

SYNTHESES OF PYRIDO[2,3-d]PYRIMIDINE NUCLEOSIDES VIA 6-ALLYLAMINO-  
URIDINES FROM 6,5'-ANHYDROURIDINE DERIVATIVE AND ALLYLAMINES

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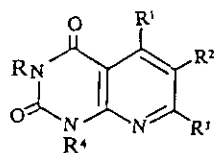
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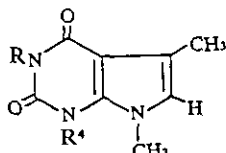
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**Abstract** ——— Pyrido[2,3-d]pyrimidine nucleosides were readily synthesized by treatment of 2',3'-O-isopropylidene-6-allylamino-uridines, which were derived from 6,5'-anhydro-2',3'-O-isopropylidene-6-hydroxyuridine and allylamines with palladium(II) acetate.

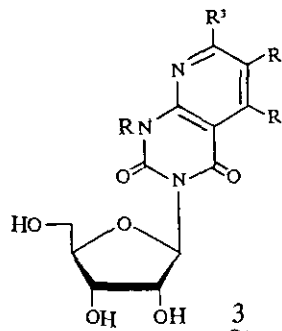
In recent years, we have interested in pyrido and pyrrolo[2,3-d]pyrimidine ring systems<sup>1)</sup> (1 and 2) which are viewed as being analogous to antibiotics (sangivamycin,<sup>2)</sup> toyocamycin<sup>3)</sup> and tubercidin<sup>4)</sup>), having potential antitumor activity. We have previously reported the synthesis of the isouridine type pyridopyrimidine nucleosides<sup>5)</sup> (3). Some of these compounds showed a significant degree of induction toward differentiation of HL-60 cells.<sup>5)</sup>



1



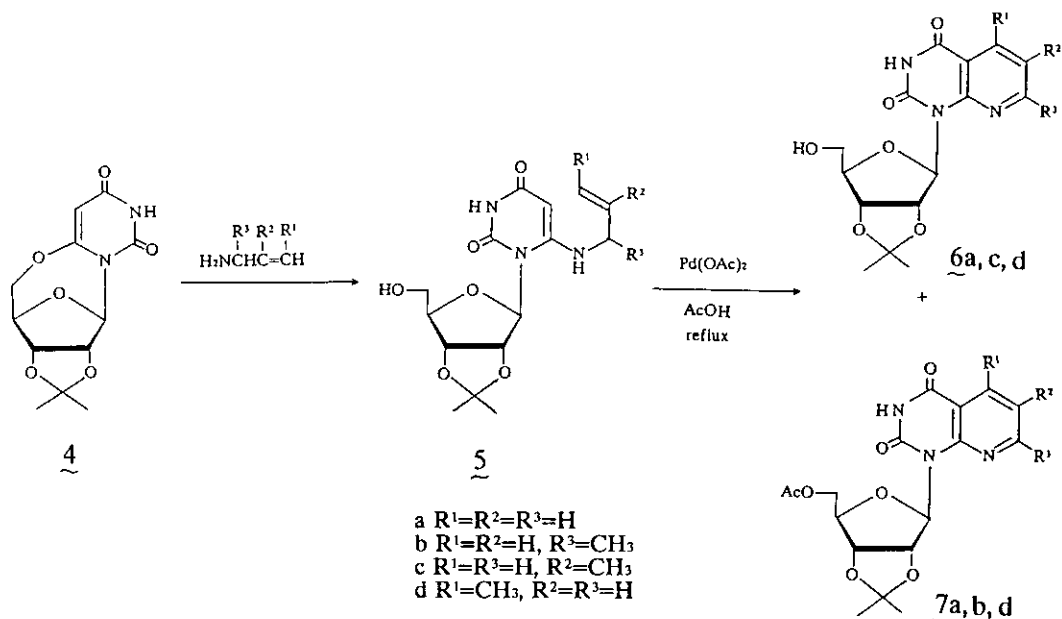
2



3

We wish to report the simple synthesis of pyrido[2,3-d]pyrimidine nucleosides (2, R<sup>4</sup>=ribofuranoside) via 6,5'-anhydro-2',3'-O-isopropylidene-6-hydroxyuridine (4)<sup>6)</sup> and allylamine with palladium(II) acetate.

Treatment of 6,5'-anhydro-2',3'-O-isopropylidene-6-hydroxyuridine (4) with allylamine at 60°C for 20 h afforded 6-allylamino-2',3'-O-isopropylideneuridine (5a, mp 214-216°C)<sup>7)</sup> in 37.4% yield. Similarly, treatment of 4 with  $\alpha$ -methylallylamine under the same conditions for 72 h led to the formation of 2',3'-O-isopropylidene-6-( $\alpha$ -methylallylamino)uridine (5b, mp 199-200°C)<sup>7)</sup> as a mixture of two stereoisomers in 32.1% yield. Furthermore, 2',3'-O-isopropylidene-6-( $\beta$ -methylallylamino)uridine (5c, mp 218-219°C)<sup>7)</sup> was obtained from the reaction of 4 with  $\beta$ -methylallylamine in 45.6% yield. 6-Crotylamino-2',3'-O-isopropylideneuridine (5d, mp 198-199°C)<sup>7)</sup> was also obtained from the reaction of 4 with crotylamine in 35.6% yield.



A mixture of 5a and palladium(II) acetate in acetic acid was refluxed for 2 h. After neutralization with saturated NaHCO<sub>3</sub> solution, the reaction mixture was extracted with AcOEt and the solution was concentrated in vacuo. The residue was subjected to silica gel column chromatography with CHCl<sub>3</sub> to afford crystalline compounds,

6a (mp 148-150°C)<sup>8)</sup> in 20.0% yield and 7a (mp 157-159°C)<sup>9)</sup> in 7.6% yield.

Compound 6a has the empirical formula, C<sub>15</sub>H<sub>17</sub>N<sub>5</sub>O<sub>6</sub>, which was derived from elemental and mass spectral analyses. <sup>1</sup>H-Nmr spectrum of 6a has a signal at  $\delta$  7.29 (dd, J=4.8

and 7.2Hz, 1H), 8.48 (dd,  $J=2.1$  and 7.2Hz, 1H) and 8.67 (dd,  $J=2.1$  and 4.8Hz, 1H) which can be attributable to the aromatic protons on a pyridine ring, and a signal at  $\delta$  5.01 (br, 1H) which can be assigned to 5'-OH proton.

From these data, the compound (6a) was assigned to be 1-(2',3'-O-isopropylidene- $\beta$ -D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione. An empirical formula,  $C_{17}H_{19}N_3O_7$ , of compound 7a was also derived from analyses data.  $^1H$ -Nmr spectrum of 7a has a signal at  $\delta$  7.30 (dd,  $J=4.8$  and 7.2Hz, 1H), 8.49 (dd,  $J=2.1$  and 7.2Hz, 1H) and 8.68 (dd,  $J=2.1$  and 7.2Hz, 1H) which can be attributable to the aromatic protons on a pyridine ring and a signal at  $\delta$  2.04 (s, 3H) which can be assigned to acetyl protons. From these data, the compound (7a) was assigned to be 1-(5'-O-acetyl-2',3'-O-isopropylidene- $\beta$ -D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione. When 5b was treated in a similar manner for 6 h, 7-methyl-1-(5'-O-acetyl-2',3'-O-isopropylidene- $\beta$ -D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (7b, mp 179-180°C)<sup>9)</sup> alone was obtained in 32.8% yield.

Furthermore, 5c was treated by palladium(II) acetate in the same manner for 30 min to give 6-methyl-1-(2',3'-O-isopropylidene- $\beta$ -D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (6c, mp 194-195°C)<sup>9)</sup> in 35.6% yield. Compound 5d was also treated by palladium(II) acetate for 3 h. The residue was subjected to silica gel column chromatography with  $CHCl_3$ , to give 5-methyl-1-(2',3'-O-isopropylidene- $\beta$ -D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (6d, mp 177-178°C)<sup>9)</sup> in 26.9% yield and 5-methyl-1-(5'-O-acetyl-2',3'-O-isopropylidene- $\beta$ -D-ribofuranosyl)-pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (7d, mp 181-182°C)<sup>9)</sup> in 10.1% yield, respectively.

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- 7) 5a: <sup>1</sup>H-Nmr (DMSO-d<sub>6</sub>) δ 1.29, 1.50(3H each, s, C-CH<sub>3</sub>), 3.55-3.77(4H, br, H-5', -NHCH<sub>2</sub>-), 4.04(1H, dt, J=3.3 and 3.9Hz, H-4'), 4.53(1H, s, H-5), 4.79(1H, dd, J=3.9 and 6.6Hz, H-3'), 5.03(1H, dd, J=3.6 and 6.6Hz, H-2'), 5.17-5.33(2H, m, CH=CH<sub>2</sub>), 5.47(1H, t, J=4.5Hz, OH-5'), 5.66-6.02(1H, m, CH=CH<sub>2</sub>), 6.28(1H, d, J=3.6Hz, H-1'), 7.18(1H, t, J=5.4Hz, NHCH<sub>2</sub>-), 10.67(1H, s, CONH).
- 5b: <sup>1</sup>H-Nmr (DMSO-d<sub>6</sub>) δ 1.28, 1.50(3H each, s, C-CH<sub>3</sub>), 1.65(3H, d, J=6.5Hz, NHCHCH<sub>3</sub>), 3.56-3.71(3H, br, NHCH-, H-5'), 4.04(1H, dt, J=3.3 and 3.9Hz, H-4'), 4.56(1H, s, H-5), 4.80(1H, dd, J=3.9 and 6.6Hz, H-3'), 5.03(1H, dd, J=3.6 and 6.6Hz, H-2'), 5.34-5.54(3H, m, CH=CH<sub>2</sub>, OH-5'), 5.55-5.70(1H, m, CH=CH<sub>2</sub>), 6.25(1H, d, J=3.6Hz, H-1'), 7.15(1H, br, NHCH-), 10.70(1H, s, CONH).
- 5c: <sup>1</sup>H-Nmr (DMSO-d<sub>6</sub>) δ 1.29, 1.50(3H each, s, C-CH<sub>3</sub>), 1.67(3H, s, C-CH<sub>3</sub>), 3.59(2H, d, J=5.4Hz, NHCH<sub>2</sub>-), 3.60-3.66(2H, br, H-5'), 4.08(1H, dt, J=3.3 and 3.9 Hz, H-4'), 4.48(1H, s, H-5), 4.82(1H, dd, J=3.9 and 6.6Hz, H-3'), 4.84, 4.87(1H each, s, C=CH<sub>2</sub>), 5.06(1H, dd, J=3.3 and 6.6Hz, H-2'), 5.55(1H, t, J=4.5Hz, OH-5'), 6.30(1H, d, J=3.3Hz, H-1'), 7.32(1H, t, J=5.4Hz, NHCH<sub>2</sub>-), 10.69(1H, s, CONH).
- 5d: <sup>1</sup>H-Nmr (DMSO-d<sub>6</sub>) δ 1.28, 1.49(3H each, s, C-CH<sub>3</sub>), 1.65(3H, d, J=6.0Hz, CH=CHCH<sub>3</sub>), 3.55-3.71(4H, br, NHCH<sub>2</sub>-, H-5'), 4.05(1H, dt, J=3.3 and 3.9Hz, H-4'), 4.56(1H, s, H-5), 4.80(1H, dd, J=3.9 and 6.6Hz, H-3'), 5.02(1H, dd, J=3.6 and 6.6Hz, H-2'), 5.37-5.70(2H, m, CH=CH-), 5.51(1H, t, J=4.5Hz, OH-5'), 6.24(1H, d, J=3.6Hz, H-1'), 7.16(1H, t, J=5.4Hz, NHCH-), 10.70(1H, s, CONH).
- 8) 6a: <sup>1</sup>H-Nmr (CDCl<sub>3</sub>) δ 1.35, 1.61(3H each, s, C-CH<sub>3</sub>), 3.87(2H, br, H-5'), 4.28(1H, dt, J=3.2 and 3.9Hz, H-4'), 5.01(1H, br, OH-5'), 5.12(1H, dd, J=3.9 and 6.6

Hz, H-3'), 5.35(1H, dd,  $J=2.7$  and 6.6Hz, H-2'), 7.14(1H, d,  $J=2.7$ Hz, H-1'), 7.29(1H, dd,  $J=4.8$  and 7.2Hz, H-6), 8.48(1H, dd,  $J=2.1$  and 7.2Hz, H-5), 8.67(1H, dd,  $J=2.1$  and 4.8Hz, H-7), 8.70(1H, br s, CONH).

6c:  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  1.37, 1.62(3H each, s,  $\text{C-CH}_3$ ), 2.42(3H, s,  $\text{C-CH}_3$ ), 3.20(1H, br, OH-5'), 3.81(1H, ddd,  $J=3.3$ , 8.4, and 12.0Hz, H-5'), 3.92(1H, dt,  $J=3.0$  and 12.0Hz, H-5'), 4.31(1H, dt,  $J=3.3$  and 3.9Hz, H-4'), 5.14(1H, dd,  $J=3.9$  and 6.6Hz, H-3'), 5.35(1H, dd,  $J=3.3$  and 6.6Hz, H-2'), 7.08(1H, br d,  $J=3.3$ Hz, H-1'), 8.28(1H, d,  $J=2.1$ Hz, H-5), 8.49(1H, d,  $J=2.1$ Hz, H-7), 8.50(1H, br, CONH).

6d:  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  1.37, 1.61(3H each, s,  $\text{C-CH}_3$ ), 2.81(3H, s,  $\text{C-CH}_3$ ), 3.24(1H, br, OH-5'), 3.82(1H, ddd,  $J=3.6$ , 8.4, and 12.0Hz, H-5'), 3.92(1H, dt,  $J=3.2$  and 12.0Hz, H-5'), 4.28(1H, dt,  $J=3.2$  and 3.9Hz, H-4'), 5.15(1H, dd,  $J=3.9$  and 6.6Hz, H-3'), 5.34(1H, dd,  $J=3.0$  and 6.6Hz, H-2'), 7.05(1H, d,  $J=5.1$ Hz, H-6), 7.16(1H, br d,  $J=3.0$ Hz, H-1'), 8.43(1H, d,  $J=5.1$ Hz, H-7), 9.00(1H, br, CONH).

9) 7a:  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  1.37, 1.57(3H each, s,  $\text{C-CH}_3$ ), 2.04(3H, s,  $\text{COCH}_3$ ), 4.23(1H, dd,  $J=7.5$  and 11.0Hz, H-5'), 4.32(1H, dt,  $J=4.2$  and 7.5Hz, H-4'), 4.41(1H, dd,  $J=4.2$  and 11.0Hz, H-5'), 5.01(1H, dd,  $J=4.2$  and 6.6Hz, H-3'), 5.31(1H, dd,  $J=1.2$  and 6.6Hz, H-2'), 7.20(1H, d,  $J=1.2$ Hz, H-1'), 7.30(1H, dd,  $J=4.8$  and 7.2Hz, H-6), 8.49(1H, dd,  $J=2.1$  and 7.2Hz, H-5), 8.68(1H, dd,  $J=2.1$  and 4.8Hz, H-7), 8.73(1H, br s, CONH).

7b:  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  1.37, 1.61(3H each, s,  $\text{C-CH}_3$ ), 2.05(3H, s,  $\text{COCH}_3$ ), 2.80(3H, s,  $\text{C-CH}_3$ ), 4.22(1H, dd,  $J=7.2$  and 11.0Hz, H-5'), 4.33(1H, dt,  $J=4.2$  and 7.2 Hz, H-4'), 4.42(1H, dd,  $J=4.2$  and 11.0Hz, H-5'), 5.01(1H, dd,  $J=4.2$  and 6.6Hz, H-3'), 5.28(1H, dd,  $J=1.2$  and 6.6Hz, H-2'), 7.03(1H, d,  $J=5.1$ Hz, H-6), 7.23(1H, br d,  $J=1.2$ Hz, H-1'), 8.43(1H, d,  $J=5.1$ Hz, H-5), 8.44(1H, br, CONH).

7d:  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  1.37, 1.60(3H each, s,  $\text{C-CH}_3$ ), 2.05(3H, s,  $\text{COCH}_3$ ), 2.81(3H, s,  $\text{C-CH}_3$ ), 4.22(1H, dd,  $J=7.5$  and 11.0Hz, H-5'), 4.33(1H, dt,  $J=4.5$  and 7.5 Hz, H-4'), 4.42(1H, dd,  $J=4.5$  and 11.0Hz, H-5'), 5.01(1H, dd,  $J=4.5$  and 6.6Hz, H-3'), 5.28(1H, dd,  $J=1.2$  and 6.6Hz, H-2'), 7.04(1H, d,  $J=6.0$ Hz, H-6), 7.22(1H, br d,  $J=1.2$ Hz, H-1'), 8.43(1H, d,  $J=6.0$ Hz, H-5), 8.49(1H, br, CONH).

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