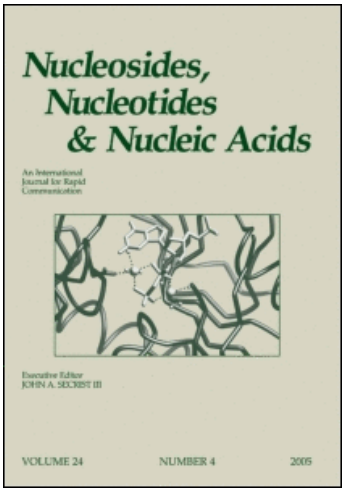

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Synthesis of *Cis*-1-[(2-Hydroxymethyl) Cyclopentyl]Uridine and Determination of its Conformation by X-Ray Crystallography and Ami Theoretical Calculations

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SYNTHESIS OF *cis*-1-[(2-HYDROXYMETHYL) CYCLOPENTYL]URIDINE AND DETERMINATION OF ITS CONFORMATION BY X-RAY CRYSTALLOGRAPHY AND AM1 THEORETICAL CALCULATIONS

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Abtract.- The title compound **1** was prepared from racemic *cis*-2-hydroxymethylcyclo pentylamine, constructing the heterocyclic base in a two-step procedure (64 % yield). The crystal structure of the compound was determined and its conformation was studied using AM1 theoretical calculations. The calculated low-energy conformations were similar to those reported for several other nucleoside analogues, and one of them closely corresponded to the X-ray structure.

Several nucleoside analogues with antiviral and/or antitumour activities, including some of those in clinical use, are 2',3'-dideoxy compounds or carbocyclic analogues in which a cyclopentane ring replaces the ribose. Recently, on the basis of published[1-4] and our own theoretical studies on the conformations of some pyrimidine nucleoside analogues, we decided to prepare carbocyclic analogues of nucleosides with the hydroxymethyl group and heterocyclic base attached to contiguous atoms of a cyclopentane ring, and to evaluate their pharmacological properties[5]. In this work we report the synthesis and crystal structure of *cis*-1-[(2-hydroxymethyl)cyclopentyl]uridine (**1**), and an AM1 theoretical study of its molecular conformation. In the theoretical study, special attention was focused on the

relative orientations of the hydroxymethyl and uridine groups with respect to the cyclopentane ring, which are important in determining biological activity.[1-3,6]

Results and Discussion

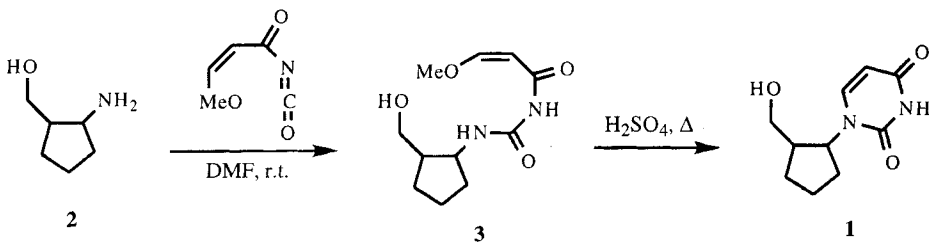
Racemic *cis* aminoalcohol **2** (Scheme 1) was prepared either from ethyl 2-oxocyclopentanecarboxylate,[7] or by cycloaddition of clorosulphonyl isocyanate to cyclopentene[8]. The *cis* stereochemistry of **2** was confirmed by ^{1}H NMR spectroscopy. Compound **1** was obtained by reaction of aminoalcohol **2** with 3-methoxy-2-propenoyl isocyanate[9] in dimethylformamide at room temperature,[10] followed by cyclization of the resulting compound **3** in refluxing sulphuric acid solution, in an overall yield of 70%.

The molecular structure of compound **1** and the atomic numbering scheme used are shown in Fig. 1. Atomic parameters for the non-hydrogen atoms are listed in Table 1, an a list of bond distances and angles is given in Table 2.

The uracil base is planar with all atoms within 0.01Å of the mean plane. The bond distances indicate that the C(2)=C(3) bond is double and that the four annular N-C bonds, which are essentially equivalent, have partial double bond character (mean distance 1.376 Å), while the N(2)-C(5) bond (1.474 Å) is a normal Nsp^2 - Csp^3 covalent bond. The C(2)-C(1)-N(1) and N(1)-C(4)-N(2) angles, that is the two internal angles at the ketonic carbon atoms, are comparable and relatively narrow (114.1(3)° and 114.6(3)°), and consequently the adjacent C(1)-N(1)-C(4) angle is very wide (127.7(3)°).

Bond lengths and angles in the cyclopentane ring are normal and need no comment. As is clearly shown in Fig. 1, this ring adopts the envelope conformation typical of cyclopentane, with four atoms essentially coplanar (within 0.006 Å) and C(7) displaced 0.566 Å out of this plane. It is noteworthy that, in order to minimize steric hindrance, this plane makes a dihedral angle of 99.8° with the mean plane calculated for the uracil ring.

In the crystal lattice, pairs of molecules related by a twofold screw axis are linked together by hydrogen-bonding interaction. Specifically the ketonic O(1) atom and the O(3) atom are separated from the symmetry-related O atoms defined by (x, y, z) ---> (-x, -1/2+y, 1/2-z) by only 2.747 Å, the corresponding O(3)···H bond and H···O(1) contact distances being 0.83 Å and 1.94 Å, respectively. In addition, the fact that O(1) and N(1) lie only 2.827 Å from the symmetry-related N and O atoms defined by (x, y, z) ---> ($\bar{x}$, $\bar{y}$, $\bar{z}$) indicates the existence of O···H-N hydrogen bonds with an O···H distance of 1.91 Å, with the result that the (x, y, z) and ($\bar{x}$, $\bar{y}$, $\bar{z}$) molecules are linked centrosymmetrically by eight-atom rings. A diagram of the molecular packing in which the H-bonds are indicated by dashed lines is shown in Fig.2.



Scheme 1

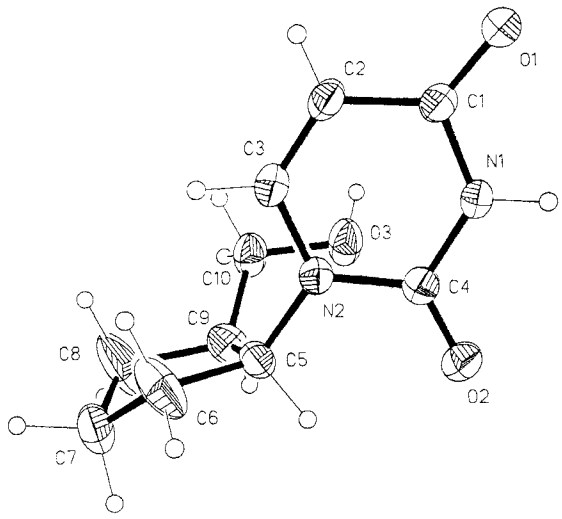


FIG. 1. Molecular structure of compound **1**; the thermal ellipsoids for the non-hydrogen atoms are of 30 % probability.

Figure 3 shows the AM1-calculated potential energy surface for the conformers of **1** obtained by varying the torsion angles χ and γ of the cyclopentane substituents (see Fig. 1).

For χ, there are two regions of minimum of energy, one corresponding to the more stable *anti* conformation, with a torsion angle between -90° and -120°, and the other to the *syn* conformation, with a torsion angle between 90° and 120°, which is 4 Kcal/mol higher in energy. These results are in agreement with those reported for other pyrimidine[1-4] and purine[6,11] nucleosides, and also with the experimental value of -98.6° deduced from the

TABLE 1. Fractional coordinates of non-hydrogen atoms, and equivalent isotropic thermal parameters (Angstrom**2). U equiv. is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U equiv.
N (1)	0.1064 (2)	0.0877 (6)	0.0868 (2)	0.042 (1)
C (1)	0.0433 (3)	0.2598 (7)	0.1067 (3)	0.043 (1)
O (1)	-0.0371 (2)	0.2490 (5)	0.0643 (2)	0.056 (1)
C (2)	0.0795 (3)	0.4395 (8)	0.1775 (3)	0.051 (1)
C (3)	0.1681 (3)	0.4322 (7)	0.2167 (3)	0.046 (1)
N (2)	0.2278 (2)	0.2553 (6)	0.1944 (2)	0.041 (1)
C (4)	0.1975 (3)	0.0705 (7)	0.1272 (3)	0.042 (1)
O (2)	0.2478 (2)	-0.0913 (5)	0.1048 (2)	0.055 (1)
C (5)	0.3233 (2)	0.2395 (8)	0.2451 (3)	0.046 (1)
C (6)	0.3760 (3)	0.471 (1)	0.2493 (5)	0.092 (2)
C (7)	0.4441 (3)	0.4545 (9)	0.3433 (4)	0.077 (2)
C (8)	0.3905 (4)	0.330 (1)	0.4187 (4)	0.130 (3)
C (9)	0.3310 (3)	0.1443 (9)	0.3581 (4)	0.058 (2)
C (10)	0.2425 (3)	0.0929 (8)	0.4068 (3)	0.057 (2)
O (3)	0.1925 (2)	-0.0885 (6)	0.3496 (2)	0.069 (1)

TABLE 2. Bond distances (Angstroms) and angles (degrees)

N(1)-C(1)	1.370 (5)	N(1)-C(4)	1.373 (5)
C(1)-O(1)	1.238 (4)	C(1)-C(2)	1.426 (6)
C(2)-C(3)	1.333 (6)	C(3)-N(2)	1.364 (5)
N(2)-C(4)	1.396 (5)	N(2)-C(5)	1.474 (4)
C(4)-O(2)	1.216 (5)	C(5)-C(6)	1.508 (7)
C(5)-C(9)	1.539 (6)	C(6)-C(7)	1.486 (7)
C(7)-C(8)	1.469 (8)	C(8)-C(9)	1.523 (8)
C(9)-C(10)	1.501 (6)	C(10)-O(3)	1.417 (5)
C(1)-N(1)-C(4)	127.7 (3)	N(1)-C(1)-C(2)	114.1 (3)
N(1)-C(1)-O(1)	119.8 (3)	O(1)-C(1)-C(2)	126.1 (4)
C(1)-C(2)-C(3)	120.1 (4)	C(2)-C(3)-N(2)	123.2 (4)
C(3)-N(2)-C(5)	122.4 (3)	C(3)-N(2)-C(4)	120.4 (3)
C(4)-N(2)-C(5)	117.1 (3)	N(1)-C(4)-N(2)	114.6 (3)
N(2)-C(4)-O(2)	122.9 (3)	N(1)-C(4)-O(2)	122.5 (4)
N(2)-C(5)-C(9)	114.8 (3)	N(2)-C(5)-C(6)	114.4 (3)
C(6)-C(5)-C(9)	105.9 (4)	C(5)-C(6)-C(7)	105.6 (4)
C(6)-C(7)-C(8)	102.3 (4)	C(7)-C(8)-C(9)	107.4 (4)
C(5)-C(9)-C(8)	103.2 (4)	C(8)-C(9)-C(10)	112.5 (4)
C(5)-C(9)-C(10)	117.9 (4)	C(9)-C(10)-O(3)	109.7 (3)

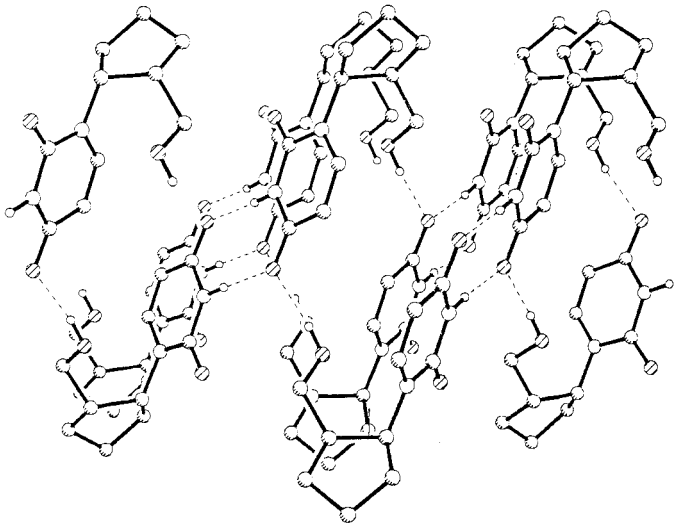


FIG. 2. Packing arrangement of compound **1**; dashed lines indicate H-bonding interactions.

X-ray structure. Note that on *anti* conformation appears to be necessary if nucleoside analogues are to have biological activity[3,6].

For γ, which describes the orientation of the exocyclic C(9)-C(10) bond, three regions of minimun energy could be distinguished: one at a γ of ca. -60°, one at 180°, and a less well-defined one between 60 and 90°.

Varying χ and γ did not produce important changes in the C(10)-C(9)-C(5)-N(2) torsion angle which always lay between +20° and +40° or -20° and -40°, nor in the geometry of the cyclopentane ring, which assumed envelope conformations with four atoms coplanar and the C(5) atom (the one bonded to the pyrimidine ring) slightly displaced from that plane. In this respect, the calculated geometry differs from the X-ray structure, in which the displaced atom is C(7). In spite of this difference, the torsion angles determined for the exocyclic bonds of the cyclopentane ring from the crystal structure (χ = -98.6° and γ = +62.6°) both lie in angular regions corresponding to energy minima in the theoretical study.

Experimental Section

A) Synthesis

Melting points are uncorrected and were determined in a Reichert Kofler thermopan or in capillary tubes in a Buchi 510 apparatus. IR spectra (KBr discs) were recorded in a

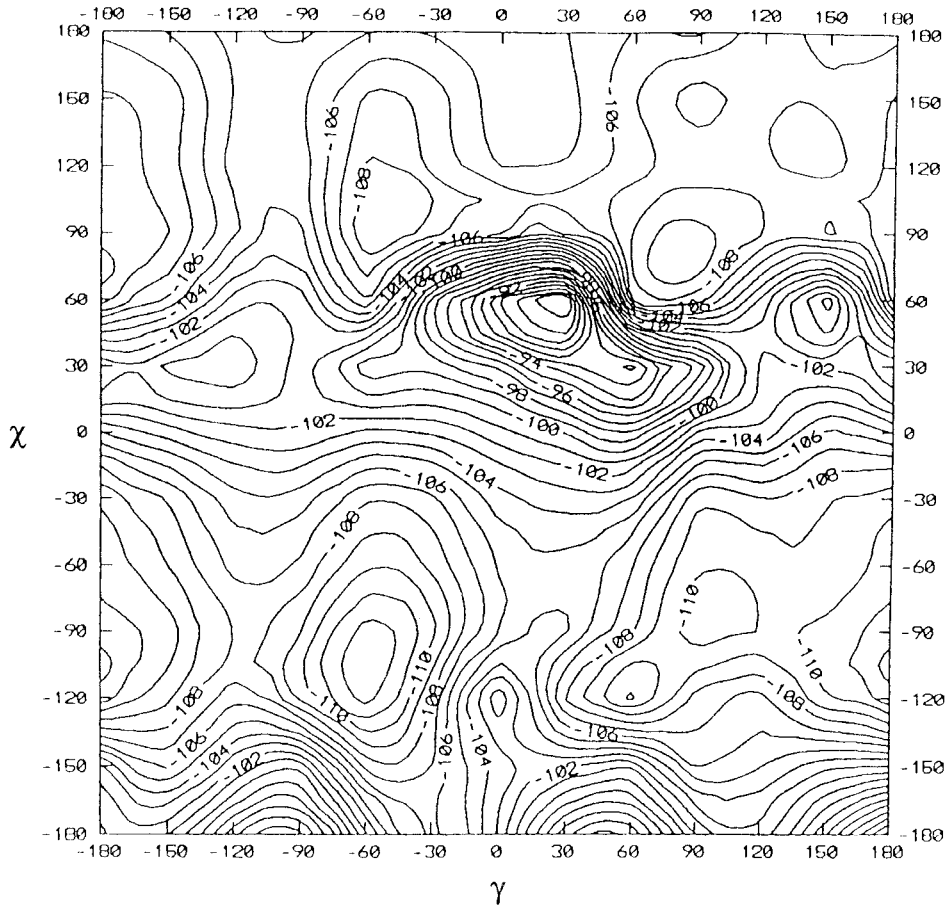


FIG. 3. AM1 calculated potential energy surface for the conformers of **1** obtained by rotation of the torsion angles χ and γ.

Perkin-Elmer 1640FT spectrometer (υ in cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded in a Bruker AMX (300 MHz) spectrometer, using TMS as internal standard (δ in ppm, J in Hz). Mass spectrometry was carried out in a Hewlett Packard 5988A spectrometer. Elemental analyses were performed by a Perkin-Elmer 240B microanalyser and were within $\pm$ 0.4% of the calculated values in all cases. Flash chromatography (FC) was performed on silica gel (Merck 60, 230-400 mesh); analytical TLC was performed on pre-coated silica gel plates (Merck 60 F254, 0.25 mm).

N-[[(2-hydroxymethyl)cyclopentyl]aminocarbonyl]-3-Methoxy-2-propenamide (3)

To a cooled (-20°C) solution of aminoalcohol **2**[7] (1.15 g, 10 mmol) in dimethyl formamide (32 mL) over 4 Å molecular sieves, was added 3-methoxy-2-propenoyl isocyanate[9] (25.5 mL of a benzene solution, 10 mmol). The mixture was stirred for 12 h at room temperature, and then the solid was filtered out. The filtrate was evaporated to afford a residue, which was purified by FC, with hexane/ethyl acetate (1:1) as eluent, to afford **3** (1.69 g, 72%). Mp 154°C. ^{1}H NMR (DMSO-d_6): 1.29-1.85 (m, 6H, $(CH_2)_3$), 2.05 (m, 1H, CH-CO), 3.33 (m, 2H, CH_2-O), 4.10 (m, 1H, CH-N), 4.42 (t, 1H, J = 5.05, OH), 5.52 (d, 1H, J = 12.32, CH-CO), 7.57 (d, 1H, J = 12.32, CH-O), 8.63 (d, 1H, J = 7.97, NH), 10.02 (s, 1H, NH). IR: 3227, 2956, 1672, 1617, 1569, 1189, 1153, 811. Anal. ($C_{11}H_{17}N_2O_4$) C, H, N.

1-[(2-Hydroxymethyl)cyclopentyl]uridine (1)

A mixture of **3** (1.50 g, 6.20 mmol) and 1M H_2SO_4 (50 mL) was refluxed for 3 h, then cooled and neutralized with 2M NaOH. The solvent was evaporated *in vacuo* to leave a solid residue, which was purified by FC, with CH_2Cl_2/MeOH (97:3) as eluent, to afford pure **1** (1.16 g; 89%): Mp 166°C. ^{1}H-NMR (DMSO-d_6): 1.23-2.25 (m, 7H, -($C\underline{H}_2$)$_3$-$C\underline{H}$-CH_2OH), 3.18 (m, 2H, CH_2O), 4.42 (bs, 1H, OH), 4.69 (q, 1H, J = 8.31, CH-N), 5.47 (d, 1H, J = 8.00, H5), 7.58 (d, 1H, J = 8.00, H6), 11.18 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6): 22.51, 27.47, 29.17, 42.64 (C2'), 58.07 (C1'), 61.04 (C6'), 100.39 (C5), 143.84 (C6), 151.91 (C2), 163.65 (C4). IR: 3370, 2954, 1703, 1687, 1384, 1047, 802. MS, m/z (I%): 210 (M^+, 59), 181 (6), 179 (M^+-CH_2OH, 7), 153 (11), 149 (10), 136 (12), 113 (M^+-C_6H_9O, 100), 96 (17), 81 (26), 80 (26), 67 (32). Anal. ($C_{10}H_{14}O_3N_2$) C, H, N.

B) Structural Study

Crystal data. $C_{10}H_{13}N_4O_3$, space group $P2_1/c$ (monoclinic); a = 14.447(6), b = 5.630(2), c = 12.817(5) Å, β = 95.25(4)°, V = 1038 Å^3, Z = 4; Dx = 1.34 Mg m^{-3}, F(000) = 468, μ (Mo Kα) = 0.6 cm^{-1}; max. crystal dimension 0.2 mm.

Data collection and refinement. Intensity data were collected on a Philips 1100 four-circle diffractometer using graphite-monochromated Mo-Kα radiation and the ϑ - 2ϑ scan method. Of the 1108 measured reflections within ϑ = 29°, 1035 unique reflections had |Fo| > 3 σ (Fo). The intensities were corrected for Lorentz and polarization effects but not for absorption because of the small dimensions of the crystal. The structure was solved by direct methods using the SHELXS-86 package[12] (ran on a Micro VAX computer) and full-matrix least-squares refinement with all non-hydrogen atoms anisotropic. H-atoms

were included as fixed contributors in calculated positions and refined with a fixed temperature factor (C-H = 1.08 Å; U_{iso} = 0.08 Å^2). Atomic scattering factors for neutral atoms were taken from International Tables for X-ray Crystallography[13]. The final R was 0.054, at which the maximum shift of the refined parameters was 0.001 times the corresponding standard deviation.

Theoretical optimization of molecular geometries was realized by the AM1 semi-empirical quantum mechanical method[14] using the AMPAC program,[15] which was run on an SGI work station. The geometry was optimized for conformers of **1** obtained by varying the torsion angles χ [C(4)-N(2)-C(5)-C(9)] and γ [O(3)-C(10)-C(9)-C(5)] (see Fig. 1) between 0° and 360° in 30° increments.

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