dried ($MgSO_4$), and concentrated under vacuum to give 274 mg (77%) of **6** as an oil. Column chromatography over Woelm grade I neutral alumina gave 241 mg (67.3%) of **6**, homogeneous in several TLC systems, $[\alpha]^{26}D$ +44.7° (*c* 1.1, CH_3OH).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.48; H, 7.31. Found: C, 70.71; H, 7.19.

Methyl 6-Deoxy-2,3-di-*O*-benzyl-4-*O*-methylsulfonyl-α-D-altropyranoside (7). A solution of 72 mg (0.2 mmol) of **6** in pyridine was treated with 460 mg of methanesulfonyl chloride at 0° for 2 days. The mixture was poured onto ice–water, and the solid was filtered and recrystallized from 2-propanol to give 72 mg (82%) of **7**, mp 85–86°, $[\alpha]^{24}D$ +54.0° (*c* 0.9, $CHCl_3$) [lit.[9] mp 85–86°, $[\alpha]^{25}D$ +53.9° (*c* 1.0, $CHCl_3$)].

Methyl 2,3-Di-*O*-benzyl-4,6-dideoxy-α-D-*arabino*-hexopyranoside (8). A. By Hydroboration of 5. Compound **5** (170 mg, 0.5 mmol) was subjected to hydroboration as described under the preparation of **6** using $NaBH_4$ and boron trifluoride etherate in diglyme. The reaction mixture was decomposed with 45 mg (0.75 mmol) of glacial acetic acid and the solution was boiled for 2 hr. The solvents were evaporated in vacuo and the product was extracted with ether, washed with $NaHCO_3$, dried ($MgSO_4$), and concentrated under vacuum to give 131 mg (76.6%) of an oil. This material was purified by column chromatography on Florisil to yield 112 mg of **8** as an oil, $n^{24}D$ 1.5325, $[\alpha]^{23}D$ +74.3° (*c* 0.9, $CHCl_3$), homogeneous on TLC.

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.78; H, 7.79.

B. From Compound 7. A solution of 150 mg (0.34 mmol) of **7** in 30 ml of acetonylacetone and 240 mg (1.6 mmol) of sodium iodide was heated at 125° for 3.5 hr with mechanical stirring. The mixture was cooled, diluted with 5 ml of water, and extracted thoroughly with petroleum ether (bp 50–70°). The petroleum ether extract was washed with sodium thiosulfate solution followed by water, dried ($MgSO_4$), and evaporated to dryness to give 123 mg of a pale yellow oil showing two major spots on TLC, probably corresponding to methyl 2,3-di-*O*-benzyl-4,6-dideoxy-4-iodo-α-D-altropyranoside and methyl 2,3-di-*O*-benzyl-4,6-dideoxy-4-iodo-α-D-idopyranoside. This material was further purified by column chromatography over Woelm grade I alumina to yield 87 mg of a mixture of the two iodo derivatives. A solution of 85 mg (0.18 mmol) of this mixture in 20 ml of anhydrous ether was treated with 130 mg of lithium aluminum hydride. The excess hydride was destroyed by the careful addition of water. The inorganic salts were removed by filtration, the filtrate was washed with water, dried ($MgSO_4$), and concentrated under vacuum, and the residue (48 mg, 76%) was evaporatively distilled to yield 31 mg of **8**, $n^{24}D$ 1.5316, $[\alpha]^{24}D$ +76.4° (*c* 1.4, CH_3OH). This material was identical with the sample prepared by the hydroboration of **5** as shown by its ir spectrum, TLC, and GC using a 5-ft 6% ethylene glycol succinate column.

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Registry No.—**1**, 55570-39-3; **2** HCl, 55570-70-2; **3**, 55570-20-2; **4**, 55570-71-3; **5**, 55570-72-4; **6**, 33159-49-8; **7**, 55570-73-5; **8**, 55570-74-6; iodomethane, 74-88-4; methanesulfonyl chloride, 124-63-0.

References and Notes

(1) For a preliminary account of this work, see C. L. Stevens and D. Chitharanjan, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, p 12C.
(2) Taken from the Ph.D. Dissertation of D. Chitharanjan, Wayne State University, 1969.
(3) For reviews on unsaturated sugars, see R. J. Ferrier, *Adv. Carbohydr. Chem.*, **20**, 67 (1965); **24**, 199 (1969).
(4) R. U. Lemieux, E. Fraga, and K. A. Watnabe, *Can J. Chem.*, **46**, 61 (1968).
(5) A. Melo, W. H. Elliott, and L. Glaser, *J. Biol. Chem.*, **243**, 1467 (1968); O. Gabriel and L. Lindquist, *ibid.*, **243**, 1469 (1968).
(6) R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, N.Y., 1970, p 189.
(7) Synthesis and Chemistry of 4-Amino-4,6-dideoxy Sugars. VII: C. L. Stevens, D. Chitharanjan, K. G. Taylor and P. M. Pillai, *J. Org. Chem.*, preceding paper in this issue.
(8) N. N. Schwartz and J. H. Blumbergs, *J. Org. Chem.*, **29**, 1976 (1964).
(9) Synthesis and Chemistry of 4-Amino-4,6-dideoxy Sugars. VI: C. L. Stevens, J. P. Dickerson, K. G. Taylor, P. Blumbergs, and P. M. Pillai, *J. Org. Chem.*, in this issue.
(10) B. Helferich and E. Himmen, *Chem. Ber.*, **61**, 1825 (1929).
(11) For the mechanism and product ratio of a similar reaction, see C. L. Stevens, K. G. Taylor, and J. A. Valicenti, *J. Am. Chem. Soc.*, **87**, 4759 (1965).

Bicyclic Nucleosides Related to Pyrimidine Nucleosides. IV. Synthesis of 4- and 6-Ribofuranosylthiazolo[5,4-*d*]pyrimidines and 4-Arabinofuranosylthiazolo[5,4-*d*]pyrimidines[1]

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Ribosylation of the bis(trimethylsilyl) derivative of thiazolo[5,4-*d*]pyrimidine-5,7-dione has afforded a mixture of α- and β-4-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione. Thiation of the β anomer was followed by methylation to afford 7-methylthio-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-5-one, which on treatment with methanolic ammonia was converted to 7-amino-4-(β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-5-one, a cytidine analog. An alternate ribosylation using a Friedel–Crafts catalyst afforded the 6-ribosyl derivative. Thiation of thiazolo[5,4-*d*]pyrimidine-5,7-dione afforded thiazolo[5,4-*d*]pyrimidin-5-one-7-thione, which was condensed with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose to afford the 4,6-diribosyl derivative.

In recent years there has been an increasing interest in the synthesis of bicyclic nucleosides with a ribofuranosyl moiety residing in the pyrimidine ring. This interest has been generated to a large extent by the isolation and identification of 3-ribosyluric acid from beef blood.[2] This interest has been directed to a large extent toward 3-ribosyl purines[3–5] but other ring systems have also been investigated.[6,7] These systems have generally afforded, in addition to the desired isomer, substantial amounts of other products. This has been found to be especially true in the case of the purines.[5] In an effort to improve the selectivity of the ribosylation reaction we have investigated and reported on the use of a bulky 8 substituent in the purine series to direct the site of ribosylation to the 3 position.[8–10] This prompted us to investigate an alternate approach to the synthesis of this type of pyrimidine analog. We have now investigated the use of the thiazolo[5,4-*d*]pyrimidine ring system in which ribosylation of the thiazole ring would result in the loss of aromaticity in that ring and should, therefore, be inhibited.[11] Using this approach, the uridine

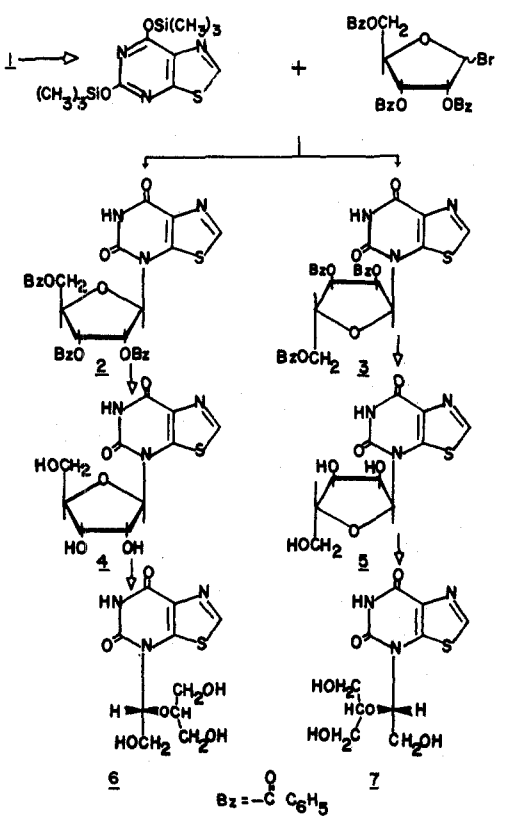
Table I
Ultraviolet Spectral Data for Certain Thiazolo[5,4-*d*]pyrimidine Nucleosides and Model Methyl Derivatives

No.	Compd	pH 1		pH 11	
		λ_{max}, nm	$\epsilon_{max} \times 10^{-3}$	λ_{max}, nm	$\epsilon_{max} \times 10^{-3}$
4	4-(β-D-Ribofuranosyl)thiazolo[5,4-*d*]-pyrimidine-5,7-dione	257	9.04	264	10.05
5	4-(α-D-Ribofuranosyl)thiazolo[5,4-*d*]-pyrimidine-5,7-dione	256.5	8.28	265	10.23
9	4-Methylthiazolo[5,4-*d*]pyrimidine-5,7-dione	261	9.80	266	10.40
11	6-Methylthiazolo[5,4-*d*]pyrimidine-5,7-dione	257	9.15	282	10.94
18	6-(β-D-Ribofuranosyl)thiazolo[5,4-*d*]-pyrimidine-5,7-dione	257	9.60	282.5	8.0

and cytidine analogs of thiazolo[5,4-*d*]pyrimidine have now been prepared. In addition, we found that the use of stannic chloride furnished the 6-ribosyl derivative.

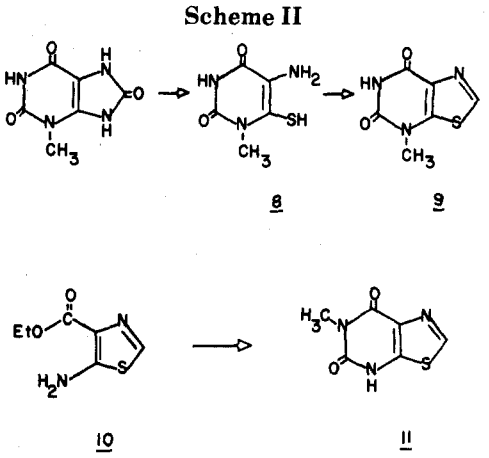
The silylation of thiazolo[5,4-*d*]pyrimidine-5,7-dione[12] (1) was accomplished with hexamethyldisilizane (HMDS) and a catalytic amount of ammonium sulfate. The silyl derivative of 1 was condensed with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in dimethylformamide at room temperature for 3 days to yield a mixture of two nucleosides which we assigned the structures 2 and 3 (vide infra) (Scheme I). The nucleoside mixture was separated by column chromatography to furnish 2 (46%) and 3 (19%) (based on unrecovered 1), which were found to have essentially identical ultraviolet spectra. We also obtained very similar R_f values for 2 and 3 [0.61 and 0.51, respectively, in chloroform–acetone (4:1)], which suggested that we had in hand a pair of anomers rather than a pair of isomers. This conclusion was also supported by the ^{1}H NMR spectra for 2 and 3, which were found to be essentially identical except for the different chemical shift values observed for the peaks assigned to the anomeric protons.[13] A removal of the protecting groups from 2 (methanolic ammonia) and 3 (methanolic sodium methoxide) afforded the nucleosides 4 and 5, respectively, which once again exhibited essentially identical ultraviolet spectra. Treatment of 4 and 5 with sodium periodate was followed by a reduction of the resultant dialdehydes with sodium borohydride to yield compounds 6 and 7, respectively. If the original nucleosides were indeed anomers (diastereoisomers), then 6 and 7 should be enantiomers with equal but opposite optical rotations.[14] The optical rotations of 6 and 7 were determined and found to be +73.3 and −75.0, respectively, which confirmed the anomeric nature of the two compounds.

Scheme I



The actual site of glycosylation for the two nucleosides was still undetermined (although we had assumed N-4) and prompted us to synthesize the two model methyl compounds, 4-methylthiazolo[5,4-*d*]pyrimidine-5,7-dione (9) and 6-methylthiazolo[5,4-*d*]pyrimidine-5,7-dione (11). The synthesis of 9 was achieved by treatment of 3-methyluric acid[15] with ammonium sulfide to give 1-methyl-6-thiouramil[16] (8). Ring closure of 8 with formic acid afforded the desired 4-methylthiazolo[5,4-*d*]pyrimidine-5,7-dione (9) (Scheme II). The synthesis of 11 was accomplished by treatment of ethyl 5-aminothiazolo-4-carboxylate[17] (10) with methyl isocyanate.[18] A comparison of the ultraviolet spectra for the deblocked nucleosides 4 and 5 with those of the methyl derivatives (Table I) established unequivocally that the nucleosides 2 and 3 were both 4-substituted derivatives as we had presumed (Scheme I).

Scheme II

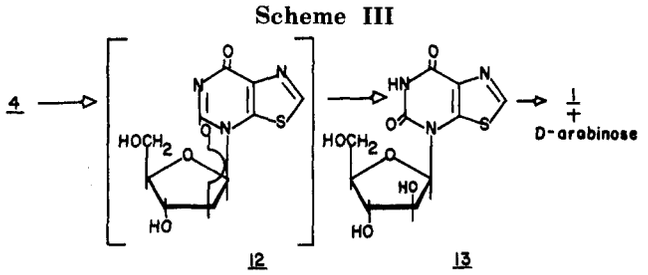


The assignment of anomeric configuration for the individual nucleosides could not be made unequivocally on the basis of ^{1}H NMR spectra, since the coupling constants for

both 4 and 5 ($J_{1',2'}$ = 6.0 and 2.8 Hz, respectively) were greater than 1 Hz.[13,19] However, a *tentative* assignment was made using ^{1}H NMR spectroscopy on the basis of the relative chemical shifts[13] observed for the anomeric protons of 4 and 5. The nucleoside with the downfield chemical shift for the anomeric proton was assigned the cis nucleoside (α) structure, i.e., 5.

This prompted us to initiate a synthesis of the 2,2′-anhydronucleoside in order to make an unequivocal anomeric assignment. Treatment of 4 with diphenyl carbonate and sodium bicarbonate in dimethylformamide at 150° for 15 min[20] gave a material which was not isolated, but was presumably the desired anhydronucleoside (12) (Scheme III).

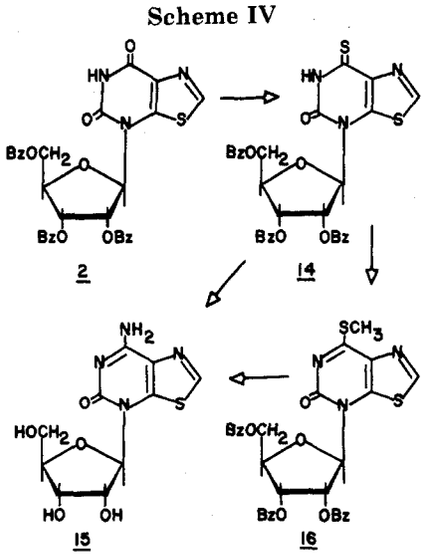
Scheme III



Treatment of 12 with 1.0 *N* sodium hydroxide furnished a nucleoside with the same ultraviolet spectra as that observed for 4 (Table I) but with a different R_f value. Hydrolysis of this nucleoside with 2 *N* hydrochloric acid and a paper chromatographic comparison of the hydrolysate with D-ribose, D-arabinose, and D-xylose showed that the sugar moiety of this nucleoside was D-arabinose. This established the structure as 4-(β-D-arabinofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (13), which also established that 4 must be the β anomer, since the intermediate anhydronucleoside derivative (12) can only be formed by a β-D-ribonucleoside.

It was necessary to functionalize the 7 position so that nucleophilic substitution by ammonia could be used in order to prepare the cytidine analog. The reaction of 2 with phosphorus pentasulfide proceeded smoothly to yield 14 (Scheme IV). The direct displacement of a thio group by

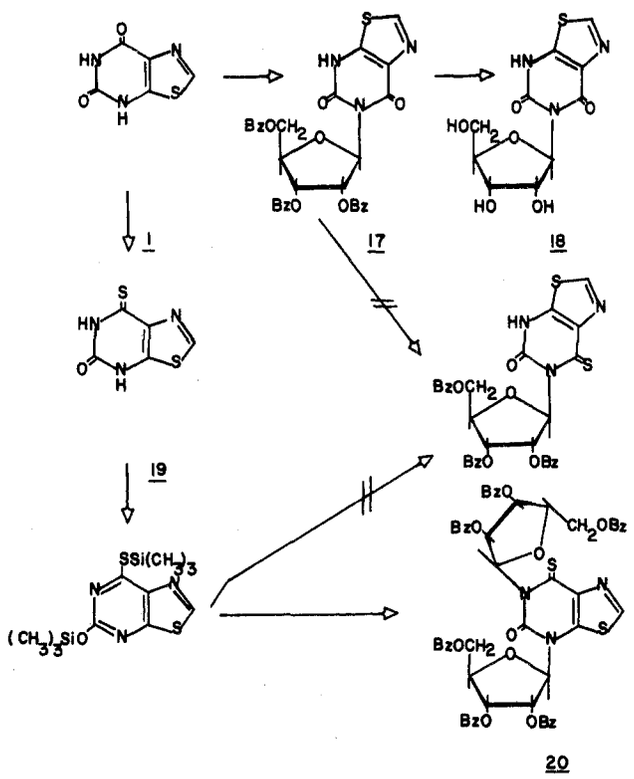
Scheme IV



ammonia has been reported for pyrimidine nucleosides[21] and 6-azapyrimidine nucleosides;[22] however, treatment of 14 with liquid ammonia at room temperature for 5 days resulted in the isolation of only a very low yield of the desired 7-amino-4-(β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-5-one (15). This prompted us to convert 14 into 7-methylthio-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-5-one (16). The site of methylation was established by ^{1}H NMR spectroscopy[13] and was further corroborated by the reaction of 16 with methanolic ammonia, which not only removed the protecting benzoyl groups but also displaced the methylthio group to give the desired cytidine analog 15.

We then initiated an alternate route using a different condensation method[23] for the preparation of the nucleoside 2 in an effort to eliminate the formation of the α anomer. Silylation of thiazolo[5,4-*d*]pyrimidine-5,7-dione (7) with hexamethyldisilizane followed by a reaction with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose in 1,2-dichloroethane in the presence of 1 equiv of stannic chloride gave a nucleoside (17), which was different from either 2 or 3. Debenzoylation of this nucleoside with sodium methoxide afforded a deblocked nucleoside which we assigned the structure 18 (Scheme V). A comparison of the ultraviolet

Scheme V



spectral data obtained for 18 with the spectral data for the model methyl compounds (9 and 11) established the site of ribosylation as N-6 for 17 and 18, with a tentative assignment of β being assigned on the basis of the $J_{1',2'}$ for 18. Although this product was unexpected, it is not without precedent, since although the reaction between bis(trimethylsilyl)lumazine and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide gave primarily 1-(β-D-ribofuranosyl)lumazine (analogous to 4), the same reaction in the presence of stannic chloride gave[6] an appreciable quantity of the 3-ribosyllumazine derivative (analogous to 17).

In an effort to prepare 7-amino-6-(β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-5-one, we attempted to thiate 17 with phosphorus pentasulfide. However, regardless of the temperature or solvent used for this reaction, only starting material was isolated. This was very surprising, since a facile thiation of 2 was observed under these same conditions. The most apparent explanation is that the presence of the 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl group on the nitrogen adjacent to the site of reaction may sterically hinder the approach of phosphorus pentasulfide at the 7 position.

In order to circumvent this difficulty, thiazolo[5,4-*d*]py-

rimidine-5,7-dione (**1**) was thiated to afford thiazolo[5,4-*d*]pyrimidin-5-one-7-thione (**19**). Silylation of **19** with bis(trimethylsilyl)acetamide followed by ribosylation in the presence of stannic chloride yielded a product which, on the basis of elemental analysis and proton magnetic resonance spectra, was assigned the diriboside structure **20**. The possibility that the sugar residues were attached to N-4 and the exocyclic sulfur was eliminated by a comparison of the ultraviolet spectral data for **20** with the uv spectral data observed for **16**, since **16** can be viewed as the methyl model of the *N*-4,7-*S*-diriboside. The other possibility in which a sugar could be attached to the exocyclic sulfur (N-6–7-S) seemed highly unlikely because of the presence of an absorption maxima at 350 nm (both pH 1 and 11) in the ultraviolet spectra of **20**. Exclusion of these two possibilities leaves the *N*-4,*N*-6-diriboside as the most likely structure for **20**.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Proton magnetic resonance spectra were obtained with a Varian A56/60 spectrophotometer and chemical shifts are reported as δ (parts per million) relative to an internal standard (tetramethylsilane or 2,2-dimethyl-2-silapentane-5-sulfonate). Ultraviolet spectra were measured with a Beckman DK-2 spectrophotometer. Thin layer chromatography was run on SilicAR 7GF (Mallinckrodt) spread to a thickness of 0.25 mm on glass plates and column chromatography was run in glass columns with sintered glass bottoms dry packed with SilicAR CC-7, 200–325 mesh (Mallinckrodt). All solvent proportions are given by volume.

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (2) and 4-(2,3,5-Tri-*O*-benzoyl-α-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (3). Thiazolo[5,4-*d*]pyrimidine-5,7-dione (**1**, 10.0 g) was silylated with hexamethyldisilizane (HMDS, 50 ml) by heating the solution at reflux temperature for 15 hr. The excess HMDS was removed by vacuum distillation and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide[8] (prepared from 29.8 g of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose) which had been dissolved in dimethylformamide (100 ml) was added to the residue. The solution was stirred at room temperature for 3 days and then poured into methanol (1 l.) containing NH_4OH (8 ml, 28% aqueous). This mixture, on standing at room temperature for 24 hr, yielded a solid which was collected by filtration. Heating this solid in a mixture of chloroform–ethanol (1:1, 1 l.) left an insoluble material which was collected by filtration and shown to be unreacted **1** (2.4 g). The filtrate was cooled to room temperature and the resulting crystals were collected by filtration to provide pure **2** [10.6 g, R_f 0.61 in chloroform–acetone (4:1)]. The methanol filtrate (from the previous filtration) was evaporated to dryness, dissolved in $CHCl_3$ (25 ml), and applied to a dry packed column (7 × 21 cm) of SilicAR CC-7. The column was eluted with chloroform–acetone (9:1, 1 l.) and fractions containing **2** (15-ml fractions, no. 36–50) were evaporated to dryness, dissolved in a mixture of chloroform–ethanol (1:1), and allowed to cool, and the solid was collected by filtration to yield an additional amount of **2**. Fractions containing pure **3** [51–75, R_f 0.51 in chloroform–acetone (4:1)] were evaporated to dryness to yield a hard foam. The filtrate from the work-up of fractions 36–50 was evaporated to dryness, dissolved in $CHCl_3$ (15 ml), and applied to a second dry packed column of SilicAR CC-7 (4.8 × 20 cm) and eluted as above to yield some additional pure **2** and **3**. Total yield of **2**, 13.0 g; mp 230–231°; ^1H NMR (DMSO-d_6) δ 11.9 (s, 1, NH), 6.42 (d, 1, $J_{1',2'}$ = 3.0 Hz, H-1').

Anal. Calcd for $C_{31}H_{23}N_3O_9S$: C, 60.67; H, 3.78; N, 6.85. Found: C, 60.87; H, 3.92; N, 7.02.

Total yield of **3**, 5.95 g; hard foam; ^1H NMR (DMSO-d_6) as above except δ 6.89 (d, 1, $J_{1',2'}$ = 4.0 Hz, H-1').

Anal. Calcd for $C_{31}H_{23}N_3O_9S$: C, 60.67; H, 3.78; N, 6.85. Found: C, 60.89; H, 4.01; N, 6.68.

4-(β-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (4). The nucleoside **2** (6.2 g) was mixed with methanolic ammonia (75 ml, saturated at −5°) in a pressure bottle and allowed to stand at room temperature for 4 days. The solution was then evaporated to dryness and the residue was extracted with ethyl acetate (100 ml in four portions), leaving a solid. Recrystallization of the solid from MeOH (60 ml) yielded 2.87 g of **4**: mp 203–205° (cloudy melt); ^1H NMR (DMSO-d_6) δ 8.95 (s, 1, H-2) 6.11 (d, 1, $J_{1',2'}$ = 6.0 Hz, H-1').

Anal. Calcd for $C_{10}H_{11}N_3O_6S$: C, 39.86; H, 3.60; N, 13.94. Found: C, 39.72; H, 3.75; N, 13.92.

4-(α-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (5). To a suspension of **3** (1.0 g) in anhydrous MeOH (20 ml) was added sodium methoxide (ca. 50 mg). This suspension was protected from moisture and stirred at room temperature for 15 hr. The crystals which had formed were collected by filtration to yield 0.36 g of a solid which was recrystallized from 95% MeOH to yield 0.3 g of **5**: mp 170° slow dec; ^1H NMR (DMSO-d_6) δ 8.76 (s, 1, H-2), 6.17 (d, 1, $J_{1',2'}$ = 2.8 Hz, H-1').

Anal. Calcd for $C_{10}H_{11}N_3O_6S$: C, 39.86; H, 3.60; N, 13.94. Found: C, 39.67; H, 3.61; N, 14.25.

Periodate Oxidation and Sodium Borohydride Reduction of 4-(β-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (4) and 4-(α-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (5). 4-(β-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (**4**, 40 mg) was suspended in 0.1 *M* sodium periodate solution (3.2 ml) in a 5-ml volumetric flask. The suspension was gently heated to dissolve the solid material and the solution was then stirred for 15 min at room temperature. Sodium borohydride (120 mg) was added to the solution in small portions and the mixture was stirred at room temperature for 30 min. The excess sodium borohydride was destroyed by the addition of 10% acetic acid (added dropwise until gas evolution ceased, ~1.4 ml). The solution was diluted to 5.0 ml, and the optical rotation of this solution was measured and found to be $[\alpha]^{27}D$ +73.3°.

4-(α-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (**5**, 40 mg) was treated in an identical fashion; the optical rotation was measured and found to be $[\alpha]^{27}D$ −75.0°.

4-Methylthiazolo[5,4-*d*]pyrimidine-5,7-dione (9). Ammonium hydroxide (28%, 75 ml) cooled in an ice bath with stirring was saturated with hydrogen sulfide gas to afford a solution of ammonium sulfide. The solution was added to a mixture of 3-methyluric acid[15] (5.2 g) and 2% NH_4OH (30 ml). The resulting suspension was stirred and then heated in a sealed container at 160° for 6 hr. The resulting solution was evaporated to dryness to yield a solid residue[16] (**8**, 4.0 g) which could be recrystallized from water. The crude solid was suspended in formic acid (85%, 70 ml) and heated at reflux temperature for 12 hr to yield 3.6 g of crude product. This solid was reprecipitated twice from dilute NH_4OH with 1 *N* HCl to yield an analytical sample of **9**, mp 350°.

Anal. Calcd for $C_6H_5N_3O_2S$: C, 39.33; H, 2.75; N, 22.95. Found: C, 39.41; H, 2.95; N, 23.20.

6-Methylthiazolo[5,4-*d*]pyrimidine-5,7-dione (11). Ethyl 5-aminothiazole-4-carboxylate (**10**, 2.0 g) and methyl isocyanate (1.5 ml) were added to pyridine (4 ml) and the suspension was heated at reflux temperature for 1 hr and then cooled to room temperature. A mixture of EtOH (5 ml) and diethyl ether (150 ml) was added to yield a solid which was collected by filtration (2.5 g). The solid (2.5 g) was added to 5% aqueous NH_4OH (40 ml) at reflux temperature and the solution was heated for 5 min. This solution was acidified with acetic acid to furnish a solid. The suspension was cooled to room temperature, and the solid was collected by filtration and recrystallized from water to yield **11**, 0.55 g, mp 348–350°.

Anal. Calcd for $C_6H_5N_3O_2S$: C, 39.35; H, 2.75; N, 22.95. Found: C, 39.00; H, 2.81; N, 22.72.

4-(β-D-Arabinofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (13). A mixture of **4** (1.0 g), diphenyl carbonate (0.88 g), and $NaHCO_3$ (0.016 g) in DMF (5 ml) was heated for 30 min in an oil bath at 150°. The suspension was poured into ether (100 ml) with stirring, and the resulting solid was collected by filtration and washed with an additional quantity of ether (50 ml). This solid [5,2′-*O*-anhydro-4-(β-D-arabinofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (**12**, 0.95 g)] was air dried, suspended in 1 *N* NH_4OH (10 ml), and stirred at room temperature for 2 hr. The solution was adjusted to pH 7.0 with 1 *N* HCl to yield crystals which were collected by filtration and washed with water (5 ml). The solid was recrystallized from water to yield 0.67 of **13**: mp over 245° slow dec; ^1H NMR (DMSO-d_6) δ 8.81 (s, 1, H-2), 6.15 (d, 1, $J_{1',2'}$ = 3.0 Hz, H-1'); uv λ_{max} ($\epsilon \times 10^{-3}$), pH 1, sh 275 nm (7.1), 258.5 (8.2); pH 11, 265 (8.6).

Anal. Calcd for $C_{10}H_{11}N_3O_6S \cdot 0.5H_2O$: C, 38.70; H, 3.89; N, 13.59. Found: C, 38.89; H, 4.07; N, 13.36.

Hydrolysis of 4-(β-D-arabinofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione. 4-(β-D-Arabinofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (**13**, 10 mg) was heated in a 2 *N* HCl solution (2 ml) on a steam bath for 3 hr and the solution was then filtered.

The filtrate was adjusted to pH 7.0 with 1 *N* NaOH and then concentrated to 1 ml. Solutions of D-arabinose, D-ribose, and D-xylose were similarly treated. The concentrated filtrates were spotted on Whatman No. 1 chromatography paper and chromatographed with 1-butanol–acetic acid–water (3:1:1). The chromatograms were sprayed with aniline–phthalic acid reagent.[24] The hydrolysis solution gave a spot at R_f 0.33, which corresponded to the R_f value for D-arabinose (R_f values for ribose and xylose were 0.43 and 0.39, respectively), thus establishing that the carbohydrate moiety of **13** was indeed D-arabinose.

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-5-one-7-thione (14). The nucleoside **2** (10.0 g) was dissolved in pyridine (125 ml) and P_2S_5 (3.6 g, 1 equiv) was then added. The solution was heated at reflux temperature for 6 hr, at which time an additional 1 equiv of P_2S_5 (3.6 g) was added. Heating was continued for an additional 6 hr, at which time the solution was evaporated to near dryness and water (200 ml) was added. This mixture was heated on a steam bath for 30 min with stirring, and the solid material was collected by filtration, washed with water (100 ml), and air dried. This solid was dissolved in chloroform (200 ml) and the chloroform solution was extracted with 0.1 *N* HCl (4 × 100 ml), saturated aqueous $NaHCO_3$ (4 × 100 ml), and water (2 × 100 ml). The $CHCl_3$ solution was then dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and washed with $CHCl_3$ and the filtrate and wash were evaporated to dryness. The residue was dissolved in $CHCl_3$ (20 ml), applied to a dry packed column of SilicAR CC-7 (7 × 25 cm), and eluted with chloroform–acetone (19:1, 1 l.) to remove the impurities which remained on the column. The eluent was evaporated to dryness, and the residue was dissolved in $CHCl_3$ (20 ml), applied to a second column of SilicAR CC-7 (7 × 20 cm), and eluted with chloroform–acetone (19:1). Fractions of 20 ml were collected, and fractions 24–75 contained pure **14**, which was crystallized from chloroform–ethanol (1:9) to yield 5.8 g of product. All other fractions containing **14** were combined, evaporated to dryness, dissolved in $CHCl_3$ (10 ml), and applied to a third column of SilicAR CC-7 (4.5 × 23 cm). Eluted as above, fractions 12–24 contained pure **14** (1.5 g) for a total yield of 7.3 g: mp 188.5–189.5°; ^{1}H NMR ($CDCl_3$) δ 8.52 (s, 1, 2); uv λ_{max} (ε × 10^{-3}), pH 1, 362 nm (18.9), sh 277 (19.5), 244 (33.7); pH 11, 326 (24.5), 275 (19.8).

Anal. Calcd for $C_{31}H_{23}N_3O_8S_2$: C, 59.12; H, 3.68; N, 6.67. Found: C, 59.25; H, 3.69; N, 6.56.

7-Methylthio-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-5-one (16). The nucleoside **14** (0.63 g) was added to sodium hydride (0.024 g) in DMF (5 ml) and the suspension was stirred at room temperature until bubbling had ceased (ca. 15 min). Methyl iodide (0.23 g, 0.1 ml) was added and the solution was stirred for an additional 1 hr. This solution was evaporated to dryness, then xylene (5 ml) was added and the suspension was again evaporated to dryness. The residue was dissolved in $CHCl_3$ (30 ml), and the $CHCl_3$ solution was extracted with water (4 × 15 ml) and then dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and washed with $CHCl_3$ (20 ml), and the combined filtrate and wash were evaporated to dryness, dissolved in $CHCl_3$ (2 ml), and applied to a dry packed column of SilicAR CC-7 (2.5 × 25 cm) and eluted with chloroform–acetone (19:1). Fractions of 20 ml were collected and fractions 6–8 contained pure **16**. These fractions were evaporated to dryness to yield a hard foam which on trituration with ether gave a solid: yield 0.60 g; ^{1}H NMR ($CDCl_3$) δ 8.37 (s, 1, H-2), 2.65 (s, 3, $-SCH_3$); uv λ_{max} (ε × 10^{-3}) pH 1, 327 nm (16.8), sh 285 (23.8), 274 (24.5), 244 (35.0); pH 11, 324 (17.1), sh 285 (25.4), 270 (26.4), 244 (40.6).

Anal. Calcd for $C_{32}H_{25}N_3O_8S_2$: C, 59.72; H, 3.92; N, 6.53. Found: C, 59.90; H, 4.20; N, 6.24.

7-Amino-4-(β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-5-one (15). Method A. The nucleoside **14** (1.0 g) was suspended in liquid ammonia (5 ml) and the reaction mixture was allowed to stand at room temperature in a sealed pressure vessel for 5 days. The excess ammonia was allowed to evaporate and the residue was extracted with ether (4 × 10 ml). Crystallization of the solid residue from water (20 ml) yielded ca. 50 mg of **15**: mp 201° slow dec; ^{1}H NMR (DMSO-d_6) δ 8.87 (s, 1, H-2), 7.90 (br m, 2, NH_2), 6.08 (d, 1, $J_{1',2'}$ = 6.0 Hz, H-1'); uv λ_{max} (ε × 10^{-3}) pH 1, 294 nm (10.1), 259 (7.6); pH 11, sh 281 (8.2), 266 (9.9),229 (17.2).

Anal. Calcd for $C_{10}H_{12}N_4O_5S\cdot H_2O$: C, 37.74; H, 4.42; N, 17.61. Found: C, 37.91; H, 4.45; N, 17.40.

Method B. The nucleoside **16** (1.5 g) was suspended in MeOH saturated with ammonia (50 ml, saturated at 0°) and the mixture was allowed to stand in a pressure bottle at room temperature for 96 hr. The crystals which had formed were collected by filtration and washed with MeOH (20 ml) to yield **15** (0.55 g). The filtrate was evaporated to dryness and the residue was extracted with carbon tetrachloride (4 × 20 ml), then recrystallized from water to yield some additional **15** for a total yield of 0.60 g; this material was shown to be identical with that obtained by method A by thin layer chromatography in chloroform–methanol (7:3) and by a comparison of ultraviolet spectra.

6-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (17). Thiazolo[5,4-*d*]pyrimidine-5,7-dione (**1**, 1.0 g) was silylated with hexamethyldisilazane (15 ml), as before, and the bis(trimethylsilyl) derivative was dissolved in 1,2-dichloroethane (100 ml). To this solution was added 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (2.7 g) followed by stannic chloride (1.5 g, 0.69 ml) and the mixture was stirred for 4 hr at room temperature. Pyridine (1 ml) was then added and the precipitate which formed was collected by filtration and washed with $CHCl_3$ (50 ml). The filtrate and wash were combined and extracted with 0.1 *N* HCl (3 × 35 ml), saturated aqueous $NaHCO_3$ (3 × 35 ml), and water (2 × 50 ml). The $CHCl_3$ solution was dried over Na_2SO_4 and filtered, the Na_2SO_4 was washed with $CHCl_3$ (50 ml), and the filtrate and wash were evaporated to dryness. The resulting syrup was dissolved in a minimum volume of $CHCl_3$ (2 ml), applied to a dry packed SilicAR CC-7 column (3.5 × 20 cm), and eluted with chloroform–acetone (4:1). The fractions containing **17** [R_f 0.53, chloroform–acetone (4:1)] were combined and evaporated to dryness, and the residue was recrystallized from ethanol–chloroform (15:1) to yield 2.0 g of product: mp 234–235°; mmp with **2** 205–215°; ^{1}H NMR ($CDCl_3$) δ 8.46 (s, 1, H-2); uv λ_{max} (ε × 10^{-3}) pH 1, sh 277 nm (17.5), 236 (32.5); pH 11, sh 295 (13.2), 277 (15.9), 230 (47.5).

Anal. Calcd for $C_{31}H_{23}N_3O_9S$: C, 60.67; H, 3.78; N, 6.85. Found C, 60.61; H, 3.77; N, 6.91.

6-(β-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidine-5,7-dione (18). Sodium methoxide (125 mg) was added to **17** (1.0 g) suspended in MeOH (20 ml). The mixture was stirred at room temperature for 15 hr, and the precipitate was collected by filtration, washed with MeOH (5 ml), and air dried (0.47 g). The filtrate and wash were neutralized with Amberlite CG-50 ion exchange resin (H^+ form), the suspension was filtered, and the resin was washed with hot MeOH (10 ml). The filtrate and wash were combined and evaporated to dryness and the residue was extracted with ether (4 × 10 ml). The solid which remained was dissolved in hot water (5 ml) by the addition of a minimum volume of concentrated NH_4OH and reprecipitated by adjusting the pH of the solution to 6.0 with 1 *N* HCl to yield some additional **18** for a total yield of 0.14 g: mp 294–296° dec; ^{1}H NMR (DMSO-d_6) δ 7.95 (s, 1, H-2), 6.23 (d, 1, $J_{1',2'}$ = 3.5 Hz, H-1').

Anal. Calcd for $C_{10}H_{11}N_3O_6S\cdot 0.5H_2O$: C, 38.70; H, 3.90; N, 13.54. Found: C, 38.74; H, 3.89; N, 13.40.

Thiazolo[5,4-*d*]pyrimidin-5-one-7-thione (19). Thiazolo[5,4-*d*]pyrimidine-5,7-dione (**1**, 10.0 g) and P_2S_5 (13.2 g) were added to pyridine (80 ml) and the mixture was heated at reflux temperature for 6 hr. An additional 1 equiv of P_2S_5 (13.2 g) was then added and the heating was continued for an additional 6 hr. The resulting solution was evaporated to dryness, water (150 ml) was added, and the suspension was heated on a steam bath with stirring for 1 hr. The resulting solid was collected by filtration and reprecipitated from hot 0.5 *N* NaOH (400 ml) with 1 *N* HCl. After cooling, the precipitate was collected by filtration, washed with water (50 ml), and dissolved in 0.1 *N* NaOH (400 ml). This solution was applied to a 2.0-cm column (diameter) containing 50 ml (wet volume) of Amberlite IRA-400 CP ion exchange resin (strong base, Cl^- form). The column was washed with 0.1 *N* NaOH (100 ml) and then **19** was eluted with 1.5 *N* NaCl which was 0.01 *N* in NaOH (1.5 l.). Acidification (pH 2) of the eluent with 1 *N* HCl yielded 5.75 g of product: mp 360°; uv λ_{max} (ε × 10^{-3}) pH 1, 342 nm (18.4), 333 (19.2), 270 (7.5); pH 11, 351 (18.5), 291 (7.8), 267 (8.2).

Anal. Calcd for $C_5H_3N_3OS_2$: C, 32.42; H, 1.63; N, 22.69. Found: C, 32.42; H, 1.62; N, 22.61.

Ribosylation of Thiazolo[5,4-*d*]pyrimidin-5-one-7-thione. Thiazolo[5,4-*d*]pyrimidin-5-one-7-thione (**19**, 2.5 g) was silylated with bis(trimethylsilyl)acetamide (9.5 ml) in 1,2-dichloroethane (25 ml) at 50° for 15 min. The solvent and excess BSA were removed by distillation and the resulting solid residue was combined with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (6.8 g) in 1,2-dichloroethane (30 ml). Stannic chloride (4.5 g, 2.0 ml) was added and the solution was stirred at room temperature for 15 hr. Pyridine (2.2 ml, 2 equiv) was added to the solution, and the resulting precipitate was removed by filtration and washed with $CHCl_3$ (100 ml). The combined filtrate and wash were extracted

with 0.1 *N* HCl (4 × 50 ml), saturated aqueous $NaHCO_3$ (4 × 50 ml), and water (2 × 50 ml). The organic phase was dried over Na_2SO_4, the Na_2SO_4 was removed by filtration and washed with $CHCl_3$ (30 ml) and the combined filtrate and wash were evaporated to dryness. The resulting syrup was dissolved in $CHCl_3$, applied to a dry packed column of SilicAR CC-7 (7 × 18 cm), and eluted with chloroform–acetone (19:1). Fractions containing the major band [R_f 0.73, chloroform–acetone (19:1), fraction no. 7–23, 20-ml fractions] were concentrated and applied to another SilicAR CC-7 (4.6 × 20 cm) column. Fractions 3–10 (20-ml fractions) from the second column contained pure **20.** These fractions were combined and evaporated to a hard foam and then triturated with ether (100 ml) to give 3.9 g of solid: mp 119–122°; ^1H NMR ($CDCl_3$) δ 8.46 (s, 1, H-2), 8.33–7.33 (m, ca. 30, $-COC_6H_5$); uv λ_{max} ($\epsilon \times 10^{-3}$) pH 1, 350 nm (14.4), sh 275 (19.5), 238 (45.3); pH 11, 350 (15.7), sh 275 (26.1), 237 (91.0).

Anal. Calcd for $C_{57}H_{43}N_3O_{15}S_2 \cdot 2H_2O$: C, 61.68; H, 4.26; N, 3.78. Found: C, 61.59; H, 4.45; N, 3.68.

Registry No.—**1,** 5082-82-6; **2,** 35867-92-6; **3,** 55520-41-7; **4,** 35867-91-5; **5,** 35867-90-4; **8,** 55520-42-8; **9,** 55520-43-9; **10,** 18903-18-9; **11,** 55520-44-0; **12,** 55520-45-1; **13,** 35867-89-1; **14,** 55520-46-2; **15,** 55520-47-3; **16,** 55520-48-4; **17,** 55520-49-5; **18,** 55520-50-8; **19,** 55520-51-9; **20,** 55520-52-0; 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide 22860-91-9; 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, 6974-32-9.

References and Notes

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(2) R. Falconer and J. M. Gulland, *J. Chem. Soc.*, 1369 (1939); H. S. Forrest, D. Hatfield, and J. M. Lagowski, *J. Chem. Soc.*, 963 (1961).
(3) D. Lipkin, C. T. Cori, and J. A. Rabi, *J. Heterocycl. Chem.*, **6,** 995 (1969).
(4) R. Lohrmann, J. M. Lagowski, and H. S. Forrest, *J. Chem. Soc.*, 451 (1964).
(5) N. J. Leonard and R. A. Laursen, *Biochemistry*, **4,** 354 (1965).
(6) G. Ritzmann, K. Harzer, and W. Pfleiderer, *Angew. Chem., Int. Ed. Engl.*, **10,** 932 (1971).
(7) B. H. Rizkalla, A. D. Broom, M. G. Stout, and R. K. Robins, *J. Org. Chem.*, **37,** 3975 (1972).
(8) C. L. Schmidt and L. B. Townsend, *J. Org. Chem.*, **37,** 2300 (1972).
(9) C. L. Schmidt and L. B. Townsend, *J. Heterocycl. Chem.*, **10,** 687 (1973).
(10) C. L. Schmidt and L. B. Townsend, *J. Chem. Soc., Perkin Trans. 1*, in press.
(11) C. L. Schmidt, W. J. Rusho, and L. B. Townsend, *Chem. Commun.*, 1515 (1971).
(12) S. J. Childress and K. L. McKee, *J. Am. Chem. Soc.*, **73,** 3862 (1951).
(13) L. B. Townsend in "Synthetic Procedures in Nucleic Acid Chemistry", Vol. II, W. W. Zorbach and R. S. Tipson, Ed., Wiley, New York, N.Y., 1973, pp 267–398.
(14) G. R. Revankar and L. B. Townsend, *J. Heterocycl. Chem.*, **7,** 1329 (1970), and references cited therein.
(15) W. Traube, *Ber.*, **33,** 3035 (1900).
(16) G. P. Hager and C. Kaiser, *J. Am. Pharm. Assoc.*, **44,** 193 (1955).
(17) A. H. Cook, I. Heilbron, and A. L. Levy, *J. Chem. Soc.*, 1598 (1947).
(18) A. H. Cook, J. D. Downer, and I. Heilbron, *J. Chem. Soc.*, 1069 (1949).
(19) R. U. Lemieux and D. R. Lineback, *Annu. Rev. Biochem.*, **32,** 155 (1963).
(20) A. Hampton and A. W. Nichol, *Biochemistry*, **5,** 2076 (1966).
(21) I. L. Doerr, J. F. Codington, and J. J. Fox, *J. Med. Chem.*, **10,** 247 (1967).
(22) V. P. Chernetskii and I. V. Alekseeva, *Chem. Heterocycl. Compd.*, **3,** 861 (1967).
(23) U. Niedballa and H. Vorbruggen, *Angew. Chem., Int. Ed., Engl.*, **9,** 461 (1970).
(24) S. M. Partridge, *Nature (London)*, **164,** 443 (1949).

C-Glycosyl Nucleosides. VII.[1] Synthesis of Some 3-β-D-Ribofuranosyl-1,2,4-oxadiazoles and 3-β-D-Ribofuranosylpyrazoles

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Two syntheses of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonamidoxime (**2a**) are described via either addition of hydroxylamine to 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide or chlorination and amination of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allose oxime. Reactions of **2a** with acetic anhydride and ethyl acetoacetate give rise to 5-substituted 3-β-D-ribofuranosyl-1,2,4-oxadiazoles, while acetaldehyde gives the related Δ^2-1,2,4-oxadiazoline. The condensation of both *O*-benzoyl and *O*-benzyl derivatives of 2,5-anhydro-D-allose with 1-chloroacetonylidenetriphenylphosphorane gives unsaturated chloro ketones that can be cyclized with hydrazine to 5-methyl-3-β-D-ribofuranosylpyrazoles. A potential route for the synthesis of pyrazoles is explored via addition of ethyl glyoxylate hydrazone to nitroolefins followed by chlorination and base-catalyzed cyclization. This has required the synthesis of a *C*-glycosyl nitroolefin via addition of nitromethane to 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allose followed by dehydration. While pyrazole synthesis was achieved in a model system, the carbohydrate derivative failed to cyclize.

The natural occurrence of a number of *C*-glycosyl nucleosides, many of which possess antibacterial or antitumor activity,[2] has prompted considerable activity directed toward the synthesis of this type of compound.[3] Our general approach has been based upon the development of a facile synthetic route for the preparation of variously protected derivatives of 2,5-anhydro-D-allose.[4] The latter compounds, which already include the critical *C*-glycosyl carbon–carbon bond, contain a reactive aldehyde function that can be elaborated into a variety of heterocyclic systems. We have, for example, described the use of these key intermediates in syntheses of 2-β-D-ribofuranosylmaleimide (showdomycin),[5] of variously substituted 4-β-D-ribofuranosylpyrazoles,[6] and of both 3- and 5-β-D-ribofuranosylisoxazoles.[1] In the present paper we further extend those studies and describe routes for the synthesis of several 3-β-D-ribofuranosyl-1,2,4-oxadiazoles and 3-β-D-ribofuranosylpyrazoles.

The most frequently encountered route for the synthesis of substituted 1,2,4-oxadiazoles involves the acylation and subsequent cyclization of amidoximes. This procedure was originally developed by Tiemann[7] some 90 years ago and has recently been reexamined by Moussebois et al.[8] The chemistry of amidoximes has been reviewed[9] and it can be seen that the most common route for their synthesis involves the condensation of nitriles with hydroxylamine.[10] For our purposes the key intermediate would be 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonamidoxime (**2a**), and this compound could be obtained by the reaction of the readily available 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide (**1**)[11,4] with hydroxylamine in methanol at 50°. Under these conditions **2a** was obtained in only 34% yield and it was necessary to effect purification by chromatography on silicic acid in order to remove several more polar by-products arising, presumably, from partial debenzoylation. While amidoximes have been prepared as substituents upon the