[1,2-*c*]pyrimidines (e.g., **2**).[3] In addition, a few *C*-glycosyl nucleosides derived from heterocycles containing bridgehead nitrogens have been described.[4] Our present concern has been the synthesis of nucleosides derived from suitably substituted derivatives of the imidazo[1,2-*a*]-1,3,5-triazine ring system (**3**), compounds which, unlike **1** and **2**, bear nitrogen atoms positionally equivalent to N^1 and N^3 of purine nucleosides. These substances can, accordingly, be looked upon as 5-aza-7-deazapurine nucleosides and are hence structurally related to other biologically interesting 7-deazapurine nucleosides such as tubercidin.[5] In this and a forthcoming paper[6] we describe our work on the synthesis of such nucleosides, part of which has previously been disclosed.[7]

The parent imidazo[1,2-*a*]-1,3,5-triazine ring system is not at all well studied. The patent literature gives reference to a number of variously substituted, and frequently reduced, derivatives.[8] A paper by Kobe et al.,[9] however, provides the only well-documented approach for the synthesis of simple 2,4-disubstituted compounds via reaction of 2-amino-1,3,5-triazines with bromoacetaldehyde. In this way several compounds substituted with alkylthio and dialkylamino groups were prepared. In view of the general paucity of simple *N*-alkylated and otherwise functionalized derivatives to serve as reference compounds for spectral analysis, we felt that direct ribosidation of derivatives of the parent ring system would be fraught with difficulties in structural assignments.[10] Since our primary objective was the synthesis of 8-ribofuranosyl



1 2



3

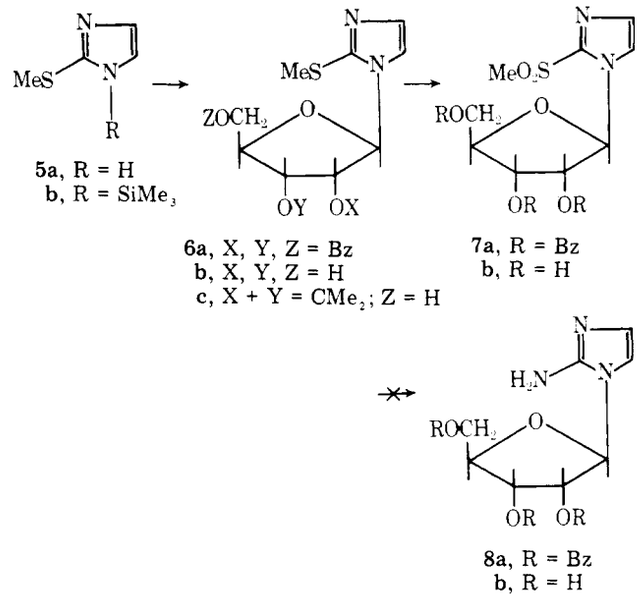
4a, R = β-D-ribofuranosyl
b, R = Me; Y = OH

derivatives (e.g., **4a**), we preferred to consider the annulation of the triazine ring onto an imidazole riboside of defined structure.

While imidazole nucleosides have been the subject of extensive study,[11] 2-amino-1-(β-D-ribofuranosyl)imidazole (**8b**), the obvious choice for annulation reactions, has not been described. The related 2-nitroimidazole nucleoside has been prepared[12] but its synthesis, as described, is rather low yielding. As an initial approach we attempted the synthesis of **8a** via displacement of a 2-methylsulfonyl function by ammonia. Nucleophilic displacement of sulfone functions from the 2 position of certain substituted imidazoles has been reported.[13] Thus, 2-methylthioimidazole (**5a**), prepared essentially as described by Markwald,[14] was converted into its trimethylsilyl derivative (**5b**) by reaction with hexamethyldisilazane in the presence of ammonium sulfate. This distillable derivative was then condensed with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide[15] in benzene at 60 °C for 1.5 h in the presence of mercuric cyanide. Following chromatography on silicic acid, 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-methylthioimidazole (**6a**) was isolated as a homogeneous foam in 53% yield. The same product could also be obtained by direct condensation of **5a** and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in acetonitrile in the presence of stannic chloride and mercuric cyanide, but in a single attempt the yield was only 40%. Debenzoylation of **6a** was achieved in almost quantitative yield using methanolic ammonium hydroxide giving crystalline 2-methylthio-1-(β-D-ribofuranosyl)imidazole (**6b**).

While the β configuration is expected for both **6a** and **6b** due to participation of the 2′-benzoyl function during the condensation reaction,[16] this could not be confirmed by NMR spectroscopy.[17] Thus, $J_{1',2'}$ for **6a** was 5.5 Hz while the $C_{1'}H$ signal for **6b** was complex due to virtual coupling to $C_{3'}H$. Conversion of **6b** to its crystalline 2′,3′-*O*-isopropylidene derivative (**6c**) led to a reduction of $J_{1',2'}$ to 3.5 Hz and to the appearance of isopropylidene methyl signals separated by 23 Hz. The latter is strongly supportive of a β configuration.[18]

Oxidation of the methylthio function of **6a** was readily achieved using an excess of *m*-chloroperbenzoic acid and gave the corresponding methylsulfone (**7a**) in essentially quantitative yield. This reaction was somewhat difficult to follow since both **6a** and **7a** have identical TLC mobilities in several solvents. Completion of the reaction could be estimated by the use of aqueous potassium permanganate spray since **6a** gave a positive test while **7a** was negative. The homogeneity of the product was apparent from its NMR spectrum, which shows the expected shift of the *S*-methyl signal at 2.55 ppm to that of the methylsulfone at 3.33 ppm. As might be expected, the anisotropic nature of the sulfone group also leads to a 0.75-ppm downfield shift of $C_{1'}H$ in going from **6a** to **7a.** Debenzoylation of **7a** was readily effected with methanolic ammonia at room temperature to give crystalline 2-methylsulfonyl-1-(β-D-ribofuranosyl)imidazole (**7b**). We were, however, unsuccessful in attempts to displace the methylsulfonyl group by treatment with methanolic ammonia at 120 °C for 16 h, with methanolic hydrazine at 100 °C for 18 h, or by fusion with formamidine acetate at 130 °C.



5a, R = H
b, R = $SiMe_3$

6a, X, Y, Z = Bz
b, X, Y, Z = H
c, X + Y = CMe_2; Z = H

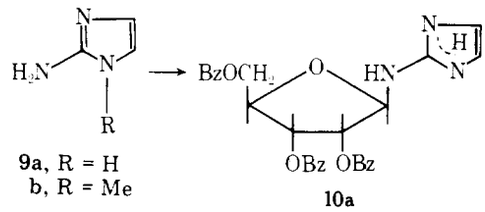
7a, R = Bz
b, R = H

8a, R = Bz
b, R = H

In view of our failure to effect nucleophilic displacement of the methylsulfonyl group in **7a,** we turned to direct ribosidation of 2-aminoimidazole since it has been shown that alkylation of 2-aminoimidazoles, 2-aminoimidazolines, and 2-aminobenzimidazoles leads to substitution on the ring nitrogen rather than the exocyclic amine.[19] A similar situation obtains with 2-aminothiazolines.[20] Accordingly, 2-aminoimidazole (**9a**) was prepared and isolated as its sulfate salt essentially according to Storey.[21] This material was condensed with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β,D-ribofuranose in the presence of stannic chloride and mercuric cyanide. A number of products were formed in this reaction, but a major one that was somewhat more polar than the others could be readily isolated by direct crystallization of the crude mixture from benzene, albeit only in 21% yield. This compound proved to be rather unstable in solution, and in view of the ready availability of the starting materials and the simple isolation procedure we have not made a serious effort to improve this yield.

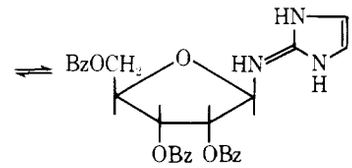
Both the ^1H- and ^{13}C-NMR spectra of the crystalline product were consistent with its being a ribofuranosylimidazole, but due to its instability we were unable to effect debenzoylation. The ^1H-NMR spectrum was unrevealing with respect to confirmation of the expected β configuration ($J_{1',2'}$ = 5 Hz), but this point was clarified by subsequent transformations. At first the ^1H-NMR spectrum in $CDCl_3$ appeared to support the expected N^1-ribofuranosyl structure (**8a**) since the imidazole ring protons (C_4H and C_5H) appeared as a pair of singlets at 6.60 and 6.64 ppm. The separation between these signals is not as large as we had anticipated, and there was no indication of the usually small (~1.5 Hz) vicinal coupling typical of imidazole derivatives.[22] Nevertheless, the nonequivalence of C_4H and C_5H supported the structure **8a** since ribosidation of the exocyclic amino group would lead to the symmetrical structure **10a,b** in which C_4H and C_5H are expected to be magnetically equivalent. Similar reasoning has been employed by Rao et al.[23] in assigning the structure of an

N-acylated derivative of **9a.** The same tentative conclusion could be reached from the ^{13}C-NMR spectrum of the product since the signals for C_4 and C_5 of the imidazole ring were magnetically nonequivalent, albeit only separated by 0.29 ppm. In spite of these data, subsequent chemical transformations and an unambiguous synthesis of **8a**[6] have unequivocally shown that the product from ribosidation of **9a** as above is, in fact, 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylamino)-imidazole (**10**). The observed magnetic nonequivalence of the imidazole ring protons could have several possible explanations. One is based upon a potential diastereotopic effect due to the chiral ribofuranosyl substituent.[24,25] Another could be the consequence of restriction of rotation of the C_2-exo N-bond due to significant contribution of the exo-imino tautomer **10b** or the presence of a hydrogen bond between a ring NH and O^4 of the furanose ring. The latter would appear to be more likely since upon heating a solution of **10** in deuterated tetrachloroethane the two singlets coalesced to a single sharp line within a remarkably narrow temperature range (85–95 °C).



9a, R = H
b, R = Me

10a



10b

Regardless of the explanation for the ribosidation of the exocyclic amino group rather than the expected ring nitrogen or for the NMR effects described above, the ribosylaminoimidazole **10** constitutes an interesting starting material for ring annulation studies which are outlined in Scheme I.

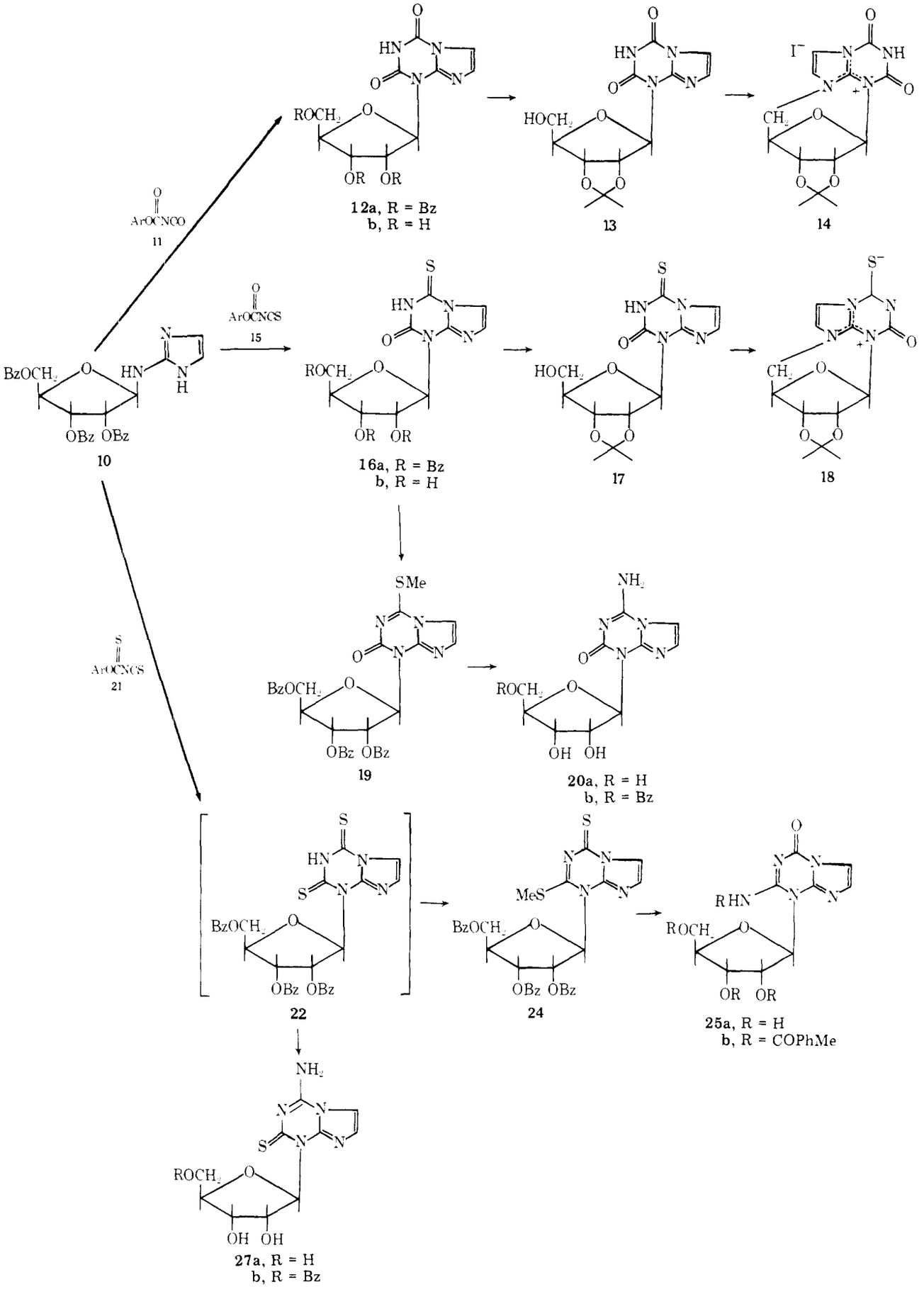
The conversion of aminoazoles to functionalized triazines has been widely explored using ethoxycarbonyl isothiocyanate and related compounds.[26] We were particularly interested in the use of the somewhat more reactive phenyl esters, and, as a model, reacted 2-amino-1-methylimidazole (**9b**)[21] with phenoxycarbonyl isocyanate (**11**) which was prepared according to Speziale et al.[27] This reaction readily gave, in 60% yield, crystalline 8-methylimidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*,8*H*)-dione (**4b**), the structure of which was quite unambiguous from analytical and spectroscopic data. A direct extension of this reaction to the condensation of **10** and **11** in dioxane at room temperature led to the chromatographic isolation of homogeneous, but noncrystalline, 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4(1*H*,3*H*)-dione (**12a**) in 70% yield. Subsequent debenzoylation using methanolic ammonium hydroxide readily gave the related free nucleoside, **12b,** in crystalline form. The UV spectrum of **12b** was markedly different from that of the 8-methyl derivative, **4b,** which provided one piece of evidence that ribosidation of **9a** had led to **10** rather than the expected **8a.**

In order to provide direct evidence for the β configuration of **10,** and hence of **12,** the latter was converted in 88% yield into its 2′,3′-*O*-isopropylidene derivative **13** through reaction with acetone and 2,2-dimethoxypropane in the presence of perchloric acid. The chemical shift differences between the isopropylidene signals (21 Hz)[18] and the small value of $J_{1',2'}$ (2 Hz)[17] were in themselves evidence for the β configuration, but further confirmation via formation of a cyclonucleoside was desired. Thus, a solution of **13** in dimethylformamide was treated at room temperature with a small excess of methyltriphenoxyphosphonium iodide and pyridine giving crystalline N^8,5′-anhydro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4(1*H*,3*H*)-dione iodide (**14**) in 70% yield. This method has previously been used for the conversion of 2′,3′-*O*-isopropylidene purine nucleosides to the corresponding N^3,5′-anhydro derivatives.[28] The electrophoretic mobilities of **14** were consistent with its ionic structure. Thus, at pH 7.6 (0.05 M ammonium bicarbonate) **13** behaves as a monoanion due to deprotonation of the heterocyclic base. The cyclonucleoside **14,** however, shows an overall slight positive character since at this pH it is a zwitterion and has a cationic mobility of 0.2 relative to N^3,5′-anhydro-2′,3′-*O*-isopropylideneadenosine,[28] which is a pure cation. In 1 M acetic acid, however, **13** is uncharged while **14** behaves as a cation. The formulation of **14** as an N^8,5′-cyclonucleoside rather than the isomeric O^2,5′-cyclonucleoside rests largely upon its cationic structure. In addition, the conversion of **13** to **14** is accompanied by substantial downfield shifts of the imidazole ring protons, which is an expected consequence of the generation of a positive charge at N^8.[29] The related conversion of 2′,3′-*O*-isopropylideneisoadenosine to the corresponding N^9,5′-cyclonucleoside has been described by Leonard and Laursen.[30]

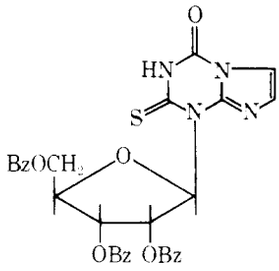
In order to prepare an analogue of **12** in which the functionalities at C_2 and C_4 were different, we investigated the reaction of **10** with phenoxycarbonyl isothiocyanate (**15**) which is prepared in situ from phenyl chloroformate and a slight excess of potassium thiocyanate in ethyl acetate essentially according to known procedures.[31] The formation of **15** was judged to be complete by GLC analysis, which showed the disappearance of phenyl chloroformate. The reaction between **10** and **15** led to a red mixture containing, by TLC analysis, one major product with a mobility similar to that of **12a** together with a number of more polar byproducts. By chromatography on a column of silicic acid the desired product (**16a**) was isolated in a homogeneous, but amorphous, form in a yield of 22%. Various attempts were made to improve the yield of this reaction through the use of different solvents and the addition of both basic (pyridine) and acidic (*p*-toluenesulfonic acid) catalysts, but without success. It has previously been shown that reaction of certain aminoazoles (e.g., 2-aminobenzimidazole and 5-aminotetrazole) with **15** leads to loss of thiocyanic acid from the intermediate thiourea to give a carbamate.[32] Since the loss of thiocyanic acid (calculated $pK_a = -1.85$[33]) would be expected to be more facile than that of cyanic acid ($pK_a = 3.46$[33]), we consider this type of side reaction to largely explain the lower yield of **16a** relative to that of **12a.**

It was not, however, immediately obvious that **16a** was a 2-oxo-4-thio derivative rather than the isomeric 2-thio-4-oxo compound **26.** Clearly either **16a** or **26** could be produced depending upon the relative nucleophilicities of the exocyclic and endocyclic nitrogens in **10** and the initial point of attack on the bifunctional reagent **15.** Some indirect evidence in favor of structure **16a** came from model reactions between **10** and *S*-phenyl chlorothioformate or ethoxycarbonyl isothiocyanate. In both cases the major products were isolated chromatographically and characterized by ^1H-NMR alone as the ring acylated products **27a** and **27b.** In each case the site of acylation was apparent since the C_1' proton appeared as a doublet of doublets with $J_{1',2'} = 5$ Hz and $J_{1',NH} = 8$ and 9 Hz, respectively. As expected, addition of D_2O led to exchange of the NH and collapse of the $C_{1'H}$ signals to doublets. Attempts to effect cyclization of **27b** to **16a** through heating in various solvents alone or in the presence of triethylamine were un-

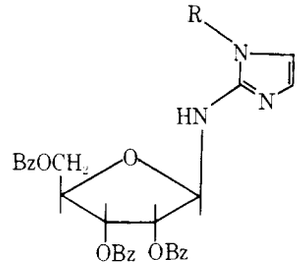
Scheme I


ArOCNCO
11
12a, R = Bz
b, R = H
13
14
ArOCNCS
15
10
16a, R = Bz
b, R = H
17
18
ArOCNCS
21
19
20a, R = H
b, R = Bz
22
24
25a, R = H
b, R = COPhMe
27a, R = H
b, R = Bz

successful, loss of thiocyanic acid and formation of the carbamate **27c** being the apparent preferred course.



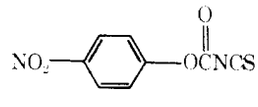
26



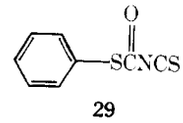
27a, R = $C(O)SC_6H_5$
b, R = $C(S)NHCO_2Et$
c, R = CO_2Et
d, R = $C(S)NHC(O)SC_6H_5$

Direct confirmation of orientation of the functions at C_2 and C_4 in **16a** came from spectroscopic examination of the crystalline debenzoylation product **16b.** The ^{1}H-NMR spectrum of **16b** in Me_2SO-d_6 showed $C_{1'}H$ as a doublet ($J_{1',2'}$ = 6 Hz) at 6.15 ppm, a position very similar to that exhibited by uridine derivatives. Extensive work has shown, however, that nucleosides having a thiono function adjacent to the site of glycosidation experience strong deshielding of the anomeric proton.[34] Thus, $C_{1'H}$ in the 2-thiono derivative **26** would be expected to appear at considerably lower field, as was found for **22.** The proton-coupled ^{13}C-NMR spectrum of **16b** was even more revealing. Cline and Townsend have recently made the important observation that a variety of nucleoside analogues show a small (3–5 Hz), three-bond coupling between the anomeric proton ($C_{1'}H$) and the carbon atoms adjacent to the site of glycosidation.[35] The spectrum of **16b** showed typical urea and thiourea type carbonyl resonances at 150.97 and 175.06 ppm, the thiocarbonyl group being characteristically the further downfield signal.[36] The proton-coupled spectrum showed the thiono carbon to be a sharp singlet while the carbonyl carbon was a doublet with ^3J = 3.9 Hz. The nature of this coupling was confirmed by single-frequency proton decoupling, irradiation at 6.15 ppm leading to collapse of the C_2 pattern to a singlet.[37] This clearly confirms that the oxo function is at C_2 and the thione at C_4 in **16.** As would be expected, the ring junction carbon (C_{8a}) appeared as a complex pattern due to small three-bond couplings to several γ protons. It is interesting that throughout this series we have been unable to detect any three-bond couplings between C_4 and C_6H.

In view of the rather low yield of **16b** obtained via the reaction of **10** and **15,** we attempted similar reactions using *p*-nitrophenoxycarbonyl isothiocyanate (**28,** from *p*-nitrophenyl chloroformate and potassium thiocyanate essentially according to Goerdeler and Gnad)[38] and the previously undescribed *S*-phenylthiocarbonyl isothiocyanate (**29**) which was prepared from *S*-phenyl chlorothioformate and potassium thiocyanate. In each case formation of the reagent was monitored by GLC and it was then used directly. The reaction between **10** and **28** was troublesome since additional purification of the product by preparative TLC was necessary in order to completely remove *p*-nitrophenol and the yield of **16a** was only 14%. On the other hand, the thiol ester **29** offers a substantial improvement over its oxygen analogue **15,** and its reaction with **10** gave **16a** in 46% yield. This is presumably a consequence of the increased tendency of the intermediate **27d** to undergo intramolecular displacement of thiophenol relative to its tendency to rearrange with loss of thiocyanic acid.



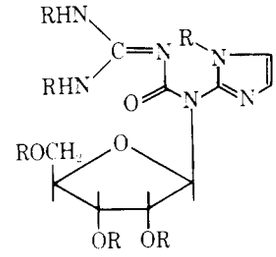
28



29

The triol, **16b,** was readily converted to its 2′,3′-*O*-isopropylidene derivative (**17**) and its β configuration was confirmed by the small value of $J_{1',2'}$ (2 Hz)[17] and by the 20 Hz separation of the isopropylidene methyl signals[18] in its ^{1}H-NMR spectrum. Treatment of **17** with methyltriphenoxyphosphonium iodide[28] in dimethylformamide led rapidly to the formation of the crystalline 5′,N^8-cyclonucleoside **18.** This compound behaved similarly to **14** during paper electrophoresis at pH 7.5 and in 1 M acetic acid, but its elemental analysis and a negative test for iodide ion indicated that, unlike **14,** it was not an iodide salt. Hence it is formulated as the zwitterion **18,** deprotonation at N^3 being a consequence of the greater acidity of the thiourea function.

Treatment of **16a** with methyl iodide and sodium bicarbonate gave the *S*-methyl derivative **19** in 75% yield. The expected site of alkylation was apparent from the ^{1}H-NMR spectrum, in which the methyl group appeared as a singlet at 2.72 ppm, a position similar to that of other methylthioamidines such as **5** and **6** (~2.5 ppm) but unlike various *N*-methylthioamides (~3.5 ppm) and *O*-methylisoureas (~3.8 ppm) in the literature.[39] Treatment of **19** with saturated methanolic ammonia at room temperature for 3 days gave crystalline 4-amino-1-(β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-2(1*H*)-one (**20a**) in 60% yield. In addition, a 12% yield of the 5′-*O*-benzoyl derivative (**20b**) was isolated from this reaction but only characterized by ^{1}H-NMR spectroscopy, which showed the expected 0.9 ppm downfield shift of the $C_{5'}$ protons relative to **20a.** As would be expected, the conversion of the 4-thiono function of **16b** to an amino group in **20a** was reflected in the ^{13}C-NMR spectrum by a shift of the C_4 signal from 175.06 to 152.89 ppm, the latter being similar to the chemical shift of the guanidine type carbon at C_2 of guanosine (154.8 ppm).[40] If **19** was treated with methanolic ammonia at 100 °C for 6 h rather than at room temperature, a product more polar than **20a** was formed and isolated in 62% yield by preparative TLC. This amorphous material, which was shown by NMR to have retained some methanol, showed only low wavelength absorption in its ultraviolet spectrum (λ_{max} 226 nm in methanol). Its ^{1}H-NMR spectrum showed the presence of a large number of exchangeable protons and upon acetylation a rather unstable hexaacetate (**30b**) was formed in which one of the acetyl methyl groups appeared at the unusual chemical shift of 2.54 ppm, a position typical of *N*-acetylimidazoles.[41] Based upon these data we suggest that this substance has the structure **30a** resulting from aminolysis of the



30a, R = H
b, R = Ac

C^4–N^5 bond of **20a** under the more vigorous conditions used. This structure is supported by both the ^{13}C- and ^{1}H-NMR spectra, which show the magnetic equivalence of both the imidazole ring carbons and the attached protons as would be expected for a symmetrical, N^2-substituted imidazole derivative.

Finally, we attempted the synthesis of the 2,4-dithione derivative **22** via reaction of **10** with *O*-phenylthiocarbonyl isothiocyanate (**21**) which was prepared in situ from *O*-phenyl chlorothioformate and potassium thiocyanate. During our

work a related preparation of **21** was described using lead thiocyanate rather than the potassium salt.[42] As in the case of the reactions of the other isothiocyanates (**15, 28,** and **29**), a number of more polar byproducts were formed in addition to the desired dithione (**22**). While **22** could be isolated in 30–35% yields by chromatography on silicic acid, it was difficult to completely free it from traces of phenol. As would be expected,[34] the presence of the 2-thione function led to strong deshielding of $C_{1'}H$, which appeared below 7.0 ppm within the aromatic proton envelope. Accordingly, the crude chromatographic product was directly treated with methanolic ammonia at room temperature, which led to both debenzoylation and displacement of the 4-thio function. Following chromatography on silicic acid crystalline 4-amino-1-(β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2(1*H*)-thione (**23a**) was isolated in an overall yield of 17% from **10.** This yield includes rehydrolysis of a small amount of the crystalline 5′-*O*-benzoate derivative (**23b**) of **23a** that was isolated as a byproduct and identified by ^{1}H-NMR (~1 ppm deshielding of the $C_{5'}$ protons relative to **23a**). The ^{1}H-NMR spectrum of **23a** confirmed that the C_4 thione had undergone displacement since $C_{1'}H$ was strongly deshielded by the adjacent thione[34] and appeared at 7.38 ppm (cf. 6.20 ppm for the 2-oxo analogue **20a**). The ^{13}C-NMR spectrum of **23a** further supported this assignment since the far downfield, thione carbon (C_2) appeared as a doublet at 182.25 ppm showing three-bond coupling of 4.4 Hz to $C_{1'}H$. It should be noted that the presence of the 2-thio function leads to a substantial deshielding of $C_{1'}$, which appears roughly 5 ppm downfield of the same carbon in the 2-oxo or 2-amino compounds. A similar shift occurs in 2,4-dithiouridine[40] and is clearly related to the known deshielding of the anomeric proton.[34]

Treatment of the slightly impure dithione, **22,** with methyl iodide and sodium bicarbonate led to selective alkylation of the C_2 thione and gave the 2-methylthio-4-thione derivative **24** which was isolated in 38% yield. As expected, removal of the anisotropic C_2 thione was accompanied by a substantial upfield shift of $C_{1'}H$ (relative to **22** or **23a**) to 6.47 ppm. Subsequent treatment of **24** with methanolic ammonia at room temperature led to aminolysis of the methylthio group and hydrolysis of the 4-thiono function. The sulfur-free product presumably arose via spontaneous hydrolysis of a 2-amino-4-imino compound and finds analogy in the facile hydrolysis of the amino group during mild acidic hydrolysis of **20a** that is described separately.[6] The structure of the resulting 2-amino-1-(β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-4(1*H*)-one (**25a**) is based upon analytical data on the tetra-*p*-toluoyl derivative (**25b**) and can be differentiated from that of the isomer **20a** by UV and NMR spectroscopy. The absence of the thione function is further supported by the absence of a far downfield ^{13}C signal similar to that in **16b** or **23a.**

The work described in this paper clearly points out the versatility of phenoxycarbonyl isocyanate and its analogues for the cyclization of aminoimidazole nucleosides. The free nucleosides **6b, 7b, 12b, 16b,** and **20a** were screened for possible biological activities,[43] but no significant antibacterial, antiviral, antifungal, or cytotoxic effects were observed in vitro. The compounds were also inactive against L-1210 leukemia and Ehrlich ascites carcinoma in mice. In a forthcoming paper[6] we extend this work to the preparation of variously substituted 8-(D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazines which are closer analogues of normal purine nucleosides.

Experimental Section

General Methods. ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectra were obtained using a Varian HA-100 spectrometer and a Bruker WH-90 spectrometer operating at 22.62 MHz, respectively, and are reported in ppm downfield of an internal standard of tetramethylsilane. We are most grateful to Dr. M. L. Maddox and Mrs. J. Nelson for obtaining these spectra. Preparative thin-layer chromatography (TLC) was conducted using 20 × 100 cm glass plates coated with a 1.3-mm layer of Merck silica gel HF. Column chromatography was done on Merck silica gel G under a pressure of 5–15 psi. Some elemental analyses were obtained from Dr. A. Bernhardt, Elbach über Engelskirchen, while most instrumental analyses were performed by the staff of our analytical laboratories, to whom we extend our thanks. Melting points were obtained on a hot-stage microscope and are corrected.

2-Methylthioimidazole (5a). Methylation of imidazole-2-thiol (2.0 g, 20 mmol) with methyl iodide (2.84 g, 20 mmol) in aqueous sodium hydroxide (10 mL of 1 M) for 30 min at room temperature was carried out essentially according to Marckwald.[14] Crystallization from water gave 2.14 g (94%) of **5a** with mp 136–138 °C (lit.[14] mp 139 °C): λ_{max} (MeOH) 218 nm (ε 7100), 245 (4700); ^{1}H NMR (pyridine-d_5) 2.60 (s, 3, SMe), 7.35 ppm (s, 2, C_4H, C_5H).

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2-methylthioimidazole (6a). (a) A mixture of **5a** (315 mg, 2.77 mmol) and ammonium sulfate (3.5 mg) in hexamethyldisilazane (1.7 mL) was heated under reflux for 1.5 h. After removal of excess reagent in vacuo at room temperature the *N*-trimethylsilyl derivative, **5b** (450 mg, 88%), was obtained by bulb-to-bulb distillation at 75–80 °C (0.5 mm). This product (2.42 mmol) was added to a solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (from 1.0 g, 1.98 mmol, of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose[15]) in benzene (40 mL) in the presence of finely ground mercuric cyanide (1.6 g, 6.3 mmol). The mixture was stirred at 60 °C for 1.5 h and then evaporated to dryness. A filtered solution of the residue in chloroform was washed with aqueous sodium bicarbonate, 30% aqueous potassium iodide, and water. The dried organic phase was evaporated and the residual syrup was chromatographed on a column of silicic acid (90 g) using CCl_4–acetone (85:15) giving 589 mg (53%) of **6a** as a homogeneous white foam: λ_{max} (MeOH) 230 nm (ε 42 900), 273 (3400), 281 (2500). Anal. Calcd for $C_{30}H_{26}N_2O_7S$ (558.52): C, 64.51; H, 4.69; N, 5.02. Found: C, 64.32; H, 4.82; N, 5.12.

(b) A mixture of **5a** (23 mg, 0.2 mmol), 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (85 mg, 0.17 mmol), stannic chloride (90 mg, 0.35 mmol), and finely powdered mercuric cyanide (90 mg, 0.35 mmol) in acetonitrile (4 mL) was stirred at 60 °C for 6 h and then under reflux for 16 h. After evaporation of the solvent, the mixture was worked up as in (a) except that purification was effected by preparative TLC using CCl_4–acetone (85:15). Elution of the major band gave 40 mg (43%) of **6a** identical to that from (a).

2-Methylthio-1-(β-D-ribofuranosyl)imidazole (6b). A solution of **6a** (2.24 g, 4 mmol) in methanol (35 mL) and concentrated ammonium hydroxide (35 mL) was kept at room temperature for 4 h and then evaporated to dryness. Crystallization of the residue from 1-propanol gave 928 mg (94%) of **6b** with mp 150–152 °C in two crops: λ_{max} (MeOH) 224 nm (ε 6200), 249 (4600). Anal. Calcd for $C_9H_{14}N_2O_4S$ (246.29): C, 43.89; H, 5.73; N, 11.38. Found: C, 43.79; H, 5.88; N, 11.31.

2-Methylthio-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-imidazole (6c). Perchloric acid (10 μL of 72%) was added to a stirred suspension of **6b** (75 mg, 0.3 mmol) in a mixture of acetone (10 mL) and 2,2-dimethoxypropane (0.3 mL). After 1 h at room temperature further portions of perchloric acid (10 μL) and 2,2-dimethoxypropane (0.7 mL) were added and after 30 min the yellow solution was neutralized by addition of 1 drop of concentrated ammonium hydroxide. The mixture was evaporated and the residue purified by preparative TLC using chloroform–methanol (9:1). Elution of the major band followed by crystallization from carbon tetrachloride gave 67 mg (77%) of **6c** with mp 88–89 °C: λ_{max} 224 nm (ε 6400), 248 (4800). Anal. Calcd for $C_{12}H_{18}N_2O_4S$ (286.28): C, 50.34; H, 6.34; N, 9.79. Found: C, 50.31; H, 6.22; N, 9.91.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2-methylsulfonylimidazole (7a). A solution of **6a** (1.25 g, 2.23 mmol) and *m*-chloroperbenzoic acid (1.2 g, 6.9 mmol) in methylene chloride (20 mL) was heated under reflux for 1 h and then cooled and washed with 10% aqueous sodium sulfite, aqueous sodium bicarbonate (twice), and water. The dried ($MgSO_4$) phase was evaporated leaving **7a** (1.32 g, 100%) as a TLC homogeneous foam (TLC, NMR) with the same R_f as **6a** but giving a negative test with aqueous potassium permanganate spray. An analytical sample was prepared by preparative TLC using CCl_4–acetone (3:1): ν_{max} (KBr) 1295, 1136 cm^{-1} (SO_2); λ_{max} (MeOH) 231 nm (ε 40 100), 274 (2800), 282 (2300). Anal. Calcd for $C_{30}H_{26}N_2O_9S$ (590.60): C, 61.01; H, 4.44; N, 4.74. Found: C, 60.98; H, 4.54; N, 4.61.

2-Methylsulfonyl-1-(β-D-ribofuranosyl)imidazole (7b). A solution of **7a** (890 mg, 1.5 mmol) in saturated methanolic ammonia was stored at room temperature for 24 h and then evaporated to dryness. An aqueous solution of the residue was extracted three times with ethyl acetate and the aqueous phase was evaporated. Crystallization

of the residue from aqueous ethanol gave 370 mg (89%) of **7b** with mp 115.5–117 °C: λ_{max} (MeOH) 237 nm (ϵ 9400). Anal. Calcd for $C_9H_{14}N_2O_6S$ (278.29): C, 38.84; H, 5.07; N, 10.07. Found: C, 38.95; H, 5.08; N, 10.10.

2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosylamino)imidazole (10). Stannic chloride (7.0 mL, 60 mmol) was added to a stirred mixture of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (15.1 g, 30 mmol), 2-aminoimidazolium sulfate (4.76 g, 36 mmol),[21] and mercuric cyanide (22.7 g, 90 mmol) in acetonitrile (800 mL) giving a clear solution. After heating at 60 °C for 2 h the solvent was evaporated and a filtered solution of the residue in chloroform was washed with 30% aqueous potassium iodide and water. The dried ($MgSO_4$) solution was evaporated and the residue crystallized from benzene giving 3.3 g (21%) of **10** which decomposed at 130–135 °C: λ_{max} (MeOH) 228 nm (ϵ 45 300), 274 (3200), 281 (2600). Anal. Calcd for $C_{29}H_{25}N_3O_7$ (527.51): C, 66.03; H, 4.78; N, 7.97. Found: C, 65.88; H, 4.87; N, 8.14.

8-Methylimidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*,8*H*)-dione (4b). A solution of phenoxycarbonyl isocyanate (0.20 mL, 1.5 mmol)[27] in dioxane (2 mL) was added dropwise over 30 min to a stirred suspension of 2-amino-1-methylimidazole (120 mg, 1.23 mmol)[21] in dioxane (20 mL). The mixture was then stirred for an additional hour and evaporated to dryness after addition of methanol (2 mL). The residue was crystallized from hot water giving 122 mg (60%) of **4b** with mp 284–286 °C: λ_{max} (0.1 N HCl) 238 nm (ϵ 10 400), 252 (9800); NMR (D_2O–TFA at 60 MHz) 3.80 (s, 3, NMe), 7.25 and 7.63 ppm (d, 1, $J_{6,7}$ = 3 Hz, C_6H, C_7H). Anal. Calcd for $C_6H_6N_4O_2$ (166.14): C, 43.37; H, 3.64; N, 33.72. Found: C, 43.20; H, 3.73; N, 33.80.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4(1*H*,3*H*)-dione (12a). A solution of phenoxycarbonyl isocyanate (0.32 mL, 2.4 mmol)[27] in dioxane (4 mL) was added dropwise over 30 min to a stirred solution of **10** (1.02 g, 2 mmol) in dioxane (15 mL) at room temperature. After a further 3 h, the solvent was evaporated and the residue was chromatographed on a column of silicic acid (160 g) using benzene–ethyl acetate (85:15) to give 830 mg (70%) of **12a** as a white foam. An analytical sample was prepared by preparative TLC using benzene–ethyl acetate (4:1): λ_{max} (MeOH) 230 nm (ϵ 43 900), 274 (3600), 282 (2600). Anal. Calcd for $C_{31}H_{24}N_4O_9$ (596.53): C, 62.41; H, 4.06; N, 9.39. Found: C, 62.30; H, 4.01; N, 9.48.

1-(β-D-Ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4(1*H*,3*H*)-dione (12b). A solution of **12a** (600 mg, 1 mmol) in methanol (5 mL) and concentrated ammonium hydroxide (10 mL) was stirred at 60 °C for 16 h and then evaporated to dryness. A solution of the residue in water was washed three times with ethyl acetate. The aqueous phase was evaporated and the residue crystallized from ethanol–acetone giving 199 mg (70%) of **12b** with mp 189–190 °C dec: An analytical sample from ethanol had mp 192–193 °C dec: λ_{max} (0.1 N HCl) 233 nm (ϵ 6200); λ_{max} (0.1 N NaOH) 224 nm (sh, ϵ 7300), 240 (sh, 4800). Anal. Calcd for $C_{10}H_{12}N_4O_6$ (284.23): C, 42.25; H, 4.26; N, 19.71. Found: C, 42.36; H, 4.35; N, 19.77.

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2,4(1*H*,3*H*)-dione (13). Perchloric acid (0.1 mL of 70%) was added to a stirred suspension of **12b** (60 mg, 0.2 mmol) in acetone (10 mL) and 2,2-dimethoxypropane (0.2 mL). After 30 min the clear solution was made alkaline with 1 N ammonium hydroxide and evaporated to dryness. The residue was purified by preparative TLC using chloroform–methanol (9:1) to give 60 mg (88%) of **13** as a homogeneous foam: λ_{max} (0.1 N HCl) 234 nm (ϵ 5800). Anal. Calcd for $C_{13}H_{16}N_4O_6$ (324.29): C, 48.15; H, 4.97; N, 17.28. Found: C, 48.06; H, 5.18; N, 16.90.

***N*^{8},5′-Anhydro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-imidazo[1,2-*a*]-1,3,5-triazine-2,4(1*H*,3*H*)-dione iodide (14).** A solution of **13** (32 mg, 0.1 mmol) and methyltriphenoxyphosphonium iodide (54 mg, 0.12 mmol)[28] in a mixture of dimethylformamide (1 mL) and pyridine (10 μL, 0.12 mmol) was kept at room temperature for 1 h and then evaporated to dryness. The residue was repeatedly triturated with ethyl acetate until the extracts were colorless and then crystallized from ethanol giving 30 mg (70%) of **14** with mp 247–249 °C dec: λ_{max} (0.01 N HCl) 219 nm (ϵ 18 300), 249 (6300). Anal. Calcd for $C_{13}H_{15}N_4O_5I$ (434.19): C, 35.96; H, 3.48; N, 12.90. Found: C, 35.83; H, 3.35; N, 12.72.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-2(1*H*)-one-4(3*H*)-thione (16a). (a) Using Phenoxycarbonyl Isothiocyanate (15). Phenyl chloroformate (1.7 mL, 14 mmol) was added to a stirred suspension of potassium thiocyanate (1.5 g, 15 mmol) in dry ethyl acetate (50 mL). After 1 h at room temperature, GLC on a 120-cm column of 3.8% UC-W at 100 °C showed the disappearance of phenyl chloroformate (retention time 1.25 min) and formation of **15** (retention time 9.5 min). A solution of **10** (5.28 g, 10 mmol) in dioxane (45 mL) was then added and the red mixture was stirred at 40 °C for 5 h. After addition of methanol (5 mL) the mixture was evaporated and a filtered chloroform solution of the residue was evaporated leaving 9.1 g of crude product. Purification of this material was effected on a column of silica gel G (1.1 kg) using benzene–ethyl acetate (91:9). Evaporation of the major UV absorbing fraction gave 1.37 g (22%) of homogeneous (TLC and NMR) **16a** as a foam that resisted crystallization. An analytical sample was prepared by preparative TLC using benzene–ethyl acetate (4:1): λ_{max} (MeOH) 218 nm (ϵ 35 300), 229 (40 100), 278 (sh, 15 800), 283 (17 000), 291 (16 400). Anal. Calcd for $C_{31}H_{24}N_4O_8S$ (612.60): C, 60.78; H, 3.95; N, 9.15. Found: C, 60.91; H, 4.06; N, 8.99.

(b) Using *p*-Nitrophenoxycarbonyl Isothiocyanate (28). *p*-Nitrophenyl chloroformate (303 mg, 1.5 mmol) was added to a stirred suspension of potassium thiocyanate (145 mg, 1.5 mmol) in ethyl acetate (5 mL). After 45 min at room temperature a solution of **10** (528 mg, 1 mmol) in dioxane (5 mL) was added and the mixture was stirred for 1.5 h. Purification as in (a) gave a product still contaminated with *p*-nitrophenol that was further purified by preparative TLC (benzene–ethyl acetate, 9:1) giving 85 mg (14%) of **16a.**

(c) Using *S*-Phenylthiocarbonyl Isothiocyanate (29). *S*-Phenyl chlorothioformate (0.19 mL, 1.5 mmol) was added to a suspension of potassium thiocyanate (160 mg, 1.6 mmol) in ethyl acetate (5 mL). After 1.25 h at room temperature, GLC on a 120-cm column of 3% OV-101 at 120 °C showed disappearance of the starting material (1.0 min) and formation of the product (5.5 min). After addition of a solution of **10** (528 mg, 1 mmol) in dioxane (5 mL) the yellow mixture was stirred for 3 h and worked up as in (a) giving 279 mg (46%) of pure **16a** identical to that above.

1-(β-D-Ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-2(1*H*)-one-4(3*H*)-thione (16b). A solution of **16a** (1.23 g, 2 mmol) in saturated methanolic ammonia was kept at room temperature for 5 days and then evaporated. A solution of the residue in methanol was evaporated to dryness in the presence of silica gel G (2 g) and the residue was applied to the top of a column containing 120 g of the same silica. Elution with a gradient of 5 to 30% methanol in chloroform gave 384 mg (64%) of **16b** with mp 178–179 °C from methanol: λ_{max} (0.1 N HCl) 214 nm (ϵ 16 500), 276 (11 100), 294 (sh, 9000); λ_{max} (0.1 N NaOH) 240 nm (sh, ϵ 4300), 288 (14 600). Anal. Calcd for $C_{10}H_{12}N_4O_5S$ (300.29): C, 39.99; H, 4.03; N, 18.66. Found: C, 40.02; H, 4.17; N, 18.53.

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-2(1*H*)-one-4(3*H*)-thione (17) and the N^8,5′-Cyclonucleoside (18). Perchloric acid (20 μL of 70%) was added to a stirred suspension of **16b** (60 mg, 0.2 mmol) in acetone (10 mL) and 2,2-dimethoxypropane (0.2 mL). After 75 min at room temperature, the clear solution was neutralized with concentrated ammonium hydroxide and evaporated. The residue was purified by preparative TLC using chloroform–methanol (19:1) giving 56 mg (82%) of the acetonide **17** as a white foam characterized by NMR: λ_{max} (MeOH, H^+) 278 nm.

A solution of **17** (65 mg, 0.19 mmol) and methyltriphenoxyphosphonium iodide (104 mg, 0.23 mmol) in dimethylformamide (2.3 mL) containing pyridine (20 μL, 0.24 mmol) was stored at room temperature for 1 h and then evaporated. The residue was purified by preparative TLC using chloroform–methanol (4:1) giving a major band that was eluted and evaporated giving 36 mg (59%) of crystalline **18** with mp 251–252 °C dec. Compound **18** behaved as a cation on paper electrophoresis at pH 4.0 and gave a negative test for iodide: λ_{max} (MeOH, H^+) 291 nm. Anal. Calcd for $C_{13}H_{14}N_4O_4S$ (322.27): N, 17.39. Found: N, 17.29.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4-methylthioimidazo[1,2-*a*]-1,3,5-triazin-2(1*H*)-one (19). A solution of **16a** (1.0 g, 1.63 mmol) and methyl iodide (0.2 mL, 3.2 mmol) in a mixture of methanol (6 mL) and dioxane (3 mL) was stirred for 24 h at room temperature in the presence of sodium bicarbonate (140 mg, 1.67 mmol) and then evaporated to dryness. The residue was chromatographed on a column of silica gel (100 g) using benzene–ethyl acetate (89:11) giving 770 mg (75%) of **19** as a homogeneous foam. An analytical sample was prepared by preparative TLC using benzene–ethyl acetate (4:1): λ_{max} (MeOH) 229 nm (ϵ 46 800), 262 (15 600), 281 (sh, 5300), 305 (2800). Anal. Calcd for $C_{32}H_{26}N_4O_8S$ (626.63): C, 61.33; H, 4.18; N, 8.94. Found: C, 61.40; H, 4.24; N, 8.89.

4-Amino-1-(β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-2(1*H*)-one (20a). A solution of **19** (753 mg, 1.2 mmol) in saturated methanolic ammonia (25 mL) was stored at room temperature for 3 days and then evaporated to dryness. Purification of the residue by preparative TLC using two developmens with chloroform–methanol (7:3) gave, after crystallization from water, 203 mg (60%) of **20a** which decomposed slowly above 220 °C: λ_{max} (0.1 N HCl) 232 nm (ϵ

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

compd	registry no.	solvent[a]	$C_{1'}H$	$C_{2'}H$	$C_{3'}H$	$C_{4'}H$	$C_{5'a}H$	$C_{5'b}H$	C_4H, C_5H, (6–10) or C_6H, C_7H (12–30)		other
6a	67463-91-6	C	6.26 (d)	5.75 (dd)	5.85 (m)	4.7 (m)	4.61 (dd)	4.75 (m)	7.00 (br s)	7.08 (br s)	2.55 (s, 3, SMe), 7.3–8.2 (m, 15, Ar)
6b	67463-92-7	P	6.45 (m)[b]	4.86 (dd) or	4.82 (dd)	4.68 (m)	4.07 (dd)	4.23 (dd)	7.25 (d)	7.91 (d)	2.52 (s, 3, SMe)
6c	67463-93-8	C	5.93 (d)	4.75 (dd)	4.88 (dd)	4.24 (m)	3.69 (dd)	3.83 (dd)	6.98 (d)	7.18 (d)	2.52 (s, 3, SMe), 1.35, 1.58 (s, 3, CMe_2)
7a	67463-94-9	C	7.01 (d)	5.80 (dd)	5.90 (dd)	4.8 (m)	4.70 (m)	4.85 (m)	7.11 (d)	7.49 (d)	3.33 (s, 3, SO_2Me), 7.2–8.2 (m, 15, Ar)
7b	67463-95-0	P	7.18 (d)	4.90 (m)	4.90 (m)	4.64 (m)	4.14 (dd)	4.29 (dd)	7.23 (d)	8.48 (d)	3.52 (s, 3, SO_2Me)
10	67463-96-1	C	5.72 (d)	5.60 (dd)	5.80 (dd)	4.66 (m)	4.66 (m)		6.60 (s)	6.64 (s)	5.8 (1, br s, NH), 7.2–8.2 (m, 15, Ar)
12a	67463-97-2	C	6.64 (d)	6.42 (dd)	6.28 (dd)	4.7 (m)	4.65 (dd)	4.85 (dd)	6.91 (d)	7.28 (d)	7.2–8.2 (m, 15, Ar)
12b	67463-98-3	D	6.11 (d)	4.78 (dd)	4.13 (dd)	3.87 (ddd)	3.6 (m)		7.01 (d)	7.48 (d)	
13	67463-99-4	D	6.36 (d)	5.33 (dd)	4.88 (dd)	4.10 (m)	3.50 (dd)	3.69 (dd)	7.02 (d)	7.47 (d)	1.32 and 1.53 (s, 3, CMe_2)
14	67464-00-0	D	6.42 (s)	5.07 (d) or	4.96 (d)	4.9 (m)	4.32 (dd)	4.83 (dd)	7.71 (d)	8.08 (d)	1.25 and 1.44 (s, 3, CMe_2)
16a	67464-01-1	C	6.64 (d)	6.40 (dd)	6.25 (m)	4.75 (m)	4.75 (m)		6.90 (d)	7.30 (d)	7.2–8.1 (m, 15, Ar)
16b	6746402-2	D	6.15 (d)	4.81 (dd)	4.12 (dd)	3.86 (m)	3.45 (dd)	3.62 (dd)	6.89 (d)	7.58 (d)	
17	67488-43-1	D	6.30 (d)	5.26 (dd)	4.83 (dd)	4.03 (m)	3.45 (dd)	3.62 (dd)	6.91 (d)	7.55 (d)	1.28 and 1.48 (s, 3, CMe_2)
18	67464-03-3	D	6.40 (s)	4.95 (d)	4.81 (m)	4.81 (m)	4.21 (dd)	4.67 (dd)	7.36 (d)	7.91 (d)	1.22 and 1.43 (s, 3, CMe_2)
19	67464-04-4	C	6.78 (d)	6.49 (dd)	6.30 (m)	4.75 (m)	4.75 (m)		6.97 (d)	7.07 (d)	2.72 (s, 3, SCH_3), 7.2–8.1 (m, 15, Ar)
20a	67464-05-5	D	6.20 (d)	5.40 (dd)	4.11 (dd)	3.84 (m)	3.50 (m)		7.02 (d)	7.62 (d)	
23a	67464-06-6	D	7.38 (d)	4.89 (dd)	4.21 (dd)	3.89 (m)	3.58 (m)		7.05 (d)	7.66 (d)	
23b	67464-07-7	D	7.41 (d)	4.95 (dd)	4.12 (m)	~4.5 (m)	4.41 (dd)	4.64 (dd)	7.13 (d)	7.70 (d)	3.16 (s, 3, MeOH)
24	67464-08-8	C	6.47 (d)	6.59 (dd)	6.45 (m)	4.8 (m)	4.69 (dd)	4.8 (m)	7.01 (d)	7.36 (d)	2.66 (s, 3, SMe), 7.2–8.1 (m, 15, Ar)
25a	67464-09-9	D	6.33 (d)	4.58 (dd)	4.0 (m)	4.0 (m)	3.52 (dd)	3.68 (dd)	6.92 (d)	7.30 (d)	
25b	67464-10-2	C	7.36 (d)	6.52 (dd)	6.35 (m)	4.8 (m)	4.8 (m)		7.02 (d)	7.42 (d)	
30a	67464-11-3	D	6.18 (d)	3.96 (dd)	3.5 (m)	3.68 (m)	3.28 (dd)	3.40 (dd)	6.79 (s)	6.79 (s)	
30b	67464-12-4	D	6.22 (d)	5.48 (dd)	5.15 (dd)	4.15 (m)	3.24 (dd)	3.95 (dd)	7.00 (d)	7.46 (d)	1.95–2.11 (m, 15, Ac_5), 2.54 (s, 3, Ac)

[a] Solvents are designated as C, $CDCl_3$; D, Me_2SO-d_6; P, pyridine-d_5. Carbinol protons are reported after addition of D_2O. [b] Virtual coupling to $C_{3'}H$.

Table II. First-Order Coupling Constants (Hz)

compd	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	$J_{4,5}$ (6–10) or $J_{6,7}$ (12–30)
6a	5.5	5.5	*a*	2	*a*	12	~1.5
6b	~5[a]	6	4.5	3.5	2.5	12	1.5
6c	3.5	6	3	3.5	3.5	12	1.5
7a	5	5	*a*	*a*	*a*	a	1.5
7b	3.5	6	*a*	3	3	12	1.5
10	5	5	*a*	*a*	*a*	*a*	0
12a	3	6	2	2	2.5	10	1.5
12b	5.5	5.5	3.5	3.5	3.5	*a*	2
13	2	6.5	3.5	3	2	13	1.5
14	0	6	6	4	1	14.5	3
16a	2.5	6.5	*a*	*a*	*a*	*a*	1.5
16b	6	5	3	4	3	12	2
17	2	6	3.5	3	2	12	1.5
18	0	6	*a*	3.5	2	14	2.5
19	3	6	*a*	*a*	*a*	*a*	1.5
20a	6	5.5	3	*a*	*a*	*a*	2
23a	6.5	5.5	3.5	*a*	*a*	*a*	1.5
23b	2.5	5.5	*a*	5.5	2.5	12	1.5
24	3	6	*a*	4.5	*a*	12.5	1.5
25a	7.5	6	*a*	3	4	13	1.5
25b	3	7	*a*	*a*	*a*	*a*	1.5
30a	5	5	*a*	3	2.5	12	0
30b	5.5	5.5	5.5	5	3.5	12	1.5

11 000), 258 (sh, 3500); λ_{max} (0.1 N NaOH) 240 nm (ε 14 400). Anal. Calcd for $C_{10}H_{13}N_5O_5$ (283.24): C, 42.40; H, 4.63; N, 24.73. Found: C, 42.45; H, 4.72; N, 24.68.

A slightly less polar byproduct was also isolated giving 54 mg (12%) of the 5′-*O*-benzoyl derivative (**20b**) as shown by ^{1}H-NMR in Me_2SO-d_6 (4.36 (dd, 1, $J_{4',5'a}$ = 5 Hz, $J_{5'a,5'b}$ = 12 Hz, $C_{5'a}H$), 4.60 ppm (dd, 1, $J_{4',5'b}$ = 5 Hz, $C_{5'b}H$)).

A comparable reaction carried out on **19** (480 mg, 0.77 mmol) in saturated methanolic ammonia at 100 °C for 6 h in a stainless steel bomb led to the formation of a major product more polar than **20.** This substance was purified by preparative TLC giving 155 mg (62%) of what is considered to be **30a** as a TLC homogeneous foam, still retaining some methanol (NMR) after drying in vacuo: λ_{max} (0.1 N HCl/MeOH) 219 nm (ε 10 350); λ_{max} (0.1 N NaOH/MeOH) 227 nm (ε 24 280). Anal. Calcd for $C_{10}H_{16}N_6O_5 \cdot 0.75$MeOH (324.31): C, 39.81; H, 5.90; N, 25.92. Found: C, 39.07; H, 5.67; N, 25.74.

Acetylation of this material (30 mg) with pyridine and acetic anhydride for 18 h at room temperature followed by preparative TLC (carbon tetrachloride–acetone, 3:2) gave 19 mg of rather unstable hexaacetate **30b** as judged by NMR analysis alone.

4-Amino-1-(β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazine-2(1*H*)-thione (23a). *O*-Phenyl chlorothioformate (6 mL, 50 mmol) was added to a solution of potassium thiocyanate (5 g, 50 mmol) in dry acetone (200 mL) giving an immediate orange-red color. After 3 min, a solution of **10** (5.28 g, 10 mmol) in acetone (40 mL) was added and the mixture was stirred at room temperature for 45 min. After evaporation of the solvent, the residue was chromatographed on a column of silica gel (1 kg) using carbon tetrachloride–ethyl acetate (92:8) giving 2.15 g (~31%) of the dithione **22** that was contaminated with a little phenol.[44] This material was dissolved in saturated methanolic ammonia and kept at room temperature for 24 h. Following evaporation of the solvents the residue was chromatographed on a column of silica gel (200 g) using a gradient of 10–20% methanol in chloroform. An initial major peak contained 204 mg (5%) of the 5′-*O*-benzoate (**23b**) with mp 168–169 °C which was identified by NMR.

A subsequent major component gave, after crystallization from methanol, 125 mg (12%) of pure **23a** as a monomethanolate which slowly decomposed above 160 °C without melting. Rehydrolysis of the 5′-*O*-benzoate with methanolic ammonia increased the overall yield of **23a** to 17%: λ_{max} (0.1 N HCl) 240 nm (sh, ε 9600), 259 (14 300), 275 (sh, 12 600), 306 (15 800); λ_{max} (0.1 N NaOH) 256 nm (ε 17 400), 283 (24 000). Anal. Calcd for $C_{10}H_{13}N_5O_4S \cdot CH_3OH$ (331.40): C, 39.86; H, 5.17; N, 21.13. Found: C, 40.00; H, 5.14; N, 21.01.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2-methylthioimidazo[1,2-*a*]-1,3,5-triazine-4(1*H*)-thione (24). Methyl iodide (0.16 mL, 2.6 mmol) was added to a solution of somewhat impure **22** (651 mg, 1.0 mmol) in a mixture of methanol (4 mL) and dioxane (2 mL) in the presence of sodium bicarbonate (100 mg, 1.2 mmol). After stirring at room temperature for 24 h further methyl iodide (100 mg) and sodium bicarbonate (50 mg) were added and the mixture was stirred at room temperature for 16 h and at 37 °C for 8 h. The mixture was evaporated and the residue was adsorbed on silica gel G (2 g) and added to the top of a column containing 60 g of the same silica packed in benzene. Elution with benzene–ethyl acetate (92:8) gave 250 mg (38%) of **24** as a foam that was homogeneous by TLC and NMR analysis: λ_{max} (MeOH) 232 nm (ε 51 000), 257 (sh, 14 100), 274 (8900), 282 (8100). Anal. Calcd for $C_{32}H_{26}N_4O_7S_2$ (642.69): C, 59.80; H, 4.08; N, 8.72. Found: C, 60.20; H, 4.13; N, 8.50.

2-Amino-1-(β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazin-4(1*H*)-one (25a). A solution of **24** (170 mg, 0.26 mmol) in saturated methanolic ammonia (5 mL) was stored at room temperature for 24 h and then evaporated to dryness. The residue was purified by preparative TLC using chloroform–methanol (4:1) and the major eluted band was precipitated from methanol with ether giving 65 mg (88%) of **25a** as an amorphous white solid. A sample reprecipitated as above showed λ_{max} (0.01 N HCl) 238 nm (sh, ε 8700), 262 (13 000) and λ_{max} (0.1 N NaOH) 223 nm (ε 22 300), 267 (sh, 2700) and gave well defined ^{1}H- and ^{13}C-NMR spectra (see Tables I–III), but acceptable elemental analyses could not be obtained. Accordingly, a sample (17 mg, 0.06 mmol) was treated overnight in pyridine (0.8 mL) with *p*-toluoyl chloride (80 μL, 0.6 mmol). The crude product was purified by preparative TLC using two developments with ethyl acetate–cyclohexane (3:7). Elution of the major band followed by crystallization from ethyl acetate–ethanol gave 21 mg (47%) of the N^2,2′,3′,5′-tetra-*p*-toluate (**25b**) with mp 174–176 °C: λ_{max} (dioxane) 239 nm (ε 53 000), 265 (sh, 19 800), 305 (22 100). Anal. Calcd for $C_{42}H_{37}N_5O_9$ (755.76): C, 66.74; H, 4.94; N, 9.27. Found: C, 66.48; H, 4.93; N, 9.18.

Registry No.—**4b,** 67464-13-5; **5a,** 7666-04-8; **5b,** 67464-14-6; **9a** sulfate, 42383-61-9; **15** (Ar = Ph), 6374-24-9; **20b,** 67464-15-7; **22,** 67464-16-8; **28,** 6473-96-7; **29,** 67464-17-9; imidazole-2-thiol, 872-35-5; 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl bromide, 16205-60-0; 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, 6974-32-9; 2,2-dimethoxypropane, 77-76-9; phenoxycarbonyl isocyanate, 5843-43-6; 2-amino-1-methylimidazole, 6646-51-1; methyltriphenoxyphosphonium iodide, 17579-99-6; phenyl chloroformate, 1885-14-9; potassium thiocyanate, 333-20-0; *p*-nitrophenyl chloroformate, 7693-46-1; *S*-phenyl chlorothioformate, 13464-19-2; *O*-phenyl chlorothioformate, 1005-56-7; *p*-toluoyl chloride, 874-60-2.

Table III. ^{13}C-NMR Chemical Shifts

compd	solvent[a]	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	C_2	C_4	C_6[b,c]	C_7[b,c]	C_{8a}[b]	other
4b	dioxane OH						155.40	170.22	107.54 or 113.07	120.00 or 113.07	151.66 146.81	31.77 (8 Me)
9a (sulfate)	D–D_2O								133.55	133.84	147.56	3 benzoyls
10	D	86.80	71.16 or 70.45	73.53	77.31	64.50						
12b	D	88.59	69.77	70.45	85.63	62.19	148.47[d]	143.76	110.92	128.12	141.25	
16b	D	88.00	69.44	71.03	85.60	62.55	150.97[d]	175.06	113.23	125.49	141.22	
18	D	90.93	83.00 or 83.74		80.75	54.13	146.81	173.40	114.79	119.93	141.06	24.32, 25.75 (CMe_2), 112.09 (CMe_2)
20a	D	88.39	69.63	70.74	85.43	62.48	149.67	152.89	109.36	128.48	143.92	
23a	D	93.76	70.15 or 70.38		85.50	62.29	182.25[d]	144.44	109.46	129.00	142.00	
25a	D	89.79	70.32 or 69.15		86.18	60.89	148.14	154.19	110.43	127.05	142.75	
30a	D	90.21	71.55	70.32	83.39	61.99	141.74	163.33	119.63	119.63	162.28	

[a] D refers to Me_2SO-d_6. [b] Compounds **9** and **10** are numbered in this table so as to show the relationship to the accompanying bicyclic compounds. Hence C_6, C_7, and C_{8a} are correctly C_4, C_5, and C_2 using imidazole numbering. [c] While the furthest downfield carbon of C_6 and C_7 has, in several cases, been shown to be coupled to the more upfield imidazole proton, we have not been able to make specific assignments. [d] Spectra of **12b**, **16b**, and **23a** were examined without proton decoupling and showed C_2 as doublets coupled to C_1H with ^3J = 3.9, 3.9, and 4.4 Hz, respectively.

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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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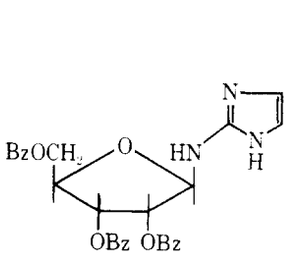
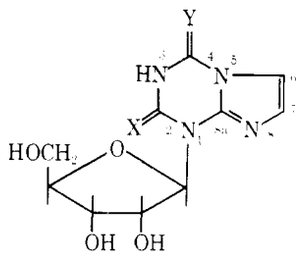
Syntheses of a number of differently ring-substituted 5-aza-7-deazapurine nucleosides are described. Stannic chloride catalyzed condensation of 2-nitroimidazole with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose surprisingly gives the α nucleosides as the predominant product. The desired β-D-ribofuranosyl 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]



1



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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