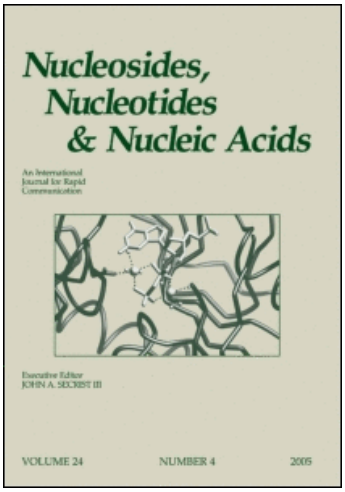


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Nucleosides. 127. Synthesis of Pyrido[2,3-d]pyrimidine Nucleosides from 5-Cyanouridine

Tsann-Long Su[a]; Kazuho Harada[a]; Kyoichi A. Watanabe[b]
[a] Laboratory of Organic Chemistry, Sloan-Kettering Institute, [b] Sloan-Kettering Division of the Graduate School of Medical Sciences, Cornell University, New York, NY

To cite this Article Su, Tsann-Long , Harada, Kazuho and Watanabe, Kyoichi A.(1984) 'Nucleosides. 127. Synthesis of Pyrido[2,3-d]pyrimidine Nucleosides from 5-Cyanouridine', Nucleosides, Nucleotides and Nucleic Acids, 3: 5, 513 — 524
To link to this Article: DOI: 10.1080/07328318408081286
URL: http://dx.doi.org/10.1080/07328318408081286

NUCLEOSIDES & NUCLEOTIDES, 3(5), 513-524 (1984)

NUCLEOSIDES. 127. SYNTHESIS OF PYRIDO[2,3-d]PYRIMIDINE NUCLEOSIDES FROM 5-CYANOURIDINE[1]

Tsann-Long Su, Kazuho Harada and Kyoichi A. Watanabe*

Laboratory of Organic Chemistry, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Division of the Graduate School of Medical Sciences, Cornell University, New York, NY 10021

Abstract. 7-Amino-6-substituted-1-(β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-diones were prepared in good yields from 5-cyanouridine by application of a novel ring transformation reaction recently developed in our laboratory. Treatment of 3-benzyloxymethyl-2',3'-O-isopropylidene-5'-O-trityl-5-cyanouridine with malononitrile, cyanoacetamide or ethyl cyanoacetate in base gave directly the pyridopyrimidine nucleosides bearing a CN, $CONH_2$ and CO_2Et at C-6, respectively. The benzyloxymethyl and trityl protecting groups were removed by hydrogenolysis and the isopropylidene group by acid hydrolysis.

The pyrido[2,3-d]pyrimidine ring system is found in a number of biologically active compounds.[2-8] However, only three publications have appeared for the synthesis of nucleoside derivatives containing this heterocyclic ring system. Thus, Broom et al.[9] first reported the synthesis of 1-ribofuranosylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 8-ribofuranosylpyrido[2,3-d]pyrimidine-2,4(3H,8H)-dione by condensation of the corresponding bis(trimethylsilyl)ated base with tri-O-acetyl-D-ribofuranosyl bromide followed by removal of protecting groups. Subsequently, they synthesized 8-β-D-ribofuranosyl-4-aminopyrido[2,3-d]pyrimidine-5(8H)-one-6-carboxamide[10] and 8-β-D-ribofuranosyl-4-aminopyrido[2,3-d]pyrimidine-7(8H)-one-5-carboxamide[11] as analogs of the antitumor antibiotic sangivamycin.[12,13]

 0732-8311/84/0305-051353.50/0

These latter syntheses also required condensation of the sugar and base.

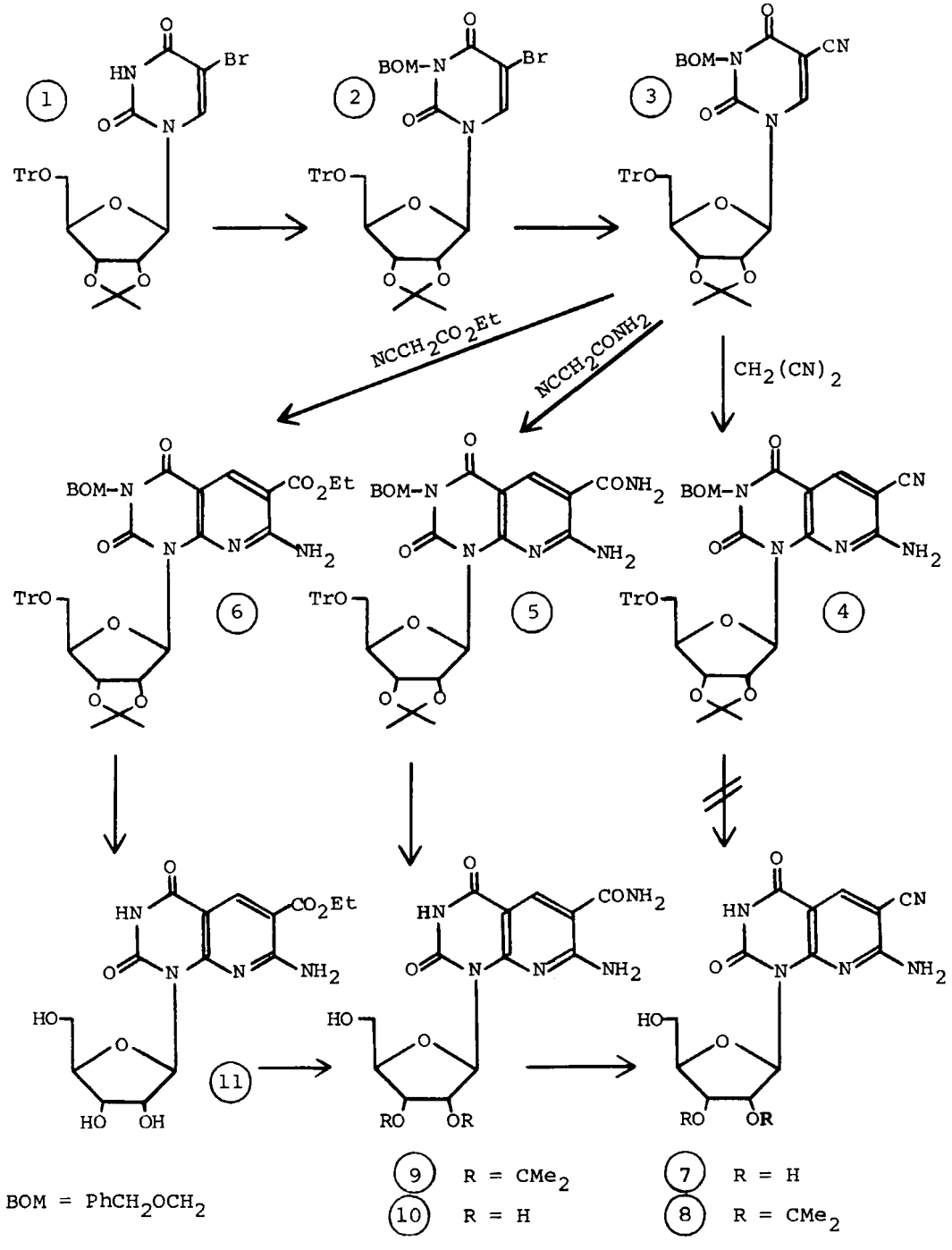
Our recent discovery[14,15] that 5-cyano-1,3-dimethyluracil can be converted in very high yields into 6-substituted-7-amino-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione in one-step by treatment with activated acetonitriles prompted us to apply this novel reaction to the synthesis of pyridopyrimidine nucleosides.

3-N-Benzyloxymethyl-2',3'-O-isopropylidene-5'-O-trityl-5-cyanouridine (**3**) (Scheme I) was chosen as the key intermediate. Since the ring transformation reaction occurs in basic medium, the N-3 position required protection by a removable protecting group in order to prevent anion formation,[16] and the sugar protecting groups must be stable to base. Compound **3** was prepared from the known and readily available 3'-O-isopropylidene-5'-O-trityl-5-bromouridine[17] (**1**) in two steps. Treatment of **1** with benzyloxymethyl chloride in N,N-dimethylformamide (DMF) in the presence of 1,8-diazabicyclo-[5,4,0]undec-7-ene (DBU) afforded the protected nucleoside **2** in high yield. Conversion of **2** to **3** was achieved by treatment of **2** with sodium cyanide in DMF.[18] Compound **3** was obtained in 80% yield as a syrup.

Treatment of **3** with malononitrile in ethanolic sodium ethoxide afforded crystalline **7-amino-3-benzyloxymethyl-6-cyano-1-(2',3'-O-isopropylidene-5'-O-trityl-β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione** (**4**) in 84% yield. The UV spectral behavior of **4** was characteristic of that for 1,3-di-substituted pyrido[2,3-d]pyrimidine-2,4(1H,3H)-diones.[15] This product contained a cyano group as evidenced by an absorption band at ν = 2220 cm^{-1} in the IR spectrum. The ^1H NMR spectrum, which showed the appearance of a new singlet at δ 8.47 for H-5 of **4** with concommitant disappearance of the H-6 signal at δ 8.05 in **3**, is also consistent with the pyridopyrimidine nucleoside structure **4** (Table I). By similar treatment of **3** with cyanoacetamide or

ethyl cyanoacetate, **7-amino-3-benzyloxymethyl-1-(2',3'-O-isopropylidene-5'-O-trityl-β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione-6-carboxamide** (**5**) and **-6-ethylcarboxylate** (**6**), respectively, were obtained in 70-75% yield.

Attempts to prepare the free nucleoside **7** by first hydrogenolysis of **4** followed by acid hydrolysis resulted in decomposition of the nucleoside. However, reduction of **5** went smoothly, and the resulting 2',3'-O-isopropylidene nucleoside **9** afforded crystalline **7-amino-1-(β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione-6-carboxamide** (**10**) on acid hydrolysis. The carboxamide group in **9** was readily converted into the cyano function under very mild conditions. Thus, treatment of **9** with trifluoroacetic anhydride in pyridine[19] afforded the 6-cyano nucleoside **8** which was then deisopropylidenated to give **7-amino-6-cyano-1-(β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione** (**7**) in crystalline form. Deprotection of **6** occurred readily, and crystalline **7-amino-1-(β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione-6-ethylcarboxylate** (**11**) was obtained in good yield. Nucleoside **11**, in turn, was converted into the carboxamide **10** by treatment with liquid ammonia at 90°C for 3 days. Thus, the reaction of **3** with malonitrile, cyanoacetamide and ethyl cyanoacetate gave the pyridopyrimidine nucleosides **4-6** which were eventually converted into the same common structure **7** (Scheme 1). The location of the glycosyl group on the pyrido[2,3-d]pyrimidine ring was not vigorously established. However, according to the mechanism proposed earlier,[14,15] ring transformation of the uridine precursor **3** should yield the 1-ribosyl derivatives **4-6**. Glycosyl N1→N8 migration is highly unlikely since it would require conversion to the less stable cross-conjugated system. Migration of this type is without precedent, while the reverse (N8→N1) has been reported.[10] These considerations support our assignment of structures **7-11** in Scheme 1 to the deprotected pyridopyrimidine



Scheme 1

nucleosides. Modification at the functional groups on the pyridopyrimidine ring is now being studied in our laboratory.

EXPERIMENTAL

General. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a JEOL-PFT-100 Spectrometer, and TMS was the internal standard for organic solvents and DDS (external) for deuterium oxide. UV and IR spectra were recorded on a Cary Model 15 Spectrometer and a Perkin-Elmer Infracord, respectively. Microanalyses were performed by M.H.W. Laboratories, Phoenix, Arizona. TLC was performed on Uniplates (Analtech, Newark, Delaware) and column chromatography on silica gel G60 (70-230 mesh, ASTM, Merck).

3-Benzyloxymethyl-2',3'-O-isopropylidene-5'-O-trityl-5-bromouridine (2)

Benzyloxymethyl chloride (4.7g, 30 mmol) was added dropwise to a mechanically stirred solution of 1[17] (14.5g, 24.3 mmol) and DBU (4.57g, 30 mmol) in dry DMF (200 mL) at 0°C. The mixture was stirred for an additional 2.5 h at 0°C, and then was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (200 mL) and water (100 mL). The organic layer was separated, washed with water (2 x 100 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was dissolved in CH_2Cl_2 and chromatographed over a column of silica gel (40 x 5 cm) using CH_2Cl_2 as the eluent. Fractions were monitored by TLC (hexane-EtOAc 3:2). Appropriate fractions were combined and evaporated *in vacuo* to give **2** (17.6g, 92%) as a syrup. All attempts at crystallization of this product failed. The spectral data of this compound are listed in Table I.

Anal. Calcd. for $C_{39}H_{37}BrN_2O_7$: C, 64.55; H, 5.14; Br, 11.01; N, 3.86. Found: C, 64.73; H, 5.33; Br, 10.89; N, 3.83.

Table 1. Spectral Characteristics of New Compounds

Comp	UV max min ($\varepsilon \times 10^3$)	^{1}H-NMR (DMSO-d_6)
2	281[a] 247nm (9.18) (2.96)	7.86(s, 1H, H-6), 7.35(m, 20H, Ph), 5.84(d, 1H, H-1', $J_{1',2'}$ = 2.4Hz), 5.48(ABq, 2H, NCH_2, J_{gem} = 10.0Hz), 4.81(m, 2H, H-2',3'), 4.70(s, 2H, $PhCH_2$), 4.38(m, 1H, H-4'), 3.39(d, 2H, H-5',5"), 1.58, 1.35(s, 3H, iPr).
3	270[a] 235 (15.0) (4.70)	8.05(s, 1H, H-6), 7.31(m, 20H, Ph), 5.74(d, 1H, H-1', $J_{1',2'}$ = 2.4Hz), 5.47(ABq, 2H, NCH_2, J_{gem} = 10.0Hz), 4.82(m, 2H, H-2',3'), 4.71(s, 2H, $PhCH_2$), 4.34(m, 1H, H-4'), 3.38(d, 2H, H-5',5"), 1.60, 1.39(s, 3H, iPr).
4	332[b] 291 (13.8) (3.66) 271 247 (11.3) (3.18) 221 (35.4)	8.47(s, 1H, H-5), 7.27(m, 20H, Ph), 5.70(bs, 2H, NH_2), 5.29(ABq, 2H, NCH_2, J_{gem} = 10.0Hz), 5.11(d, 1H, H-1', $J_{1',2'}$ = 0.2Hz), 4.89(m, 1H, H-2'), 4.59(s, 2H, $PhCH_2$), 4.40(m, 2H, H-3',4'), 3.18-3.56(m, 2H, H-5',5"), 1.59(s, 3H, iPr), 1.34(s, 3H, iPr).
5	331[b] 302 (11.9) (4.64) 287 257 (12.5) (3.10) 225sh (31.3)	8.54(s, 1H, H-5), 7.30(m, 20H, Ph), 6.40(bs, 2H, NH_2), 5.30(ABq, 2H, NCH_2, J_{gem} = 10.0Hz), 5.12(d, 1H, H-1', $J_{1',2'}$ = 0.2Hz), 4.90(m, 1H, H-2'), 4.57(s, 2H, $PhCH_2$), 4.37-4.45(m, 2H, H-3',4'), 3.37(m, 2H, H-5',5"), 1.60(s, 3H, iPr), 1.35(s, 3H, iPr).

6	333[b] (13.3) 286 (12.5) 231 (35.1)	300 (3.61) 262 (4.44)	8.91(s, 1H, H-5), 7.30(m, 20H, Ph), 5.77(bs, 2H, NH_2), 5.28(ABq, 2H, NCH_2, J_{gem} = 10.0Hz), 5.19(d, 1H, H-1', $J_{1',2'}$ = 0.2Hz), 4.90(m, 1H, H-2'), 4.60(s, 2H, $PhCH_2$), 4.39(q, 2H, CH_2Me), 4.30-4.45(m, 2H, H-3',4'), 3.35(m, 2H, H-5',5"), 1.59(s, 3H, iPr), 1.41(t, 3H, CH_2Me), 1.34(s, 3H, iPr).
7	331[b] (15.7) 283 (14.8) 228 (48.0)	298 (4.44) 258 (5.27)	11.56(s, 1H, 3-NH), 8.34(s, 1H, H-5), 7.93(bs, 2H, NH_2), 6.55(d, 1H, H-1', $J_{1',2'}$ = 3.0Hz), 4.58(dd, 1H, H-2', $J_{1',2'}$ = 3.0, $J_{2',3'}$ = 6.0Hz), 4.21 (t, 1H, H-3', $J_{2',3'} = J_{3',4'}$ = 6.0Hz), 4.04(bs, 3H, 2',3',5'-OH), 3.41-3.96(m, 3H, H-4',5',5").
10	331[b] (12.4) 284 (13.1) 228 (23.0)	299 (4.24) 258 (3.66)	12.23(s, 1H, 3-NH), 8.56(s, 1H, H-5), 8.27(bs, 2H, NH_2), 7.42(bs, 2H, NH_2), 6.61(d, 1H, H-1', $J_{1',2'}$ = 3.0Hz), 5.08(d, 1H, OH), 4.83(d, 1H, OH), 4.62 (m, 2H, H-2', 5'-OH; after D_2O exchange, dd, $J_{1',2'}$ = 3.0, $J_{2',3'}$ = 6.0Hz), 4.22(m, 1H, H-3'), 3.43-3.72(m, 3H, H-4',5',5").
11	333[b] (14.5) 284 (14.9) 230 (29.4)	293 (3.38) 259 (5.06)	11.49(s, 1H, 3-NH), 8.54(s, 1H, H-5), 8.26(bs, 2H, NH_2), 6.60(d, 1H, H-1', $J_{1',2'}$ = 2.7Hz), 5.07(d, 1H, OH), 4.86(d, 1H, OH), 4.59(m, 2H, H-2', 5'-OH; after D_2O exchange, dd, $J_{1',2'}$ = 2.7, $J_{2',3'}$ = 6.0Hz), 4.25(q, 2H, CH_2Me), 4.21-4.42(m, 2H, H-3',4'), 3.54(m, 2H, H-5',5"), 1.33(t, 3H, CH_2Me).

a) in EtOH, b) in MeOH. Chemical shifts in ppm (δ), signals, s(singlet), d(doublet), t(triplet), q(quartet), m(multiplet), dd(double doublet), bs(broad singlet). Values given for coupling constants are first order.

3-Benzoyloxymethyl-2'-3'-O-isopropylidene-5'-O-trityl-5-cyano-uridine (3)

A mixture of 2 (18.0g, 24.8 mmol) and NaCN (3.0g, 37.2 mol) in DMF (200 mL) was heated at 80°C for 5 h, then concentrated in vacuo. The residue was partitioned between water (500 mL) and EtOAc (200 mL). The aqueous layer was separated and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with water (3 x 200 mL), dried (Na_2SO_4), evaporated, and the residue chromatographed using n-hexane-EtOAc (17:3 v/v) as the eluent. Compound 3 (13.2g, 80%) was obtained as a syrup. See Table I for the spectral data of this product.

Anal. Calcd. for $C_{40}H_{37}N_3O_7$: C, 71.52; H, 5.55; N, 6.24. Found: C, 71.31; H, 5.67; N, 6.24.

7-Amino-3-benzyloxymethyl-1-(2',3'-O-isopropylidene-5'-O-trityl-β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione-6-carboxylic acid.

Derivatives. (a) 6-Carbonitrile (4)

A solution of 3 (5.0g, 7.4 mmol) and malononitrile (737 mg, 11.2 mmol) in NaOEt/EtOH (prepared by dissolving 343 mg of Na in 100 mL of EtOH) was heated at reflux for 30 min. After cooling the mixture to room temperature, crystalline precipitates were collected by filtration and recrystallized from $CHCl_3$-EtOH to afford 4 (4.61g, 84%), mp 153-154°C (dec). See Table I for spectral data.

Anal. Calcd. for $C_{43}H_{39}N_5O_7 \cdot 2/5\ CHCl_3$: C, 66.36; H, 5.11; N, 8.92. Found: C, 66.51; H, 5.13; N, 8.99. The presence of $CHCl_3$ in the sample was detected by ^1H NMR taken in DMSO-d_6.

(b) 6-Carboxamide (5).

In a similar manner but using cyanoacetamide (938 mg) as the nucleophile, the 6-carboxamide analog 5 (4.0g, 71%) was obtained, mp 149-150°C (dec). Table I lists the spectral characteristics of this compound.

Anal. Calcd. for $C_{43}H_{41}N_5O_8 \cdot 1/2\ CHCl_3$: C, 64.07; H, 5.09; N,

8.59. Found: C, 63.96; H, 5.09; N, 8.59.

(c) 6-Carboxylic Acid Ethyl Ester (6).

This compound **6** was obtained by treatment of **3** (5.0g) with ethyl cyanoacetate (1.26g) at reflux for 15 min. The reaction mixture was diluted with water (100 mL), and the precipitates were collected by decantation of the supernatant. The residue was dissolved in $CHCl_3$, the solution dried (Na_2SO_4), and purified by chromatography on a silica gel column (5 x 40 cm) using hexane-EtOAc (7:3 v/v) as the eluent. Compound **6** (4.13g, 74%) was obtained as an amorphous powder.

Anal. Calcd. for $C_{45}H_{44}N_4O_9 \cdot H_2O$: C, 67.33; H, 5.74; N, 6.98. Found: C, 67.38; H, 5.63; N, 6.74.

7-Amino-1-(2',3'-O-isopropylidene-β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione-6-carboxamide (9)

A mixture of **5** (2.00g, 2.65 mmol), 10% Pd/C (1.80g), EtOH (150 mL) and EtOAc (150 mL) was shaken at room temperature for 40 h in a Parr hydrogenator in a hydrogen atmosphere with an initial pressure of 40 p.s.i. The catalyst was removed by filtration, and washed with EtOH (3 x 100 mL). The combined filtrate and washings were concentrated to dryness in vacuo. The resulting powder (1.35g) was washed well with ether (5 x 50 mL) to give 692 mg (74%) of **9**, mp > 300°C. The product was used directly in the next step.

7-Amino-6-cyano-1-(2',3'-O-isopropylidene-β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (8)

Trifluoroacetic anhydride (0.51 mL, 3.78 mmol) was added to a stirred, ice-cooled solution of **9** (450 mL, 1.14 mmol) in anhydrous dioxane (60 mL) and dried pyridine (0.55 mL, 6.84 mmol) at such a rate that the temperature was kept below 5°C. The mixture was stirred an additional 3 h at room temperature, then poured onto ice-water (100 mL), and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with water (3 x 50 mL), dried (Na_2SO_4), and concentrated to dryness in vacuo to

give 329 mg (77%) of **8**, mp > 300°C. IR (KBr) 2220 cm^{-1} (CN).

7-Amino-6-cyano-1-(β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (7)

A mixture of **8** (113 mg, 0.30 mmol) in EtOH (25 mL) and 18% HCl/MeOH (10 mL) was stirred at room temperature for 2 h. Compound **7** precipitated from the mixture was collected by filtration, and recrystallized from DMF-MeOH to give 83 mg (82%) of pure product, mp > 300°. See Table I for spectral characteristics.

Anal. Calcd. for $C_{13}H_{13}N_5O_6$: C, 46.33; H, 3.79; N, 20.91. Found: C, 46.57; H, 3.91; N, 20.89.

7-Amino-1-(β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione-6-carboxamide (10)

In a similar manner as above, **10** was obtained from **9** by acid hydrolysis of the isopropylidene group, mp > 300°C. The spectral characteristics of **10** are listed in Table I.

Anal. Calcd. for $C_{13}H_{15}N_5O_7 \cdot 1/2\ H_2O$: C, 43.10; H, 4.45; N, 19.33. Found: C, 43.36; H, 4.42; N, 19.43.

7-Amino-1-(β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione-6-carboxylic acid ethyl ester (11)

To a solution of **6** (753 mg, 1 mmol) in EtOH (120 mL) and EtOAc (30 mL) was added 10% Pd/C (700 mg), and the mixture was hydrogenated in a Parr hydrogenator at room temperature at an initial pressure of 40 psi. After 20 h, the catalyst was removed by filtration and washed well with EtOH. The combined filtrate and washings were concentrated to dryness. The residue was treated with 5% HCl/MeOH (20 mL) overnight at room temperature. The solvent was removed *in vacuo*, and the residue crystallized from DMF-EtOH to afford **11**, (166 mg, 44%), mp > 340°C. See Table I for the spectral data.

Anal. Calcd. for $C_{15}H_{18}N_4O_8 \cdot H_2O$: C, 45.00; H, 5.03; N, 13.99. Found: C, 44.88; H, 4.86; N, 13.80.

Conversion of 11 to 10

A mixture of **11** (15 mg, 0.042 mmol) in liquid NH_3 (10 mL) was heated in a sealed tube at 90°C for 3 days. The NH_3 was allowed to evaporate, and the solid residue was recrystallized from DMF-EtOH to afford **10** (9 mg, 65%), mp > 300°C. The IR spectrum of this product was identical to that of authentic sample of **10** prepared from **9** (vide supra).

ACKNOWLEDGEMENT

The authors are indebted to Dr. Jack J. Fox of this Institute for his warm and continued interest.

REFERENCES

1. This investigation was supported in part by funds from the National Cancer Institute, U. S. Department of Health and Human Services (Grants CA-08748 and 18601).
2. Hurbert, B. S.; Ferone, R.; Hermann, T. A.; Hitchings, G. H.; Barnett, M.; Busby, S. R. M. J. Med. Chem., 1968, 11, 711; Irwin, W. J.; Wibberley, D. B. Advan. Heterocycl. Chem., 1969, 10, 149.
3. Anderson, G. L.; Shim, J. L.; Broom, A. D. J. Org. Chem., 1976, 41, 1095; Ogura, H.; Sakaguchi, Chem. Pharm. Bull., 1973, 21, 2014; Grivsky, E. M.; Lee, S.; Sigel, C. W.; Duch, D. S.; Nichol, C. A. J. Med. Chem., 1980, 23, 327; Duch, D. S.; Edelstein, M. P.; Bowers, S. W.; Nichol, C. A.; Cancer Res., 1982, 42, 3987; Temple, C.; Elliott, R. D.; Montgomery, J. A. J. Org. Chem., 1982, 47, 761.
4. Matsumoto, J.; Minami, S. J. Med. Chem., 1975, 18, 74; Suzuki, N. Chem. Pharm. Bull., 1980, 28, 761.
5. Davoll, J.; Clarke, J.; Elslager, E. F. J. Med. Chem., 1972, 15, 837.
6. Althuis, T. H.; Moore, P. F.; Hess, H. J. J. Med. Chem., 1979, 22, 44.
7. Bennett, L. R.; Blankley, C. J.; Fleming, R. W.; Smith, R. D.;

Tessmann, D. K. J. Med. Chem., 1981, 24, 382.

8. Kretzschmar, E. Pharmazie, 1980, 35, 253.

9. Rizkalla, B. H.; Broom, A. D.; Stout, M. G.; Robins, R. K. J. Org. Chem., 1972, 37, 3975.

10. Rizkalla, B. H.; Broom, A. D. J. Org. Chem., 1972, 37, 3980.

11. Anderson, G. L.; Broom, A. D. J. Org. Chem., 1977, 42, 997.

12. Rao, K. V.; Renn, D. W. Antimicrob. Agents Chemother., 1963, 77.

13. For comprehensive reviews, see Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, 1970, p. 323; "Nucleosides as Biological Probes," Wiley-Interscience, New York, 1979, p. 158.

14. Su, T.-L.; Watanabe, K. A. J. Heterocycl. Chem., 1982, 19, 1261.

15. Su, T.-L.; Watanabe, K. A. J. Heterocycl. Chem., 1984, 21, 0000.

16. Hirota, K.; Watanabe, K. A.; Fox, J. J. J. Heterocycl. Chem., 1977, 14, 537; J. Org. Chem., 1978, 43, 1198.

17. Rosenthal, A.; Dodd, R. H. Carbohyd. Res., 1980, 85, 15.

18. Inoue, H.; Ueda, T. Chem. Pharm. Bull., 1978, 26, 2657.

19. Campagna, F.; Carotti, A.; Casini, G. Tetrahedron Lett., 1977, 1813.

Received July 2, 1984.