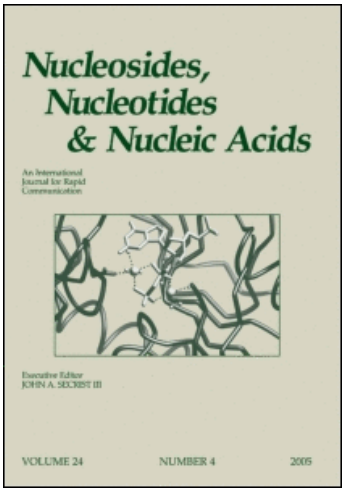

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The Synthesis of Two Novel Ring-Expanded Xanthine Nucleosides Containing the Imidazo[4,5-*e*][1,4]Diazepine Ring System

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THE SYNTHESIS OF TWO NOVEL RING-EXPANDED XANTHINE NUCLEOSIDES CONTAINING THE IMIDAZO[4,5-e][1,4]DIAZEPINE RING SYSTEM

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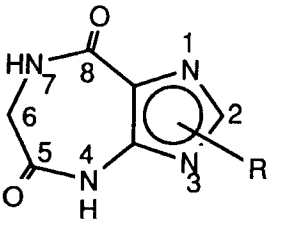
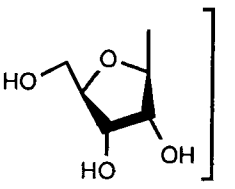
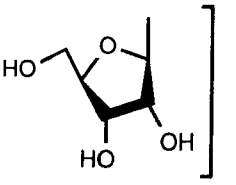
ABSTRACT: The synthesis of two regioisomeric nucleosides, 4,5,7,8-tetrahydro-6H-3-(β-D-ribofuranosyl)imidazo[4,5-e][1,4]diazepin-5,8-dione (**2**) and its 1-glycosyl analogue (**3**) is reported. They were prepared by ribosydation of the heterocyclic aglycon **4** which in turn was synthesized in three steps from 4(5)-nitroimidazole-5(4)-carboxylic acid (**5**). Distinction between the two isomers was achieved by an unequivocal synthesis of **2**.

In 1986, we reported[1] a general method for the synthesis of a family of novel, ring-expanded ("fat") purine analogues bearing the 5:7-fused imidazo[4,5-e][1,4]diazepine ring system; the xanthine analogue **1** being one among them. Two years later, another group[2] came up with an alternative route for the same ring system. We now wish to report the synthesis of the corresponding riboside analogues **2** and **3**,



1; R = 1 or 3-Me

2; R = 3- 

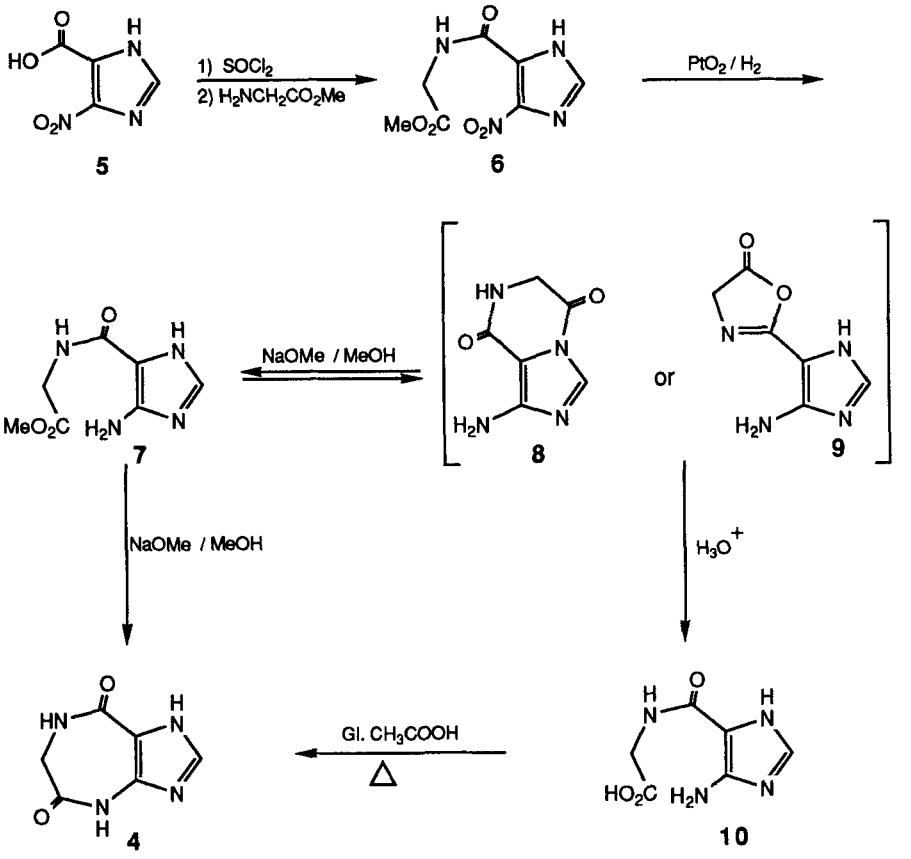
3; R = 1- 

4; R = H

which are the logical precursors to other ring-expanded purine nucleosides containing the same ring skeleton. With their structural resemblance to the natural counterparts, these nucleosides are potentially rich source of substrates or inhibitors of enzymes of purine metabolism as well as of those requiring energy cofactors. Because of their unique structural features, steric constraints, and conformational characteristics,[3] they are also potential probes for structure and function of nucleic acids.

The Vorbrüggen ribosidation[4] of **4** is the obvious route to access **2** and **3**. To that end, compound **7**, the precursor of **4**, was prepared from the nitro-carboxyimidazole (**5**) by conventional procedures (Scheme I).

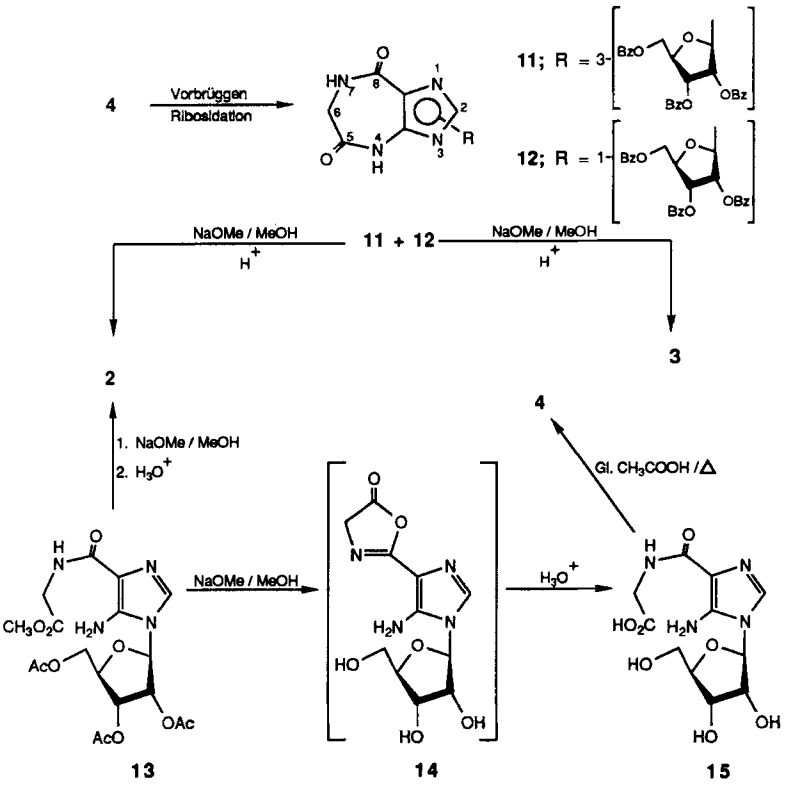
SCHEME I



However, all attempts to ring-close **7** to **4**, using freshly prepared solutions of sodium methoxide in methanol provided two products: the desired **4** along with the ring-open carboxylic acid **10** in a ≈ 2:1 ratio. The product ratio did not change even after carefully excluding moisture from the reactants and the medium. Apparently, **7** is in equilibrium with a species such as **8** or **9** (or both) which falls apart to **10** upon acid work-up. The facile ring-opening of 2-substituted-5(4H)-oxazolones by a variety of nucleophiles at both C=O and C=N junctions is well documented.[5] Nevertheless, **10** could be conveniently ring-closed to **4** by heating in glacial acetic acid. Attempts to ring-close **7** with glacial acetic acid provided only the starting material.

As anticipated, the Vorbrüggen procedure[4] (Scheme II) provided the two regioisomeric nucleosides **11** and **12**. Deprotection of the hydroxy groups with sodium methoxide/methanol yielded the desired ribosides **2** and **3**, respectively. The two isomers were distinguished by an

SCHEME II



unequivocal synthesis of **2** from the known nucleoside **13**[6] by ring-closure with sodium methoxide/methanol. This procedure, as in the case of aglycon **4**, also yielded the ring-open riboside **15**, presumably via **14**. Heating **15** in glacial acetic acid gave **4**. Single-crystal X-ray diffraction analyses[7] of **2** and **3** revealed that while the base-ribose conformational array[3] of **2** is syn, it is anti in **3**. Likewise, whereas **2** has the C2'-endo-C3'-exo sugar pucker, it is reversed in **3**.

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were recorded at 80 or 500 and 125 MHz, respectively. The reported spectral data are relative to Me_4Si as an internal reference standard. Multiplicity of ^{13}C NMR signals is based on off-resonance ^1H decoupled spectra. Electron impact (EI) were recorded at 70 eV. Elemental microanalyses were performed by Atlantic Microlab, Inc., Norcross, Georgia. Melting points are uncorrected. Dry solvents were prepared as follows: methanol, ether, toluene, and xylene were distilled over sodium metal; acetonitrile was distilled from CaH_2, followed by distillation from P_2O_5; DMF and DMSO were distilled under reduced pressure from CaH_2; THF was first dried over KOH and then distilled over sodium. All Dry solvents were stored over 3 or 4 Å molecular sieves.

4(5)-Nitro-5(4)-(N-methoxycarbonylmethyl)carbamoyl-1H-imidazole (6). In a flame-dried three-neck r.b. flask, fitted with a $CaCl_2$ guard tube, was placed **5** (5 g, 31.8 mmol). Thionyl chloride (20 mL, 0.27 mol) was introduced through a serum cap and the reaction mixture was heated to 50 °C with continuous stirring for 24 h. The mixture was rotary evaporated under anhydrous conditions, and the residue was co-evaporated with dry toluene three times, when a highly hygroscopic yellow powder—the acid chloride—was obtained. Without further purification, this powder was placed in a three-neck r.b.flask, maintained under N_2. Dry CH_3CN (15 mL) was added, followed by the addition of a cold CH_2Cl_2 solution of glycine methyl ester (3 g, 33 mmol) which was freshly liberated from the corresponding hydrochloride salt in 20 mL of CH_2Cl_2 by treatment with triethylamine at 0 °C. The reaction mixture was stirred at room temperature for 10 h. The mixture was evaporated to dryness on a rotary evaporator, and the residue was dissolved in boiling MeOH (100 mL), treated with decolorizing charcoal,

and filtered. Concentration and cooling of the filtrate afforded a solid which was recrystallized from MeOH as off-white shining crystals of **6** (5.5 g, 76%), mp 221–223 °C: ^{1}H NMR (Me_2SO-d_6) δ 9.22–9.20 (t, J_{NH-CH2} = 4.5 Hz, 1 H, NH, exchangeable with D_2O), 7.88 (s, 1 H, imidazole CH); 4.11 (d, J_{CH2-NH} = 5.5 Hz, 2, CH_2), 3.67 (s, 3 H, –OMe); IR (KBr), 3318, 1732, 1656, 1510, 1508 cm^{-1}; mass spectrum m/e 228 (M^+), 197, 169, 140; UV (MeOH) λ_{max} 303 nm. Anal. Calcd for $C_7H_8N_4O_5$: C, 36.85; H, 3.53; N, 24.56. Found: C, 36.76; H, 3.55; N, 24.48.

4(5)-Amino-5(4)-(N-methoxycarbonylmethyl)carbamoyl-1H-imidazole (7). Compound **6** (1 g, 4.3 mmol) was dissolved in absolute MeOH (150 mL), and transferred to a 500-mL hydrogenation bottle. About 0.1 g of PtO_2.monohydrate was added, and the bottle shaken in a Parr hydrogenation apparatus at 40 psi for 30 min. The reaction mixture was filtered through a pad of Celite. A tlc of the filtrate (silica gel, $CHCl_3$–MeOH, 8:1) showed the formation of a slightly lower moving (than the starting material), and strongly I_2-staining component. The filtrate was evaporated to dryness and the residue was purified by flash chromatography on silica gel (40–63 μm), using 8:1 $CHCl_3$–MeOH as the eluting solvent system. The pure solid obtained was recrystallized from MeOH–ether as a white amorphous powder of **7** (238 mg, 28%), mp 162–164 °C: ^{1}H NMR (Me_2SO-d_6) δ 7.68–7.55 (t, J_{NH-CH2} = 6.0 Hz, 1 H, NH, exchangeable with D_2O), 7.04 (s, 1 H, CH of imidazole), 5.5 (br s, 2 H, NH_2, exchangeable with D_2O), 3.97–3.89 (d, J_{CH2-NH} = 6.0 Hz, 2 H, CH_2), 3.63 (s, 3 H, OMe); IR (KBr) 3370, 3340, 3258, 1714, 1624, 1532 cm^{-1}; mass spectrum m/e 198 (M^+), 166, 139, 110, 82; UV (MeOH) λ_{max} 268.5 nm. Anal. Calcd for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.38; H, 5.10; N, 28.23.

4(5)-Amino-5(4)-(N-carboxymethyl)carbamoyl-1H-imidazole (10) and 4,5,7,8-Tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione (4). Dry MeOH (8 mL), freshly distilled over sodium, was introduced in a three-neck flask, maintained under N_2. Freshly cut Na metal (100 mg, 4.3 mg.atom) was added with stirring to form a clear solution. Compound **7** (200 mg, 1 mmol) was added in portions and the reaction mixture was heated to reflux for 25 h. It was cooled, acidified with 1 N HCl to pH 6.5, diluted with methanol, treated with decolorizing charcoal, and filtered. The colorless filtrate, upon evaporation to dryness on a rotary evaporator, gave a white solid residue which was recrystallized from H_2O to afford white needles of **4** (98 mg, 59%), mp

> 300°C: ^{1}H NMR (Me_2SO-d_6) δ 12.87 (s, 1 H, NH, exchangeable with D_2O), 10.72 (s, 1 H, NH, exchangeable with D_2O), 7.85-7.75 (t, J_{NH-CH2} = 5.0 Hz, 1 H, NH, exchangeable with D_2O), 7.70 (s, 1 H, imidazole CH), 3.67-3.66 (d, J_{CH2-NH} = 5.2 Hz, 2 H, CH_2); ^{13}C NMR (Me_2SO-d_6) δ 168.23 (s, C=O), 162.33 (s, C=O), 141.63 (s, junctional C next to 7-ring NH), 137.13 (d, imidazole C-2), 111.37 (s, junctional C next to 7-ring C=O), 46.3 (t, CH_2); IR (KBr) 3412, 1672, 1650 cm^{-1}; mass spectrum m/e 166 (M^+), 137, 110, 82; UV (H_2O) λ_{max} 268.5 nm (ε = 7.2 x 10^3), (pH 12.8) 293 (7.6 x 10^3). Anal. Calcd for $C_6H_6N_4O_2 \cdot \frac{1}{4} H_2O$: C, 42.20; H, 3.80; N, 32.81. Found: C, 42.50; H, 3.88; N, 32.95.

The aqueous filtrate from the above recrystallization was evaporated to dryness by azeotroping with toluene several times. The residue was suspended in excess dry MeOH, and the white solid (NaCl) was filtered. The filtrate, upon standing in a freezer overnight, afforded white crystals of **10** (53 mg, 29%), mp 220 °C (dec): ^{1}H NMR (Me_2So-d_6) δ 7.65-7.63 (t, J_{NH-CH2} = 5.0 Hz, 1 H, NH, exchangeable with D_2O), 7.11 (s, 1 H, CH of the imidazole), 5.52 (br s, 2 H, NH_2, exchangeable with D_2O); 3.85-3.84 (d, J_{CH2-NH} = 5.5 Hz, 2 H, CH_2); IR (KBr) 3600-3200 (br), 1650, 1632 cm^{-1}; mass spectrum m/e 184 (M^+), 166, 137, 110, 82; UV (MeOH) λ_{max} 266.5 nm, (pH = 5.4) 267.0 (ε 4.9 x 10^3), (pH = 12.8) 275.5 (7.3 x 10^3), (pH = 0.5) 266.5 (5.6 x 10^3). Anal. Calcd for $C_6H_8N_4O_3$: C, 39.13; H, 4.47; N, 30.42. Found: C, 39.14; H, 4.37; N, 30.32.

Ring-closure of 10 with Glacial Acetic Acid. The procedure used was analogous to the one reported.[2] The spectral data of the compound were identical with those of **4** obtained above.

4,5,7,8-Tetrahydro-6H-3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl) imidazo[4,5-e][1,4]diazepine-5,8-dione (11) and 4,5,7,8-Tetrahydro-6H-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazo[4,5-e][1,4]diazepine-5,8-dione (12). Vorbrüggen Ribosydation[4] of 4. A suspension of **4** (0.4 g, 2.4 mmol) and $(NH_4)_2SO_4$ (50 mg) in 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (35 mL) was refluxed under N_2 for 5-6 h to form a clear solution. The solution was cooled and evaporated to dryness. The residue was co-evaporated with dry toluene (3 x 10 mL) and the dry residue was dissolved in freshly distilled dry CH_3CN (30 mL). To this solution, maintained under N_2, were added 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose, followed by HMDS (0.8 mL, 3.79 mmol), chlorotrimethylsilane (0.48 mL, 3.78 mmol), triflic acid (1.0 mL, 11.3

mmol). The reaction mixture was stirred at room temperature for 17 h, when a TLC [silica gel, toluene: acetic acid: H_2O (5:5:1)] indicated the formation of two major UV absorbing spots. The mixture was diluted with CH_2Cl_2 (100 mL) and washed successively with saturated $NaHCO_3$ solution and H_2O (50 mL). The aqueous phase was extracted once with CH_2Cl_2 (50 mL). The combined CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was mixed with silica gel (2.5 g, 40–63 μm), evaporated to dryness, and the residue was loaded onto a flash chromatography column of silica gel (100 g, 40–63 μm) and the column was eluted first with a mixture of EtOAc–toluene (1:1) to afford **12**, followed by EtOAc–toluene (9:1) to give **11**.

Compound **11** was further purified by trituration with hexane–Et_2O, followed by recrystallization from hexane–CH_2Cl_2, white powder, yield 200 mg (14%), mp 143–145 °C with sintering at 135 °C: ^{1}H NMR (Me_2SO–d_6) δ 10.96 (s, 1 H, exchangeable with D_2O, N^4–H), 8.07 (s, 1 H, imidazole CH), 8.04–7.34 (m, 16 H, 1 H exchangeable with D_2O, 3 x OC_6H_5 + N^7–H), 6.40–6.35 (d, J_{CH-CH} = 4.6 Hz, 1 H, anomeric CH), 6.05–6.0 (m, 2 H, ribose CH's), 4.85–4.70 (m, 3 H, ribose CH's + CH_2), 3.66 (m, 2 H, sharp singlet with D_2O exchange, 7-ring CH_2).

Trituration with Et_2O, followed by recrystallization from hexane–EtOAc gave **12** as a white powder (0.75 g, 51%), mp 129–131 °C: ^{1}H NMR (Me_2SO–d_6) δ 10.86 (s, 1 H, exchangeable with D_2O, N^4–H), 8.2 (s, 1 H, imidazole CH), 8.06–7.42 (m, 16 H, 1 H exchangeable with D_2O, 3 x OC_6H_5 + N^7–H), 6.76–6.71 (d, J_{CH-CH} = 3.5 Hz, 1 H, anomeric CH), 6.02–5.97 (m, 2 H, ribose CH's), 4.75 (br s, 3 H, ribose CH's + CH_2), 3.67–3.64 (m, 2 H, sharp singlet with D_2O exchange, 7-ring CH_2).

4,5,7,8-Tetrahydro-6H-3-(β-D-ribofuranosyl)imidazo[4,5-e][1,4]-diazepine-5,8-dione (2). To a three-neck flask, maintained under N_2, was introduced dry MeOH (15 mL). Freshly cut sodium (20 mg, 0.87 mg.atom) was added with stirring to form a clear solution. Compound **11** (200 mg, 0.32 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was evaporated to dryness, and the residue was dissolved in H_2O, and neutralized with 0.5 N HCl. The reaction mixture was evaporated to dryness by azeotroping with toluene, and the residue was extracted with hot dry MeOH. Concentration of MeOH extracts, followed by precipitation with $CHCl_3$ gave a white powder which was recrystallized from MeOH into white crystals of **2** (79 mg, 81%), mp: changes color at 150 °C and decomposes

gradually at >170 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.87 (s, 1 H, imidazole CH), 7.82 (t, J_{NH-CH2} = 5.4 Hz, 1 H, NH, exchangeable with D_2O), 5.66-5.65 (d, J_{CH-CH} = 6 Hz, 1 H, anomeric CH), 5.21-5.20 (d, J_{OH-CH} = 4.5 Hz, 1 H, ribose OH, exchangeable with D_2O), 4.23-4.20 (t, J_{CH-CH} = 5.45 Hz, 1 H, ribose CH), 4.06-4.05 (d, J_{OH-CH} = 3.5 Hz, 1 H, ribose OH, exchangeable with D_2O), 4.07-4.04 (dd, J_{OH-CH} = 4.5 & 3.5 Hz, 1 H, ribose OH, exchangeable with D_2O), 3.93-3.91 (dd, J_{CH-CH} = 3 Hz, 1 H, ribose CH), 3.67-3.56 (m, 5 H, ribose CH + CH_2 + 7-ring CH_2); ^{13}C NMR (Me_2SO-d_6) δ 168.95 (s, C=O), 164.50 (s, C=O), 134.02 (d, imidazole C-2), 131.89 (s, junctional C next to 7-ring NH), 122.44 (s, junctional C next to 7-ring C=O), 88.06 (d, ribose CH), 85.44 (d, ribose CH), 74.31 (d, ribose CH), 70.01 (d, ribose CH), 60.83 (t, ribose CH_2), 45.59 (t, ring CH_2); IR (KBr) 3360-2700 (br), 1690, 1640 cm^{-1}; UV λ_{max} (pH 6.1) 263 nm (ε 7.1 x 10^3), (pH 13.2) 294 (8 x 10^3), 247 (9.2 x 10^3). Anal. Calcd for $C_{11}H_{14}N_4O_6 \cdot 3/4\ H_2O$: C, 42.38; H, 5.01; N, 17.97: Found: C, 42.32; H, 5.02; N, 17.99.

4,5,7,8-Tetrahydro-6H-1-(β-D-ribofuranosyl)imidazo[4,5-e][1,4]-diazepine-5,8-dione (3). It was prepared from **12** by the procedure described above for compound **2**. It was recrystallized from $CHCl_3$-MeOH as shiny, white crystals, yield 84%, mp 275-278 °C: ^{1}H NMR (Me_2SO-d_6) δ 10.78 (s, 1 H, NH, exchangeable with D_2O), 8.24 (s, 1 H, imidazole CH), 8.07-8.05 (t, J_{NH-CH2} = 5.2 Hz, 1 H, NH, exchangeable with D_2O), 6.21-6.20 (d, J_{CH-CH} = 4.0 Hz, 1 H, anomeric CH), 5.43-5.42 (d, J_{OH-CH} = 5.2 Hz, 1 H, ribose OH, exchangeable with D_2O), 5.078-5.065 (d, J_{OH-CH} = 5.2 Hz, 1 H, ribose OH, exchangeable with D_2O), 5.05-5.04 (d, J_{OH-CH} = 5.6 Hz, 1 H, ribose OH, exchangeable with D_2O), 4.10-4.08 (m, 1 H, ribose CH), 4.04-4.03 (m, 1 H, ribose CH), 3.87-3.85 (m, 1 H, ribose CH), 3.71-3.67 (m, 2 H, CH_2), 3.66-3.56 (m, 2 H, CH_2); ^{13}C NMR (Me_2SO-d_6) δ 168.65 (s, C=O), 161.85 (s, C=O), 143.18 (s, junctional C next to 7-ring NH), 137.75 (d, imidazole C-2), 110.82 (s, junctional C next to 7-ring C=O), 89.24 (d, ribose CH), 84.20 (d, ribose CH), 75.58 (d, ribose CH), 68.97 (d, ribose CH), 60.24 (t, ribose CH_2), 45.84 (t, ring CH_2); IR (KBr) 3500-3000 (br), 1682, 1632 cm^{-1}; UV λ_{max} (pH 7.2) 267.5 nm (ε 7.2 x 10^3), (pH 12.8) 294 (8 x 10^3), (pH 0.69) 263.5 (7.6 x 10^3). Anal. Calcd for $C_{11}H_{14}N_4O_6$: C, 44.25; H, 4.69; N, 18.77: Found: C, 44.27; H, 4.79; N, 18.73.

4,5,7,8-Tetrahydro-6H-3-(β-D-ribofuranosyl)imidazo[4,5-e][1,4]-diazepine-5,8-dione (2) and 5-Amino-4-(N-carboxymethyl)carbamoyl-1-β-D-ribofuranosylimidazole (15). Ring-closure of 13 with Sodium Methoxide/Methanol. Dry MeOH (100 mL), which was freshly distilled over sodium, was introduced in a three-neck flask, maintained under a stream of N_2. Freshly cut sodium (1.0 g, 43.5 mg.atom) was added with stirring to form a clear solution. Compound **13** (3.5 g, 7.6 mmol) was added in portions and the reaction mixture was heated at reflux for 6 h. TLC [silica gel, $CHCl_3$-MeOH (3:2)] indicated the formation of two new UV absorbing compounds. The reaction mixture was cooled, neutralized with 1N HCl, and evaporated to dryness. The residue was purified by flash chromatography on silica gel (40-63 μm), employing (a) $CHCl_3$-MeOH (3:1) to collect the faster eluting **2**, followed by (b) $CHCl_3$-MeOH (1:1) to collect the slower eluting **15**.

Compound **2** was recrystallized from MeOH as white crystals (1.2 g, 53%). Melting point and spectral data of this compound were identical to those of **2** obtained from **11**, described above.

Compound **15** was isolated as the sodium salt and recrystallized from acetonitrile into a white powder (0.4 g, 17 %), ^1H NMR (Me_2SO-d_6) δ 7.45-7.44 (t, J_{NH-CH2} = 4.2 Hz, 1 H, NH, exchangeable with D_2O), 7.32 (s, 1 H, imidazole CH), 5.8 (br s, 2 H, NH_2, exchangeable with D_2O), 5.46-5.44 (d, J_{CH-CH} = 4.8 Hz, 1 H, anomeric CH), 5.3-5.15 (br, 3 H, 3 x OH, exchangeable with D_2O), 4.27-4.24 (t, 1 H, ribose CH), 4.04-4.02 (m, 1 H, ribose CH), 3.88-3.87 (m, 1 H, ribose CH), 3.71-3.69 (d, J_{CH2-NH} = 4.2 Hz, 2 H, side-chain CH_2), 3.57-3.56 (m, 2 H, ribose CH_2); IR (KBr) 3400-3100 (br), 1630-1560 (br) cm^{-1}; UV λ_{max} (pH 6.8) 266 (ε 12.9 x 10^3), (pH 12.5) 266.5 (12.8 x 10^3), (pH 0.7) 269.5 (10.2 x 10^3).

Anal. Calcd for $C_{11}H_{15}N_4O_7Na$: C, 39.08; H, 4.97; N, 16.08. Found: C, 39.01; H, 4.46; N, 16.56.

Thermolysis of 15 in Glacial Acetic Acid. A mixture of **15** (100 mg, 2.9 mmol) and glacial acetic acid (10 mL) was heated at reflux for 18 h. The reaction mixture was cooled and rotary evaporated to dryness. Coevaporation of the residue with toluene (3 x 3 mL), followed by trituration with a small amount of H_2O gave white crystals, whose TLC behavior, melting point, and HPLC mobility were identical to those of **4**, obtained by ring closure of **7** or **10**, described above.

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