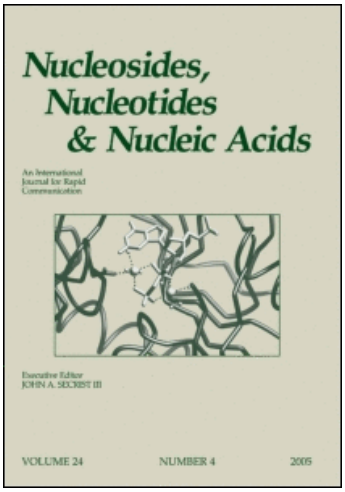

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Synthesis of Ring-Expanded Xanthines and Xanthosines Containing the Imidazo[4,5-d][1,3]diazepine Ring System

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SYNTHESIS OF RING-EXPANDED XANTHINES AND XANTHOSINES CONTAINING THE IMIDAZO[4,5-d][1,3]DIAZEPINE RING SYSTEM

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ABSTRACT: Syntheses of 4,5,6,8-tetrahydro-1H,7H-imidazo[4,5-d][1,3]-diazepine-5,8-dione (**9**), its 3-benzyl derivative (**8**), and 3- and 1-ribosyl derivatives, (**12**) and (**13**), respectively, are reported. Single-crystal X-ray analyses of **8** and **9** are also presented.

Ring-expanded ("fat") purine heterocycles, nucleosides, and nucleotides are of chemical, biochemical, and biophysical interest.[1-3] From a chemical standpoint, their synthesis and investigation of physico-chemical properties are important. Attempted synthesis of "fat" adenine analogue (**1**) resulted in the discovery of two novel rearrangements.[1] While **2** was found to be more stable than **1**, its synthesis nevertheless proved to be far from trivial.[2] From a biophysical perspective, ring-expanded purines are potentially excellent probes for steric and conformational constraints of the nucleic acid double-helix. In this context, exploring syn/anti base-ribose and endo/exo sugar pucker conformations of nucleosides (primary structure), as well as helical structure, stability, and conformation of polynucleotides (secondary structure) containing the heterocyclic

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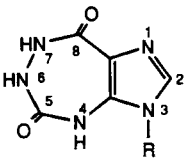

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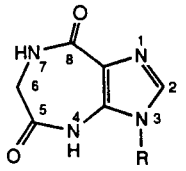

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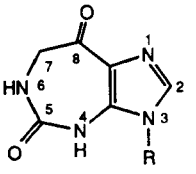

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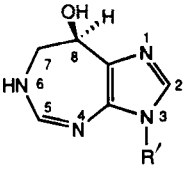

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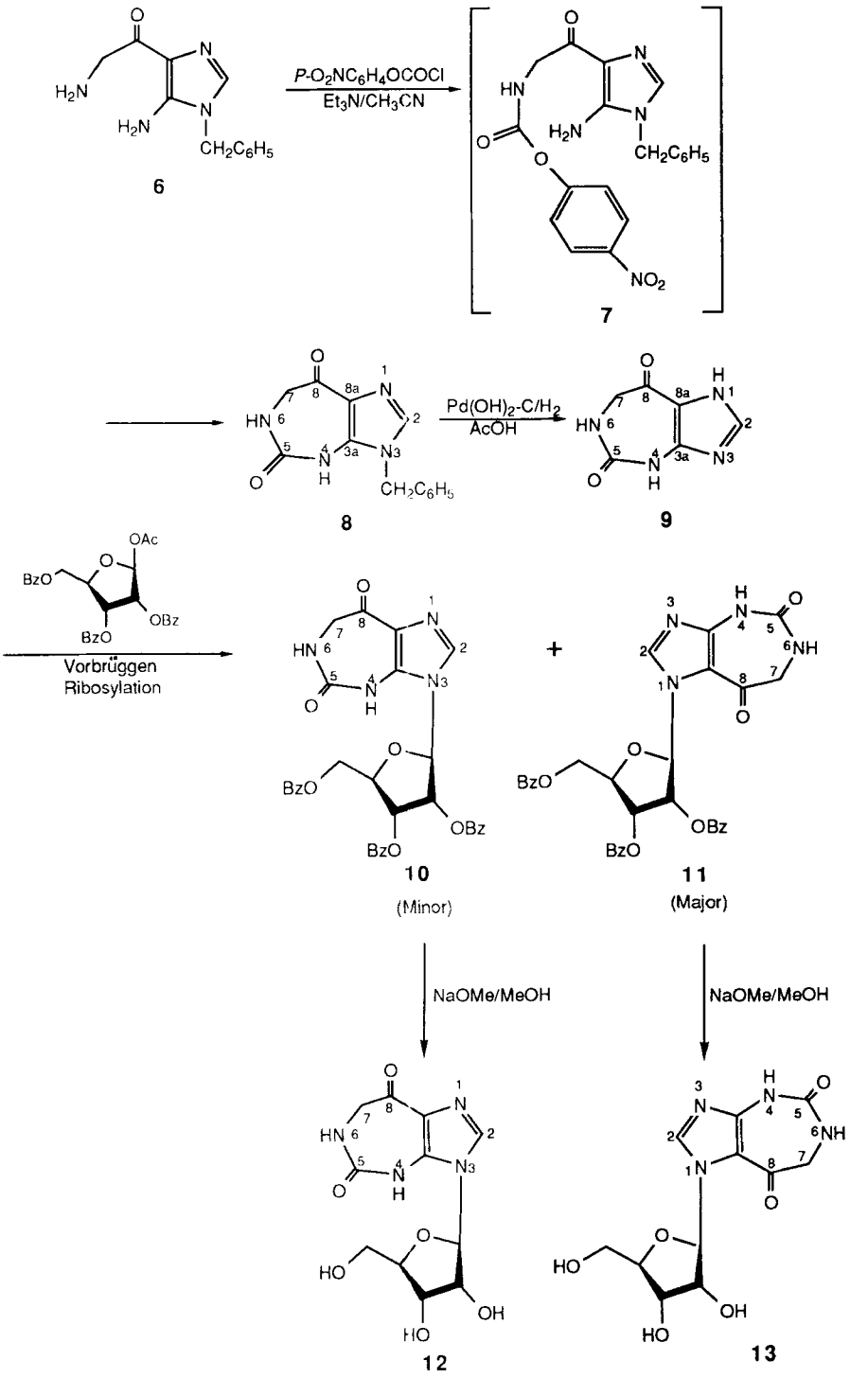
Coformycin: R′ = β-D-ribofuranosyl
Pentostatin: R′ = 2′-deoxy-β-D-ribofuranosyl

system 3 proved to be interesting and rewarding.[3] We now report the synthesis of two other ring-expanded nucleosides, 12 and 13, which contain the heterocyclic system 4, and are structural analogues of 3. The ring skeleton of 4, the imidazo[4,5-d][1,3]diazepine nucleus, is present in the naturally occurring synergistic antitumor antibiotics, coformycin and pentostatin (5),[4] that are the strongest known inhibitors of adenosine deaminase ($K_i \approx 10^{-11}$).[5] We also report here the single-crystal X-ray structures of the aglycon 9 and its 3-benzyl derivative 8. In view of a number of alleged seven-membered and larger ring heterocycles that were later found to be only 5- or 6-membered ring systems,[6] structure confirmation by single-crystal X-ray diffraction analyses was warranted.

The target ring system 4 was synthesized as follows (**Scheme I**): The diamine 6[4f] was ring-closed with p-nitrophenyl chloroformate to give the 3-benzyl derivative 8. The latter upon debenzylation by catalytic hydrogenation yielded the parent ring-expanded xanthine 9. The structures of both 8 and 9 were confirmed by single-crystal X-ray diffraction analyses. The ORTEP views along with the employed atom numbering schemes for compounds 8 and 9 are shown in **Figure 1**. As

SCHEME I



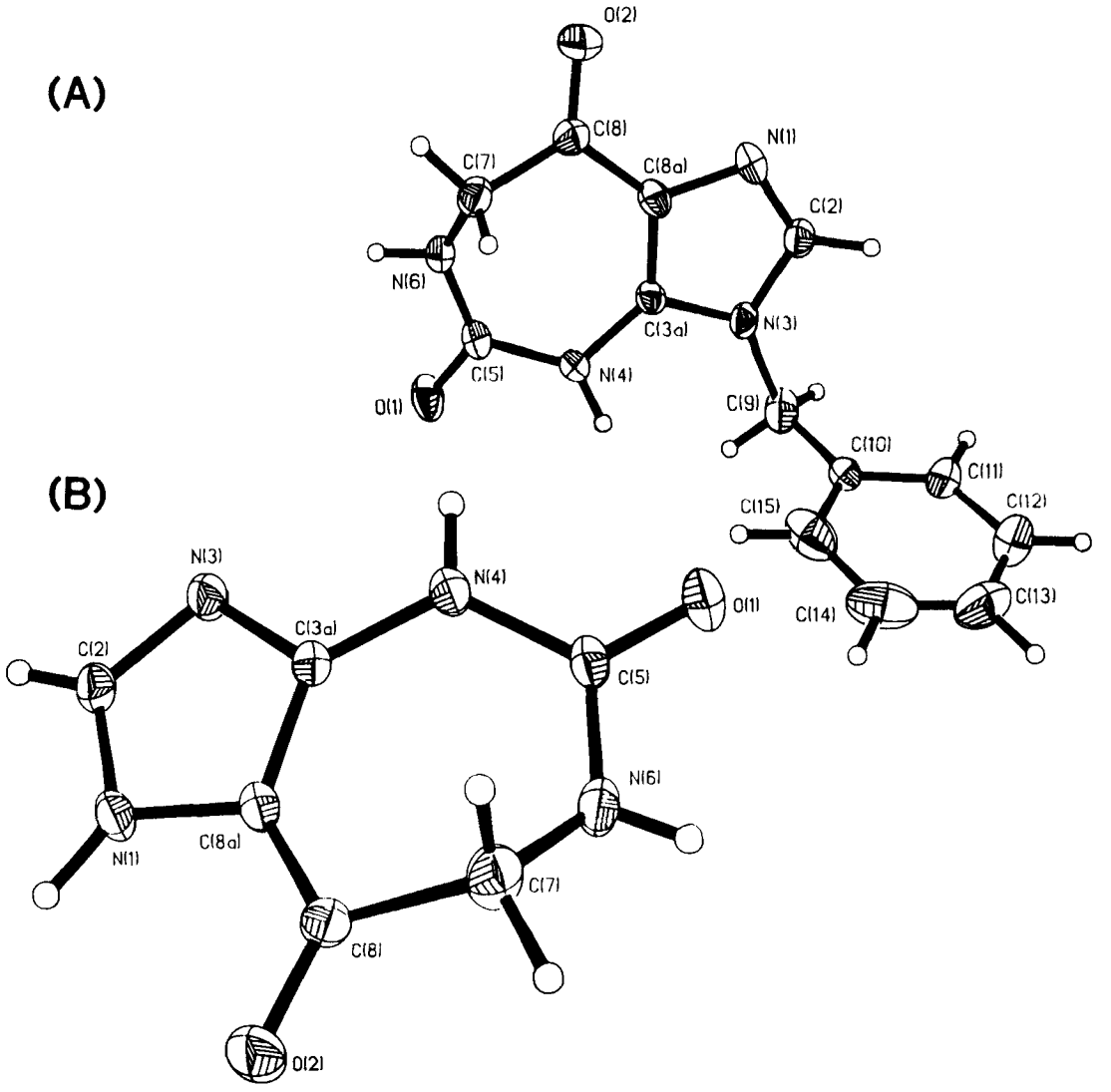


FIG. 1: The ORTEP view showing the atom numbering scheme and thermal ellipsoids at the 30% probability level of (a) **8** and (b) **9**.

anticipated, the seven-membered ring in each is puckered. While the two bonds of the diazepine ring attached to the two carbons at the ring-junction are essentially coplanar with the imidazole ring, the C-5 atom of **8** and **9** showed deviations of 0.7033 and 0.7080 Å, respectively, from a least squares plane, calculated by inclusion of N-1, C-2, N-3,

C-3a, N-4, C-7, C-8, O-1, and O-2 atoms. Furthermore, the C-5 (C=O) to C-8 (C=O) torsional angle is ≃ 75°±3. In the unsubstituted compound **9**, the imidazole hydrogen was located at the 1-position, whereas the precursor **8** had the benzyl group at the 3-position. The crystal structure of **9** revealed the presence of a molecule of water in the unit cell. There were two types of hydrogen bonds, one involving two molecules of **9** with two intermolecular hydrogen bonds of distance N(3)....N(4) = 2.898 Å each, and the other involving a water molecule and four separate molecules of **9** with intermolecular hydrogen bonds of distances $H_2O(3)....N(6)$ = 2.949 Å, $H_2O(3)....O(1)$ = 2.757 Å, $H_2O(3)....N(1)$ = 2.791 Å, $H_2O(3)....O(2)$ = 2.736 Å.

Ribosylation of **9** by the Vorbrüggen method[7] yielded two regioisomeric nucleosides **10** and **11** in a 1:3 ratio with a 50% total yield. The two isomers were distinguished from each other based upon the anticipated and observed lower field ^{1}H NMR signal for H-2 of **11** as compared with that of **10**; the electron-withdrawing C-8 carbonyl group of **11** and the electron-donating N-H group at position-4 of **10** would cause, respectively, deshielding and shielding of the H-2 proton through resonance. We have recently observed a similar effect in the analogous regioisomeric nucleosides containing the ring system **3**.[3b] Deprotection of the sugar hydroxyl groups of **10** and **11** with sodium methoxide/methanol afforded the two target nucleosides **12** and **13**.

Our results of ribosylation differ considerably from those reported for a similar ribosylation of the corresponding hypoxanthine analogue of **9**,[4c] wherein a single nucleoside, the inosine analogue of **10**, has been reported to have been isolated. Our repeated attempts gave only a mixture of **10** and **11**, the latter being the major product.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded at 80 or 500 MHz, on an IBM NR/80 or a General Electric GN-500 spectrometer, respectively. The reported spectral data are relative to Me_4Si as an internal reference standard. Electron impact (EI) mass spectra were recorded at 70 eV on a Hewlett Packard 5988A mass spectrometer. X-Ray diffraction analyses were carried out at the Department of Chemistry, Southern Methodist University, Dallas, TX on an automatic Nicolet R_{3m}/V diffractometer.

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; acetonitrile was distilled from CaH_2, followed by distillation over 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.

3-Benzyl-4,5,6,8-tetrahydro-7H-imidazo[4,5-d][1,3]diazepine-5,8-dione (8). 2-Amino-1-(1-benzyl-5-amino-1H-imidazol-4-yl)ethanone dihydrochloride[5f] (900 mg, 3.0 mmol) was dissolved in H_2O (20 mL) and was cooled in an ice-water bath. Aqueous NaOH solution (2 N) was added dropwise with constant stirring until the pH of the solution reached 13-14. The solution was extracted with AcOEt (3 X 25 mL), and the combined extracts were dried over anhydrous $MgSO_4$. Filtration, followed by rotary evaporation of the filtrate under reduced pressure, gave a solid which was recrystallized from toluene as pale yellow crystals of **6** (400 mg, 1.7 mmol, 60%), mp 156-162 °C: ^1H NMR (Me_2SO-d_6) δ 7.26 (m, 6, Ph-H + imidazole CH), 6.5 (s, 2, NH_2 aromatic, exchangeable with D_2O), 5.09 (s, 2, benzyl CH_2), 3.69 (s, 2, side-chain CH_2), 1.7 (br s, 2, NH_2 aliphatic, exchangeable with D_2O); IR (KBr) 3400, 3360, 3260, 3100, 1650 cm^{-1}; mass spectrum (70 eV) m/z 230 (M^+), 201, 173, 91; UV λ_{max} (MeOH) 297 nm, (pH 13) 297.

A mixture of **6** (322 mg, 1.4 mmol) and dry CH_3CN (30 mL) was warmed, under N_2, in a three-necked flask, fitted with a reflux condenser and a guard tube, to form a clear solution. p-Nitrophenyl chloroformate (297 mg, 1.47 mmol) was added, whereupon a white solid separated. After addition of triethylamine (0.32 mL, 28.7 mmol), the white solid dissolved to give a clear solution. The solution was stirred at reflux for 5 h when most of **8** separated as a solid. The reaction mixture was cooled and the solid obtained was collected by filtration and was washed with cold CH_3CN, followed by Et_2O. The solid was recryastallised from EtOH as colorless crystals of **8** (210 mg, 0.82 mmol, 59%), mp 214 °C (dec): ^1H NMR (Me_2SO-d_6) δ 9.79 (s, 1, NH-4, exchangeable with D_2O), 7.63 (s, 1, imidazole CH), 7.3 (m, 6, Ph-H + NH-6, exchangeable with D_2O), 5.36 (s, 2, benzyl CH_2), 3.65 (d, J = 4.9 Hz, 2, ring CH_2, changing to a singlet upon D_2O exchange); IR (KBr) 3400, 3100, 3000, 1700, 1650 cm^{-1}; mass spectrum (70 eV) m/z 256 (M^+), 200, 91; UV λ_{max} (MeOH) 284.5 nm, (pH 13) 333.5.

Anal. Calcd for $C_{13}H_{12}N_4O_2 \cdot 1/4\ H_2O$: C, 59.88; H, 4.79; N, 21.49. Found: C, 60.01; H, 4.84; N, 21.59.

4,5,6,8-Tetrahydro-1H,7H-imidazo[4,5-d][1,3]diazepine-5,8-dione (9). Compound (8) (510 mg, 2 mmol) was dissolved in dry acetic acid (10 mL) in a hydrogenation bottle. To this solution was added $Pd(OH)_2$ on carbon (20%, 80 mg), and the mixture was hydrogenated in a Parr hydrogenator at 40 psi for 16 h. The catalyst was removed by filtration through Celite and was washed with acetic acid (5 mL). The filtrate, along with the washings, was evaporated to dryness under reduced pressure to obtain a colorless residue. It was triturated with cold water, and the solid which separated was collected by filtration. It was recrystallized from water as colorless crystals of 9 (275 mg, 1.65 mmol, 83%), mp > 310 °C: ^{1}H NMR (Me_2SO-d_6) δ 12.88 (br s, 1, NH-1, exchangeable with D_2O), 9.75 (s, 1, NH-4, exchangeable with D_2O), 7.74 (s, 1, imidazole CH), 7.14 (br s, 1, NH-6, exchangeable with D_2O), 3.65 (d, J = 4.5 Hz, 2, ring CH_2, changing to a singlet upon D_2O exchange); IR (KBr) 3350–2950, 1750–1650 cm^{-1}; mass spectrum (70 eV) m/z 166 (M^+), 138, 110, 83; UV λ_{max} (H_2O) 278.5 nm, (pH 13–14) 304.0.

Anal. Calcd for $C_6H_6N_4O_2$: C, 43.38; H, 3.64; N, 33.72. Found: C, 43.29; H, 3.65; N, 33.66.

3-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-4,5,6,8-tetrahydro-7H-imidazo[4,5-d][1,3]diazepine-5,8-dione (10) and 1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-4,5,6,8-tetrahydro-7H-imidazo[4,5-d][1,3]diazepine-5,8-dione (11). A mixture of 9 (500 mg, 3 mmol) and 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (1.51 g, 3 mmol) in dry CH_3CN (30 mL) was stirred at room temperature for 10 min, under N_2, in a three-necked flask equipped with a reflux condenser and a guard tube filled with anhydrous $CaCl_2/CaSO_4$. Freshly distilled 1,1,1,3,3,3-hexamethyldisilazane (0.7 mL, 3.3 mmol), freshly distilled chlorotrimethylsilane (0.45 mL, 3.6 mmol) and trifluoro-methane sulfonic acid (0.3 mL, 3.6 mmol) were added consecutively to the above mixture whereupon it became slightly warm. The reaction was monitored by TLC (toluene:acetic acid:water 5:5:1). After stirring for 1 h at room temperature, the TLC showed partial completion of the reaction. The reaction mixture was heated at reflux for 2 h to obtain a clear solution whose TLC showed two different UV-absorbing spots. The solution was cooled, CH_3CN (10 mL) and CH_2Cl_2 (30 mL) were added, and the mixture was extracted with saturated aqueous solution of $NaHCO_3$. The organic layer was separated,

and the aqueous layer was once again extracted with CH_2Cl_2 (10 mL), and the combined organic extracts were washed with saturated aqueous solution of NaCl. The organic layer was dried over anhydrous $MgSO_4$, filtered, and the filtrate was evaporated to dryness under reduced pressure to obtain a solid.

The above solid, a mixture of two compounds, was dissolved in CH_2Cl_2 (10 mL), and the solution was mixed with silica gel (40-63 μm, 2 g) and rotary evaporated to dryness. The residue was suspended in CH_2Cl_2 (10 mL), and the resulting slurry was loaded onto a flash chromatography column packed with silica gel (40-63 μm, 100 g) in CH_2Cl_2. The column was eluted with a mixture of CH_2Cl_2-EtOAc (1:1) (250 mL) at 10 mL/min at 6 psi, followed by a mixture of EtOAc-isopropanol (9:1) (200 mL). The appropriate UV-absorbing fractions were pooled and evaporated to dryness. The residue was triturated with EtOAc and the colorless solid obtained was collected by filtration. It was further purified by recrystallization from CH_2Cl_2-petroleum ether (40-60°) to obtain colorless crystals of **11** (525 mg, 0.86 mmol, 35%), mp 239 °C: ^{1}H NMR (Me_2SO-d_6) δ 9.94 (d, J = 1.95 Hz, 1, NH-4, exchangeable with D_2O), 8.23 (s, 1, imidazole CH), 7.63 (m, 16, Ph-H + NH-6, exchangeable with D_2O), 6.69 (d, J = 2.7 Hz, 1, anomeric H), 5.95 (s, 2, ribose-H), 4.8 (s, 3, ribose-H), 3.65 (d, J = 4.8 Hz, 2, ring CH_2, singlet upon D_2O exchange).

Anal. Calcd for $C_{32}H_{26}N_4O_9 \cdot \frac{1}{2}\ H_2O$: C, 62.03; H, 4.39; N, 9.04. Found: C, 62.05; H, 4.17; N, 9.02.

The column was further eluted with EtOAc-isopropanol (4:1) at 10 mL/min at 6 psi. The fractions collected were found to be a mixture of two compounds. All the fractions were pooled and evaporated to dryness under reduced pressure. The residue obtained was dissolved in $CHCl_3$ (2 mL) and loaded onto a Chromatotron™ plate (1 mm thickness, Kieselgel 60 GF_{254}). It was eluted with a mixture of $CHCl_3$-MeOH (4:1). The appropriate UV-absorbing fractions were pooled and rotary evaporated to dryness to obtain **10** as a pinkish solid (225 mg, 0.37 mmol, 15%), mp 252 °C: ^{1}H NMR (Me_2SO-d_6) δ 9.99 (s, 1, NH-4, exchangeable with D_2O), 8.02-7.40 (m, 17, Ph-H + imidazole CH + NH-6, exchangeable with D_2O), 6.63 (d, J = 6.0 Hz, 1, anomeric H), 6.04-5.93 (m, 2, ribose-H), 4.79-4.68 (m, 3, ribose-H), 3.65 (d, J = 4.8 Hz, 2, ring CH_2, singlet upon D_2O exchange).

Anal. Calcd for $C_{32}H_{26}N_4O_9 \cdot 1H_2O$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.39; H, 4.22; N, 8.88.

3-β-D-Ribofuranosyl-4,5,6,8-tetrahydro-7H-imidazo[4,5-d][1,3]-diazepine-5,8-dione (12). To a well-stirred solution of **10** (100 mg, 0.16 mmmol) in dry MeOH (5 mL) and CH_2Cl_2 (1 mL) in a 25 mL three-necked flask equipped with a reflux condenser and maintained under N_2, was added dropwise a freshly prepared solution of NaOMe in MeOH (3 mL) until the pH of the solution reached 13-14 (litmus). The mixture was stirred at room temperature for 30 min, cooled in an ice-water bath, and carefully neutralized to pH 6-7 with acetic acid. The solvents were removed under reduced pressure, the residue was washed with Et_2O and triturated with cold H_2O to obtain **12** as colorless crystals (33 mg, 0.11 mmol, 69%), mp >250 °C: ^{1}H NMR (Me_2SO-d_6) δ 9.89 (br s, 1, NH-4, exchangeable with D_2O), 7.8 (s, 1, imidazole CH), 7.58 (br s, 1, NH-6, exchangeable with D_2O), 5.80 (d, J = 7.0 Hz, 1, anomeric H), 4.3-3.48 (m, ribose-H + ribose OH), 3.65 (d, J = 4.0 Hz, 2, ring CH_2, singlet upon D_2O exchange).

1-β-D-Ribofuranosyl-4,5,6,8-tetrahydro-7H-imidazo[4,5-d][1,3]-diazepine-5,8-dione (13). This compound was prepared from **11** (300 mg, 0.49 mmol), using the procedure described above for **12**. The product was recrystallized from water to give colorless crystals of **13** (111 mg, 0.37 mmol, 76%), mp 266 °C (dec.): 1H NMR (Me_2SO-d_6) δ 9.77 (br s, 1, NH-4, exchangeable with D_2O), 8.28 (s, 1, imidazole CH), 7.21 (br s, 1, NH-6, exchangeable with D_2O), 6.24 (d, J = 2.7 Hz, 1, anomeric H), 5.34 (d, J = 4.9 Hz, 1, ribose-OH, exchangeable with D_2O), 5.0 (t, 2, ribose-OH, exchangeable with D_2O), 3.65-4.05 (m, 5, ribose-H), 3.65 (d, J = 4.6 Hz, 2, ring CH_2, singlet upon D_2O exchange); UV λ_{max} (H_2O) 239.5, 291.5 nm, (pH 13) 294.0, 341.0, (pH 2) 287.5.

Anal. Calcd for $C_{11}H_{14}N_4O_6$: C, 44.30; H, 4.73; N, 18.78; Found: C, 44.25; H, 4.74; N, 18.69.

Single Crystal X-ray Diffraction Analyses of Compounds 8 and 9. Suitable crystals were grown through slow crystallization from the appropriate solvents (see pertinent experimental data above). The unit cell dimensions were obtained by a least-squares fit of the angles of 25 centered reflections in the range of 10° <2θ <25°. Intensity data were collected by using a θ/2θ scan type in the range of 3° <2θ <50°, using graphite monochromated Mo Kα (λ = 0.71073 Å) radiation. Three standard reflections monitored after every 100 reflections did not show

Table I. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2x10^3$) for compound 8

	x	y	z	U(eq)
O(1)	5429(4)	3762(4)	-1973(4)	55(4)
O(2)	3495(3)	3449(4)	882(5)	63(4)
N(1)	4887(5)	4679(4)	1441(5)	45(4)
N(3)	5960(4)	5003(4)	773(5)	39(4)
N(4)	5635(4)	4134(4)	-470(5)	39(4)
N(6)	4435(4)	3328(4)	-1023(6)	43(4)
C(2)	5585(5)	5125(6)	1462(6)	42(5)
C(3a)	5444(5)	4404(5)	291(5)	33(4)
C(5)	5152(5)	3727(5)	-1191(5)	38(5)
C(7)	4090(5)	3017(5)	-149(6)	43(5)
C(8)	4070(5)	3562(5)	501(6)	39(5)
C(8a)	4776(5)	4206(5)	713(6)	39(5)
C(9)	6759(5)	5456(6)	637(6)	52(5)
C(10)	7202(5)	5316(5)	1334(6)	38(5)
C(11)	7603(5)	5845(5)	1998(6)	49(5)
C(12)	8044(7)	5752(7)	2641(8)	75(7)
C(13)	8087(8)	5127(9)	2628(10)	80(8)
C(14)	7716(9)	4591(9)	2012(12)	93(9)
C(15)	7261(7)	4679(6)	1343(9)	75(7)

Table II. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2x10^3$) for compound 9

	x	y	z	U(eq)
O(1)	2382(3)	13770(1)	611(1)	41(1)
O(2)	8535(3)	9409(2)	2215(1)	48(1)
O(3)	8958(3)	15346(2)	1534(1)	40(1)
N(1)	5627(3)	7791(2)	1087(1)	32(1)
N(3)	2146(3)	8667(2)	407(1)	31(1)
N(4)	1933(3)	11239(2)	758(1)	32(1)
N(6)	5324(3)	12631(2)	1401(1)	38(1)
C(2)	3701(4)	7478(2)	591(1)	32(1)
C(3a)	3144(3)	9819(2)	826(1)	27(1)
C(5)	3188(3)	12608(2)	919(1)	31(1)
C(7)	5712(4)	11634(2)	2017(1)	41(1)
C(8a)	5332(3)	9318(2)	1259(1)	30(1)
C(8)	6733(3)	10045(2)	1845(1)	32(1)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table III. Bond lengths (Å) and bond angles (°) for compound 8

O(1)-C(5)	1.251 (11)	O(2)-C(8)	1.230 (13)
N(1)-C(2)	1.278 (12)	N(1)-C(8a)	1.379 (12)
N(3)-C(2)	1.365 (14)	N(3)-C(3a)	1.363 (9)
N(3)-C(9)	1.462 (11)	N(4)-C(3a)	1.379 (13)
N(4)-C(5)	1.400 (10)	N(6)-C(5)	1.320 (11)
N(6)-C(7)	1.435 (11)	C(3a)-C(8a)	1.381 (14)
C(7)-C(8)	1.489 (15)	C(8)-C(8a)	1.445 (10)
C(9)-C(10)	1.488 (15)	C(10)-C(11)	1.382 (12)
C(10)-C(15)	1.395 (19)	C(11)-C(12)	1.386 (19)
C(12)-C(13)	1.352 (27)	C(13)-C(14)	1.331 (21)
C(14)-C(15)	1.427 (25)		

C(2)-N(1)-C(8a)	105.1(9)	C(2)-N(3)-C(3a)	106.1(7)
C(2)-N(3)-C(9)	123.5(7)	C(3a)-N(3)-C(9)	130.3(8)
C(3a)-N(4)-C(5)	124.7(9)	C(5)-N(6)-C(7)	127.0(8)
N(1)-C(2)-N(3)	113.5(8)	N(3)-C(3a)-N(4)	121.5(8)
N(3)-C(3a)-C(8a)	105.5(8)	N(4)-C(3a)-C(8a)	133.0(7)
O(1)-C(5)-N(4)	117.4(8)	O(1)-C(5)-N(6)	123.2(7)
N(4)-C(5)-N(6)	119.4(8)	N(6)-C(7)-C(8)	113.9(8)
O(2)-C(8)-C(7)	122.0(7)	O(2)-C(8)-C(8a)	121.9(9)
C(7)-C(8)-C(8a)	116.0(9)	N(1)-C(8a)-C(3a)	109.8(7)
N(1)-C(8a)-C(8)	123.6(9)	C(3a)-C(8a)-C(8)	126.3(9)
N(3)-C(9)-C(10)	113.7(7)	C(9)-C(10)-C(11)	119.9(10)
C(9)-C(10)-C(15)	123.5(9)	C(11)-C(10)-C(15)	116.5(10)
C(10)-C(11)-C(12)	122.0(12)	C(11)-C(12)-C(13)	119.7(11)
C(12)-C(13)-C(14)	121.8(17)	C(13)-C(14)-C(15)	119.2(18)
C(10)-C(15)-C(14)	120.7(12)		

Table IV. Bond lengths (Å) and bond angles (°) for compound 9

O(1)-C(5)	1.232 (2)	O(2)-C(8)	1.228 (2)
N(1)-C(2)	1.323 (2)	N(1)-C(8a)	1.389 (2)
N(3)-C(2)	1.323 (2)	N(3)-C(3a)	1.363 (2)
N(4)-C(3a)	1.379 (2)	N(4)-C(5)	1.375 (2)
N(6)-C(5)	1.347 (2)	N(6)-C(7)	1.457 (3)
C(3a)-C(8a)	1.381 (2)	C(7)-C(8)	1.516 (3)
C(8a)-C(8)	1.425 (2)		

C(2)-N(1)-C(8a)	107.1(1)	C(2)-N(3)-C(3a)	104.5(1)
C(3a)-N(4)-C(5)	126.5(1)	C(5)-N(6)-C(7)	127.3(2)
N(1)-C(2)-N(3)	113.2(2)	N(3)-C(3a)-N(4)	118.7(1)
N(3)-C(3a)-C(8a)	110.7(1)	N(4)-C(3a)-C(8a)	130.6(2)
O(1)-C(5)-N(4)	119.6(2)	O(1)-C(5)-N(6)	121.8(2)
N(4)-C(5)-N(6)	118.6(1)	N(6)-C(7)-C(8)	115.1(2)
N(1)-C(8a)-C(3a)	104.5(1)	N(1)-C(8a)-C(8)	124.4(2)
C(3a)-C(8a)-C(8)	130.3(2)	O(2)-C(8)-C(7)	121.4(2)
O(2)-C(8)-C(8a)	122.9(2)	C(7)-C(8)-C(8a)	115.5(1)

any significant change in intensity during data collection. Intensities were corrected for Lorentz and polarization effects but not for absorption. The structures were determined by direct methods and all non-hydrogen atoms were found by using the program package SHELXTL-PLUS[8] and subsequent difference Fourier techniques. Full-matrix least-squares refinements were performed. Neutral atom scattering factors and anomalous scattering correction terms were taken from the International Tables for X-ray Crystallography.[9] The hydrogen atoms were located from difference Fourier maps and were included in the final refinement with fixed isotropic thermal parameters and with geometric constraints for CH_2 and phenyl protons, where applicable. The structure of **8** is of relatively lower quality as compared with that of **9** due to the high thermal motion of carbons in the phenyl ring. Refinement proceeded to convergence by minimizing the function $\Sigma w(|F_o| - |F_c|)^2$, where the weight, w, is $\sigma(F)^{-2}$. The discrepancy indices $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, and $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w(|F_o|)^2]^{1/2}$ are presented below in crystallographic data. The final atomic coordinates, bond lengths, and bond angles for **8** and **9** are collected in **Tables I-IV.**

Crystallographic Data. A. Compound 8: $C_{13}H_{12}N_4O_2$, $M_r = 256.3$, $D_x = 1.410$ g cm^{-3}, space group R3, $a = 20.872$ (6) Å, $b = 20.872$ (7) Å, $c = 14.404$ (3) Å, $\alpha = 90.0$, $\beta = 90.0$, $\gamma = 120.0$, $V = 5434$ (3) Å^3, $\mu = 0.093$ mm^{-1}. Final $R = 8.79\%$, $R_w = 13.10\%$, S = 4.73, for 747 observed [$I \geq 3\sigma(I)$] reflections, R = 9.91% for all 907 unique data. Maximum and minimum difference Fourier residuals = 2.12 and -0.28 eÅ^{-3}, respectively.

B. Compound 9: $C_6H_6N_4O_2 \cdot H_2O$, $M_r = 184.2$, space group $P2_{1/c}$, $a = 4.734$ (2) Å, $b = 8.798$ (4) Å, $c = 18.700$ (8) Å, $\beta = 90.64$ (3), $V = 778.5$ (5) Å^3, $\mu = 0.120$ mm^{-1}. Final $R = 4.30\%$, $R_w = 6.71\%$, S = 0.22 for 1128 observed [$I \geq 3\sigma(I)$] reflections, R = 5.07% for all 1381 unique data. Maximum and minimum difference Fourier residuals = 0.25 and -0.41 eÅ^{-3}, respectively.

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Supplementary Material Available: Anisotropic displacement coefficients, H-atom coordinates with isotropic displacement coefficients, selected torsion angles, and the calculated and observed structure factors for **8** and **9** are collected in **Supplementary Tables 1-8**, and are available from the journal upon request.

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