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## Nucleosides, Nucleotides and Nucleic Acids

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### Nucleophilic N<sup>1</sup> → N<sup>3</sup> Rearrangement of 5'-O-Trityl-O<sup>2</sup>,3'-Cycloanhydrothymidine

Xian-Bin Yang<sup>a</sup>; Konrad Misiura<sup>a</sup>; Wojciech J. Stec<sup>a</sup>; Marek J. Potrzebowski<sup>a</sup>; Sławomir Kaźmierski<sup>a</sup>; Michał Wieczorek<sup>b</sup>; Wiesław R. Majzner<sup>b</sup>; Grzegorz D. Bujacz<sup>b</sup>

<sup>a</sup> Polish Academy of Sciences, Centre of Molecular and Macromolecular Studies, Łódź, Poland <sup>b</sup>

Technical University in Łódź, Institute of General Food Chemistry, Łódź, Poland

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**NUCLEOPHILIC N<sup>1</sup> → N<sup>3</sup> REARRANGEMENT OF  
5'-O-TRITYL-O<sup>2</sup>,3'-CYCLOANHYDROTHYMIDINE\***

Xian-Bin Yang<sup>a</sup>, Konrad Misiura<sup>a</sup>, Wojciech J. Stec<sup>a\*</sup>, Marek J. Potrzebowski<sup>a</sup>,  
Sławomir Kazmierski<sup>a</sup>, Michał Wieczorek<sup>b</sup>, Wiesław R. Majzner<sup>b</sup>, Grzegorz D. Bujacz<sup>b</sup>

<sup>a</sup>*Polish Academy of Sciences, Centre of Molecular and Macromolecular Studies,  
Sienkiewicza 112, 90-363 Łódź, Poland*

<sup>b</sup>*Technical University in Łódź, Institute of General Food Chemistry,  
Stefanowskiego 4/10, 90-924 Łódź, Poland*

**Abstract.** 5'-O-Trityl-O<sup>2</sup>,3'-cycloanhydrothymidine (**1**) heated at 150°C in the presence of O,O-diethyl phosphate or O,O-diethyl phosphorothioate anions undergoes rearrangement into N<sup>3</sup>-isomer (**2**); its structure was established by both advanced NMR methods and X-ray crystallographic studies. The most probable mechanism of **1**→**2** rearrangement relies upon reversibility of glycosidic bond cleavage process.

The chemistry of 5'-O-trityl-O<sup>2</sup>,3'-cycloanhydrothymidine (**1**)<sup>1–8</sup> has received much attention due to the significance of **1** as a substrate in the synthesis of various 3'-substituted thymidine analogues with prospective application as therapeutics. For instance 3'-azido-3'-deoxythymidine (AZT), an approved drug against the AIDS, can be synthesized *via* reaction of **1** with lithium or sodium azide.<sup>9–10</sup> Moreover, anhydronucleosides like **1** are useful substrates for the preparation of 3'-amino-3'-deoxyribonucleosides,<sup>11</sup> which are further used in the synthesis of oligo(nucleoside phosphoramidate)s.<sup>12–13</sup> Recently, compound **1** was examined as a model substrate for nucleophilic substitution at the 3'-carbon atom by O,O-diethyl phosphate or O,O-diethyl phosphorothioate anions.<sup>14</sup> It was found that instead of expected 3'-O-phosphorylated products, the isomeric compound, 5'-O-trityl-O<sup>2</sup>,3'-cycloanhydro-N<sup>3</sup>-thymidine (**2**), was formed. Compound **2** was postulated as an

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\* This paper is dedicated to the memory of Professor Alexander Krayevsky

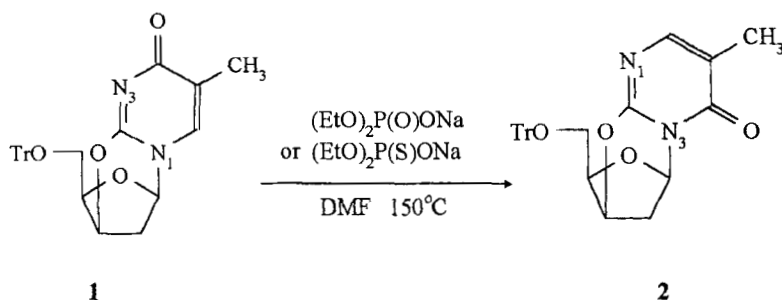
intermediate formed during  $N^1 \rightarrow N^3$  rearrangement observed at the AZT syntheses<sup>15,16</sup> and recently by Liotta and coworkers<sup>17</sup> who suggested the presence of **2** as a by-product in the stereocontrolled synthesis of nucleosides *via* intramolecular glycosylation.

Here we present the synthesis and complete structural elucidation of **2** by means of advanced NMR methods and X-ray analysis. The differences of the chemical shifts of protons and carbons in NMR spectra of compound **1** and **2** are studied as well as their X-ray crystal and molecular structures. The mechanism of observed rearrangement  $1 \rightarrow 2$  is also discussed.

## RESULTS AND DISCUSSION

The synthesis of 5'-O-trityl- $O^2,3'$ -cycloanhydrothymidine (**1**) was performed by triflate modification of the Horowitz<sup>2</sup> method. Such modification allowed to get **1** with 87% yield in a one-pot reaction of 5'-O-tritylthymidine with trifluoromethanesulfonyl chloride (triflic chloride) in the presence of 4-dimethylaminopyridine.

The resulting cycloanhydride **1** was then heated in the presence of an excess of sodium O,O-diethyl phosphate or phosphorothioate in DMF solution. No reaction was observed (TLC assay) when the reaction mixture was kept at 100°C for 18 h. However, increasing the temperature up to 150°C and time to 28 h caused total disappearance of substrate and the formation of a new product **2**. This new product showed higher mobility on TLC than starting **1**.



SCHEME 1

Compound **2** was isolated from the reaction mixture by silica gel chromatography in 23% yield. The low yield of **2** is probably caused by partial detritylation of **1** and **2** occurring

during prolonged heating. Structure of **2** was tentatively assigned as the 5'-O-trityl-O<sup>2</sup>,3'-cycloanhydro-N<sup>3</sup>-thymidine on the basis of the following data: a) IR spectrum of **2** exhibits a band at 1677 cm<sup>-1</sup> showing that a carbonyl function is still present; b) maximum of UV absorption of **2** in CH<sub>3</sub>CN at 283 nm, indicated that a modification of the aglycon part of molecule had occurred<sup>18</sup>; c) overall <sup>1</sup>H-NMR spectral pattern is akin to that of **1**; d) elemental analysis (C: 74.40%, H: 5.67%, N: 6.08%) and mass spectroscopic data [high resolution mass spectrum (EI): 466.1876] suggested that **2** is isomeric with **1**. This conclusion was fully confirmed by the advanced 2D NMR and X-ray diffraction analysis (*vide infra*).

### NMR Studies of **1** and **2**.

The complete assignment of the <sup>1</sup>H-NMR chemical shifts for **1** and **2** was done by means of <sup>1</sup>H-<sup>1</sup>H Pulse Field Gradient (PFG) COSY experiment. The <sup>1</sup>H-NMR was also used to establish the connectivity between protons on the basis of analysis of the geminal and vicinal couplings. The values of appropriate chemical shifts and coupling constants are collected in Table 1.

In <sup>1</sup>H-NMR spectrum, the anomeric proton of **2** appeared at 6.75 ppm. The comparison of chemical shifts for **2** and **1** showed that for the latter compound the H-1' signal is upfield about 1.29 ppm. The large difference in chemical shifts of anomeric protons in **1** and **2** may arise from hydrogen bonding between H-1' and oxygen atom attached to C-4 in compound **2** as supported by X-ray studies. The distance between H-1' and C-4 oxygen for compound **2** is 2.37 Å. The calculated bond length is in range excepted for hydrogen bonds and observed difference in chemical shifts for **1** and **2** and is consistent with reference data.<sup>19</sup> The presence of intra- and intermolecular C-H...O hydrogen bond was previously a matter of controversy<sup>20</sup> but recently this phenomenon is well-established<sup>21</sup> and supposed to have many implications in biology.<sup>22-24</sup>

The anomeric protons of **1** and **2** resonates as doublets, indicating that both H-1' are coupled only with H-2'α. The lack of coupling between H-1' and H-2'β in compound **1** and **2** could be explained assuming that the H1'-C-C-H2'β dihedral angle is close to 90°. In fact, the dihedral angles estimated from X-ray are 65.2° for compound **1**, 71.5° and 69.5° for compound **2**, respectively. For compound **1** the H-2'α appeared at higher

Table 1 <sup>1</sup>H-NMR Chemical shifts and coupling constants in compounds 1 and 2

Position	Compound 1		Compound 2	
	$\delta_{\text{H}}$ (ppm) <sup>a</sup>	Coupling Constants(Hz)	$\delta_{\text{H}}$ (ppm) <sup>a</sup>	Coupling Constants(Hz)
H-1'	5.46 (d)	<sup>3</sup> J <sub>1',2<math>\alpha</math></sub> =3.7	6.75 (d)	<sup>3</sup> J <sub>1',2<math>\alpha</math></sub> =4.0
H-2' $\alpha$	2.36 (dd)	<sup>2</sup> J <sub>2<math>\alpha</math>,2'<math>\beta</math></sub> =-12.7, <sup>3</sup> J <sub>2<math>\alpha</math>,1'</sub> =3.7, <sup>3</sup> J <sub>2<math>\alpha</math>,3</sub> =2.8	2.45 (dddd)	<sup>2</sup> J <sub>2<math>\alpha</math>,2'<math>\beta</math></sub> =-12.9, <sup>3</sup> J <sub>2<math>\alpha</math>,1'</sub> =4.0, <sup>3</sup> J <sub>2<math>\alpha</math>,3</sub> =2.6
H-2' $\beta$	2.64 (dddd)	<sup>2</sup> J <sub>2'<math>\beta</math>,2'<math>\alpha</math></sub> =-12.7, <sup>3</sup> J <sub>2'<math>\beta</math>,3</sub> =1.2	2.33 (dd)	<sup>2</sup> J <sub>2'<math>\beta</math>,2'<math>\alpha</math></sub> =-12.9, <sup>3</sup> J <sub>2'<math>\beta</math>,3</sub> =1.4
H-3'	5.12 (m)		5.17 (m)	
H-4'	4.26 (td)	<sup>3</sup> J <sub>4',5<math>\alpha</math></sub> =6.6, <sup>3</sup> J <sub>4',3</sub> =3.5	4.26 (td)	<sup>3</sup> J <sub>4',5<math>\alpha</math></sub> = <sup>3</sup> J <sub>4',5'<math>\beta</math></sub> =6.8, <sup>3</sup> J <sub>4',3</sub> =2.4
H-5' $\alpha$ <sup>b</sup>	3.35 (d)	<sup>3</sup> J <sub>5<math>\alpha</math>,4'</sub> =6.6	3.39 (dd)	<sup>2</sup> J <sub>5<math>\alpha</math>,5'<math>\beta</math></sub> =-12.0, <sup>3</sup> J <sub>5<math>\alpha</math>,4'</sub> =6.8
H-5' $\beta$ <sup>b</sup>	3.35 (d)	<sup>3</sup> J <sub>5'<math>\beta</math>,4'</sub> =6.6,	3.26 (dd)	<sup>2</sup> J <sub>5'<math>\alpha</math>,5'<math>\beta</math></sub> =-12.0, <sup>3</sup> J <sub>5'<math>\beta</math>,4'</sub> =6.8
CH <sub>3</sub> -5	1.92 (d)	<sup>3</sup> J <sub>CH<sub>3</sub>-5,6</sub> =1.1	1.96 (d)	<sup>3</sup> J <sub>CH<sub>3</sub>-5,6</sub> =1.1
H-6	6.91 (d)	<sup>3</sup> J <sub>6,CH<sub>3</sub>-5</sub> =1.1	7.45 (d)	<sup>3</sup> J <sub>6,CH<sub>3</sub>-5</sub> =1.1

<sup>a</sup>The chemical shifts of trityl protons are omitted. <sup>b</sup>The H-5' $\alpha$  and H-5' $\beta$  proton signal are assigned according to literature.<sup>26</sup>

field (2.36 ppm) than H-2'β (2.64 ppm). These data are consistent with the axial-equatorial shielding rule. The opposite trend was observed for compound **2**. The H-2'α appeared at a lower field (2.45 ppm) compared to H-2'β (2.33 ppm). The upfield shifting of H-2'β resonance for **2** is apparent if we assume that this proton is in shielding zone of the carbonyl group C(4)=O(4). As concluded, the distance between C4 and H-2'β is equal to 3.85 Å while analogous distance between C4 and H-2'α is found to be 4.67 Å. The shielding effect of the carbonyl group should be also considered in case of the anomeric proton where the distance between C4 and H1' is only 2.76 Å.<sup>25</sup> However two opposite effects have to be taken into consideration in this case. As seen the deshielding effect of the hydrogen bonding plays the dominate role. Moreover, it is worthy to note two different coupling patterns observed for C-5' with C-4' protons in <sup>1</sup>H-NMR spectra in compounds **1** and **2** (*A<sub>2</sub>M* and *ABM*, respectively).

To find the specific and diagnostic differences between **1** and **2**, a detailed analysis of <sup>13</sup>C-NMR spectra was performed. With known <sup>1</sup>H-NMR chemical shifts and proton-proton couplings, the assignments of protonated carbons (one bond C-H connectivities) were carried out employing PFG-HMQC technique.<sup>26</sup> The chemical shifts of quaternary carbon of thymidine atoms were established by means of PFG HMBC (heteronuclei multi-bond correlation)<sup>27</sup> experiment. This method is a very sensitive probe of <sup>1</sup>H-<sup>13</sup>C long range connectivities, therefore the complete assignments of <sup>13</sup>C-NMR chemical shifts was possible. The <sup>13</sup>C-NMR data are given in Table 2.

Figure 1 shows the <sup>1</sup>H-<sup>13</sup>C PFG HMBC spectrum of **1** recorded at room temperature in chloroform-d. Inspection of this spectrum revealed that there are cross peaks between protons CH<sub>3</sub>-5 (δ=1.92 ppm), H-6 (δ=6.91 ppm) and carbonyl carbon C-4 (δ=171.67 ppm) *via* three bonds. There is no cross peak between H-1' (δ=5.46 ppm) and C-4, whereas the cross peak between H-1' (δ=5.46 ppm) and C-6 (δ=135.29 ppm) was detected. Figure 2 presents the <sup>1</sup>H-<sup>13</sup>C PFG HMBC spectrum of compound **2**.

An inspection of this spectrum indicates the presence of connectivities between H-1' (δ=6.75 ppm), CH<sub>3</sub>-5 (δ=1.96 ppm), H-6 (δ=7.45 ppm) and C-4 carbonyl carbon (δ=160.93 ppm). There is no cross peak between H-1' and C-6 (δ=150.48 ppm). These spectral features unambiguously confirm the correctness of structural assignment for compound **2**. Comparison of <sup>13</sup>C-NMR chemical shifts of compounds **1** and **2** indicates

**Table 2** <sup>13</sup>C-NMR Chemical shifts assignments for compounds **1** and **2**

Position <sup>a</sup>	Compound <b>1</b>			Compound <b>2</b>		
	δ <sub>c</sub> (ppm)	HMBC	δ <sub>c</sub> (ppm)	HMBC	δ <sub>c</sub> (ppm)	HMBC
C-1'	87.89	5.46(H-1')	H-2'α, H-3', H-4', H-6'	77.91	6.75(H-1')	H-2'α
C-2'	33.41	2.36(H-2'α) 2.64(H-2'β)		32.80	2.45(H-2'α) 2.33(H-2'β)	
C-3'	76.74	5.12(H-3')	H-1', H-2'β, H-4', H-5'α	76.87	5.17(H-3')	H-1', H-2'β H-4', H-5'α, 5'β
C-4'	84.31	4.26(H-4')	H-1', H-2'β, H-3', H-5'α	84.38	4.26(H-4')	H-1', H-2'β, H-5'α, H-5'β
C-5'	62.25	3.35(H-5'α)	H-4'	62.01	3.39(H-5'α) 3.26(H-5'β)	H-4'
C-2	153.23		H-1', H-3', H-6	152.20		H-1', H-3', H-6
C-4	171.67		CH <sub>3</sub> -5, H-6	160.93		H-1', H-6, CH <sub>3</sub> -5
C-5	117.96		CH <sub>3</sub> -5, H-6	117.07		CH <sub>3</sub> -5, H-6
C-6	135.29	6.91(H-6)	H-1', CH <sub>3</sub> -5	150.48	7.45(H-6)	CH <sub>3</sub> -5
CH <sub>3</sub> -5	13.26	1.92(CH <sub>3</sub> -H)	H-6	12.96	1.96(CH <sub>3</sub> -5)	H-6

The chemical shifts of trityl group carbons are omitted.

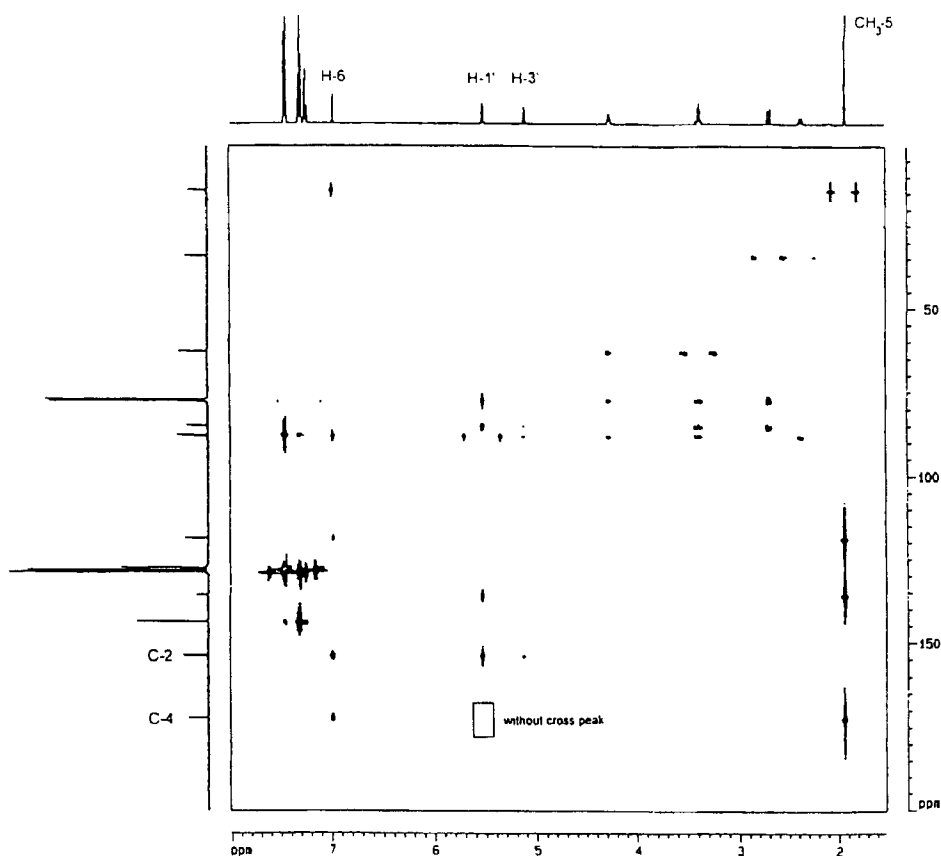


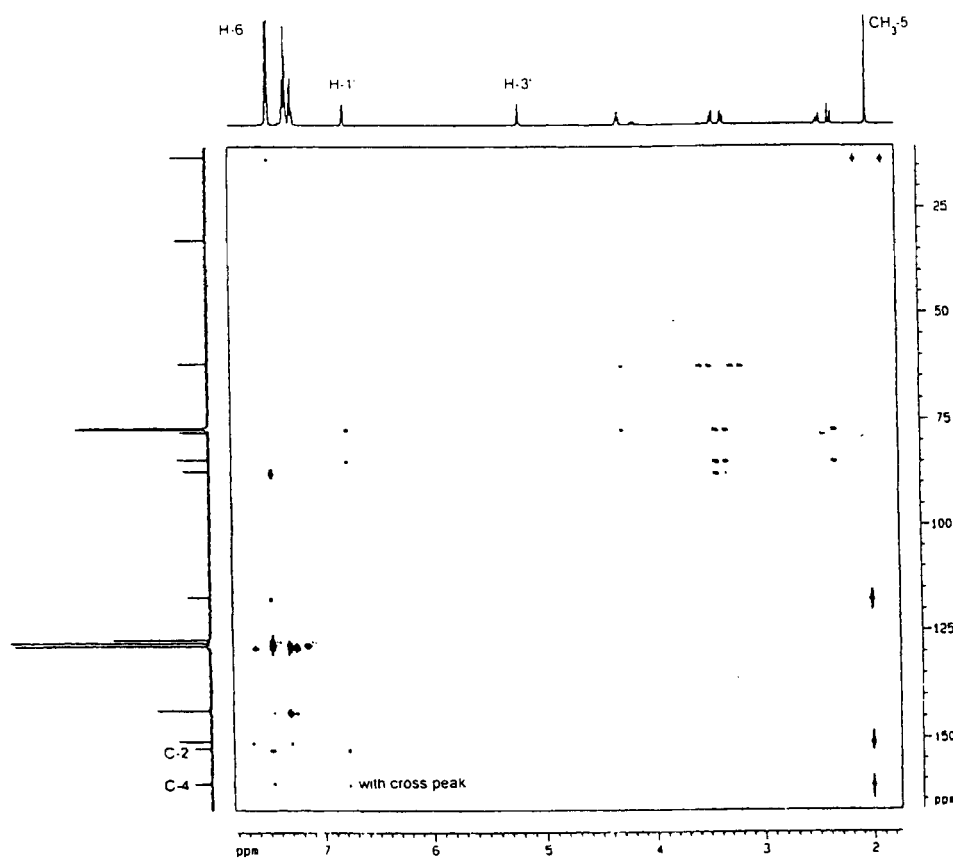
FIG. 1  $^1\text{H}$ - $^{13}\text{C}$  PFG HMBC spectrum of 5'-O-trityl- $\text{O}^2,3'$ -cycloanhydrothymidine (**1**)

the significant differences for C-4 and C-6 atoms. In compound **2** the resonance signal of C-4 is shifted about 10.7 ppm to high field and signals of C-6 is shifted a 15.2 ppm to lower field as compared with that of **1**. Such distinction of the chemical shifts can be caused by ring current effect of the phenyl groups of trityl residue.

### X-ray Crystallographic Analysis of **1** and **2**

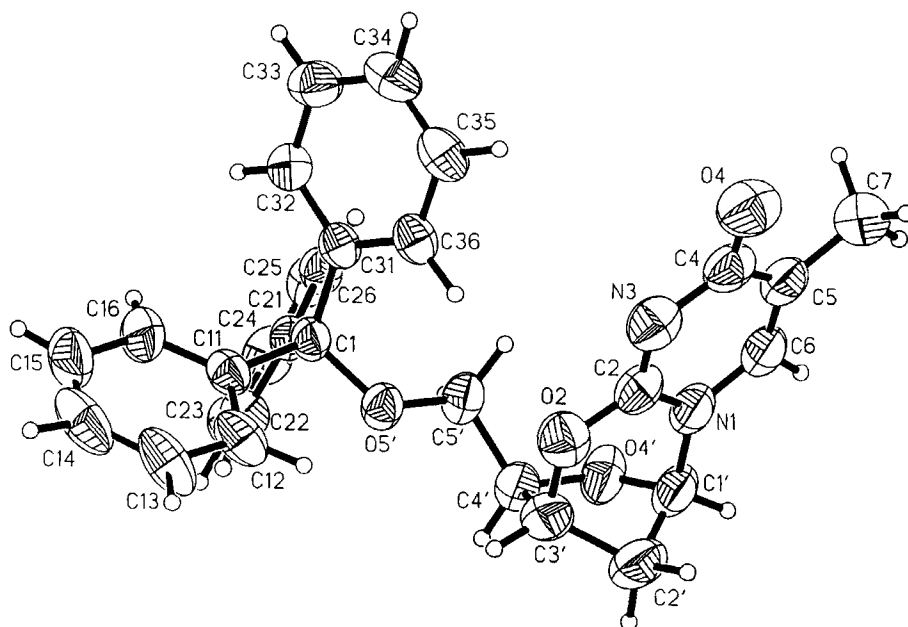
For X-ray analysis compounds **1** and **2** were crystallized from ethyl alcohol under a slow saturation with n-hexane. Figures 3, 4, and 5 show the overall view of compounds **1** and **2** along with the numbering scheme for all the atoms constituting the independent part of the unit cell. The experimental details are collected in Table 3



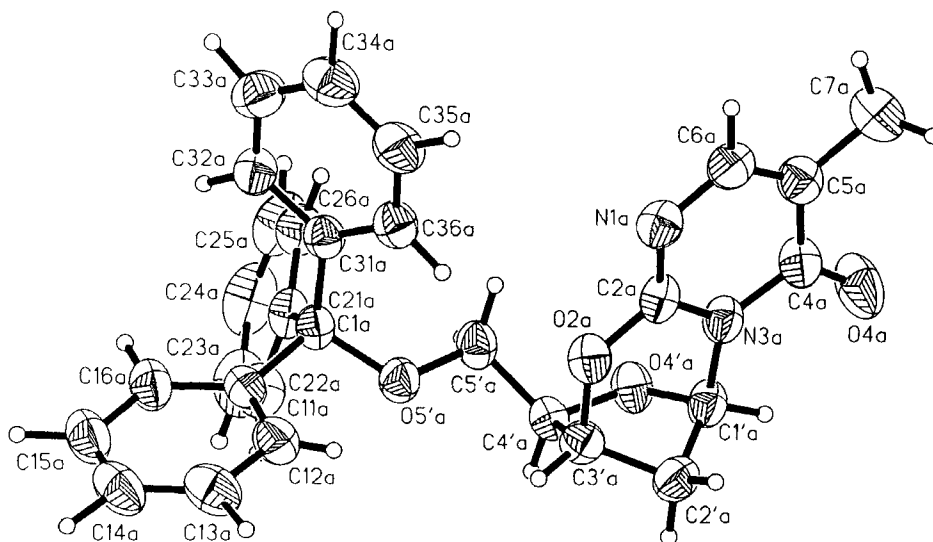


**FIG. 2**  $^1\text{H}$ - $^{13}\text{C}$  PFG HMBC spectrum of 5'-O-trityl- $\text{O}^2,3'$ -cycloanhydro- $\text{N}^3$ -thymidine (**2**)

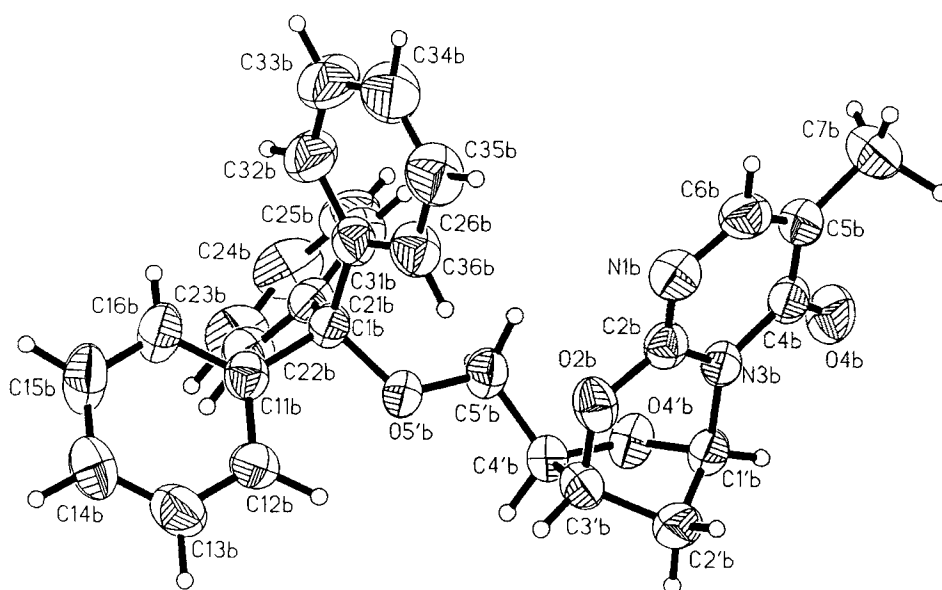
Compound **1** contains one molecule in the asymmetric part, while in compound **2** the asymmetric part is made up of two nucleoside molecules and one solvent molecule. The absolute configuration in the sugar moiety and the relative position in respect to the thymidine ring were obtained for both compounds. As expected the absolute configuration on the C3' atom in both **1** and **2** is *R*. In order to describe the conformation of the sugar ring for both compounds, the asymmetry parameters based on the torsion angles have been calculated. The conformation of the deoxyribose ring for both compounds has the shape of a deformed envelope with C2' atom in the *flap* position. Molecule **2a** is more deformed in comparison to **2b** and the molecule of compound **1**). The deviation of atoms C3' and C2' from the plane containing atoms C1', O4' and C4' describes the form of the



**FIG. 3** The molecular structure of 5'-O-trityl-O<sup>2</sup>,3'-cycloanhydrothymidine (**1**)



**FIG. 4** The molecular structure of 5'-O-trityl-O<sup>2</sup>,3'-cycloanhydro-N<sup>3</sup>-thymidine, form a (**2a**)



**FIG. 5** The molecular structure of 5'-O-trityl-O<sup>2</sup>,3'-cycloanhydro-N<sup>3</sup>-thymidine form b (**2b**)

ring on **1**-C2' *exo*, **2a**-C2' *exo*; C3' *endo* and **2b**-C2' *exo*. The base-sugar bridge C3'-O4'-C4 and C3'-O2-C2 in **1** and **2**, respectively, creates an additional six-membered ring connected to the ribose which stabilizes the conformation of the sugar moiety. The suppression of the structural flexibility of the ribose ring was described for several modified nucleosides containing an intramolecular bridge between base and sugar.<sup>28</sup> The total lack of pseudorotation was observed for the compound containing the bridge C2'-X-C(base). Some level of flexibility of the ribose ring remained for compound with C3'-X-C(base) base sugar bridge.<sup>29</sup> Comparing bond lengths and valency angles for **1** and **2**, we were able to establish that the difference in corresponding geometrical parameters is smaller than 3 $\sigma$ . The exception is 6 $\sigma$  difference for C1'-O4' bonds with lengths 1.404(3) $\text{\AA}$ , 1.423(3) $\text{\AA}$  and 1.418(4) $\text{\AA}$  for molecules **1**, **2a** and **2b** respectively. The observed bond lengths and angles are also similar to that found for related structures (*i.e.* 3' $\alpha$ -diethylphosphono-3' $\beta$ -hydroxy-5'-O-tritylthymidine) deposited in the Cambridge Crystallographic Database.<sup>30</sup>

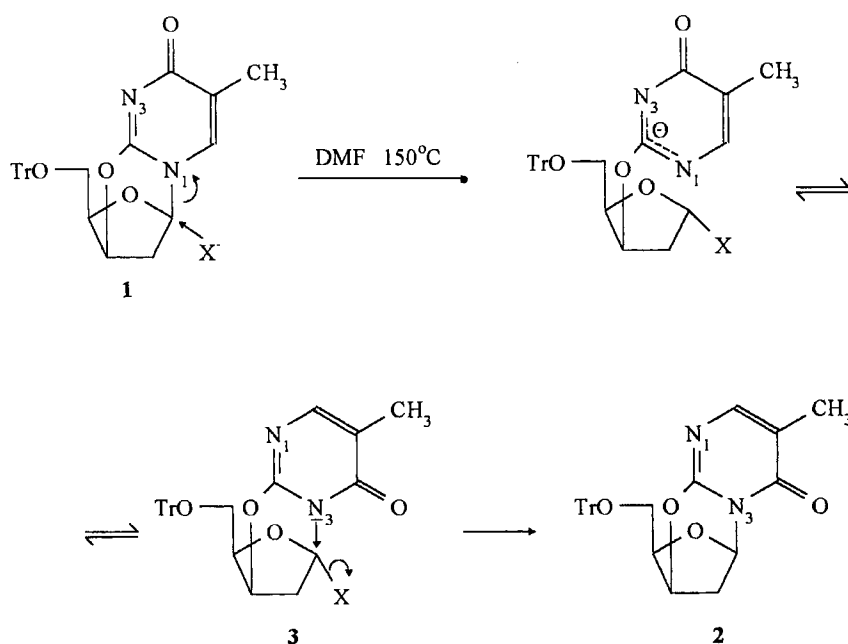
**Table 3** Crystal data and experimental details

Compound	1	2
Molecular formula	C <sub>29</sub> H <sub>26</sub> N <sub>2</sub> O <sub>4</sub>	C <sub>29</sub> H <sub>26</sub> N <sub>2</sub> O <sub>4</sub> +½C <sub>2</sub> H <sub>6</sub> O
Formula weight	466.52	489.55
Crystallographic system	monoclinic	monoclinic
Space group	P2 <sub>1</sub>	P2 <sub>1</sub>
a (Å)	8.751(3)	15.612(5)
b (Å)	13.530(4)	9.094(3)
c (Å)	10.698(4)	18.428(7)
β (°)	111.83(3)	107.83(3)
V (Å <sup>3</sup> )	1175.8(7)	2490.6(14)
Z	2	4
D <sub>c</sub> (g/cm <sup>3</sup> )	1.318	1.306
μ [cm <sup>-1</sup> ]	7.12	7.11
Crystal dimensions (mm)	0.25x0.25x0.45	0.10x0.20x0.25
Maximum 2θ (°)	150	148
Radiation, λ (Å)	CuKα, 1.54184	CuKα, 1.54184
Scan mode	ω/2θ	ω/2θ
Scan width (°)	0.75+0.14 tanθ	0.80+0.14 tanθ
<i>hkl</i> ranges:	<i>h</i> = -10 10 <i>k</i> = 0 16 <i>l</i> = -13 13	0 19 -11 10 -23 21
DECAY correction:	min: 1.00006 max: 1.08912 ave: 1.04223	not applied
EAC correction:	min: 0.9442 max: 0.9990 ave: 0.9740	0.9259 0.9976 0.9674
No. of reflections:	unique 2521	9911
refine with <i>I</i> >0σ( <i>I</i> )	2505	9209
observed with <i>I</i> >2σ( <i>I</i> )	2416	7894
No. of parameters refined	420	894
Largest diff. peak (eÅ <sup>-3</sup> )	0.423	0.187
Largest diff. hole (eÅ <sup>-3</sup> )	-1.193	-0.196
<i>R</i> <sub>obs</sub>	0.0368	0.0498
<i>wR</i> <sub>obs</sub>	0.0873	0.1321
Weighting coeff.*	<i>m</i> 0.0451 <i>n</i> 0.0775	0.0958 0.0448
Extinction coeff.**	<i>k</i> 0.0101(9)	0.0047(4)
<i>S</i> <sub>obs</sub>	1.062	1.083
shift/esd max	0.000	-0.004
Absolute structure	<i>R</i> <sub>C1'</sub> , <i>R</i> <sub>C3'</sub> , <i>R</i> <sub>C4'</sub>	<i>R</i> <sub>C1'</sub> , <i>R</i> <sub>C3'</sub> , <i>R</i> <sub>C4'</sub>
Flack parameter χ	-0.18(20)	0.06(18)
<i>R</i> <sub>int</sub>	0.0577	0.0504
<i>T</i> <sub>meas</sub>	293(2)	293(2)
<i>F</i> (000)	492	1036

\* weighting scheme  $w=[\sigma^2(\text{Fo}^2)+(m*\text{P})^2+n*\text{P}]^{-1}$  where  $\text{P}=[\max(0,\text{Fo}^2)+2\text{Fc}^2]/3$ \*\* extinction method SHELXL, extinction expression  $\text{Fc}^*=k\text{Fc}[1+0.001x\text{Fc}^2\lambda^3/\sin(2\theta)]^{-1/4}$

### Mechanism of Rearrangement 1→2

The mechanism of the ring-opening process by which **1** rearranges to **2** in the presence of sodium O,O-diethyl phosphate or O,O-diethyl phosphorothioate is of interest in view of the synthetic application of transglycosylation reactions.<sup>31</sup> In a blank experiment, when **1** was heated without presence of phosphate or phosphorothioate and no formation of **2** was observed, we proved nucleophilic (not thermal) mechanism of this rearrangement. In our interpretation nucleophilic attack of the O,O-diethyl phosphate or O,O-diethyl phosphorothioate anion takes place at C-1' with the cleavage of the glycosidic bond providing intermediate **3** (Scheme 2).



SCHEME 2

Dispersion of the negative charge between N-1 and N-3 gives rise to resonance stabilized intermediate. An attack of the N-3 anion at C-1' occurs with the reconstitution of the nucleosidic bond accompanied by simultaneous release of diethyl phosphate or

diethyl phosphorothioate anion, resulting in formation of rearranged product **2**. Higher thermodynamic stability of **2** compared to **1** was also proved by semi-empirical (PM-3) molecular calculations.<sup>32</sup> The heats of formation in vacuum of **1** and **2** are 75.5 and 102.9 kJ/mol, respectively. Glycosidic rearrangement N-1  $\rightarrow$  N-3 in anhydronucleosides has been reported to occur under strong acidic conditions,<sup>33,34</sup> although it also takes place to a small extent in nucleophilic substitutions by azide anion.<sup>15,16</sup>

## EXPERIMENTAL

### 5'-O-Trityl-O<sup>2</sup>,3'-cycloanhydrothymidine (**1**)

To a stirred solution of 5'-O-tritylthymidine (920 mg, 1.9 mmole) and 4-dimethylaminopyridine (700 mg, 5.75 mmole) in dry dichloromethane (10 ml) at -20°C was added trifluoromethanesulfonyl chloride (0.24 ml, 2.25 mmole) over a period of 5 min. After 10 min the temperature was allowed to rise up to -5°C, and stirring was continued for 15 min. TLC control indicated that the starting material disappeared, and a new less polar compound was formed ( $R_f$  0.49, chloroform:ethanol=19:1, v/v). Reaction mixture was left at room temperature. Gradual disappearance of the compound with  $R_f$  0.49 was observed accompanied with the appearance of another compound with  $R_f$  0.07 (chloroform:ethanol, 19:1, v/v). After 2.5 h the reaction was complete. Solvent was then removed to dryness, the residue was dissolved in *ca.* 5 ml of chloroform and this solution was applied on silica gel column for chromatography [silica gel, 230-400 mesh, 60 g, eluted with chloroform (50 ml), then chloroform containing 0-5% of methanol]. The appropriate fractions (TLC control,  $R_f$  0.07, chloroform:ethanol =19:1, v/v) were combined and evaporated to dryness, providing 770 mg of the title compound in 87% yield. The obtained compound **1** was crystallized from ethanol, m.p. 230-231°C (*lit.*<sup>7</sup> 226-229°C),  $[\alpha]_D + 9.1$  (c 2.8, CHCl<sub>3</sub>).

### 5'-O-Trityl-O<sup>2</sup>,3'-cycloanhydro-N<sup>3</sup>-thymidine (**2**)

To a stirred solution of 5'-O-trityl-O<sup>2</sup>,3'-cycloanhydrothymidine (**1**, 466 mg, 1 mmole) in anhydrous DMF (5 ml) was added sodium O,O-diethyl phosphate or phosphorothioate (5 mmole). The stirred reaction mixture was maintained at reflux temperature for 28 h. After cooling to room temperature, the brown solution was

concentrated to dryness *in vacuo*. The residue was suspended in chloroform (150 ml) and the resulting solution was washed with water (3 x 30 ml), dried with anhydrous  $\text{MgSO}_4$  and the solvent was evaporated to dryness. The crude product was purified by silica gel column chromatography (silica gel, 230-400 mesh, 10 g) using the following eluting system:  $\text{CH}_2\text{Cl}_2$  (50 ml),  $\text{CH}_2\text{Cl}_2:\text{CHCl}_3=1:1$  (50 ml),  $\text{CHCl}_3$  (50 ml),  $\text{CHCl}_3$  containing 0-5% MeOH. Appropriate fractions (TLC control,  $R_f$  0.46, chloroform: ethanol=19:1, v/v) were combined and evaporated to dryness, providing 107 mg of the product as a colorless solid in 23% yield. This compound was crystallized from ethanol, m.p. 223-224°C;  $[\alpha]_D$  -100 (c 0.5,  $\text{CHCl}_3$ ); elemental analysis: found C% 74.40%, H% 5.67%, N% 6.08%; required C% 74.72, H% 5.62, N% 6.01%; High Resolution EI-MS for  $\text{C}_{29}\text{H}_{26}\text{O}_4\text{N}_2$ : calcd. 466.1893, found 466.1876.

### NMR experiments

Compounds **1** and **2** were dissolved in  $\text{CDCl}_3$  and NMR spectra were acquired at room temperature. The  $^1\text{H}$  NMR spectra were recorded on a Bruker AC-200 spectrometer at 200.13 MHz with a spectral width 2994 Hz.  $^{13}\text{C}$  NMR spectra were recorded on a Bruker DRX-500 spectrometer at 125.77 MHz with a spectral width 17 kHz. All two-dimensional experiments made in this work (COSY, HMQC, HMBC) were carried with Pulse Field Gradients (PFG) on a Bruker DRX-500 spectrometer in order to reduce the time of measurements and to improve the quality of spectra (e.g. reducing the  $T_1$  noise).

### X-ray experiments

Crystal and molecular structure of **1** and **2** were determined using data collected at room temperature on a CAD4 diffractometer with graphite monochromatized  $\text{CuK}\alpha$  radiation. Compounds **1** and **2** crystallize in the monoclinic system, in space group  $\text{P}2_1$ . Crystal data and experimental details are shown in Table 3. The lattice constants were refined by least-squares fit of 25 reflections in the  $\theta$  range  $19.61^\circ$ - $29.36^\circ$  for **1** and  $18.79^\circ$ - $28.68^\circ$  for **2**. The decline in intensity of three control reflections (4,5,-3; 0,4,-4; -2,4,-4) and (3,-2,5; 2,-1,8; 4,-2,3) were 15.7% during 55.5 hours of exposure time and 0.1% during 157.3 hours, for **1** and **2** respectively.

For compound **1** intensity correction was applied (DECAY program)<sup>35</sup>. For both compounds an empirical absorption correction was applied by the use of the  $\psi$ -scan method (EAC program).<sup>35,36</sup> A total of 2505 for **1** and 9209 for **2** reflections with  $I \geq 0\sigma(I)$  were used to solve the structures by direct methods<sup>37</sup> and to refine them by full matrix least-squares using  $F^2$  parameter.<sup>38</sup> Hydrogen atoms were found on different Fourier maps and refined isotropically, except hydrogens at solvent molecule (for compound **2**) that were placed geometrically at idealized positions and set as riding with fixed thermal parameters equal to 1.33 times of the equivalent isotropic thermal parameter of the parent-atom. Anisotropic thermal parameters were applied for all nonhydrogen atoms.

The final refinement converged to  $R=0.0368$  for 420 refined parameters and 2416 reflections with  $I \geq 2\sigma(I)$  for **1** and  $R=0.0498$  for 894 refined parameters and 7894 observed reflections with  $I \geq 2\sigma(I)$  for **2**. The absolute configurations at the chiral atoms were established as  $R_{C1'}$ ,  $R_{C3'}$ , and  $R_{C4'}$ . The absolute structure was determined by the Flack method<sup>39</sup> with results  $\chi=-0.18(20)$  for **1** and  $0.06(18)$  for **2**.

The authors have deposited atomic coordinates, bond lengths, and bond angles for these structures with the Cambridge Crystallographic Data Centre.<sup>40</sup>

### Molecular Modeling

PM-3 and AM1 calculations were carried out using HyperChem<sup>TM</sup> 5.0 software.

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