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

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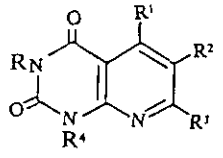
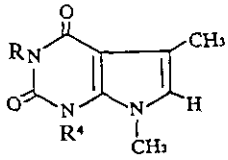
Abstract ——— Pyrido[2,3-d]pyrimidine nucleosides were readily synthesized by treatment of 2',3'-O-isopropylidene-6-allylamino-uridines, which were derived from 6,5'-anhydro-2',3'-O-isopropylidene-6-hydroxyuridine and allylamines with palladium(Ⅱ) acetate.

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



1



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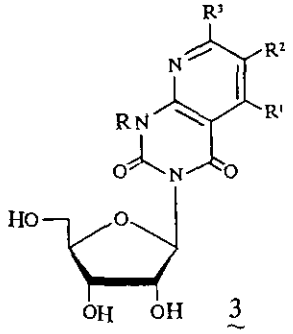
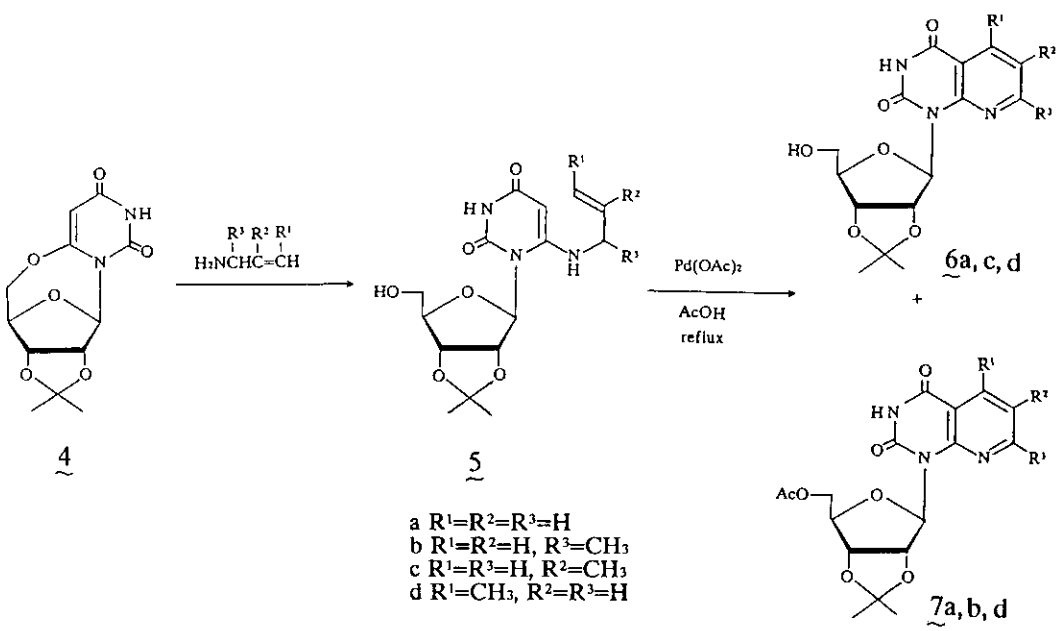


3

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

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



4

5

a R^1=R^2=R^3=H
b R^1=R^2=H, R^3=CH_3
c R^1=R^3=H, R^2=CH_3
d R^1=CH_3, R^2=R^3=H

A mixture of 5a and palladium(Ⅱ) acetate in acetic acid was refluxed for 2 h. After neutralization with saturated $NaHCO_3$ 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 $CHCl_3$ to afford crystalline compounds, 6a (mp 148-150℃)[8] in 20.0% yield and 7a (mp 157-159℃)[9] in 7.6% yield.

Compound 6a has the empirical formula, $C_{15}H_{17}N_3O_6$, which was derived from elemental and mass spectral analyses. ^{1}H-Nmr spectrum of 6a has a signal at δ 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 δ 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-β-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. ^{1}H-Nmr spectrum of 7a has a signal at δ 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 δ 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-β-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-β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (7b, mp 179-180℃)[9] 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-β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (6c, mp 194-195℃)[8] 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-β-D-ribofuranosyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (6d, mp 177-178℃)[8] in 26.9% yield and 5-methyl-1-(5'-O-acetyl-2',3'-O-isopropylidene-β-D-ribofuranosyl)-pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (7d, mp 181-182℃)[9] in 10.1% yield, respectively.

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7) 5a: ^{1}H-Nmr (DMSO-d_6) δ 1.29, 1.50(3H each, s, C-CH_3), 3.55-3.77(4H, br, H-5', -NHCH_2-), 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_2), 5.47(1H, t, J=4.5Hz, OH-5'), 5.66-6.02(1H, m, CH=CH_2), 6.28(1H, d, J=3.6Hz, H-1'), 7.18(1H, t, J=5.4Hz, NHCH_2-), 10.67(1H, s, CONH).

5b: ^{1}H-Nmr (DMSO-d_6) δ 1.28, 1.50(3H each, s, C-CH_3), 1.65(3H, d, J=6.5Hz, NHCHCH_3), 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_2, OH-5'), 5.55-5.70(1H, m, CH=CH_2), 6.25 (1H, d, J=3.6Hz, H-1'), 7.15(1H, br, NHCH-), 10.70(1H, s, CONH).

5c: ^{1}H-Nmr (DMSO-d_6) δ 1.29, 1.50(3H each, s, C-CH_3), 1.67(3H, s, C-CH_3), 3.59 (2H, d, J=5.4Hz, NHCH_2-), 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_2), 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_2-), 10.69(1H, s, CONH).

5d: ^{1}H-Nmr (DMSO-d_6) δ 1.28, 1.49(3H each, s, C-CH_3), 1.65(3H, d, J=6.0Hz, CH=CHCH_3), 3.55-3.71(4H, br, NHCH_2-, 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: ^{1}H-Nmr ($CDCl_3$) δ 1.35, 1.61(3H each, s, C-CH_3), 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=2.7Hz, 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}H-Nmr ($CDCl_3$) δ 1.37, 1.62(3H each, s, C-CH_3), 2.42(3H, s, 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=3.3Hz, H-1'), 8.28(1H, d, J=2.1Hz, H-5), 8.49(1H, d, J=2.1Hz, H-7), 8.50(1H, br, CONH).

6d: ^{1}H-Nmr ($CDCl_3$) δ 1.37, 1.61(3H each, s, C-CH_3), 2.81(3H, s, 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=5.1Hz, H-6), 7.16(1H, br d, J=3.0Hz, H-1'), 8.43(1H, d, J=5.1Hz, H-7), 9.00(1H, br, CONH).

9) 7a: ^{1}H-Nmr ($CDCl_3$) δ 1.37, 1.57(3H each, s, C-CH_3), 2.04(3H, s, $COCH_3$), 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=1.2Hz, 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}H-Nmr ($CDCl_3$) δ 1.37, 1.61(3H each, s, C-CH_3), 2.05(3H, s, $COCH_3$), 2.80 (3H, s, 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=5.1Hz, H-6), 7.23(1H, br d, J=1.2Hz, H-1'), 8.43(1H, d, J=5.1Hz, H-5), 8.44(1H, br, CONH).

7d: ^{1}H-Nmr ($CDCl_3$) δ 1.37, 1.60(3H each, s, C-CH_3), 2.05(3H, s, $COCH_3$), 2.81 (3H, s, 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=6.0Hz, H-6), 7.22(1H, br d, J=1.2Hz, H-1'), 8.43(1H, d, J=6.0Hz, H-5), 8.49(1H, br, CONH).

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