SYNTHESIS OF 2-IMINO-3-[1-(β-D-RIBOFURANOSYL)OXO]-1H,5H-1,5-BENZODIAZEPINE THROUGH CONDENSATION OF O-PHENYLENEDIAMINE WITH FORMYLISOXAZOLE GLYCOSIDE

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Abstract—The synthesis of 3-[1-(β-D-ribofuranosyl)oxo]-1H,5H-1,5-benzodiazepine (3) and 2-imino-3-[1-(β-D-ribofuranosyl)oxo]-1H,5H-1,5-benzodiazepine (8) is described. The cyclocondensation of enaminone glycoside (1) with o-phenylenediamine afforded benzodiazepine (2) in 64% yield. The reaction of formylisoxazole (4) with o-phenylenediamine led to three products, iminobenzodiazepine (5), benzimidazole (6), and enaminone nitrile (7) in 33%, 27%, and 9% yields, respectively. Removal of the sugar protecting groups in 2 and 5 with aqueous sodium carbonate in methanol gave the deprotected C-nucleosides (3 and 8).

Recently we have reported the syntheses of the 4-[1-(β-D-ribofuranosyl)oxo]-1,3-dihydro-2H-1,5-benzodiazepin-2-ones through condensation of 1,2-diaminobenzenes with furanone glycoside. In this paper, we want to describe the novel synthesis of 3-[1-(β-D-ribofuranosyl)oxo]-1H,1,5-benzodiazepines through the condensation of the enaminone aldehyde (1) and isoxazole aldehyde (4) with o-phenylenediamine. Compounds (1 and 4) can be obtained from enaminone glycoside by our previously published procedure. Condensation of the enaminone aldehyde (1) with o-phenylenediamine in methanol-chloroform (10:1) at room temperature for 9 days gave 3-[1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)oxo]-1H,1,5-benzodiazepine (2) in 64% yield. Higher reaction temperatures gave lower yields. 2 was characterized by the elemental analysis and 1H/13C NMR spectra. The 1H NMR spectrum of 2 exhibited signals at δ 14.37 (d, J = 6.6 Hz, NH) and δ 8.82 (d, J = 6.6 Hz, diazepine ring proton). The removal of the sugar protecting groups in compound (2) was readily accomplished with
aqueous sodium carbonate to produce benzodiazepine (3) in 49% yield. The stereochemistry of the C-1' position in compound (3) was confirmed as to be β by NOE experiment (Scheme 1).

Reagents and conditions: a. o-phenylenediamine, MeOH/CHCl₃, rt, 9 days; b. aq. Na₂CO₃, MeOH, rt, 23 h; c. o-phenylenediamine, CHCl₃, rt, 3 days.

Scheme 1.
Condensation of isoxazole aldehyde (4) with o-phenylenediamine in chloroform at room temperature gave 2-imino-3-[1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)oxo]-1H,5H-1,5-benzodiazepine (5) and 4-(2-benzimidazolyl)-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)isoxazole (6) in 33% and 27% yields as the major products and small amounts of 2-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-3-(2-amino)anilino-1-oxo-2-propene-2-carbonitrile (7) in 9% yield. Structure assignment of 5, 6, and 7 was supported by 1H and 13C NMR spectra. In particular, 1H NMR spectrum of 5 showed three NH protons at δ 9.00, 10.97, and 12.39 (disappear on the addition of deuterium oxide). The proton signal on diazepine ring at δ 8.47 (H-4) showed HMBC correlations to the carbon at δ 152 (C-2) and δ 189 (carbonyl). These data indicate the ring system of 1,5-benzodiazepine in 5. In the 1H NMR spectrum of 7 the signal for olefinic proton appeared at δ 7.82 (d, J=13.3 Hz). The presence of an intramolecular NH chelated proton is clearly observed at δ 12.30 (d, J=13.3 Hz). The IR spectrum of 7 showed an absorption band at 2212 cm⁻¹ due to the nitrile group. A plausible explanation for the formation of 5 involves nucleophilic attack by o-phenylenediamine on the aldehyde carbon of the isoxazole moiety of 4 with subsequent formation of Schiff's base [I] which then undergoes cyclization to tricyclic compound [II]. Ring opening of II produce benzodiazepine [III], which is converted to 5 by hydrogen shift (Scheme 2).

Removal of protecting groups in compound (5) with aqueous sodium carbonate in methanol was readily accomplished and afforded the benzodiazepine (8) and benzimidazole (9) in 48% and 12% yields, respectively. From a stereochemical point of view the diazepine ring of 8 can be regarded as a cycloheptadiene system, oscillating between two limiting pseudo-boat conformations, which interconvert through a quasi-planar transition state. In the NOE experiment of 8, strong NOE correlations were observed between the N₂ proton and imino proton, between N₁ proton and benzene ring proton as shown in Figure 1. These data indicated the preference of conformation (8A). In the 1H NMR spectrum of 9, the signal corresponding to the methine proton of position 2 was not observed. The missing signal may be attributed to exchange occurring between tautomeric forms.³ The ring contraction of 1,5-benzodiazepine into benzimidazole under basic condition was reported by Okamoto and Ueda.⁴ The stereochemistry of the C-1' position in compounds (8 and 9) was confirmed as to be β by NOE experiments (Scheme 1). Thus, the NOE indicates that the β-ribofuranoside configuration has been preserved during the reaction sequence.
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EXPERIMENTAL

Fast-atom bombardment MS spectra (FABMS) were run on a JMS-HX 110 spectrometer. The $^1$H and $^{13}$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. The IR spectra were measured with a FT/IR-230 (Jasco) spectrophotometer. Analytical TLC was performed on glass plates coated with a 0.5-mm layer of Silica Gel GF$_{254}$ (E. Merck). The compounds were detected by UV light (254 nm).

3-[1-(2,3,5-Tri-O-benzoyl-$^\beta$-D-ribofuranosyl)oxo]-1H-1,5-benzodiazepine (2): To a solution of 1 (224.5 mg, 0.36 mmol) in 10:1 MeOH-CHCl$_3$ (20 mL) was added o-phenylenediamine (40 mg, 0.36 mmol). The mixture was stirred at rt for 9 days, and then the reaction mixture was evaporated. The residue was purified by PTLC with CHCl$_3$ as eluent. This afforded 108.5 mg (64%) of 2 as an orange yellow solid (from methanol); mp 165-166°C.

$^1$H NMR (CDCl$_3$): δ 4.58 (dd, 1 H, J = 4.2, 12.1 Hz, H-5'a), 4.81 (m, 1 H, H-4'), 4.92 (dd, 1 H, J = 4.2, 12.1 Hz, H-5'b), 5.35 (d, 1 H, J = 2.4 Hz, H-1'), 5.80 (dd, 1 H, J = 4.9, 7.1 Hz, H-3'), 6.20 (dd, 1 H, J = 2.4, 4.9 Hz, H-2'), 7.14-8.08 (m, 19 H, Ph), 8.82 (d, 2 H, J = 6.6 Hz, H-2, 4), 14.37 (dd, 1 H, J = 6.6 Hz, NH, exchanged with D$_2$O); $^{13}$C NMR (CDCl$_3$): δ 63.8 (C-5'), 72.7, 74.5, 79.7, 83.1 (C-1', 2', 3', 4'), 107.8 (C-3), 115.9, 126.7, 128.3-133.6 (C-6, 7, 8, 9, 5a, 9a, Ph), 137.0, 151.9 (C-2, C-4), 165.3, 165.6, 166.1, 190.6 (C=O). Anal. Calcd for C$_{36}$H$_{28}$N$_2$O$_8$ • 0.5 H$_2$O; C, 69.11; H, 4.67; N, 4.48. Found: C, 69.31; H, 4.60; N, 4.61.

3-[1-(^$\beta$-D-Ribofuranosyl)oxo]-1H-1,5-benzodiazepine (3): To a solution of 2 (64.2 mg, 0.105 mmol)
in 2:1 MeOH-CHCl₃ (4 mL) was added 10% aq. Na₂CO₃ (0.4 mL). The mixture was stirred at rt for 23 h, and then the reaction mixture was evaporated. The residue was chromatographed on a column of silica gel with 99:1 CHCl₃-MeOH as eluent. This afforded 15.6 mg (49%) of 3 as an orange yellow solid (methanol); mp 133-135°C; [α]D -1.3° (c 0.1, Me₂SO); ¹H NMR [(CD₃)₂SO]: δ 3.58 (m, 2 H, H-5'), 3.85 (m, 2 H, H-3', 4'), 4.10 (dd, 1 H, J = 5.0, 5.0 Hz, H-2'), 5.08 (d, 1 H, J = 5.0 Hz, H-1'), 7.24, 7.60 (each m, each 2 H, H-6, 7, 8, 9), 8.90 (d, 2 H, J = 6.3 Hz, H-2, 4'), 14.90 (dd, 1 H, J = 6.3, 6.3 Hz, NH, exchanged with D₂O); ¹³C NMR [(CD₃)₂SO]: δ 61.7 (C-5'), 71.3, 83.0 (C-3', 4'), 74.0 (C-2'), 79.2 (C-1'), 108.0 (C-3), 115.6, 124.2, 126.7, 126.8 (C-6, 7, 8, 9), 136.5, 136.6 (C-5a, 9a), 152.5, 162.0 (C-2, C-4), 194.4 (C=O). Anal. Calcd for C₁₅H₁₆N₂O₅: C, 59.21; H, 5.30; N, 9.21. Found: C, 60.06; H, 5.05; N, 9.15.

2-Imino-3-[1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)oxo]-1H,5H-1,5-benzodiazepine (5), 4-(2-Benzimidazolyl)-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)isoxazole (6) and E-1-(2,3,5-Trι-O-benzoyl-β-D-ribofuranosyl)-3-(2-amino)anilino-1-oxo-2-propene-2-carbonitrile (7). To a solution of 4 (131.1 mg, 0.24 mmol) in CHCl₃ (10 mL) was added o-phenylenediamine (26 mg, 0.24 mmol). The mixture was stirred at rt for 3 days, and then the reaction mixture was evaporated. TLC (CHCl₃) showed that the dark yellow syrup contained three major components (Rf 0.25, 0.20, and 0.22). The mixture was separated by PTLC with CHCl₃ as eluent.

**Compound (5):** yellow foam; yield 40.0 mg (33%); Rf 0.25; IR (KBr) 1726 (C=O) cm⁻¹; ¹H NMR [(CD₃)₂SO]: δ 4.55 (dd, 1 H, J = 3.5, 12.3 Hz, H-5'a), 4.63 (dd, 1 H, J = 3.5, 12.3 Hz, H-5'b), 4.79 (m, 1 H, H-4'), 5.65 (d, 1 H, J = 4.8 Hz, H-1'), 5.83 (dd, 1 H, J = 4.8, 4.8 Hz, H-3'), 6.12 (dd, 1 H, J = 4.8, 4.8 Hz, H-2'), 7.13-7.99 (m, 19 H, Ph), 8.47 (dd, 1 H, J = 7.1, 14.8 Hz, H-4), 9.00 (dd, 1 H, J = 7.1, 7.1 Hz, H-5, exchanged with D₂O), 10.97 (dd, 1 H, J = 7.1, 14.8 Hz, =NH, exchanged with D₂O), 12.39 (s, 1 H, H-1, exchanged with D₂O); ¹³C NMR [(CD₃)₂SO]: δ 63.6 (C-5'), 72.4, 75.4, 78.9, 80.7 (C-1', 2', 3', 4'), 97.8 (C-3), 111.8 (C-9), 116.9 (C-6), 121.1, 121.6 (C-7, 8), 128.6-133.7 (Ph), 132.1, 141.2 (C-5a, 9a), 151.5 (C-2), 157.6 (C-4), 164.8, 164.8, 165.5, 189.3 (C=O). FABMS (nitrobenzyl alcohol as matrix). Found: [M + H]⁺ m/z 632.2028. Calcd for C₃₆H₃₀N₃O₈: [M + H]⁺ 632.2033.

**Compound (6):** colorless foam; yield 32.5 mg (27%); Rf 0.20; ¹H NMR (CD₃COCD₃): δ 4.77 (dd, 1 H, J = 4.0, 12.2 Hz, H-5'a), 4.88 (dd, 1 H, J = 4.0, 12.2 Hz, H-5'b), 4.98 (m, 1 H, H-4'), 6.18 (dd, 1 H, J = 5.5, 5.5 Hz, H-3'), 6.25 (dd, 1 H, J = 5.5, 5.5 Hz, H-2'), 6.58 (d, 1 H, J = 5.5 Hz, H-1'), 7.23-8.13 (m, 19 H, imidazole ring, Ph), 9.07 (s, 1 H, H-3), 12.00 (br, NH, exchanged with D₂O); ¹³C NMR (CDCl₃): δ 63.4 (C-5), 71.8, 74.6, 76.3, 81.3 (C-1', 2', 3', 4'), 111.3 (C-4), 123.2-134.0 (imidazole ring, Ph), 141.8 (C-2 imidazole), 150.8 (C-3), 163.0 (C-5), 165.3, 165.8, 166.3 (C=O). Due to the unstable nature of this compound, a good elemental analysis could not be obtained.

**Compound (7):** yellow foam; yield 10.5 mg (9%); Rf 0.22; IR (KBr) 2212 (CN), 1728 (C=O) cm⁻¹; ¹H NMR
(CDCl₃): δ 3.70 (br, 2 H, NH₂, exchanged with D₂O), 4.63 (dd, 1 H, J = 4.3, 11.3 Hz, H-5'a), 4.78 (m, 2 H, H-4', 5'b), 5.34 (d, 1 H, J = 4.3 Hz, H-1'), 5.83 (dd, 1 H, J = 5.6, 5.6 Hz, H-3'), 5.98 (dd, 1 H, J = 4.3, 5.6 Hz, H-2'), 6.86 (m, 2 H, Ph), 7.05 (d, 1 H, J = 7.8 Hz, Ph), 7.13 (dd, 1 H, J = 7.8, 7.8 Hz, Ph), 7.33-7.58 (m, 9 H, Ph), 7.82 (d, 1 H, J = 13.3 Hz, H-3'), 7.91-8.10 (m, 6 H, Ph), 12.30 (d, 1 H, J = 13.3 Hz, NH, exchanged with D₂O); ¹³C NMR (CDCl₃): δ 64.0 (C-S), 72.7, 73.7, 80.3, 62.7 (C-1', 2', 3', 4'), 83.4 (C-2), 118.3 (CN), 118.0, 119.5, 120.3, 125.9, 128.2-138.1 (Ph), 155.4 (C-3), 165.3, 166.2, 193.1 (C=O). FABMS (nitrobenzyl alcohol as matrix). Found: [M + H]⁺ m/z 632.2063. Calcd for C₃₆H₃₀N₃O₈: [M + H]⁺ 632.2033.

2-lmino-3-[1-(β-D-ribofuranosyl)oxo]-1H,5H-1,5-benzodiazepine (8) and 2-(β-D-Ribofuranosyl)-oxo-2-formylethane-2-benzimidazole (9): To a solution of 5 (145.5 mg, 0.23 mmol) in 5:1 MeOH-CHCl₃ (15 mL) was added 10% aq. Na₂CO₃ (4.5 mL) and CHCl₃ (5 mL). The mixture was stirred at rt for 1 day, and then the reaction mixture was evaporated. TLC (CHCl₃) showed that the dark yellow syrup contained two major components (Rf 0.22, and 0.31). The mixture was separated by PTLC with 99:1 CHCl₃-MeOH as a eluent. Compound (8): yellow solid; yield 35.5 mg (48%); mp 197-199°C (from methanol); R₁ 0.22; [α]D -80.1° (c 0.7, Me₂SO); ¹H NMR [(CD₃)₂SO]: δ 3.49 (dd, 1 H, J = 3.9, 11.7 Hz, H-Sa), 3.61 (dd, 1 H, J = 3.9, 11.7 Hz, H-5'b), 3.92 (m, 2 H, H-3, 4'), 4.17 (dd, 1 H, J = 4.7, 4.7 Hz, H-3'), 4.87 (br, 1 H, OH, exchanged with D₂O), 4.91 (d, 1 H, J = 4.7 Hz, H-1'), 4.97 (br, 1 H, OH, exchanged with D₂O), 5.22 (br, 1 H, OH, exchanged with D₂O), 7.11 (m, 2 H, Ph), 7.53 (dd, 1 H, J = 2.7, 6.3 Hz, Ph), 7.61 (dd, 1 H, J = 2.7, 6.3 Hz, Ph), 8.35 (dd, 1 H, J = 6.8, 14.6 Hz, H-4), 8.81 (dd, 1 H, H-4, exchanged with D₂O), 10.87 (dd, 1 H, J = 6.8, 6.8 Hz, H-5, exchanged with D₂O), 11.7, 116.9, 121.1, 121.2 (C-6, 7, 8, 9), 132.0, 135.1, 141.1 (C-5a, 9a), 151.8, 156.2 (C-2, 4), 192.8 (C=O). Anal. Calcd for C₁₅H₁₇N₅O₅·0.5 H₂O: C, 54.87; H, 5.53; N, 12.80. Found: C, 54.94; H, 5.58; N, 12.34. Compound (9): colorless foam; yield 9.0 mg (12%); R₁ 0.31; [α]D -68.1° (c 0.2, Me₂SO); ¹H NMR [(CD₃)₂SO]: δ 3.69 (dd, 1 H, J = 3.2, 12.1 Hz, H-5'a), 3.90 (dd, 1 H, J = 3.2, 12.1 Hz, H-5'b), 4.05 (m, 1 H, H-4'), 4.16 (dd, 1 H, J = 4.9, 4.9 Hz, Hz-H-3'), 4.28 (dd, 1 H, J = 4.9, 4.9 Hz, H-2'), 4.97 (br, 2 H, OH, exchanged with D₂O), 5.18 (d, 1 H, J = 4.9 Hz, H-1'), 5.24 (br, 1 H, OH, exchanged with D₂O), 7.31, 7.73 (each dd, each 2 H, J = 3.2, 6.1 Hz, H-4, 5, 6, 7), 9.88 (s, 1 H, CHO), 13.15 (br, 1 H, benzimidazole H-1, exchanged with D₂O); ¹³C NMR [(CD₃)₂SO]: δ 61.8 (C-5'), 71.3, 74.5, 82.5, 84.1 (C-1', 2', 3', 4'), 79.2 (C-2), 99.0, 113.0, 123.6, 128.3, 129.2 (benzimidazole C-4, 5, 6, 7, 8, 9), 148.9 (benzimidazole C-2), 184.5 (CHO), 192.5 (C=O). FABMS (nitrobenzyl alcohol as matrix). Found: [M + H]⁺ m/z 321.1072. Calcd for C₁₅H₁₇N₂O₆: [M + H]⁺ 321.1087.
REFERENCES


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