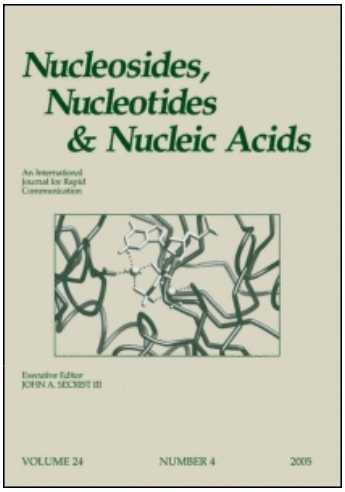

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STRUCTURES OF TWO SEVEN-MEMBERED RING PYRIMIDINE NUCLEOSIDE DERIVATIVES

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ABSTRACT. Crystal structure analyses of 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-tetrahydro-2H-1,3-diazepine-2,4(3H)-dione (I) and 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-6,7-dihydro-2H-1,3-diazepine-2(3H)-one (II) show that the major conformational differences between them lie in the aglycone moiety. In I the aglycone is twisted with C(6) and C(7) above, and C(5) below, the plane of the ring. In II the aglycone has a sofa conformation with C(7) above the plane of the ring. The ribose conformation in both compounds is C(1')-exo-C(2')-endo ($^2T_1$), the C(4')-C(5') orientation is gauche-gauche, and the glycoside linkage is high-anti (χ = -104.5(3)° I, -95.2(5)° II, respectively).

The crystal structures of two ring-expanded pyrimidine nucleoside analogues (FIG. 1) were determined to investigate the conformational behavior of seven-membered ring bases. After removal of the benzoyl groups, compound II is a potent inhibitor of cytidine deaminase (CD) [1]. The binding affinity of seven-membered ring nucleosides towards CD increases by more than an order of magnitude over that of six-membered ring pyrimidine analogues, suggesting that the stereochemistry of the aglycone is important for binding to the enzyme active site. CD has been a target of considerable interest due to its ability to inactivate cytidine-derived drugs [1,2], such as cytosine arabinoside [3] and 5-azacytidine [4]. Knowledge of the conformational preference of the seven-membered ring bases in these nucleoside analogues can lead to a better understanding of the enzyme active site, and to the design of more effective inhibitors.

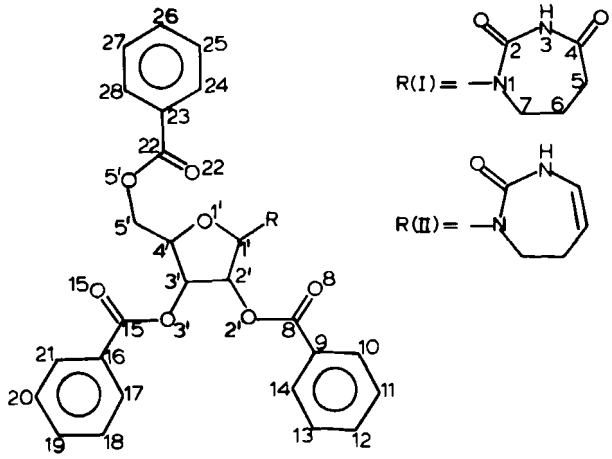

FIGURE 1. Structural formulas for I and II.

EXPERIMENTAL

Crystals of both compounds were grown from a 2-propanol solution by slow evaporation. Accurate cell dimensions were calculated from least-squares refinement of 25 reflections. Crystal data are: (I) $C_{31}H_{28}N_2O_9$, M_r = 572.51, $P2_12_12_1$, a = 15.327(2), b = 17.353(2), c = 10.630(2) Å, V = 2827.2(1) Å^3, Z = 4, D_x = 1.340 gcm^{-3}, λ(CuKα) = 1.5418 Å, μ = 7.915 cm^{-1}, F(000) = 1200; (II) $C_{31}H_{28}N_2O_8$, M_r = 556.52, $P2_12_12_1$, a = 15.379(2), b = 16.858(2), c = 10.902(1) Å, V = 2826.4(2) Å^3, Z = 4, D_x = 1.306 gcm^{-3}, λ(MoKα) = 0.71073 Å, μ = 0.889 cm^{-1}, F(000) = 1168. Data were collected at room temperature (293 K) on an Enraf Nonius CAD-4 diffractometer with Ni-filtered CuKα radiation for I; and a Nicolet P3 diffractometer using MoKα radiation for II. The crystals were stable and showed no deterioration during data collection. The data were corrected for Lorentz and polarization effects, but not for extinction or absorption effects. There were 3305 unique reflections for I, of which 2790 had I>3.5σ(I); and there were 2828 unique reflections for II, of which 2113 had I>3.5σ(I) [5]. Compound I was solved by direct methods (SHELX84) [6]. Since the crystal structures of I and II are isomorphous, the structure solution of II was obtained by refinement of atom positions from I. Parameters were refined by full matrix least-squares techniques using anisotropic thermal parameters for the non-

TABLE 1. Atomic coordinates (X10^4) and equivalent isotropic thermal parameters (X10) for 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-tetrahydro-2H-1,3-diazepine-2,4(3H)-dione (I).

ATOM	X/a(σ)	Y/b(σ)	Z/c(σ)	BISO(Å²)*	ATOM	X/a(σ)	Y/b(σ)	Z/c(σ)	BISO(Å²)*
C(2)	-1047(2)	1714(2)	5938(3)	37(1)	C(24)	2785(3)	2536(2)	6704(4)	47(1)
C(4)	-1196(2)	3103(2)	6607(4)	47(1)	C(25)	2860(4)	3255(3)	7218(5)	64(1)
C(5)	-449(3)	3355(2)	5769(5)	55(1)	C(26)	2764(4)	3366(3)	8512(6)	72(2)
C(6)	434(3)	3061(2)	6208(4)	49(1)	C(27)	2594(4)	2748(4)	9254(5)	68(2)
C(7)	381(2)	2223(2)	6572(4)	42(1)	C(28)	2544(3)	2019(3)	8774(4)	52(1)
C(8)	1027(2)	2705(2)	2624(3)	37(1)	C(1')	202(2)	1270(2)	4799(3)	33(1)
C(9)	639(2)	3129(2)	1527(3)	40(1)	C(2')	901(2)	1633(2)	3966(3)	32(1)
C(10)	1051(3)	3788(2)	1123(4)	52(1)	C(3')	1327(2)	919(2)	3410(3)	34(1)
C(11)	726(4)	4191(3)	80(5)	63(1)	C(4')	1347(2)	379(2)	4547(3)	36(1)
C(12)	1(4)	3910(3)	-544(4)	62(1)	C(5')	2197(3)	330(2)	5244(4)	46(1)
C(13)	-402(4)	3259(3)	-163(4)	61(1)	N(1)	-179(2)	1769(2)	5728(3)	36(1)
C(14)	-95(3)	2858(3)	909(4)	50(1)	N(3)	-1405(2)	2326(2)	6628(3)	45(1)
C(15)	811(3)	798(2)	1295(3)	38(1)	O(2)	-1500(2)	1184(2)	5598(3)	49(1)
C(16)	99(3)	477(2)	511(3)	42(1)	O(4)	-1627(2)	3550(2)	7203(3)	68(1)
C(17)	137(4)	637(3)	-782(4)	61(1)	O(8)	1719(2)	2850(2)	3060(3)	58(1)
C(18)	-527(5)	382(3)	-1552(5)	82(2)	O(15)	1383(2)	1202(2)	935(2)	55(1)
C(19)	-1211(5)	-29(3)	-1082(6)	76(2)	O(22)	2519(3)	551(2)	7661(3)	79(1)
C(20)	-1258(4)	-211(3)	221(6)	68(1)	O(1')	673(2)	659(1)	5398(2)	40(1)
C(21)	-581(3)	49(3)	987(4)	51(1)	O(2')	515(1)	2134(1)	3045(2)	35(1)
C(22)	2532(2)	1114(2)	7021(3)	41(1)	O(3')	719(2)	581(1)	2519(2)	36(1)
C(23)	2631(2)	1905(2)	7478(3)	38(1)	O(5')	2423(2)	1076(1)	5756(2)	42(1)

*BISO=Beq=$4/3\Sigma_i\Sigma_j\beta_{ij}(a_i a_j)$

hydrogen atoms. Hydrogen atoms were located in difference Fourier syntheses, given isotropic thermal parameters one unit greater than the heavy atom to which they are bonded and then refined. The final difference Fourier maps for I and II showed no peaks greater than 0.11 eÅ^{-3}. The final R for I is 0.056 and for II is 0.057. Atomic scattering factors were taken from International Tables for X-ray Crystallography [7]. All calculations were performed on a Vax 11/780 computer using the Enraf-Nonius crystallographic package. Final positional and isotropic thermal parameters for I and II are listed in Tables 1 and 2.

RESULTS AND DISCUSSION

The molecular conformations of the title compounds and their superposition are illustrated in FIGS. 2 and 3, respectively. The superposition was accomplished by a least-squares fit of the complete ribose, N(1), C(2), N(3), and C(4) using FITMOL [8]; and showed final positional

TABLE 2. Atomic coordinates (X10^4) and equivalent isotropic thermal parameters (X10) for 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-6,7-dihydro-2H-1,3-diazepine-2(3H)-one (II).

ATOM	X/a(σ)	Y/b(σ)	Z/c(σ)	BISO(Å^2)*	ATOM	X/a(σ)	Y/b(σ)	Z/c(σ)	BISO(Å^2)*
C(2)	-1188(4)	1484(4)	6076(5)	38(2)	C(24)	2694(5)	2494(5)	6592(7)	60(2)
C(4)	-1487(5)	2872(5)	6770(7)	59(2)	C(25)	2764(5)	3269(6)	6958(9)	74(3)
C(5)	-795(7)	3308(5)	6525(8)	69(3)	C(26)	2693(6)	3458(6)	8185(10)	78(3)
C(6)	103(5)	3016(4)	6303(7)	59(2)	C(27)	2551(5)	2867(7)	9020(8)	76(3)
C(7)	192(4)	2157(4)	6597(6)	43(2)	C(28)	2481(5)	2092(5)	8667(6)	57(2)
C(8)	888(4)	2647(3)	2828(5)	36(1)	C(1')	73(3)	1156(3)	4911(4)	33(1)
C(9)	567(4)	3026(3)	1683(5)	37(1)	C(2')	770(3)	1544(3)	4138(4)	30(1)
C(10)	990(4)	3688(4)	1272(6)	52(2)	C(3')	1252(4)	823(3)	3633(4)	34(1)
C(11)	737(6)	4039(5)	160(8)	64(2)	C(4')	1236(4)	267(3)	4716(5)	35(1)
C(12)	87(7)	3713(5)	-487(7)	68(3)	C(5')	2058(5)	188(4)	5435(6)	47(2)
C(13)	-345(6)	3058(4)	-91(6)	62(2)	N(1)	-342(3)	1651(2)	5798(4)	35(1)
C(14)	-111(4)	2707(4)	1011(6)	47(2)	N(3)	-1608(3)	2062(3)	6767(5)	49(2)
C(15)	901(4)	741(3)	1513(5)	37(2)	O(2)	-1562(2)	887(3)	5750(4)	51(1)
C(16)	234(4)	445(3)	628(4)	36(1)	O(8)	1527(3)	2848(3)	3364(4)	60(1)
C(17)	352(5)	601(4)	-604(6)	51(2)	O(15)	1502(3)	1164(3)	1248(3)	46(1)
C(18)	-264(6)	369(5)	-1445(6)	64(2)	O(22)	2384(4)	517(3)	7789(4)	75(2)
C(19)	-995(6)	-17(5)	-1063(7)	63(2)	O(1')	550(2)	535(2)	5509(3)	39(1)
C(20)	-1115(5)	-188(5)	164(7)	65(2)	O(2')	399(2)	2025(2)	3194(3)	34(1)
C(21)	-496(5)	34(4)	1003(6)	53(2)	O(3')	736(2)	489(2)	2668(3)	35(1)
C(22)	2414(4)	1057(4)	7082(5)	47(2)	O(5')	2296(2)	973(3)	5873(3)	48(1)
C(23)	2544(4)	1899(4)	7432(5)	44(2)					

*BISO = Beq = $4/3\Sigma_i\Sigma_j\beta_{ij}(a_ia_j)$

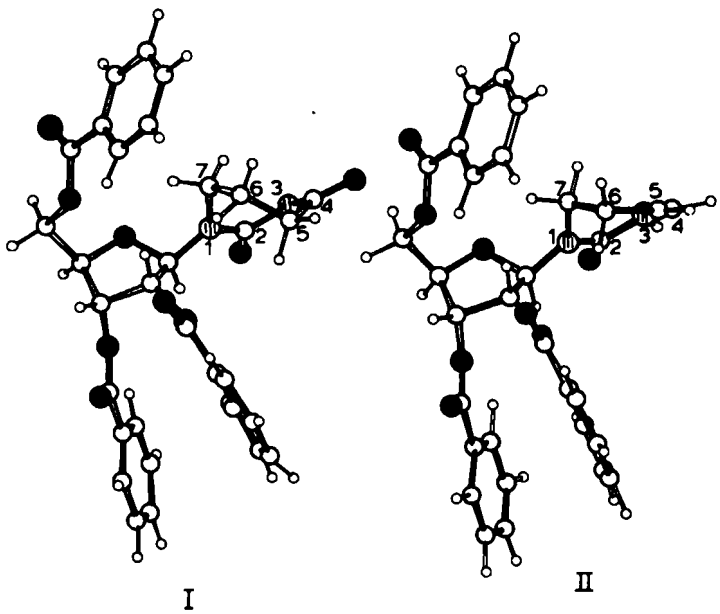

FIGURE 2. Conformation of the title compounds.

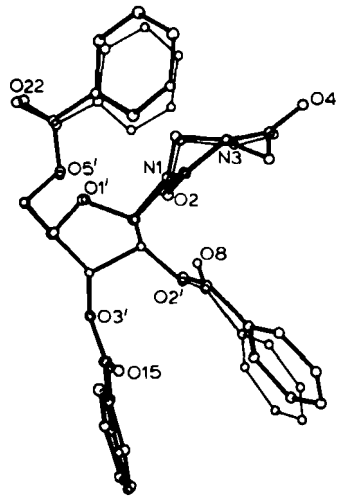

FIGURE 3. Superposition of I (heavy line) and II (narrow line).

differences in the range of 0.033 to 0.114 Å for the atom pairs. Atom pairs not involved in the least-squares fit had positional differences within the range 0.025 to 0.784 Å. As shown, there is homology between the nucleoside moieties, and there are only minor differences in the orientation of the benzoyl protecting groups. Bond lengths and bond angles for the nucleoside are shown in FIG. 4.

These data are the first structural information of diazepine-containing nucleosides. The conformational differences of the aglycone (FIG. 2, TABLE 3) result from the base in I being twisted with C(6) and C(7) above, and C(5) below, the face of the ring; while in II the base has a sofa conformation with C(7) above the ring plane. The ribose ring puckering is described by the pseudorotation parameters P (phase angle) and τ_m(maximum puckering amplitude) [9] (TABLE 3), and correspond to a C(1′)-exo-C(2′)-endo ($^2T_1$) conformation for both structures. The endocyclic torsion angles of the ribose are represented by τ (TABLE 3) and the conformation around C(4′)-C(5′) is gauche-gauche, as shown by ψ_1 and ψ_2.

The orientation of the ribose with respect to the aglycone is high anti, where χ (O(1)′-C(1′)-N(1)-C(2)) is -104.5(3)° and -95.2(5)° for I and II, respectively. Most C(3′)-endo pyrimidine nucleosides and their 5-substituted derivatives exist in an anti conformation [10] due to the

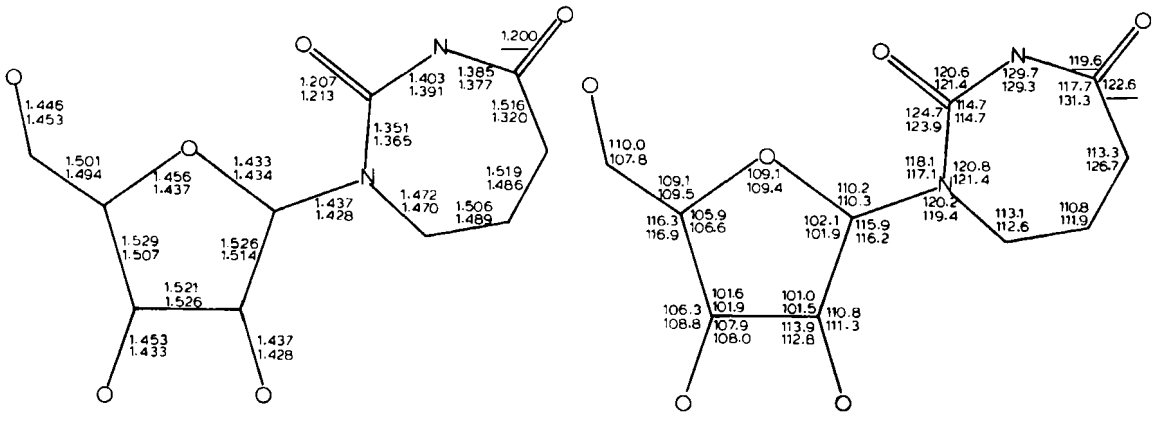

FIGURE 4. Bond lengths and bond angles of the ribose and aglycone for compounds I and II are listed first and second, respectively.

TABLE 3. Torsion angles of the aglycone and ribose.

Angle	Compounds I	II
Aglycone		
N(3)-C(2)-N(1)-C(7)	24.6(4)°	27.8(7)
N(1)-C(2)-N(3)-C(4)	36.1(5)	31.9(9)
C(5)-C(4)-N(3)-C(2)	-2.8(6)	-28.5(13)
N(3)-C(4)-C(5)-C(6)	-67.6(5)	-7.6(15)
C(4)-C(5)-C(6)-C(7)	44.7(5)	-9.9(12)
C(5)-C(6)-C(7)-N(1)	39.2(5)	64.0(8)
C(6)-C(7)-N(1)-C(2)	-87.3(4)	-87.1(7)
Ribose		
τ_0[O(1')-C(1')]	-31.2(3)	-31.4(5)
τ_1[C(1')-C(2')]	44.3(3)	42.5(5)
τ_2[C(2')-C(3')]	-40.1(3)	-37.8(5)
τ_3[C(3')-C(4')]	22.3(3)	19.6(5)
τ_4[C(4')-O(1')]	5.7(3)	7.4(5)
ψ_1[O(1')-C(4')-C(5')-O(5')	-57.7(4)	-63.5(6)
ψ_2[C(3')-C(4')-C(5')-O(5')	61.9(4)	57.9(6)
P(phase angle)	154.5(3)	152.1(5)
τ_m(max. pucker)	44.4(3)	42.8(5)

repulsive interaction between the ribose ring and the 2-oxo substituent of the pyrimidine base. A C(2′)-endo conformation of the ribose relieves this steric hindrance, thus both a syn and anti orientation is observed. The χ range normally observed for C(2′)-endo structures is between -100 to -160° and 25 to 60° for anti and syn, respectively [11]. For pyrimidine nucleosides χ is more closely restricted to an anti domain from -120 to -160° [11]; there is steric hindrance between hydrogen atoms of the pyrimidine, C(6)-H, and the ribose, C(2′)-H in the region of -100°. Therefore, the observation of a high-anti-C(1′)-exo-C(2′)-endo is unusual. Because of the high-anti orientation, the intramolecular contacts between the aglycone C(7) and the ribose ring are minimized. Despite differences in base conformation, C(7) is equidistant between C(2′) and O(1′) (3.0 Å) in both structures.

There is an intermolecular N(3)...O(8) hydrogen bond of 2.908(1) and 2.899(6) Å in I and II, respectively.

In summary, these ring-expanded pyrimidine nucleosides have an unusual high-anti glycoside orientation and C(1′)-exo-C(2′)-endo ribose pucker. The relative position of C(7) with respect to the ribose ring is the same in both structures, even though the base conformation is twisted in the dione (I) and sofa in the 2-one-4-ene (II) analogue. These results suggest that the enzyme active conformation is the same for both.

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SUPPLEMENTARY MATERIAL

Tables of hydrogen coordinates, anisotropic thermal parameters, observed and calculated structure factors and a complete list of bond distances, bond angles and torsion angles are available from VC.

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