Synthesis of 6-Amino-1,2,3-triazolo[4,5-*c*]pyridin-4(5*H*)one (8-Aza-3-deazaguanine) and 6-Amino-1-(β-D-ribofuranosyl)-1,2,3-triazolo[4,5-*c*]pyridin-4(5*H*)one (8-Aza-3-deazaguanosine) *via* Novel Ring Closure Procedures

Rich. B. Meyer, Jr., (1a), Ganapathi R. Revankar, P. Dan Cook, (1b), Kenneth W. Ehler (1c), Martin P. Schweizer (1d) and Roland K. Robins*

Cancer Research Center, Department of Chemistry, Brigham Young University, Provo, Utah 84602

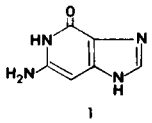
Received August 27, 1979

The total synthesis of 6-amino-1,2,3-triazolo[4,5-*c*]pyridin-4(5*H*)one (8-aza-3-deazaguanine, **3**) and 6-amino-1-(β-D-ribofuranosyl)-1,2,3-triazolo[4,5-*c*]pyridin-4(5*H*)one (8-aza-3-deazaguanosine, **22**) has been described for the first time by a novel base-catalyzed ring closure of 4(5)-cyanomethyl-1,2,3-triazole-5(4)carboxamide (**14**) and methyl 5-cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,3-triazole-4-carboxylate (**17**), respectively. Under the catalysis of DBU, 2,4-dinitrophenylhydrazone of dimethyl 1,3-acetonedicarboxylate (**7**) was converted to methyl 5-methoxycarbonylmethyl-1-(2,4-dinitroanilino)-1,2,3-triazole-4-carboxylate (**12**) *via* dimethyl 2-diazo-3-iminoglutarate (**8**). Catalytic reduction of **12** gave methyl 4(5)methoxycarbonylmethyl-1,2,3-triazole-5(4)carboxylate (**11**) from which methyl 4(5)carbamoylmethyl-1,2,3-triazole-5(4)carboxylate (**10**) was obtained by ammonolysis. Dehydration of **10** provided methyl 4(5)cyanomethyl-1,2,3-triazole-5(4)carboxylate (**13**) which on amination gave **14**. The 1,2,3-triazole nucleosides **17**, **18** and **19** were obtained from the stannic chloride-catalyzed condensation of the trimethylsilyl **13** and a fully acylated β-D-ribofuranose. The yield and ratio of the ribofuranosyl derivatives of **13** markedly depends on the ratio of stannic chloride used. The structures of the nucleosides **22** and **23** were established by a combination of NOE, ^{1}H-nmr and ^{13}C-nmr spectroscopy.

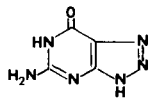
J. Heterocyclic Chem., **17**, 159 (1980).

Introduction.

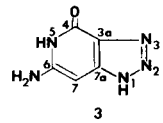
Since the original isolation of the antibiotics toyocamycin, tubercidin and sangivamycin in the early 1960's and subsequent structural elucidation of these antibiotics as 7-deazapurine (pyrrolo[2,3-*d*]pyrimidine) nucleosides, the developments (both chemical and biochemical) in the area of deazapurine nucleosides have been considerable (2). Ensuing interest in the chemical synthesis of such 1-, 3- and 7-deazapurine nucleosides represents one of the most recently explored areas of research in nucleic acid chemistry. Many of these deazapurine derivatives have proven to be of considerable interest in antitumor and antiviral chemotherapy. Recent demonstration by Robins, *et al.* (3) that 3-deazaguanine (6-aminoimidazo-[4,5-*c*]pyridin-4(5*H*)one, **1**) and its ribonucleoside and nucleotide possess potent and broad spectrum antiviral (4) and antitumor (5) activity is a convincing example. Furthermore, 7-(β-D-ribofuranosyl)-3-deazaguanine (6-amino-3-β-D-ribofuranosylimidazo[4,5-*c*]pyridin-4(5*H*)one) has shown significant antibacterial activity (6) against gram-negative bacteria.



1



2



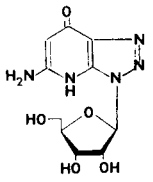
3

The chemical synthesis of 5-amino-1,2,3-triazolo[4,5-*d*]-pyrimidin-7(6*H*)one (8-azaguanine, **2**) in 1945 by Roblin, *et al.* (7) and the discovery of its antibacterial (7), antiviral (8) as well as antitumor (9) activities generated early interest in 8-azapurines. This guanine analog later came into prominence through the pioneering work of Kidder and co-workers (10). Pathocidin, an antifungal antibiotic isolated in 1961 from a species of streptomyces, was found to be 8-azaguanine (11) and has provided a valuable tool for the molecular biologist since it is readily incorporated into the ribonucleic acids (12). 8-Azahypoxanthine has also been shown (13) to have potent activity against Adenocarcinoma 755 in mice. The reported biological and chemotherapeutic activity of various 8-azapurine nucleosides (2,14) has claimed increasing attention in recent years.

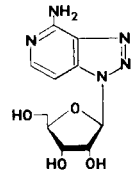
Important biological activity of aza/deaza analogs of guanine and its metabolites is anticipated from ever increasing knowledge of guanine nucleotide metabolism in microbial and mammalian systems (15). The synthesis of 6-amino-1,2,3-triazolo[4,5-*c*]pyridin-4(5*H*)one (8-aza-3-deazaguanine, **3**) and its ribonucleoside is of particular interest since this molecule is structurally related to both the chemotherapeutically potent analogs 3-deazaguanine and 8-azaguanine. This type of compound has potential

0022-152X/80/010159-11$02.25

for use as a biochemical probe in the study of the substrate specificity of enzymes involved in the metabolism of guanosine and related derivatives, since the N-1 atom of guanine or guanosine analog is probably essential to function as either a substrate or an inhibitor of purine nucleoside phosphorylase (PNPase) (15b). Although the



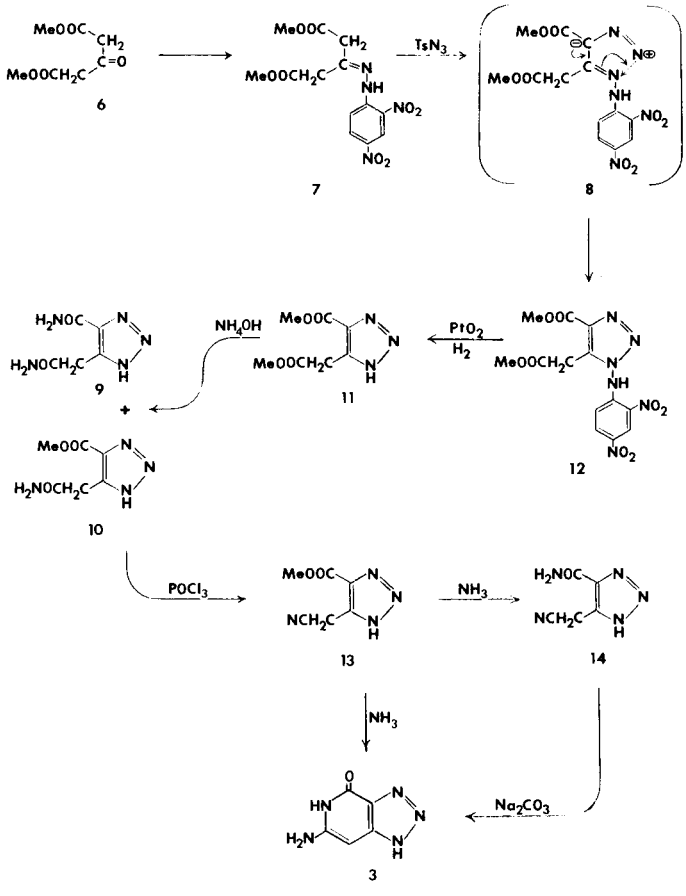
4



5

syntheses of 8-aza-1-deazaguanosine (5-amino-3-β-D-ribofuranosyl-1,2,3-triazolo[4,5-*b*]pyridin-7-one, **4**) (16) and 8-aza-3-deazaadenosine (4-amino-1-β-D-ribofuranosyl-1,2,3-triazolo[4,5-c]pyridine, **5**) (17) have been described, the preparation of either 8-aza-3-deazaguanine or 8-aza-3-deazaguanosine has to date not been realized. We now report the total synthesis of 8-aza-3-deazaguanine and 8-aza-3-deazaguanosine, by a combination of novel ring closure procedures.

SCHEME I



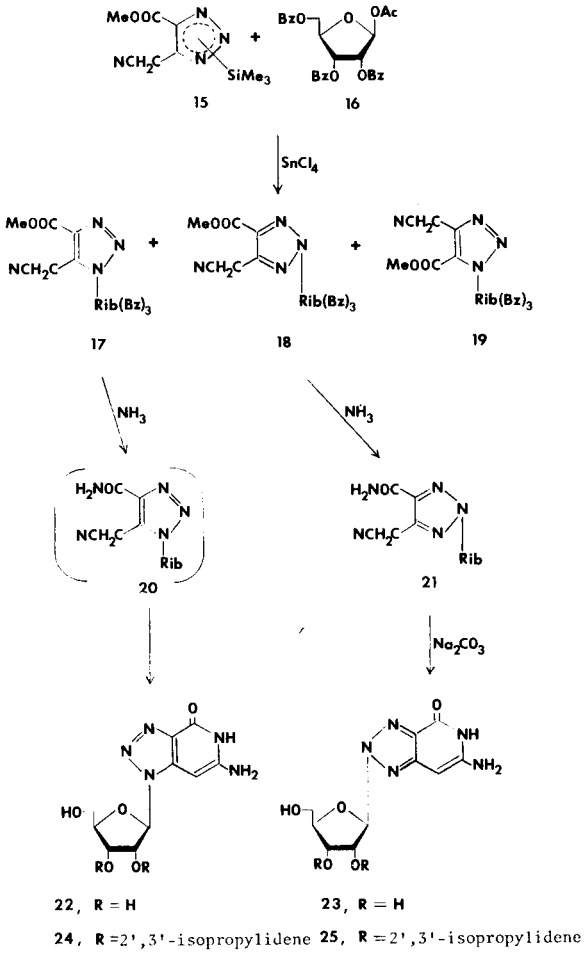
Results and Discussion.

The synthesis of the parent 1,2,3-triazolo[4,5-c]-pyridine ring system might be approached by the well-documented ring-annulation of an appropriately functionalized 3,4-diaminopyridine (18) or a 1,2,3-triazole derivative. We envisaged the latter approach as the most straightforward and admirably suited route to 8-aza-3-deazaguanine (**3**) and its ribonucleoside (**22**). The synthesis of methyl 4(5)methoxycarbonylmethyl-1,2,3-triazole-5(4)carboxylate (**11**), which is amenable to further ring closure to **3**, *via* the elegant procedure employed for the preparation of 3-deazaguanine (**1**) (3) was our first choice. Several of our initial attempts to effect a 1,3-cycloaddition of suitably substituted azide to an enolate of dimethyl 1,3-acetonedicarboxylate (**6**) presented formidable problems. The strategy for the successful synthesis, however, involved the cyclization of a dimethyl 2-diazo-3-iminoglutarate (**8**). Under the catalysis of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), the 2,4-dinitrophenylhydrazone of dimethyl 1,3-acetonedicarboxylate (**7**) was converted to the intermediate diazo derivative (**8**) with *p*-toluenesulfonyl azide. The intermediate **8**, which was not isolated, immediately cyclized to give methyl 5-methoxycarbonylmethyl-1-(2,4-dinitroanilino)-1,2,3-triazole-4-carboxylate (**12**) in 90% yield. This cyclization is analogous to the reported conversion of α-diazoimines, generated oxidatively from 1,2-bishydrazones, to 1-amino-1,2,3-triazoles (19). Catalytic reduction of **12** in the presence of platinum oxide readily gave **11** in over 82% yield. The ^{1}H nmr spectrum is in support of this structure.

Ammonolysis of **11** with concentrated ammonium hydroxide at room temperature readily gave, in addition to the expected (20) methyl 4(5)carbamoylmethyl-1,2,3-triazole-5(4)carboxylate (**10**), the diamide 4(5)carbamoylmethyl-1,2,3-triazole-5(4)carboxamide (**9**). However, this reaction appears to be temperature dependent, since treatment of **11** with cold (0-5°) concentrated ammonium hydroxide furnished exclusively **10**. The mixture of compounds **9** and **10** could be separated by fractional crystallization; the less soluble (in ethanol) diamide **9** crystallizes first. The structure of **10** was established by ^{1}H nmr by observing the methylene resonance shift from δ 4.06 ppm (relative to TMS) in **11** to 3.87 ppm in **10** and 3.90 ppm in **9**. Furthermore, the more upfield of the two methyl ester resonances in **11** (3.67 ppm) was missing in **10** while the downfield methyl resonance (3.86 ppm) was superimposed on the methylene of **10**. It has been shown previously (20) that the downfield of the two methyl resonances of methyl 4(5)methoxycarbonylmethylimidazole-5(4)carboxylate was attributable to the aromatic ester. The key intermediate in the synthesis of **3** or its ribonucleoside is methyl 4(5)cyanomethyl-1,2,3-triazole-5(4)carboxylate (**13**), and was obtained in good yield by

dehydration of **10** with boiling phosphoryl chloride. The structure of **13** was confirmed by observing a nitrile and ester absorption band at 2260 and 1715 cm^{-1}, respectively, in the ir spectrum. The downfield shift of the methylene resonance to 4.34 ppm is further proof of the structure of **10**. Treatment of **13** with liquid ammonia at 100-110° for 10 hours provided 4(5)cyanomethyl-1,2,3-triazole-5(4)-carboxamide (**14**). The ir spectrum of **14** also possessed a nitrile band at 2220 cm^{-1} as well as an amide carbonyl band at 1655 cm^{-1}, in place of the ester carbonyl band of **13**. Compound **14** was smoothly cyclized by refluxing with aqueous sodium carbonate solution (3) to give **3** in 59% yield. By allowing the ammonolysis of **13** to proceed for 8 days at elevated temperature, a 16.5% yield of **3** was obtained, in addition to 75% yield of **14**. The assignment of the 8-aza-3-deazaguanine structure was based on the elemental analysis and ^1H nmr studies. An additional aromatic proton resonance at δ 5.42 ppm due to C_7H, an aromatic amine resonance at δ 5.87 ppm, and the absence of a methylene resonance at δ 4.36 ppm was observed for **3**, which was present in the triazole **14**. Furthermore, the uv spectrum of **3** exhibited the characteristic large bathochromic shifts expected due to the annulation of the pyridone moiety to the triazole ring.

SCHEME II



The next target was the synthesis of 8-aza-3-deazaguanosine (**22**). In recent years, the more stable 1-acyloxy derivatives of protected furanoses in place of 1-halo sugars have been widely employed to couple with trimethylsilylated heterocyclic bases in the presence of a Lewis-acid catalyst (particularly stannic chloride) to obtain the blocked nucleosides (21). We employed this elegant procedure for the preparation of **22**. The conventional trimethylsilylation (22) of **13**, which involved heating the base with hexamethyldisilazane (HMDS) in the presence of the catalyst ammonium sulfate gave the syrupy trimethylsilyl derivative (**15**). Without extensive purification **15** was condensed with 1 equivalent of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**16**) in the presence of 0.72 molar equivalent of anhydrous stannic chloride in 1,2-dichloroethane at ambient temperature for 25 hours. Under these conditions and after silica gel column chromatography, a 93.8% yield of crystalline nucleoside material was obtained, identified as methyl 5-cyanomethyl-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,3-triazole-4-carboxylate (**18**). Careful investigation furnished chromatographic evidence of the formation of at least two other nucleoside materials in very minor amounts (<1.5%); presumably the positional isomers. No attempt was made to isolate these minor products. However, the condensation of 1 equivalent of **15** with 1 equivalent of **16** and 1.44 molar equivalent of stannic chloride in 1,2-dichloroethane at ambient temperature for 20 hours afforded the three isomeric nucleosides **17** (13.5%), **18** (77.0%) and **19** (3.5%), in a distribution much more favorable for our specific needs. This product distribution, which is affected by the amount of stannic chloride, is similar to the stannic chloride catalyzed ribosylation of methyl 4(5)cyanomethyl-1-trimethylsilylimidazole-5(4)carboxylate (3) and 4(5)cyano-5(4)cyanomethyl-1-trimethylsilylimidazole (21e), although not to such a marked extent. A stannic chloride-silylated aglycon complex which may allow regioselective ribosylation may be operative here (3,21e). Longer reaction times and higher temperatures did not improve the yield of **17**. Debenzoylation of **18** with concomitant amination of the ester function was achieved in good yield by the treatment of **18** with methanolic ammonia at room temperature to obtain crystalline 5-cyanomethyl-2-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (**21**). Ring closure of **21** in boiling 5% aqueous sodium carbonate gave 6-amino-2(β-D-ribofuranosyl)-1,2,3-triazolo[4,5-*c*]pyridin-4(5*H*)one (**23**). The ^1H nmr spectrum of **23** revealed an aromatic proton resonance at δ 5.43 ppm for C_7H, an aromatic amine resonance at δ 5.66 ppm and absence of a

methylene resonance at δ 4.38 ppm, which was present in the starting triazole nucleoside (**21**). Because of the paucity of the intermediate **19**, no attempt was made to further cyclize it.

When **17** was treated with liquid ammonia at 100° for 15 hours, a 37.0% yield of very fluorescent 8-aza-3-deazaguanosine (**22**) was obtained. Although tlc of the reaction mixture indicated a fairly clean reaction, the isolation and purification of **22** was difficult. A combination of column chromatography and preparative tlc resulted in the isolation of analytically pure **22** in low yield. Reaction of **17** with methanolic ammonia under milder reaction conditions (**25**° for 20 hours) gave a complex reaction mixture from which the isolation of **22** was much more cumbersome and gave a lower yield.

Although the anomeric configuration of **22** and **23** could tentatively be assigned as β on the basis of several empirical rules (23), and the general recognition that coupling in the presence of a Lewis-acid of silylated base with sugars having a 2-acyloxy function leads almost exclusively (at low temperatures) to the β-anomers of the nucleosides (21), these could not be used for the unequivocal assignment of anomeric configuration. The ^{1}H nmr spectrum of **23** in DMSO-d_6 revealed a doublet for the anomeric proton centered at δ 5.96 ppm with a coupling constant of 4.5 Hz, which suggested the preparation of the 2′,3′-*O*-isopropylidene derivative in order to reduce the magnitude of the coupling constant to within the acceptable limits (24). Isopropylidenation (25) of **23** with 2,2-dimethoxypropane in the presence of perchloric acid in anhydrous acetone at room temperature furnished 6-amino-2-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,3-triazolo[4,5-*c*]pyridin-4(5*H*)one (**25**). The ^{1}H nmr spectrum of **25** in DMSO-d_6 exhibited a coupling constant of 2.0 Hz for the anomeric doublet and also revealed the difference in proton chemical shifts between the methyl signals of the isopropylidene group to be 0.19 ppm, a difference characteristic of β-configuration (26). To establish the anomeric configuration of **22**, 8-aza-3-deazaguanosine was similarly converted to 6-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,3-triazolo[4,5-*c*]pyridin-4(5*H*)one (**24**). The difference between the ^{1}H nmr chemical shifts observed for the isopropylidene methyl groups of **24** was 0.20 ppm (Δδ) which is in good agreement with the reported (26) values for β-ribonucleosides. Based on these data, the β-configuration for **22, 23** and hence for **17** and **18** was assigned.

We then initiated studies designed to provide unambiguous assignments for the site of ribosylation in **22** and **23** by using proton and carbon-13 nmr spectroscopy. The rationale for employing carbon-13 and proton nmr techniques in the present study is based upon the success several laboratories have experienced for the determination of glycosylation site in various fused nitrogen heterocycles. One such method has involved changes in the chemical shifts of carbon atoms located at positions α and β to the site of nitrogen substitution (21d, 27). Another criterion involves the change in vicinal through - nitrogen ^{13}C-H coupling constants in the heterocyclic ring upon substitution of the intervening nitrogen atom (28) or observation of vicinal coupling between α carbons of the heterocycle and anomeric protons of the glycon (15b,21d). Yet a third method used as an aid in assigning glycosylation site concerns the nuclear Overhauser effect (NOE) between spatially close protons in the aglycon and in the glycon moiety (particularly the anomeric proton) (17). In the present study we have utilized all three of the above mentioned methods for structure determination of the N-1 and N-2-β-D-ribofuranosyl derivatives of 6-amino-1,2,3-triazolo[4,5-*c*]pyridin-4(5*H*)one.

^{13}C-nmr Results; Peak Assignments.

In Tables I and II we summarize the carbon-13 chemical shift and ^{13}C-^{1}H coupling constant data for the three compounds of concern, **3, 22** and **23**. Assignment of the five carbon resonances in the base was straight forward. In the proton coupled spectra the singlet at lowest field was ascribed to the carbonyl carbon at position 4. At highest field, C-7 produced a doublet of 170 Hz due to direct coupling to H-7. The remaining resonances, two doublets and a singlet, were differentiated in the coupled spectrum in the following way: The largest doublet, 4.8 Hz due to vicinal coupling to H-7, was assigned to C-3a. With respect to the remaining two carbons, C-6 and C-7a, it would be anticipated that both would display two-bond couplings to H-7. However, it has been observed in systems such as cytosine, that the two bond ^{13}C-^{1}H interaction between amino substituted carbons and protons on adjacent carbons is usually too small to be detected (<0.5 Hz) (29). We have thus assigned the singlet at 76.6 ppm to C-6 and the doublet (1.8 Hz) at 83.7 ppm to C-7a. It should be noted that no long range splitting due to nitrogen bound hydrogens was observed for the three compounds. This is presumably due to exchange. No precautions were taken to remove water from the solvent.

In a similar fashion, the resonances due to the base carbons in the N-2 glycosyl isomer (**23**) were assigned from the proton-coupled spectrum. The ribose carbon resonance designations were taken from the literature (30). The peak due to C-7 which falls in the ribose region was established by noting the 170 Hz direct coupling constant, as seen for this carbon in the base, as contrasted to the 140-150 Hz couplings which the ribose carbons display. The peak assigned to C-1′ has a larger coupling (168 Hz) also, but this resonance appears at such a low field it could not possibly be C-7.

Assignment of the carbon-13 spectrum of the N-1

glycosyl isomer (**22**) generally proceeded in the same way. In this case, however, the situation was somewhat different in that the multiplicity was greater for C-6 and C-7a than in **3** and **23**, namely a doublet and a quartet. The latter was assigned to C-7a since the possibility exists for two bond coupling to H-7 and three bond interactions with H-1′. It is interesting to note that in this case the two bond interaction between H-7 and C-6 results in a measurable coupling constant of 1.2 Hz.

Assignment of Ribosylation Sites.

The designation in Table II of $^{2}J_{C\text{-}7a,H\text{-}7}$ = 1.8 Hz and $^{3}J_{C\text{-}7a,H\text{-}1'}$ = 1.0 Hz for the compound listed as the N-1 isomer is somewhat arbitrary in that we did not attempt selective proton decoupling experiments, primarily due to the long machine times necessary to obtain suitable coupled spectra for 1 KHz sweep widths (18-20,000 scans requiring 26 hours/spectrum). The 1.8 Hz coupling was tentatively assigned to the two bond interactions based upon similarity in magnitude to those found for the aglycon and the compound listed as the N-2 isomer.

The important point to be made here is that two long range interactions are observed at C-7a, one involving H-1′, which necessarily means that the ribofuranosyl moiety must be attached to the N-1 nitrogen. The coupling constant is less than observed in other systems (15b) but it must be recognized that this interaction is strongly dependent upon the orientation of carbohydrate and heterocyclic moieties about the glycosidic bond (28). Thus, if the time average conformation is intermediate between anti and syn, the torsional angle between C-7a and H-1′ about the glycosidic bond could be close to 90° resulting in a vicinal coupling constant close to zero Hz. The situation could thus arise in which lack of a measurable interaction between H-1′ and an α-carbon could frustrate the determination of ribosylation site due to the particular glycosidic torsional conformation. For this reason we rely upon consideration of all three criteria, ^{13}C-shifts, long range ^{13}C-^{1}H coupling and NOE as a basis for our site assignments. It should be noted at this juncture that the compound we designate as the N-2 glycosyl isomer displayed no measurable coupling between C-7a and H-1′.

In Table I we have compared the various chemical shifts between the base and two nucleosides. Note the large positive α-shift (+7.6 ppm) for C-7a in the nucleoside designated as the N-1 isomer, with a much smaller upfield shift seen for the same carbon in the designated N-2 isomer. The two β-carbons, C-3a, C-7, in the case of the N-1 isomer were little affected by ribosylation. For the N-2 isomer, the β-carbons C-3a and C-7a respectively, displayed a negative 3.2 ppm shift and a positive 1.6 ppm shift. Previous work has shown that carbons α to N-substitution are invariably shifted substantially to higher field, whereas β-carbons, although normally shifting 1-2 ppm downfield, can also move 1-2 ppm upfield (15b,27). The data in Table I is thus consistent with the ribosylation assignment.

Proton Nmr Results.

Table III contains pmr data of the two nucleosides **22** and **23** including the NOE results. The assignments for the portion of interest were very straightforward, since H-7 gave a sharp single proton singlet, H-1′ a doublet and NH_2 a broad two-proton singlet which decreased upon adding deuterium oxide to the DMSO-d_6 solution indicating readily exchangeable protons. When H-1′ was irradiated in the sample labeled N-1 isomer, a 12% increase in the area of the peak due to H-7 was observed. No such increase was observed with the N-2 isomer. These results clearly corroborate our glycosylation assignments based upon the carbon-13 data, for only in the case of N-1 ribosylation are H-7 and H-1′ in close enough proximity for enhancement to occur.

Additional information on the chemical nature of the two nucleosides can be gleaned from the proton chemical shift data. In going from N-2 to N-1 substitution, one removes the deshielding influence of the lone pair electrons of one nitrogen, which is reflected in the 0.18 ppm shift upfield for H-1′. Interestingly, C-1′ shifts upfield over 6.0 ppm, as is seen in Table I. Even more interesting is the very large downfield shift of the NH_2 resonance, going from N-2 to N-1 ribosyl attachment. In the latter molecule manipulation of molecular models serves to illustrate that the amino protons can readily hydrogen bond to the 5′-oxygen atom, a situation not possible in the N-2 isomer. However, in order for the NH_2 protons to undergo

Table I

Carbon-13 Chemical Shifts, from Internal Dioxane

Compound	Chemical Shift, δ, ppm									
	C-3a	C-4	C-6	C-7	C-7a	C-1′	C-2′	C-3′	C-4′	C-5′
3	62.8	89.8	76.6	1.0	83.7					
22	63.2	89.4	84.6	0.8	76.1	23.7	6.5	4.2	19.4	+4.6
23	66.0	90.6	85.2	4.0	82.1	30.0	8.3	4.5	19.8	+4.4
Δδ, **3-22**	-0.4	+0.4	-8.0	+0.2	+7.6					
Δδ, **3-23**	-3.2	-0.8	-8.6	-3.0	+1.6					

Table II

^{13}C-^{1}H Coupling Constants, Hz

Compound	C-3a	C-6	C-7	C-7a	C-1′	C-2′	C-3′	C-4′	C-5′
3	H-7 = 4.8		H-7 = 170	H-7 = 1.8	H-1′= 165	H-2′ = 150	H-3′ = 150	H-4′ = 150	H-5′,5″ = 140
22	H-7 = 4.8	H-7 = 1.2	H-7 = 170	H-7 = 1.8 H-1′ = 1.0					
23	H-7 = 6.0		H-7 = 170	H-7 = 1.8	H-1′ = 168	H-2′ = 150	H-3′ = 150	H-4′ = 150	H-5′,5″ = 140

Table III

90 MHz Proton Nmr Results

Compound	Chemical shifts in ppm, from internal dioxane H-7	NH_2	H-1′	NOE H-7 (a)
22	1.93	2.64	2.24 (b)	12%
23	1.93	2.06	2.42 (c)	0

(a) Increase in peak area upon irradiation of H-1′. (b) $^{3}J_{1'-2'}$ = 4.8 Hz. (c) $^{3}J_{1'-2'}$ = 3.9 Hz.

Table IV

p*K*a Values of Certain Guanine and Guanosine Analogs

	p*K*a (acidic)
Guanine	9.3
Guanosine	9.2
3-Deazaguanine	11.2
3-Deazaguanosine	11.2
3-Aza-3-deazaguanine, **3**	10.3
8-Aza-3-deazaguanosine, **22**	10.3
8-β-D-Ribofuranosyl-8-aza-3-deazaguanine, **23**	10.4

hydrogen bonding interaction with the 5′-oxygen in the N-1 isomer, the glycosidic conformation has to be in an "abnormal" syn range where X is about 180°. This corresponds to an angle Φ, around the glycosidic bond of about 80°, which would yield a very low $^{3}J_{C\text{-}7a,H\text{-}1'}$ as observed. In addition, the NOE between H-7 and H-1′ would be modest, as is found. These results strongly suggest that the nucleoside **22** is 6-amino-1-(β-D-ribofuranosyl)-1,2,3-triazolo[4,5-c]pyridin-4(5*H*)one and **23** is the 2-(β-D-ribofuranosyl) isomer.

Because of the proposed (15b) relationship between pKa's and biological activity of guanine analogs, it was of interest to measure the p*K*a's of **3**, **22** and **23**. The natural substrate guanine has a p*K*a value of 9.3 and one would expect an increase in the p*K*a value if a ring nitrogen atom was replaced by a methine group, as was observed in the case of biologically active 3-deazaguanine and 3-deazaguanosine (Table IV). A similar increase in p*K*a values was also observed in the 8-aza-3-deazaguanine series. The biological activity of these compounds will be reported elsewhere.

EXPERIMENTAL

General Procedures.

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H nmr) spectra were recorded at 60 MHz on a Hitachi Perkin-Elmer R-20A Spectrometer in DMSO-d_6 using DSS as an internal standard. Ultraviolet spectra (uv, sh = shoulder) were recorded on a Cary Model 15 spectrophotometer and

infrared spectra (ir) on a Perkin-Elmer 257 spectrophotometer (potassium bromide pellets). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Thin-layer chromatography (tlc) was run on silica gel 60 F-254 (EM Reagents) plates. ICN Woelm silica gel (70-230 mesh) was used for column chromatography. All solvents used were reagent grade. Detection of components on tlc was by ultraviolet light and with 10% sulfuric acid in methanol spray followed by heating. Evaporations were carried out under reduced pressure with the bath temperature below 30°. Samples of **3**, **22** and **23** were dissolved in DMSO-d_6 (Stohler Isotopes) with gentle heating. Both **3** and **23** were 1.0 *M*. solutions, whereas **22** was 0.67 *M*. Since DMSO completely disrupts base stacking interactions which might lead to changes in chemical shifts (31) it is valid to compare the measured shifts directly.

The 25 MHz ^{13}C-spectra were taken at ambient temperature (32-34°) on a Varian XL-100 spectrometer equipped with a 620/L computer. The data table was 8192 points. Sweep widths were generally 5 KHz for decoupled spectra and those coupled spectra where scalar couplings from directly bonded protons were measured. For determination of long range coupling constants, 1 KHz sweeps were utilized. The recycle time between pulses was 5 seconds, about the value estimated for the T_1's of the bridgehead quaternary carbons. One thousand to ten thousand transients were summed and transformed for proton decoupled spectra while 2,000-20,000 scans were collected for coupled spectra (the decoupler was gated off during acquisition of the FID so the NOE was retained). Chemical shifts were measured from internal dioxane. Proton spectra were also obtained on a Varian EM390 spectrometer. p*K*a values were measured spectrophotometrically.

Dimethyl 1,3-Acetonedicarboxylate (2,4-Dinitrophenyl)hydrazone (**7**).

To an ice-cooled solution of 2,4-dinitrophenylhydrazine (198.1 g., 1.0 mole) in concentrated sulfuric acid (400.0 ml.) was added water (800.0 mole) followed by methanol (2.0 l) dropwise with efficient stirring. Dimethyl 1,3-acetonedicarboxylate (**6**, 174.1 g., 1.0 mole) was added dropwise to the mixture and the stirring continued for an additional 2 hours. The copious yellow suspension was cooled (0-5°) and collected by filtration under suction as dry as possible. The crude product was washed with cold water (8 x 250 ml.) until the filtrate was neutral. Crystallization of the product from large excess of methanol provided 315.0 g. (in two crops, 88.9%) of **7** as yellow needles, m.p. 96-97°; ^{1}H nmr (DMSO-d_6): δ 3.65-3.90 (m, 10, C*H*$_2$, C*H*$_3$), 7.88 (d, 1, J = 9.5 Hz, C$_6$*H*), 8.49 (dd, 1, J = 9.5 Hz, J = 3.0 Hz, C$_5$*H*), 8.92 (d, 1, J = 3.0 Hz, C$_3$*H*), 11.37 (s, 1, N*H*); uv λ max (*p*H 1 and 7): 223 nm (ε 13,200), 258 (10,800), 362 (20,800); uv λ max (*p*H 11) 230 nm (ε 13,900), 242 sh (12,800), 332 (9,700); ir (potassium bromide): 870, 915, 1130, 1330, 1410, 1430, 1505, 1580, 1605, 1715 cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}N_4O_8$ (354.27): C, 44.07; H, 3.98; N, 15.82. Found: C, 44.09; H, 3.87; N, 15.81.

Methyl 5-Methoxycarbonylmethyl-1-(2,4-dinitroanilino)-1,2,3-triazole-4-carboxylate (**12**).

To a warm solution (~50°) of **7** (177.1 g., 0.5 mole) and *p*-toluenesulfonyl azide (108.5 g., 0.55 mole) in ethyl acetate (1.5 l) was added 1,5-diazabicyclo[5.4.0]undec-5-ene (83.7 g., 0.55 mole) in one portion with efficient stirring. The solution was stirred at ambient temperature for 1 hour and then extracted with 0.5 *N* hydrochloric acid (3 x 800 ml.) followed by water (3 x 800 ml.). The organic layer was dried over anhydrous sodium sulfate. The residue obtained after the removal of ethyl acetate was crystallized from a mixture of methanol and methoxyethanol (1:1, v/v) to provide 171.1 g. (90.0%) of **12**, m.p. 164-165°; ^{1}H nmr (DMSO-d_6): δ 3.55 (s, 3, C*H*$_3$), 3.92 (s, 3, C*H*$_3$), 4.15 (s, 2, C*H*$_2$), 6.42 (d, 1, J = 9.0 Hz, C$_6$*H*), 8.41 (dd, 1, J = 9.0 Hz, J = 2.0 Hz, C$_5$*H*), 8.97 (d, 1, J = 2.0 Hz, C$_3$*H*), 11.45 (s, 1, N*H*); uv λ max (*p*H 1): 213 nm (ε 21,200), 261 (12,300), 312 (12,700); uv λ max (*p*H 7): 215 nm (ε 22,300), 256 sh (10,400), 315 (13,500), 391 (15,000); uv λ max (*p*H 11): 229 nm (ε 18,500), 255 sh (8,400), 392 (22,700); ir (potassium bromide): 1000, 1050, 1300, 1340, 1410, 1490, 1580, 1610, 1720, 1740, 3250 cm^{-1}.

Anal. Calcd. for $C_{13}H_{12}N_6O_8$ (380.27): C, 41.06; H, 3.18; N, 22.10. Found: C, 40.79; H, 3.09; N, 22.06.

Methyl 4(5)Methoxycarbonylmethyl-1,2,3-triazole-5(4)carboxylate (**11**).

A solution of **12** (22.5 g., 0.059 mole) in acetic acid (30.0 ml.) and methoxyethanol (150.0 ml.) was treated with platinum oxide (0.80 g.) and the mixture was hydrogenated in a Parr apparatus at 35 psi at ambient temperature for 4 hours. The mixture was filtered through a Celite pad which was washed with methoxyethanol (2 x 25 ml.). The combined organic layer was treated with 0.25 *N* hydrochloric acid (250.0 ml.) and then extracted with ethyl acetate (3 x 200 ml.). The residue obtained from evaporation of the dried (magnesium sulfate) extracts was crystallized from ethyl acetate-toluene, using decolorizing carbon, to provide 9.7 g. (82.3%) of **11**, m.p. 127-129°; ^{1}H nmr (DMSO-d_6): δ 3.67 (s, 3, C*H*$_3$), 3.86 (s, 3, C*H*$_3$), 4.06 (s, 2, C*H*$_2$); uv λ max (*p*H 1): 223 nm (ε 9,100); uv λ max (*p*H 7): 235 nm (ε 8,900); uv λ max (*p*H 11): 234 nm (ε 8,700); ir (potassium bromide): 800, 940, 1000, 1100, 1160, 1195, 1220, 1245, 1310, 1410, 1420, 1575, 1710, 1730, 2600, 2850 cm^{-1}.

Anal. Calcd. for $C_7H_9N_3O_4$ (199.17): C, 42.21; H, 4.55; N, 21.10. Found: C, 42.01; H, 4.52; N, 20.95.

4(5)Carbamoylmethyl-1,2,3-triazole-5(4)carboxamide (**9**) and Methyl 4(5)Carbamoylmethyl-1,2,3-triazole-5(4)carboxylate (**10**). Method 1.

A solution of **11** (39.8 g., 0.20 mole) in concentrated ammonium hydroxide (250.0 ml.) was allowed to stand at room temperature in a stoppered flask for 8 hours and then evaporated to dryness. The residue was suspended in hot water (~100 ml.) and adjusted to *p*H 4 with 2 *N* hydrochloric acid and again evaporated to dryness. Fractional crystallization of the residue from ethanol provided methyl 4(5)carbamoylmethyl-1,2,3-triazole-5(4)carboxylate (**10**, 20.0 g., 54.3%) as the more soluble, higher R_f product (chloroform:acetone, 8:2 or methanol:chloroform 9:1, v/v): m.p. 188° dec.; ^{1}H nmr (DMSO-d_6): δ 3.87 (s, 5, C*H*$_2$, C*H*$_3$), 7.05 (br, s, 1, N*H*), 7.55 (br, s, 1, N*H*), 12.05 (br, s, 1, N*H*); uv λ max (*p*H 1): 208 nm (ε 9,000), 222 (8,500); uv λ max (*p*H 7): 224 nm, sh (ε 7,600), 233 (8,300); uv λ max (*p*H 11): 238 nm (ε 9,800); ir (potassium bromide): 780, 830, 950, 995, 1030, 1130, 1200, 1250, 1260, 1330, 1400, 1430, 1485, 1600, 1675, 1720, 2750, 3400 cm^{-1}.

Anal. Calcd. for $C_6H_8N_4O_3$ (184.16): C, 39.13; H, 4.38; N, 30.43. Found: C, 38.96; H, 4.31; N, 30.61.

4(5)Carbamoylmethyl-1,2,3-triazole-5(4)carboxamide (**9**).

This compound (11.0 g., 32.5%) was the more insoluble, lower R_f value product of m.p. 255°; ^{1}H nmr (DMSO-d_6): δ 3.90 (s, 2, C*H*$_2$), 7.05, 7.47, 7.60, 7.88 (br, s, N*H*): uv λ max (*p*H 1): 210 nm (ε 9,500); uv λ max (*p*H 7): 212 nm, sh (ε 7,500), 230 (7,600); uv λ max (*p*H 11) 238 nm (ε 8,700); ir (potassium bromide): 705, 760, 940, 995, 1090, 1145, 1180, 1220, 1265, 1335, 1390, 1420, 1500, 1565, 1605, 1640, 1665,

2650, 3120, 3275 cm^{-1}.

Anal. Calcd. for $C_5H_7N_5O_2$ (169.15): C, 35.50; H, 4.17; N, 41.41. Found: C, 35.39; H, 4.11; N, 41.32.

Method 2.

To precooled (0-5°) concentrated ammonium hydroxide (100 ml.) in a pressure bottle was added finely powdered **11** (16.5 g., 0.083 mole) and the stoppered flask was allowed to stand in the refrigerator overnight with occassional shaking. The solution was evaporated to dryness and the residue was suspended in water (35 ml.). The *p*H of the aqueous mixture was adjusted to 3 with 2*N* hydrochloric acid. The mixture was again evaporated to dryness. The dry residue was crystallized from ethanol using decolorizing carbon to yield exclusively **10** (15.0 g., 98.4%), m.p. 187-188° dec. with identical R_f, ir, ^1H nmr, uv and satisfactory elemental analyses as for the product obtained by method 1.

Methyl 4(5)Cyanomethyl-1,2,3-triazole-5(4)carboxylate (**13**).

A mixture of **10** (36.8 g., 0.20 mole) and freshly distilled phosphoryl chloride (300 ml.) was heated under reflux for 1.5 hours under anhydrous conditions. The excess phosphoryl chloride was removed *in vacuo* and the residual syrup was triturated with several protions of petroleum ether (30-60°, 5 x 100 ml.). The residue was dissolved with cooling in ice-water (200 ml.) and adjusted to *ca* *p*H 6-7 with solid sodium bicarbonate. The *p*H stabilized dark aqueous solution was extracted with ethyl acetate (5 x 200 ml.) and the combined organic layer dried over anhydrous sodium sulfate. Evaporation of the solvent provided 30.0 g. of yellow oil which solidified on cooling. Crystallization of the solid with the aid of decolorizing carbon from water provided 26.0 g. (78.3%) of **13** as stout needles, m.p. 113-114° (after drying at 80° over phosphorus pentoxide for 5 hours); ^1H nmr (DMSO-d_6): δ 3.93 (s, 3, CH_3), 4.34 (s, 2, CH_2), 7.0 (br, s, 1 N*H*); uv λ max (*p*H 1): 211 nm, sh (ε 6,000), 222 (7,100); uv λ max (*p*H 7): 233 nm (ε 9,200); uv λ max (*p*H 11): 235 nm (ε 9,500); ir (potassium bromide): 785, 820, 940, 985, 1100, 1200, 1255, 1355, 1400, 1440, 1525, 1715, 2260, 2920, 3220 cm^{-1}.

Anal. Calcd. for $C_6H_6N_4O_2$ (166.14): C, 43.37; H, 3.64; N, 33.73. Found: C, 43.44; H, 3.73; N, 33.72.

4(5)Cyanomethyl-1,2,3-triazole-5(4)carboxamide (**14**).

A mixture of **13** (16.6 g., 0.1 mole) and liquid ammonia (150.0 ml.) was heated (100-110°) in a steel bomb (300 ml. size) for 10 hours. The ammonia was allowed to evaporate and a vacuum was applied to the residue for several hours to remove the last traces of the solvent. The residue was suspended in hot water and the *p*H adjusted to 6 with 2*N* hydrochloric acid. The residue obtained from removal of the water was crystallized from water with the aid of decolorizing carbon to afford **14** as light yellow needles, 12.3 g. (81.4%), m.p. 165-166°; ^1H nmr (DMSO-d_6): δ 4.36 (s, 2, CH_2), 7.65 (s, 1, N*H*), 7.95 (s, 1, N*H*), 12.4 (br, s, 1, N*H*); uv λ max (*p*H 1): 207 nm (ε 8,200), 217 sh (7,600); uv λ max (*p*H 7): 217 nm, sh (ε 6,100), 233 (7,800); uv λ max (*p*H 11): 234 nm (ε 8,500); ir (potassium bromide): 690, 770, 785, 930, 1130, 1200, 1365, 1395, 1430, 1520, 1600, 1655, 1680, 2220, 3100, 3400 cm^{-1}.

Anal. Calcd. for $C_5H_5N_5O$ (151.13): C, 39.73; H, 3.33; N, 46.34. Found: C, 39.59; H, 3.28; N, 46.51.

6-Amino-1,2,3-triazolo[4,5-*c*]pyridin-4(5*H*)one (8-Aza-3-deazaguanine, **3**). Method 1.

A mixture of **14** (15.1 g., 0.1 mole) and 10% aqueous sodium carbonate (100.0 ml.) was heated under gentle reflux for 1 hour. The cooled reaction mixture was neutralized to *p*H 6 with 2*N* hydrochloric acid and evaporated to dryness. The residue was triturated with a small amount of cold water and then crystallized from aqueous ethanol (charcoal) to provide light-beige needles, 9.0 g. (59.5%), m.p. > 310° dec. (after drying at 80° over phosphorus pentoxide for 10 hours); ^1H nmr (DMSO-d_6): δ 5.42 (s, 1, C_7H), 5.87 (s, 2, NH_2), 10.60 (br, s, 1, N*H*), 12.66 (br, s, 1, N*H*); uv λ max (*p*H 1): 211 nm (ε 18,500), 275 (8,800), 298 sh (3,800); uv λ max (*p*H 7): 212 nm (ε 18,800), 274 (9,700), 299 sh (4,600); uv λ max (*p*H 11): 222 nm (ε 18,700), 263 (6,500), 304 (4,400); ir (potassium bromide): 775, 840, 890, 1015, 1245, 1260, 1350, 1415, 1595, 1640, 1685, 2950, 3315, 3400 cm^{-1}.

Anal. Calcd. for $C_5H_5N_5O$ (151.13): C, 39.73; H, 3.33; N, 46.34. Found: C, 39.58; H, 3.40; N, 46.38.

Method 2.

A mixture of **13** (16.6 g., 0.1 mole) and liquid ammonia (150 ml.) was heated (100-110°) in a steel bomb (300 ml. size) for 8 days. The ammonia was allowed to evaporate, and a vacuum was applied to the residue to remove last traces of solvent. The residue was dissolved in hot water and the *p*H adjusted to 6 with 2*N* hydrochloric acid. The aqueous solution was treated with charcoal, filtered, evaporated to a small volume and allowed to stand at 0° overnight. The light-beige crystals that deposited were collected to provide 2.5 g. (16.5%) of **3**, m.p. > 310° dec. with identical R_f, ir, ^1H nmr and uv as for the product obtained by method 1.

The above filtrate was evaporated to dryness and the residue triturated with a small amount of cold water and crystallized from aqueous ethanol to provide 11.3 g. (74.8%) of 4(5)cyanomethyl-1,2,3-triazole-5(4)carboxamide, identical to **14** prepared as described previously.

Methyl 5-Cyanomethyl-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,3-triazole-4-carboxylate (**18**).

A mixture of dry **13** (5.25 g., 0.031 mole, dried at 80° over phosphorus pentoxide under vacuum, overnight), freshly distilled hexamethyldisilazane (25.0 ml.) and a few crystals of ammonium sulfate (25 mg.) was heated at reflux temperature for 15 hours with the exclusion of moisture. The clear, slightly brown solution was fractionated by distillation to remove excess of HMDS and the residual solid, which eventually melts, was presumed to be the trimethylsilyl derivative (**15**) and was used without further purification. To a solution of **15** in anhydrous 1,2-dichloroethane (200 ml.) was added 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**16**, 16.0 g., 0.031 mole) followed by anhydrous stannic chloride (5.8 g., 0.022 mole). The reaction mixture was protected from moisture and stirred for 25 hours at ambient temperature. The pale yellow reaction mixture was then poured into cold, 10% aqueous sodium bicarbonate solution (400 ml.) containing chloroform (250 ml.) with efficient stirring and keeping the mixture basic at all times. The resulting emulsion was filtered through a Celite pad which was washed with chloroform (5 x 25 ml.). The combined organic layer was washed with saturated aqueous sodium bicarbonate solution (100 ml.) followed by water (2 x 150 ml.) before it was dried over anhydrous sodium sulfate. The solvent was evaporated and the residual light yellow foam was dissolved in chloroform (15 ml.). The solution was applied to an open-bed silica gel column (4 x 40 cm) packed in benzene and the column was eluted with benzene:ethyl acetate (4:1, v/v). The fractions containing the major nucleoside product were pooled and the solvent evaporated to leave homogeneous cream colored foam (18.5 g.) which was crystallized from a large excess of methanol using decolorizing carbon as white

micro-needles, 18.1 g. (93.8%): m.p. 129-130°; ^{1}H nmr (DMSO-d_6): δ 3.96 (s, 3, CH_3), 4.40 (s, 2, CH_2), 7.06 (d, 1, J = 4.5 Hz, C$_1$'H), and other sugar protons; uv λ max (*p*H 1): 235 nm (ε 12,200); uv λ max (ethanol): 231 nm (ε 18,200), 270 sh (9,200); uv λ max (*p*H 11) 228 nm (ε 14,700), 275 sh (5,500); ir (potassium bromide): 1605, 1725, 2260, 3010, 3430 cm^{-1}.

Anal. Calcd. for $C_{32}H_{26}N_4O_9$ (610.58): C, 62.95; H, 4.29; N, 9.18. Found: C, 62.87; H, 4.37; N, 8.96.

Methyl 5-Cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,3-triazole-4-carboxylate (**17**), Methyl 4-Cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,3-triazole-5-carboxylate (**19**) and (**18**).

The procedure described above for the preparation of **18** was followed except that 1.44 molar equivalents of stannic chloride was used instead of 0.72 molar equivalent and the reaction was allowed to proceed for 20 hours at ambient temperature. Tlc (silica gel, benzene-ethyl acetate, 4:1, v/v) indicated completion of the reaction. Column chromatography (silica gel, 3.5 x 85 cm, packed in benzene and eluted with benzene-ethyl acetate, 4:1, v/v) provided **18** as the first major fraction, 14.9 g. (77.0%), m.p. 129-130°. This material was identical with the isomer previously prepared.

Further elution of the column with benzene-ethyl acetate (4:1) provided 0.67 g. (3.5%) of **19** as pale yellow, homogeneous foam, m.p. 78-80° (softens); ^{1}H nmr (DMSO-d_6): δ 3.94 (s, 3, CH_3), 4.35 (s, 2, CH_2), 7.08 (d, 1, J = 3.0 Hz, C$_1$'H), and other sugar protons.

Anal. Calcd. for $C_{32}H_{26}N_4O_9$ (610.58): C, 62.95; H, 4.29; N, 9.18. Found: C, 63.19; H, 4.34; N, 8.89.

Compound **17** was isolated from the last fraction as colorless foam, 2.6 g. (13.5%), m.p. 85-86° (softens); ^{1}H nmr (DMSO-d_6): δ 3.92 (s, 3, CH_3), 4.34 (s, 2, CH_2), 6.86 (d, 1, J = 4.0 Hz, C$_1$'H), and other sugar protons.

Anal. Calcd. for $C_{32}H_{26}N_4O_9$ (610.58): C, 62.95; H, 4.29; N, 9.18. Found: C, 62.79; H, 4.45; N, 8.96.

5-Cyanomethyl-2-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (**21**).

A suspension of **18** (18.32 g., 0.03 mole) in cold (-10°) anhydrous methanol (200 ml.) containing liquid ammonia (150 ml.) in a pressure bottle was allowed to stand at room temperature with stirring for 30 hours. The methanolic ammonia was evaporated to dryness and the residual semi-solid was triturated with boiling benzene (5 x 50 ml.). The benzene insoluble solid was collected and air-dried to yield 8.0 g. of crude product which was crystallized from water, using decolorizing carbon, as light-beige needles, 7.2 g. (84.8%), m.p. 180-181°; ^{1}H nmr (DMSO-d_6): δ 4.38 (s, 2, CH_2), 6.00 (d, 1, J = 5.0 Hz, C$_1$'H), 7.86 (s, 1, NH), 8.13 (s, 1, NH), and other sugar protons; uv λ max (*p*H 1): 232 nm (ε 11,300); uv λ max (*p*H 7): 232 nm (ε 10,600); uv λ max (*p*H 11): 232 nm (ε 13,600); ir (potassium bromide): 1605, 1665, 2260, 3440, 3500, 3550 cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}N_5O_5$ (283.24): C, 42.41; H, 4.63; N, 24.73. Found: C, 42.61; H, 4.82; N, 24.57.

6-Amino-2-(β-D-ribofuranosyl)-1,2,3-triazolo[4,5-*c*]pyridin-4(5*H*)-one (**23**).

A suspension of **21** (2.83 g., 0.01 mole) in absolute ethanol (20.0 ml.) was heated under reflux while 5% aqueous sodium carbonate solution (20.0 ml.) was added dropwise, at the end of which a clear solution was obtained. Heating was continued for an additional 50 minutes. The cooled, slightly yellow solution was neutralized to *p*H 6 with glacial acetic acid before evaporating to dryness. The residue was collected, washed with cold water (2 x 5 ml.) followed by ethanol (3 x 5 ml.) and then crystallized from aqueous ethanol as pale yellow micro-needles to yield 2.20 g. (77.7%), m.p. 231-232° dec.; ^{1}H nmr (DMSO-d_6): δ 5.43 (s, 1, C$_7$$H$), 5.66 (s, 2, N$H_2$), 5.96 (d, 1, J = 4.5 Hz, C$_1$'H), 11.33 (br, s, 1, NH), and other sugar protons; uv λ max (*p*H 1): 228 nm, sh (ε 8,200), 249 (13,300); uv λ max (*p*H 7): 222 nm (ε 17,200), 268 (9,600), 340 sh (3,100); uv λ max (*p*H 11): 233 nm (ε 20,000), 263 sh (3,100), 348 sh (2,800); ir (potassium bromide): 1615, 1640, 1685, 3360, 3450, 3510 cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}N_5O_5$ (283.24): C, 42.40; H, 4.63; N, 24.73. Found: C, 42.25; H, 4.77; N, 24.60.

6-Amino-1-(β-D-ribofuranosyl)-1,2,3-triazolo[4,5-*c*]pyridin-4(5*H*)-one (8-Aza-3-deazaguanosine, **22**).

Method 1.

Compound **17** (1.22 g., 0.002 mole) and liquid ammonia (20 ml.) were heated in a steel bomb (50 ml.) for 15 hours at 100°. The ammonia was allowed to evaporate at room temperature, and the residual solid was triturated with boiling benzene (5 x 20 ml.). The benzene insoluble solid was dissolved in minimum of water and chromatographed on a silica gel column (2.5 x 30 cm) packed in chloroform. The column was eluted with chloroform:-methanol (4:1, v/v) to provide slightly impure **22**, which was rechromatographed on preparative tlc using ethyl acetate:water:-1-propanol (4:2:1, v/v, upper phase) to provide 0.21 g. (37%) of analytically pure (after crystallization from water), very fluorescent 8-aza-3-deazaguanosine, m.p. 230° (starts decomposing); ^{1}H nmr (DMSO-d_6): δ 5.49 (s, 1, C$_7$$H$), 5.83 (d, 1, J = 4.5 Hz, C$_1$'H), 6.10 (s, 2, NH_2), 10.65 (br, s, 1, NH), and other sugar protons; uv λ max (*p*H 1): 218 nm (ε 8,800), 246 sh (2,800), 286 (16,000); uv λ max (*p*H 7): 217 nm (ε 12,600), 287 (16,900); uv λ max (*p*H 11): 227 nm (ε 14,900), 285 (6,300), 312 (4,800); ir (potassium bromide): 1050, 1625, 1675, 3180, 3340, 3420 cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}N_5O_5.H_2O$ (301.26): C, 39.87; H, 5.01; N, 23.24. Found: C, 40.07; H, 4.79; N, 23.35.

Method 2.

A suspension of **17** (0.61 g., 0.001 mole) in cold (0 to -5°) anhydrous methanol (15 ml.) containing liquid ammonia (10 ml.) in a pressure bottle was allowed to stand at room temperature with stirring for 20 hours. The methanolic ammonia was evaporated to dryness and the residual solid was triturated with boiling benzene (5 x 10 ml.). The benzene insoluble solid was found to be a mixture of four components from which 80 mg. (28.2%) of **22** was isolated by repeated column chromatography (silica gel, chloroform:methanol, 4:1, v/v) and crystallization. This material was identical with 8-aza-3-deazaguanosine prepared by method 1.

6-Amino-2-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,3-triazolo-[4,5-*c*]pyridin-4(5*H*)one (**25**).

2,2-Dimethoxypropane (0.35 ml.) and 70% perchloric acid (0.10 ml.) were added to dry acetone (35 ml.). The mixture was protected from moisture and stirred at room temperature for 5 minutes before **23** (0.28 g., 0.001 mole) was added in one portion. The mixture was stirred for 5 hours and the reddish-orange solution was adjusted to *ca. p*H 7 with 10% aqueous sodium carbonate. The solution was evaporated to dryness *in vacuo* to a syrup which was chromatographed on a silica gel column (2 x 25 cm). Elution with ethyl acetate:water:1-propanol (4:2:1, v/v, upper phase) provided the isopropylidene derivative (0.20 g., 62.5%) as an orange colored foam. Crystallization from aqueous ethanol gave an analytical sample of m.p. 236-238° dec.; ^{1}H nmr (DMSO-d_6): δ 1.36 (s, 3, CH_3), 1.55 (s, 3, CH_3), 5.45 (s, 1, C$_7$$H$), 5.66 (s, 2, N$H_2$), 6.26 (d, 1, J = 2.0 Hz, C$_1$'H), 11.53 (br, s, 1, NH); uv λ max (*p*H 1): 228

nm, sh (ε 7,900), 248 (8,700); uv λ max (*p*H 7): 223 nm (ε 21,300), 267 (7,100), 339 sh (2,300); uv λ max (*p*H 11): 232 nm (ε 22,300), 263 sh (3,200), 348 sh (2,300); ir (potassium bromide): 1080, 1140, 1615, 1640, 1680, 3420, 3480, 3560 cm^{-1}.

Anal. Calcd. for $C_{13}H_{17}N_5O_5$ (323.30): C, 48.29; H, 5.30; N, 21.66. Found: C, 48.01; H, 5.43; N, 21.48.

6-Amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,3-triazolo-[4,5-*c*]pyridin-4(5*H*)one (**24**).

By following the procedure described above for the preparation of **25**, compound **22** (70 mg.) was reacted with 2,2-dimethoxypropane (0.1 ml.) in acetone (10 ml.) containing a drop of perchloric acid. Crystallization of the product from aqueous ethanol gave 52 mg. of **24**, m.p. >235° dec.; ^{1}H nmr (DMSO-d_6): δ 1.41 (s, 3, C*H*$_3$), 1.61 (s, 3, C*H*$_3$), 5.51 (s, 1, C$_7$*H*), 5.96 (d, 1, J = 2.5 Hz, C$_1$'*H*), 6.21 (s, 2, N*H*$_2$), 10.68 (br, 1, N*H*); uv λ max (*p*H 1): 220 nm (ε 1,300), 286 (1,600); uv λ max (*p*H 7): 218 nm (2,200), 286 (1,600); uv λ max (*p*H 11): 227 nm (ε 3,900), 286 (1,300), 312 sh (1,300); ir (potassium bromide): 1080, 1140, 1615, 1675, 3420, 3480, 3550 cm^{-1}.

Anal. Calcd. for $C_{13}H_{17}N_5O_5$ (323.30): C, 48.29; H, 5.30; N, 21.66. Found: C, 48.16; H, 5.23; N, 21.52.

Acknowledgments.

The authors wish to thank Howard Cottam and Doug Reinhart for technical assistance and large-scale preparation of the intermediates.

REFERENCES AND NOTES

(1a) Department of Pharmaceutical Chemistry, University of California, San Francisco, CA 94143; (b) Warner-Lambert/Parke-Davis Pharmaceutical Research Division, Ann Arbor, MI 48106; (c) Department of Chemistry, University of Nevada, Reno, NV 89507; (d) Department of Medicinal Chemistry, The University of Utah, Salt Lake City, Utah 84112.

(2) G. R. Revankar and R. K. Robins, in "Chemistry of Nucleosides and Nucleotides" Vol. II, R. K. Robins and L. B. Townsend, Eds., Plenum Publishing Corp., New York, N. Y., in press.

(3) P. D. Cook, R. J. Rousseau, A. M. Mian, P. Dea, R. B. Meyer, Jr., and R. K. Robins, *J. Am. Chem. Soc.*, **98**, 1492 (1976).

(4a) R. W. Sidwell, L. B. Allen, J. H. Huffman, J. T. Witkowski, P. D. Cook, R. L. Tolman, G. R. Revankar, L. N. Simon, and R. K. Robins, *Chemotherapy*, **6**, 279 (1976); (b) L. B. Allen, J. H. Huffman, P. D. Cook, R. B. Meyer, Jr., R. K. Robins, and R. W. Sidwell, *Antimicrob. Agents Chemother.*, **12**, 114, (1977); (c) P. D. Cook, L. B. Allen, D. G. Streeter, J. H. Huffman, R. W. Sidwell, and R. K. Robins, *J. Med. Chem.*, **21**, 1212 (1978).

(5a) T. A. Khwaja, L. Kigwana, R. B. Meyer, Jr., and R. K. Robins, *Proc. Am. Assoc. Cancer Res.*, **16**, 162 (1975); (b) T. A. Khwaja and J. Varven, *ibid.*, 17, 200 (1976); (c) A. M. Mian and T. A. Khwaja, 2nd Joint Conf. of CIC/ACS, Medicinal Chem. Division, Montreal, Canada, May 1977, Abstract #15; (d) P. Schwartz, D. Hammond, and T. A. Khwaja, *Proc. Am. Assoc. Cancer Res.*, **18**, 153 (1977).

(6) T. R. Matthews, D. W. Yotter, P. D. Cook, R. W. Sidwell, R. K. Robins, and P. F. Dougherty, 16th Intersceince Conf. on *Antimicrob. Agents Chemother.*, Chicago, Ill., 1976, Abstract #425, 426.

(7) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole, and J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **67**, 290 (1945).

(8) R. E. F. Matthews and J. D. Smith, *Adv. Virus Res.*, **3**, 49 (1955).

(9a) R. W. Brockman and S. Chumley, *Biochim. Biophys. Acta*, **95**, 365 (1965); (b) J. F. Henderson, *Biochem. Pharacol.*, **12**, 551 (1963).

(10a) G. W. Kidder and V. C. Dewey, *J. Biol. Chem.*, **179**, 181 (1949); (b) G. W. Kidder, V. C. Dewey, R. E. Parks, Jr., and G. L. Woodside, *Science*, **109**, 511 (1949); (c) G. W. Kidder, V. C. Dewey, R. E. Parks, Jr., and G. L. Woodside, *Cancer Res.*, **11**, 204 (1951).

(11a) K. Anzai and S. Suzuki, *J. Antibiot.*, **14A**, 253 (1961); (b) K. Anzai, J. Nagatsu, and S. Suzuki, *ibid.*, **14A**, 340 (1961).

(12a) J. H. Mitchell, H. E. Skipper, and L. L. Bennett, Jr., *Cancer Res.*, **10**, 647 (1950); (b) R. E. F. Matthews, *Nature*, **171**, 1065 (1953); (c) I. Lasnitzki, R. E. F. Matthews, and J. D. Smith, *ibid.*, **173**, 346 (1954); (d) H. G. Mandel and P. E. Carlo, *J. Biol. Chem.*, **201**, 335 (1953); (e) R. W. Brockman, C. Sparks, D. J. Hutchison, and H. E. Skipper, *Cancer Res.*, **19**, 177 (1959); (f) R. W. Brockman, L. L. Bennett, Jr., M. S. Simpson, A. R. Wilson, J. R. Thomson, and H. E. Skipper, *ibid.*, **19**, 856 (1959).

(13) R. K. Robins, *J. Med. Chem.*, **7**, 186 (1964).

(14a) P. W. Allan and L. L. Bennett, Jr., *Proc. Am. Assoc. Cancer Res.*, **11**, 2 (1970); (b) W. Hutzenlaub, R. L. Tolman, and R. K. Robins, *J. Med. Chem.*, **15**, 879 (1972); (c) C. W. Smith, R. W. Sidwell, R. K. Robins, and R. L. Tolman, *ibid.*, **15**, 883 (1972); (d) L. L. Bennett, Jr., M. H. Vail, P. W. Allen, and W. R. Laster, Jr., *Cancer Res.*, **33**, 465 (1973); (e) R. D. Elliott and J. A. Montgomery, *J. Med. Chem.*, **19**, 1186 (1976).

(15a) C. I. Pogson, *Am. J. Clin. Nutr.*, **27**, 380 (1974); (b) L. B. Townsend, B. L. Cline, R. P. Panzica, P. E. Fagerness, L. W. Roti Roti, J. D. Stoeckler, G. W. Crabtree, and R. E. Parks, Jr., *Lecutres in Heterocyclic Chem.*, Vol. IV, R. N. Castle and I. Lalezari, Eds., HeteroCorp., Orem, UT (1978), S-79.

(16a) B. L. Cline, R. P. Panzica, and L. B. Townsend, *J. Heterocyclic Chem.*, **13**, 1365 (1976); (b) B. L. Cline, R. P. Panzica, and L. B. Townsend, *J. Org. Chem.*, **43**, 4910 (1978).

(17) J. A. May, Jr. and L. B. Townsend, *ibid.*, **41**, 1449 (1976).

(18a) Z. Talik and E. Plazek, *Rocz. Chem.*, **30**, 1139 (1956); (b) K. B. deRoos and C. A. Salemink, *Rec. Trav. Chim.*, **90**, 1166 (1971); (c) C. Temple, Jr., B. H. Smith, and J. A. Montgomery, *J. Org. Chem.*, **37**, 3601 (1972); (d) C. Temple, Jr., B. H. Smith, and J. A. Mongomery, *ibid.*, **38**, 1095 (1973).

(19a) G. Wittig and A. Krebs, *Chem. Ber.*, **94**, 3260 (1961); (b) S. Hauptman, H. Wilde, and K. Moser, *Tetrahedron Letters*, 3295 (1967).

(20) R. K. Robins, J. K. Horner, C. V. Greco, C. W. Noell, and C. G. Beamers, *J. Org. Chem.*, **28**, 3041 (1963).

(21a) U. Neidballa and H. Vorbrüggen, *Angew. Chem., Int. Ed. Engl.*, **9**, 461 (1970); (b) U. Neidballa and H. Vorbrüggen, *J. Org. Chem.*, **39**, 3654, 3660, 3672 (1974), and references cited therein; (c) K. A. Watanabe, D. H. Hollenberg and J. J. Fox, *J. Carbohydr. Nucleosides Nucleotides*, **1**, 1 (1974); (d) S.-H. Kim, D. G. Bartholomew, L. B. Allen, R. K. Robins, G. R. Revankar, and P. Dea, *J. Med. Chem.*, **21**, 883 (1978); (e) P. D. Cook and R. K. Robins, *J. Org. Chem.*, **43**, 289 (1978).

(22) E. Wittenburg, *Z. Chem.*, **4**, 303 (1964).

(23a) B. R. Baker, *Chem. Biol. Purines, Ciba Found. Symp.*, **1956**, 120 (1957); (b) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (c) J. A. Montgomery, *Carbohydr. Res.*, **33**, 184 (1974), and references cited therein.

(24) L. B. Townsend, in "*Synthetic Procedures in Nucleic Acid Chemistry*", Vol. 2, W. W. Zorbach and R. S. Tipson, Eds., Wiley-Interscience, New York, N. Y. (1973), p. 331.

(25) G. R. Revankar and L. B. Townsend, *J. Chem. Soc., C*, 2440 (1971).

(26a) J.-L. Imbach, J.-L. Barascut, B. L. Kam, B. Rayner, C. Tamby, and C. Tapiero, *J. Heterocyclic Chem.*, **10**, 1069 (1973); (b) J.-L. Imbach, J.-L. Barascut, B. L. Kam, and C. Tapiero, *Tetrahedron Letters*, 129 (1974).

(27a) G. P. Kreishman, J. T. Witkowski, R. K. Robins, and M. P. Schweizer, *J. Am. Chem. Soc.*, **94**, 5894 (1972); (b) P. Dea, G. R. Revankar, R. L. Tolman, R. K. Robins, and M. P. Schweizer, *J. Org. Chem.*, **39**, 3226 (1974); (c) P. Dea and R. K. Robins, in "Chemistry and Biology of Nucleosides and Nucleotides", R. Harmon, R. K. Robins, and L. B. Townsend, Eds., Academic Press, New York, N. Y., 1978, p. 301; (d) M.-T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzica, and L. B. Townsend, *J. Am. Chem. Soc.*, **97**, 4627, 4636 (1975).

(28) P. Dea, G. P. Kreishman, M. P. Schweizer, J. T. Witkowski, R. Nunlist, and M. Bramwell, in "Proceedings of the 1st International Conference on Stable Isotopes in Chemistry, Biology and Medicine", P. D. Klein and S. V. Petersen, Eds., USAEC Technical Information Center, Oak Ridge, Tenn., 1973, p. 84.

(29) M. P. Schweizer, E. B. Banta, J. T. Witkowski, and R. K. Robins, *J. Am. Chem. Soc.*, **95**, 3770 (1973).

(30a) A. J. Jones, D. M. Grant, M. W. Winkley, and R. K. Robins, *ibid.*, **92**, 4079 (1970); (b) H. H. Mantsch and I. C. P. Smith, *Biochem. Biophys. Res. Commun.*, **46**, 808 (1972).

(31) S. I. Chan, M. P. Schweizer, P. O. P. Ts'o, and G. K. Helmkamp, *J. Am. Chem. Soc.*, **86**, 4182 (1964).