The Synthesis of Thieno[2,3-*d*]pyrimidine Nucleosides related to the Naturally Occurring Nucleosides Cytidine and Uridine

By **Vemanna D. Patil, Dean S. Wise,** and **Leroy B. Townsend,*** Department of Medicinal Chemistry, College of Pharmacy and Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, and Department of Medicinal Chemistry and Department of Chemistry, University of Utah, Salt Lake City, Utah 84112, U.S.A.

Several ribofuranosyl nucleosides of the thieno[2,3-*d*]pyrimidine ring system have been prepared by condensation of the persilylated base with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in 1,2-dichloroethane in the presence of stannic chloride. These nucleosides are analogues of uridine and cytidine. The synthesis of the arabinofuranosides of 4-aminothieno[2,3-*d*]pyrimidin-2-one and 4-amino-5-methylthieno[2,3-*d*]pyrimidin-2-one from a cyclonucleoside intermediate is described.

DUE largely to the isolation and characterization of 3-(ribofuranosyl)uric acid [1,2] and the isolation from patients treated with allopurinol of 7-(D-ribofuranosyl)pyrazolo-[3,4-*d*]pyrimidine-4,6-dione,[3,4] which was found to inhibit pyrimidine *de novo* biosynthesis, we have undertaken [5,6] the synthesis of nucleosides of bicyclic heterocycles which possess a pyrimidine ring analogously substituted to uracil, cytidine, *etc.* as part of the ring system. These nucleoside derivatives have been designed with the ribofuranosyl moiety positioned on the pyrimidine ring, in an effort to mimic the natural pyrimidine nucleosides rather than purine nucleosides, and therefore to compete for enzymes in the pyrimidine biosynthetic pathway. We have found [6] that certain 2-substituted-6-(β-D-ribofuranosyl)oxazolo[5,4-*d*]pyrimidin-7-one derivatives give rise to growth-inhibition activity in both L-1210 and *Escherichia coli in vitro* cell screens. This activity has prompted us to investigate the synthesis of the uridine and cytidine analogues of the closely related thieno[2,3-*d*]pyrimidine bicyclic ring system.

RESULTS AND DISCUSSION

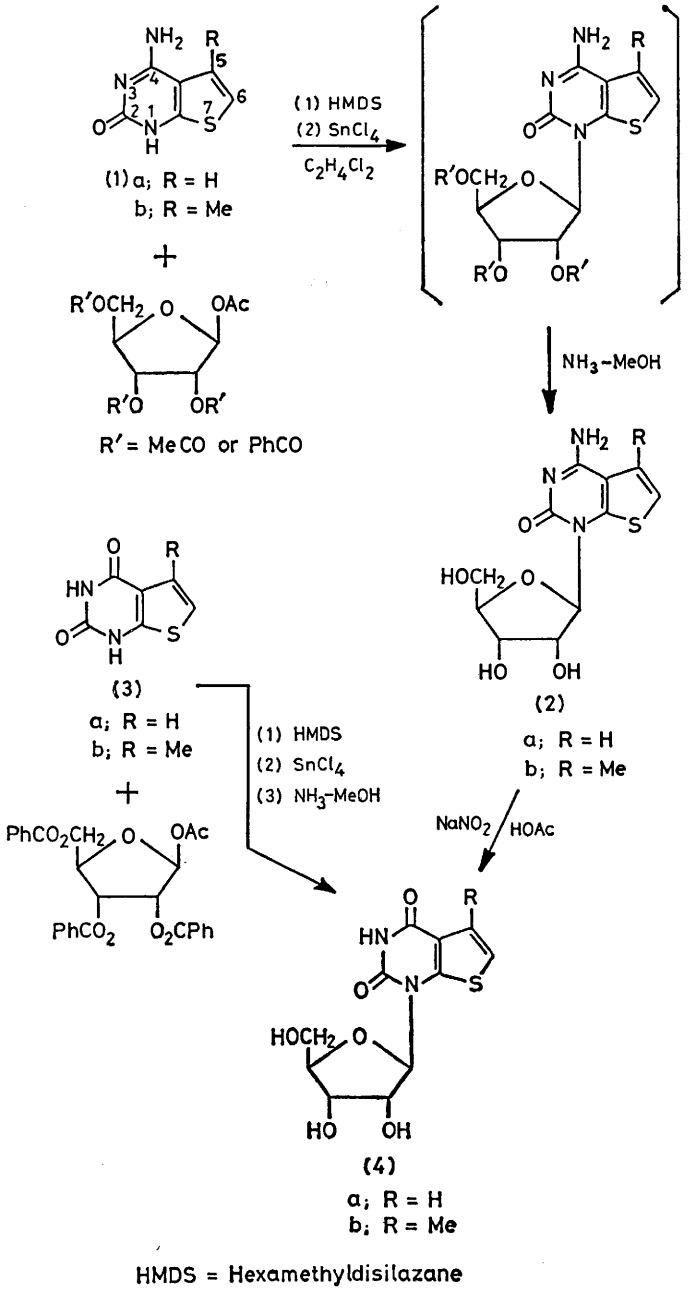
A key intermediate for the synthesis of this series of cytidine analogues was 4-aminothieno[2,3-*d*]pyrimidin-2-one (1a). This heterocycle (1a) was prepared routinely in 70—75% yield by fusing [7] a mixture of 2-amino-3-cyanothiophen [8] with urea at 170—180 °C; 4-amino-5-methylthieno[2,3-*d*]pyrimidin-2-one [8] (1b) was prepared similarly. The synthetic route we envisaged for the preparation of these nucleosides required the conversion of (1a) and (1b) into their bis(trimethylsilyl) derivatives. The silylation of (1a) was accomplished with hexamethyldisilazane in the presence of a catalytic amount of ammonium sulphate in excellent yield, while silylation of 4-amino-5-methylthieno[2,3-*d*]pyrimidin-2-one (1b) could only be accomplished using *NO*-bis(trimethylsilyl)-acetamide.

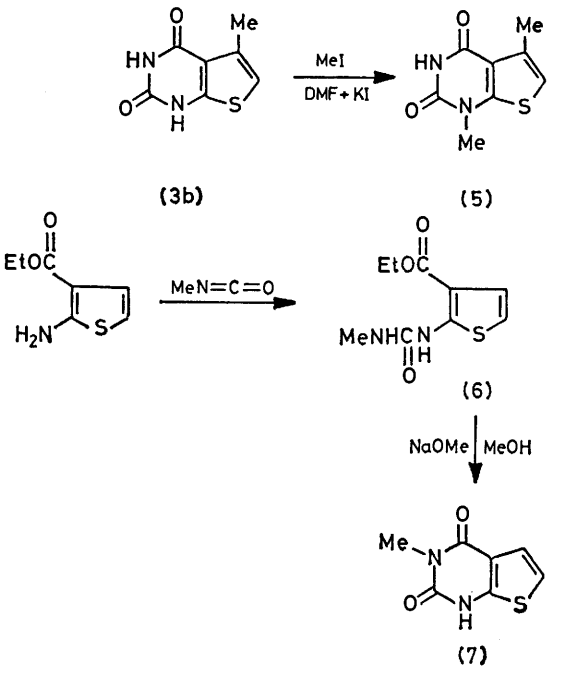
Coupling of the silyl derivative of (1a) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in 1,2-dichloroethane in the presence of 1.5 equiv. stannic chloride [9] proceeded cleanly, and a blocked nucleoside was isolated as a syrup. All attempts to crystallize this syrup were unsuccessful. However, removal of the acetyl groups by treatment of this intermediate with methanolic ammonia afforded the crystalline nucleoside (2a) in 40% yield. When the same condensation conditions were repeated using the carbohydrate 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, the yield of the free nucleoside was only moderately increased to 47%. The condensation of (1b) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, again by the method of Niedballa and Vorbruggen,[9] and subsequent removal of the benzoyl groups with methanolic ammonia, provided the nucleoside (2b) in 60% overall yield.

In order to prepare the analogous uridine derivatives, persilylated thieno[2,3-*d*]pyrimidine-2,4-dione [prepared from thieno[2,3-*d*]pyrimidine-2,4-dione [8] (3a)] or persilylated 5-methylthieno[2,3-*d*]pyrimidine-2,4-dione [prepared from 5-methylthieno[2,3-*d*]pyrimidine-2,4-dione [8] (3b)] were condensed with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in 1,2-dichloroethane at room temperature in the presence of stannic chloride. Debenzoylation of the blocked nucleosides was achieved in methanolic ammonia to afford the desired 1-(β-D-ribofuranosyl)thieno[2,3-*d*]pyrimidine-2,4-dione (4a) or 5-methyl-1-(β-D-ribofuranosyl)thieno[2,3-*d*]pyrimidine-2,4-dione (4b), respectively, as crystalline compounds which may be viewed as 5,6-disubstituted uridine analogues.

Although (2a), (2b), (4a), and (4b), due to the mode of synthesis, were assumed to be the 1-β-D ribofuranosides, the assignments for the actual site of ribosylation, and the configuration about the anomeric carbon, were equivocal. In order to substantiate the site of ribosylation, the most utilized procedure, that of preparing the model methyl derivatives and comparing the u.v. spectra, was undertaken. The monomethylation of (3b) was achieved by treatment with methyl iodide in DMF at room temperature in the presence of KI to provide 1,5-dimethylthieno[2,3-*d*]pyrimidine-2,4-dione (5). The synthesis of 3-methylthieno[2,3-*d*]pyrimidine-2,4-dione (7) was accomplished by treatment of ethyl 2-aminothiophen-3-carboxylate [7] with methyl isocyanate and subsequent ring-closure of the intermediate ureido-(6) with methanolic sodium methylate. Unfortunately, although a similarity in the structure of the u.v. spectra of (4b) and (5), and a dissimilarity between (4b) and (7) was apparent, a 5-nm difference (see Table 1) in $\lambda_{max.}$ between the nucleosides (4a) and (4b) and the model methyl-heterocycle (5) was not considered significant

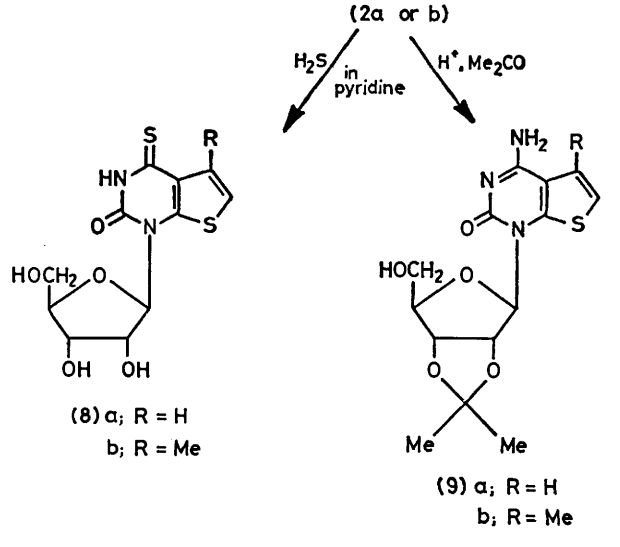
enough to allow the unequivocal assignment of the site of ribosylation by this method as N-1. However, the actual site of ribosylation was subsequently obtained by performing a series of chemical transformations upon the nucleosides (2a) and (2b). On treatment of (2a) or (2b) with sodium nitrite in glacial acetic acid, a facile deamination occurred and furnished (4a) or (4b), respectively, which indicated that (2a) and (2b) were *N*-ribosylated at the same site as (4a) and (4b). It is known that the presence of an anisotropic thione group adjacent to the site of ribosylation [10,11] imparts a strong deshielding of the C-1′-H in the ^{1}H n.m.r. spectra of these compounds relative to their oxo-analogues parts.





Sulphohydrolysis [12] with H_2S in pyridine led to a facile conversion of the NH_2 groups of (2a) and (2b) into the thione groups of (8a) and (8b). In the nucleosides (8a) and (8b), no anisotropic perturbation of the C-1′-H due to the thione group was observed; in fact, a small upfield shift was observed for the anomeric protons of (8a) and (8b) when compared to (4a) and (4b). Thus, the lack of deshielding established their structures as 1-(β-D-ribofuranosyl)-4-thioxothieno[2,3-*d*]pyrimidin-2-one (8a) and 5-methyl-1-(β-D-ribofuranosyl)-4-thioxothieno[2,3-*d*]pyrimidin-2-one (8b), and thus (see above) that the site of ribosylation was N-1 in the nucleosides (2a) and (2b), and also (4a) and (4b).

The method of Niedballa and Vorbruggen [9] reportedly leads almost exclusively to the β-nucleosides, and in this present report the products of these various glycosid-



ation condensations [(2a), (2b), (4a), and (4b)] were found to be only one component when monitored by t.l.c. during the course of the reaction. However, the ^{1}H n.m.r. spectra of these compounds did not permit a direct confirmation [13,14] of the β-configuration since in all cases except (4b) the values of J(H-1′–H-2′) were 5 Hz. Thus, the preparation of the 2′,3′-isopropylidene derivatives of (2a) and (2b) was undertaken in an effort to reduce the magnitude of the coupling constants [J(H-1′–H-2′)] to within acceptable limits. The isopropylidene derivatives (9a) and (9b) were prepared by treating (2a) and (2b) with dry acetone and catalytic amounts of perchloric acid. The ^{1}H n.m.r. spectrum (Table 2) of (9b) in $(CD_3)_2SO$ exhibited a doublet [J(H-1′–H-2′) 1 Hz] at δ 5.85 for the anomeric proton and the difference between the chemical shift of the *exo*- and *endo*-methyl groups for the 2′,3′-*O*-isopropylidene group of *ca.* 0.2 p.p.m. for both (9a) and (9b) is indicative of β-D-ribonucleosides.[15]

TABLE 1

Spectral data for thieno[2,3-*d*]pyrimidine nucleosides and methyl model compounds

Compound	$\lambda_{max.}$/nm (ε × 10^{-3}) MeOH	pH 1	pH 11	^{1}H n.m.r. (δ) H-1′	J(H-1′–H-2′)/Hz	H-5, H-6
(1a)	276 (4.0), 264 (7.0), 228 (28.7)	303 (5.3), 235 (31.1)	274 (10.0), 226 (24.4)			7.17, 7.5
(2a)	295 (4.3), 265sh (6.8), 231 (32.3)	308 (6.9), 260sh (8.4), 238 (30.5)	295 (5.4), 255sh (8.4), 233 (34.1)	5.98	5	7.1, 7.46
(2b)	301 (3.8), 237 (30.4)	317 (5.0), 263sh (10.6), 243 (25)	301 (4.0), 239 (31.01)	5.85	5	6.75
(4a)	285 (4.5), 245sh (5.4), 226 (24)	287 (4.8), 255sh (6.0), 228 (24.6)	285 (4.5), 245sh (6.9), 229 (24.6)	5.98	5	7.25s
(4b)	295 (5.3), 234 (27)	297 (5.7), 236 (28.3)	293 (4.4), 232 (29.8)	6.08	3	6.7
(5)	290 (2.1), 259sh (2.6), 228 (12.2)	292 (4.5), 260 (6.11), 231 (25.5)	290sh (2.9), 261 (6.7), 230 (25.5)			
(7)	278 (3.8), 256 (6.0), 223 (29.1)	277 (3.8), 252 (6.9), 225 (30.9)	299 (6.2), 265 (9.6), 226 (26.6)			
(8a)	341 (19.0), 280 (8.2), 248.5 (14.2)	352 (19.0), 249 (17.1)	331 (16.8), 299 (11.7), 249 (15.8)	5.91	5	7.18, 7.35
(8b)	347 (20.1), 280 (11.4), 253 (20.3)	353 (17.8), 305 (13.5), 252 (23.1)	337 (18.6), 301 (14.2), 256 (23.6), 231 (18.8)	5.9	6	6.91
(10a)	286 (7.6), 268 (7.3), 228 (28.9)	286 (8.2), 268 (8.3), 235sh (26.4), 225 (29.5)	295 (5.7), 265sh (7.3), 234 (34.9)	6.83	5	7.68, 8.08
(10b)	293 (5.0), 241 (23.9)	293 (4.6), 243 (23.9)	301 (4.3), 239 (30.5)	6.73	3	
(11a)	297 (5.1), 267sh (6.9), 233 (34.7)	315 (6.6), 243 (31.1)	297 (5.1), 267sh (6.1), 234 (34.1)	6.16	4	7.2, 7.5
(11b)	302 (3.8), 240 (28.5)	321 (4.4), 264sh (9.1), 244 (23.5)	301 (4.1), 239 (28.5)	6.17	4	6.63

TABLE 2

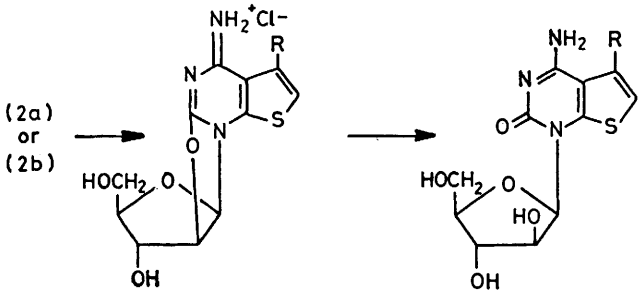
^{1}H N.m.r. spectral data (δ) of 2′,3′-*O*-isopropylidenes of some thieno[2,3-*d*]pyrimidin-2-one 1-ribonucleosides (J/Hz in parentheses)

Compound	Me	ΔδMe	H-1′
(9a)	1.33, 1.53	0.20	5.90 (3)
(9b)	1.26, 1.48	0.22	5.85 (1)

Hence (2a) and (2b) may be unequivocally assigned the structures 4-amino-1-(β-D-ribofuranosyl)thieno[2,3-*d*]pyrimidin-2-one and 4-amino-5-methyl-1-(β-D-ribofuranosyl)thieno[2,3-*d*]pyrimidin-2-one, respectively, and (4a) and (4b) as 1-((β-D-ribofuranosyl)thieno[2,3-*d*]pyrimidine-2,4-dione and 5-methyl-1-(β-D-ribofuranosyl)thieno[2,3-*d*]pyrimidine-2,3-dione, respectively.

We were also interested in preparing the arabinoside of the cytidine series of these thieno[2,3-*d*]pyrimidine nucleosides due to the marked chemotherapeutic activity of cytosine arabinoside.[16] Fusion of (2a) or (2b) with diphenyl carbonate [17] in DMF resulted in extensive decomposition. However, treatment of (2a) or (2b) with 2-acetoxyisobutyryl chloride [18] in acetonitrile at room temperature for 1 h and subsequent treatment of the resulting crude 3′-*O*-acetyl-5′-dioxolanone intermediate with methanolic hydrogen chloride afforded 2,2′-anhydro-1-(β-D-arabinofuranosyl)-4-iminothieno-[2,3-*d*]pyrimidine hydrochloride (10a) or 2,2′-anhydro-

1-(β-D-arabinofuranosyl)-4-imino-5-methylthieno-[2,3-*d*]pyrimidine hydrochloride (10b) in 71 and 63% yields, respectively. The anhydro-bridge of (10a) and (10b) was readily cleaved in each case using 0.3N sodium hydroxide solution to furnish the desired 4-amino-1-(β-D-arabinofuranosyl)thieno[2,3-*d*]pyrimidin-2-one (11a) and 4-amino-5-methyl-1-(β-D-arabinofuranosyl)thieno-[2,3-*d*]pyrimidin-2-one (11b).



EXPERIMENTAL

Melting points were determined with a Thomas-Hoover apparatus. The ^{1}H n.m.r. spectra were obtained on a JEOL C60h spectrometer and an EM-390-MHz spectrometer using sodium 4,4-dimethyl-4-silapentane-1-sulphonate (DSS) as an internal standard, [$^2H_6$]DMSO as solvent, and chemical shifts are expressed in δ from DSS. The u.v. spectra were recorded on a Beckman Acta CIII spectrometer. T.l.c. was run on glass plates coated with 250 μm of SilicAR 7GF (Mallinkrodt). The analytical and physical data for the new compounds are in Table 3.

4-Aminothieno[2,3-d]*pyrimidin-2-one* (1a).—2-Amino-3-cyanothiophen [8] (6.2 g) was thoroughly mixed with urea (12.4 g), and the mixture then heated to 170—180 °C. The mixture melted after 15 min, re-solidified after 45 min, and heating was then continued for an additional 5 min. The solid was ground in a mortar, methanol added, and the solid then filtered off. The pale yellow solid was dried at 50 °C *in vacuo* to yield 6.3 g (75%) of (1a), m.p. 355—356 °C (decomp.).

General Procedure for the Synthesis of Thieno[2,3-d]*pyrimidine Ribonucleosides* [(2a), (2b), (4a), *and* (4b)].—*Method* 1. Silylation of the heterocycles (1a), (3a), and (3b) was carried out by heating the appropriate heterocycle (0.02 mol) in hexamethyldisilazane (80 ml) in the presence of a catalytic amount of $(NH_4)_2SO_4$ at reflux temperature for 5—6 h. The silylation of (1b) was carried out using *NO*-bis(trimethylsilyl)acetamide (10 ml) in 1,2-dichloroethane (30 ml) at room temperature for 3—4 h. The excess of silylating agent was removed by distillation, and the silylated base was dissolved in 1,2-dichloroethane (60 ml). In a separate round-bottom flask (200 ml), 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (10.12 g, 0.02 mol) was dissolved in 1,2-dichloroethane (60 ml), to which stannic chloride (4 ml) was added, and the reaction mixture was stirred at room temperature in a sealed flask for 30 min. This mixture was then added to a solution of the above silylated base in one portion. The flask was sealed, and the solution stirred for 18—20 h at room temperature. In order to avoid the heavy emulsion which is generally formed during the extraction of the reaction mixture with sodium hydrogencarbonate, pyridine (4 ml) was added to complex the excess of stannic chloride. The reaction mixture was stirred for 4 h, and the precipitate which had formed was collected by filtration through a Celite pad. The precipitate was washed with chloroform (2 × 30 ml), and the combined filtrates were then washed successively with saturated sodium hydrogencarbonate solution (2 × 120 ml) and water (2 × 80 ml). The chloroform phase was dried over anhydrous sodium sulphate, the drying agent was removed by filtration, and the chloroform mixture evaporated under reduced pressure to afford a syrup. Attempts to crystallize these blocked nucleosides were unsuccessful. A solution of the blocked nucleoside in methanolic ammonia (methanol saturated with ammonia at 0 °C, 240 ml) was allowed to stand at room temperature for 20 h with occasional shaking. The solution was filtered, and the filtrate evaporated *in vacuo* to yield

TABLE 3

Analytical and physical data for thieno[2,3-*d*]pyrimidine nucleosides

Compound	M.p. (°C)	Yield (purified)(%)	Molecular formula *	Analysis (%) Required C	Required H	Required N	Found C	Found H	Found N
(1a)	355—356	75	$C_6H_5N_3OS$	40.90	3.44	23.88	41.0	3.4	23.85
(2a)	227—228	48	$C_{11}H_{13}N_3O_5S\cdot H_2O$	41.68	4.77	13.26	41.9	4.75	13.5
(2b)	224—225	60	$C_{12}H_{15}N_3O_5S$	45.00	4.83	12.41	44.7	4.8	12.6
(4a)	212—214	30	$C_{11}H_{12}N_2O_6\cdot H_2O$	41.52	4.40	8.81	41.55	4.35	8.8
(4b)	234—235	51	$C_{12}H_{14}N_2O_6S$	45.80	4.49	8.91	46.05	4.7	8.85
(5)	262—263	71	$C_8H_8N_2O_2S$	49.08	4.11	13.28	49.25	4.3	13.35
(7)	340—342 (sublimes)	86	$C_7H_6N_2O_2S$	46.25	3.32	14.38	46.2	3.3	14.6
(8a)	200—201	62	$C_{11}H_{12}N_2O_5S_2\cdot H_2O$	39.53	4.19	8.38	39.8	4.1	8.3
(8b)	178—179	50	$C_{12}H_{14}N_2O_5S_2$	43.64	4.24	8.49	43.5	4.5	8.4
(9a)	180—181	53	$C_{14}H_{17}N_3O_5S\cdot 2H_2O$	44.80	5.68	11.20	44.8	5.65	11.2
(9b)	215—216 (softens at 180)	50	$C_{15}H_{19}N_3O_5S\cdot 0.5H_2O$	49.46	5.49	11.54	49.6	5.5	11.4
(10a)	262—263 (decomp.)	71	$C_{11}H_{12}N_3ClO_4S\cdot H_2O$	39.36	4.17	12.52	39.4	4.15	12.45
(10b)	239—240	63	$C_{12}H_{14}N_3ClO_4S\cdot 0.5H_2O$	42.30	4.41	12.33	42.25	4.5	12.15
(11a)	238	57	$C_{11}H_{13}N_3O_5S\cdot 0.5H_2O$	42.86	4.54	13.63	43.0	4.7	13.3
(11b)	240	48	$C_{12}H_{15}N_3O_5S\cdot 1.5H_2O$	42.36	5.29	12.35	42.65	5.15	12.4

*All analyses containing water were verified by ^{1}H n.m.r. spectroscopy.

a solid material which was collected by filtration. Recrystallization from water (2a) and methanol [(2b, (4a), and (4b)] yielded the pure nucleosides. (See Table 3 for m.p.s and yields.)

4-Amino-1-(β-D-ribofuranosyl)thieno[2,3-d]*pyrimidin-2-one* (2a). *Method* 2. The same general procedure described above was repeated using 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (0.02 mol). The yield of deblocked nucleoside (1a) was 40%.

1-(β-D-Ribofuranosyl)thieno[2,3-d]*pyrimidine-2,4-dione* (4a). *Method* 2. Compound (2a) (100 mg) was dissolved in glacial acetic acid (5 ml) and added dropwise with stirring at −5 to −10 °C to a 5-ml aqueous solution of sodium nitrite (300 mg) and stirred for an additional 2 h. An additional 5-ml of aqueous sodium nitrite (500 mg) solution was added; the reaction was stirred for an additional 16 h, at which time t.l.c. showed only the product. The solution was evaporated to dryness *in vacuo* and the residue was triturated with methanol (25 ml) and the insoluble salts removed by filtration. The methanolic solution was submitted to chromatography and the product eluted from a column of SilicAR CC-7 (2 × 10 cm) with a mixture of $CHCl_3$–MeOH (7 : 3). Fractions containing the product, as determined by t.l.c., were pooled, evaporated to dryness *in vacuo*, and recrystallized from methanol to yield a nucleoside which was identical in m.p., u.v., and n.m.r., to (4a).

5-Methyl-1-(β-D-ribofuranosyl)thieno[2,3-d]*pyrimidine-2,4-dione* (4b). *Method* 2. Compound (4b) was prepared in the same manner as (4a) by treatment of (2b) with sodium nitrite in glacial acetic acid.

1,5-Dimethylthieno[2,3-d]*pyrimidine-2,4-dione* (5). Compound (3b) [8] (1 mmol) and a catalytic amount of ammonium sulphate (2 mg) were suspended in hexamethyldisilazane (10 ml) and refluxed for 4 h. The excess of hexamethyldisilazane was removed *in vacuo* and the residue suspended in dimethylformamide (10 ml) containing methyl iodide (2 ml). The reaction was stirred at ambient temperature for 16 h. Removal of the methyl iodide and dimethylformamide *in vacuo* and treatment of the residue with absolute ethanol (10 ml) furnished crystalline (5). Recrystallization from ethanol furnished an analytical sample (160 mg).

3-Methylthieno[2,3-d]*pyrimidine-2,4-dione* (7).—Methyl isocyanate (6 mmol) and triethylamine (1 ml) were added to a solution of 2-amino-3-ethoxycarbonylthiophen [8] (3 mmol) in dry benzene (20 ml). The solution was refluxed for 15 h. After removal of the solvent *in vacuo*, the resulting residue was mixed with 2 ml of warm ethyl ether and cooled to effect crystallization. The resulting ureido-compound (m.p. 137—138 °C) was combined with sodium methoxide (2 mmol) in methanol (30 ml) and refluxed for 4 h. The solution was cooled, neutralized with Dowex 50 H^+ resin, and then suction-filtered. The resin was washed with warm methanol (25 ml) and the combined filtrates were reduced to dryness *in vacuo* and the resulting residue recrystallized from ethanol.

4-Amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)thieno[2,3-d]*pyrimidin-2-one* (9a).—Compound (2a) (100 mg) was suspended in dry acetone (100 ml), cooled to −5 °C, and 70% perchloric acid (2 drops) was then added. The solution was allowed to warm to room temperature and stirred for an additional 2 h. Solid sodium hydrogencarbonate (2 g) was then added and the stirring continued for 30 min. The solid was collected by filtration, and the residue washed with acetone (20 ml). The combined filtrates were evaporated to dryness *in vacuo* at *ca.* 45 °C and triturated with chloroform (30 ml). The residue was crystallized from water to yield colourless needles of (9a) (60 mg, 53.2%).

4-Amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-5-methylthieno[2,3-d]*pyrimidin-2-one* (9b). Compound (9b) was prepared in the same manner as (9a), by treating (2b) (100 mg) with dry acetone (100 ml) in the presence of perchloric acid (2 drops). This procedure furnished (9b) (56 mg, 50%) as white needles from water.

1-(β-D-Ribofuranosyl)-4-thioxothieno[2,3-d]*pyrimidin-2-one* (8a).—In a stainless steel reaction vessel, compound (3a) (200 mg) in water (3 ml) and pyridine (3 ml) was cooled to −70 °C and liquid H_2S was added to bring the volume to 15 ml. The container was sealed and heated at 40 °C for 110 h. The reaction mixture was evaporated to dryness and triturated with water. The residue was crystallized from water to yield pale yellow needles of (8a) (130 mg, 61.9%).

5-Methyl-1-(β-D-ribofuranosyl)4-thioxothieno[2,3-d]*pyrimidin-2-one* (8b).—Compound (8b) was prepared in the same manner as (8a) by treating (2b) (200 mg) with liquid H_2S, in pyridine (3 ml) (total volume 15 ml). This procedure furnished (8b) (50% yield) as pale yellow needles from methanol.

2,2′-Anhydro-1-(β-D-arabinofuranosyl)-4-iminothieno[2,3-d]*pyrimidine Hydrochloride* (10a). 2-Acetoxyisobutyryl chloride (2.2 ml) was added to (2a) (1 g) in a suspension of acetonitrile (7 ml), and the reaction mixture stirred at room temperature for 1 h. The solvent was largely evaporated, and the residue triturated twice with diethyl ether to give a crude 5′-dioxolanone derivative. This solid was dissolved in 0.2% methanolic hydrogen chloride (120 ml) and stored at room temperature for 3 days before evaporation of the solvent. The residue was crystallized from methanol as white needles of (10a) (750 mg, 71%).

2,2′-Anhydro-1-(β-D-arabinofuranosyl)-5-methyl-4-iminothieno[2,3-d]*pyrimidine Hydrochloride* (10b).—Compound (10b) was prepared in the same manner as (10a) by heating (2b) (750 mg) in acetonitrile (15 ml) with α-acetoxyisobutyryl chloride (2 ml). The procedure furnished (10b) (500 mg, 63%) as white needles from methanol.

4-Amino-1-(β-D-arabinofuranosyl)thieno[2,3-d]*pyrimidin-2-one* (11a).—Compound (10a) (300 mg) was treated with sodium hydroxide solution (1 ml of 1N diluted to 3 ml), and the reaction mixture stirred for 1 h. The solution became clear; the precipitate which then appeared was collected by filtration and recrystallized from water to furnish colourless needles of (11a) (160 mg, 57%).

4-Amino-1-(β-D-arabinofuranosyl)-5-methylthieno[2,3-d]*pyrimidin-2-one* (11b).—Compound (11b) was prepared in the same manner as (11a) by treating (10b) (330 mg) with sodium hydroxide solution (1 ml of 1N diluted to 3 ml). This procedure furnished (11b) (150 mg 48% yield) as needles on recrystallization from water.

This investigation was supported by the National Cancer Institute, Department of Health, Education and Welfare.

[9/977 *Received*, 25*th June*, 1979]

REFERENCES

[1] H. S. Forrest, D. Hatfield, and J. M. Lagowski, *J. Chem. Soc.*, 1961, 963; R. Lohrmann, J. M. Lagowski, and H. S. Forrest, *J. Chem. Soc.*, 1964, 451.

[2] A. R. Davis, E. B. Newton, and S. R. Benedict, *J. Biol. Chem.*, 1922, **54**, 595; R. Falconer, and J. M. Gulland, *J. Chem. Soc.*, 1939, 1369; and more recently M. M. Jezewska, B. Gorzkowski, and T. Sawicka, *Acta Biochim. Polon.*, 1967, **14**, 71.

[3] T. A. Krenitsky, G. B. Elion, R. A. Strelitz, and G. H. Hitchings, *J. Biol. Chem.*, 1967, **242**, 2675.
[4] T. D. Beardmore and W. N. Kelley, *J. Lab. Clin. Med.*, 1971, **78**, 696.
[5] C. L. Schmidt and L. B. Townsend, *J. Heterocyclic Chem.*, 1973, **10**, 687; C. L. Schmidt and L. B. Townsend, *J.C.S. Perkin I*, 1975, 1257; C. L. Schmidt and L. B. Townsend, *J. Org. Chem.*, 1975, **40**, 2476.
[6] V. D. Patil, D. S. Wise, L. B. Townsend, and A. Bloch, *J. Medicin. Chem.*, 1974, **17**, 1282.
[7] K. Gewald, *Chem. Ber.*, 1965, **98**, 3571.
[8] A. A. Chacke, University of North Carolina, Dissertation, 1965 (*Diss. Abs.*, 1965, **26**, 7).
[9] A. Niedballa and H. Vorbruggen, *J. Org. Chem.*, 1974, **39**, 3654, and references cited therein.
[10] R. A. Long and L. B. Townsend, *Chem. Comm.*, 1970, 1087.
[11] H. Vorbruggen, P. Strehlke, and G. Schulz, *Angew. Chem. Internat. Edn.*, 1969, **8**, 976.
[12] T. Ueda, K. Miura, M. Imazawa, and K. Odajima, *Chem. Pharm. Bull.* (*Tokyo*), 1974, **22**, 2377.
[13] L. B. Townsend in 'Synthetic Procedures in Nucleic Acid Chemistry,' vol. II, eds. W. Werner Zorbach and R. Stuart Tipson, Interscience, New York, N.Y., 1973, pp. 267—370.
[14] R. U. Lemieux, *Ann. Rev. Biochem.*, 1963, **32**, 155.
[15] J. L. Imbach, J. L. Barascut, B. K. Kam, and C. Tapiero, *Tetrahedron Letters*, 1974, 129.
[16] G. D. Gray, *Ann. New York Acad. Sci.*, 1975, **255**, 372.
[17] A. Hampton and A. W. Nichol, *Biochemistry*, 1966, **5**, 2076.
[18] A. F. Russell, M. Prystasz, E. K. Hamamura, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, 1974, **39**, 2182.