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Ring Contractions of 5-Diazouracils. I. Conversions of 5-Diazouracils into 1,2,3-Triazoles by Hydrolysis and Methanolysis

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The hydrolysis of $O^{5'}$-6(*S*)-cyclo-5-diazouridine (**1**) to 1-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (**2**) and carbon dioxide was shown to proceed via initial attack at C-2 by using oxygen-18 label in the C-4 position. Similar reactions of $O^{5'}$-6(*S*)-cyclo-5-diazo-2′-deoxyuridine (**5**), 5-diazouracil-6-methanolate (**7**), and 5-diazo-1-methyluracil-6-methanolate (**11**) gave the expected triazole derivatives. The unsuccessful hydrolysis of $O^{5'}$-6(*S*)-cyclo-5-diazo-3-methyluridine (**13**) was shown to be due to the absence of an initial attack by water. Methanolysis of **1** gave **2**, methyl 1-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxylate (**16**), and methyl carbamate (**17**). Methanolysis of **11** gave 1-methyl-1,2,3-triazole-4-carboxamide (**12**), **17**, and methyl 1-methyl-1,2,3-triazole-4-carboxylate (**18**). Methanolysis of **7** gave methyl *N*-(1,2,3-triazol-4-ylcarbonyl)carbamate (**20**) which established that these ring contractions proceeded via a N-1–C-2 bond cleavage. Diazotization of O^{2}-2′-cyclo-5-amino-5′-deoxyuridine (**28**) gave a product which suggested that these ring contractions require the formation of a tautomeric carbinolamidine prior to nucleophilic attack. Methanolysis of 5-(3,3-dimethyl-1-triazeno)uridine (**36**) gave **2** and **16**. This reaction was probably the result of direct nucleophilic attack on **36** rather than a prior decomposition of the triazeno group to a diazo group since 5-(3,3-dimethyl-1-triazeno)-1,3-dimethyluracil (**38**) was recovered quantitatively under similar reaction conditions. A partial hydrolysis of **11** labeled with oxygen-18 at C-2 showed a retention of isotopic label and suggested that the transition state for ring opening involved a partial C–N bond cleavage rather than the formation of a tetrahedral intermediate. The results are discussed in terms of a mechanism in which a proton at N-3 of the uracil ring must tautomerize to the O-2 position and the diazo ether derivative of this tautomer must be formed prior to ring opening.

Our initial interest in this area involved a structural reinvestigation[1] of 5-diazouracils and their possible synthetic utility for the preparation of 5-substituted uracil derivatives. This had been suggested[2] in the literature and a few reports of nucleophilic displacement reactions had been published.[3–5] Our preliminary studies, to determine the susceptibility of the diazo group of $O^{5'}$-6(*S*)-cyclo-5-diazouridine[1] (**1**) toward nucleophilic displacement, revealed that displacement reactions did not occur at low temperatures. In an effort to find a suitable solvent for conducting displacement reactions at elevated temperatures, we investigated the stability of **1** in acetonitrile at 100°. We observed a ring contraction of **1** to afford 1-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide[6] (**2**). We could find no precedent for this unusual reaction in the literature, which prompted us to initiate a study on the scope and mechanism of this reaction.

Results and Discussion

A solution of **1** in acetonitrile was heated in a stainless steel reaction vessel at 100° and the solution was then allowed to stand at ambient temperature to afford a white solid (**2**). Initial data indicated that **1** had been converted to uridine via a simple nitrogen elimination, since there was observed an absence of absorption bands in the 4.65-μ region of the ir spectrum and specific peaks [B + H (112), B + 2H (113), S (133), M − 30 (214)] in the low-resolution mass spectrum were essentially identical with those reported for uridine.[7] However, the uv spectrum of **2** revealed the absence of any absorption maximum in the 230–346-nm region. Elemental analyses (C, H, N) for **2** were found to be consistent with the empirical formula $C_8H_{12}N_4O_5$ and established that a ring carbonyl group had been lost instead of diatomic nitrogen. The structure of **2** was established on the basis of the following data.

The ^{1}H NMR spectrum (Figure 1) of **2** revealed a pattern of peaks in the δ 3.5–6.5 region which were indicative[8] of a ribofuranosyl moiety. The presence of D-ribose was confirmed by the treatment of **2** with dilute acid, followed by a direct paper chromatographic comparison of the hydrolysate with similarly treated samples of D-ribose, D-arabinose, and D-xylose (Table I). The facile hydrolysis of **2** suggested a *N*-glycosyl bond. The ^{1}H NMR spectrum (Figure 1) of **2** revealed the presence of two broad singlets (δ 7.75 and 7.50) which were exchanged on the addition of deuterium oxide to the ^{1}H NMR sample. This was suggestive of a carboxamide group and additional evidence for the presence of an amide group was obtained by a positive hydroxylamine–ferric chloride test.[9] Only one unassigned absorption peak remained in the ^{1}H NMR spectrum and it was assumed to be an aromatic proton on the basis of its chemical shift (δ 8.80). These data were all consistent with a disubstituted, five-membered heterocycle with three ring nitrogens (triazole). The formation of a triazole could occur by loss of the carbonyl group in the C-2 position of **1** followed by annulation between N-1 and the diazo group. If ring opening and rearrangement had occurred in the proposed manner, then the structure must be 1-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide[10–12] (**2**). A rigorous comparison of this nucleoside with an authentic sample prepared

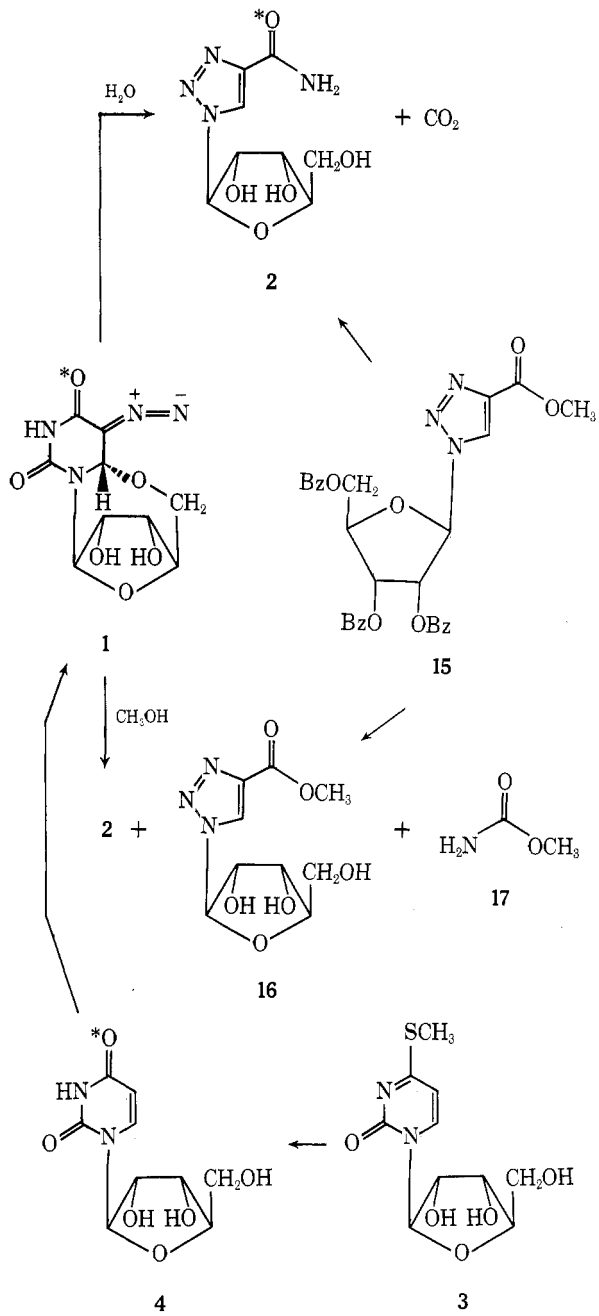


Table I
Chromatographic Comparison of the Hydrolysate[a] of 2 with Authentic Pentoses

Compd	R_f A[b]	R_f B[b]
Hydrolysate of **2**	0.303	0.206
D-Ribose	0.305	0.209
D-Arabinose	0.250	0.138
D-Xylose	0.244	0.244

[a] 10-mg samples in 1 *N* hydrochloric acid (2 ml) were heated on a steam bath for 30 min and then neutralized by the addition of 0.8 *N* sodium hydroxide. Samples were then applied to Whatman No. 1 chromatography paper and developed (descending) a distance of 18 in. Components were detected as dark spots by spraying with an aniline–phthalic acid mixture[c] followed by heating for 10 min at 120°. [b] Solvent systems: A, 1-butanol–acetic acid–water (3:1:4 v:v:v, organic phase); B, 1-butanol–acetic acid–water (3:1:1 v:v:v). [c] S. M. Partridge, *Nature (London)*, **164**, 443 (1949).

Table II
Comparison of
1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxamide (2)

	From 1	From 15
Mp, °C	202–204	202–204
Uv, λ_{max} (water)	210 nm (ε 12212)	210 nm (ε 12444)
Ir, μ	2.96 (NH_2) 5.97 (C=O)	2.96 (NH_2) 5.97 (C=O)
^{1}H NMR (Figure 1), δ	8.8 (s, 1 H5)	8.8 (s, 1 H5)
$[\alpha]^{26}D$ (*c* 1, H_2O)	−61.0°	−61.6°
TLC,[a] R_f A	0.45	0.45
B	0.39	0.39
C	0.66	0.66
EI MS[b] M	244/0	244/0
M − CH_2O	214/1.8	214/2.0
B + C_2H_4	155/3.7	155/3.8
B + CH_2O	141/3.0	141/3.3
B + 2H	113/21.5	113/21.6
B + H	112/100.0	112/100.0
CI MS (CH_4)		
M + C_3H_5	285/7	285/7
M + C_2H_5	273/30	273/4
MH	245/38	245/24
BH_2	113/100	113/100

[a] Thin layer chromatography was performed on 5 × 20 cm glass plates coated to a thickness of 0.25 mm with Mallinckrodt SilicAR 7GF. Solvent systems: A, chloroform–methanol (3:1 v:v); B, ethyl acetate–ethanol (9:1 v:v); C, ethyl acetate–1-propanol–water (4:1:2 v:v:v, organic phase). [b] M = molecular ion; B = base moiety. Reported as *m/e*/rel intensity.

by one of the reported[10] procedures established that these compounds were identical in every respect (Table II).

A quantitative yield of starting material (1) was recovered when this reaction was repeated using anhydrous acetonitrile, which suggested that water was required for the ring opening and ring contraction. A quantitative yield of **2** was obtained when water (5%) was included in the reaction, which established that water was indeed an essential reactant. Therefore, ring opening was the result of hydrolysis, with two possible positions (C-2 and C-4) at which nucleophilic attack by water followed by ring opening could occur. Either route would lead to a carbamic acid derivative which should decarboxylate[13] under the reaction conditions and evolve carbon dioxide. This prompted us to collect gases from the reaction mixture by attaching an evacuated glass bulb to the bleed valve of the reaction vessel, which allowed the gases to escape into the bulb. A mass spectrum, of the contents of the bulb, revealed that carbon dioxide had in fact been evolved as evidenced by a molecular ion at *m/e* 44.

The nucleoside (1) labeled with oxygen-18 at the C-4 position was required to establish which carbonyl group of **1** had been eliminated. Acid-catalyzed hydrolysis of 1-(β-D-ribofuranosyl)-4-methylthio-2-pyrimidone[14] (**3**) in oxygen-18 enriched (10%) water furnished the uridine (*4) required for the preparation of *1. Compound *4 was converted to *1 by bromination, amination, and subsequent diazotization[1] without a loss of isotopic label (Table III). Reaction of *1 gave *2 under the above conditions and a mass spectrum of *2 (Table III) demonstrated a complete retention of label. The isotopic content of *2 was determined by calculating the relative percentage of the second isotope peak of the ion fragment at *m/e* 214 (M − 30). The isotopic content of *2, by an analysis of the B + 2H ion fragment, was precluded since an additional small ion fragment occurs at the same mass in the spectrum of **2**. However, it was possible to assign the isotope of *2 to the carboxamide group since there was very little possibility of oxygen migration from the C-4 position of 1 to the ribofuranose moiety of **2**. Further studies demonstrated no involvement of the carbohy-

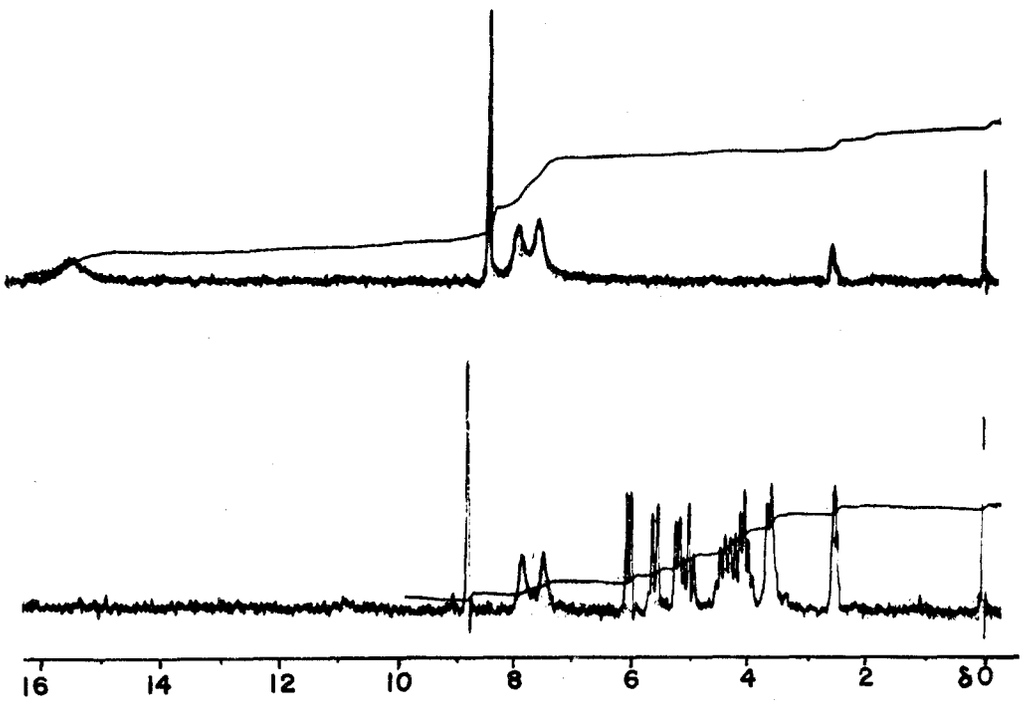


Figure 1. ^{1}H NMR spectra (Me_2SO-d_6) of 1,2,3-triazole-4-carboxamide (8) (top) and 1-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (2) (bottom).

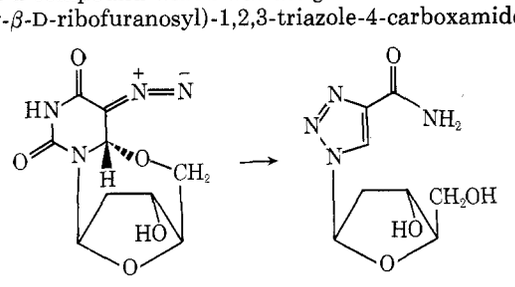
Table III
Oxygen-18 Enrichments[a]

Compd	Ion measured, *m/e*	% oxygen-18
*3	226 (M − H_2O)	9.75
*1	139 (BH)	8.70
*2	214 (M − 30)	8.70
*40	126 (M)	5.65
*11	153 (M − CH_3O)	5.39
*11 + *41[b]	153 (M − CH_3O or M − OH)	4.91

[a] Corrected for the natural abundance of oxygen-18. [b] Mixture obtained from partial reaction of 11* with water (see text).

drate moiety in the reaction and with the isotope being assigned to the carboxamide group, several conclusions were drawn from the observed retention of label. This indicated that the carboxamide group of **2** originated from the N-3 and C-4 positions of **1**, that the carbonyl group in the C-2 position of **1** was eliminated during the reaction, and also that the C-4 oxygen atom of **1** was not exchanged by solvent (water) under the reaction conditions.

A solution of $O^{5'}$-6(*S*)-cyclo-5-diazo-2′-deoxyuridine[1] (**5**) in 5% aqueous acetonitrile was heated at 100° for 18 hr to afford a compound which was assigned the structure 1-(2-deoxy-β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (**6**)

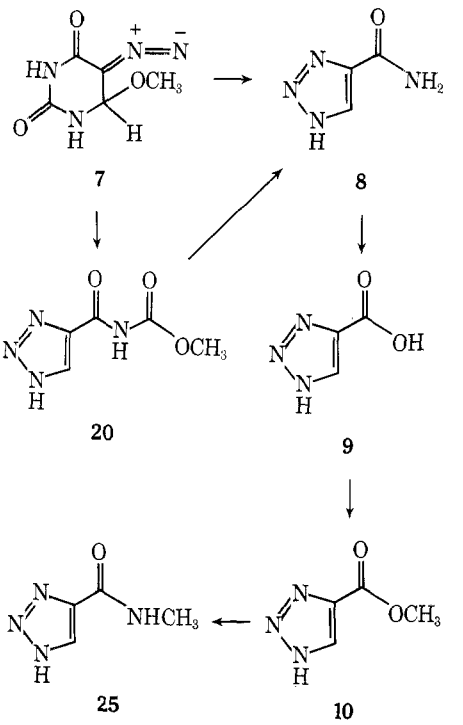


5 **6**

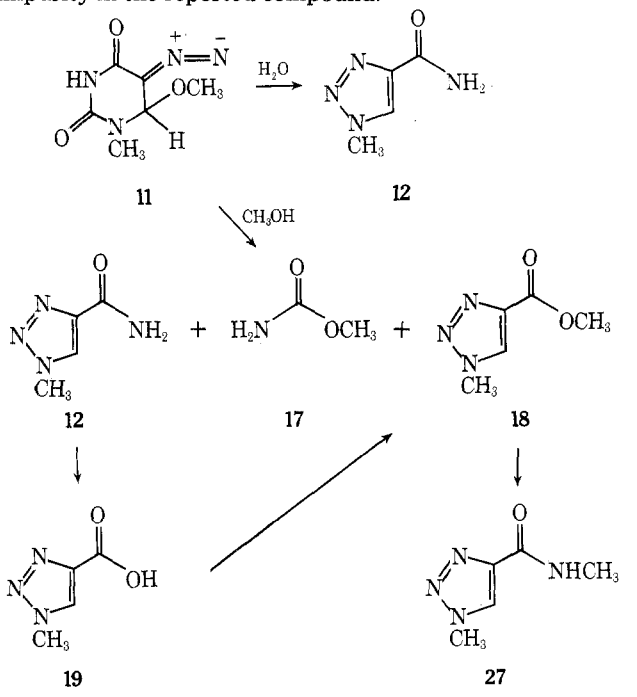
by a comparison of its spectral data with the spectral data of **2**. The anomeric proton of **6** appeared as a pseudotriplet ($J_{1'2'}$ = 6 Hz) having a peak width of 12 Hz and allowed assignment[15] of the β configuration to **6**. This demonstrated that the 2′-hydroxyl group was not involved in the reaction and that compounds such as deoxynucleosides (which are particularly sensitive to hydrolysis,[22,23] glycosyl bond cleavage) can be converted to 1,2,3-triazoles by this method. This was of considerable interest since the syntheses of 1-glycosyl-1,2,3-triazoles have been previously accomplished by cycloaddition of various glycosyl azides with substituted acetylenes[10,16-20] and by the acid-catalyzed fusion[11] of 4-substituted 1,2,3-triazoles with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose. It is of interest that **2** is a structural isomer of the broad spectrum antiviral nucleoside 1-(β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide.[21] The synthesis of **6** by the reported methods (vide supra) would have furnished complex isomeric mixtures. It would appear that the preferred synthesis of 1-glycosyl-1,2,3-triazoles would be by ring contraction of 5-diazouracils.

5-Diazouracil-6-methanolate[1] (**7**) was heated at 100° for 18 hr in 5% aqueous acetonitrile to give a solid which had a melting point similar to that reported[24] for 1,2,3-triazole-4-carboxamide (**8**). A ^{1}H NMR spectrum (Figure 1) revealed two broad exchangeable singlets (δ 7.93 and 7.63), an aromatic proton (δ 8.48), and a broad, exchangeable peak (δ 15.6) which was assigned to a tautomeric ring proton. Elemental analyses (C, H, N) correlated with the empirical formula $C_3H_4N_4O$ and the ir and uv spectra of **8** were consistent with the assigned structure. Compound **8** was also converted to 1,2,3-triazole-4-carboxylic acid (**9**) by treatment with sodium hydroxide and into methyl 1,2,3-triazole-4-carboxylate (**10**) by esterification of **9**. The physical properties of these two compounds were in good agreement with the values reported[25-27] in the literature. This also established that an alkyl group at N-1 was not necessary for the ring contraction to occur.

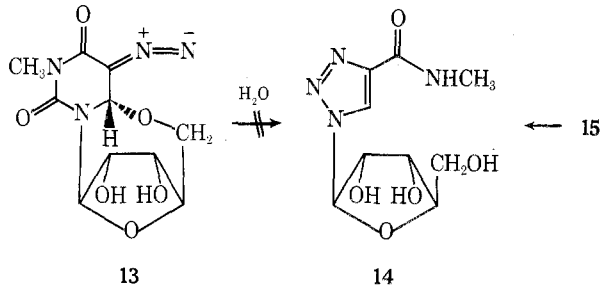
Reaction of 5-diazo-1-methyluracil-6-methanolate[28] (**11**) under similar conditions gave a compound which we assumed was 1-methyl-1,2,3-triazole-4-carboxamide (**12**). However, the structure assignment for **12** was complicated by a discrepancy between our observed physicochemical



properties and those reported[29] for **12** in the literature. This required us to unequivocally establish the structure of our product. A preliminary communication[30] from our laboratory has established the structure of our product as **12**. The difference in physicochemical properties between **12** obtained by the ring contraction of **11** and **12** as reported[29] in the literature may be due to the presence of an isomeric impurity in the reported compound.



There was no detectable reaction when $O^{5'}$-6(*S*)-cyclo-5-diazo-3-methyluridine[31] (**13**) was heated at 100° in 5% aqueous acetonitrile. Although a disappearance of starting material did occur when the temperature was increased to 150°, the major product was a tar, with two minor components being detected by thin layer chromatography. These minor components had the same mobility, in three solvent systems, as 3-methyluracil and 3-methyluridine. If **13** had undergone a ring contraction similar to those described above, the product would have been 1-(β-D-ribofuranosyl)-1,2,3-triazole-4-*N*-methylcarboxamide (**14**). Treatment of methyl 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,3-triazole-4-carboxylate[10] (**15**) with methylamine furnished **14**.



A chromatographic comparison of **14** with the above mixture showed no detectable amount of **14**. This was of considerable interest since the only difference between **1** and **13** was the presence of a methyl group at N-3. An experiment in which **13** was heated at 100° for 18 hr in 5% aqueous acetonitrile with water enriched (10%) in oxygen-18 furnished only unreacted **13** which was analyzed by mass spectroscopy for oxygen-18 content. The mass spectrum failed to show any ion fragments with a second isotope larger than that due to the natural abundance of oxygen-18 and established that water had not attacked C-2. The failure of 5-diazouracils, with a methyl group at N-3, to undergo ring contraction was investigated further (vide infra).

The above studies suggested that hydrolysis by water should furnish carbamic acid intermediates upon ring opening. It appeared that we could isolate the carbamic acid intermediates as their methyl esters, if the nucleophile responsible for hydrolysis was changed from water to methanol. This would establish the presence of carbamates and identify the initial bond broken in the ring-opening process.

A solution of **1** in anhydrous methanol was heated at 100° for 18 hr and cooled to room temperature, and a thin layer chromatogram of the solution revealed the presence of two nucleoside products. The minor component had the same chromatographic mobility as **2**. The major component was not visible under ultraviolet light (254 nm) but could be detected by charring with 10% sulfuric acid. These two components were separated by dry pack column chromatography and the minor component was found to be identical in all respects with **2**. Elemental analyses for the major component were consistent with the empirical formula $C_9H_{13}N_3O_6$, which did not support an esterified carbamic acid intermediate. A ^1H NMR spectrum of the major component revealed a pattern of peaks in the δ 3.5–3.6 region which were indicative[8] of a ribofuranosyl moiety and an aromatic proton at δ 8.83. However, the two broad exchangeable singlets for the amide group of **2** were replaced by a methyl group absorption at δ 3.82, which suggested that the compound was methyl 1-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxylate (**16**). An independent synthesis of **16** was accomplished by treatment of **15** with sodium methoxide in methanol and the two samples were found to be identical in every respect.

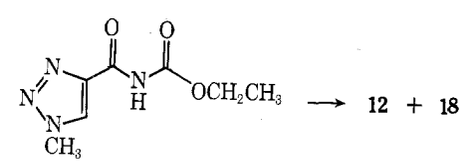
The formation of **16** by this reaction was of considerable interest, since the study of **1** labeled with oxygen-18 at C-4 had established that C-4 was not attacked by water. It would appear that the carbamate ester (if formed) had been hydrolyzed under the reaction conditions to give a mixture (**2** and **16**), and that methyl carbamate (**17**) must also be present in the reaction mixture. The reaction was repeated and the crude reaction mixture was examined for the presence of a third component by ^1H NMR spectroscopy, which revealed the presence of **2** and **16** in the ratio 5:1.

Two additional peaks were observed [δ 3.54 (s, 3) and 6.38 (bs, 2)], with the integrated intensities of the methyl group of **16** being equal to the integrated intensity of the absorption at δ 3.54. These data were consistent with the formation of methyl carbamate (**17**) in an equimolar ratio with **16.** Methyl carbamate (**17**) was subsequently isolated from the reaction mixture by sublimation and found to be identical with a commercial sample.[32]

The methanolysis of **11** gave a mixture of **12** (major product), **17,** and methyl 1-methyl-1,2,3-triazole-4-carboxylate (**18**), although a higher temperature (135°) was required for completion in 18 hr. A conversion of **12** to 1-methyl-1,2,3-triazole-4-carboxylic acid (**19**) was accomplished by treatment with sodium hydroxide and esterification of **19** by treatment with methanol in the presence of dry hydrogen chloride gave **18.** Identification of **18** from the mixture was made by a comparison of **18** prepared by this independent synthesis from **12** (vide supra).

5-Diazouracil-6-methanolate (**7**) was heated at 132° in 5% methanolic acetonitrile[33] to give a product which was characterized as methyl *N*-(1,2,3-triazol-4-ylcarbonyl)-carbamate (**20**) on the basis of the following data. Elemental analyses and a molecular ion at *m/e* 170 in the mass spectrum were consistent with the empirical formula $C_5H_6N_4O_3$. The ^1H NMR spectrum revealed the presence of a methyl group (δ 3.77), an aromatic proton (δ 8.74), and a very broad exchangeable absorption centered at approximately δ 10.6 which was consistent with the presence of at least one NH proton. The empirical formula and downfield chemical shift of the aromatic proton from the peak for the aromatic proton of **8** (Δδ 0.29) suggested that the major difference between **20** and **8** was the group at the C-4 position which was deshielding the C-5 proton of **20.** The structure for **20** was consistent with these data and additional confirmation was obtained by hydrolysis of **20** with sodium hydroxide to give **8.**

The isolation and characterization of **20** from this reaction established that initial ring opening had occurred between N-1 and C-2. Although we assumed that the ring contractions of other 5-diazouracils had occurred by ring opening in the same position, we elected to show that the *N*-formyl methylcarbamate functional group could be hydrolyzed in methanol to afford a mixture of methyl ester and amide. This was accomplished by heating a solution of ethyl *N*-(1-methyl-1,2,3-triazol-4-ylcarbonyl)carbamate[34] (**21**) in methanol at 135° to give a mixture of **12** and **18.**



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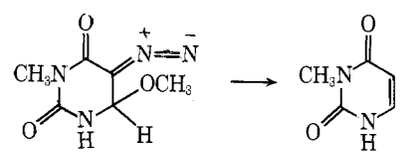

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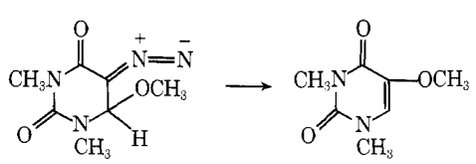

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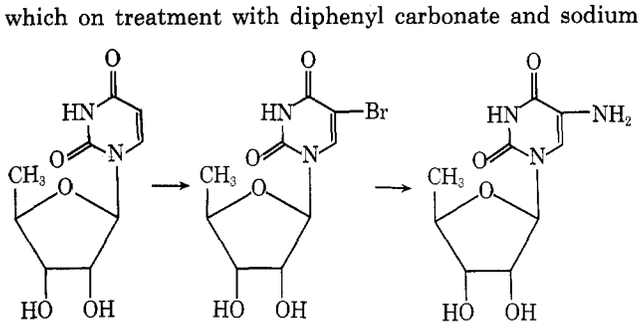
Similar reactions of 5-diazo-3-methyluracil-6-methanolate[28] (**22**) and 5-diazo-1,3-dimethyluracil-6-methanolate[28] (**23**) with methanol did not afford the expected triazole derivatives. When **22** was heated at 100° with 5% methanolic acetonitrile, the only product which could be isolated was 3-methyluracil[35] (**24**). The expected products, **10** and 1,2,3-triazole-4-*N*-methylcarboxamide (**25**) (prepared by treatment of **10** with methylamine), were used for a direct comparison (TLC, ^1H NMR) with the reaction mixture obtained from **22** and established that neither of these triazoles were present in detectable amounts.

A similar reaction of **23** gave only 5-methoxy-1,3-dimethyluracil[36] (**26**). The expected products, **18** and 1-methyl-1,2,3-triazole-4-*N*-methylcarboxamide (**27**) (prepared by treatment of **18** with methylamine), were used for a direct comparison (^1H NMR) with the reaction mixture obtained from **23** and established that neither of these triazoles were present in detectable amounts.

The difference between **13, 22,** and **23** (which do not give triazoles) and **1, 5, 7,** and **11** (which do give triazoles) is replacement of the N-3 proton by a methyl group. The unsuccessful conversion of 5-diazouracils having a methyl group at N-3 (**13, 22** and **23**) to triazoles was attributed to the absence of nucleophilic attack at C-2 in the case of **13.** However, failure of the N-3 alkylated compounds to form triazoles cannot be accounted for on the basis of inductive effects alone, since it was shown that the presence of methyl, hydrogen, ribose, and 2-deoxyribose at N-1 did not significantly alter the formation of triazoles. The difference between these two series of compounds can be rationalized if it is assumed that a proton at N-3 must first tautomerize to the C-2 oxygen atom to form a carbinolamidine, which then undergoes attack by water. Unfortunately, there are no reports in the literature which can be cited in favor of this proposal, but data which supported this proposal were obtained by a study of the diazotization of O^2-2′-cyclo-5-amino-5′-deoxyuridine (**28**).

5′-Deoxyuridine[37] (**29**) was treated with bromine in the presence of acetic anhydride and acetic acid to furnish a syrup which gave 5-bromo-5′-deoxyuridine (**30**) after treatment with methanolic ammonia. Treatment of **30** with liquid ammonia furnished 5-amino-5′-deoxyuridine (**31**), which on treatment with diphenyl carbonate and sodium



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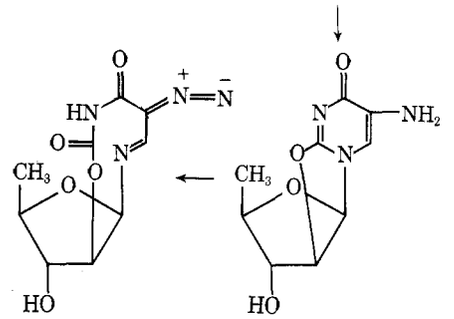

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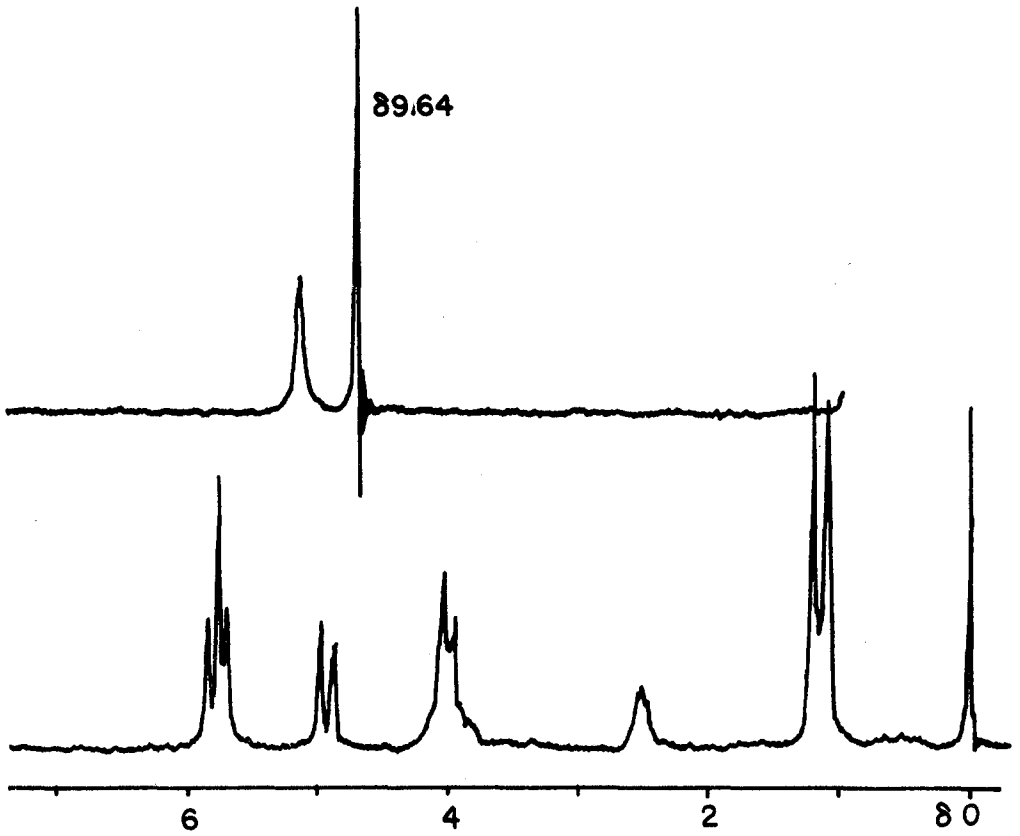


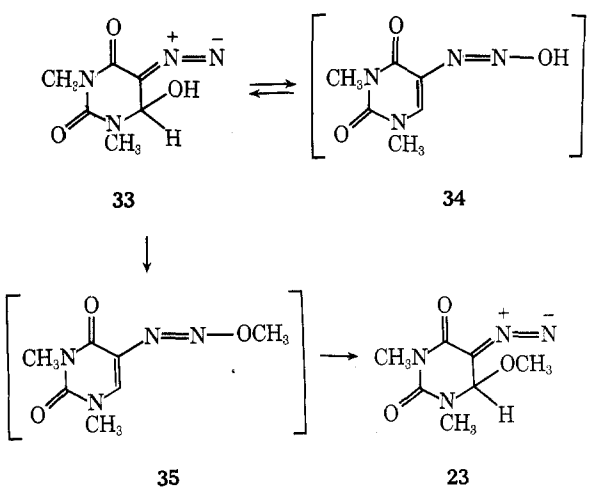
Figure 2. ^{1}H NMR spectrum (Me_2SO-d_6) of diazo compound **32**. The top spectrum is a continuation of the bottom spectrum with an upfield offset of 300 Hz.

bicarbonate in *N,N*-dimethylacetamide gave **28**. The structural characterizations of **30** and **31** were accomplished by comparisons of their physicochemical properties with those of the corresponding uridine derivatives. The structural assignment for **28** was facilitated by the appearance of two absorption maxima (289 and 258 nm) in the ultraviolet absorption spectrum. Treatment of **28** with nitrous acid gave a compound which was characterized as 5-diazo-10-hydroxy-9-methyl(7a*S*,9*S*,10*S*,10a*R*)tetrahydrofurano[2,3-*h*]-1,3,7-perhydro-3*H*-oxadiazonin-6-ene-2,4-dione (**32**) on the basis of the following data. Elemental analyses gave the empirical formula $C_9H_{10}N_4O_5$. The molecular ion was observed at *m/e* 255 (MH^+) in the chemical ionization mass spectrum (CH_4 reagent gas). A strong absorption at 4.65 μ in the ir spectrum which was characteristic[1] of similar structures and a loss of diatomic nitrogen (*m/e* 227, MH − N_2) in the CI mass spectrum supported the presence of a diazo group. The CI mass spectrum also revealed the presence of a large ion fragment (*m/e* 211) which corresponded to a loss of carbon dioxide and suggested the presence of an acyclic carbamate structure as a portion of the molecule. The ultraviolet absorption maximum of **32** occurred at higher energy (248 nm) with a larger extinction coefficient (ϵ 36200) than those observed for 5-diazouracils[1] and suggested that the 5-diazouracil chromophore had been drastically altered. The ^{1}H NMR spectrum (Figure 2) of **32** confirmed the structural assignment by revealing the presence of an NH proton (δ 10.1), a single hydroxyl group proton (δ 5.77) and a strong vicinal coupling (J = 6.0 Hz) for the carbohydrate 1 and 2 protons. The N=CH proton of **32** was also found downfield from the C-6 proton of anhydro-5-diazouracil[1] (δ 9.64, $\Delta\delta$ 0.51) and established that diazotization of **28** had not resulted in glycosidic bond cleavage. Therefore, the structure **32** was consistent with the data and established that diazotization of **28** had occurred with hydrolytic ring opening between N-1 and C-2.

An examination of structure **28** reveals the similarity between this structure and the tautomer which could be formed by migration of an N-3 proton of 5-diazouracils to the O-2 position. The observed hydrolytic ring opening of **28** by diazotization would appear to lend credence to the above argument that the carbinolamidine tautomer of 5-diazouracils is the actual specie which undergoes ring opening during hydrolysis and methanolysis.

The unsuccessful conversion of **22** to triazoles on methanolysis is not necessarily due to a lack of ring opening of an N-1/O-2 carbinolamidine tautomer. Our data have only established that the methanolysis of **22** gives the product of nitrogen elimination and, therefore, that an alternate reaction occurs at a rate faster than the reaction which would lead to triazoles.

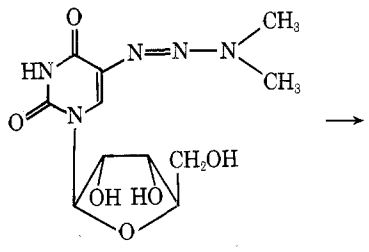
We have previously[28] presented evidence for an equilibrium in water between 5-diazo-1,3-dimethyluracil-6-hydrate (**33**) and the isomeric diazotic acid (**34**). We also pro-



33 **34**

35 **23**

posed[28] that diazo ether derivatives (e.g., **35**) were intermediates in the conversions of 5-diazouracil-6-hydrates to the 6-methanolate derivatives (e.g., **23**). The question of whether the diazotic acids or diazo ethers with structures similar to **34** and **35** were the actual species which underwent hydrolysis and methanolysis during the ring contractions prompted us to study the reaction of 5-(3,3-dimethyl-1-triazeno)uridine[1] (**36**) with methanol. Compound **36** may be viewed structurally as being very similar to **34** and **35** with the major difference being that the diazotic acid or ester has been isolated as its *N,N*-dimethyltriazeno derivative. A solution of **36** in dry methanol was heated in an oil bath at 90° and TLC of the reaction mixture revealed the presence of two nucleoside components (same chromatographic mobilities as **2** and **16**), which were separated and identified as **2** (3%) and **16** (74%) by comparisons with authentic samples. Small amounts of methyl carbamate (**17**) and 1,1-dimethylurea (**37**) were also isolated from the reaction mixture. The formation of **37** would appear to be the result of an elimination of dimethylamine from **36** followed by a reaction of dimethylamine with methyl carbamate (**17**).



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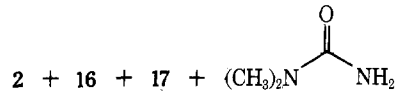

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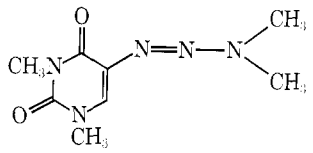
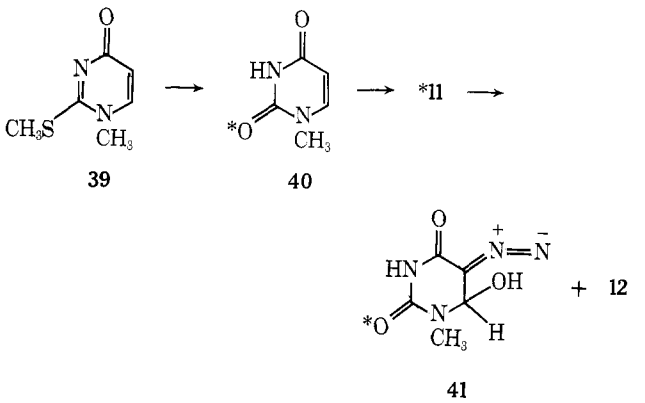
A similar experiment in which 5-(3,3-dimethyl-1-triazeno)-1,3-dimethyluracil[28] (**38**) was heated at 85° in dry



38

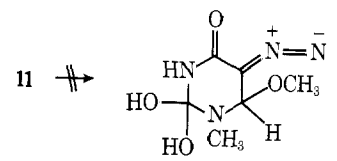
methanol resulted in the recovery of unchanged **38**. This would suggest that the reaction of **36** to give **2** and **16** was most likely the result of direct methanolysis of **36** rather than an initial decomposition of the 5-(3,3-dimethyl-1-triazeno) group to the corresponding 5-diazouracil.

We decided to study the nature of the structural requirements for attack by water. The most feasible approach, without doing a kinetic study, was to study an incomplete reaction of **11** with water, in which the C-2 position of **11** had been labeled with oxygen-18. Acid-catalyzed hydrolysis of 1-methyl-2-methylthio-4-pyrimidone[35] (**39**) in oxygen-18 enriched (10%) water furnished [2-^{18}O]-1-methyluracil (***40**), which then was converted to ***11** by the previously reported procedures[28,35] without loss of oxygen-18 isotope (Table III). The reaction of ***11** with 5% aqueous acetonitrile gave a mixture which was characterized by its ^{1}H NMR spectrum and revealed the presence of starting material (**11**), the product of C-6 exchange with water[28] (**41**), and **12** in the ratio 1:1:3. Therefore, the reaction had progressed to more than half completion and a mass spectrum of this mixture was examined for isotopic content. It could



39 **40** **41**

not be determined whether the specie observed in the mass spectrum was ***11**, ***41**, or a mixture of the two, since the spectra of both compounds gave the ion fragment *m/e* 153 (M − OCH_3 or M − OH) as the highest mass peak. The important feature was the presence of isotopic label in an abundance similar to the isotopic label originally present in ***11**. This established that an exchange of the C-2 oxygen atom had not occurred under the reaction conditions and suggested that the transition state may involve a predominance of carbon–nitrogen bond cleavage for ring opening rather than the formation of a tetrahedral intermediate with two hydroxyl groups (e.g., **42**) attached to C-2 (in equilibrium) prior to the transition state.[38] The presence of **41** in the reaction mixture also established that an exchange of the C-6 substituent (methoxyl in the case of **11**) can occur prior to ring opening.



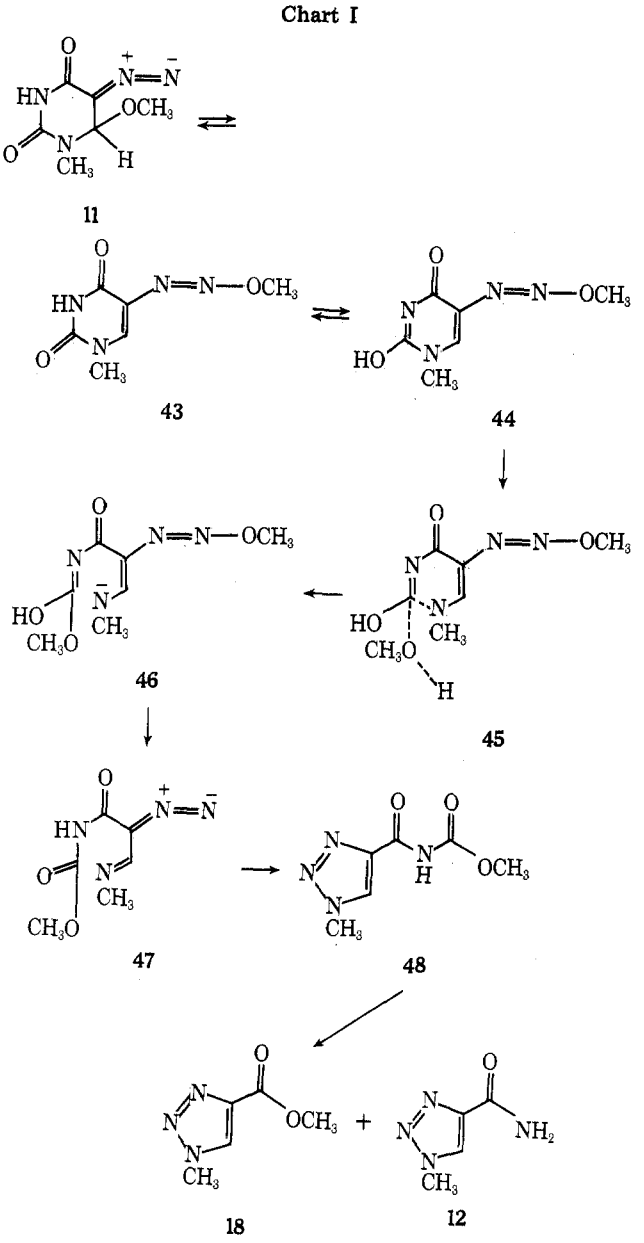
42

The results described above are consistent with the outline of Chart I, which illustrates the reaction of **11** with methanol. In this chart, **11** is in mobile equilibrium with its isomeric diazo ether (**43**). The diazo ether **43** is in tautomeric equilibrium with **44** which undergoes the rate-determining attack by methanol at C-2 to give the anion **46** with the transition state (**45**) involving partial N-1–C-2 bond cleavage. Tautomerism of **46** and elimination of methoxide ion by an electron shift gives **47**, which then rotates about the 5-6 bond and annulates between N-1 and the diazo group to give methyl *N*-(1-methyl-1,2,3-triazol-4-ylcarbonyl)carbamate (**48**). Compound **48** is assumed to be unstable under the reaction conditions and is converted into **18** and **12**.

The outline illustrated in Chart I provides a rational account of the experimental observations. It accounts for the exchange of the C-6 methoxyl group of **11** for a hydroxyl group during the partial hydrolysis of ***11**, the failure of the N-3 methylated compounds to be converted to triazoles, and for the observed conversion of the triazeno derivative **36** into triazoles on heating in methanol. Isotopic retention during the partial hydrolysis of ***11** is also accounted for by the transition state **45**. Annulation of **47** has ample precedence in the literature.[39–41] The intermediacy of **48** in the reaction of **11** with methanol is consistent with the isolation of **20** and with the competitive formation of esters and amides during methanolysis of N-1 alkylated 5-diazouracils.

By evoking the intermediacy of **46–48** the chart also accounts for the lack of 1,2,3-triazole-4-carboxylic acids dur-

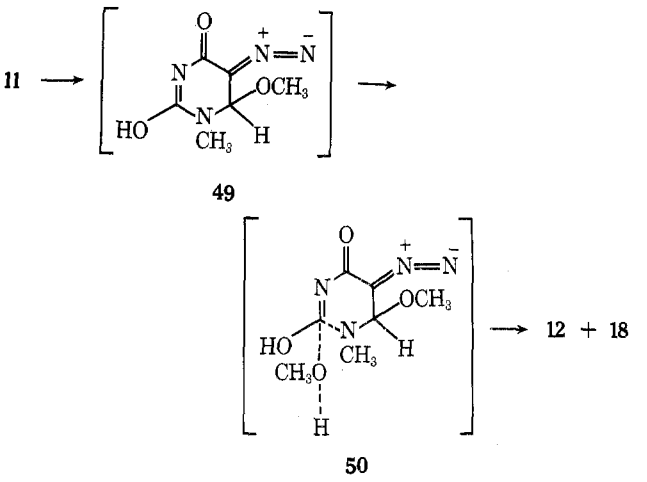
Chart I



ing the hydrolysis of 5-diazouracils, since the similar carbamic acid intermediates may decarboxylate[13] at a rate faster than the rate of hydrolysis to the acids. In contrast to decarboxylation, these intermediates may undergo competitive ester exchange and methanolysis to give both **12** and **18**.

We caution that this agreement of experiment with the model does not prove that the model is absolutely correct. However, we feel that it justifies using the model as a basis for interpretation at this time.

If the model is correct in its broader aspects, it may yet be faulty in detail. To be specific, our experiments do not require **44** to be the only intermediate which ring opens after attack by methanol. We cannot exclude the possibility that **11** first tautomerizes to afford **49**, which then undergoes a rate-limiting attack by methanol as illustrated by the transition state **50**. We find this transition state (**50**) attractive on the grounds that the driving force for ring opening between N-1 and C-2 would be the extended conjugation resulting after ring opening and expulsion of the C-6 methoxyl group. However, this transition state (**50**) is unattractive on the grounds of the stability of the *N,N*-dimethyltriazeno group (which is not hydrolyzed under the



reaction conditions), the facile conversion of **36** into triazoles, and also by the detectable[28] equilibrium between **33** and the isomeric diazotic acid (**34**) in aqueous solution.

Experimental Section

Ultraviolet spectra were recorded on a Beckman DK-2 or Beckman Acta CIII recording spectrophotometer. Infrared spectra were determined on a Beckman IR8 spectrophotometer in compressed potassium bromide disks and ^{1}H NMR spectra (Me_2SO-d_6 and Me_2SO-d_6–deuterium oxide) on a Varian A56/60 instrument using 2,2-dimethylsilapentane-5-sulfonate (DSS) as internal standard and chemical shifts are expressed as parts per million (δ) from DSS. Electron impact mass spectra were recorded on a Hewlett-Packard 5930A Dodecopole instrument, ion source and direct inlet temperatures of 190°, ionizing energy 70 eV. Chemical ionization mass spectra were recorded on a Varian CH 7 instrument, modified for high-pressure operation,[42] using methane reagent gas, ion source and direct inlet temperatures of 190°, reagent gas pressure in the ion source 0.5 Torr. All samples for mass spectra were introduced by direct probe. Specific rotations were determined on a Perkin-Elmer 141 digital readout polarimeter. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Anhydrous methanol was obtained by distillation from calcium hydride and anhydrous acetonitrile was obtained by distillation from phosphorus pentoxide. These solvents were stored over activated Linde type 3A 4–8 mesh molecular sieves. Concentrations in vacuo were performed at or below 40°. Thin layer chromatography was performed on 5 × 20 cm glass plates coated to a thickness of 0.25 mm with Mallinckrodt SilicAR 7GF. Samples for elemental analyses were dried at 0.5 Torr in an Abderhalden apparatus using phosphorus pentoxide as the desiccant and the solvent as indicated.

Hydrolysis of $O^{5'}$-6(*S*)-Cyclo-5-diazouridine (1) to Afford 1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxamide (2). $O^{5'}$-6(*S*)-Cyclo-5-diazouridine[1] (**1**, 100 mg) was finely powdered in a mortar and added to 5% (v/v) aqueous acetonitrile (10 ml). The mixture was sealed in a stainless steel reaction vessel, heated for 18 hr in an oil bath which was maintained at 100°, and then allowed to cool to room temperature. The bleed outlet of the reaction vessel was connected to a 100-ml gas collection bulb which had been flushed with nitrogen and evacuated to 0.2 Torr. The bleed valve of the reaction vessel was opened and carbon dioxide was allowed to collect in the bulb. The reaction mixture was evaporated to dryness in vacuo to give **2** (89.4 mg, quantitative), mp 198–201°. A small sample was recrystallized for analysis from hot methanol and dried for 18 hr at the reflux temperature of toluene (Table II).

Anal. Calcd for $C_8H_{12}N_4O_5$: C, 39.35; H, 4.95; N, 22.94. Found: C, 39.42; H, 5.24; N, 22.60.

[4-^{18}O]Uridine (*3). 4-Thiouridine[43] (2.18 g) was methylated by the literature[14] procedure to give 4-methylthiouridine (**4**, 3.42 g) as a hard foam which may have contained some sodium iodide. This foam was used for the preparation of *3 without further purification. The foam was dissolved in a mixture of oxygen-18 enriched (10%) water (2 ml) and ethanol (25 ml) and concentrated hydrochloric acid (4 drops) was then added to the solution. The mixture was heated to reflux temperature, reflux temperature was maintained for 2 hr, and the solution then evaporated in vacuo to afford a hard foam. The foam was coevaporated with ethanol (25 ml), then dissolved in hot ethanol (3 ml) and the solution was ap-

plied to the top of a column (2 × 43 cm) of silica gel which had been packed in chloroform. The column was eluted with a chloroform–methanol mixture (3:1 v/v), with 100-ml fractions being collected. Fractions 7–12 contained uridine as determined by TLC in the same solvent system. These fractions were combined and concentrated in vacuo to afford a hard foam. This foam was dissolved in ethanol (8 ml) and then allowed to stand at 5° for 48 hr to give **38** (1.10 g, 55%), mp 167–169° (lit.[44] mp 164–165°) (see Table III).

Hydrolysis of $O^{5'}$-6(*S*)-Cyclo-5-diazo-2′-deoxyuridine (5) to Afford 1-(2-Deoxy-β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (6). 5-Diazo-2′-deoxyuridine[1] (**5**, 275 mg) was added to 5% (v/v) aqueous acetonitrile (15 ml) and the solution sealed in a stainless steel reaction vessel. The reaction vessel was heated for 18 hr in an oil bath maintained at 100° and then allowed to stand at room temperature for 18 hr. The colorless crystals which had separated from solution were collected by filtration and dried for 2 hr at the reflux temperature of methanol to give **6** (219 mg, 90%): mp 151–152°; uv λ_{max} (methanol) 210 nm (ϵ 11900); ^{1}H NMR δ 8.77 (s, 1, H5), 7.85 (bs, 1, NH), 7.53 (bs, 1, NH), 6.59 (t, 1, W = 12, 1′H); ir 2.96 (NH_2), 5.97 μ (C=O); MS *m/e* 198/2.9 (M − 30), 139/15 (B + 29), 117/49 (S), 113/13 (B + 2H), 112/23 (B + H).

Anal. Calcd for $C_8H_{12}N_4O_4$: C, 42.11; H, 5.30; N, 24.55. Found: C, 42.00; H, 5.01; N, 24.25.

Hydrolysis of 5-Diazouracil-6-methanolate (7) to Afford 1,2,3-Triazole-4-carboxamide (8). 5-Diazouracil-6-methanolate[2] (**7**, 1 g) was dissolved in a mixture of acetonitrile (250 ml) and water (10 ml) by heating slightly on a steam bath. The solution was sealed in a stainless steel reaction vessel, heated for 18 hr at 100° (internal temperature), and allowed to cool to room temperature and the mixture was evaporated to dryness in vacuo. The solid was recrystallized from glacial acetic acid (20 ml) to give **8** (638 mg, 98%), mp 261–263° (lit.[24] mp 253–254°), uv λ_{max} (water) 197 nm (ϵ 9400).

Anal. Calcd for $C_3H_4N_4O$: C, 32.15; H, 3.60; N, 49.98. Found: C, 32.39; H, 3.83; N, 49.95.

1,2,3-Triazole-4-carboxylic Acid (9). 1,2,3-Triazole-4-carboxamide (**8**, 2.82 g) was dissolved in 0.99 *N* sodium hydroxide (56.2 ml) and the solution was heated for 7 days on a steam bath. An additional quantity of 0.99 *N* sodium hydroxide (25.5 ml) was then added to the solution and heating was continued for another 24 hr. The solution was allowed to cool to room temperature and then acidified by the addition of 0.96 *N* hydrochloric acid (84.2 ml). Colorless crystals separated from the solution after standing for 18 hr at 5° and were collected by filtration to give **9** (1.64 g, 58%), mp 230–233° (lit.[25,26] mp 222–224° and 214–215°), uv λ_{max} (water) 211 nm (ϵ 6800).

Methyl 1,2,3-Triazole-4-carboxylate (10). Compound **9** (1.24 g) was added to a solution of dry hydrogen chloride (2 g) in methanol (100 ml). The mixture was heated at reflux temperature for 3.5 hr and then evaporated to dryness in vacuo. The residue was coevaporated with methanol (2 × 20 ml) and then crystallized by trituration with chloroform (20 ml at −30°) for 30 min. The insoluble white solid was collected by filtration and recrystallized from hot methanol (10 ml) to give **10** (1.05 g, 76%): mp 144–145° (lit.[27] mp 145°); uv λ_{max} (water) 219 nm (ϵ 8100); ir 3.17 (NH), 5.8 μ (C=O) [lit.[27] 3.2 (NH) and 5.8 μ (C=O)].

Hydrolysis of 5-Diazo-1-methyluracil-6-methanolate (11) to Afford 1-Methyl-1,2,3-triazole-4-carboxamide[30] (12). 5-Diazo-1-methyluracil-6-methanolate[30] (**11**, 500 mg) was dissolved in 5% (v/v) aqueous acetonitrile (15 ml) and the solution was placed in a stainless steel reaction vessel. The sealed reaction vessel was heated for 3.5 hr in an oil bath maintained at 100° and then allowed to stand at ambient temperature for 18 hr. The white solid which had separated from solution was collected by filtration and washed with methanol (5 ml) to give **12** (266 mg, 78%), mp 261–263°. A small sample was recrystallized from methanol for analysis and dried for 18 hr at the reflux temperature of toluene, melting point unchanged, uv λ_{max} (water) 210 nm (ϵ 11800).

Anal. Calcd for $C_4H_6N_4O$: C, 38.09; H, 4.80; N, 4.42. Found: C, 38.19; H, 4.56; N, 44.45.

Methanolysis of $O^{5'}$-6(*S*)-Cyclo-5-diazouridine (1) to Afford Methyl Carbamate (17), Methyl 1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxylate (16), and 1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxamide (2). $O^{5'}$-6(*S*)-Cyclo-5-diazouridine[1] (**1**, 300 mg) was dissolved in anhydrous methanol (20 ml) and the solution sealed in a stainless steel reaction vessel. The reaction vessel was heated for 18 hr in an oil bath maintained at 100° and then allowed to cool to room temperature. SilicAR CC7 (2.5 g) was added to the solution and the resulting mixture was evaporated to dryness in vacuo and the residue applied to the top of a vacuum packed dry column (1 × 18 cm) of SilicAR CC7. The column was eluted with a chloroform–methanol mixture (5:1 v/v), with 5-ml fractions being collected. Fraction 3 was evaporated to dryness in vacuo and the residue was allowed to sublime at ambient temperature and pressure to give methyl carbamate (**17**): mp 54–55°; ir 2.88 (NH_2) and 5.90 μ (C=O); MS *m/e* 75/41 (M), 59/3 (M − NH_2), 44/100 (M − CH_3O); ^{1}H NMR δ 3.54 (s, 3, CH_3) and 6.47 (bs, 2, NH_2). A commercial sample of **17** had identical properties. The yield of **17** was determined from the ^{1}H NMR spectrum of the crude reaction mixture obtained from another run (see text). Fractions 5–7 contained **16** as determined by TLC in the same solvent system and were combined, evaporated to dryness in vacuo, and recrystallized from methanol (3 ml) to give **16** (208 mg, 75%): mp 150–153°; uv λ_{max} (methanol) 214 nm (ϵ 11000); $[\alpha]^{26}D$ −55.0° (*c*, 1, water).

Anal. Calcd for $C_9H_{13}N_3O_6$: C, 41.70; H, 5.06; N, 16.21. Found: C, 41.61; H, 5.07; N, 16.22.

Fractions 11–13 contained **2** and were evaporated to dryness in vacuo and the residue recrystallized from methanol (3 ml) to give **2** (20.2 mg, 8%) as determined by TLC in the same solvent system, mp 198–200°, uv λ_{max} (water) 210 nm (ϵ 11400).

1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxamide (2). Compound **16** (14.8 mg, obtained by methanolysis of **1**) was added to methanol which had been previously saturated at 0° with ammonia (10 ml). The reaction vessel was tightly stoppered, and the mixture was allowed to stand at room temperature for 18 hr and then evaporated in vacuo to dryness to give pure **2** (quantitative), mp 202–204°, TLC and ir spectrum identical with those of a sample of **2** obtained from the reaction of **15** with methanolic ammonia.

Methyl 1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxylate (16). Compound **15** (495 mg) was dissolved in methanol (25 ml) and sodium methoxide (5 mg) was then added. The solution was stirred at room temperature for 3.5 hr and then neutralized by the addition of an excess of dry ice. The solution was evaporated in vacuo to afford a syrup which crystallized on trituration with diethyl ether (20 ml) for 1 hr. The white solid was collected by filtration, recrystallized from methanol (4 ml), and dried for 4 hr at the reflux temperature of toluene to give **16** (139 mg, 62%): mp 151–153°; uv λ_{max} (water) 214 nm (ϵ 10700); $[\alpha]^{26}D$ −55.9° (*c* 1, water).

Anal. Calcd for $C_9H_{13}N_3O_6$: C, 41.70; H, 5.06; N, 16.21. Found: C, 41.75; H, 5.08; N, 16.05.

Methanolysis of 5-Diazo-1-methyluracil-6-methanolate (11) to Afford 1-Methyl-1,2,3-triazole-4-carboxamide[30] (12), Methyl 1-Methyl-1,2,3-triazole-4-carboxylate (18), and Methyl Carbamate (17). 5-Diazo-1-methyluracil-6-methanolate[28] (**11**, 2.58 g) was dissolved in dry methanol (20 ml). The solution was sealed in a stainless steel reaction vessel, heated for 18 hr in an oil bath maintained at 135°, and then allowed to cool to room temperature. The white solid which had separated from solution was collected by filtration and washed with methanol (5 ml) to give **12** (1.12 g, 63%), mp 261–263°, uv λ_{max} (water) 210 nm (ϵ 11000). The filtrate was concentrated to 10 ml in vacuo and allowed to stand at room temperature for 2 hr to give **18** (292 mg, 15%), mp 158–161°. A small sample of **18** was recrystallized from methanol for analysis and dried for 3.5 hr at the reflux temperature of toluene, melting point unchanged, uv λ_{max} (water) 215 nm (ϵ 10200).

Anal. Calcd for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.77. Found: C, 42.79; H, 5.22; N, 30.04.

The filtrate was evaporated to dryness in vacuo and the residue was extracted with chloroform (15 ml). The chloroform extract was evaporated to dryness in vacuo and the residue was sublimed at 70° (16 Torr) to give **17** (53 mg, 6%), mp 52–53°, ir and ^{1}H NMR spectra identical with those of a commercial[32] sample.

1-Methyl-1,2,3-triazole-4-carboxamide (12). Compound **18** (75 mg, from the methanolysis of **11**) was added to a solution of methanol which had been previously saturated at −5° with ammonia (5 ml). The reaction vessel was tightly stoppered and the mixture was allowed to stand at room temperature for 18 hr. The solution was then evaporated to dryness in vacuo, the residue was triturated with methanol (1.5 ml) for 30 min, and the insoluble material was collected by filtration to give **12** (64.4 mg, 96%), mp 260–262°, uv λ_{max} (water) 210 nm (ϵ 11300).

Methyl-1,2,3-triazole-4-carboxylic Acid (19). Compound **12** (900 mg) was added to 0.99 *N* sodium hydroxide (8.30 ml). The solution was heated for 24 hr at reflux temperature, cooled to room temperature, and then acidified by the addition of 0.96 *N* hydrochloric acid (8.60 ml). The solution was allowed to stand at 5° for 18 hr and the white solid which had separated from solution was collected by filtration to give **19** (796 mg, 88%), mp 240–242°. An

additional quantity of **19** (82 mg, 97%), mp 240–242°, was obtained by concentrating the filtrate to 5 ml at reflux temperature and then allowing the solution to stand at 5° for 18 hr. A small sample was recrystallized from water for analysis and dried for 5 hr at the reflux temperature of toluene, melting point unchanged, uv λ_{max} (water) 211 nm (ϵ 8600).

Anal. Calcd for $C_4H_5N_3O_2$: C, 37.80; H, 3.97; N, 33.06. Found: C, 37.71; H, 4.18; N, 33.18.

Methyl 1-Methyl-1,2,3-triazole-4-carboxylate (18). 1-Methyl-1,2,3-triazole-4-carboxylic acid (**19**, 853 mg) was added to a mixture of dry hydrogen chloride (0.5 g) and methanol (25 ml). The mixture was heated for 18 hr at reflux temperature and the solution was then evaporated to dryness in vacuo. The residue was coevaporated with methanol (2 × 25 ml), dissolved in hot methanol (20 ml), and then allowed to stand at 5° for 18 hr to give **18** (793 mg, 84%), mp 159–161°. A small sample was recrystallized for analysis from methanol and dried for 3 hr at the reflux temperature of benzene, melting point unchanged, uv λ_{max} (water) 215 nm (ϵ 10200).

Anal. Calcd for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.77. Found: C, 42.48; H, 5.16; N, 29.56

Methanolysis of 5-Diazouracil-6-methanolate (7) to Afford Methyl *N*-(1,2,3-Triazol-4-ylcarbonyl)carbamate (20). 5-Diazouracil-6-methanolate[1] (**7**, 500 mg) was dissolved in a mixture of methanol (1 ml) and acetonitrile (19 ml). The solution was sealed in a stainless steel reaction vessel, heated for 18 hr in an oil bath maintained at 132°, and then allowed to cool to room temperature. The solution was evaporated to dryness in vacuo to give **20** (500 mg, quantitative), mp 194–196°. A small sample was recrystallized from methanol for analysis and dried for 2.5 hr at the reflux temperature of toluene, mp 202–204°, uv λ_{max} (water) 228 nm (ϵ 10600).

Anal. Calcd for $C_5H_6N_4O_3$: C, 35.30; H, 3.55; N, 32.93. Found: C, 35.39; H, 3.63; N, 33.09.

Hydrolysis of Methyl *N*-(1,2,3-Triazol-4-ylcarbonyl)carbamate (20) to Afford 1,2,3-Triazole-4-carboxamide (8). Methyl *N*-(1,2,3-triazol-4-ylcarbonyl)carbamate (**20**, 146 mg) was added to 1.73 of 0.99 *N* sodium hydroxide. The solution was heated on a steam bath for 24 hr and then allowed to cool to room temperature. The solution was acidified by the addition of 1.02 *N* hydrochloric acid (1.69 ml) at which time a gas was evolved. The solution was evaporated to dryness in vacuo and the white solid which remained was then triturated with water (1 ml). The insoluble material was collected by filtration and dried for 1.5 hr at the reflux temperature of toluene to give **8** (47.7 mg, 50%), mp 256–259°, uv λ_{max} (water) 197 nm (ϵ 9300).

1,2,3-Triazole-4-*N*-methylcarboxamide (25). Compound **10** (500 mg) was dissolved in a solution of methanol which had been previously saturated at 30° with methylamine (15 ml). The solution was sealed in a stainless steel reaction vessel, heated for 18 hr in an oil bath maintained at 80°, and allowed to cool to room temperature. The solution was evaporated to dryness in vacuo, and the residue was coevaporated with methanol (2 × 10 ml) and then allowed to stand at 5° for 18 hr to give colorless crystals which were collected by filtration. The crystals were recrystallized from hot ethanol (20 ml) and dried at the reflux temperature of toluene for 18 hr to give **26** (375 mg, 83%), mp 258–261°, uv λ_{max} (water) 211 nm (ϵ 9900).

Anal. Calcd for $C_4H_6N_4O$: C, 38.09; H, 4.80; N, 44.42. Found: C, 38.11; H, 4.74; N, 44.62.

1-Methyl-1,2,3-triazole-4-*N*-methylcarboxamide (27). Compound 18 (342 mg) was added to a solution of methanol which had been previously saturated at 30° with methylamine (20 ml). The solution was sealed in a stainless steel reaction vessel, heated for 18 hr in an oil bath maintained at 80°, and then allowed to cool to room temperature. The solution was evaporated to dryness in vacuo and the residue coevaporated with methanol (10 ml). The solid was recrystallized from methanol (15 ml) to give **27** (297 mg, 87%), mp 215–216°. A small sample was recrystallized from methanol for analysis and dried for 3 hr at the reflux temperature of toluene, melting point unchanged, uv λ_{max} (water) 214 nm (ϵ 11700).

Anal. Calcd for $C_5H_8N_4O$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.99; H, 5.79; N, 39.84.

Methanolysis of 5-(3,3-Dimethyl-1-triazeno)uridine (36) to Afford Methyl Carbamate (17), *N,N*-Dimethylurea (37), Methyl 1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxylate (16), and 1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxamide (2). 5-(3,3-Dimethyl-1-triazeno)uridine[1] (**36**, 590 mg) was dissolved in dry methanol (25 ml). The solution was sealed in a stainless steel reaction vessel, heated for 18 hr in an oil bath maintained at 90°, and then allowed to cool to room temperature. The solution was examined by TLC (chloroform–methanol, 5:1 v/v) and appeared to contain two nucleoside components: a major component with a R_f of 0.8 (ester **18**) and a minor component with R_f 0.2 (amide **2**). SilicAR CC7 (3 g) was added to this solution. The mixture was evaporated to dryness in vacuo and the residue was applied to the top of a vacuum packed dry column (2 × 20 cm) of SilicAR CC7 (50 g). The column was eluted with the same solvent and 1-ml fractions were collected. Fractions 1–6 contained a brown oil which was sublimed at ambient temperature and 16 Torr to give **17** (2 mg, 1.4%), mp 51–53°. The sublimation apparatus was then immersed in an oil bath at 120° and evacuated to 16 Torr. Compound **37** (36 mg, 17%) condensed on the cold finger: mp 165–169° (lit.[44] mp 182°); ir 3.05 and 3.15 (NH_2), 6.25 μ (C=O); ^{1}H NMR δ 2.70 (s, 6, 2-CH_3) and 5.60 (bs, 2, NH_2); MS *m/e* 88/57 (M), 72/9 (M − NH_2), 44/100 [$N(CH_3)_2$ and M − $N(CH_3)_2$]. Fractions 7–13 contained the faster moving nucleoside component (**16**, 334 mg, 69% after recrystallization from methanol): mp 153–155°; uv λ_{max} (water) 214 nm (ϵ 10600); $[\alpha]^{26}D$ −57.0° (*c* 1, water). Fractions 18–24 contained a mixture of three components (as determined by TLC in the same solvent system). An additional quantity of **16** (22.4 mg, 76%, mp 151–153°) was obtained from these fractions by crystallization from methanol (2 ml). Fractions 25–44 contained only one compound and were evaporated to dryness in vacuo to give **2** (13.4 mg, 3%), mp 202–204°, uv λ_{max} (water) 210 nm (ϵ 12000).

[2-^{18}O]-1-Methyluracil (*40). 1-Methyl-2-methylthio-4-pyrimidone[35] (**39**, 4.68 g) was added to a solution of oxygen-18 enriched (10%) water (1.55 ml) and ethanol (20 ml) and concentrated hydrochloric acid (0.04 ml) was then added. The mixture was heated at reflux for 18 hr, an additional quantity (0.5 ml) of concentrated hydrochloric acid was then added, and heating at reflux temperature was continued for an additional 2 days. The mixture was allowed to cool to room temperature, and the white solid which had separated from solution was collected by filtration, washed with ethanol (3 ml), and recrystallized from water (35 ml) to give ***40** (3.21 g, 85%), mp 231–233. The filtrate was evaporated to dryness in vacuo, the residue was dissolved in water (4 ml), and the pH of the solution was adjusted to 7 with 1 *N* sodium hydroxide. The solution was then evaporated to dryness in vacuo and the residue recrystallized from water (1 ml) to give an additional quantity of ***40** (313 mg, 94%), mp 231–233°. The literature[35] reports mp 232–233° for 1-methyluracil.

5-Bromo-5′-deoxyuridine (30). 5′-Deoxyuridine[37] (**29**, 500 mg) was added to acetic anhydride (3 ml) and the mixture was cooled to 10°. A solution of bromine (380 mg) in acetic acid (0.3 ml) was added to the mixture and the solution was allowed to stand at 5° for 20 hr. Additional bromine (1 drop) was then added, the solution was evaporated to a syrup in vacuo, and the syrup was stored in vacuo (16 Torr) for 48 hr using potassium hydroxide pellets as the desiccant. A solution (25 ml) of methanol, which had been previously saturated at −5° with ammonia, was added to the syrup. The vessel was tightly stoppered and the mixture was allowed to stand at room temperature for 20 hr. The solution was evaporated to a syrup in vacuo, and the syrup was dissolved in ethanol (5 ml) and allowed to stand at room temperature for 18 hr to give **30** (518 mg, 77%), mp 181–183°. A small sample was recrystallized from ethanol for analysis and dried at the reflux temperature of toluene for 5 hr, mp 184–185°, uv λ_{max} (methanol) 279 nm (ϵ 9900).

Anal. Calcd for $C_9H_{11}N_2O_5Br$: C, 35.07; H, 3.60; N, 9.09. Found: C, 34.80; H, 3.41; N, 9.21.

5-Amino-5′-deoxyuridine (31). 5-Bromo-5′-deoxyuridine (**30**, 1.16 g) and anhydrous liquid ammonia (15 ml) were heated at 50° in a stainless steel reaction vessel for 24 hr and the ammonia was then removed in vacuo to give a hard foam. This foam was dissolved in 1 *N* hydrochloric acid (12 ml), the solution was passed through a column (1.5 × 17 cm) of Dowex 50W-X2 (H^+) ion exchange resin, and the column was washed with water (75 ml). The column was then eluted with 1 *N* hydrochloric acid and 10-ml fractions were collected. Fractions 4–11 were combined and evaporated to a thick suspension in vacuo. This suspension was coevaporated with ethanol (2 × 100 ml). The solid was recrystallized from ethanol (50 ml) with sufficient water (approximately 5 ml) being added to effect solution at reflux temperature which furnished the hydrochloride salt of **31** (744 mg, 71%): mp 225° dec; uv λ_{max} (water) 294 nm (ϵ 7700), (pH 1) 264 nm (ϵ 11000).

Anal. Calcd for $C_9H_{13}N_3O_5$·HCl·0.5H_2O: C, 37.44; H, 5.24; N, 14.56. Found: C, 37.62; H, 5.24; N, 14.51.

The hydrochloride salt of **31** (710 mg) was dissolved in water (25 ml) and the pH of the solution adjusted to 7 by the addition of

Dowex 1X2 (OH^-) ion exchange resin. The resin was removed by filtration and washed with water (10 ml) and the filtrate evaporated to dryness in vacuo. The solid was recrystallized from water (5 ml) and dried for 6 hr at the reflux temperature of toluene to give **31** (565 mg, 92%), mp 226–228°, uv λ_{max} (water) 293 nm (ϵ 8000), (pH 1) 265 nm (ϵ 10000).

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.45; H, 5.39; H, 17.28. Found: C, 44.55; H, 5.20; N, 17.26.

O^2-2′-Cyclo-5-amino-5′-deoxyuridine (28). 5-Amino-5′-deoxyuridine (**31**, 2.44 g), diphenyl carbonate (3.89 g), and sodium bicarbonate (163 mg) were combined and *N,N*-dimethylacetamide (10 ml) added to the mixture. The mixture was heated for 25 min in an oil bath maintained at 170° and then added dropwise with good stirring to diethyl ether (200 ml). The solid was collected by filtration, washed with diethyl ether (160 ml), recrystallized from methanol (125 ml), and dried for 12 hr at the reflux temperature of toluene to give **28** (1.92 g, 85%), mp 262–263°, uv λ_{max} (methanol) 289 nm (ϵ 7200) and 258 (6300).

Anal. Calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 48.03; H, 4.94; N, 18.66.

Diazotization of O^2-2′-Cyclo-5-amino-5′-deoxyuridine (28) to Give Diazo Compound 32. Compound **28** (806 mg) was added to 1.02 *N* hydrochloric acid (5.27 ml) at 0° and 0.95 *M* aqueous sodium nitrite solution (4.15 ml) was added dropwise to the mixture over a period of 8 min while maintaining the temperature at 0–2°. After the addition was complete, the mixture was stirred in the cold for 30 min and then added to 35 ml of a chloroform–acetonitrile (3:2 v/v) mixture. The resulting mixture was stirred at room temperature for 10 min, the organic layer was decanted, and the aqueous layer was again stirred for 10 min with 35 ml of the chloroform–acetonitrile mixture. The organic layer was decanted, and the aqueous layer was concentrated to 6 ml in vacuo and then extracted with 3 × 15 ml of the chloroform–acetonitrile mixture. The organic solutions were then combined, dried ($MgSO_4$) at 5° for 18 hr, and then concentrated to a syrup in vacuo. The syrup was dissolved in hot 1-propanol (6 ml) and the solution allowed to stand at 5° for 18 hr to give light yellow crystals which were collected by filtration and dried for 3 hr at the reflux temperature of methanol to give **32** (542 mg, 60%): mp 148–149°; uv λ_{max} (methanol) 249 nm (ϵ 30,000); ir 2150 cm^{-1} (diazo).

Anal. Calcd for $C_9H_{10}N_4O_5$: C, 42.53; H, 3.97; N, 22.04. Found: C, 42.59; H, 4.23; N, 21.89.

1-(β-D-Ribofuranosyl)-$O^{5'}$-6(*S*)-Cyclo-5-diazo-1,6-dihydro-3-methylpyrimidine-2,4(6*H*)-dione [$O^{5'}$-6(*S*)-Cyclo-5-diazo-3-methyluridine, 13]. 5-Amino-3-methyluridine[45] (1.0 g) was dissolved in 50% (v) aqueous acetic acid (8.90 ml) and the solution was cooled to 0° in an ice–salt bath. A 6.9% aqueous solution of sodium nitrite (3.70 ml) was added dropwise to the solution over a peroid of 12 min while maintaining the temperature at 0–2°. After the addition was complete, the solution was stirred in the cold for 10 min and then concentrated to a syrup in vacuo. The syrup was coevaporated first with toluene (2 × 20 ml), then ethanol (2 × 20 ml), the residue was dissolved in hot ethanol (20 ml), and the solution was allowed to stand at 5° for 18 hr to give **13** (790 mg, 76%), mp 192–193°. A small sample was recrystallized from ethanol for analysis and dried for 18 hr at the reflux temperature of toluene: melting point unchanged; uv λ_{max} (methanol) 265 nm (ϵ 17000); ir 4.73 μ (diazo).

Anal. Calcd for $C_{10}H_{12}N_4O_6$: C, 42.29; H, 4.24; N, 19.73. Found: c, 42.24; H, 4.24; N, 19.73.

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(31) The synthesis of **13** is described in the Experimental Section of this paper. The structural assignment for **13** was accomplished by a method similar[1] to that used for the structural assignment for **1**.
(32) A commercial sample of **17** was purchased from J. T. Baker Co., Plainsville, N.J.
(33) Reaction of **7** in refluxing methanol with the inclusion of triethylamine (10 mol %) gave a product which had the same chromatographic mobility as uracil. A chromatographic comparison of the reaction mixture with **20** revealed that **20** was not formed in a detectable amount. This precluded a kinetic study of possible base catalysis and suggested that ring opening does not proceed by an ElcB mechanism.
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