Syntheses and Structure Assignments of Six Azolinone Ribonucleosides

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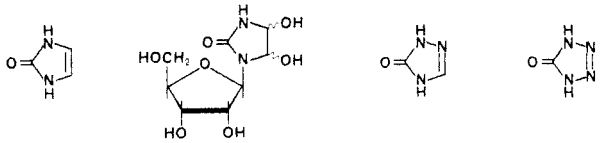
N-Ribosidation of a series of azolinones was achieved via silylation and $SnCl_4$ catalysis. N-Ribosidation of 4-imidazolin-2-one gave 1-β-D-ribofuranosyl-4-imidazolin-2-one; of 1,2,4-triazolin-3-one gave 2- and 4-β-D-ribofuranosyl-1,2,4-triazolin-3-one, and 2,4-di-β-D-ribofuranosyl-1,2,4-triazolin-3-one; and of 2-tetrazolin-5-one gave 1-β-D-ribofuranosyl-2-tetrazolin-5-one and 1,4-di-β-D-ribofuranosyl-2-tetrazolin-5-one. Structure assignments were based on NMR and mass spectra, microanalytical data, and interconversions. The triazolinone monoriboside isomer structures were differentiated by ^{13}C NMR long-range coupling patterns, and the assignments were confirmed by X-ray crystallography. New syntheses were developed for several of the ribonucleosides by fashioning the azolinone rings from 2,3,5-tri-*O*-benzoylribofuranosyl isocyanate.

The imidazolidin-2-one nucleus appears in products of the γ-radiolysis of cytosine[2] and of the oxidation of uric acid.[3] The 4-imidazolin-2-one nucleus (1), through 1-carbamoyl-4-imidazolin-2-one, served as a precursor for the synthesis of the cytosine radiolysis products.[4] It is possible that the γ-radiolysis products of cytidine[2] will include, by analogy, *cis*- and *trans*-1-carbamoyl-3-β-D-ribofuranosyl-4,5-dihydroxyimidazolidin-2-one and, by facile hydrolysis of the carbamoyl group, the corresponding 1-β-D-ribofuranosyl-4,5-dihydroxyimidazolidin-2-one (2). Because of our interest in these compounds, we have directed attention first to the synthesis of the *N*-ribosyl derivatives of 4-imidazolin-2-one (1) and the related 1,2,4-triazolin-3-one (3) and 2-tetrazolin-5-one (4). Interest is also



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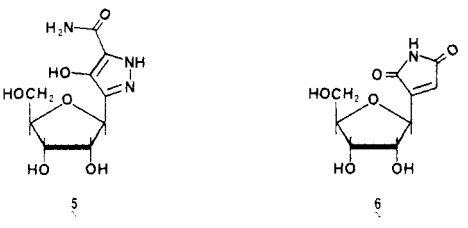
stimulated in these compounds by the existence of biologically and therapeutically active ribonucleosides that contain five-membered-ring heterocycles. These include the natural antibiotics pyrazofurin (pyrazomycin, 5),[5-8] which has antiviral and antitumor activity; showdomycin (6),[9-12] an antibacterial agent and an inhibitor of Ehrlich ascites tumor cells; and bredinin (7),[13-15] which inhibits the growth of *Candida albicans* and vaccinia virus, is cytotoxic to lymphoma cell line L5178Y, and is an immunosuppressive agent; and the synthetic broad-spectrum antiviral compound ribavirin (virazole, 8).[16-19] Other *N*-ribosyl derivatives that have been synthesized include those of the five-membered-ring imidazoles,[20,21] triazoles,[22-27] tetrazoles,[28,29] and thiazoles.[30,31]



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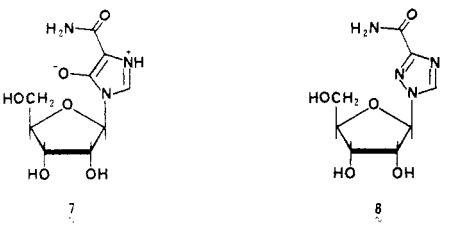

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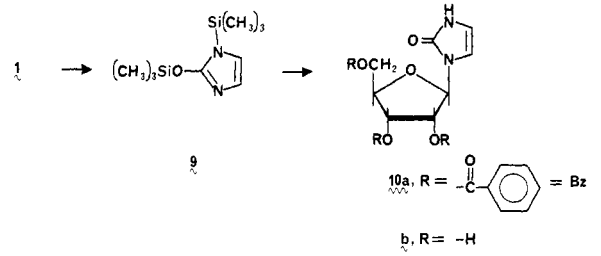
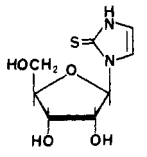
Among the five-membered-ring heterocycles, 4-imidazolin-2-one (**1**), 1,2,4-triazolin-3-one (**3**), and 2-tetrazolin-5-one (**4**) bear close resemblance to the pyrimidinones, and pyrimidinones have been N-ribosidated efficiently by the Vorbrüggen method,[32-34] which accordingly directed our course of synthesis.[35] Trimethylsilylation of 4-imidazolin-2-one (**1**) with hexamethyldisilazane and trimethylsilyl chloride in anhydrous pyridine yielded a sublimable solid, identified as 1-(trimethylsilyl)-2-[(trimethylsilyl)oxy]imidazole (**9**). Reaction of **9** with 1-*O*-



1 → 9 → 10a, R = Bz; b, R = H

acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in 1,2-dichloroethane/acetonitrile with $SnCl_4$ as catalyst gave 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-4-imidazolin-2-one (**10a**) as the major ribonucleoside product. Deprotection with methanolic ammonia furnished 1-β-D-ribofuranosyl-4-imidazolin-2-one (**10b**). Analysis of the ^{13}C NMR spectrum of **10b** was useful in assigning N-ribosidation sites of other products in this series. The resonances for the ribosyl carbons were in the expected range.[36-38] For the imidazolidinone ring, the C4 and C5 resonances were in close proximity, 110.2 and 109.1 ppm from tetramethylsilane in the decoupled spectrum, but were easily distinguishable in the proton-coupled ^{13}C spectrum. In the latter, the 110.2-ppm resonance appeared as a doublet of doublets, J = 199.7 and 9.3 Hz, due to coupling with H4 and H5, respectively, whereas the 109.1-ppm resonance was split by H5 and H4 (J = 199.7 and 10.2 Hz) and also showed three-bond coupling, J = 4.8 Hz, to the anomeric proton of the sugar attached to the adjacent nitrogen. The ^{13}C assignments are therefore in the order listed above. Compound **10b** is of ancillary interest due to the recent finding that a substituted glycosyl-4-imidazolin-2-one makes up part of the structure of the antibiotic nikkomycin X.[39] The synthesis of 1-β-D-ribofuranosyl-4-imidazoline-2-thione (1-β-D-ribofuranosylimidazole-2-thione) (**11**) by the Vorbrüggen method has also been described.[40]



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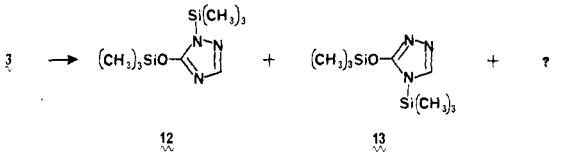
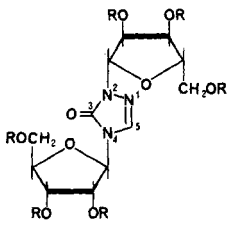
N-Ribosidation of 1,2,4-triazolin-3-one (**3**) was carried out by the same procedure that was used for 4-imidazolin-2-one (**1**). Trimethylsilylation of **3** gave a low-melting, distillable solid consisting, on the basis of comparison with **9**, of 2- and 4-(trimethylsilyl)-3-[(trimethylsilyl)oxy]-1,2,4-triazole (**12** + **13**) and possibly the third, the 1-trimethylsilyl, isomer. N-Ribosidation, followed by



3 → 12 + 13 + ?

workup and column chromatography, yielded three ribonucleoside products consisting of one diribonucleoside and two monoribonucleosides. The relative proportions of these products were highly variable, depending upon the reaction conditions. A diribonucleoside has been reported as an attendant product with **11** in the N-ribosidation of 4-imidazoline-2-thione.[40] We could assign the structure of the deprotected diribonucleoside from the trimethylsilylated 1,2,4-triazolin-3-one (**3**) as 2,4-di-β-D-ribofuranosyl-1,2,4-triazolin-3-one (**14b**) on the basis of elemental analysis, mass spectrum, and a comparison of its ^{13}C NMR spectrum with the spectra of the two mono-*N*-ribosyl derivatives. When the ^{13}C NMR spectrum of **14b** was determined in $(CD_3)_2SO$, the proton-coupled resonance of C5 appeared as a doublet of doublets due to one-bond and three-bond coupling at 134.2 ppm, whereas in D_2O, the C5 resonance disappeared in the fourier transform pulsed spectrum, which indicated that exchange of deuterium for hydrogen had occurred at C5.[41] Confirmation of the assigned structure was obtained by N-ribosidation of **15a** to give **14a** in good yield. If the possibility of O-ribosidation is rejected, as indicated by the close proximity of the two 1′-carbons in the ^{13}C NMR spectrum of **14b** in $(CD_3)_2SO$, the only site on **15a** which is available for ribosidation is the N2 position.



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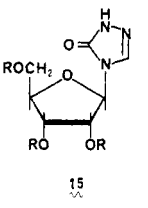

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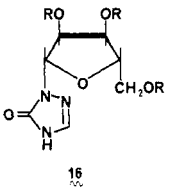
14, 15, 16a, R = Bz; b, R = H



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Of the N-tribenzoylribosidated triazolinones, the isomer of highest R_f on thin-layer chromatography (silica, 5% EtOH/$CHCl_3$) was deprotected to yield the N-ribosidated triazolinone that showed C5 in the ^{13}C NMR spectrum in D_2O as a doublet of doublets, J = 221 and 6 Hz. These values correspond to one-bond and three-bond couplings. The carbonyl carbon showed coupling to more than one proton at three-bond distance. These coupling patterns identify this *N*-ribosyl derivative as 4-β-D-ribofuranosyl-

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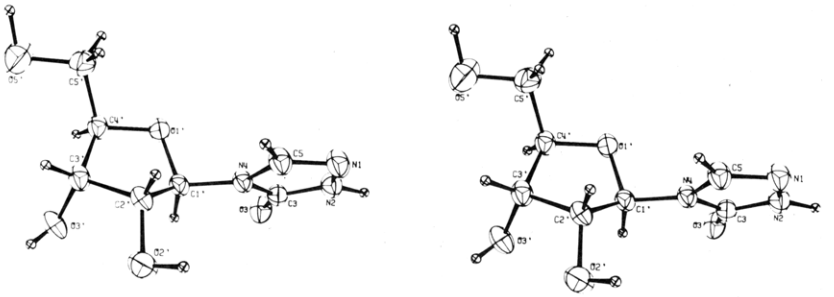

Figure 1. Stereoscopic view of a single molecule of 4-β-D-ribofuranosyl-1,2,4-triazolin-3-one (**15b**).

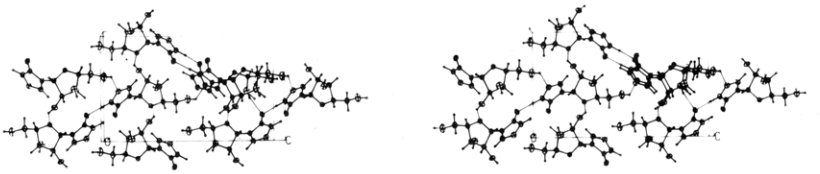

Figure 2. Stereoscopic view of the packing of 4-β-D-ribofuranosyl-1,2,4-triazolin-3-one (**15b**).

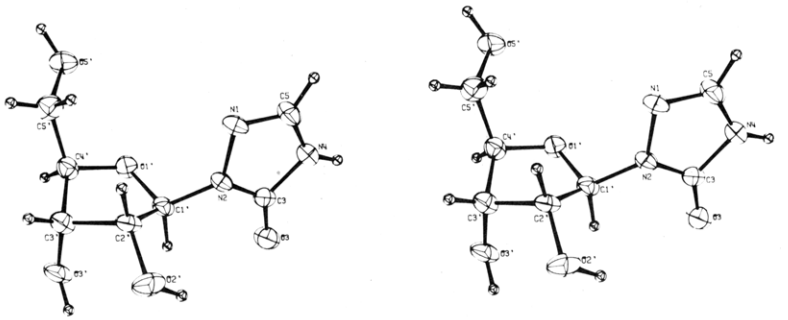

Figure 3. Stereoscopic view of a single molecule of 2-β-D-ribofuranosyl-1,2,4-triazolin-3-one (**16b**).

1,2,4-triazolin-3-one (**15b**), in a singular solution to the structure problem, since only in **15b** are both C3 and C5 coupled to the anomeric proton three bonds distant. The ^{13}C NMR of the second deprotected mono-*N*-ribosyl derivative showed C5 as a doublet, J = 219 Hz, due to one-bond coupling, and C3 as a multiplet, leading to assignment of its structure as 2-β-D-ribofuranosyl-1,2,4-triazolin-3-one (**16b**). The structure assignments of these two isomers were verified by X-ray crystallography. Slow crystallization from CH_3CN/CH_3OH gave X-ray quality crystals of both **15b** and **16b**.

X-ray crystallography of the compound assigned structure **15b** confirms both the position of N-ribosidation and the configuration at C1′ (β). A stereoscopic view of the molecule is given in Figure 1, together with the atom numbering used in the analysis. The atoms of the nitrogen-containing heterocyclic ring are coplanar and show shortening of bond lengths, consistent with some aromatic character. The C3–N4 bond length of 1.392 (4) Å is close to the 1.380 Å found in 3,5-diaryl-1,2,4-oxadiazoles by Albinati and Brückner,[42] who pointed out that the latter value is typical for N-containing aromatic compounds. The N2–C3 and N4–C5 bonds are shortened due to the adjacent C3–O3 and N1–C5 double bonds.[43,44] The plane of N1, N2, C3, N4, C5, O3 (Table I) is somewhat deformed. If O3 is excluded from the plane calculation, better coplanarity of the ring atoms is observed; the deviation of O3 from the plane of the ring atoms is observed; the deviation of O3 from the plane of the ring atoms is relatively large (0.048 (3) Å). In the O-containing heterocyclic ring the C4′–C5′ bond is somewhat shorter than the 1.54 (3) Å length predicted, but some shortening is expected since the C5 thermal parameters are large. The other bond lengths in the ribosyl ring are within 4 standard deviations of their expected values.[43] The conformation of the furanose ring is C2′-endo. The conformation about the C1′–N4 bond is best defined by the value of χ = 84.73° (O1′–C1′–N4–C5).[45]

Table I. Best Planes Calculations for 4-β-D-Ribofuranosyl-1,2,4-triazolin-3-one (15b)

atoms in plane	deviation from plane, Å	atoms in plane	deviation from plane, Å
N1	-0.0075	N1	0.0005
N2	0.0096	N2	0.0022
C3	0.0113	C3	-0.0044
N4	0.0084	N4	0.0033
C5	-0.0129	C5	-0.0042
O3	-0.0109	other atoms	
		O3	-0.0405
χ^2 = 94.58		χ^2 = 7.35	

Table II. Intermolecular Hydrogen Bonds in 4-β-D-Ribofuranosyl-1,2,4-triazolin-3-one (15b)

A–H···B	A–H	H···B	<A–H···B	A···B
N2–H2···O3	1.00	1.78	170	2.770
O2′–HO2′···O1′	1.04	2.09	146	3.012
O3′–HO3′···O3	0.76	2.04	167	2.790
O5′–HO5′···N1	1.04	2.03	139	2.892

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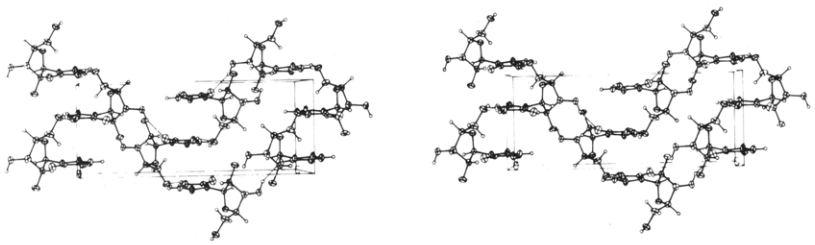


Figure 4. Stereoscopic view of the packing of 2-β-D-ribofuranosyl-1,2,4-triazolin-3-one (**16b**).

Table III. Best Planes Calculations for 2-β-D-Ribofuranosyl-1,2,4-triazolin-3-one (16b)

atoms in plane	deviation from plane, Å	atoms in plane	deviation from plane, Å
N1	−0.0008	N1	−0.0103
N2	−0.0005	N2	0.0070
C3	−0.0233	C3	−0.0054
N4	−0.0093	N4	−0.0023
C5	0.0207	C5	0.0121
O3	0.0104	other atoms	
		O3	0.0436
χ^2 = 70.11		χ^2 = 18.31	

There is no intramolecular hydrogen bonding in the structure; however, extensive intermolecular hydrogen bonding exists. As indicated in Table II, O3 is involved in a strong hydrogen bond to an H2 and less strongly to an HO3′ of neighboring molecules. The packing diagram (Figure 2) shows the hydrogen bonding with thin lines. The molecules are packed in three mutually perpendicular 2_1 screw axes with no stacking of the heteroaromatic bases.

The stereoscopic view of **16b** provided by X-ray crystallography is shown in Figure 3. In this structure also, the atoms in the N-heterocyclic ring are nearly coplanar and the ring exhibits some aromatic character. The bond lengths of the heterocycles of **15b** and **16b** are nearly the same. The significant differences (3 SD) are a 0.02 Å increase in the N1–N2 bond length and a 0.02 Å decrease in the N1–C5 and N4–C5 bond lengths in **16b** compared with those in **15b**. The N–C3 bonds are not affected. The N1–C5 bond length differences are consistent with hydrogen bonding to N1 in **15b** causing electron withdrawal from the bond.

The planarity of the heterocyclic ring including O3 in **16b** (Table III) is somewhat improved over that in **15b**; there is weaker intermolecular hydrogen bonding to O3 in **16b**. Exclusion of O3 from the calculations gives some improvement in ring coplanarity but not by as great an increment as observed for **15b**. The conformation of the furanose ring is C2′-endo, and the conformation about the C1′–N2 bond is expressed by the value of χ = 63.98° (O1′–C1′–N2–N1).[45]

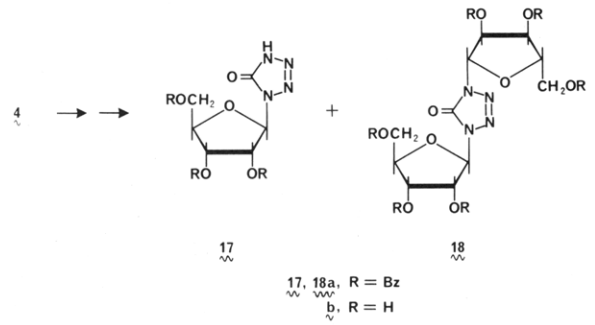
There are no intramolecular hydrogen bonds in the crystal structure of **16b**, and there are three intermolecular hydrogen bonds (Table IV). The packing diagram (Figure 4) indicates that the stacking interaction between adjacent heterocycles may be significant. Calculations show adjacent bases to be at an angle of 16.7° to each other, with an average distance of 3.50 Å between them. The rings are stacked with the C5 atom of one ring approximately in the center of the ring above it.

N-Ribosidation of 2-tetrazolin-5-one (**4**), using the Vorbrüggen procedure, gave, as expected, 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-tetrazolin-5-one (**17a**) and

Table IV. Intermolecular Hydrogen Bonds in 2-β-D-Ribofuranosyl-1,2,4-triazolin-3-one (16b)

A–H···B	A–H	H···B	<A–H···B	A···B
N4–H4···O5′	0.86	2.16	161	2.986
O3′–HO3′···O3	0.90	2.01	157	2.867
O5′–HO5′···N1	0.94	2.03	163	2.986

1,4-bis(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-tetrazolin-5-one (**18a**). Methanolic ammonia deprotection of **17a**



gave 1-β-D-ribofuranosyl-2-tetrazolin-5-one (**17b**) plus an ammonia adduct with properties consistent with the structure 1-carbamoyl-4-ribofuranosyltetrazene (Rib-NH-N=N-NH-$CONH_2$). The tetrazene could logically result from ammonia attack on the carbonyl of the tetrazolinone and subsequent ring opening. The coupled ^{13}C NMR spectrum of **17b** in D_2O showed the carbonyl carbon as a singlet, consistent with the expected syn conformation between C5 and H1′. The positions of the resonances were very similar to those seen in the diribonucleoside, confirming the position of ribosidation as N1. Deprotection of **18a** gave 1,4-di-β-D-ribofuranosyl-2-tetrazolin-5-one (**18b**) as a glass. While the carbonyl carbon did not show the expected three-bond coupling within the resolution of the instrument, there was only one set of ribosyl resonances, indicating the equivalence of the two ribosyl moieties and, accordingly, N1 and N4 as the sites of N-ribosidation.

Selective syntheses were developed for several of the ribonucleosides on the basis of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl isocyanate (**19**) as a common precursor. Previously, compound **19** has been used in the synthesis of ribofuranosyl ureas[46] and ribonucleoside analogues,[47] and the corresponding isothiocyanate has been used in the synthesis of a series of sulfur-containing nucleosides including the thione analogues of **15b** and **16b**.[27,48,49]

Cyanic acid, when treated with α-aminoacetaldehyde diethyl acetal (**20**), gave α-ureidoacetaldehyde diethyl acetal which closed to **1** in the presence of acid.[50] With

(45) Prusiner, P.; Sundaralingam, M. *Acta Crystallogr., Sect. B* **1976**, *32*, 419.

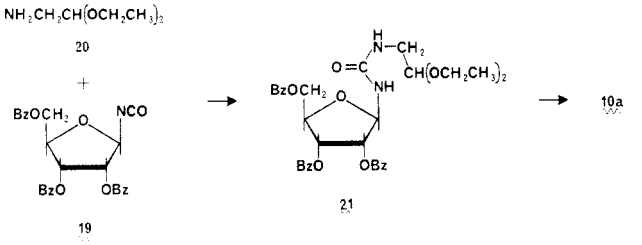
(46) Ukita, T.; Hamada, A.; Yoshida, M. *Chem. Pharm. Bull.* **1964**, *12*, 454.

(47) Píškala, A.; Šorm, F. *Collect. Czech. Chem. Commun.* **1964**, *29*, 2060.

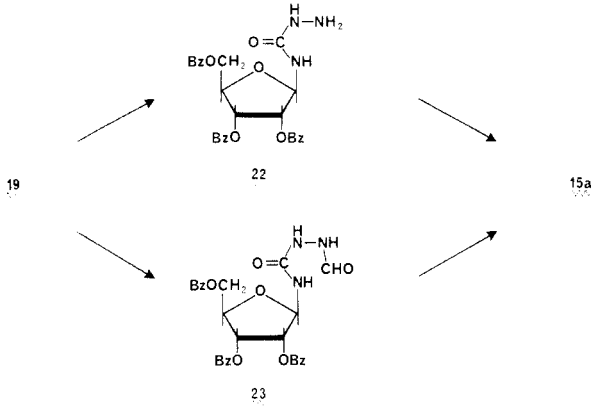
(48) Takahashi, H.; Nimura, N.; Ogura, H. *Chem. Pharm. Bull.* **1979**, *27*, 1130, 1143, 1147.

(49) Takahashi, H.; Nimura, N.; Obata, N.; Sakai, H.; Ogura, H. *Chem. Pharm. Bull.* **1979**, *27*, 1153.

the synthesis of unsubstituted **1** as the model, **20** was added to a toluene solution of **19**. Chromatography of the reaction mixture gave *N*-(2,2-diethoxyethyl)-*N'*-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)urea (**21**). Stirring of **21** in toluene with a catalytic amount of *p*-toluenesulfonic acid gave **10a** in overall yield of 18% from 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose.



Similar methodology was used in the synthesis of **15a**. Ring closure of 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-semicarbazide (**22**) with triethyl orthoformate was expected to give **15a**. Compound **22** had been synthesized by Hřebabecký, Točík, and Beránek[51] from 3-β-D-ribofuranosyl-2,4-thiazolidinedione. We found that the reaction of **19** with anhydrous hydrazine provided an alternate route. Attempted ring closure of **22** with triethyl orthoformate in the presence of an acid catalyst gave a small amount of the desired **15a** but produced predominantly hydrolysis products. Reaction of **19** with formyl hydrazide gave 1-formyl-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-semicarbazide (**23**). Ring closure was accomplished by dehydrative silylation with hexamethyldisilazane in pyridine to give **15a** in 71% yield.



In conclusion, we have provided syntheses of a series of azolinone ribonucleosides that may have interesting properties in the biological systems in which they are being tested. We have utilized ^{13}C NMR spectroscopy in the assignment of positions of substitution in the *N*-nucleosides, along with X-ray single-crystal analysis and interconversions of mono- to di-*N*-ribofuranosyl derivatives.

Experimental Section

Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 337 grating infrared spectrophotometer with polystyrene as the standard. Nuclear magnetic resonance spectra were recorded on JEOL FX-60, Varian EM 390, HR 220, and/or HA 100 spectrometers using either tetramethylsilane or 3-(trimethylsilyl)tetradeuteriopropionic acid sodium salt as internal standards for ^1H NMR and tetramethylsilane or dioxane as internal standards for ^{13}C NMR. Mass spectra were obtained on a Varian CH-5 spectrometer (low resolution) and a Varian MAT 731 spectrometer (field desorption) coupled with a 620i computer and a STATOS recorder. Microanalyses were determined by Josef Nemeth and his associates or by Midwest Microlab, Ltd. Thin-layer chromatography was carried out on Macherey-Nagel precoated silica gel plates with fluorescent indicator. Brinkmann 0.05–0.2-mm silica gel was used for column chromatography.

4-Imidazolin-2-one (1). α-Aminoacetaldehyde diethyl acetal (**20**) (50 g, 376 mmol) was poured over 80 g of ice and 76 mL of cold (−40 °C) 5 N HCl was added.[50] A solution of potassium cyanate (45.7 g, 564 mmol) in 100 mL of water was added slowly to the reaction mixture, and the reaction mixture was heated at reflux for 2 h. Concentration of the solvent to 20 mL gave α-ureidoacetaldehyde diethyl acetal as a white precipitate, which was collected and added to 1 L of 0.1 N H_2SO_4 under nitrogen. The solution was stirred at 25 °C for 2 days. Barium hydroxide was used to neutralize the solution, and the resulting $BaSO_4$ precipitate was removed by filtration. Concentration of the solvent to 60 mL gave **1** (16.8 g, 53%) as a white precipitate. Chromatography (10% MeOH/$CHCl_3$) provided pure **1**: mp 230–258 °C dec; ^1H NMR ($(CD_3)_2SO$) δ 6.20 (s, 2, 4; and 5 H), 9.69 (br, 2, 2 NH); ^{13}C NMR ($(CD_3)_2SO$) δ 155.1 (d, J = 0.5 Hz, C=O), 108.6 (dd, J = 197.2, 9.4 Hz, 4 and 5 C).

1-(Trimethylsilyl)-2-[(trimethylsilyl)oxy]imidazole (9). Dry 4-imidazolin-2-one (**1**; 9.73 g, 116 mmol) was suspended in dry pyridine (25 mL), and 25 mL of hexamethyldisilazane was added according to the method of Wiemer.[35] A catalytic amount of trimethylsilyl chloride (about 0.5 mL) was then added to the suspension. The reaction was heated at reflux for 7 h, at which point most of the solid had dissolved. The solvent was removed in vacuo, and the residue was sublimed in a Kugelrohr apparatus to give white needles of **9** (20.51 g, 78%): sublimation temperature 105 °C (1.5 mm); ^1H NMR ($(CD_3)_2SO$) δ 0.33 (s, 18, 2 $Si(CH_3)_3$), 6.20 (s, 2, 4, and 5 H).

Anal. Calcd for $C_9H_{20}N_2OSi_2$: C, 47.32; H, 8.82; N, 12.26. Found: C, 47.30; H, 8.80; N, 12.32.[35]

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4-imidazolin-2-one (10a). To 1-(trimethylsilyl)-2-[(trimethylsilyl)oxy]imidazole (**9**; 10.25 g, 45 mmol) dissolved in a mixture of 1,2-dichloroethane and acetonitrile (100 mL/100 mL) was added 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose (22.68 g, 45 mmol) that had been previously dried (78 °C, 24 h, 1 mm).[35] The resulting suspension was cooled to 0 °C in an ice bath. Stannic chloride (6 mL) was added, and the solution was stirred at 0 °C for 5 h under anhydrous conditions. The reaction was quenched with a saturated $NaHCO_3$ solution in water, and the tin precipitate was removed by filtration through Celite. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo to give a thick oil. Recrystallization twice from acetonitrile gave **10a** (3.01 g, 13%) in analytical purity. Chromatography (0–8% EtOH/$CHCl_3$) of the residues gave a further crop (1.44 g, 6%) for a total yield of 19%: mp 203–205 °C; ^1H NMR ($(CD_3)_2SO$) δ 4.70 (m, 3, 4′, and 5′ H), 6.02 (m, 3, 1′, 2′, and 3′ H), 6.49 (t, 1, J = 2.8 Hz, 4 H), 6.69 (dd, 1, J = 2, 2.8 Hz, 5 H), 7.30–8.15 (m, 15, benzoyl H), 10.23 (br, 1, ring NH); field-desorption mass spectrum, m/e 528 (M^+).

Anal. Calcd for $C_{29}H_{24}N_2O_8$: C, 65.91; H, 4.58; N, 5.30. Found: C, 66.00; H, 4.57; N, 5.47.

Deprotection of O-benzoylated ribonucleosides was accomplished by the following general procedure. The protected ribonucleoside was added to methanol (1 g of ribonucleoside/100 mL MeOH) and the resulting suspension was cooled in an ice bath. Anhydrous ammonia was bubbled through the suspension until saturation was achieved. The reaction mixture was stirred at room temperature until TLC (5% EtOH/$CHCl_3$) indicated completion of the reaction, normally 24–48 h. Removal of the solvent in vacuo gave either an oil or a solid residue. This residue was washed with hot toluene to remove methyl benzoate and benzamide, and the insoluble residue was crystallized from the appropriate solvent to give the pure deprotected ribonucleoside.

1-β-D-Ribofuranosyl-4-imidazolin-2-one (10b). Deprotection of **10a** and crystallization from CH_3OH/CH_3CN gave **10b** (76%): mp 170–173 °C; ^1H NMR ($(CD_3)_2SO$) δ 3.53 (s, 2, 5′ CH), 3.77–4.15 (m, 3, 2′, 3′, and 4′ CH), 4.85–5.15 (m, 3, OH), 5.39 (d, 1, J = 5.4 Hz, anomeric H), 6.41 (d, 1, J = 3 Hz, 4 (or 5) H), 6.59 (d, 1, J = 3 Hz, 5 (or 4) H), 10.02 (br, 1, NH); ^{13}C NMR (D_2O) δ 154.0 (m, C=O), 110.2 (dd, J = 199.7, 9.3 Hz, 4 C), 109.1 (ddd, J = 199.7, 10.2, 4.8 Hz, 5 C), 85.7 and 84.2 (1′ and 4′ C, probably in that

(50) Duschinsky, R.; Dolan, L. A. *J. Am. Chem. Soc.* **1946**, *68*, 2350.
(51) Hěbabecký, H.; Točík, Z.; Beránek, J. *Collect Czech. Chem. Commun.* **1979**, *44*, 1475.

order[36-38]), 73.0 (2′ and 3′ C), 61.4 (5′ C); mass spectrum, *m/e* (relative intensity, 70 eV) 216 (4, M^+), 113, 97, 84 (100, $C_3H_4N_2O$).

Anal. Calcd for $C_8H_{12}N_2O_5$: C, 44.45; H, 5.59; N, 12.96. Found: C, 44.30; H, 5.87; N, 12.68.

1,2,4-Triazolin-3-one (3). A suspension of semicarbazide hydrochloride (9.0 g, 81 mmol) in 68 mL of triethyl orthoformate (60.5 g, 408 mmol) was heated at reflux for 2.5 h, according to the procedure of Kröger et al.[52] The mixture was cooled and filtered, yielding 6.24 g (91%) of **3**. Recrystallization from ethanol gave white flakes: mp 235–237 °C (lit.[53] mp 232–234 °C); IR (KBr) 1695 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 7.70 (s, 1, CH), 11.30 (br, 2, ring NH); ^{13}C NMR (D_2O) δ 156.5 (d, J = 5.8 Hz, C=O), 137.3 (d, J = 215 Hz, 5 C); mass spectrum, *m/e* (relative intensity, 70 eV) 85 (100, M^+), 42 (87, M^+ – HNCO).

2- and 4-(Trimethylsilyl)-3-[(trimethylsilyl)oxy]-1,2,4-triazole (12 and 13). To a suspension of 1,2,4-triazolin-3-one (**3**; 2.18 g, 26 mmol) in 22 mL of anhydrous pyridine were added 22 mL of HMDS and 0.5 mL of trimethylsilyl chloride. The suspension was heated at reflux under dry nitrogen for 4 h, at which point the reaction mixture was a clear solution. Removal of the solvent under vacuum at 50 °C gave a pale-yellow oil. Distillation of this oil in a Kugelrohr apparatus gave an oil which solidified to colorless needles upon cooling (5.67 g, 96%): sublimation temperature 62 °C (0.15 mm); ^1H NMR ($(CD_3)_2SO$) δ 0.43–0.54 (m, $SiCH_3$), 7.15 and 7.24 (s, base CH of two isomers).

N-Ribosidation of 2- and 4-(Trimethylsilyl)-3-[(trimethylsilyl)oxy]-1,2,4-triazole (12 and 13). In a typical N-ribosidation procedure a solution of 2- and 4-(trimethylsilyl)-3-[(trimethylsilyl)oxy]-1,2,4-triazole (**12** and **13**, 38 mmol) in 50 mL of anhydrous dichloroethane was added to a mixture of 100 mL of anhydrous CH_3CN and 50 mL of anhydrous dichloroethane. To this solution was added 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose (15.22 g, 30.2 mmol), and the resulting suspension was cooled in an ice bath. Tin(IV) chloride (4 mL, 34 mmol) was added and the reaction mixture was warmed slowly to room temperature with stirring. After 5 h, TLC (5% MeOH/$CHCl_3$) indicated that all of the starting material had reacted. The reaction was quenched by the slow addition of a suspension of an excess of $NaHCO_3$ in 200 mL of water. Upon completion of gas evolution the mixture was diluted with 400 mL of dichloroethane and filtered to remove the tin salt. The solid was washed with 50 mL of hot dichloroethane, and the wash was added to the filtrant. The organic and aqueous layers were separated, and the aqueous layer was extracted (2 × 50 mL) with dichloroethane. After the organic layers were combined and dried over Na_2SO_4, the solvent was removed under vacuum to give a white crystalline solid. This solid was dissolved in acetonitrile and absorbed onto 20 g of silica gel. The solvent was removed in vacuo, and the solid was added to a column (500 g, 0–5% EtOH/$CHCl_3$) for chromatography. The chromatography was followed by TLC (5% EtOH/$CHCl_3$), and three major products were observed, collected, and crystallized from CH_3CN. These products were identified as the following: R_f 0.5, 2,4-bis(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolin-3-one (**14a**; 4.66 g, 29% from ribofuranose); R_f 0.3, 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolin-3-one (**15a**; 3.40 g, 21%); R_f 0.25, 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolin-3-one (**16a**; 0.16 g, 1%).

Ratios and yields of the N-ribosidation products vary with solvent, reagent ratios, and reaction times.

The use of 2.2 equiv of 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose per mole of the silylated heterocycle increased the yield of the 2,4-bisribosidated product (**14a**) to 45% with a 48-h reaction time. If the same reaction was quenched after 3 h, the 4-ribosidated isomer (**15a**) was obtained in 26% yield.

The use of 1,2-dichloroethane as the reaction solvent produced a slower reaction but favored the formation of the 2-ribosidated isomer (**16a**). With a reaction time of 6 days, the yield of **16a** was optimized at 17%.

2,4-Bis(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolin-3-one (14a): mp 239–241 °C; ^1H NMR ($CDCl_3$) δ 4.53–4.80 (m, 6, 4′ and 5′ CH), 5.67–6.20 (m, 6, 1′, 2′, and 3′ CH), 7.20–7.50 and 7.70–8.10 (m, 30, benzoyl H), 8.61 (s, 1, base CH); mass spectrum, *m/e* (relative intensity, 70 eV) 445 (1, $(C_6H_5CO)_3C_5H_6O_4^+$), 122 (6, $C_6H_5CO_2H^+$), 105 (100, $C_6H_5CO^+$), 77 (26, $C_6H_5^+$); field-desorption mass spectrum, *m/e* 974 (M^+).

Anal. Calcd for $C_{54}H_{43}N_3O_{15}$: C, 66.59; H, 4.45; N, 4.31. Found: C, 66.50; H, 4.43; N, 4.69.

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolin-3-one (15a): mp 198–200 °C; ^1H NMR ($(CD_3)_2SO$) δ 4.6–4.8 (m, 3, 4′ and 5′ CH), 5.90–6.23 (m, 3, 1′, 2′, and 3′ CH), 7.33–8.06 (m, 15, benzoyl H), 8.14 (s, 1, base CH); mass spectrum, *m/e* (relative intensity, 70 eV) 445 (16, $M^+ - C_2H_2N_3O$), 105 (100, $C_6H_5CO^+$), 77 (17, $C_6H_5^+$); field-desorption mass spectrum, *m/e* 530 ($M^+ + 1$).

Anal. Calcd for $C_{28}H_{23}N_3O_8$: C, 63.51; H, 4.38; N, 7.94. Found: C, 63.34; H, 4.59; N, 8.18.

2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolin-3-one (16a): mp 249–252 °C; ^1H NMR ($(CD_3)_2SO$) δ 4.5–4.8 (m, 3, 4′ and 5′ H), 5.93–6.07 (br s, 3, 1′, 2′, and 3′ H), 7.3–8.1 (m, 16, ArH and base CH); mass spectrum, *m/e* (relative intensity, 70 eV) 445 (9, $M^+ - C_2H_3N_3O$), 105 (100, $C_6H_5CO^+$), 77 (22, $C_6H_5^+$); field-desorption mass spectrum, *m/e* 530 ($M^+ + 1$).

Anal. Calcd for $C_{28}H_{23}N_3O_8$: C, 63.51; H, 4.38; N, 7.94. Found: C, 63.21; H, 4.32; N, 7.87.

2,4-Di-β-D-ribofuranosyl-1,2,4-triazolin-3-one (14b) was obtained by deprotection of **14a** and was recrystallized from methanol (79%): mp 180–182 °C; IR (KBr) 1637 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 3.56 (m, 4, 5′ H), 3.88–4.36 (m, 6, 2′, 3′, and 4′ H), 4.90 (t, 1, 5′ OH), 5.05–5.16 (m, 3, OH), 5.37–5.56 (m, 4, anomeric H and 2 OH), 9.27 (s, 1, base CH); ^{13}C NMR ($(CD_3)_2SO$) δ 158.7 (m, C=O), 134.2 (dd, J = 212, 3 Hz, base CH), 86.6 and 85.5 (C-1 and C-4), 73.6, 73.1, 70.1, and 70.0 (C-2 and C-3), 61.3 (C-5); ^{13}C NMR (D_2O) δ 159.8 (d, J = 3.2 Hz, C=O), 93.0, 87.7, 85.1 and 84.7 (C-1 and C-4), 73.7 and 69.4 (C-2 and C-3), 60.8 and 60.5 (C-5); mass spectrum, *m/e* (relative intensity, 70 eV) 217 (1.8, $M^+ - C_5H_8O_4$), 187 (6.8, $M^+ - C_6H_{10}O_5$), 133 (96, $C_5H_9O_4^+$), 86 (100, base + 1^+); field-desorption mass spectrum, *m/e* 349 (M^+).

Anal. Calcd for $C_{12}H_{19}N_3O_9$: C, 41.26; H, 5.48; N, 12.03. Found: C, 41.39; H, 5.54; N, 12.30.

4-β-D-Ribofuranosyl-1,2,4-triazolin-3-one (15b). Recrystallization from methanol/acetonitrile of the product from the deprotection of **15a** gave **15b** in analytical purity (82%): mp 173–175 °C; IR (KBr) 1655 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 3.50 (m, 2, 5′ CH), 3.81, 3.99, 4.22 (3 m, 3, 2′, 3′, and 4′ CH), 4.88 (t, 1, 5′ OH), 5.01 (d, 1, OH), 5.25 (d, 1, J = 6 Hz, anomeric H), 5.29 (d, 1, OH), 8.02 (s, 1, base CH), 11.65 (br, 1, NH); ^{13}C NMR (D_2O) δ 154.6 (m, C=O), 136.5 (dd, J = 221, 6 Hz, base CH), 86.2 and 84.6 (C-1′ and C-4′), 73.1 and 70.0 (C-2′ and C-3′), 61.1 (C-5′); mass spectrum, *m/e* (relative intensity, 70 eV) 217 (1.1, M^+), 187 (6.5, $M^+ - CH_2O$), 133 (83, $C_5H_{10}O_4^+$), 86 (100, base + 1^+).

Anal. Calcd for $C_7H_{11}N_3O_5$: C, 38.71; H, 5.11; N, 19.35. Found: C, 38.56; H, 5.15; N, 19.52.

2-β-D-Ribofuranosyl-1,2,4-triazolin-3-one (16b). Deprotection of **16a** gave **16b** (50%). Recrystallization from methanol/acetonitrile gave an analytical sample: mp 146.5–147.5 °C; ^1H NMR ($(CD_3)_2SO$) δ 3.41 (m, 3, 5′ H and 5′ OH), 3.75, 3.98, 4.25 (3 m, 3, 2′, 3′, and 4′ CH), 4.60–5.20 (br, 2, 2′ and 3′ OH), 5.37 (d, 1, J = 4.5 Hz, 1′ H); ^{13}C NMR (D_2O) δ 155.0 (d, J = 5 Hz, C=O), 137.1 (d, J = 218.8 Hz, C-5), 86.2, 84.2 (C-4′ and C-1′), 72.5, 70.5 (C-2′ and C-3′), 61.6 (C-5′); mass spectrum, *m/e* (relative intensity, 70 eV) 218 (1.26, $M^+ + 1$), 217 (0.68, M^+), 187 (8.2, $M^+ - CH_2O$), 86 (100, $C_2H_4N_3O^+$).

Anal. Calcd for $C_7H_{11}N_3O_5$: C, 38.71; H, 5.11; N, 19.35. Found: C, 38.86; H, 5.05; N, 19.57.

N-Ribosidation of 4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolin-3-one (15a). A suspension of **15a** (0.42 g, 0.8 mmol) in 6 mL of HMDS, 10 mL of anhydrous pyridine, and about 0.25 mL of trimethylsilyl chloride was heated at reflux for 4 h. The resulting solution was cooled and the solvent was removed under vacuum to give a white solid. This solid was dissolved in 17 mL of anhydrous 1,2-dichloroethane and 2 equiv of 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose (0.80 g, 1.6 mmol) was added. The solution was cooled on ice and 0.5 mL of $SnCl_4$ was added, giving an immediate precipitate. The reaction was followed by TLC (2.5% EtOH/$CHCl_3$). After 24 h, the reaction was quenched with a saturated $NaHCO_3$ solution, giving a suspension which was filtered through Celite. The tin salts were washed with 1,2-dichloroethane (2 × 30 mL). The organic layer

(52) Kröger, C.-F.; Selditz, P.; Mutscher, M. *Chem. Ber.* **1965**, *98*, 3034.
(53) Kröger, C.-F.; Hummel, L.; Mutscher, M.; Beyer, H. *Chem. Ber.* **1965**, *98*, 3025.

was separated and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a yellow solid. Chromatography (110 g, $CHCl_3$) and collection of the fractions having spots which ran with 2,4-bis(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolin-3-one (**14a**), followed by evaporation of the solvent, gave a white solid (0.28 g, 0.29 mmol, 36%) identical with **14a** by ^1H NMR.

Crystallographic Analysis of 4-β-D-Ribofuranosyl-1,2,4-triazolin-3-one (15b) and 2-β-D-Ribofuranosyl-1,2,4-triazolin-3-one (16b). Both compounds crystallized slowly from CH_3CN/CH_3OH at room temperature. The reflections were observed on a Syntex $P2_1$ automated diffractometer equipped with a graphite monochromator using Cu Kα (λ = 1.5418 Å). The variable-scan option was used at 4–20°/min for **15b** and 2–58.6°/min for **16b**. Three standard reflections were monitored every 57 reflections; an examination of these at the end of the data collection showed insignificant crystal decomposition. The data were corrected for Lorentz and polarization effects.[54] Because of crystal twinning in **15b**, Friedel pairs were averaged.

The structures were solved by the MULTAN program.[55] All of the hydrogen atom positions were observed in difference maps, including those of the hydroxyl groups. All hydrogen atoms were fixed at difference Fourier positions and they were assigned a constant isotropic thermal parameter of 5.0. The scattering curves were taken from th e analytical expression used in the "International Tables for X-ray Crystallography".[56]

For **15b**, reflections were collected on a crystal of dimensions 0.50 × 0.40 × 0.10 mm to give the following data: $C_7H_{11}N_3O_5$, mol wt 217.2, orthorhombic, $P2_12_12_1$ (D_2^4), a = 5.726 (1) Å, b = 9.294 (2), Å, c = 16.583 (2) Å, volume = 882.5 Å^3, $F(000)$ = 456, ρ_{calcd} (Z = 4) = 1.63 g cm^{-3}, μ (Cu Kα) = 11.60 cm^{-1}. Of 1011 reflections, 984 were considered observed at $3.92\sigma(I)$.[57] Full-matrix least-squares refinements on the positional and anisotropic thermal parameters of the nonhydrogen atoms converged to agreement factors R = 0.054, R_w = 0.068.[58] The final value of $E = [\sum w(|F_o| - |F_c|)^2/(m - n)]^{1/2}$, where m is the number of observations and n is the number of variables, was 1.76. A final difference map showed no peak greater than 0.35 e/Å^3.

The crystal properties of **16b**, observed for a crystal 0.75 × 0.30 × 0.15 mm, were as follows: $C_7H_{11}N_3O_5$, mol wt 217.2, orthorhombic, $P2_12_12_1$ (D_2^4), a = 7.073 (3) Å, b = 7.373 (4) Å, c = 17.475 (7) Å, volume = 911.3 Å^3, $F(000)$ = 456, ρ_{calcd} (Z = 4) = 1.584 g cm^3, μ (Cu Kα) = 11.24 cm^{-1}. For **16b**, 780 of 821 reflections processed were considered observed. The parameters of the nonhydrogen atoms converged to agreement factors R = 0.057, R_w = 0.076.[58] The final value of E was 1.90, and the final difference map showed no peak greater than 0.32 e/Å^3.

2-Tetrazolin-5-one (4) was prepared by a modification of the procedure reported by Lieber and Enkoji.[59] Aminotetrazole hydrate (10.3 g, 100 mmol) was dissolved in a mixture of 200 mL of water, 10 mL of concentrated H_2SO_4, and 100 g of ice. After the mixture had been cooled to 5 °C, $NaNO_2$ (7.65 g, 111 mmol) in 50 mL of water was added, and the reaction mixture was stirred for 30 min. Cupric sulfate (38 g, 152 mmol) in 200 mL of water was added to the reaction. The mixture was stored in the refrigerator overnight. A small amount of precipitate was filtered from the solution, dissolved in 10 mL of concentrated HCl, and added to the original filtrate. Hydrogen sulfide was bubbled through the reaction mixture for 10 min, the CuS was removed by filtration, and the process was repeated until CuS no longer formed upon addition of hydrogen sulfide. The reaction mixture was heated to near boiling, and barium chloride (84 g, 343 mmol) was added to precipitate the sulfate. The solution was cooled, and the $BaSO_4$ was removed by filtration. Evaporation of the filtrate gave a yellow solid (21 g). Extraction of this solid with acetone in a Soxhlet apparatus, followed by evaporation of the acetone, yielded 5.22 g (61%) of **4**: mp 243–245 °C (lit.[59] mp 257–258 °C dec); IR (KBr) 1670 cm^{-1}; mass spectrum, m/e (relative intensity, 70 eV) 86 (100, M$^+$), 43 (51, HNCO).

Anal. Calcd for CH_2N_4O: C, 13.95; H, 2.33; N, 65.12. Found: C, 14.25; H, 2.32; N, 65.45.

N-Ribosidation of 2-Tetrazolin-5-one (4). To dry 2-tetrazolin-5-one (**4**; 3.07 g, 0.036 mol) were added 25 mL of HMDS, 30 mL of anhydrous pyridine, and 10 drops of trimethylsilyl chloride. The reaction mixture was heated at reflux for 3 h, during which time the solid gradually dissolved. The reaction mixture, was cooled, and the solvent was removed on a rotary evaporator to give a white solid (some of which distilled during solvent removal), which was assumed to be 1-(trimethylsilyl)-5-[(trimethylsilyl)oxy]tetrazole. This solid was immediately dissolved in 100 mL of dry 1,2-dichloroethane, anhydrous 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose (14.90 g, 0.030 mol, 0.82 equiv) was added, and the solution was cooled on ice. Addition of 2 mL of $SnCl_4$ resulted in the immediate formation of a precipitate. The reaction was followed by TLC (diethyl ether) and stirring was continued for 42 h at room temperature. The TLC monitoring then showed two major ribose-containing spots, at R_f 0.35 and 0.28. The reaction was quenched with 200 mL of saturated $NaHCO_3$ solution in water. To the suspension was added NaCl to saturate the aqueous layer, and ether was added until separation of the phases was achieved with the organic layer above the aqueous layer. This procedure made filtration easier. The liquids were poured away from the tin salts and filtered. Acetonitrile was added to the tin salts, and the mixture was heated to reflux and then filtered to remove any residual product from the salts. The organic layer was separated and evaporated to give an oil. Chromatography (500 g, 0–4% $EtOH/CHCl_3$) cleanly separated the two major products. The first product from the column was collected, and the solvent was evaporated to give an oil. The oil was dissolved in 3 mL of CH_3CN and 15 mL of CH_3OH was added. The needles that separated from the solution at room temperature were collected. Recrystallization from CH_3CN/CH_3OH gave an analytical sample of 1,4-bis(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-tetrazolin-5-one (**18a**; 2.26 g, 0.0023 mol, 16%).

Collection of the second product and evaporation of the solvent gave a white solid. Recrystallization from acetonitrile gave needles of analytically pure 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-tetrazolin-5-one (**17a**; 8.09 g, 0.015 mol, 52%).

When the mole ratio of 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose to **4** was increased to 2.03:1, the yield of **18a** was increased to 92%.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2-tetrazolin-5-one (17a): mp 173–175 °C; ^1H NMR ($(CD_3)_2SO$) δ 4.58–4.66 (m, 2, 5′ H), 4.85–4.86 (m, 1, 4′ H), 6.03–6.06 (m, 1, 2′ (or 3′) H), 6.16–6.23 (m, 2, 1′ and 3′ (or 2′) H), 7.41–4.69 and 7.89–8.00 (m, 15, benzoyl H); mass spectrum, m/e (relative intensity, 70 eV) 122 (8, $C_7H_6O_2^+$), 105 (100, $C_6H_5CO^+$), 77 (19, $C_6H_5^+$), 43 (10, HNCO); field-desorption mass spectrum, m/e 531 (M + 1$^+$).

Anal. Calcd for $C_{27}H_{22}N_4O_8$: C, 61.13; H, 4.18; N, 10.56. Found: C, 60.80; H, 4.10; N, 10.58.

1,4-Bis(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-tetrazolin-5-one (18a): mp 134–135.5 °C; ^1H NMR ($CDCl_3$) δ 4.57–4.75 (m, 6, 4′ and 5′ H), 6.05–6.18 (m, 6, 1′, 2′, and 3′ H), 7.18–8.20 (m, 30, benzoyl H); mass spectrum, m/e (relative intensity, 70 eV) 122 (15, $C_7H_6O_2^+$), 105 (100, $C_6H_5CO^+$), 77 (31, $C_6H_5^+$), 44 (20, H_2NCO^+).

Anal. Calcd for $C_{53}H_{42}N_4O_{15}$: C, 65.30; H, 4.34; N, 5.75. Found: C, 65.09; H, 4.27; N, 5.80.

1-Carbamoyl-4-β-D-ribofuranosyl-2-tetrazene was obtained during the methanolic ammonia deprotection of **17a** for 24 h at room temperature. Extraction of the oil residue with toluene, followed by precipitation from methanol by carbon tetrachloride, gave an analytically pure solid: mp 160–163 °C dec; ^1H NMR ($(CD_3)_2SO$) δ 3.28–3.66 (m, 2, 5′ H), 3.85 (m, 1, 4′ H), 4.11 (m, 1, 3′ (or 4′) H), 4.50 (m, 1, 2′ (or 3′) H), 5.48 (d, 1, J = 4.5 Hz, 1′ H), 5.88 (br, NH, H_2O); ^{13}C NMR (D_2O) δ 129.6 and 128.7 (C=O, cis and trans), 86.4 and 84.6 (1′ and 4′ C), 73.2 and 70.4 (2′ and 3′ C), 61.7 (5′ C); field-desorption mass spectrum, m/e 236 (M + 1$^+$).

Anal. Calcd for $C_6H_{13}N_5O_5$: C, 30.64; H, 5.57; N, 29.78. Found: C, 31.04; H, 5.59; N, 29.89.

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1-β-D-Ribofuranosyl-2-tetrazolin-5-one (17b) was obtained by methanolic ammonia deprotection of **17a** at −10 °C for 5 days as a hygroscopic powder after chromatography (ether to CH_3OH) and precipitation from methanol with ethyl acetate: ^1H NMR ($(CD_3)_2SO$) δ 3.41 (dd, 1, J = 5.2, 11.8 Hz, 5′ H), 3.55 (dd, 1, J = 4.1, 11.8 Hz, 5′ H), 3.87 (m, 1, 4′ H), 4.13 (t, 1, J = 4.5 Hz, 3′ H), 4.48 (t, 1, J = 4.8 Hz, 2′ H), 5.17 (br, OH and HN), 5.50 (d, 1, J = 4.8 Hz, 1′ H); ^{13}C NMR ($(CD_3)_2SO$) δ 159.8 (C=O), 86.9 and 85.2 (1′ and 4′ C), 72.6 and 70.9 (2′ and 3′ C), 62.5 (5′ C); field-desorption mass spectrum, m/e 219 $(M + 1)^+$; high-resolution field-desorption mass spectrum, m/e 219.0767 ($C_6H_{11}N_4O_5$, $(M + 1)^+$).

1,4-Di-β-D-ribofuranosyl-2-tetrazolin-5-one (18b) was obtained by the methanolic ammonia deprotection of **18a**. Extraction of the benzoyl-containing compounds into toluene left **18b** as an oil which was purified by chromatography (acetone to 50% acetone:methanol) and rigorously dried to give a glass: ^1H NMR (D_2O) δ 3.73 (m, 4, 5′ H), 4.14 (m, 2, 4′ H), 4.42 (t, 2, J = 5.4 Hz, 3′ H), 4.72 (m, 2, 2′ H), 5.75 (d, 2, J = 4.2 Hz, 1′ H); ^{13}C NMR (D_2O) δ 150.3 (s, C=O), 87.5 and 84.8 (1′ and 4′ C), 72.9 and 70.1 (2′ and 3′ C), 61.2 (5′ C); field-desorption mass spectrum, m/e 351 $(M + 1^+)$.

Anal. Calcd for $C_{11}H_{18}N_4O_9$: C, 37.72; H, 5.18; N, 15.99. Found: C, 37.90; H, 5.38; N, 15.74.

Silver isocyanate was prepared within a few days time of when it was to be used. Silver nitrate (12.3 g, 82 mmol) and potassium cyanate (7.0 g, 86 mmol) were each dissolved in 12 mL of water.[60] The two solutions were cooled on ice and slowly mixed with vigorous stirring. The precipitate was filtered and washed with cold water (3 × 10 mL) and then with acetone (3 × 20 mL). After air-drying in the dark for 3 h, the white powder was placed in a light-tight container and stored under vacuum in a desiccator until use (12.2 g, 87%).

2,3,5-Tri-O-benzoylribofuranosyl Chloride. In a typical synthesis of 2,3,5-tri-O-benzoylribofuranosyl chloride, the procedure of Kissman et al.[61] was followed. Dry 1-O-acetyl-2,3,5-tri-O-benzoylribofuranose (25 g, 50 mmol) was added to 1100 mL of anhydrous ether. The resulting suspension was cooled in a salt water/ice bath and anhydrous HCl was bubbled into the reaction mixture until either the ribofuranose was completely dissolved or until the temperature of the ether suspension fell below 4 °C. The reaction mixture was stored at −5 °C for 72 h, after which the ether and HCl were removed in vacuo at or below 25 °C. Anhydrous toluene (2 × 30 mL) was added to the resulting oil and was evaporated under vacuum to remove residual acetic acid. The remaining oil was immediately dissolved in the anhydrous solvent required for the next reaction.

2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl Isocyanate (19). 2,3,5-Tri-O-benzoylribofuranosyl chloride (synthesized from 15.32 g (30.4 mmol) of 1-O-acetyl-2,3,5-tri-O-benzoylribofuranose) was dissolved in 500 mL of anhydrous toluene and dry, finely powdered silver isocyanate (12.20 g, 71.8 mmol) was added.[47] The reaction mixture was heated at reflux with vigorous stirring for 3 h. After the reaction had been cooled to room temperature, the silver salts were filtered and washed with dry toluene. The washings and the reaction solvent were combined and used immediately in a subsequent reaction.

***N*-(2,2-Diethoxyethyl)-*N*′-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)urea (21).** α-Aminoacetaldehyde diethyl acetal **20** (2.25 g, 16.9 mmol) was added to a solution of 2,3,5-tri-O-benzoyl-β-D-ribofuranos-1-yl isocyanate (**19**; prepared from 16.7 mmol of D-1-O-acetyl-2,3,5-tri-O-benzoylribofuranose) in 400 mL of toluene. After the mixture was stirred for 24 h at room temperature, the reaction appeared complete by TLC (5% EtOH/$CHCl_3$). The solvent was evaporated under vacuum, leaving a viscous oil. Chromatography (400 g, 0–0.5% EtOH/$CHCl_3$) followed by crystallization from toluene/hexane, gave **21** (5.17 g, 50%). An analytical sample was obtained by slow recrystallization: mp 119–122 °C; ^1H NMR ($CDCl_3$) δ 1.17 (t, 6, 2 CH_3), 3.13–3.73 (m, 6, 3 CH_2 of diethoxyethyl), 4.41–4.61 (m, 4, acetal CH and 4′ and 5′ CH), 5.40 (t, 1, NH), 5.57–6.05 (m, 3, 1′, 2′, and 3′ CH), 6.23 (d, 1, NH), 7.18–8.10 (m, 15, benzoyl CH); mass spectrum, m/e (relative intensity, 70 eV) 322 (2), 105 (100, $C_6H_5CO^+$), 103 (35), 77 (20, $C_6H_5^+$), 75 (14), 47 (18, $C_2H_5OH_2^+$); field-desorption mass spectrum, m/e 621 (M^+).

Anal. Calcd for $C_{33}H_{36}N_2O_{10}$: C, 63.86; H, 5.85; N, 4.51. Found: C, 63.78; H, 5.89; N, 4.33.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-4-imidazolin-2-one (10a). To a solution of *N*-(2,2-diethoxyethyl)-N′-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)urea (**21**; 3.52 g, 5.7 mmol) in 500 mL of anhydrous toluene was added a catalytic amount (2 mg) of *p*-toluenesulfonic acid. The reaction mixture was stirred at room temperature and the disappearance of starting material was followed by TLC (5% EtOH/$CHCl_3$). After 96 h the solvent was evaporated to give an oil. Chromatography (0–1% EtOH/$CHCl_3$) gave **10a** (1.04 g, 35%) identical with the compound produced by ribosidation of **1**.

4-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)semicarbazide (22). A solution of 2,3,5-tri-O-benzoyl-β-D-ribofuranos-1-yl isocyanate (**19**; (synthesized from 8.05 g (16 mmol) of 1-O-acetyl-2,3,5-tri-O-benzoylribofuranose) in 200 mL of anhydrous toluene was added slowly to a solution of anhydrous hydrazine (2.09 g, 65 mmol) in 100 mL of isobutyl alcohol at 0 °C. The reaction mixture was stirred at 0 °C for 5 min, during which time residual ionic silver in the toluene was reduced, giving a black suspension. The reaction was quenched by the extraction of unreacted hydrazine into water (2 × 100 mL). Evaporation of the solvent resulted in a gray solid, to which 300 mL of boiling toluene was added. Hot filtration, followed by washing the glassware with hot toluene (2 × 50 mL), gave a colorless solution, which upon cooling gave **22** (4.95 g, 60%) in analytical purity: mp 167.5–169.5 °C (lit.[51] mp 171–172 °C); ^1H NMR ($(CD_3)_2SO$) δ 4.21 (s, 2, NH_2), 4.58 (m, 3, 4′ and 5′ CH), 5.74–5.82 (m, 3, 1′, 2′, and 3′ CH), 7.33–8.11 (m, 17, benzoyl CH and amide NH); mass spectrum, m/e (relative intensity, 70 eV) 214 (1), 122 (40, $C_6H_5CO_2H$), 105 (100, $C_6H_5CO^+$), 77 (48, $C_6H_5^+$), 74 (3, $CH_4N_3O^+$); field-desorption mass spectrum, m/e 519 (M^+).

Anal. Calcd for $C_{27}H_{25}N_3O_8$: C, 62.42; H, 4.85; N, 8.09. Found: C, 62.20; H, 4.77; N, 7.92.

Ring Closure of 4-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)semicarbazide (22; 0.042 g, 0.08 mmol) in 20 mL of triethyl orthoformate with 1 drop of 99% formic acid as a catalyst was followed by TLC (5% EtOH/$CHCl_3$). After 1 h at reflux, the starting material had disappeared and a spot corresponding to the desired 4-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolin-3-one (**15a**) had appeared. The predominant product was faster moving than **15a** and was assumed to be a decomposition product. Addition of more acid (2 drops) and continued heating (1 h) resulted in the decomposition of the previously formed **15a**.

1-Formyl-4-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)semicarbazide (23). To 750 mL of a toluene solution of 2,3,5-tri-O-benzoyl-β-D-ribofuranos-1-yl isocyanate (**19**; synthesized from 0.046 mol of 1-O-acetyl-2,3,5-tri-O-benzoylribofuranose) was added formic acid hydrazide (6.08 g, 0.101 mol, 2.2 equiv). The reaction was stirred at room temperature for 24 h and followed by TLC (5% EtOH/$CHCl_3$) which showed two major spots at R_f 0.9 and 0.08. The excess formic acid hydrazide was extracted into water (2 × 60 mL). Evaporation of the solvent gave a gray oil which was dissolved in CH_3CN and filtered to remove residual silver, and the CH_3CN was evaporated to give a clear oil. Chromatography (300 g, 0–8% EtOH/$CHCl_3$) separated several products. The product at R_f 0.08 on TLC was collected and the solvent was evaporated to give an oil. Crystallization from toluene gave **23** (13.60 g, 0.025 mol, 54%) in analytical purity as colorless needles: mp 169–171 °C; ^1H NMR ($(CD_3)_2SO$) δ 4.57 (s, 3, 4′ and 5′ CH), 5.61–5.83 (m, 3, 1′, 2′, and 3′ CH), 7.40–8.09 (m, 16, benzoyl CH and formyl H), 8.33, 8.56, 9.69 (s, 3, NH); mass spectrum, m/e (relative intensity, 70 eV) 322 (2), 105 (100, $C_6H_5CO^+$), 77 (22, $C_6H_5^+$), 60 (11, NH_2NHCHO^+); field-desorption mass spectrum, m/e 548 ($M^+ + 1$).

Anal. Calcd for $C_{28}H_{25}N_3O_9$: C, 61.42; H, 4.60; N, 7.67. Found: C, 61.34; H, 4.49; N, 7.59.

4-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolin-3-one (15a). To 1-formyl-4-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)semicarbazide (**23**; 0.46 g, 0.85 mmol) in 20 mL of anhydrous pyridine were added 5 mL of HMDS and 0.5 mL of trimethylsilyl chloride. The resulting solution was heated at reflux for 10 h. Removal of the solvent under vacuum gave a yellow solid.

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Chromatography (60 g, 0–2% EtOH/$CHCl_3$) of the product mixture, followed by recrystallization from acetonitrile, gave pure **15a** (0.32 g, 71%).

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Registry No. **1**, 5918-93-4; **3**, 930-33-6; **4**, 16421-52-6; **9**, 80049-39-4; **10a**, 67908-99-0; **10b**, 67908-94-5; **12**, 80049-40-7; **13**, 80049-41-8; **14a**, 80049-42-9; **14b**, 80049-43-0; **15a**, 80049-44-1; **15b**, 80049-45-2; **16a**, 80049-46-3; **16b**, 80049-47-4; **17a**, 80049-48-5; **17b**, 80049-49-6; **18a**, 80049-50-9; **18b**, 80049-51-0; **19**, 21823-89-2; **20**, 645-36-3; **21**, 80063-08-7; **22**, 71397-61-0; **23**, 80049-52-1; potassium cyanate, 590-28-3; α-ureidoacetaldehyde diethyl acetal, 80049-53-2; β-D-1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose, 6974-32-9; semicarbazide hydrochloride, 18396-65-1; triethyl orthoformate, 122-51-0; aminotetrazole, 4418-61-5; 1-(trimethylsilyl)-5-[(trimethylsilyl)oxy]tetrazole, 34907-74-9; 1-carbamoyl-4-β-D-ribofuranosyl-2-tetrazene, 80049-54-3; β-D-2,3,5-tri-*O*-benzoylribofuranosyl chloride, 29706-90-9; silver isocyanate, 3315-16-0; hydrazine, 302-01-2; formic acid hydrazide, 624-84-0.

Supplementary Material Available: Tables listing positional and thermal parameters, bond lengths, bond angles, and torsion angles from the X-ray structure solutions for compounds **15b** and **16b** (10 pages). Ordering information is given on any current masthead page.

Intramolecular Photoarylations of *N*-(Haloaryl)ethyl β-Enaminones

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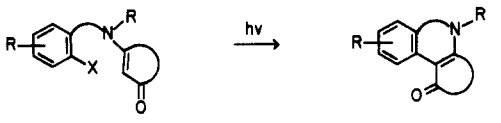
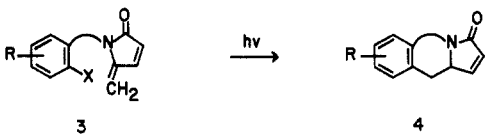
The photochemistry of several *N*-(haloaryl)ethyl β-enaminones was investigated in order to develop methods for preparation of tricyclic enaminone systems. The efficiencies of intramolecular photoarylations of the haloaryl systems were found to be dependent upon the wavelength of irradiation. Accordingly, irradiations of the haloaryl β-enaminones **9a,c,d,f** with Pyrex-filtered light leads to formation of the reduced N-cyclized and C-cyclized products **9b** or **9e**, **8a** or **8b**, and **10a** or **10b**, respectively. The major products in these processes are the reduced materials. In contrast, irradiations of the bromoaryl enaminones **9c** or **9f** with Vycor-filtered light results in high yielding conversions to the C-cyclized tricyclic enaminones **10a** and **10b** in synthetically useful yields ranging from 50% to 85%. A discussion of reasons for these wavelength dependencies is given in terms of excited-state discrimination in these bichromophoric systems. Possible reaction mechanisms are considered. The origin of another major product, **11**, generated by irradiation of **9f** with Vycor-filtered light, is also discussed.

Photocyclizations of *N*-haloaryl-substituted enaminones (**1** → **2**) and related enamides (**3** → **4**) have been employed

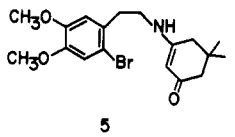


1 **2**



3 **4**

in the synthesis of a variety of heterocyclic compounds.[2,3] The reactions, in most cases, are efficient and thus useful in the preparation of complex structures found in natural products or their precursors. In recent studies,[4] we required simple methods for synthesis of the tricyclic β-enaminones **10a** and **10b**. Reports by Kibayashi and his co-workers[2] suggested that intramolecular photoarylations of appropriately substituted *N*-(haloaryl)ethyl enaminones **9** might be of use in this regard.[5] However, the reported variability of the yields of these processes left some doubt about the success of this adventure. For example, although irradiation of dioxane solutions of **5** with Pyrex-filtered



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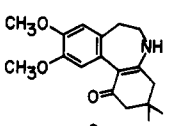
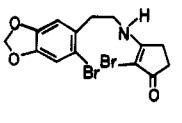
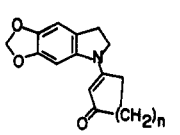


6



7



8a n=2
8b n=1

light for 125 h leads to generation of the cyclized product **6** in 91% yield, photolysis of the cyanopentenone analogue **9f** formed the dibromide **7** (4%) and hydroindole **8a** (29%) as the sole photoproducts. Equally inconsistent behavior

(1) To whom inquiries should be addressed at the University of Maryland.

(2) (a) Iida, H.; Aoyagi, S.; Kibayashi, C., *J. Chem. Soc. Perkin Trans. 1* **1977**, 120–122. (b) Iida, H.; Yuasa, Y., Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1978**, 766–767. (c) Iida, H.; Yuasa, Y., Kibayashi, C. *J. Org. Chem.* **1979**, *44*, 1236–1241.

(3) Bernhard, H. O.; Sniekus, V., *Tetrahedron Lett.* **1971**, 4867–4870. Ise, I. Sniekus, V., *J. Chem. Soc., Chem. Commun.* **1976**, 505–506.

(4) Preliminary results of this work have been reported at the Southeast–Southwest Regional Meeting of the American Chemical Society New Orleans, 1980; abstract ORGN 364.

(5) (a) Other approaches involving intramolecular additions to benzynes appear possible.[5b] (b) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1979**, *44*, 1074–1080.

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