Heteroatom Chemistry
Volume 9, Number 6, 1998

The X-ray Crystal and Molecular Structure of 5′-Bromo-5′-deoxythymidine

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Received 26 November 1997; revised 13 March 1998

ABSTRACT: *5′-Bromo-5′-deoxythymidine (***1***) crystallizes with four molecules in a monoclinic unit cell of space group C2. The ribose ring adopts an envelope conformation, transient between* $^{1}_{0}T$ *and* E_0 *(O4′-exo), with the C1′ atom being in the flap position. In the crystal lattice, the molecules are connected by intermolecular one-dimensional chains of hydrogen bondings from the hydroxyl hydrogen H3′(O3′) to the carbonyl oxygen O4. The differences in conformation and a hydrogen-bonding system of* **1** *with comparison to the structure of thymidine are observed.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9: 591–596, 1998

INTRODUCTION

As the result of systematic studies on the relation between the structure and reactivity of nucleosides, nucleotides, and their structural analogs, we have focused our attention on 5′-halogeno-5′-deoxynucleosides. Since the 1970s, they have played an important role in the development of nucleoside analogs synthesis because they can be relatively easily transformed into deoxy-, amino-, thio-, unsaturated, and other derivatives [1]. They can be treated as versatile alkylating agents toward thio- and selenophosphoric acids, and thus, they also can be useful in the preparation of DNA analogs [2]. We recently used 5′-bromo-5′-deoxynucleosides, including **1**, for the synthesis of 3′-O-thymidylyl(5′-deoxy-5′-selene-thymidylyl)-Se-phosphoroselenolate, its O-methyl ester and methanephosphonate derivatives [3, 4].

In this article, we present an X-ray crystallographic analysis of 5′-bromo-5′-deoxythymidine (**1**) [5] and its comparison with 2′-deoxythymidine. The differences, both in molecular geometry and significantly in the structures of lattices, are discussed.

Experimental

The X-ray crystal and molecular structure of **1** was determined by the use of the intensity data collected at room temperature for the θ range 1–75° from a crystal of dimensions 0.15 × 0.25 × 0.60 mm on an Enraf-Nonius CAD4 diffractometer [6] with graphite monochromatized CuKα radiation (λ = 1.54178 Å, scan mode $\omega/2\theta$, scan with 1.33 + 0.14 tan θ). Compound **1** crystallizes in the monoclinic system, space group C2, with a = 25.540 (7) Å, b = 5.525 (2) Å, c = 8.921 (2) Å, β = 109.10 (2)°. Other crystal data for $C_{10}H_{13}O_4N_2Br$ are V = 1190(9) Å^3, $F(000)$ = 616, Z = 4, D_c = 1.704(2) g/cm^3, M_r = 305.14, μ(CuKα) = 48.2 cm^{-1}. Ranges of hkl were h = −32–32, k = −6–0, and l = −11–11.

The lattice constants were diffractometrically

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This project is partially assisted by the State Committee for Scientific Research (KBN, Grant 3 TO9A 031 011).

CCC 1042-7163/98/060591-06

determined from 25 reflections in the θ range 17.1–35.6°. The decline in intensities of three control reflections ($-5, -1, 4$; $1, -1, 4$; $4, -2, 3$) was 3.7% during 38.2 hours of exposure; intensity data were corrected by the use of the DECAY program [7], with correction factors min. = 1.00002, max. = 1.01918, and aver. = 1.00949. The empirical absorption correction was applied by the use of the ψ-scan method (EAC program) [7, 8]; the correction factors were min. = 0.8428, max. = 0.9991, and aver. = 0.9388. From a total of 2703 measured reflections, 1350 unique reflections were obtained ($R_{\text{int}} = 0.0405$), of which 1328 with $I \geq 3\sigma(I)$ were used in structure analysis.

The structure was solved by direct methods and refined by full-matrix least-squares (SHELXTL/PC) using F's [9, 10]. Hydrogen atoms were found in a difference Fourier map and set as riding with fixed isotropic thermal parameters equal to $U = 0.08$ Å^2. Anisotropic thermal parameters were applied for all nonhydrogen atoms. The final refinement converged to $R = 0.066$ and $R_w = 0.076$ with weight $w^{-1} = \sigma^2(F) + 0.005\,F^2$ for 155 refined parameters, with a goodness-of-fit parameter equal to $S = 1.2967$. Final residual peak and hole were 1.114 eÅ^{-3} (near the bromide atom) and -0.752 eÅ^{-3}, respectively.

The absolute structure of **1** was determined independently by the use of three methods: the Rogers η-test [9, 11], the Hamilton test [11, 12], and calculation of the Flack parameter x [13, 14]. The obtained results were as follows: Rogers method: $\eta = 0.84(18)$, $\eta_{\text{inv}} = -0.83(18)$; the Hamilton test: $R_{\text{ratio}} = 1.024$, $N = 1173$, the probability of the opposite(inv) configuration being $\alpha < 10^{-6}$; Flack parameter $x = 0.01(5)$, unequivocally confirming the configuration shown in Figure 1. The absolute configurations at C1′, C3′, and C4′ atoms are $R_{\text{C1}'}$, $S_{\text{C3}'}$, and $R_{\text{C4}'}$, respectively.

Further details of the crystal structure investigation are available on request from the Cambridge Crystallographic Data Centre [15].

RESULTS AND DISCUSSION

The asymmetric part of the unit cell of **1** consists of one molecule. The molecular structure of **1** with the atom numbering is shown in Figure 1. Atomic coordinates and equivalent isotropic thermal parameters are given in Table 1. Selected bond lengths and angles are listed in Table 2.

In the crystal lattice, the molecules of **1** are connected by hydrogen-bonding chains from the hydroxyl hydrogen H3′(O3′) to the carbonyl oxygen O4 of the next molecule (symmetry: $x, y - 1, z - 1$). The chains are along the diagonal line of the plane bc (see Figure 2). The geometry of these hydrogen bonds is as follows: O3′-H3′, 0.86 (1) Å; H3′ ··· O4, 1.90 (1) Å; O3′ ··· O4, 2.727 (7) Å; and O3′-H3′ ··· O4, 161 (2)°.

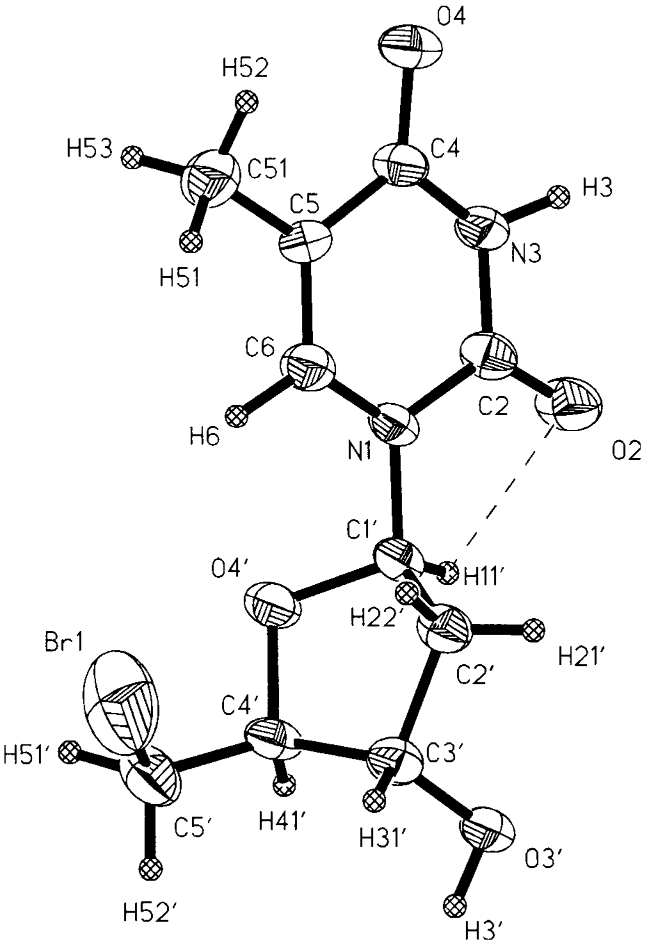

FIGURE 1 Molecular structure and atomic-numbering scheme of 5′-bromo-5′-deoxythymidine (thermal ellipsoids drawn at the 50% probability level). Intramolecular hydrogen contact C1′–H11′ ··· O2 is shown.

The intermolecular hydrogen-bonding system between the 3′-hydroxyl hydrogen of the deoxyribose ring and the carbonyl oxygen O4 of the thymine ring has a strong influence on deformation of the geometry of the thymine ring (C5–C4–N3 and O4–C4–C5 angles equal 116.5 (5)° and 123.4 (5)°, respectively) and on elongation of the double bond O4–C4 [1.246 (7) Å], when compared with the length of the C2–O2 double bond [1.199 (8) Å, Table 2].

The shortest intramolecular hydrogen contact exists between the carbonyl oxygen O2 of the thymine ring and the hydrogen atom H11′ bonded to carbon C1′ of the ribose ring. The geometry of this contact is the following: C1′–H11′, 0.99 (1) Å; H11′ ··· O2, 2.24 (1) Å; C1′ ··· O2, 2.728 (7) Å; C1′–H11′ ··· O2, 110 (2)°; and C2–O2 ··· H11′, 66 (2)°.

TABLE 1 Atomic Coordinates and Equivalent Isotropic Displacement Coefficients $U_{(eq)}$(Å^2)

$$U_{(eq)} = (1/3)\ \Sigma_i \Sigma_j U_{ij}\ a_i^* a_j^* a_i a_j$$

Atom	*x*	*y*	*z*	$U_{(eq)}$
Br1	0.9537(1)	0.7440[a]	0.2465(1)	0.0882(5)
N1	0.8385(2)	0.6673(10)	0.5714(4)	0.0295(7)
C2	0.7981(2)	0.6452(11)	0.6450(5)	0.0302(8)
O2	0.7603(2)	0.5052(11)	0.6001(4)	0.0445(8)
N3	0.8055(2)	0.7971(11)	0.7709(4)	0.0320(7)
C4	0.8448(2)	0.9741(12)	0.8233(4)	0.0339(8)
O4	0.8447(2)	1.1072(11)	0.9359(4)	0.0490(10)
C5	0.8854(2)	0.9939(12)	0.7415(4)	0.0330(8)
C51	0.9307(2)	1.1769(14)	0.7951(6)	0.0456(10)
C6	0.8796(2)	0.8383(12)	0.6198(5)	0.0333(8)
C1′	0.8317(2)	0.5251(11)	0.4302(4)	0.0302(10)
C2′	0.8123(2)	0.6626(12)	0.2755(5)	0.0347(8)
C3′	0.8292(2)	0.4946(12)	0.1662(4)	0.0325(8)
O3′	0.7851(1)	0.3255(11)	0.1018(4)	0.0453(10)
C4′	0.8808(2)	0.3617(11)	0.2784(5)	0.0329(8)
C5′	0.9346(3)	0.4027(14)	0.2539(7)	0.0476(12)
O4′	0.8848(1)	0.4357(9)	0.4367(3)	0.0385(7)
H3	0.7729(10)	0.7851(20)	0.7945(10)	0.08[b]
H51	0.9390(10)	1.2337(20)	0.6965(10)	0.08[b]
H52	0.9185(10)	1.3095(20)	0.8440(10)	0.08[b]
H53	0.9642(10)	1.1075(20)	0.8713(10)	0.08[b]
H6	0.9105(10)	0.8686(20)	0.5639(10)	0.08[b]
H11′	0.8082(10)	0.3903(20)	0.4424(10)	0.08[b]
H21′	0.7741(10)	0.6891(20)	0.2372(10)	0.08[b]
H22′	0.8319(10)	0.8134(20)	0.2855(10)	0.08[b]
H31′	0.8390(10)	0.6006(20)	0.0839(10)	0.08[b]
H3′	0.7966(10)	0.2462(20)	0.0351(10)	0.08[b]
H41′	0.8726(10)	0.1884(20)	0.2712(10)	0.08[b]
H51′	0.9691(10)	0.3294(20)	0.3339(10)	0.08[b]
H52′	0.9315(10)	0.3328(20)	0.1501(10)	0.08[b]

[a] The *y* coordinate of Br1 atom was fixed to set the origin.
[b] Thermal parameters U_{iso} were fixed for all hydrogen atoms.

TABLE 2 Bond Lengths and Valence Angles in **1**

Bond Lengths (*Å*)

Br1-C5′	1.954(8)	C1′-O4′	1.427(6)	N3-C4	1.369(8)
C4′-C5′	1.478(9)	C3′-O3′	1.431(7)	C4-C5	1.454(7)
C3′-C4′	1.554(7)	N1-C1′	1.446(6)	C5-C6	1.354(7)
C2′-C3′	1.508(8)	N1-C2	1.398(8)	O2-C2	1.199(8)
C1′-C2′	1.510(6)	N1-C6	1.373(8)	O4-C4	1.246(7)
C4′-O4′	1.441(6)	C2-N3	1.365(7)	C5-C51	1.493(8)

Valence Angles (°)

Br1-C5′-C4′	114.0(5)	C6-N1-C1′	120.6(5)
C5′-C4′-O4′	109.3(5)	C2-N1-C6	121.2(5)
C3′-C4′-C5′	117.8(5)	O2-C2-N1	122.5(5)
O3′-C3′-C4′	109.9(4)	O2-C2-N3	123.5(5)
O3′-C3′-C2′	107.9(4)	N1-C2-N3	114.1(5)
C2′-C3′-C4′	103.7(4)	C2-N3-C4	127.5(5)
C1′-C2′-C3′	101.7(4)	O4-C4-N3	120.2(5)
C2′-C1′-O4′	103.6(4)	O4-C4-C5	123.4(5)
C1′-O4′-C4′	107.3(4)	N3-C4-C5	116.5(5)
C3′-C4′-O4′	105.7(4)	C4-C5-C6	116.5(5)
N1-C1′-C2′	115.6(4)	C4-C5-C51	119.7(5)
N1-C1′-O4′	108.1(4)	C6-C5-C51	123.8(5)
C2-N1-C1′	117.7(4)	N1-C6-C5	124.1(5)

The conformation of the molecule of **1** can be described in detail by values of the torsion angles listed in Table 3.

The endocyclic torsion angles and asymmetry parameters calculated on the basis of these angles [15] show that the five-membered ribose ring (C1′-C2′-C3′-C4′-O4′) adopts a deformed envelope conformation, transient between $^{1}_{0}T$ and E_0 (O4′-exo)[17], with a torsion angle C2′-C3′-C4′-O4′ of 7.0 (5)°, with the C1′ atom being in the flap position. The dihedral angle between the ring plane passing through O4′, C1′, C2′ atoms and the least-squares plane passing through C2′, C3′, C4′, O4′ atoms is equal to 40.5 (3)°. The dihedral angle between the latter plane and the thymine ring plane is equal to 75.0 (2)°.

The three-dimensional arrangement of the thymine ring with respect to the deoxyribose ring in the molecule of **1** (shown in the Newman projection perpendicular to the N1–C1′ bond (see Figure 3a) shows that the oxygen atom O4′ of the ribose ring is *anticlinal* to the thymine carbon C2 [140.0(5)°] and *synclinal* to the thymine carbon C6 [47.6(6)°]. This results in the antiorientation of the pyrimidine ring relative to the sugar moiety. This arrangement is similar to that observed in the molecule of thymidine [15, 18] (Figure 3b).

The comparison of other structural features of **1** with the structure of thymidine [15, 18] revealed that these compounds crystallize in different systems: **1** is monoclinic and crystallizes in space group C2, but thymidine is orthorhombic, with space group $P2_12_12_1$. The unit cells in both structures are composed of four molecules. The conformation of thymidine is different from the conformation established for **1**. The values of endocyclic torsion angles and asymmetry parameters [16], given in Table 3, show that the five-membered deoxyribose rings in thymidine and in **1** adopt a deformed envelope conformation, but the difference is in the atom that opens the envelope: In thymidine, the carbon atom C3′ is in the flap position, but in **1**, the carbon atom C1′ occupies that position.

In the deoxyribose ring of thymidine, the dihedral angle between the ring plane passing through C2′, C3′, C4′ atoms and the least-squares plane passing through the C1′, C2′, C4′, O4′ atoms is equal to 36.6°. The dihedral angle between the latter plane and the thymine ring plane is equal to 74.3 (2)°.

Analysis of the inter- and intramolecular hydrogen contacts in the crystals of thymidine shows the similarities of intermolecular contact between the hydroxyl hydrogen H3′(O3′) and the carbonyl oxy-

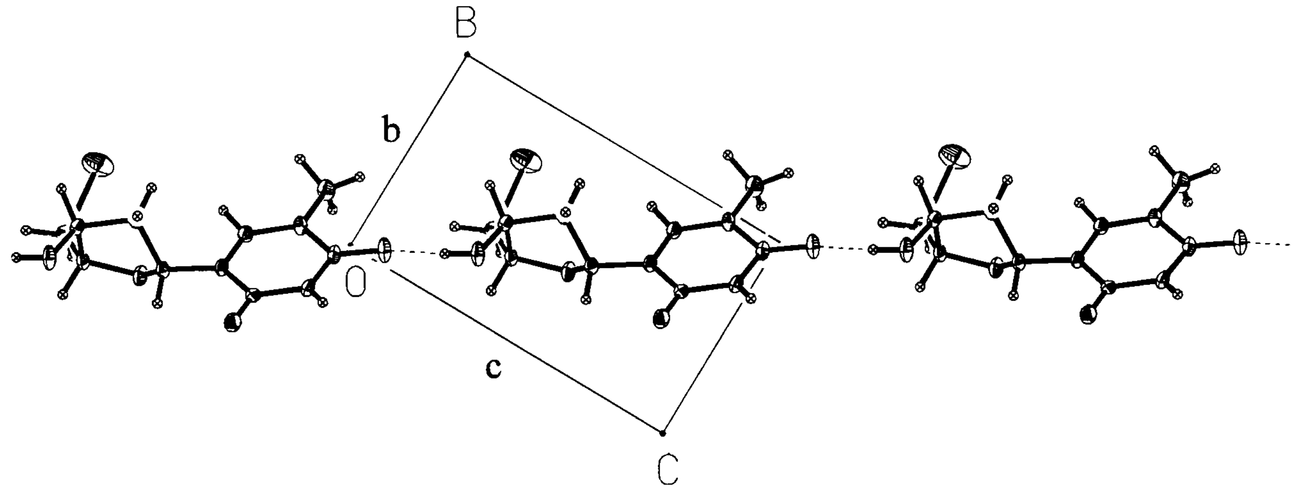

FIGURE 2 The hydrogen-bonding chains between the ribose and thymine rings in the crystal lattice of **1** (dashed lines), lying along the diagonal line of the plane *bc*. The projection is perpendicular to the unit-cell *a* axis. Thermal ellipsoids are drawn at the 25% probability level.

TABLE 3 Selected Torsion Angles for **1**: Conformation of the Ribose Ring of **1** in Comparison with Thymidine

(a) Conformation of the Ribose Ring in **1** *and Thymidine: Torsion Angles (°)*

	Compound **1**	*Thymidine*
C2′-C3′-C4′-O4′	7.0(5)	33.2
C1′-C2′-C3′-C4′	−29.2(5)	−36.9
C3′-C2′-C1′-O4′	42.3(5)	27.8
C2′-C1′-O4′-C4′	−39.2(5)	−7.0
C1′-O4′-C4′-C3′	19.9(5)	−16.7

Asymmetry Parameters [16]

	Compound **1**	*Thymidine*
ΔC_5(O4′)	37.4(2)	46.3
ΔC_5(C1′)	6.9(2)	40.7
ΔC_5(C2′)	24.6(2)	19.6
ΔC_5(C3′)	46.7(2)	8.3
ΔC_5(C4′)	52.0(2)	33.2
ΔC_2(O4′-C1′)	30.1(2)	58.7
ΔC_2(C1′-C2′)	11.5(2)	41.1
ΔC_2(C2′-C3′)	48.7(2)	7.8
ΔC_2(C3′-C4′)	67.3(2)	28.5
ΔC_2(C4′-O4′)	60.2(2)	53.9

(b) Other Interesting Torsion Angles for **1**

Br1-C5′-C4′-C3′	51.9(6)	N1-C1′-C2′-C3′	160.4(4)
Br1-C5′-C4′-O4′	−68.7(5)	N1-C1′-O4′-C4′	−162.4(4)
C1′-O4′-C4′-C5′	147.5(5)	C2-N1-C1′-C2′	104.5(5)
C2′-C3′-C4′-C5′	−115.3(5)	C2-N1-C1′-O4′	−140.0(5)
O3′-C3′-C2′-C1′	87.3(5)	C6-N1-C1′-C2′	−68.0(6)
O3′-C3′-C4′-C5′	129.6(5)	C6-N1-C1′-O4′	47.6(6)
O3′-C3′-C4′-O4′	−108.1(5)		

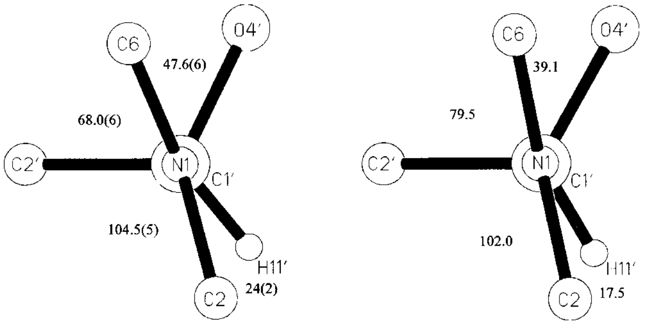

FIGURE 3 The Newman projection around the N1–C1′ bond: (a) in the molecule of **1** and (b) in the molecule of thymidine [15, 18].

gen O4 of thymine and 1 (symmetry: $-x$, $0.5 + y$, $0.5 - z$). The geometry of that contact in thymidine is similar (O3′–H3′, 0.93 Å; H3′ ··· O4, 1.82 Å; O3′ ··· O4, 2.746 Å; and angle O3′–H3′ ··· O4 176.1°), but a difference in the direction of these hydrogen-bonding chains in the crystal lattice of both structures (see Figures 2 and 4) is observed. In the crystal lattice of thymidine, these chains are situated along the unit-cell *b* axis (Figure 4).

The intermolecular hydrogen-bonding chains between the deoxyribose hydroxyl hydrogen H3′(O3′) and the thymine carbonyl oxygen O4 have a similar influence on deformation of the geometry of the thymine ring for both thymidine and 1. The deformation of the corresponding (C5-C4-N3 and O4-C4-C5) valence angles in thymidine is greater than in 1, and the elongation of the O4–C4 double bond is smaller (the respective C5-C4-N3 and O4-C4-

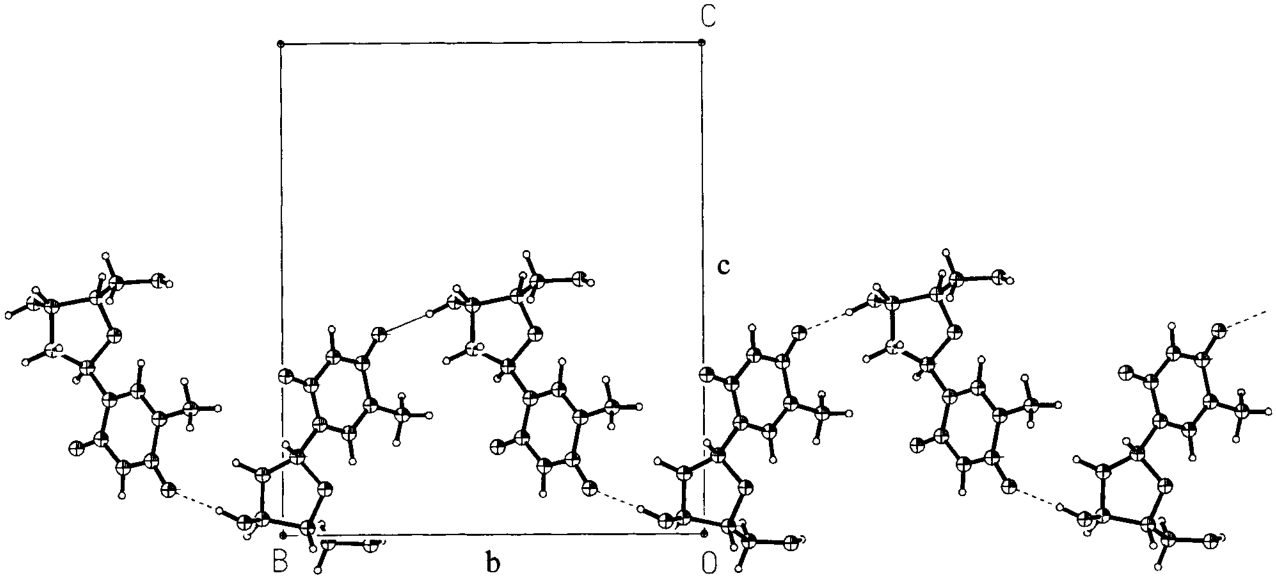

FIGURE 4 The hydrogen-bonding chains between the ribose and thymine rings in the crystal lattice of thymidine (dashed lines), lying along the unit-cell *b* axis. The projection is perpendicular to the unit-cell *a* axis.

TABLE 4 Two Hydrogen Contacts in Thymidine with Distances H ··· A Not Greater than ·· 2.20 Å [15]

D–H ·· A	*D–H* (*Å*)	*H ·· A* (*Å*)	*D ·· A* (*Å*)	*D–H ·· Å* (°)	*Symmetry*
N3–H(N3) ··· O3′	0.953	1.897	2.843	171.5	0.5 − *x*, 1 − *y*, *z* − 0.5
O5′–H(O5′) ··· O5′	0.843	1.959	2.798	173.5	*x* − 0.5, 0.5 − *y*, 1 − *z*

C5 angles being 115.7° and 124.6°, and the O4–C4 double bond length being 1.230 Å). The respective C2–O2 double bond length is slightly greater (1.206 Å).

In the molecule of thymidine, other important contacts are present, which are not observed in the structure of **1** (in **1**, besides that which was previously described, other inter- or intramolecular contacts are greater than 2.37 Å). The parameters for two important hydrogen bonds in the structure of thymidine, with the H ··· A distance not greater than 2.20 Å, are collected in Table 4. An analogous (as in **1**) intramolecular contact C2–O2 ··· H11′ has the following geometry: C1′–H11′, 0.97 Å; H11′ ··· O2, 2.29 Å; C1′ ··· O2, 2.748 Å; C1′–H11′ ··· O2, 108°; and C2–O2 ··· H11′, 81°.

The presence of a heavy, strongly electronegative bromine atom in molecule **1** affects intermolecular contacts within the crystal lattice. The molecules of **1** form linear chains, bound with intermolecular hydrogen bonds O3′–H3′ ··· O4–C4 along the diagonal line of the plane *bc* (Figure 2). Conversely, in thymidine, the same hydrogen bond results in a spiral chain formation (Figure 4).

ACKNOWLEDGMENTS

The authors are indebted to Professor Wojciech J. Stec for encouragement and helpful discussions.

SUPPLEMENTARY DATA

Tables of observed and calculated structure factors, anisotropic thermal parameters, and torsion angles, together with projections of intermolecular contacts for **1** and thymidine (15 pages) are available.

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[5] J. P. H. Verheyden, J. G. Moffat, *J. Org. Chem.*, *37*, 1972, 2289. Preparation of **1**: Thymidine (0.243 g, 1 mmol) and Ph_3P (0.393 g, 1.5 mmol) were dried overnight on high vacuum and dissolved in dry pyridine (2 mL). To this mixture, CBr_4 (0.5 g, 1.5 mmol) was added. After 2.5 hours, reaction was completed (TLC assay). Water and $CHCl_3$ were poured to the reaction mixture, and the product was extracted with several portions of $CHCl_3$, dried with $MgSO_4$, and purified by means of silica gel column chromatography (Kieselgel 60, 230–400 mesh, eluent $CHCl_3$–MeOH, 96:4); yield 70%. Pure product was crystallized from $CHCl_3$. T_m 143–146°C (not corrected).

MS DI (70 eV): 304, 306; ^{1}H NMR (200 MHz) δ (Py-d_5): 2.40–2.63 (m, $C_{2'}H$), 3.86 (dd, $C_{5'}H$), 4.40 (m, $C_{4'}H$), 4.85 (dt, $C_{3'}H$), 6.80 (dd, $C_{1'}H$).

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