Arch. Pharm. Res. **15**(1), 87-90 (1992)

Synthesis of Substituted Pyridine-2,4-dione Nucleosides

Joon Kwang Lee, Jeong Hee Won, Jung Sup Park,
Chang Ho Hwang, K. H. Chung* and Eung K. Ryu*
*Departmet of Pharmacy, Chungbuk National University, Cheong Ju, 360-763, Korea *Division of Organic Chemistry, Korea Research Institute of Chemical Technology P.O. Box 9, Daedeog-Danji, Taejon 305-606, Korea*

(Received March 7, 1992)

Abstract □ The syntheses of novel heterocyclic base modified pyrimidine nucleosides are described. 5,6-Dimethyl-4-hydroxy-3-methoxy-1-(β-D-ribofuranosyl)-2(1H)-pyridinone **7** was synthesized by condensation of silylated 5,6-dimethyl-4-hydroxy-3-methoxy-2(1H)-pyridinone with β-D-ribofuranose-1-acetate-2,3,5-tribenzoate in dichloroethane in the presence of Lewis acid followed by debenzoylation. The 2,2′-anhydro-5,6-dimethyl-2-hydroxy-3-methoxy-1-β-D-arabinofuranosyl-4-pyridinone **8** was obtained from the reaction of the free ribonucleoside **7** and diphenyl carbonate in DMF. None of these compounds showed any significant antiviral and antitumor activities *in vitro* tests.

Keywords □ 5,6-dimethyl-4-hydroxy-3-methoxy-2(1H)-pyridinone, 5,6-dimethyl-4-hydroxy-3-methoxy-1-(β-D-ribofuranosyl)-2(1H)-pyridinone, 2,2′-anhydro-5,6-dimethyl-2-hydroxy-3-methoxy-1-β-D-arabinofuranosyl-4-pyridinone.

3-Deazapyrimidine analogs of pyrimidine nucleosides modified at the 3 position of pyrimidine ring by replacement of a carbon atom were first synthesized by Bruce L. Currie *et al.*[1-4] Although the 3-deazapyrimidine analogs showed cytotoxic activity and antitumor activity against Leukemia L 1210, *E. coli* K12 and *E. coli* B culture, 3-substituted 3-deazapyrimidine nucleosides have been reported only few examples[5,6].

In the course of the study of piericidin analogs, we synthesized many new 2,4-pyridinediones[7]. Herein we report the synthesis of new pyridinedione nucleosides and their biological activities.

EXPERIMENTAL SECTION

Melting points were measured with a Thomas Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNM-PMX 60 or Varian FT 300 A spectrometer, using tetramethylsilane (TMS) as an internal standard. Chemical shift values from TMS were recorded on δ scale. Mass spectra were determined with a GC/MS-QP 1000 spectrometer. TLC was performed on Merck silica gel 60F-254 plates in solvent (A, $CHCl_3$/MeOH = 10:1; B, ethyl acetate/hexane = 1:4; C, ethyl acetate/isopropanol/H_2O = 4:1:2, upper layer). Column chromatography was carried out on Merck silica gel 60 (230-400 mesh).

2,4-Bis (trimethylsilyloxy)-5,6-dimethyl-3-methoxypyridine 5

A suspension of 5,6-dimethyl-4-hydroxy-3-methoxy-2(1H)-pyridinone (**4** 2.68g, 15.9 mmol), ammonium sulfate (0.26g), and HMDS (20 m*l*) was heated to reflux under nitrogen atomosphere, until the solid became clear solution. The reaction mixture was evaporated under reduced pressure to leave an oil. The residue was distilled at 112°C/0.7 mm Hg to give 4.60g (92.5%) of the product as a colorless viscous oil.

5,6-Dimethyl-4-hydroxy-3-methoxy-1-(2,3,5-tribenzoyl-β-D-ribofuranosyl)-2(1H)-pyridinone 6

To a mixture of silylated pyridine **5** (4.60g, 12.9 mmol) and 1-*O*-acetyl-2,3,5-tribenzoyl-β-D-ribofuranose (6.05g, 12.9 mmol) in anhydrous 1,2-di-chloroethane (60 m*l*) was added $SnCl_4$ (2.28 m*l*, 19.7 mmol) in dichloroethane (10 m*l*) at 0°C. The mixture was stirred at room temperature for 1 day, then poured into saturated aqueous sodium bicarbonate solution (50 ml), and stirred for 30 min. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and the solvent was removed *in vacuo*. The residue was chromatographed on a silica gel column with chloroform/acetone (9:1) as eluent to give 6.70g (85%) of compound **6** as a white foam, mp. 88-90℃: ^{1}H-NMR ($CDCl_3$) δ 2.00 (s, 3H, 6-CH_3), 2.35 (s, 3H, 5-CH_3), 3.85 (s, 3H, OCH_3), 4.65 (m, 2H, H-5'), 4.75 (m, 1H, H-4'), 5.90 (s, 1H, H-1'), 6.70 (dd, 1H, H-3'), 6.80 (m, 1H, H-2'), 6.90 (s, 1H, D_2O exchangeable), 7.35-8.00 (m, 15H, aromatic); MS *m/z* 615 (M^+); Anal. calcd for $C_{34}H_{31}N_1O_{10}$ H_2O: C, 64.65; H, 5.27; N, 2.22 Found: C, 64.74; H, 4.94; N, 2.03.

5,6-dimethyl-4-hydroxy-3-methoxy-1-(β-D-ribofuranosyl)-2(1H)-pyridinone 7

A solution of compound **6** (2g, 3.2 mmol) and 0.1M sodium methoxide in methanol (32.6 ml) was stirred for 4h at room temperature. The reaction mixture was neutralized with Dowex IRC-50 H^+ resin. The resin was filtered off and washed with methanol (10 ml). After removal of the solvent *in vacuo*, the residue was chromatographed on a silica gel column with a upper layer of ethyl acetate/isopropanol/H_2O (4:1:2) to give 0.85g (86.5%) of hygroscopic compound **7** as a white foam, mp 63-65℃: ^{1}H-NMR (DMSO-d_6) δ 1.95 (s, 3H, 6-CH_3), 2.25 (s, 3H, 5-CH_3), 3.30 (s, 1H, D_2O exchangeable), 3.45 (m, 2H, H-5'), 3.65 (s, 3H, OCH_3), 3.75 (t, 2H, H-2',3'), 4.65 (dd, 1H, H-4'), 4.95 (s, 1H, D_2O exchangeable), 5.15 (s, 1H, D_2O exchangeable) , 6.75 (d, 1H, H-1'), 10.20 (br.s, 1H, D_2O exchangeable); MS *m/z* 301 (M^+).

2,2'-anhydro-5,6-Dimethyl-2-hydroxy-3-methoxy-1-β-D-arabinofuranosyl-4-pyridinone 8

To a solution of compound **7** (100 mg, 0.33 mmol) in anhydrous DMF (0.31 ml) were added diphenyl carbonate (90 mg, 0.41 mmol) and sodium bicarbonate (1.5 mg, 0.018 mmol). The mixutre was heated with stirring for 30 min in an oil-bath preheated at 150℃. The reaction mixture was cooled to 60℃ and then poured into ether (10 ml) with vigorous stirring. The tan precipitate was dissolved in methanol (5 ml) and triturated with ether (10 ml). The white precipitate was filtered, washed with ether, and dried over P_2O_5 *in vacuo* to give 67 mg (70%) of product as a white solid, mp 230-232℃: ^{1}H-NMR (DMSO-d_6) δ 1.85 (s, 3H, 6-CH_3), 2.30 (s, 3H, 5-CH_3), 3.30 (s, 2H, H-5'), 3.70 (s, 3H, OCH_3), 3.90 (t, 1H, D_2O exchangeable), 4.45 (dd, 1H, H-4'), 5.10 (d, 1H, H-2'), 5.14 (m, 1H, H-3'), 5.45 (d, 1H, D_2O exchangeable), 6.25 (d, 1H, H-1'); MS *m/z* 283 (M^+): Anal. calcd for $C_{13}H_{17}N_1O_6$: C, 54.88; H, 6.02; N, 4.60. Found: C, 55.12; H, 6.05; N, 4.94.

5,6-Dimethyl-4-hydroxy-3-methoxy-1-[3',5'-O-(tetraisopropyldisiloxandiyl)-β-D-ribofuranosyl]-2(1H)-pyridinone 9

To a suspension of compound **7** (0.2g, 0.66 mmol) in dried pyridine (6 ml) at 5℃ was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (0.23 ml, 0.73 mmol). The mixutre was stirred under a nitrogen atomosphere at room temperature for 3h. After removal of the solvent, the residue was dissolved in chloroform (50 ml), washed with water (50 ml×2), dried over anhydrous sodium sulfate, and the solution was filtered. The filtrate was concentrated *in vacuo* to a small volumn and subjected to chromatography using a silica gel column and ethyl acetate/hexane (1:5) as eluent. Fractions containing the product were combined and evaporated to give 0.3g (85.7%) of compound **9** as a viscous oil: ^{1}H-NMR ($CDCl_3$) δ 1.05 (m, 28H, isopropyl), 2.00 (s, 3H, 6-CH_3), 2.35 (s, 3H, 5-CH_3), 3.50 (d, 1H, D_2O exchangeable), 3.85 (s, 3H, OCH_3), 3.95 (m, 1H, H-4'), 4.10 (m, 2H, H-5'), 4.75 (m, 1H, H-3'), 5.20 (m, 1H, H-2'), 5.70 (d, 1H, H-1'), 6.40 (s, 1H, D_2O exchangeable); MS *m/z* 544 (M^+).

RESULTS AND DISCUSSION

5,6-Dimethyl-4-hydroxy-3-methoxy-2(1H)-pyridinone **4** was synthesized by the known procedure (Fig. 1)[7]. The silylated pyridine **5** was obtained from the reaction of compound **4**, hexamethyldisilazane (HMDS), and ammonium sulfate as a catalyst under refluxing condition. This silylated pyridine **5** was glycosylated with β-D-ribofuranose-1-acetate-2,3,5-tribenzoate by addition of tin (IV) chloride[8,9] in 1,2-dichloroethane to give 5,6-dimethyl-4-hydroxy-3-methoxy-1-(β-D-2',3',5'-tribenzoylribofuranosyl)-2(1H)-pyridinone **6** in 85% yield as shown in Fig. 2. In this reaction α-isomer was not formed, which might be explained by the steric effect of bulky pyridone ring along with neighboring participation ef-

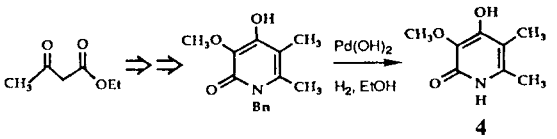

Fig. 1. Synthesis of 5,6-dimethyl-4-hydroxy-3-methoxy-2(1H)-pyridinone.

fect of 2′-*O*-benzoyl group.

The debenzoylation of compound **6** with an aqueous methanolic ammonium solution for 48h or 0.1N sodium ethoxide in ethanol for 3h at room temperature furnished a very hygroscopic 5,6-dimethyl-4-hydroxy-3-methoxy-1-β-D-ribofuranosyl-2(1H)-pyridinone **7** in 85% yield and 2,2′-anhydro-5,6-dimethyl-2-hydroxy-3-methoxy-1-β-D-arabinofuranosyl-4-pyridinone **8** as a byproduct in 3-4% yield.

Treatment of compound **7** wtih diphenyl carbonate in DMF gave 2,2′-anhydronucleoside **8** in 70% yield. The structure of **8** was confirmed by ^{1}H-NMR spectrum representing with a shift of 1′-H from δ 5.75 to 6.25 and by the high resolution mass spectrum revealing the molecular weight (*m/z* 283, M^+; $C_{13}H_{17}N_1O_6$) lacking 18 mass units (H_2O) from **7**. This anhydronucleoside **8** failed to react with 0.1N aqueous sodium hydroxide solution, whereas other anhydronucleosides have been reported to convert easily to the corresponding arabinosides under the same conditions[2,10].

In addtion, we had attempted to synthesize 2′-deoxynucleoside from **7** according to the literature procedures[11-14]. For example, the nucleoside **7** treated with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPSCl_2$) in pyridine at room temperature to give the 3′,5′-tetraisopropyldisiloxandiyl protected derivative 5,6-dimethyl-4-hydroxy-3-methoxy-1-[(3′,5′-*O*-tetraisopropyldisiloxandiyl)-β-D-ribofuranosyl]-2(1H)-pyridinone **9** in high yield. Attempts of reaction of **9** and 1,1′-thiocarbonyldiimidazole (TCDI) in DMF failed to give the expected its 2′-thiocarbonylimidazole derivative, a precursor of 2′-deoxynucleoside.

The synthesized compounds, **4**, **5**, **6**, **7**, and **8** were tested for antiviral activities against HSV-1 and antitumor activities against L1210 and P388 tumor cells *in vitro*. None of the compounds showed antiviral (ED_{50}>250 μg/m*l*) and antitumor activities (ID_{50}>100 μg/m*l*).

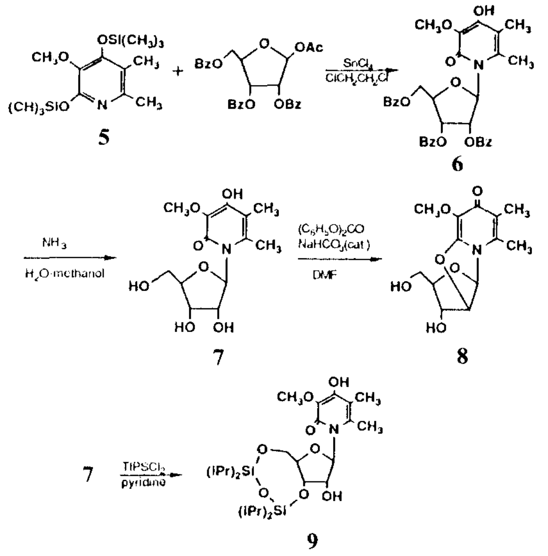

Fig. 2. Synthesis of pyridinedione nucleoside derivatives.

ACKNOWLEDGEMENTS

We wish to thank the Korea Science and Engineering Foundation for financial support of this work.

LITERATURE CITED

1. Robins, M. J. and Currie, B. L.: Synthesis of 3-deazauridine [4-hydroxy-1-(β-D-ribofuranosyl)-2-pyridone]. *Chem. Commun.*, 1547 (1968).
2. Currie, B. L. and Robins, R. K.: The synthesis of 3-deazapyrimidine nucleosides related to uridine and cytidine and their derivatives. *J. Heterocycl. Chem.*, 7, 323 (1970).
3. Currie, B. L., Robins, M. J. and Robins, R. K.: The synthesis of 3-deazaorotidine and related nucleoside derivatives of 4-hydroxy-2-pyridones. *J. Heterocycl. Chem.*, **8**, 221 (1970).
4. Robins, M. J., Currie, B. L., Robins, R. K. and Broom, A. D.: Novel nucleophilic displacement of benzoate by sulfur during thiation of 3-deazauridine tribenzoate. *Can. J. Chem.*, **49**, 3067 (1971).
5. Robins, M. J. and Lee, Ian S. K.: Nucleic acid related compounds. 3-deazauridine stannous chloride catalysis of cis-diol *vs* phenolic base methylation with diazomethane. *J. Med. Chem.*,

18, 1070 (1975).

6. McNamara, Dennis J.: Synthesis, antitumor activity, and antiviral activity of 3-substituted 3-deazacytidine and 3-substituted 3-deazauridine. *J. Med. Chem.*, **33**, 2006 (1990).
7. Chung, K. H., Cho, K. Y., Takahashi, N. and Yoshida, S.: A facile synthesis of substituted 4-hydroxy-2-pyridones, *Heterocycles*, **32**, 463 (1988).
8. Niedballa, U. and Vorbruggen, H.: A general synthesis of N-glycosides I. Synthesis of pyrimidine nucleosides. *J. Org. Chem.*, **39**, 3654 (1974).
9. Vorbruggen, H., Krolikiewicz, K. and Bennua, B.: Nucleoside synthesis XXII. Nucleoside synthesis with trimethylsilyl triflate and perchlorate as catalysts. *Chem. Ber.*, **114**, 1234 (1981).
10. Fox, J. J., Miller, N. and Wempen, I.: Nucleosides XXIX. 1-β-D-arabinofuranosyl-5-fluorocytosine and related arabinonucleosides *J. Med. Chem.*, **8**, 101 (1966).
11. Pankiewicz, Krzysztof., Matsuda Akira and Wstanabe Kyoichi A.: Nucleosides 121. Improved and general synthesis of 2′-deoxy C-nucleosides. Synthesis of 5-(2-deoxy-β-D-erythro-pentofuranosyl)-uracil, -1-methyluracil, -1,3-dimethyluracil, and -isocytosine. *J. Org. Chem.*, **47**, 485 (1982).
12. Robins, M. J., Wilson, J. S. and Hansske, F.: Nucleic acid related compounds 42. A general procedure for the efficient deoxygenation of secondary alcohols. Regiospecific and stereoseletive conversion of ribonucleosides to 2′-deoxynucleosides. *J. Am. Chem. Soc.*, **105**, 4059 (1983).
13. Falco, E. A. and Fox, J. J.: Nucleosides XLVIII. Synthesis of 1-(5-deoxy-β-D-arabinofuranosyl) cytosine and related compounds. *J. Med. Chem.*, **11**, 148 (1968).
14. Kawasaki, A. M., Wotring, L. L. and Townsend, L. B.: Synthesis and cytotoxicity studies of 8-amino-6-methyl-2-β-D-ribofuranosyl-1,2,3,5,6,7-hexaazaacenaphthalene (7-Aza-TCN) and the corresponding 2′-deoxy- and arabinonucleoside analogues. *J. Med. Chem.*, **33**, 3170 (1990).