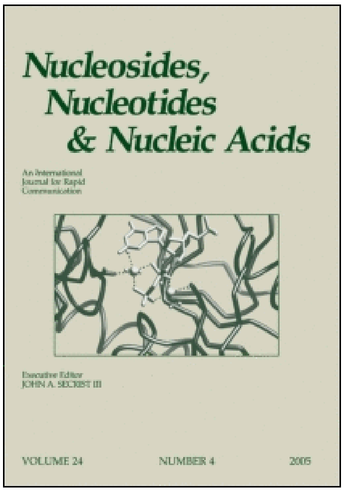

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SYNTHESIS AND STRUCTURAL STUDY OF PYRIMIDYL CARBOCYCLIC ANALOGUES OF NUCLEOSIDES BASED ON CYCLOPENTENE RINGS

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ABSTRACT

A series of 1,2-disubstituted carbonucleoside analogues of pyrimidine and 5-halopyrimidines with the unsaturated carbocycle cyclopentene was synthesized. AIM theory was applied to analyse the conformational and electronic effects of 5-halogenation.

In continuance with our study of carbocyclic analogues of nucleosides (CANs) having a five-membered carbocycle bearing the base and hydroxymethyl group at adjacent positions (1), we have prepared racemic mixtures of *cis*-pyrimidyl and *cis*-5-halopyrimidyl derivatives with a double bond between positions 2 and 3 of the carbocycle (Scheme 1).

The starting material (±)-6-azabicyclo[3.2.0]hept-3-en-7-one (**1**) was obtained by $2+2$ cycloaddition of cyclopentadiene (2 mol) to chlorosulfonyl isocyanate (1 mol) in dry ethyl ether at -60°C. Transformation of **1** into the uridine analogue **4** was achieved in three steps with an overall yield of 31%, the key step being the reductive opening of the amide bond of **1** using an open-chain uracil precursor as the requisite electron-withdrawing N substituent (2). Treatment of **1** with 3-methoxyacryloyl isocyanate in dry benzene afforded the corresponding carbamoyl derivative **3**. Reduction of **3** with excess $NaBH_4$ in methanol and

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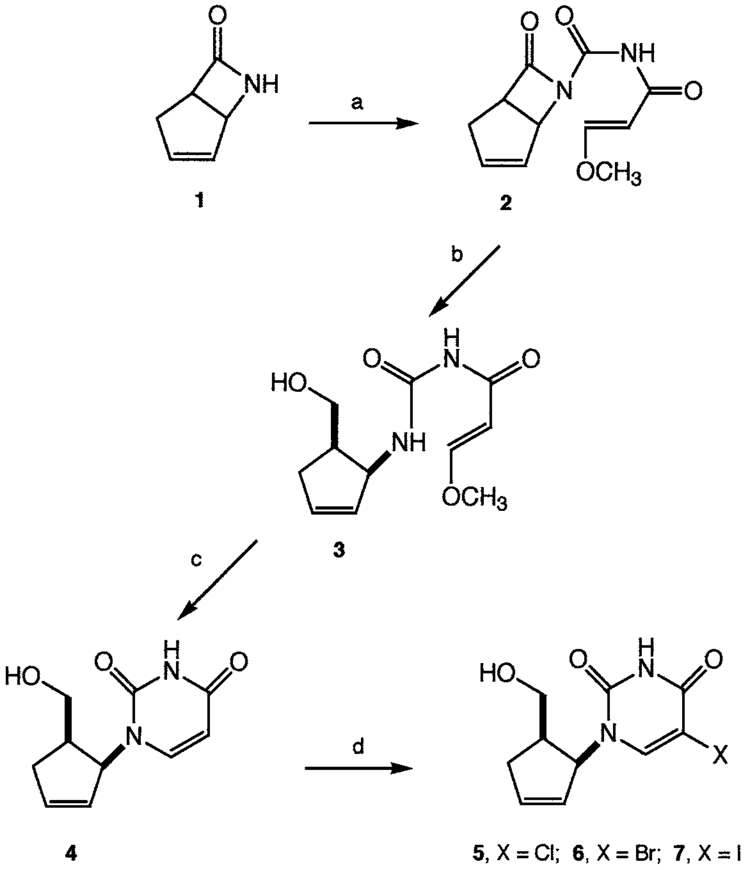
*Corresponding author.



Scheme 1. a: 3-methoxyacryloyl isocyanate, benzene, 60°C, 3 h (60%); b: $NaBH_4$, MeOH, r.t. 20 min (74%); c: H_2SO_4 2 M, reflux, 3 h (68%); d: NCS, DMF, r.t. 24 h (41%); NBS, DMF, r.t. 1 h (52%); NIS, AcOH, 80°C, 8 h (29%).

subsequent acidic ring closure afforded the desired pyrimidyl CAN **4**. Position **5** of the uracil ring was then halogenated with NXS (X = Cl, Br, I). Chlorination (to **5**, 41%) and bromination (to **6**, 52%) being carried out at room temperature in DMF and iodination (to **7**, 29%) at 80°C in acetic acid.

Computations carried out to compare the structures of the unhalogenated compound **4** and the 5-fluoro derivative afforded very similar results for both molecules at both AM1 and HF/6–31G* levels. In all cases essentially the same 18 conformers were found ranked in the same order by energy. In all these conformers the cyclopentene ring adopts the envelope form, thus maximizing the distance between the base and the carbon bearing the hydroxymethyl group (C2′). In the most stable conformer (Fig. 1) the hydroxyl group is hydrogen-bonded to the uracil O2 oxygen; the most significant dihedral angles are 267,0° for C2-N1-C1′-C2′, 197,7° for O6′-C6′-C2′-C3′ and 295,8° for H-O6′-C6′-C2′. The electronic effects of

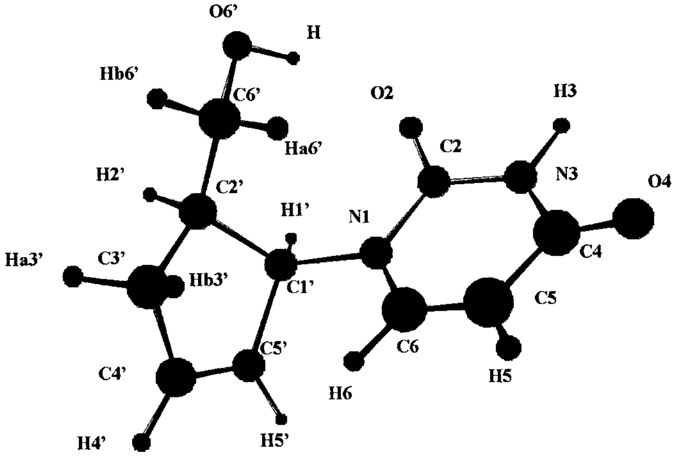


Figure 1.

5-halogenation were examined by applying AIM theory (3), using HF/6–31 ++ G** wave functions of the most stable conformer of compound **4** and their 5-fluoro and 5-chloro derivatives. The computed bond and integrated atomic properties indicate that 5-halogenation does not give rise to any significant modification of the electronic properties of the cyclopentene ring. Main changes in electron distribution are localized on atoms C4, C5 and C6; whereas H6, O4 and N**1** exhibit smaller, though significant, variations (Table 1).

The electron population in the C5 region is depleted (ΔN (Ω) negative values) and more space-localized (negative relative values of the first moment of the electron population, r (1), volume, v; and Shannon entropy (4), Sh) upon 5-halogenation. The positive ΔN (C5) value obtained for the chlorinated compound can be interpreted as due to the reorganization of the interatomic surfaces after halogenation which results in an electron charge transfer to C5 from the remaining neighboring

Table 1. Most Important Varitation of the Atomic Properties Due to 5-Halogenation of Compound **4**. Cl′ is Included Because it is the Most Affected Atom of the Cyclopentene Ring

	$10^3\Delta N(\Omega)$/a.u.		$10^2\Delta r^1(\Omega)$/a.u.		$\Delta v(\Omega)/cm^3mol^{-1}$		$\Delta Sh(\Omega)$		$\Delta E(\Omega)/Kcalmol^{-1}$	
Ω	f-h	cl-h	f-h	cl-h	f-h	cl-h	f-h	cl-h	f-h	cl-h
O4	−24	−13	−6	−4	−2.5	−2.5	−0.01	−0.01	15.8	33.1
C4	−79	−68	−15	−12	−1.8	−1.7	−0.06	−0.05	27.0	40.5
C5	−485	23	−86	−4	−21.8	−12.5	−0.28	−0.02	181.7	11.4
C6	−119	−120	−24	−24	−2.6	−5.0	−0.06	−0.07	27.0	40.5
H6	−28	−26	−4	−4	−1.0	−1.3	−0.02	−0.04	10.3	7.5
N1	−11	−6	−2	−1	−0.4	−0.2	0.00	0.00	3.0	13.9
C1′	5	11	1	2	0.3	0.3	0.00	0.01	−4.7	4.9

atoms. It has been also found as on important destabilization of C5, C6, C4 and H6 atoms.

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