30315-51-6; *p*-toluenesulfenyl chloride, 98-59-9; *d*-(10)-camphorsulfonic acid, 3144-16-9.

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Synthesis of C-Nucleosides. 13.[1] *s*-Triazolo[4,3-*a*]- and -[1,5-*a*]pyridine Derivatives

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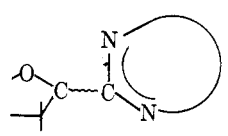
s-Triazolo[4,3-*a*]- and -[1,5-*a*]pyridine C-nucleosides are obtained in one step from 2-pyridylhydrazines and ribofuranosyl thioformimidate. The structures of these compounds are determined with ultraviolet, ^1H and ^{13}C NMR, mass, and circular dichroism spectra.

Glycosyl thioformimidates have proved in our hands to be convenient intermediates for the total synthesis of C-nucleosides. Their condensation with α or ortho aminonitrile derivatives, for instance, gave nucleosides of type **1** (imidazoles, purines, pyrazolopyrimidines)[2] in one step. We decided then to study the feasibility of using the same thioimidates to prepare heterocycles of type **2**, i.e. 1,2,4-triazoles[3] and fused triazoles.



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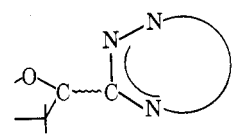

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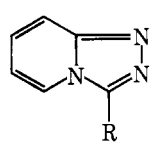
Representative of this new class of heterocycles is the triazolo[4,3-*a*]pyridine **3**. This structure is of particular in-



3

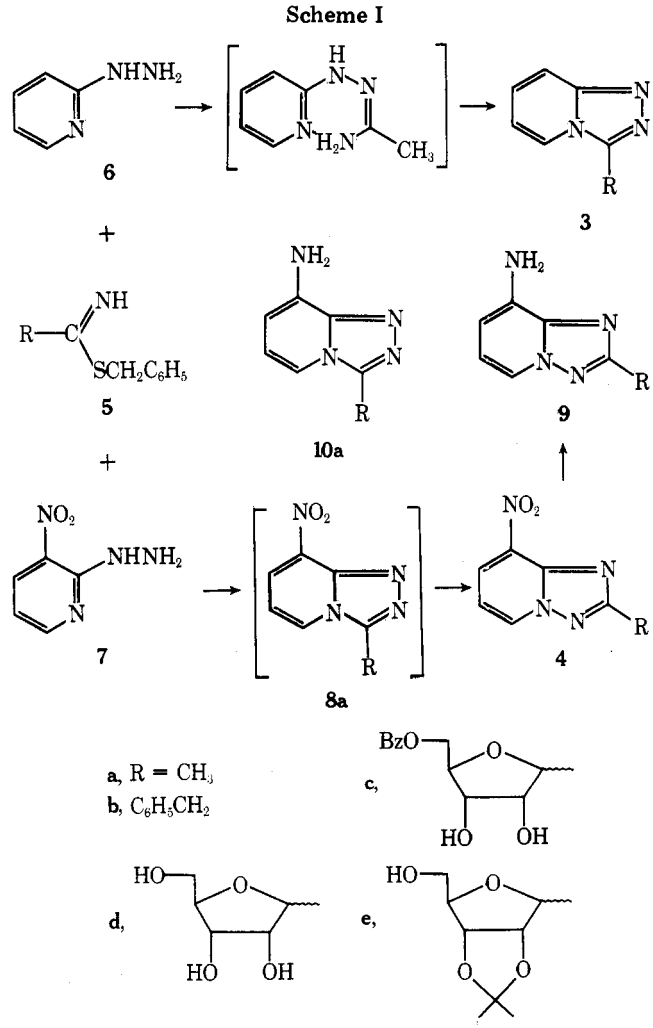
terest since on one hand it contains the 1,2,4-triazole moiety of ribavirine, and on the other hand it may be regarded as an unusual deaza analogue of formycines. C-Nucleosides containing a bridgehead nitrogen atom are unknown.[17] Their synthesis was undertaken in view of their possible biological activities.

3-Alkyl and aryl *s*-triazolo[4,3-*a*]pyridines **3** have been synthesized by cyclization of 2-pyridylhydrazines with carboxylic acid derivatives: anhydrides,[4] chlorides,[5,6] ortho esters,[5] or from the 2-pyridylhydrazone of aromatic aldehydes.[6-8] When the 2-pyridylhydrazine is substituted with an electron-withdrawing NO_2 group in position 3, the ring closure with ortho esters gives the expected 3-alkyl-8-nitro-*s*-triazolo[4,3-*a*]pyridines **3** which isomerized easily into *s*-triazolo[1,5-*a*]pyridines **4**.[9]

Results

In order to develop a reaction that could be extended to carbohydrate chemistry, we condense benzyl thioacetimidate (**5a**) (Scheme I) with 2-pyridylhydrazine (**6**): with 10% of pyridine in chloroform at room temperature, the reaction

Scheme I



yields the noncyclized intermediate acetamidrazone whereas using reflux in pyridine, the yield of cyclization goes up to 79% of 3-methyl-*s*-triazolo[4,3-*a*]pyridine (**3a**), previously described.[4] In the same conditions, benzyl phenylthioacetim-

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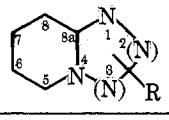
Table I. Ultraviolet Absorption Spectral Data

Compd	s-Triazolo[4,3-a]pyridine, λ_{max} (ϵ) in H_2O				Compd	s-Triazolo[1,5-a]pyridine, λ_{max} (ϵ) in H_2O	
3a	267 (3300)	286 (3300)			4a	230 (14600)	330 (6400)
3b	268 (4300)	287 (3600)			4b	230 (16400)	326 (6000)
β-3c	263 (4600)	271 (5300)	280 (4500)	295 (3400)	4c	243 (9800)	328 (5200)
α-3c	265 (4100)	271 (4800)	280 (3900)	296 (3000)			
β-3d	265 (4400)	270 (4700)	280 (4000)		4d	235 (13800)	328 (5500)
α-3d	261 (3600)	272 (4500)	280 (3800)				
8a	225 (14000)	360 (4300)					
10a	225 (12700)	297 (11600)			9a	270 (10400)	294 (6800)
					9b	272 (10400)	294 (7200)
					9c	280 (9700)	299 (6900)
					9d	275 (9000)	295 (6000)

Table II. ^{13}C Chemical Shifts of Quaternary Carbons (ppm from Me_4Si)



Compd	C-2	C-3	C-8	C-8a
10a		145.4$_7$	136.1$_5$	145.7$_6$
β-3d		149.6$_4$		144.5$_5$
9a	162.1$_2$		136.8$_8$	145.1$_1$
9d	162.6$_0$		136.5$_7$	143.6$_5$
4d	166.6$_9$		135.5$_0$	144.3$_9$

idate (**5b**) yields 48% of 3-benzyl-*s*-triazolo[4,3-*a*]pyridine (**3b**).

The reaction proceeds differently between 3-nitro-2-pyridylhydrazine (**7**) and thioimidate **5a**: instead of the expected 8-nitro-*s*-triazolo[4,3-*a*]pyridine (**8a**),[9] we obtain the isomerized heterocycle, i.e., the triazolo[1,5-*a*]pyridine **4a**. The structure of **4a**[9,10] is established on the basis of its spectral characteristics (uv, ^{13}C NMR), and also by comparison with authentic samples prepared according to the literature. 2-Benzyl-8-nitro-*s*-triazolo[1,5-*a*]pyridine (**4b**) is obtained in the same way (65%) from **5b** and **7**.

The structural assignment is made once again after reduction of the nitro heterocycles over palladium on charcoal. The *s*-triazolo[1,5-*a*]pyridine **4a** is then hydrogenated into **9a**,[10] which is different from the *s*-triazolo[4,3-*a*]pyridine **10a**[9] obtained from **8a**. The spectral data show that amino benzyl derivative **9b** belongs also to the *s*-triazolo[1,5-*a*]pyridine series.

The condensation of benzyl 5-*O*-benzoyl-D-ribofuranosyl thioformimidate (**5c**) with **6** gives a mixture of *s*-triazolo[4,3-*a*]pyridines α- and β-**3c** (63%) which was separated on silica gel chromatography (β/α 90/10). The benzoyl group is quantitatively removed with methanolic ammonia at room temperature giving 3-D-ribofuranosyl-*s*-triazolo[4,3-*a*]pyridines α- and β-**3d**.

The cyclization of **5c** with 3-nitro-2 pyridylhydrazine (**7**) leads to 58% of the β anomer of the *s*-triazolo[1,5-*a*]pyridine **4c**; we have not isolated the α anomer among the by-products obtained from the chromatographic fractions (<2%). Compound **4c** is debenzoylated into 2-β-D-ribofuranosyl-8-nitro-*s*-triazolo[1,5-*a*]pyridine (**4d**). The catalytic reduction of **4c** gives the corresponding 8-amino derivative **9c** which is converted into 2-β-D-ribofuranosyl-8-amino-*s*-triazolo[1,5-*a*]pyridine (**9d**).

The isopropylidene derivatives **3e**, **4e**, and **9e** are prepared for configuration assignment using ^1H NMR.

Discussion

As observed previously,[2c] the condensation reactions of the ribofuranosyl thioformimidate **5c** give a mixture of anomers with the β anomer strongly predominant (**3c**) or exclusive (**4c**).

The main problem with the reported synthetic sequences is to ascertain (1) the structure of the heterocycles, i.e., *s*-triazolo[4,3-*a*]pyridine **3** or *s*-triazolo[1,5-*a*]pyridine **4**; (2) the structure and configuration of the nucleosides. These structural assignments are built mainly on uv spectra, ^1H and ^{13}C NMR, mass spectra, and circular dichroism.

1. Structure of the Heterocycles. A first structural determination of the heterocycles **3** and **4** is easily made with the uv spectra, owing to the authentic samples **3a**, **8a**, **10a** (*s*-triazolo[4,3-*a*]pyridine) and **4a**, **9a** (*s*-triazolo[1,5-*a*]pyridine), the structure of which having been previously established with numerous correlations.[5,9,10] Table I shows that the two series exhibit absorption maxima at different wavelengths.

^{13}C NMR spectra allow one to assign unambiguously the two series of compounds *s*-triazolo[4,3-*a*]pyridine of type **3** and *s*-triazolo[1,5-*a*]pyridine of type **4** (Table II). As a matter of fact, the chemical shift of a carbon nucleus at position 2 is about 15–20 ppm downfield as compared to that of a carbon at position 3, in similar heterocycles.[11] This fact is due to the presence of the bridgehead nitrogen at position 4 which does not induce a low-field shift for a neighboring carbon as large as that due to a cyclic nitrogen bearing a lone pair of electrons. It has been recently used successfully[12] for similar assignments among *s*-triazolo[4,3-*a*]- and *s*-triazolo[1,5-*a*]pyrimidines.

Table III gives the ^1H NMR spectra of the model compounds.

Table III. ^1H NMR (Chemical Shifts in ppm from Me_4Si) in Me_2SO-d_6 (5×10^{-3} M) at 34° of *s*-Triazolopyridine Model Compounds

Compd	H_5	H_6	H_7	H_8	NH_2	R = CH_3	$C_6H_5CH_2$	
3a	8.35	6.96	7.33	7.71		2.68		
3b	8.34	6.93	7.33	7.76			7.29	4.55
4a	9.30	7.34	8.63			2.58		
4b	9.32	7.35	8.63				7.33	4.29
8a	8.81	7.19	8.40			2.76		
9a	7.99	6.81	6.53		5.80	2.43		
9b	8.03	6.83	6.53		5.80		7.30	4.13
10a	7.55	6.71	6.22		5.90	2.61		

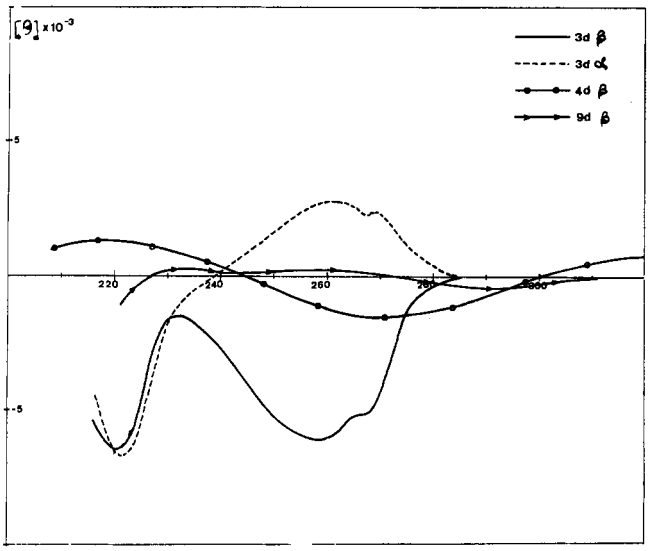


Figure 1. CD spectra of nucleosides in water.

2. Structure and Configuration of the Nucleosides. The structures of the nucleosides are confirmed by the mass spectra: all the ribonucleosides show the molecular ion M and the characteristic peaks of a furanose at M − 30. The C–C bond is established by the reduced intensity of ions at B + 2H and the abundant ions arising from the fragmentation of O–$C_{1'}$, $C_{2'}$–$C_{3'}$ bonds and O–$C_{4'}$, $C_{1'}$–$C_{2'}$ bonds:[2c] the major peak is at B + 30 for *s*-triazolo[4,3-*a*]pyridines **3d** and at B + 44 for *s*-triazolo[1,5-*a*]pyridines **4d** and **9d.** In a couple of anomers such as **3d,** the configuration is based on the relative intensities of ions at M − 30:[2c] the β anomer exhibits a higher intensity than the α anomer.

The circular dichroism spectra (Figure 1) give opposite Cotton effects for α-**3d** and β-**3d.** The *s*-triazolo[1,5-*a*]pyridines present very weak Cotton effects. This may be explained by the orientation of the base with regard to the sugar: molecular models show that the *s*-triazolo[1,5-*a*]pyridines should have more rotational mobility around the glycosyl bond than their [4,3-*a*]triazolo isomers.

The possibility of assignment of the anomeric configuration by ^{1}H NMR is dependent upon the nature of the compounds. In the C-nucleosides of type **3** (Table IV) the α and β anomers are clearly distinguished by the difference in the chemical shift of the H-1′ proton[13] and in the $J_{1',2'}$ coupling constant (Table VI) for the unsubstituted nucleosides **3d.** The difference in chemical shift values for the methyl resonances in the isopropylidene derivatives[14] **3e,** and especially **4e** (since only one anomer has been isolated), is indicative of the configuration: $\Delta\delta CH_3 < 0.15$ for α anomer; $\Delta\delta CH_3 > 0.15$ for β anomer. The last effect is presumably due to different ring current effects from the base and to steric hindrance as observed for the H-5 resonances. Proton chemical shift and coupling constant values in the compounds of type **3,** as well as in the other series of C-nucleosides (types **4** and **9,** Table V), are, however, depending on several structural parameters. Besides the anomer configuration, the position of ribose substitution and the syn-trans conformation of the gylcosidic bond govern the NMR properties. The full analysis of these phenomena is beyond the scope of the present paper.

Experimental Section

Melting points were determined with a Kofler microscope and were uncorrected. Ultraviolet spectra were recorded with a Perkin-Elmer 237 or a Cary 118C. NMR spectra were obtained using a Varian XL-100 with tetramethylsilane as internal reference. Mass spectra were obtained with a Varian CH-7 or MS-9. Optical activities were measured with a Perkin-Elmer 241 MC polarimeter and circular dichroism spectra were recorded with a Roussel-Jouan ll-185 dichrograph. Chromatographic columns were packed with Silicar 100 mesh grade l; 0.25 mm thick TLC plates were prepared with Merck Kieselgel $HF_{254+366}$ and visualized with an uv light at 254 nm.

3-Methyl-*s*-triazolo[4,3-*a*]pyridine (3a). A solution of 5.5 g (50 mmol) of 2-pyridylhydrazine (**6**) and 10.1 g (50 mmol) of benzyl thioacetimidate (**5a**)[15] in 90 ml of pyridine was stirred for 2 h at room temperature and refluxed for an additional 1 h. The residue of evaporation was recrystallized with benzene–cyclohexane (1/1) to yield 5.3 g (79%) of **3a,** mp 132 °C (lit.[4] mp 134 °C).

2-Pyridyl-N_2-acetamidrazone Hydrochloride. Hydrazine **6** (5.5 g, 50 mmol) was added to a solution of 10.1 g (50 mmol) of **5a** in 100 ml of chloroform and 7.9 g (100 mmol) of pyridine. The solution was kept at room temperature for 20 h; the precipitate was filtered and washed with hot chloroform, 9 g (96%), mp 170 °C.

Anal. Calcd for $C_7H_{11}N_4Cl$ (186.5): C, 45.04; H, 5.89; N, 30.02; Cl, 19.03. Found: C, 44.93; H, 5.82; N, 29.81; Cl, 19.12.

3-Benzyl-*s*-triazolo[4,3-*a*]pyridine (3b). The same procedure as for **3a** was followed, 2.2 g (20 mmol) of **6** and 5.6 g (20 mmol) of **5b.**[16] The residue was treated with carbon black and recrystallized from benzene, 2 g (48%), mp 165–166 °C.

Anal. Calcd for $C_{13}H_{11}N_3$ (209): C, 74.62; H, 5.30; N, 20.08. Found: C, 74.53; H, 5.45; N, 19.81.

2-Methyl-8-nitro-*s*-triazolo[1,5-*a*]pyridine (4a). The condensation as above with 3.1 g (20 mmol) of 3-nitro-2-pyridylhydrazine (**7**) and **5a** gave 82% of **4a,** mp 195–196 °C (benzene).[9,10]

2-Benzyl-8-nitro-*s*-triazolo[1,5-*a*]pyridine (4b). The same procedure with 4.62 g (30 mmol) of **7** and 8.3 g (30 mmol) of **5b** gave 4.95 g (65%) of **4b,** mp 137–143 °C (cyclohexane).

Table IV. ^{1}H NMR of *s*-Triazolo[4,3-*a*]pyridine C-Nucleosides

Compd	H_5	H_6	H_7	H_8	$H_{1'}$	$H_{2'}$	$H_{3'}$	$H_{4'}$	$H_{5'a}$	$H_{5'b}$	CH_3,	C_6H_5
α-3c	8.53	6.92	7.36	7.73	5.70			4.60–4.30			*o*	8.02
											m,p	7.60
β-3c	8.42	6.84	7.31	7.70	5.37	4.85		4.45–4.25			*o,m,p*	7.50
α-3d	8.50	6.89	7.35	7.71	5.58	4.24	4.21	4.05	3.68	3.50		
β-3d	8.69	6.96	7.39	7.78	5.21	4.55	4.08	3.95	3.57	3.51		
α-3e	8.59	6.97	7.37	7.74	5.81	5.07	4.91	4.33	3.62		1.34	1.22
β-3e	8.54	7.00	7.41	7.78	5.53	5.58	4.85	4.12	3.17		1.53	1.36

Table V. ^{1}H NMR of *s*-Triazolo[1,5-*a*]pyridine C-Nucleosides

Compd	H_5	H_6	H_7	NH_2	$H_{1'}$	$H_{2'}$	$H_{3'}$	$H_{4'}$	$H_{5'a}$	$H_{5'b}$	CH_3, C_6H_5	
4c	9.26	7.38	8.66		5.03			4.55–4.20			*o*	7.95
											m,p	7.50
4d	9.37	7.41	8.69		4.94	4.33	4.09	3.93	3.62	3.51		
4e	9.38	6.43	8.50		5.16		4.83	4.17	3.53	3.47	1.54	1.35
9c	8.01	6.88	6.58	5.81	4.91			4.55–4.15			*o*	7.95
											m,p	7.50
9d	8.07	6.88	6.59	5.83	4.81	4.31	4.04	3.86	3.57	3.47		
9e	8.08	6.91	6.60	5.91	5.00	5.15	4.77	4.07	3.50	3.40	1.52	1.33

Table VI. Coupling Constants (Hz)

Compd	$J_{5,6}$	$J_{5,7}$	$J_{5,8}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$
3a	6.9	1.2	1.1	6.5	1.2	9.2						
3b	7.0	1.2	1.2	6.5	1.2	9.3						
4a	6.8	1.3		8.0								
4b	6.7	1.2		8.0								
8a	7.0	1.0		7.5								
9a	6.6	1.1		7.6								
9b	6.5	1.2		7.6								
10a	6.6	0.8		7.2								
α-**3c**	7.2	1.2	1.2	6.5	1.2	9.4	3.0					
β-**3c**	7.0	1.2	1.2	6.5	1.2	9.2	3.8	4.0				
α-**3d**	7.0	1.2	1.1	6.5	1.1	9.3	3.5	3.5	7.6	2.5	4.4	12.0
β-**3d**	7.0	1.0	1.2	6.5	1.1	9.3	6.9	5.2	4.0	3.2	4.0	12.0
α-**3e**	7.2	1.2	1.2	6.5	1.1	9.4	4.2	6.3	0.7	5.0		
β-**3e**	7.2	1.2	1.0	6.4	1.0	9.4	3.8	5.8	1.5	5.6		
4c	6.7	1.2		7.9			3.7					
4d	6.8	1.2		8.0			5.2	4.8	5.1	4.0	5.2	11.7
4e	6.8	1.1		6.8				5.9	2.8	5.7		
9c	6.6	1.1		7.6			3.8					
9d	6.5	1.0		7.5			5.4	5.2	5.0	4.5	5.5	11.8
9e	6.7	1.1		7.5			3.9	6.2	2.9	5.8		

Anal. Calcd for $C_{13}H_{10}N_4O_2$ (254): C, 61.41; H, 3.96; N, 22.04. Found: C, 61.70; H, 3.92; N, 22.30.

2-Benzyl-8-amino-s-triazolo[1,5-a]pyridine (9b). **4b** (2.54 g, 10 mmol) was hydrogenated in 100 ml of ethanol at room temperature and atmospheric pressure over Pd/C (0.5 g, 30%). The solution was filtered and evaporated into a residue which was recrystallized with cyclohexane, 1.12 g (50%), mp 97–98 °C.

Anal. Calcd for $C_{13}H_{12}N_4$ (224): C, 69.62; H, 5.39; N, 24.99. Found: C, 69.57; H, 5.34; N, 24.93.

Compounds **8a, 10a,** and **9a** were prepared according to the literature.[9,10]

3-(5′-O-Benzoyl-α- and -β-D-ribofuranosyl)-s-triazolo[4,3-a]pyrine (3c). A solution of 7.41 g (17.5 mmol) of thioformimidate **5c**[2b] and 1.91 g (17.5 mmol) of **6** in 70 ml of pyridine was heated at reflux for 15 h. The solution was evaporated, and the residue was dissolved in aqueous methanol and neutralized with NaOH (1 N).

Evaporation to dryness and column chromatography (200 g, 44 × 4 cm) (EtOAc–EtOH, 9/1) gave β-**3c** and α-**3c.**

(a) β-**3c** (3.56 g, 57%), mp 60 °C, R_f 0.78 ($CHCl_3$–EtOH, 25/4).

Anal. Calcd for $C_{18}H_{17}N_3O_5$ (355): C, 60.84; H, 4.82; N, 11.83. Found: C, 60.86; H, 5.15; N, 12.11.

MS M·+ *m/e* 355; $[\alpha]^{25}D$ − 162° (*c* 0.39, DMF); CD $[\theta]_{239}$ −17 000, $[\theta]_{250}$ −11 500, $[\theta]_{261}$ −13 000, $[\theta]_{270}$ −8000, $[\theta]_{283}$ 0, $[\theta]_{290}$ −600.

(b) α-**3c** (0.40 g, 6%), mp 90 °C; R_f 0.67 ($CHCl_3$–EtOH, 25/4).

Anal. Calcd for $C_{18}H_{17}N_3O_5$ (355): C, 60.84; H, 4.82; N, 11.83. Found: C, 60.55; H, 5.02; N, 11.60.

MS M·+ *m/e* 355; $[\alpha]^{25}D$ = −9° (*c* 0.22, DMF); CD $[\theta]_{237}$ −7000, $[\theta]_{253}$ 0, $[\theta]_{272}$ +2500, $[\theta]_{286}$ +2000, $[\theta]_{321}$ 0.

3β-D-Ribofuranosyl-s-triazolo[4,3-a]pyridine (β-3d). The debenzoylation of β-**3c** with methanolic ammonia at room temperature during 72 h gave quantitatively β-**3d,** mp 198–200 °C (MeOH), R_f 0.36 ($CHCl_3$–EtOH, 5/1).

Anal. Calcd for $C_{11}H_{13}N_3O_4$ (251): C, 52.58; H, 5.22; N, 16.73. Found: C, 52.39; H, 5.51; N, 16.97.

MS M·+ *m/e* 251 (8%), 234 (2%) M − 17, 221 (20%) M − 30, 162 (96%) B + 44, 148 (100%) B + 30, 120 (21%) B + 2; $[\alpha]^{25}D$ −114° (*c* 0.51, H_2O); CD $[\theta]_{221}$ −6500, $[\theta]_{232}$ −1500, $[\theta]_{259}$ −6000, $[\theta]_{265}$ −5200, $[\theta]_{285}$ 0.

3α-D-Ribofuranosyl-s-triazolo[4,3-a]pyridine (α-3d). As above, α-**3c** gave α-**3d,** mp 100 °C, R_f 0.24 ($CHCl_3$–EtOH, 5/1).

Anal. Calcd for $C_{11}H_{13}N_3O_4$ (251): C, 52.58; H, 5.22; N, 16.73. Found: C, 51.90; H, 5.69; N, 16.25.

MS M·+ *m/e* 251 (10%), 234 (1%) M − 17, 221 (2%) M − 30, 162 (66%) B + 44, 148 (100%) B + 30, 120 (13%) B + 2; CD $[\theta]_{222}$ −6700, $[\theta]_{239}$ 0, $[\theta]_{261}$ +2900, $[\theta]_{269}$ +2500, $[\theta]_{285}$ 0; $[\alpha]^{25}D$ −15° (*c* 0.08, H_2O).

2-(5′-O-Benzoyl-β-D-ribofuranosyl)-8-nitro-s-triazolo-[1,5-a]pyridine (4c). A solution of 5.75 g (13.6 mmol) of **5c** and 2.1 g (13.6 mmol) of **7** in 60 ml of pyridine was heated at reflux for 15 h. The same procedure as for **3c** gave after column chromatography ($CHCl_3$–EtOH, 96/4) 3.17 g of **4c,** mp 133–135 °C (EtOH), R_f 0.41 ($CHCl_3$–EtOH, 10/1).

Anal. Calcd for $C_{18}H_{16}N_4O_7$ (400): C, 54.00; H, 4.03; N, 14.00. Found: C, 54.21; H, 4.21; N, 14.14.

MS M·+ *m/e* 400; $[\alpha]^{25}D$ −28° (*c* 0.51, DMF); CD $[\theta]_{230}$ −9000, $[\theta]_{236}$ 0, $[\theta]_{250}$ −2700, $[\theta]_{278}$ −520, $[\theta]_{300}$ −1900.

2β-D-Ribofuranosyl-8-nitro-s-triazolo[1,5-a]pyridine (4d). A solution of methanolic ammonia of **4c** gave quantitatively after 72 h **4d,** mp 194–195 °C (EtOH), R_f 0.25 ($CHCl_3$–EtOH, 10/1).

Anal. Calcd for $C_{11}H_{12}N_4O_6$ (296): C, 44.59; H, 4.05; N, 18.91. Found: C, 44.95; H, 4.25; N, 18.67.

MS M·+ *m/e* 296 (1%), 278 (3%) M − 18, 265 (3%) M − 31, 207 (100%) B + 44, 193 (53%) B + 30, 165 (2%) B + 2; $[\alpha]^{25}D$ −42° (*c* 0.49, H_2O); CD $[\theta]_{218}$ +1300, $[\theta]_{245}$ 0, $[\theta]_{268}$ −1500, $[\theta]_{300}$ 0.

2-(5′-O-Benzoyl-β-D-ribofuranosyl)-8-amino-s-triazolo-[1,5-a]pyridine (9c). A methanolic solution of 1 g of **4c** was hydrogenated over Pd/C (10%) at room temperature and atmospheric pressure. After filtration, the solvent was evaporated and the residue chromatographed on silica gel (EtOAc–EtOH, 95/5) to yield 0.70 g (76%) of **9c,** mp 70 °C, R_f 0.69 ($CHCl_3$–EtOH, 5/1).

Anal. Calcd for $C_{18}H_{18}N_4O_5$ (370): C, 58.37; H, 4.90; N, 15.13. Found: C, 58.03; H, 5.39; N, 14.89.

MS M·+ *m/e* 370; $[\alpha]^{25}D$ −16° (*c* 0.50, DMF); CD $[\theta]_{222}$ −11 500, $[\theta]_{250}$ 0, $[\theta]_{278}$ −15 000, $[\theta]_{300}$ 0.

2β-D-Ribofuranosyl-8-amino-s-triazolo[1,5-a]pyridine (9d). The debenzoylation during 1 week of **9c** gave **9d,** mp 65 °C, R_f 0.33 ($CHCl_3$–EtOH, 5/1).

Anal. Calcd for $C_{11}H_{14}N_4O_4$ (266): C, 49.62; H, 5.30; N, 21.04. Found: C, 49.87; H, 5.69; N, 20.88.

MS M·+ *m/e* 266 (13%), 249 (3%) M − 17, 236 (6%) M − 30, 177 (100%) B + 44, 163 (32%) B + 30, 135 (8%) B + 2; $[\alpha]^{25}D$ −34° (*c* 0.49, H_2O); CD $[\theta]_{227}$ 0, $[\theta]_{230}$ +260, $[\theta]_{260}$ +250, $[\theta]_{273}$ 0, $[\theta]_{293}$ −450.

A general procedure was used for the 2′,3′-O-isopropylidene nucleosides.[2b]

β-**3e,** R_f 0.70 ($CHCl_3$–EtOH, 25/4) (foam).

Anal. Calcd for $C_{14}H_{17}N_3O_4$ (291): C, 57.73; H, 5.88; N, 14.43. Found: C, 57.38; H, 6.34; N, 14.06.

α-**3e,** R_f 0.55 ($CHCl_3$–EtOH, 25/4) (foam).

Anal. Calcd for $C_{14}H_{17}N_3O_4$ (291): C, 57.73; H, 5.88; N, 14.43. Found: C, 57.48; H, 5.80; N, 14.54.

4e, mp 163 °C, R_f 0.90 ($CHCl_3$–EtOH, 10/1).

Anal. Calcd for $C_{14}H_{16}N_4O_6$ (336): C, 50.00; H, 4.80; N, 16.66. Found: C, 50.39; H, 5.05; N, 16.31.

9e, mp 60 °C R_f 0.61 ($CHCl_3$–EtOH, 10/1) (foam).

Registry No.—3a, 1004-65-5; **3b,** 59696-86-5; α-**3c,** 59696-87-6; β-**3c,** 59696-88-7; α-**3d,** 59696-89-8; β-**3d,** 59696-90-1; α-**3e,** 59696-91-2; β-**3e,** 59696-92-3; **4a,** 7169-91-7; **4b,** 59696-93-4; **4c,** 59696-94-5; **4d,** 59696-95-6; **4e,** 59696-96-7; **5a,** 59696-97-8; **5b,** 53331-09-2; **5c,** 50908-31-1; **6,** 4930-98-7; **7,** 15367-16-5; **8a,** 31040-10-5; **9a,** 7169-93-9; **9b,** 59696-98-9; **9c,** 59696-99-0; **9d,** 59697-00-6; **9e,** 59697-01-7; **10a,** 31040-12-7; 2-pyridyl-N_2-acetamidrazone HCl, 59697-02-8.

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6-Oxa Analogues of Pyrimidines and Pyrimidine Nucleosides. Synthesis of 5-Amino-6*H*-1,2,4-oxadiazin-3(2*H*)-one, 2-β-D-Ribofuranosyl-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione, and Related Derivatives

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Treatment of 6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**1**, 6-oxadihydrouracil) with phosphorus pentasulfide in dioxane gave 6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**2**, 4-thio-6-oxadihydrouracil). Amination of **2** with ammonia in dioxane gave 5-amino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**3**, 6-oxadihydrocytosine). Treatment of **2** with dimethylamine in dioxane afforded 5-dimethylamino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**5**). The stannic chloride catalyzed condensation of 3,5-bis(trimethylsilyloxy)-6*H*-1,2,4-oxadiazine (**6**) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**7a**) or 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**7b**) gave the corresponding blocked 6-oxadihydrouridines 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8a**) and 2-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8b**). 2-β-D-Ribofuranosyl-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**8c**, 6-oxadihydrouridine) was obtained by the removal of the acetyl blocking groups of **8b** with methanolic hydrogen chloride. Thiation of **8a** with phosphorus pentasulfide in dioxane afforded 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**12**), which upon treatment with dimethylamine in dioxane gave 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-dimethylamino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**13**). The stannic chloride catalyzed condensation of 3-trimethylsilyloxy-5-dimethylamino-6*H*-1,2,4-oxadiazine (**14**) with **7a** also afforded **13**. The ^{13}C NMR spectra of several of the above 6*H*-1,2,4-oxadiazin-3(2*H*)-ones are reported and have been utilized to support structural assignments.

6*H*-1,2,4-Oxadiazine-3,5(2*H*,4*H*)-dione (**1**) and 6-methyl-6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione, 6-oxa analogues of uracil and thymine, respectively, have previously been synthesized.[1] These analogues are actually isosteres of 5,6-dihydrouracil and 5,6-dihydrothymine in which the 6-methylene group has been replaced by an oxygen such that these compounds can be considered as 6-oxadihydrouracil (**1**) and 6-oxadihydrothymine. It has been shown, however, that 6-oxadihydrouracil (**1**) is an apparent competitive antagonist of uracil, and not of dihydrouracil, in bacterial systems.[2] In an effort to further investigate the chemical and biochemical properties of the 6*H*-1,2,4-oxadiazin-3(2*H*)-one ring system, we have synthesized the 6-oxa analogues of 4-thiouracil, cytosine, and *N*,*N*-dimethylcytosine as well as the 6-oxa analogue of uridine, the first 6*H*-1,2,4-oxadiazine nucleoside.

Reaction of 6*H*-1,2,4-oxadiazine-3,5(2*H*,4*H*)-dione (**1**) with phosphorus pentasulfide in refluxing, anhydrous dioxane afforded 6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**2**, 4-thio-6-oxadihydrouracil) in 55% yield. Elemental analysis established that **2** was a monothio derivative of **1**. The shift in the uv maximum from 220 nm (ε 1250) to 272 nm (ε 15 900) upon thiation was similar to that found upon thiation of 5,6-dihydrouracils.[3] That the 6*H*-1,2,4-oxadiazine ring had remained intact was shown by the almost quantitative reconversion of **2** to **1** by boiling water. Thiation of **1** was expected to give the 5-thio derivative in analogy to the thiation of 5,6-dihydrouracils.[3] Unequivocal assignment of the structure of 6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**2**) is based on subsequent transformation of **2** to 5-amino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**3**) as described below.

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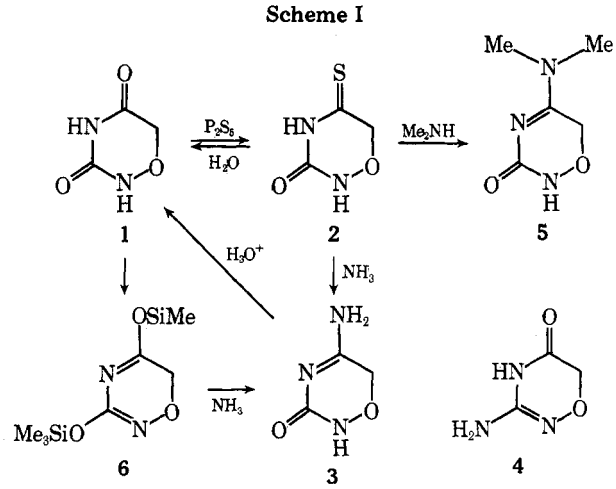
Scheme I



Reaction of 6*H*-1,2,4-oxadiazin-3(2*H*)-one-5(4*H*)-thione (**2**) with ammonia in dioxane at room temperature resulted in conversion to 5-amino-6*H*-1,2,4-oxadiazin-3(2*H*)-one (**3**, 6-oxadihydrocytosine) in 90% yield. The highly reactive nature of the thio group of **2** is analogous to that found for 1-alkyl-