A NOVEL SYNTHESIS OF C-NUCLEOSIDES HAVING PYRROLO[1,2-β]-PTERIDINE, 6- AND 8-DEAZAPYRROLO[1,2-β]-PTERIDINE RING SYSTEMS FROM 6-HYDROXY-6-(2,3,5-TRI-O-BENZOYL-β-D-RIBOFURANOSYL)-2H-PYRAN-3(6H)-ONE

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Abstract —— A versatile intermediate pyranulose glycoside (1) for C-nucleoside synthesis was treated with 4,5-diaminopyrimidine in AcOH to give 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrrolo[1,2-β]-pteridine (2) in 58% yield. However, treatment of 1 with 4,5,6-triaminopyrimidine in TFA afforded the 4-aminopteridine (4) without formation of the pyrrolo[1,2-β]-pteridine. Similar reaction of 2,3- and 3,4-diaminopyridines with 1 in AcOH led to formation of 8- and 6-deazapyrrolo[1,2-β]-pteridines (5 and 6), respectively. Removal of the sugar protecting groups in 2, 5, and 6 with sodium carbonate gave the deprotected C-nucleosides (7, 8 and 9).

During our efforts to develop a general synthetic method for C-nucleosides, we have prepared an extremely useful intermediate, viz, 6-hydroxy-6-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2H-pyran-3(6H)-one (1), from which some ring transformations with a variety of amines have been reported.1 We now describe the preparation of C-nucleosides having tricyclic systems, pyrrolo[1,2-β]-pteridine, pyrido[2,3-e]pyrrolo[1,2-α]pyrazine (8-deazapyrrolo[1,2-β]-pteridine), pyrido[3,4-e]pyrrolo[1,2-α]pyrazine (6-deazapyrrolo[1,2-β]-pteridine), through the cyclocondensation of 1 with 1,2-diaminoheterocycles (pyrimidines and pyridines). The structure of pyrrolo[1,2-β]-pteridine is somewhat similar to that of 5,10-methylenetetrahydrofolic acid, which participates in one carbon transfer reaction in vivo. The tricyclic C-nucleosides may show interesting and/or improved biological effects. Two previous syntheses of pyrrolo[1,2-β]-pteridine derivatives have been reported by different routes,2,3 and here we also report a facile
one-pot synthesis of this ring system, as a part of our program of synthesis of C-nucleoside.

The starting pyranulose glycoside (1) used in this work was prepared from the furan glycoside by the procedure previously reported.\textsuperscript{1a} The cyclocondensation of the pyranulose glycoside (1) with 4,5-diaminopyrimidine in acetic acid at room temperature for 3 days gave 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrrolo[1,2-\textit{f}]pteridine (2) as a major reaction product in 58% yield without any formation of the isomeric pyrrolo[1,2-\textit{e}]pteridine isomer (2'). Structural determination of 2 was made by MS and NMR experiments. The \textsuperscript{1}H NMR spectrum of 2 showed two doublets at \(\delta\) 7.04 \(\left(J = 3.1\ \text{Hz}\right)\) and \(\delta\) 7.33 \(\left(J = 3.1\ \text{Hz}\right)\) characteristic of the pyrrole moiety. The C-5a \((\delta_C 152.6)\) shows correlation with H-4 \((\delta_H 9.11)\), H-7 \((\delta_H 9.31)\), and H-9 \((\delta_H 9.75)\) in the \textsuperscript{1}H-\textsuperscript{13}C long-range COSY spectrum of 2. These data indicate the ring system of pyrrolo[1,2-\textit{f}]pteridine in 2.

Solvent: (a), acetic acid; (b), TFA.

The \textsuperscript{1}H-\textsuperscript{13}C long range COSY experiments of compounds (2, 4, 5, and 6).
In trifluoroacetic acid (TFA), 2 was obtained in 32% yield as the main product and its α isomer (3) was obtained in 2% yield. The stereochemistry of the C-1’ position in compounds (2 and 3) was confirmed by NOE experiments. Irrigation of the H-1’ (δ 6.24) in 3 gave a 10.1% enhancement of the signal at δ 6.35 assignable to the H-2’. This enhancement was not observed for 2.

Next, the cyclocondensation of the pyranulose glycoside (1) with 4,5,6-triaminopyrimidine in TFA at room temperature gave 4-amino-6-[3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-3-oxopropyl]pteridine (4) in 39% yield without formation of the corresponding tricyclic compound. The position of the ribofuranosyl group in 4 was confirmed by a $^1$H-$^{13}$C long-range COSY experiment. The C-8α (δC 162.7) shows correlation with H-2 (δH 8.91) and H-7 (δH 8.69). This data indicated that the ribofuranosyl moiety is linked at the 6 position. A plausible explanation for the formation of 4 involves nucleophilic attack by the more basic 5-amino group of 4,5,6-triaminopyrimidine on the carbonyl carbon of the pyranone moiety of 1 with subsequent formation of a Schiff’s base (I), which then isomerizes to give II. Dehydration of II would lead to tricyclic compound (III), which is then opened to give the unstable ring-opened intermediate (IV). IV is converted to 4 by a proton shift (Scheme 2). We think that the formation of 2 proceeds by the same mechanism as that for the formation of pyrroloquinoxaline described in a previous paper.1a

The pyranulose glycoside (1) reacted with 2,3-diaminopyridine in acetic acid at room temperature for 3 days, gave 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrido[2,3-e]pyrrolo[1,2-a]pyrazine (5) in 33% yield. The $^1$H NMR spectrum of 5 clearly showed two doublets at δ 6.90 ($J = 4.1$ Hz) and δ 7.05 ($J = 4.1$ Hz) characteristic of the pyrrole moiety. When the similar reaction of 1 with 3,4-diaminopyridine was performed, corresponding tricyclic compound (6), 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrido[4,3-e]pyrrolo[1,2-a]pyrazine, was obtained in 39% yield.
Structural determination of 5 and 6 was made by MS and \textsuperscript{1}H-\textsuperscript{13}C long-range COSY experiments (Scheme 1). Roba and his collaborators\textsuperscript{4} have synthesized pyrido[2,3-e]pyrrolo[1,2-a]pyrazine ring system by intramolecular cyclization of 3-(1-pyrrolyl)-2-pycolinyl azide. The ring structure of 6, pyrido[4,3-e]pyrrolo[1,2-a]pyrazine, comes into new entry of a novel heterocyclic system. The removal of the sugar protecting groups in compounds (2, 5, and 6) was readily accomplished with aqueous sodium carbonate to afford the compounds (7, 8, and 9). The stereochemistry of the C-1\textsuperscript{\textprime} position in compounds (7, 8, and 9) was confirmed as to be \p by NOE experiments (Figure 1). Thus, the NOE indicates that the \p-ribofuranoside configuration have been preserved during the reaction sequence.

![Figure 1. NOE experiments of compounds (7, 8, and 9).](image)

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EXPERIMENTAL

MS spectra were taken on a Hitachi M-80 instrument by direct insertion at 70 eV; fast-atom bombardment MS spectra (FABMS) were run on a JMS-HX 110 spectrometer. The \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were measured with a JNM-A-400 or an A-600 (JEOL) spectrometer, with tetramethylsilane as an internal standard. Optical rotations were measured with a Jasco DIP-370 polarimeter (10-cm cell) at 25 °C. Analytical TLC was performed on glass plates coated with a 0.5-mm layer of Silica Gel GF\textsubscript{254} (E. Merck). The compounds were detected by UV light (254 nm).
1-(2,3,5-Tri-O-benzoyl-α-D-ribofuranosyl)pyrrolo[1,2-β]pteridine (2): To a solution of 1 (103.2 mg, 0.185 mmol) in acetic acid (5 mL) was added 4,5-diaminopyrimidine (24.1 mg, 0.221 mmol) and the mixture was stirred at rt for 3 days. The reaction mixture was neutralized with saturated NaHCO₃ solution and then extracted with CHCl₃ (3X10 mL). The extracts were combined, washed with water, dried over MgSO₄, and evaporated to dryness. The residual syrup was purified by PTLC with CHCl₃-MeOH (49:1) as eluent. This afforded 65.9 mg (58%) of 2 as a pale yellow foam; ¹H NMR (CDCl₃) δ 4.56 (dd, 1 H, J = 3.5, 12.3 Hz, H-Sa), 4.77 (dd, 1 H, J = 3.5, 12.3 Hz, H-Sb), 4.94 (m, 1 H, H-4'), 5.79 (d, 1 H, J = 3.1 Hz, H-1'), 6.03 (dd, 1 H, J = 3.5, 12.3 Hz, H-Sa), 7.04 (d, 1 H, J = 3.1 Hz, H-1'), 6.43 (dd, 1 H, J = 4.6, 6.6 Hz, H-2'), 7.04 (d, 1 H, J = 3.1 Hz, H-2'), 7.33 (d, 1 H, J = 3.1 Hz, H-3), 7.26-8.02 (m, 15 H, Ph), 9.11 (s, 1 H, H-4), 9.31 (s, 1 H, H-7), 9.75 (s, 1 H, H-9); ¹³C NMR (CDCl₃) δ 66.3 (C-S), 72.6 (C-3), 73.0 (C-2'), 74.4 (C-1'), 81.0 (C-4'), 110.6 (C-2'), 115.3 (C-3'), 123.0-133.7 (C-1, 3a, 9a, Ph), 147.8 (C-9), 152.6 (C-5a), 153.6 (C-7), 155.1 (C-4), 164.8, 165.3, 166.2 (C=O). HRFABMS Found: MH+ 615.1855 Calcd for C₃₉H₃₂N₆O₉; MH 615.1880 Nitrobenzyl alcohol (NBA) as matrix.

1-(2,3,5-Tri-O-benzoyl-α-D-ribofuranosyl)pyrrolo[1,2-β]pteridine (3): In the same manner (reaction solvent was used TFA) as described above for 2, 5.5 mg (2%) of 3 was obtained as a foam from 218.4 mg (0.391 mmol) of 1 and 4,5-diaminopyrimidine together with 76.8 mg (32%) of 2. Compound 3: ¹H NMR (CDCl₃) δ 4.76 (dd, 1 H, J = 4.4, 12.1 Hz, H-Sa), 4.84 (dd, 1 H, J = 3.7, 12.1 Hz, H-Sb), 4.93 (m, 1 H, H-4'), 6.07 (dd, 1 H, J = 5.4 Hz, H-3'), 6.24 (d, 1 H, J = 5.4 Hz, H-1'), 6.35 (dd, 1 H, J = 5.4 Hz, H-2'), 7.08 (d, 1 H, J = 4.4 Hz, H-2), 7.26-8.12 (m, 16 H, H-3, Ph), 9.11 (s, 1 H, H-4), 9.23 (s, 1 H, H-7), 9.72 (s, 1 H, H-9); ¹³C NMR (CDCl₃) δ 64.0 (C-5'), 72.9 (C-3'), 73.1 (C-2'), 75.4 (C-1'), 79.3 (C-4'), 110.6 (C-2'), 117 7 (C-3'), 123.3-133.7 (C-1, 3a, 9a, Ph), 147.8 (C-9), 152.6 (C-5a), 153.6 (C-7), 155.1 (C-4), 165.1, 165.5, 165.8 (C=O). HRFABMS Found: MH+ 648.2119 Calcd for C₃₉H₃₂N₆O₉; MH 648.2119 Nitrobenzyl alcohol (NBA) as matrix.

4-Amino-6-[3-(2,3,5-tri-O-benzoyl-α-D-ribofuranosyl)-3-oxopropyl]pteridine (4): In the same manner (TFA as the solvent) as described above for 2, 170.9 mg (39%) of 4 was obtained as a yellow foam from 373.7 mg (0.669 mmol) of 1 and 4,5,6-triaminopyrimidine; ¹H NMR (CDCl₃) δ 3.12-3.45 (m, 4 H, CH₂CH₂), 4.61 (dd, 1 H, J = 4.2, 12.3 Hz, H-5'a), 4.76 (m, 1 H, H-4'), 4.83 (d, 1 H, J = 5.1 Hz, H-1'), 4.90 (dd, 1 H, J = 3.1, 12.3 Hz, H-5'b), 5.69 (dd, 1 H, J = 5.4 Hz, H-3'), 5.85 (dd, 1 H, J = 5.4 Hz, H-2'), 7.27-8.04 (m, 15 H, Ph), 8.69 (s, 1 H, H-7), 8.91 (s, 1 H, H-2); ¹³C NMR (CDCl₃) δ 28.2, 35.7 (CH₂CH₂), 63.5 (C-5'), 72.3 (C-3'), 72.7 (C-2'), 80.5 (C-1'), 85.4 (C-4'), 123.0-133.7 (C-4a, Ph), 152.2 (C-7), 152.4 (C-4'), 154.4 (C-6), 158.1 (C-2), 162.7 (C-8a), 165.3, 165.5, 165.1, 205 5 (C=O). HRFABMS Found: MH+ 648.2119 Calcd for C₃₉H₃₂N₆O₉; MH 648.2094. NBA as matrix.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)pyrrolo[2,3-e]pyrrolo[1,2-a]pyrazine (5): This compound was prepared from 1 and 2,3-diaminopyridine as described above for 2: colorless oil, 33%; ¹H NMR (CDCl₃): δ 4.60 (dd, 1 H, J = 2.9, 12.1 Hz, H-5'a), 4.79 (dd, 1 H, J = 2.9, 12.1 Hz, H-5'b), 4.91 (m, 1 H, H-4'), 5 83
General Procedure for the Deprotection. Sufficient amount of methanolic sodium carbonate (0.5 mmol) was added to the protected C-nucleoside (0.04 mmol) in MeOH (2 mL). The mixture was kept at room temperature for 5 h, and evaporated under reduced pressure. The residue was purified by PTLC to afford the corresponding deprotected free C-nucleoside.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)pyrido[3,4-e]pyrrolo[1,2-a]pyrazine (6): This compound was prepared from 1 and 3,4-diaminopyridine as described above for 2: colorless oil, 39%; \( \text{H NMR (CDCl}_3\)}: \( \delta \) 4.60 (dd, 1 H, \( J = 3.5, 12.2 \) Hz, \( \text{H-5'a} \)), 4.75 (dd, 1 H, \( J = 3.5, 12.2 \) Hz, \( \text{H-5'b} \)), 4.94 (m, 1 H, \( \text{H-4} \)), 5.93 (d, 1 H, \( J = 7.8 \) Hz, \( \text{H-1} \)), 6.02 (dd, 1 H, \( J = 3.4, 5.6 \) Hz, \( \text{H-3} \)), 6.40 (dd, 1 H, \( J = 5.6, 7.8 \) Hz, \( \text{H-2'} \)), 6.97 (d, 1 H, \( J = 4.2 \) Hz, \( \text{H-2} \)), 7.05 (d, 1 H, \( J = 4.2 \) Hz, \( \text{H-3} \)), 7.30-8.06 (m, 15 H, Ph), 7.84 (d, 1 H, \( J = 5.4 \) Hz, \( \text{H-6} \)), 8.69 (d, 1 H, \( J = 5.4 \) Hz, \( \text{H-7} \)), 8.89 (s, 1 H, \( \text{H-4} \)), 9.87 (s, 1 H, \( \text{H-9} \)); \( \text{C NMR (CDCl}_3\)}: \( \delta \) 63.9 (C-5), 72.7 (C-3), 73.2 (C-2), 74.6 (C-1), 80.9 (C-4), 109.4 (C-2), 114.5 (C-3), 122.8 (C-6), 125.7-133.6 (C-1, 3a, 9a, Ph), 140.2 (C-9), 141.8 (C-5a), 145.7 (C-7), 150.1 (C-4), 165.2, 165.5, 167.0 (C=O). HRFABMS Found: MH' 614.1924 Calcd for C_{36}H_{68}N_{2}O_{7}; MH 614.1935. NBA as matrix.

1-((β-D-Ribofuranosyl)pyrrolo[1,2-f]pteridine (7): colorless solid, mp 247 °C (decomp) (from methanol); 41%; [α]_D -37.0° (c 0.4, Me_2SO); \( \text{H NMR (CDCl}_3\)}: \( \delta \) 3.49 (m, 2 H, H-5), 4.05 (m, 2 H, H-3'), 4.12, 4.86, 5.34 (each br, 3 H, OH exchanges with D_2O), 4.44 (dd, 1 H, \( J = 4.8, 7.1 \) Hz, H-2'), 5.28 (d, 1 H, \( J = 7.1 \) Hz, H-1'), 7.26 (d, 1 H, \( J = 4.2 \) Hz, H-2), 7.33 (d, 1 H, \( J = 4.2 \) Hz, H-3), 9.20, 9.28 (each br, 3 H, H-4, 7), 9.75 (s, 1 H, H-9); \( \text{C NMR (CDCl}_3\)}: \( \delta \) 61.6 (C-5), 71.2 (C-3), 73.8 (C-2'), 75.6 (C-1'), 85.4 (C-4'), 111.1 (C-2'), 115.6 (C-3), 122.9, 128.1, 134.4 (C-1, 3a, 9a), 148.1 (C-9), 152.3 (C-5a), 153.9 (C-7), 154.5 (C-4). HRFABMS Found: MH' 301.0937 Calcd for C_{16}H_{18}N_{2}O_{4}; MH 301.0966. Triethanolamine as matrix.

1-((β-D-Ribofuranosyl)pyrido[2,3-e]pyrrolo[1,2-a]pyrazine (8): colorless solid, mp 239 °C (decomp) (from methanol); 36%; [α]_D -96.5° (c 0.4, Me_2SO); \( \text{H NMR (CDCl}_3\)}: \( \delta \) 3.50 (m, 2 H, H-5'), 4.05 (m, 2 H, H-3', -4'), 4.43 (m, 1 H, H-2'), 4.84, 5.21 (each br, 3 H, OH exchanged with D_2O), 5.19 (d, 1 H, \( J = 7.3 \) Hz, H-1'), 7.13 (d, 1 H, \( J = 4.2 \) Hz, H-2), 7.17 (d, 1 H, \( J = 4.2 \) Hz, H-3), 7.66 (dd, 1 H, \( J = 4.5, 8.4 \) Hz, H-8), 8.70 (dd, 1 H, \( J = 1.5, 4.5 \) Hz, H-7), 8.82 (dd, 1 H, \( J = 1.5, 8.4 \) Hz, H-9), 9.09 (s, 1 H, H-4); \( \text{C NMR (CDCl}_3\)}: \( \delta \) 61.6
(C-5'), 71.1 (C-3'), 73.7 (C-2'), 75.4 (C-1'), 85.3 (C-4'), 108.1 (C-2), 115.0 (C-3), 122.5 (C-8), 126.0 (C-9), 124.5, 127.4, 132.5 (C-1, 3a, 9a), 146.3 (C-7), 147.7 (C-5a), 149.1 (C-4). HRFABMS Found: MH* 302.1141 Calcd for C_{19}H_{16}N_{2}O_{4}: MH 302.1186. NBA as matrix.

1-(β-D-Ribofuranosyl)pyrido[3,4-e]pyrrolo[1,2-a]pyrazine (9): colorless solid, mp 271 °C (decomp) (from methanol); 22%; [α]_D {-32.1} (c 0.3, Me_2SO); ^1H NMR [(CD_3)_2SO]: δ 3.50 (m, 2 H, H-5'), 4.06 (m, 2 H, H-3', 4'), 4.45, 5.26 (each br, 3 H, OH exchanged with D_2O), 4.83 (dd, 1 H, J = 5.5 Hz, H-2'), 5.21 (d, 1 H, J = 5.5 Hz, H-1'), 7.19 (d, 1 H, J = 4.8 Hz, H-2), 7.22 (d, 1 H, J = 4.8 Hz, H-3), 7.82 (d, 1 H, J = 5.1 Hz, H-6), 8.64 (d, 1 H, J = 5.1 Hz, H-7), 9.07 (s, 1 H, H-9); ^13C NMR [(CD_3)_2SO]: δ 61.6 (C-5'), 71.1 (C-3'), 73.7 (C-2'), 75.6 (C-1'), 85.3 (C-4'), 109.6 (C-2), 114.6 (C-3), 122.2 (C-6), 125.2, 128.1, 132.2 (C-1, 3a, 9a), 140.2 (C-9), 141.3 (C-5a), 145.4 (C-7), 150.3 (C-4). HRFABMS Found: MH 300.0894 Calcd for C_{19}H_{16}N_{2}O_{4}: MH 300.0994. Triethanolamine as matrix.

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