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Pyrido[2,3-*d*]pyrimidines. II. Synthesis of Ribonucleosides of 4-Oxo- and 2,4-Dioxopyrido[2,3-*d*]pyrimidines[1]

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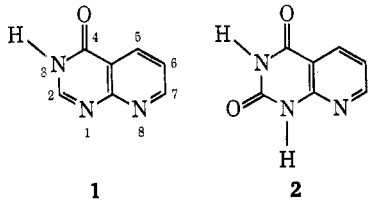
The syntheses of 1-β-D-ribofuranosyl-4-oxopyrido[2,3-*d*]pyrimidine and 1- and 8-β-D-ribofuranosyl-2,4-dioxopyrido[2,3-*d*]pyrimidine are described. The site of ribosylation in each case is assigned by uv and pmr comparisons with requisite *N*-methyl model compounds. The assignment of anomeric configuration is based upon pmr spectroscopy. A facile N-8 → N-1 ribosyl rearrangement is described.

Significant antitumor activity against Walker muscular carcinosarcoma in rats has recently been demonstrated for 4-oxopyrido[2,3-*d*]pyrimidine[2] (**1**, NSC 112518) and 2,4-dioxopyrido[2,3-*d*]pyrimidine[2] (**2**, NSC 112519). It was, therefore, of interest to undertake the synthesis of certain ribonucleoside derivatives of **1** and **2** as potential antitumor and antiviral agents.



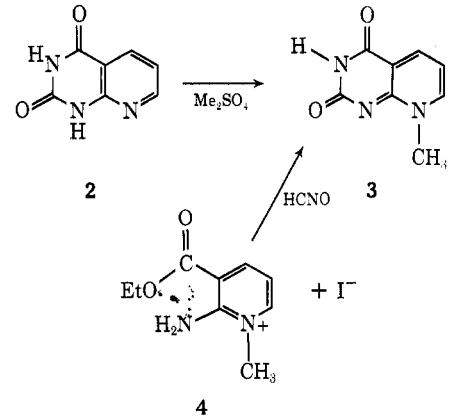
1 **2**

Despite the extensive literature describing the synthesis of pyrido[2,3-*d*]pyrimidines,[3] there are no reported examples of nucleosides of this ring system. Ribonucleosides of the related quinazoline ring system have been previously reported.[4]

There are three possible sites of N-alkylation on the pyrido[2,3-*d*]pyrimidine nucleus, namely, positions 1, 3, and 8. In a study involving the chemical synthesis of nucleosides of **1** and **2**, therefore, it was necessary to obtain model compounds in order to ascertain the position of N-ribosylation. *N*-Methyl derivatives, which have been widely used as models in the proof of site of substitution of the sugar moiety of nucleosides,[5] were chosen as the appropriate model compounds. The synthesis of ribonucleosides of **1** and **2** and the necessary *N*-methyl model compounds comprises the basis for this report.

Results and Discussion

***N*-Methyl Model Compounds.**—As noted above, three sites of N-alkylation are possible for both **1** and **2**. It was necessary, therefore, to synthesize two *N*-methyl isomers of each in order to unambiguously determine the site of N-ribosylation by physical methods. Examination of the structure of 2,4-dioxopyrido[2,3-*d*]pyrimidine (**2**) suggested that alkylation in neutral aprotic media should result in selective alkylation at N-8, since N-1 and N-3 are amide-type nitrogens –CONH– which already bear a proton. Methylation of **2** with dimethyl



2 **3**

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(1) (a) Paper I in this series: J. L. Shim, R. Niess, and A. D. Broom, *J. Org. Chem.*, **37**, 578 (1972). (b) Supported by Research Grant T491 from American Cancer Society, Research Grant CA 12823 from the National Cancer Institute, NIH, and Training Grant CA 5209 from the National Cancer Institute, NIH.

(2) R. K. Robins and G. H. Hitchings, *J. Amer. Chem. Soc.*, **77**, 2267 (1955).

(3) For a recent review, see W. J. Irwin and D. B. Wibberley, *Advan. Heterocycl. Chem.*, **10**, 149 (1969).

(4) (a) M. G. Stout and R. K. Robins, *J. Org. Chem.*, **33**, 1219 (1968); (b) M. G. Stout and R. K. Robins, *J. Heterocycl. Chem.*, **6**, 89 (1969).

(5) A. M. Michelson, "The Chemistry of Nucleosides and Nucleotides," Academic Press, New York, N. Y., 1963.

TABLE I

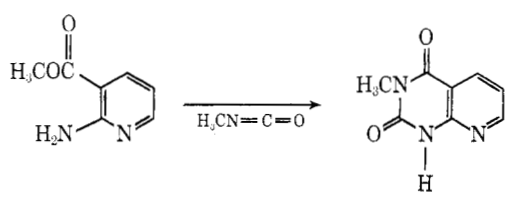
PROTON MAGNETIC RESONANCE FREQUENCIES (δ) FOR VARIOUS PYRIDO[2,3-*d*]PYRIMIDINE DERIVATIVES

Compd no.	Solvent	C-2 H	C-5 H	C-6 H	C-7 H	N-3 CH_3	N-8 CH_3	C-1′ H
1	DMSO-d_6	8.22 (s)	8.40 (d of d)	7.45 (q)	8.83 (d of d)			
2	DMSO-d_6		8.17 (d of d)	8.17 (q)	8.50 (d of d)			
2	A[a]		8.00 (d of d)	6.91 (q)	8.25 (d of d)			
3	A[a]		8.23 (d of d)	6.97 (t)	8.37 (d of d)		3.76 (s)	
5	DMSO-d_6		8.01 (d of d)	7.01 (q)	8.40 (d of d)	3.20 (s)		
5	A[a]		8.00 (d of d)	6.83 (q)	8.33 (d of d)	3.30 (s)		
6	DMSO-d_6	8.50 (s)	8.36 (m)	7.46 (q)	8.86 (d of d)	3.50 (s)		
7	DMSO-d_6	8.20 (s)	8.57 (d)	7.32 (t)	8.70 (d)		4.05 (s)	
10	DMSO-d_6		8.25 (d of d)	7.26 (m)	8.55 (d of d)			6.56 (d), $J_{1',2'}$ = 3.5 Hz
12	DMSO-d_6	8.41 (s)	8.41 (d of d)	7.46 (q)	8.83 (m)			6.03 (d), $J_{1',2'}$ = 3 Hz
14	DMSO-d_6		8.31 (d of d)	6.93 (t)	8.88 (d of d)			6.38 (s)
14	A[a]		8.21 (d of d)	6.86 (t)	8.45 (d of d)			6.30 (s)

[a] A, mixture of D_2O–DMSO-d_6 (75:25). All other spectra were run in DMSO-d_6 solution; DSS as internal reference. All spectra were obtained on a 60-MHz Jeol nmr instrument; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

sulfate in anhydrous dimethylformamide indeed gave the expected 8-methyl derivative **3**. Compound **3** was established as the 8-methyl derivative by an unambiguous synthetic procedure. Methylation of ethyl 2-aminonicotinate[6] according to Hirai[7] gave 2-amino-3-carbethoxy-1-methylpyridinium iodide (**4**). Condensation of **4** with cyanic acid gave **3**. The uv and pmr spectra of **3** prepared by either route were superimposable.

The synthesis of 3-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidine (**5**) had been previously reported by Capuano, *et al.*[8] Attempts to repeat this procedure resulted only in the recovery of starting material; the product described as melting at 226° was not obtained. However, when methyl 2-aminonicotinate was refluxed with methyl isocyanate in pyridine, a 76% yield of the desired product **5** having a melting point of 274–275°



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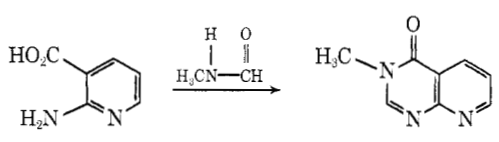
was obtained. This product gave the correct elemental analysis for **5**; the pmr spectrum showed a singlet (three protons) at δ 3.2 corresponding to the *N*-methyl group at position 3.

A somewhat similar procedure involving a high-temperature condensation of 2-aminonicotinic acid with *N*-methylformamide afforded 3-methyl-4-oxopyrido-[2,3-*d*]pyrimidine (**6**).



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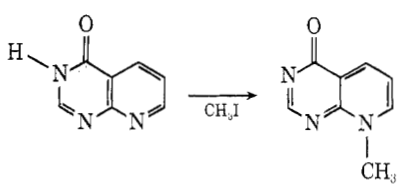
Methylation of 4-oxopyrido[2,3-*d*]pyrimidine (**1**) with methyl iodide in dimethyl sulfoxide gave only the 8-methyl derivative **7** in 57% yield plus starting material. This demonstrated that the most nucleophilic center in **1**



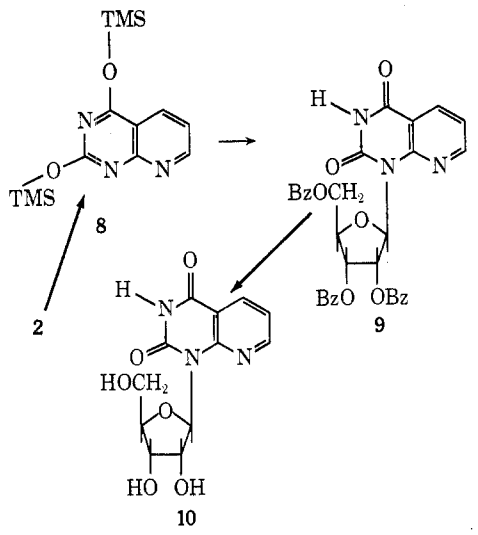
1 **7**

is N-8, at least under the conditions employed in this alkylation reaction. The assignment of the site of alkylation as N-8 rather than N-1 was based on pmr spectroscopy. It is known that N-methylation of pyridine[9] and also fused ring systems containing a pyridine ring[10] causes downfield shifts of the pyridine ring γ-position proton signals and either upfield or downfield shifts of the α-proton signals (the "α effect").[10b] Examination of the data in Table I reveals that the signal for the C-5 H (pyridine ring γ position) of **7** appears 0.17 ppm *downfield* from the corresponding signal in **1** and the C-7 H signal occurs 0.13 ppm upfield relative to that of **1**. In the case of 3-methyl-4-oxopyrido[2,3-*d*]pyrimidine (**6**) and 1-ribosyl derivative (*vide infra*), a pronounced downfield shift of the C-2 proton resonance was observed, as expected,[11] but there was essentially no change in the chemical shift of the pyridine ring proton resonances (C-5, C-6, C-7, Table I) relative to the parent compound **1**.

Nucleosides.—The use of trimethylsilyl derivatives of nitrogen heterocycles in nucleoside syntheses[12,13] circumvents difficulties associated with the low solubility and high melting point of the pyrido[2,3-*d*]pyrimidines used in this work. The present study required the attachment of a β-D-ribofuranosyl moiety to position 1 of 2,4-dioxopyrido[2,3-*d*]pyrimidine (**2**). Trimethylsilylation of **2** with hexamethyldisilazane gave 2,4-bis(trimethylsilyloxy)pyrido[2,3-*d*]pyrimidine (**8**). Integration of the pmr spectrum of **8** indicated the presence of six Si-CH_3 groups. Treatment of **8** with freshly prepared 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in dry acetonitrile gave a complex mixture from which 2,4-dioxo-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-

(6) H. H. Fox, *J. Org. Chem.*, **17**, 547 (1952).
(7) H. Hirai, *Chem. Pharm. Bull.*, **14**, 861 (1966).
(8) L. Capuano, M. Welter, and R. Zander, *Chem. Ber.*, **102**, 3698 (1969).
(9) R. J. Chuck and E. W. Randal, *J. Chem. Soc. B*, 261 (1967).
(10) (a) D. J. Blears and S. S. Danyluk, *Tetrahedron*, **23**, 2927 (1967); (b) J. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1969, p 82.
(11) A. D. Broom and R. K. Robins, *J. Org. Chem.*, **24**, 1025 (1969).
(12) M. W. Winkley and R. K. Robins, *ibid.*, **33**, 2822 (1968).
(13) L. Birkhofer, A. Ritter, and H. P. Keuhltan, *Angew. Chem.*, **75**, 209 (1963).

pyrido[2,3-*d*]pyrimidine (**9**) was isolated by a chromatographic procedure. Treatment of **9** with methanolic sodium methoxide gave 2,4-dioxo-1-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (**10**). The pre-

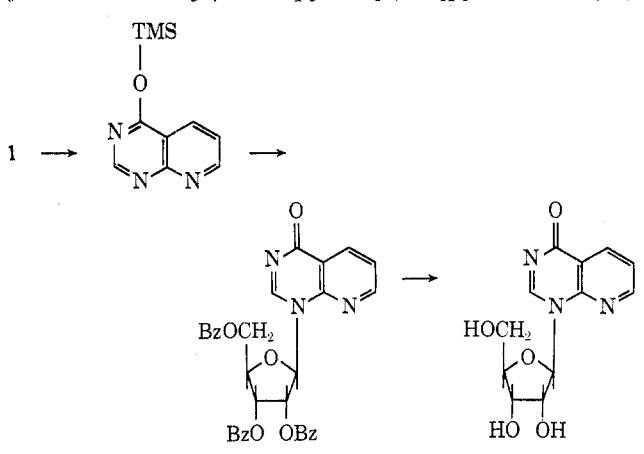


TMS = trimethylsilyl, Bz = benzoyl

dominate formation of the β anomer would be expected on the basis of previous studies in the quinazoline series[4] and of Baker's "trans rule."[14] The configurational assignment of **10** was supported by the small coupling constant of the anomeric proton ($J_{1',2'}$ = 3.5 Hz).[15]

Assignment of the site of ribosylation was made by uv comparisons with the *N*-methyl model compounds previously described. The uv spectra of 2,4-dioxo-3-methylpyrido[2,3-*d*]pyrimidine (**5**) were quite similar to those of **2** at pH 1 and 7 (Table II). At pH 11, however, a 23-nm bathochromic shift in the long wavelength absorption maximum of **5** relative to **2** was observed. Since the monoanion of each was present in this alkaline medium, this established N-3 H in compound **2** as the more acidic proton. The uv spectrum of **10** at pH 11 was dissimilar to those of **5**, **3**, and the 8-(β-D-ribofuranosyl) derivative **14** (*vide infra*), but quite similar to that of **2** (Table II). This firmly established that **10** is, in fact, the N-1-substituted nucleoside.

A similar procedure was used for the synthesis of 1-(β-D-ribofuranosyl)-4-oxopyrido[2,3-*d*]pyrimidine (**12**).



(14) B. R. Baker, *et al.*, *J. Org. Chem.*, **19**, 1786 (1954).

(15) R. U. Lemieux and D. R. Lineback, *Annu. Rev. Biochem.*, **32**, 155 (1963).

TABLE II

ULTRAVIOLET ABSORPTION DATA FOR VARIOUS PYRIDO[2,3-*d*]PYRIMIDINE DERIVATIVES

Compd no.	pH 1 λ_{max}, nm	pH 1 ϵ_{max}	pH 7 λ_{max}, nm	pH 7 ϵ_{max}	pH 11 λ_{max}, nm	pH 11 ϵ_{max}
1	270	4200	270	4,200	280	4,200
	317	7950	317	4,200	323	7,400
2	305	8000	306	8,050	263	9,150
					310	8,950
3[a]	237	5850	237	6,300	257	10,100
	311	9700	271	11,400	356.5	8,150
			353	8,500		
5	305	6700	304	6,750	265	11,200
					333	5,150
6	270	3950	270	5,600	270	6,150
	278	3850	299	6,350	290	6,850
	320	8200	309 (s)	4,500	309 (s)	4,900
7	220	9500	247	7,200	246	8,600
	277	3300	285	1,750	284 (s)	1,750
	328	9650	360	7,750	361	8,600
10	301	6800	301	6,800	235	13,200
					261.5	3,850
					305	7,500
12	245 (s)	5500	263	5,550	269	6,100
	317	5300	300	5,000	300	5,000
			313	3,600	313	3,800
14[a]	237	6450	272	16,200	258	10,100
	306	7750	356.5	13,500	359	7,500

[a] Acidic spectra were obtained in 1*N* HCl, pH ~0.

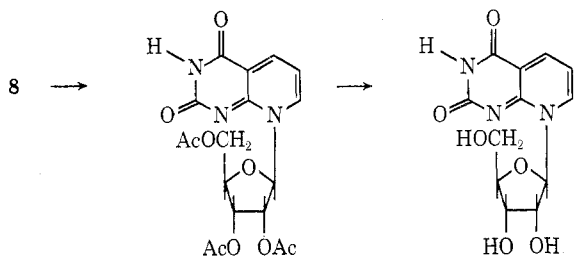
Assignment of position of ribosylation in **12** was based on uv and pmr spectrometry. The uv spectrum of **12** at pH 11 (Table II) was unlike those of 3-methyl-4-oxopyrido[2,3-*d*]pyrimidine (**6**) and the 8-methyl derivative (**7**). This confirms that **12** is the 1-ribosyl derivative. This assignment is further supported by the pmr data (Table I). As previously noted (*vide supra*) ribosylation at N-1 or methylation at N-3 leads to a downfield shift of the H-2 resonance, and alkylation at N-8 markedly alters the pyridine proton signals without changing the signal for H-2. Examination of the pmr data reveal that the spectrum of **12** is similar to that of 3-methyl-4-oxopyrido[2,3-*d*]pyrimidine (**6**) and totally unlike that of the 8-methyl derivative **7**, Since the uv data clearly eliminated 3-ribosylation, the assignment of **12** as a 1-substituted nucleoside is confirmed. A small coupling constant for the anomeric proton ($J_{1',2'}$ = 3.0 Hz) again permitted assignment of the β configuration.[15]

It was previously noted that methylation of compounds **1** and **2** in nonaqueous, essentially neutral media occurred at the most nucleophilic nonprotonated site (the N-8 position). Ribosylation of **1** and **2** under similar conditions gave, on the other hand, the 1-ribosyl derivatives. This result may be explained on the basis that bromo sugars usually contain HBr carried along in the isolation procedure. Furthermore, they are unstable, giving HBr on decomposition. The presence of HBr in solution with either **1** or **2** would result in N-protonation at position 8, thus directing alkylation with the sugar to the pyrimidine ring.

The synthesis of the 8-ribosyl derivative of **2** was achieved only by using the condensation procedure of Furukawa and Honjo.[16] A solution of **8** in dry chlorobenzene was treated with tetra-*O*-acetyl-β-D-ribofura-

(16) Y. Furukawa and M. Honjo, *Chem. Pharm. Bull.*, **16**, 1076 (1968).

nose and anhydrous aluminum chloride at room temperature to give the 8-ribosyl derivative **13**. Deblocking with methanolic ammonia gave 2,4-dioxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (**14**).



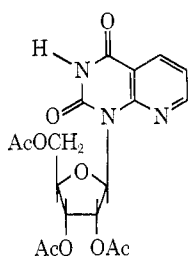
13 **14**

Ac = −COCH$_3$

Assignment of the position of alkylation with the sugar in **14** as N-8 was based on the close similarity between the uv spectra of **14** and of 2,4-dioxo-8-methylpyrido[2,3-*d*]pyrimidine (**3**) at pH 0, 7, and 11.[17]

Further confirmation of 8-ribosylation in **14** was obtained from the pmr data (Table I). As noted earlier, the pmr signal of H-5 is the most sensitive to N-8 substitution. The signals for H-5 of both the 8-methyl (**3**) and 8-ribosyl (**14**) derivatives appear 0.2 ppm downfield from those of the parent compound **2** and the 3-methyl derivative (**5**). The β configuration was confirmed by the observation that the signal for the anomeric proton appeared as a rather broad singlet ($J_{1',2'}$ < 1 Hz).[15,18]

Alteration of the reaction conditions for the preparation of **13** by adding dropwise a solution of tetra-*O*-acetyl-D-ribofuranose in chlorobenzene to a hot mixture of **8** and $AlCl_3$ in chlorobenzene gave mainly the 1-ribosyl derivative (**15**). This may be explained by



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assuming that **15** is the more thermodynamically stable product and that a facile rearrangement from N-8 to N-1 may be taking place at the higher temperature. This was confirmed by heating for 3 min a mixture of **13**, $AlCl_3$, and chlorobenzene. A rapid rearrangement occurred to give only **15** as judged by thin layer chromatography. Analogous N-3 → N-9 alkyl and glycosyl migrations have been described for purine derivatives.[19,20]

It is of interest that, while application of the $AlCl_3$ procedure[16] for nucleoside synthesis from **2** gave the desired **13**, this and every other procedure attempted with 4-oxopyrido[2,3-*d*]pyrimidine (**1**) gave mostly the 1-ribosyl derivatives; none of the 8-ribosyl isomer was formed in any case. This may well be attributed to an extremely facile rearrangement of an 8-ribosyl to a 1-ribosyl derivative in this case. This argument receives support from the finding that, in the case of 4-oxoquinazoline, which lacks the pyridine nitrogen at N-8,[4] and 6-methylpyrimidines,[12] alkylation is directed to N-3 rather than N-1.

Experimental Section

2,4-Dioxo-8-methylpyrido[2,3-*d*]pyrimidine (3). Method A.—To a suspension of 800 mg of **2**[2] (6.12 mmol) in 25 ml of *N*,*N*-dimethylformamide was added 2.0 ml of dimethyl sulfate. The reaction mixture was heated on a steam bath for 24 hr. The clear dark red solution was poured into 600 ml of methylene chloride with continuous stirring. The yellow precipitate was filtered and washed with methylene chloride. The precipitate was suspended in acetone and neutralized with concentrated aqueous ammonium hydroxide. The precipitate was filtered, dissolved in 25 ml of boiling water, and kept at 5° for crystallization. The yellow fine powder was filtered, washed with a little cold water, and air-dried to give 550 mg (48.9%), mp >360°. *Anal.* Calcd for $C_8H_7N_3O_2$: C, 54.25; H, 3.96; N, 23.74. Found: C, 54.53; H, 4.31; N, 23.91.

Method B.—2-Amino-3-carboxyethyl-*N*-methylpyridinium iodide[7] (301 mg, 1.0 mmol) was dissolved in 15 ml of ethanol. Potassium cyanate (160 mg, 2.20 mmol) and 2.0 ml of glacial acetic acid were added, and refluxing was continued for a total of 24 hr. The precipitate was filtered, washed with ethanol, and air-dried. The solid was crystallized from water to yield 120 mg (68.5%), mp >360°. Uv and pmr spectra were identical with those of the compound prepared by method A.

2,4-Dioxo-3-methylpyrido[2,3-*d*]pyrimidine (5). Method A.—Methyl 2-aminonicotinate (1.0 g, 6.6 mmol) was dissolved in 25 ml of pyridine. Methyl isocyanate (1.0 ml) was added, and the mixture was refluxed for 16 hr. The dark red solution was evaporated to dryness. The residue was refluxed with 40.0 ml of ethanol, and the precipitate was filtered. The precipitate was crystallized from 30 ml of a methanol–H_2O mixture to yield 0.9 g (76%), mp 274–275°. A sample was dried *in vacuo* over refluxing toluene for elemental analysis. *Anal.* Calcd for $C_8H_7N_3O_2 \cdot 0.5H_2O$: C, 51.60; H, 4.31; N, 22.65. Found: C, 51.70; H, 4.31; N, 22.99.

Method B.—2,4-Dioxopyrido[2,3-*d*]pyrimidine (1.0 g, 6.2 mmol) was dissolved in 100 ml of 1 *N* aqueous NaOH. Dimethyl sulfate (882 mg, 7 mmol) was added, and the mixture was stirred at room temperature for 4 hr. Another 882-mg portion of dimethyl sulfate was added. The mixture was stirred overnight. The solution was acidified with glacial acetic acid to pH 5 and filtered. A yellow precipitate formed upon concentrating the filtrate to 60 ml. The precipitate was filtered, washed with little cold water, and crystallized from water to yield 160 mg (15%), mp 274–275°. A mixture melting point was not depressed.

3-Methyl-4-oxopyrido[2,3-*d*]pyrimidine (6).—2-Aminonicotinic acid (1.0 g, 7.25 mmol) and 2 g of *N*-methylformamide (33.6 mmol) were heated together at an oil bath temperature of 180° for 5 hr. The solution solidified on cooling, and the product was recrystallized from ethanol. The small needles were filtered, washed with a little cold ethanol, and air-dried to yield 600 mg (51.2%), mp 204–205°. *Anal.* Calcd for $C_8H_7N_3O$: C, 59.60; H, 4.35; N, 26.10. Found: C, 59.65; H, 4.64; N, 26.21.

8-Methyl-4-oxopyrido[2,3-*d*]pyrimidine (7).—To a solution of 800 mg of 4-oxopyrido[2,3-*d*]pyrimidine (5.45 mmol) dissolved in 25 ml of dry dimethyl sulfoxide was added 2.0 ml of methyl iodide. The solution was stirred at room temperature for 36 hr

(17) (a) Whereas compound **14** showed a λ_{max} at 359 nm at pH 1 or 7, the λ_{max} of **3** shifted from 353 to 311 nm upon changing the pH from 7 to 1. This difference at pH 1 was apparently due to the difference in pK_a of **3** *vs.* **14** created by the electron-withdrawing effect of the ribosyl group relative to a methyl group. By comparison with a methyl substituent, a ribosyl moiety has a net electron-withdrawing (−*I*) effect. This is demonstrable by a comparison of the greater basiciy of 9- methylhypoxanthine (pK_a = 1.86) relative to inosine (pK_a = 1.2). Adjustment of solutions of **3** and **14** to pH of about 0 resulted in the disappearance of the absorption at 350–360 nm with the concomitant appearance of a peak at 306 nm for **14** and 311 nm for **3**, supporting the assignment of N-8 substitution in **14**. (b) A. R. Katritzky, "Physical Methods in Heterocyclic Chemistry," Vol. I, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, p 100.

(18) Coupling constants of 1.0 Hz or less are unusual in the β-D-ribofuranoside series, but by no means unprecedented. See, for example, R. J. Rousseau, R. K. Robins, and L. B. Townsend, *J. Heterocycl. Chem.*, **4**, 311 (1967).

(19) M. Miyaki and B. Shimizu, *Chem. Pharm. Bull.*, **18**, 732 (1970).

(20) B. Shimizu and M. Miyaki, *ibid.*, **18**, 579 (1970).

in a stoppered flask. The dark red solution was poured into 700 ml of methylene chloride with continuous stirring. The yellow precipitate was filtered and air-dried. The precipitate was dissolved in water and neutralized with concentrated ammonium hydroxide solution to pH 7.0. Acetone was added and the clear solution was kept at 5° for crystallization. The long yellow crystals were filtered, washed with acetone, and dried to yield 650 mg (57%), mp 253–254° dec. *Anal.* Calcd for $C_8H_7N_3O$: C, 59.60; H, 4.35; N, 26.10. Found: C, 59.49; H, 4.62; N, 26.41.

General Method for the Preparation of the Trimethylsilyl Derivatives of 2,4-Dioxo- and 4-Oxopyrido[2,3-*d*]pyrimidine.—The appropriate pyrido[2,3-*d*]pyrimidine was dried by refluxing in toluene (Dean-Stark water trap), and the mixture was cooled. A few crystals of ammonium sulfate and 2.0 ml of hexamethyldisilazane for every 1 g of base were added. The mixture was refluxed for 24 hr, the solution was filtered, and the filtrate was evaporated to near dryness under reduced pressure. The residue was distilled *in vacuo* at oil bath temperature of 160–170°. The solidified distillate was collected and stored in a stoppered flask in the refrigerator for use.

2,4-Dioxo-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (9).—To a solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (obtained from 47 g of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-ribofuranose and 40 g of dry hydrobromic acid)[21] in 500 ml of dry acetonitrile, 17.0 g of molecular sieves (4A, 1/16-in. pellets) and 26.2 g of 2,4-bis(trimethylsilyloxy)pyrido[2,3-*d*]pyrimidine (85.0 mmol) were added. The flask was stoppered, and the mixture was stirred for 72 hr. The mixture was filtered, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 130 ml of ethanol and 40 ml of water and heated to reflux for 5 min. The solution was evaporated to dryness. The solid residue was triturated with 300 ml of chloroform for 2 days. The chloroform solution was filtered and evaporated to dryness to give 40 g of solid. A 5-g sample of this solid residue was dissolved in 10 ml of chloroform and applied to a column of silicAR 7 G (1 m in length and 10 cm in diameter, holding 2 lb of silicAR 7 G). The column was eluted with chloroform. The first 1300 ml of elute was discarded. The next 400 ml contained a mixture of two compounds. A third fraction (200 ml) contained only the desired compound. This fraction was evaporated to dryness, and the oily residue was crystallized from benzene–cyclohexane to yield 0.8 g (15%), mp 114°. *Anal.* Calcd for $C_{33}H_{25}N_3O_9$: C, 65.12; H, 4.12; N, 6.93. Found: C, 64.93; H, 4.28; N, 6.75.

2,4-Dioxo-1-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (10).—A 0.4-g sample of **9** was dissolved in 30 ml of methanol saturated with ammonia at 0°. The flask was sealed and kept at room temperature overnight. The solution was evaporated under reduced pressure, and the residue was crystallized from methanol to yield 150 mg (75%), mp 193–194°. *Anal.* Calcd for $C_{12}H_{13}N_3O_6$: C, 48.90; H, 4.42; N, 14.25. Found: C, 48.75; H, 4.52; N, 14.12.

4-Oxo-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (11).—To the 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide obtained from 11.5 g of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose[21] in 120 ml of dry acetonitrile, 4.9 g of 4-trimethylsilyloxypyrido[2,3-*d*]pyrimidine (22.4 mmol) suspended in 15.0 ml of acetonitrile was added with stirring. Stirring was continued overnight. The clear solution was evaporated to dryness, and the solid was dissolved in 75 ml of boiling ethanol. Distilled water (20 ml) was added, and the solution was cooled to room temperature over 4 hr and filtered to give 6.6 g, mp 190–194°. Crystallization several times from a benzene–cyclohexane mixture gave a product of mp 194–195°. *Anal.* Calcd for $C_{33}H_{25}N_3O_8$: C, 67.00; H, 4.26; N, 7.10. Found: C, 67.61; H, 4.36; N, 7.22.

4-Oxo-1-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (12).—To a solution of 0.108 g of sodium methoxide in 25 ml of methanol was added 500 mg of **11**. The solid was dissolved by heating on a steam bath. The solution was left at room temperature overnight. The solvent was removed *in vacuo*, and the powder was extracted with ether and filtered. The residue was dissolved in methanol and Amberlite 120 (prewashed with methanol) added with stirring until the solution was neutral. The mixture was filtered and the filtrate was concentrated and kept at 5° overnight. The precipitate was filtered, washed with cold methanol, and air-dried to yield 0.200 g (85.5%), mp 174°. A sample was recrystallized from an isopropyl alcohol–water mixture. The crystals were dried *in vacuo*. *Anal.* Calcd for $C_{12}H_{13}N_3O_5 \cdot 0.5H_2O$: C, 50.00; H, 4.87; N, 14.6. Found: C, 49.99; H, 4.77; N, 14.53.

2,4-Dioxo-8-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (13).—2,4-Bistrimethylsilyloxypyrido[2,3-*d*]pyrimidine (3.75 g, 12.2 mmol), prepared by the general method, was added to 250 ml of dry chlorobenzene. The mixture was stirred for 3 min and 3.05 g of tetra *O*-acetyl-β-D-ribofuranose (9.6 mmol) was added. Anhydrous aluminum chloride (1.63 g, 11.2 mmol) was added gradually, and the mixture was cooled in an ice bath and neutralized with methanolic ammonia to apparent pH 7.0 (pHydrion paper). The mixture was filtered and the precipitate triturated well with 800 ml of $CHCl_3$ and filtered. The combined filtrate was evaporated under reduced pressure to a syrupy residue. The residue was dissolved in 2.0 l. of boiling diethyl ether. The solution was filtered, concentrated to 300 ml, and kept overnight. The fine yellow powder was filtered, washed with ether, and recrystallized from ethyl acetate to yield 1.20 g (30.3%), mp 99–100°. *Anal.* Calcd for $C_{18}H_{19}N_3O_9 \cdot 0.5H_2O$: C, 50.20; H, 4.66; N 9.78. Found: C, 50.45; H, 4.71; N, 9.49.

2,4-Dioxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (14).—Compound **13** (150 mg, 0.38 mmol) was dissolved in 25 ml of methanol saturated with ammonia at 0°. The flask was sealed and left at room temperature overnight. The crystals were filtered and washed with little cold methanol to yield 75 mg. Another crop was obtained from the filtrate by evaporation to dryness under reduced pressure and crystallization from a minimum volume of methanol. The precipitate was filtered to yield 90 mg (combined yield 82%), mp 235° dec. *Anal.* Calcd for $C_{12}H_{13}N_3O_6 \cdot H_2O$: C, 46.00; H, 4.80; N, 13.22. Found: C, 46.05; H, 4.75; N, 13.53.

Registry No.—**1**, 24410-19-3; **2**, 21038-66-4; **3**, 36259-09-3; **5**, 24541-54-6; **6**, 36259-11-7; **7**, 36259-12-8; **9**, 36259-13-9; **10**, 36259-14-0; **11**, 36259-15-1; **12**, 36259-16-2; **13**, 36208-02-3; **14**, 36208-03-4.

(21) W. W. Zorbach and R. S. Tipson, "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, Wiley-Interscience, New York, N. Y., 1968, p 161.