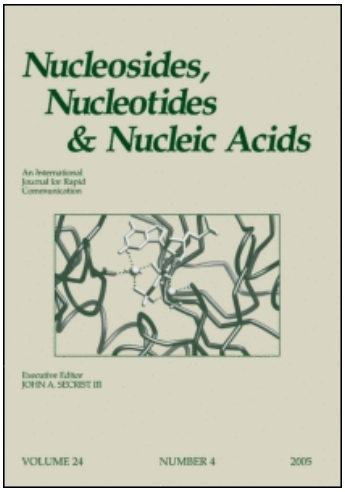

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Jokić, Milan , Raza, Zlatica and Katalenić, Darinka(2000) 'The Synthesis of Novel 6,5- and 6,6-Membered Fused Heterocyclic Compounds Derived from Thymine', Nucleosides, Nucleotides and Nucleic Acids, 19: 9, 1381 — 1396
To link to this Article: DOI: 10.1080/15257770008033849
URL: http://dx.doi.org/10.1080/15257770008033849

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 19(9), 1381–1396 (2000)

THE SYNTHESIS OF NOVEL 6,5- AND 6,6-MEMBERED FUSED HETEROCYCLIC COMPOUNDS DERIVED FROM THYMINE

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Abstract: Novel pyrimido[1,2-a]pyrimidinones **14**, **15** and **16** and imidazo[1,2-a] pyrimidinones **19** and **20**, designed as conformationally constrained analogues of 1-(3-amino-2-hydroxypropyl)thymine and 1-(2-amino-3-hydroxypropyl)thymine, respective ly, were synthesized by the ring-opening/ ring-closure rearrangement of the corresponding byciclic oxygen-containing amino compounds **12** and **17**.

Nucleosides and their analogues, as derivatives of natural pyrimidines and purines, have gained increasing importance through their biological activity particularly as antiviral and anticancer compounds.[1] Several derivatives that do not have a sugar moiety or a ring structure (acyclic or aliphatic nucleosides) have emerged as a new class of antiviral agents which function mostly as inhibitors of viral reverse transcriptase (RT), or DNA polymerase.[2] In contrast to the purine acyclic nucleosides, pyrimidine acyclic nucleosides have not shown significant antiviral activity.[3] Nonetheless, pyrimidine acyclic nucleosides, 1-[(hydroxyethoxy)methyl)]-6-(phenylthio)thymine [HEPT] derivatives, so called nonnucleoside inhibitors have been found to be active against HIV-1 RT.[4] Extensive structure-activity studies have been conducted on this new inhibitors.[5] However, studies on the synthesis of cyclic variants in the HEPT series are rare.[6] In the past few years the fused pyrimidines have aroused much attention owing to the wide range of biological activity of these compounds.[7] Many potential drugs have been modeled on them, particularly in cancer and virus research.[8] This encouraged us to extend our work with restricted acyclic pyrimidines[9,10] and to

synthesize novel 6,5- and 6,6-membered fused heterocyclic compounds as potential antiviral agents. The preparation of polycyclic molecules containing uracil or thymine ring possess significant synthetic challenges. In our earlier work, we have reported on a general strategy for the formation of pyrimido[2,1-b][1,3]oxazolones and pyrimido[2,1-b][1,3]oxazinones (O^2,2'- and O^2,3'-anhydro compounds or anhydrides, respectively) derived from thymine[9] and uracil[10], which features intramolecular cyclisation reactions of suitably activated aliphatic pyrimidine analogues. On the other hand, we have found that intramolecular nucleophilic substitution of the O^2,2'-cyclo linkage in cyclonucleosides with an *in situ* generated amino group as an internal nucleophile constitutes an excellent route to nitrogen-containing tricyclic nucleosidic systems (Figure 1).[11] These two facts prompted us to study the transformations of amino derivatives of O^2,2'- and O^2,3'-anhydrides derived from *N*-1 substituted thymine into the corresponding nitrogen-isosteres. In the present communication, we describe utility of this approach for the preparation of novel pyrimido[1,2-a]pyrimidinones and imidazo[1,2-a] pyrimidinones.

The general approach utilized in the synthesis of N^2,3'- and N^2,2'-anhydrides involves the use of azido derivatives of O^2,2'- and O^2,3'-anhydro compounds. Previously, the synthesis of O^2,2'-anhydro-1-(2,3-dihydroxypropyl)thymine (**3**), O^2,2'-anhydro-1-(3-azido-2-hydroxyropyl)thymine (**5**) and, O^2,3'-anhydro-1-(2,3-dihydroxy propyl)thymine (**7**) have been described using sulphonyl derivatives of 1-(2,3-dihydro xypropyl)thymine as intermediates.[9] This synthetic method involved numerous reaction steps and poor yields. Now, we present a new and less fastidious synthetic approach to prepare the azides **5** and **11** (Scheme 1). 1-Allylthymine[12a] **1** was converted to the corresponding dibromide **2** (80.7%), treated with DBU in CH_2Cl_2 to achieve cyclisation to the novel O^2,2'-anhydro-3'-bromo derivative **4** in 83.6% yield. The maximums of UV absorption of bromo derivative **4** (λ_{max} =229 and 259 nm) and the absence of 3-NH signal in ^{1}H NMR spectrum indicate the cyclic structure. The NMR spectra (^{1}H and ^{13}C) of **4** are in good agreement with the spectral data of the known five-membered anhydro derivatives[9] **3** and **5**. ^{13}C NMR data for 2,2'-anhydro derivatives are presented in Table 1. Reaction of bromo intermediate **4** with NaN_3 in DMF led to the nucleophilic displacement with formation of azido derivative **5** in a very good yield. This material was identical by IR, UV, NMR spectra and thin layer R_F values with the previously

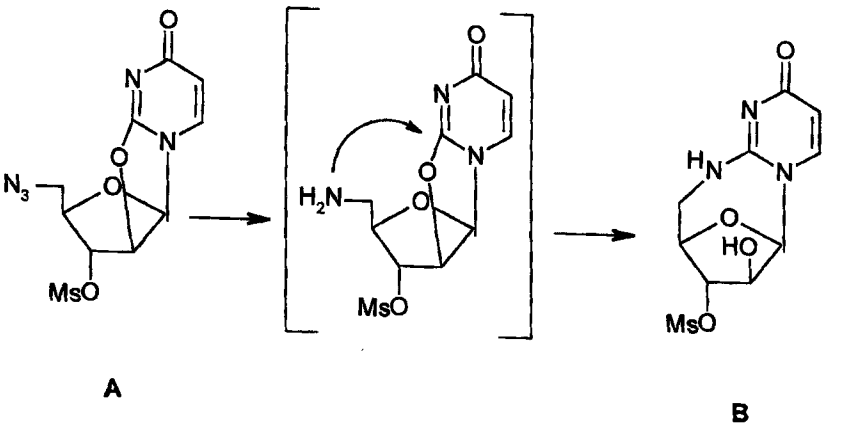
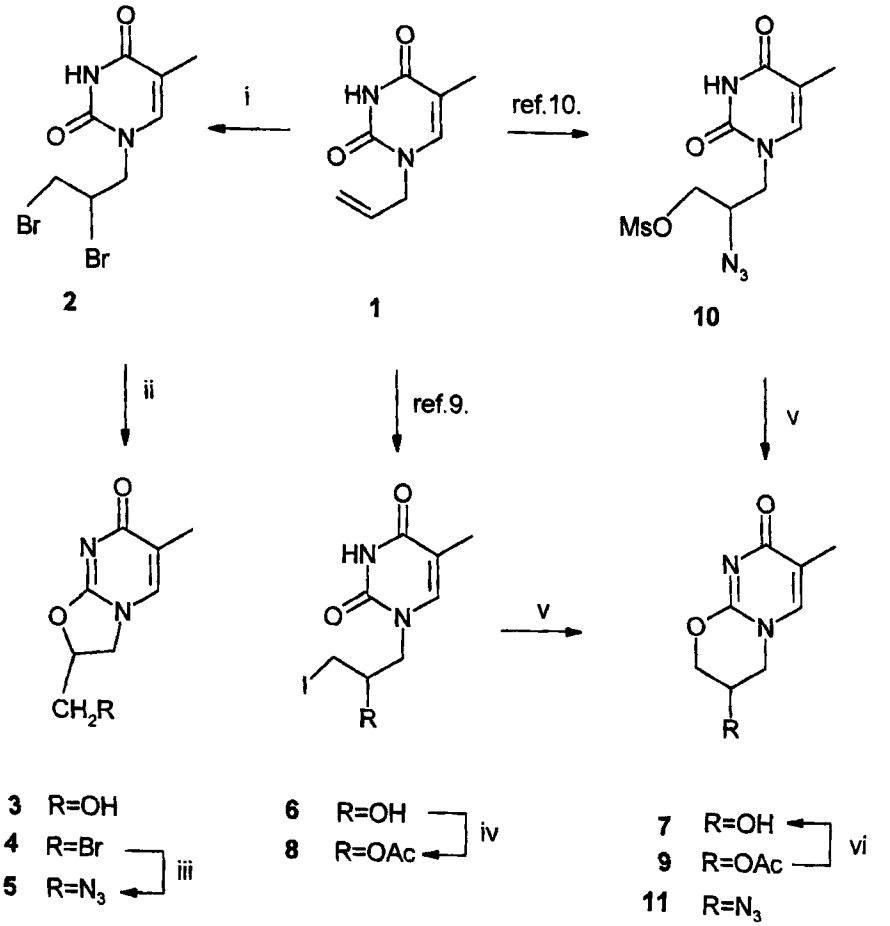


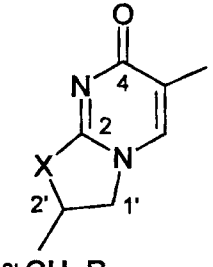
Figure 1



Reagents and conditions: i, Br_2, CH_2Cl_2; ii, DBU, CH_2Cl_2, r.t.,3 h; iii, NaN_3, DMF, 90°C, 3 h; iv, Ac_2O, Py; v, DBU, CH_2Cl_2, r.t., overnight; vi, NH_3, MeOH

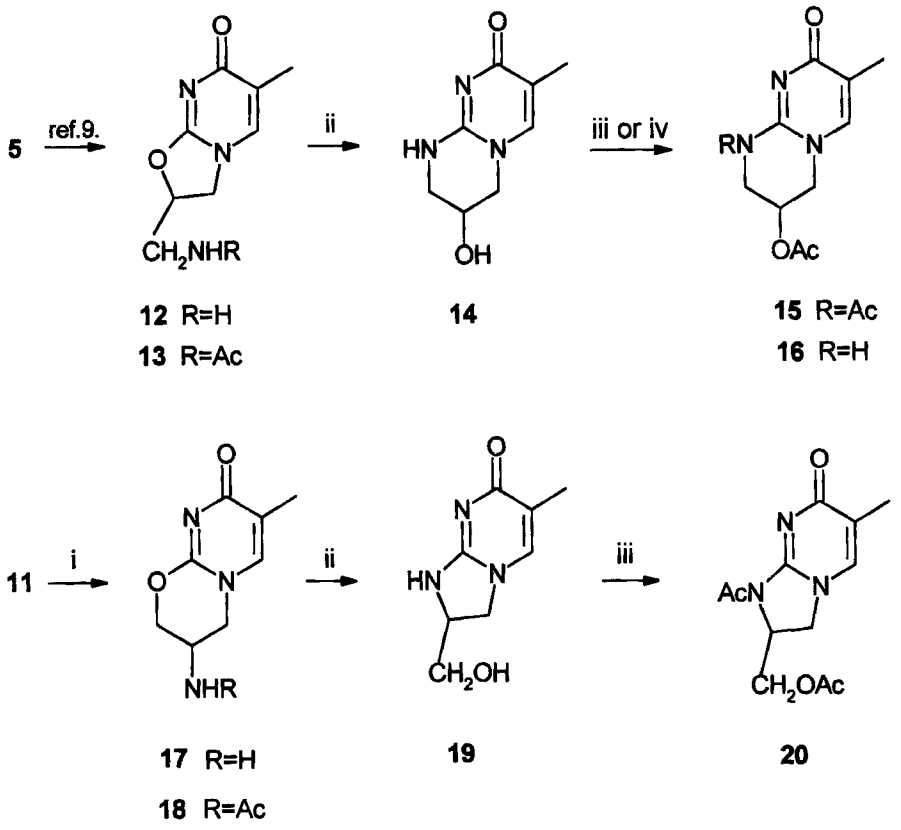
Scheme 1

Table 1. ^{13}C NMR chemical shifts (in ppm) of 2,2'-anhydro derivatives in DMSO-d_6



	C-4	C-2	C-6	C-5	C-2'	C-3'	C-1'	CH_3-5	NAc (CO;CH_3)	OAc (CO;CH_3)
3 X=O; R=OH	171.62	160.28	133.81	115.89	79.04	61.12	47.29	13.43		
4 X=O; R=Br	171.86	160.13	134.05	116.23	76.72	34.73	50.01	13.60		
5 X=O; R=N_3	171.39	159.71	133.75	115.86	76.86	52.09	48.13	13.43		
12 X=O; R=NH_2	172.04	160.39	134.38	115.73	80.14	43.53	48.34	13.66		
13 X=O; R=NHAc	172.23	160.42	134.48	116.18	77.81	40.97	48.75	13.69	170.67; 22.55	
19 X=NH; R=OH	172.03	158.82	134.45	112.87	53.98	62.97	48.99	13.98		
20 X=NAc; R=OAc	167.80	152.49	135.54	116.21	53.03	63.11	47.34	13.78	170.50; 24.70	169.35; 20.50

syntesized[9] **5**. After the successful synthesis of **5** from **1**, attention was focussed on the preparation of azido derivative **11** from suitably activated O^2,3'-anhydro substrate **7**. Compound **7** can be synthesized, in 57% yield, by intramolecular cyclisation of 1-(2-hydroxy-3-iodopropyl)thymine (**6**).[9] In an attempt to prevent the 2',3'-epoxydation, the 2'-OH group of **6** was acetylated, giving the 2'-*O*-acetyl derivative[12b] **8**. The reaction of the iodo-acetate **8** with DBU gave the 2'-*O*-acetyl O^2,3'-anhydro derivative **9**, which after deprotection gave almost quantitatively the requisite substrate **7**. However, activation of O^2,3'-anhydro compound **7** by mesylation failed to produce the expected mesyl intermediate in appreciable yield. As judged from analitical t.l.c. considerable decomposition occurred during the mesylation. An alternative for the preparation of azide **11** is the standard DBU cyclisation of 2'-azido-3'-mesylate **10** prepared in six steps from **1** by a sequence established for uracil derivatives.[10] The bicyclic azide **11** was obtained as a sole product. The formation of cyclic azido compounds **11** from acyclic azide **10** was evidenced by the characteristic UV absorption peak at 254 nm, indicating the quinone-like structure, and the absence of 3-NH and 3'-*O*-Ms signals in ^{1}H NMR spectrum. Moreover, in the ^{13}C NMR spectrum the signals for C-4 and C-2 of **11** appeared at lower field than the corresponding signals of aliphatic derivative **10** ($\Delta\delta$ 6 and 2 ppm, respectively), in accordance to the anhydro bond formation. In view of the facile conversion of O^2,2'-anhydro-5'-azido uridine **A** to imino compound **B** under catalytic hydrogenation of azido group[11] (Figure 1) it was of interest to explore the hydrogenation of azido-anhydro compounds **5** and **11**. Expecting a similar aryl-oxygen fission and rings interconversion under reductive conditions, MeOH solutions of **5** and **11**, respectively, were treated with H_2 over Pd-black (Scheme 2). No isomerization occurred and amino derivatives **12**[9] and **17**, respectively, were obtained in very good yield. These amino compounds were characterized as the 3'-*N*-acetyl[9] **13** and 2'-*N*-acetyl **18** derivative, respectively. Obviously, cyclic amines **14** and **19** cannot be formed from amino-anhydro derivatives **12** and **17**, respectively, under those reaction conditions. The ring-opening/ ring-closure rearrangement reactions of the amino-anhydro derivatives **12** and **17** were investigated under a range of conditions, and were found to be an acid-promoted reaction. The best reagent was found to be benzoic acid in DMF. Under optimal conditions at 100°C the recyclisations **12** → **14** and **17** → **19** were complete within 3 hours. It is reasonable to postulate that the reaction mechanism is closely



Reagents and conditions: i, H_2, Pd-black, MeOH; ii, BzOH, DMF, 100°C, 3h; iii, Ac_2O, Py, r.t., 16h, iv, Ac_2O, Py, r.t., 4h.

Scheme 2

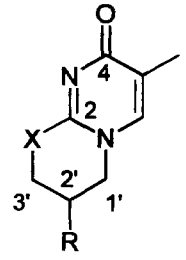
related to that of isomerization of 4-aminobenzofuranes to 4-hydroxyindoles.[13] The whole reaction sequence represents a special type of ring transformation (ring transformation by chain transfer) where a ring and a chain moiety in the starting materials are transformed to each other giving the products. The transformation of *O*-anhydrides **12** and **17** to *N*-anhydrides **14** and **19**, respectively, was evidenced by the appearance of the bathochromic shifts of the UV absorption peaks ($\Delta\lambda$ 9 and 21 nm, respectively), indicating that a modification of the nucleobase structure had occurred. The similarity of the UV spectra of *N*-bridged compounds **14** and **19** and 2,3'-imino-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine[14] suggests that all of them exist in *p*-

quinonoid form (2-amino-4-oxo). The ^1H and ^{13}C NMR data for the nitrogen-bridged compounds **14** and **19** are consistent with the structures assigned and can be compared with those of 6,6- and 5,6-membered fused ring oxygen isosteres. The ^1H NMR spectra of **14** and **19** showed the absence of signals in ≈ 3.5 ppm region, corresponding to protons of 3'- and 2'-amino groups of **12** and **17**, respectively. At 7.59 ppm for **14** and 7.72 ppm for **19** the characteristic peaks of amino groups are observed, each corresponding to one proton. Whereas the peaks of 3-NH protons in the 11 ppm region are not observed, it follows that in DMSO-d_6 heterocycles **14** and **19** have an amino structure. The signals appearing at 5.42 ppm as a broad singlet and at 5.09 ppm as a broad triplet for **14** and **19**, respectively, are attributed to the 2° and 1° OH groups. In the ^{13}C NMR spectra the chemical shifts of C-2 resonance for the *N*-bridged compounds **14** and **19** (152 and 158 ppm, respectively) are found at higher field than the C-2 chemical shifts for the corresponding *O*-anhydro compounds **7** and **3** (154 and 160 ppm, respectively), in accordance with the greater electronegativity of oxygen *vs.* nitrogen. As expected, the C-3' signal in **14** and C-2' in **19** are shifted considerably upfield ($\Delta\delta \approx$ 25 ppm) when compared with the corresponding signals of O^2,3'- and O^2,2'-anhydro compounds **7** and **3**, respectively, (Table 1 and 2).

In order to obtain further convincing evidence in support of the existence of the amino tautomeric forms of novel heterocyclic compounds **14** and **19**, we examined the acylation reactions. Treatment of **14** with excess acetic anhydride in pyridine at room temperature for 16 hours gave the diacetyl derivative **15**. The existence of two singlets at 1.98 and 2.44 ppm, in ^1H NMR spectrum of **15**, for the acetoxy and acetamido groups, respectively, confirms the amino structure of **14**. Although we have succeeded in isolation and characterization of diacetyl **15**, it was relatively unstable and hydrolysed slowly to the *O*-acetate **16.** The monoacetate **16** was prepared independetly by selective acetylation of cyclic aminoalcohol **14** for 4 hours. In similar manner, the five-membered cyclic amine **19** gave the stable diacetyl derivative **20.** As suggested by the ^1H NMR spectrum of diacetate **20**, structure **19** is also represented in amino tautomeric form.

In conclusion, this intramolecular process has shown its potential for construction of polycyclic systems from simple precursors. Further work involving a comparison of the imino-bridged bicyclic compounds **14** and **19** with oxygen isosteres **17** and **12**, as well as the investigations of the biological activity, are currently in progress.

Table 2. ^{13}C NMR chemical shifts (in ppm) of 2,3'-anhydro derivatives in DMSO-d_6



	C-4	C-2	C-6	C-5	C-3'	C-2'	C-1'	CH_3-5	NAc ($CO;CH_3$)	OAc ($CO;CH_3$)
7 X=O; R=OH	170.46	153.76	138.81	117.30	69.97	58.74	52.88	12.68		
9 X=O; R=OAc	170.03	153.86	139.06	118.04	67.34	62.50	50.19	13.09		170.84; 20.82
11 X=O; R=N_3	170.82	153.76	139.06	118.10	67.31	50.87	50.30	13.07		
17 X=O; R=NH_2	171.98	156.98	142.08	120.23	72.95	43.29	55.07	13.57		
18 X=O; R=NHAc	170.16	154.15	139.40	117.83	67.95	40.45	50.79	13.09	171.11; 22.49	
14 X=NH; R=OH	170.29	152.22	138.47	113.92	44.52	58.71	53.06	13.45		
15 X=NAc; R=OAc	169.70	150,17	139.86	118.27	45.21	65.42	51.46	13.34	171.42; 25.27	169.99; 20.73
16 X=NH; R=OAc	169.63	151.83	137.60	114.49	41.42	62.30	49.48	12.83		170.12; 20.44

EXPERIMENTAL

General. All the solvents were dried and redistilled shortly before use. Thin-layer chromatography (t.l.c.) was performed on silica gel *60 F_{254}* (Merck) plastic sheets in a CH_2Cl_2-MeOH 9:1 mixture unless otherwise stated; detection by UV light, I_2 vapors or by spraying with ninhydrine reagent. Preparative t.l.c. was performed on silica gel (type 60 F $_{254,}$ Merck) plates activated at 110°C for 1 h; developed in dichlormethane-methanol (9:1), recovery with acetone unless otherwise stated. Melting points, uncorrected, were taken with a Kofler hot-stage apparatus. IR spectra were recorded for KBr pellets on a Perkin-Elmer 297 spectrometer. UV spectra were taken for solutions in 96% EtOH on a Philips PUB700 UV/visible spectrophotometer. ^1H and ^{13}C NMR spectra (in DMSO-d_6, δ in ppm and *J* in Hz) were recorded on a Varian Gemini 300 (300/75 MHz) using standard Gemini software package. The spectra were referenced to residual DMSO-d_6 signal (2.51 (^1H) or 39.6 (^{13}C), respectively). The multiplicites of ^{13}C signals were determined by DEPT or APT experiments. Compounds **1**, **3**, **5**, **6**, **7**, **8**, **10**, **12** and **13** were prepared as described in the our previous papers.[9,10,12]

1-(2,3-Dibromopropyl)thymine (2). A solution of 1-allylthymine[12a] (**1**) (520 mg, 3.13 mmol) in CH_2Cl_2 (60 ml) was treated with bromine (0.2 ml) dissolved in CH_2Cl_2 (20 ml) for 1 h and then stirred at room temperature for additional 3 h until disapperance of starting material (t.l.c.). The solvent was removed under reduced pressure and residue was crystallized from methanol (670 mg). An additional quantity of the product (154 mg) was separated by preparative t.l.c. (ether, two developments) of the methanole filtrate. The overall yield was 824 mg (80.7%), R_F 0.92 or 0.31 (in ether), m.p. 150-151°C (from $CHCl_3$ / n-hexane); λ_{max} 267 nm (log ε 3.98); IR ν_{max} : 3410, 3160, 3015, 2736, 1820, 1708, 1480, 1426, 1366, 1259 cm^{-1}; ^1H NMR δ: 11.37 (1H, br s, D_2O exch., NH), 7.51 (1H, d, $J_{6,Me}$ 1.0, H-6); 4.77-4.69 (1H, m, H-2'), 4.23 (1H, dd, $J_{A,B}$ 14.3, $J_{A,2'}$ 4.7, H_A-1'), 4.04-3.93 (3H, m, H_B-1', H-3'), 1.77 (3H, d, $J_{Me,6}$ 1.0, CH_3-5); ^{13}C NMR δ: 164.50 (C-4), 151.21 (C-2), 141.77 (C-6), 108.71 (C-5). 52.35 (C-1'), 50.73 (C-2'), 39.88 (C-3'), 12.01 (CH_3-5). Anal. calc. for $C_8H_{10}N_2O_2Br_2$ (326.02): C 29.47, H 3.09, N 8.59, Br 49.03. Found: C 29.50, H 3.11, N 8.45, Br 49.08.

***O^2*,2'-Anhydro-1-(3-bromo-2-hydroxypropyl)thymine (4),{2-(bromomethyl)-6-methyl-2,3-dihydro-7*H*-pyrimido[2,1-b][1,3]oxazol-7-one}*.** DBU (0.2 ml, 1.3

* Sistematic name in { }

mmol) was added dropwise to a solution of the dibromide **2** (350 mg, 1.07 mmol) in CH_2Cl_2 (20 ml) and the mixture was stirred at room temperature for 3 h. The crystalline product was filtered off (200 mg) and additional quantity (15 mg) being obtained from the filtrate after it had been purified by preparative t.l.c.. The overall yield was 215 mg (83.6%), R_F 0.59, m.p. 186-188°C (from methanol / ether); λ_{max} 229.0 and 259.0 nm (log ε 3.78 and 3.84); IR ν_{max}: 3428, 3057, 3035, 1965, 1668, 1610, 1552, 1504, 1445, 1375, 1300, 1282, 1249, 1160, 1138, 1119, 982 cm^{-1}; ^1H NMR δ: 7.66 (1H, s,H-6), 5.30-5.23 (1H, m, H-2'), 4.38 (1H, dd, $J_{A,B}$ 10.0, $J_{A,2'}$ 9.7, H_A-1'), 3.97 (1H, dd, $J_{B,A}$ 9.7, $J_{B,2'}$ 5.6, H_B-1'), 3.95 (1H, dd, $J_{A,B}$ 11.52, $J_{A,2'}$ 4.4, H_A-3'), 3.89 (1H, dd, $J_{B,A}$ 11.5, $J_{B,2'}$ 4.7, H_B-3'), 1.79 (3H, s, CH_3-5). Anal. calc. for $C_8H_9N_2O_2Br$ (245.08): C 39.20, H 3.70 N 11.43, Br 32.61. Found : C 39.46, H 3.85, N 11.38, Br 32.43.

O^2,2'-Anhydro-1-(3-azido-2-hydroxypropyl)thymine[9] (5), {2-(azidomethyl)-6-methyl-2,3-dihydro-7*H*-pyrimido[2,1-b][1,3]oxazol-7-one}. A suspension of O^2,2'-anhydro bromide **4** (215 mg, 0.88 mmol) and sodium azide (114 mg, 1.76 mmol) in anhydrous DMF (10 ml) was heated at 90°C for 1 h. The precipitate was filtered off and the filtrate evaporated to dryness under reduced pressure. The residue was purified by preparative t.l.c. to give product (160 mg, 88%) identical (mixed m.p., IR and NMR spectra) with previously synthesized.[9]

O^2,3'-Anhydro-1-(2,3-dihydroxypropyl)thymine[9] (7), {3-hydroxy-7-methyl-3,4-dihydro-2*H*,8*H*-pyrimido[2,1-b][1,3]oxazin-8-one}. A solution of acetate **9** (115 mg, 0.52 mmol) in saturated methanolic ammonia (5 ml) was stirred at room temperature for 3 h . The solvent was removed under reduced pressure and crysttalline residue was triturated with acetone (2x5 ml) and diethyl ether (2x5 ml) to give *title compound* (83 mg, 88.9% 9) identical (mixed m.p., IR and NMR spectra) with previously synthesized.[9]

1-(2-Acetoxy-3-iodopropyl)thymine[12b] (8). A solution of 1-(2-hydroxy-3-iodo propyl) thymine[9] (**6**) (500 mg, 1.61 mmol) and freshly destilled acetic anhydride (1 ml) in anhydrous pyridine (20 ml) was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue separated by preparative t.l.c. giving the product (490 mg, 86.3%) identical (mixed m.p., IR and ^1H NMR spectra) with previously synthesized.[12b] ^{13}C NMR δ: 169.85 (CO of OAc). 164.53 (C-4), 151.26 (C-2), 141.72 (C-6), 108.80 (C-5), 70.42 (C-2'), 50.41 (C-1'), 20.59 (CH_3 of OAc), 11.84 (CH_3-5), 4.86 (C-3').

O^2,3'-Anhydro-1-(2-acetoxy-3-hydroxypropyl)thymine (9), {7-methyl-8-oxo-3,4-dihydro-2*H*,8*H*-pyrimido[2,1-b][1,3]oxazin-3-yl acetate}. To a solution of 3'-iodo acetate[12b] **8** (200 mg, 0.89 mmol) in CH_2Cl_2 (20 ml) DBU (0.17 ml, 1.1 mmol) was added dropwise and the mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the crystalline residue was triturated with methanol (3x 5 ml) to give *title compound* **9** (82 mg). An additional quantity (26 mg) being obtained from the combined mother liquors after it had been evaporated to dryness and purified by preparative t.l.c. (two developments). The overall yield was 108 mg (84.8%), R_F 0.36, m.p. 191-193°C (from methanol). λ_{max} 233.1 and 253.6 nm (log ε 3.99 and 3.93); IR ν_{max}: 3432, 1738, 1678, 1623, 1531, 1514, 1380, 1329, 1288, 1246, 1180, 1092, 1030 cm^{-1}; ^1H NMR δ: 7.41 (1H, d, $J_{6,Me}$ 1.3, H-6), 5.44-5.34 (1H, m, H-2'), 4.57 (1H, dd, $J_{A,B}$ 12.0, $J_{A,2'}$ 1.0, H_A-3'), 4.42 (1H, ddd, $J_{B,A}$ 12.0, $J_{B,2'}$ 2.7, $J_{B,B1'}$ 2.1, H_B-3'), 4.26 (1H, dd, $J_{A,B}$ 13.5, $J_{A,2'}$ 3.3, H_A-1'), 3.97 (1H, ddd, $J_{B,A}$ 13.5, $J_{B,2'}$ 2.2, $J_{B,B3'}$ 2.1, H_B-1'), 2.06 (3H, s, CH_3 of OAc). 1.78 (3H, d, $J_{Me,6}$ 1.3, CH_3-5). Anal. calc. for $C_{10}H_{12}N_2O_4$ (224.21): C 53.57, H 5.40, N 12.50. Found: C 53.32, H 5.61, N 12.20.

1-(2-Azido-3-methylsulphonyloxypropyl)thymine (10). To a solution of 1-(2-azido-3-hydroxypropyl)thymine[10] (200 mg, 0.88 mmol) in anhydrous and freshly distilled pyridine (5 ml) methanesulphonylchloride (0.1 ml, 1.4 mmol) was added and mixture was stirred at 3-5°C for 16 h. The solvent was azeotropically removed under reduced pressure in the presence of toluene. Preparative t.l.c. (two developments) afforded **10** (217 mg, 81.6%), R_F 0.65, m.p. 110-112°C (from methanol/ether). λ_{max} 266.5 nm (log ε 3.79); IR ν_{max}: 3450, 2125, 1680, 1470, 1354, 1243, 1178 cm^{-1}; ^1H NMR δ: 11.37 (1H, br s, D_2O exch., NH), 7.50 (1H, d, $J_{6,Me}$ 1.0, H-6); 4.43 (1H, dd, $J_{A,B}$ 13.8, $J_{A,2'}$ 6.3, H_A-3'), 4.29-4.22 (2H, m, H_B-3', H-2'), 3.89 (1H, dd, $J_{A,B}$ 14.1, $J_{A,2'}$ 4.2, H_A-1'), 3.74 (1H, dd, $J_{B,A}$ 14.1, $J_{B,2'}$ 7.5, H_B-1'), 3.25 (3H, s, CH_3 of OMs),1.76 (3H, d, $J_{Me,6}$ 1.0, CH_3-5); ^{13}C NMR δ: 164.61 (C-4), 151.43 (C-2), 141.75 (C-6), 109.14 (C-5). 69.43 (C-3'), 58.76 (C-2'), 47.54 (C-1'), 36.91 (CH_3 of OMs) 12.06 (CH_3-5). Anal. calc. for $C_9H_{13}N_5O_5S$ (303.30): C 35.64, H 4.32, N 23.09. Found: C 35.91, H 4.43, N 23.01.

O^2,3'-Anhydro-1-(2-azido-3-hydroxypropyl)thymine (11), {3-azido-7-methyl-3,4-dihydro-2*H*,8*H*-pyrimido[2,1-b][1,3]oxazin-8-one}. To a solution of 1-(2-azido-3-methyl sulphonyloxypropyl)thymine **10** (102 mg, 0.34 mmol) in CH_2Cl_2 (10 ml) DBU (0.08 ml, 0.5 mmol) was added dropwise and the mixture was stirred at room

temperature for 16 h. The solvent was removed under reduced pressure and the residue separated by preparative t.l.c. (two developments) giving 45 mg (64.7%) of the product **11**, R_F 0.19, m.p. 147-149°C (from methanol / ether); λ_{max} 231.2 and 254.1 nm (log ε 3.71 and 3.64); IR ν_{max}: 3450, 2112, 1666, 1530, 1500, 1446, 1377, 1310, 1276, 1260, 1170 cm^{-1}; ^1H NMR δ: 7.43 (1H, d, $J_{6,Me}$ 1.5, H-6), 4.67-4.62 (1H, m, H-2'), 4.55 (1H, dd, $J_{A,B}$ 11.7, $J_{A,2'}$ 2.7, H_A-3'), 4.45 (1H, ddd, $J_{B,A}$ 11.7, $J_{B,2'}$ 2.4, $J_{B,B1'}$ 2.4, H_B-3'), 4.22 (1H, dd, $J_{A,B}$ 13.5, $J_{A,2'}$ 3.6, H_A-1'), 3.94 (1H, ddd, $J_{B,A}$ 13.5, $J_{B,2'}$ 2.4, $J_{B,B3'}$ 2.4, H_B-1'), 1.78 (3H, d, $J_{Me,6}$ 1.5, CH_3-5). Anal. calc. for $C_8H_9N_5O_2$ (207.19): C 46.37, H 4.38, N 33.80. Found: C 46.19, H 4.62, N 33.67.

***N*²,3'-Anhydro-1-(2,3-dihydroxypropyl)-5-methylisocytosine (14), {7-hydroxy-3-methyl-6,7,8,9-tetrahydro-2*H*-pyrimido[1,2-a]pyrimidin-2-one}.** To a solution of 2-(aminomethyl)-6-methyl-2,3-dihydro-7*H*-pyrimido[2,1-b][1,3]oxazol-7-one[9] (**12**) (60 mg, 0.33 mmol) in DMF (4 ml) benzoic acid (40 mg, 0.33 mmol) was added and stirred at 100°C for 3 h. The solvent was removed under reduced pressure, the residue was triturated with acetone (2x5 ml) to give *title compound* (37 mg ,61.6%), R_F 0.04, m.p. 291-293°C (from methanol); λ_{infl} 268.5 nm (log ε 3.28); IR ν_{max}: 3270, 2908, 1677, 1622, 1571, 1510, 1415, 1321, 1206, 1170, 1105 cm^{-1}; ^1H NMR δ: 7.59 (1H, br s, D_2O exch., NH), 7.11 (1H, d, $J_{6,Me}$ 0.9, H-6); 5.42 (1H, br s, D_2O exch., OH); 4.41-4.08 (1H, m, H-2'); 3.85-3.80 (1H, m, H_A-1'); 3.61-3.56 (1H, m, H_B-1'); 3.30-3.26 (1H, m, H_A-3'); 3.13-3.09 (1H, m, H_B-3'); 1.70 (1H, d, $J_{Me,6}$ 0.9, CH_3-5). Anal. calc. for $C_8H_{11}N_3O_2$ (181.19): C 53.03, H 6.12, N 23.19. Found: C 53.28, H 6.30, N 22.91.

***N*²-Acetyl-*N*²,3'-anhydro-1-(2-acetoxy-3-hydroxypropyl)-5-methylisocytosine (15), {1-acetyl-7-methyl-8-oxo-1,3,4,8-tetrahydro-2*H*-pyrimido[1,2-a]pyrimidin-3-yl acetate}.** Compound **14** (80 mg, 0.44 mmol) in anhydrous pyridine (5 ml) was treated with acetic anhydride (0.47 ml, 5 mmol) at room temperature for 16 h. The mixture was evaporated to dryness under reduced pressure and traces of pyrimidine were removed by coevaporation with toluene (2x5 ml). The residual syrup was purified by preparative t.l.c. to give oily product (87 mg,74.5%), R_F 0.49, wich crystalized upon standing, m.p. 201-203°C; λ_{max} 229 nm (log ε 4.26), λ_{infl} 254.1 nm (logε 3.99); IR ν_{max}: 3420, 1730, 1692, 1661, 1634, 1535, 1489, 1468, 1442, 1405, 1377, 1334,1288, 1245 cm^{-1} ; ^1H NMR δ: 7.63 (1H, d, $J_{6,Me}$ 1.2, H-6); 5.45-5.41 (1H, m, H-2'); 4.15 (1H, dd, $J_{A,B}$ 13.8, $J_{A,2'}$ 3.0, H_A-1'); 4.01 (1H, dd, $J_{B,A}$13.8, $J_{B,2'}$ 2.7, H_B-1'); 3.93-3.81 (2H, m, H-

3'); 2.44 (3H, s , CH_3 of NAc), 1.98 (3H, s , CH_3 of OAc), 1.83 (3H, d, $J_{Me,6}$ 1.2, CH_3-5). Anal. calc. for $C_{12}H_{15}N_3O_4$ (265.26): C 54.33, H 5.70, N 15.84. Found: C 54.05, H 5.81, N 16.07.

***N*²,3'-Anhydro-1-(2-acetoxy-3-hydroxypropyl)-5-methylisocytosine (16), {7-methyl-8-oxo-1,3,4,8-tetrahydro-2*H*-pyrimido[1,2-a]pyrimidin-3-yl acetate}.** A solu tion of **14** (40 mg, 0.22 mmol) in anhydrous pyridine (3 ml) and acetic anhydride (0.025 ml, 0.26 mmol) was stirred at room temperature for 4 h. Evaporation of the mixture to dryness and coevaporation with toluene (2x5 ml) left a residue which on trituration with methanol (3x3 ml) afforded a crystalline product **16** (35 mg, 71.3%), R_F 0.19, m.p. > 300°C (from methanol). λ_{infl} 268.1 nm (log ε 3.59); IR ν_{max}: 3435, 2900, 1728, 1672, 1620, 1580, 1504, 1425, 1380, 1330, 1312, 1259, 1242 cm^{-1}; ^1H NMR δ: 7.82 (1H, br s, D_2O exch., NH), 7.16 (1H, d, $J_{6,Me}$ 1.2, H-6), 5.26-5.23 (1H, m, H-2'); 4.04 (1H, dd, $J_{A,B}$ 13.5, $J_{A,2'}$ 2.4, H_A-1'), 3.84 (1H, ddd, $J_{B,A}$13.5, $J_{B,2'}$ 2.7, $J_{B,3'B}$ 2.4, H_B-1'), 3.47 (1H, dd, $J_{A,B}$ 13.2, $J_{A,2'}$ 2.1, H_A-3'), 3.31 (1H, ddd, $J_{B,A}$13.2, $J_{B,2'}$ 2.4, $J_{B,1'B}$ 2.4, H_B-3'), 2.04 (3H, s , CH_3 of OAc), 1.71 (3H, d, $J_{Me,6}$ 1.2, CH_3-5). Anal. calc. for $C_{10}H_{13}N_3O_3$ (223.23): C 53.80, H 5.87, N 18.83. Found: C 53.93, H 5.92, N 18.74.

***O*²,3'-Anhydro-1-(2-amino-3-hydroxypropyl)thymine (17), {3-amino-7-methyl -3,4-dihydro-2*H*,8*H*-pyrimido[2,1-b][1,3]oxazin-8-one}.** Pd-black (30 mg) was added to a solution of azide **11** (50 mg, 0.24 mmol) in methanol (20 ml) and the mixture was stirred under H_2 (0.36 MPa) at room temperature for 3 h. The catalyst was filtered off on a short celite column and the filtrate evaporated to give a oily product (39 mg), showing very low chromatographic mobility. ^1H NMR δ: 7.36 (1H, s, H-6); 4.31 (1H, dd, $J_{A,B}$ 10.7, $J_{A,2'}$ 2.65, H_A-3'), 4.05 (1H, ddd, $J_{B,A}$10.7, $J_{B,2'}$ 5.6, $J_{B,1'B}$ 1.4, H_B-3'), 3.97 (1H, dd, $J_{A,B}$ 11.9, $J_{A,2'}$ 4.0, H_A-1'), 3.59 (1H, ddd, $J_{B,A}$11.9, $J_{B,2'}$ 3.6, $J_{B,3'B}$ 1.4, H_B-1'), 3.31 (2H, br s, D_2O exch., NH_2), 3.23-3.16 (1H, m, H-2'), 1.77 (3H, s, CH_3-5).

***O*²,3'-Anhydro-1-(2-acetamido-3-hydroxypropyl)thymine (18), {7-methyl-8-oxo-3,4-dihydro-2*H*,8*H*-pyrimido[2,1-b][1,3]oxazin-3-yl acetamid}.** A solution of amine **17** (39 mg, 0.21 mmol) in anhydrous pyridine (2 ml) and acetic anhydride (0.21 ml, 2.2 mmol) was stirred at room temperature for 16 h. The mixture was evaporated to dryness under reduced pressure and traces of pyrimidine were removed by coevaporation with toluene (2x5 ml). The residual syrup was purified by preparative t.l.c. (CH_2Cl_2:MeOH=8:2, two developments) to give product (33 mg, 68.8%), R_F 0.07,

m.p. 176-178°C (from methanol); λ_{max} 232.5 and 253.9 nm (log ε 3.68 and 3.63), IR ν_{max}: 3420, 1730, 1692, 1661, 1634, 1535, 1489, 1468, 1442, 1405, 1377, 1334,1288, 1245 cm^{-1}; ^1H NMR δ: 8.55 (1H, d, $J_{NH,2'}$ 6.23, D_2O exch.,NH), 7.39 (1H, s, H-6), 4.44 (1H, dd, $J_{A,B}$ 11.1, $J_{A,2'}$ 2.1, H_A-3'), 4.35-4.38 (1H, m, H-2'), 4.25 (1H, ddd, $J_{B,A}$11.1, $J_{B,2'}$ 1.8, $J_{B,1'B}$ 1.5, H_B-3'), 4.14 (1H, dd, $J_{A,B}$ 12.9, $J_{A,2'}$ 4.2, H_A-1'), 3.76 (1H, ddd, $J_{B,A}$12.9, $J_{B,2'}$ 2.2, $J_{B,1'B}$ 1.5, H_B-1'), 1.85 (3H, s, CH_3 of NHAc), 1.78 (3H, s, CH_3-5). Anal. calc. for $C_{10}H_{13}N_3O_3$ (223.23): C 53.80, H 5.87, N 18.83. Found: C 53.62, H 5.96, N 18.57.

N^2,2'-Anhydro-1-(2,3-dihydroxypropyl)-5-methylisocytosine (19), {2-(hydroxy methyl)-6-methyl-1,2,3,7-tetrahydroimidazo[1,2-a]pyrimidin-7-one}. To a soluti on of amine **17** (80 mg, 0.44 mmol) in DMF (5 ml) benzoic acid (53 mg, 0.44 mmol) was added and stirred at 100°C for 3 h. The solvent was removed under reduced pressure, the residue was triturated with acetone (2x5 ml) to give product **19** (59 mg ,73.8%), R_F 0.06, m.p. 286-288°C (from methanol). λ_{max} 221.1 and 274.4 nm (logε 3.88 and 3.47); IR ν_{max}: 3190, 2895, 1674, 1610, 1553, 1470, 1359, 1309, 1290, 1128 cm^{-1}; ^1H NMR δ: 7.73 (1H, br s, D_2O exch., NH), 7.36 (1H, s, H-6), 5.10 (1H, t, $J_{OH,3'}$ 4.2, D_2O exch., OH), 4.08 (1H, dd, $J_{A,B}$ 9.6, $J_{A,2'}$ 9.0, H_A-1'), 3.94-3.86 (1H, m, H-2'), 3.80 (1H, dd, $J_{B,A}$ 9.6, $J_{B,2'}$ 5.4, H_B-1'), 3.43-3.33 (2H, m, H-3') 1.70 (3H, s, CH_3-5). Anal. calc. for $C_8H_{11}N_3O_2$ (181.19): C 53.03, H 6.12, N 23.19. Found: C 53.13, H 6.27, N 22.91.

N^2-Acetyl-N^2,2'-anhydro-1-(3-acetoxy-2-hydroxypropyl)-5-methylisocytosine (20), {(1-acetyl-6-methyl-7-oxo-1,2,3,7-tetrahydroimidazo[1,2-a]pyrimidin-2-yl) methyl acetate}. To a solution of **19** (40 mg, 0.22 mmol) in anhydrous pyridine (3 ml) acetic anhydride (0.24 ml, 2.5 mmol) was added and stirred at room temperature for 16 h. Solvent was evaporated under reduced pressure and traces of pyridine were removed by coevaporation with toluene (2x5 ml). The resultant residue was separated by preparative t.l.c. giving the oily product **20** (48 mg, 82.2%), R_F 0.53, which crystalized upon standing, m.p. 140-142°C. λ_{max} 223.2 and 252.9 nm (log ε 4.44 and 4.09); IR ν_{max}: 3440, 2925, 1740, 1690, 1658, 1620, 1546, 1482, 1400, 1275, 1234, 1145, 1042 cm^{-1}; ^1H NMR δ: 7.68 (1H, s, H-6), 4.85-4.79 (1H, m, H-2'), 4.34 (1H, dd, $J_{A,B}$ 11.7, $J_{A,2'}$ 4.2, H_A-1'), 4.19 (1H, dd, $J_{B,A}$ 11.7, $J_{B,2'}$ 3.3, H_B-1'), 4.18 (1H, dd, $J_{A,B}$ 10.8, $J_{A,2'}$ 9.6, H_A-3'), 3.93 (1H, dd, $J_{B,A}$ 10.8, $J_{B,2'}$ 3.0, H_B3'), 2.52 (3H, s, CH_3 of NAc, obscured by those of DMSO), 1.92 (3H, s, CH_3 of OAc) 1.81 (3H, s , CH_3-5); ^1H NMR (CD_3OD) δ: 7.74

(1H, dd , $J_{6,Me}$ 1.1, H-6), 4.99 (1H, m, H-2', obscured by methanolic OH), 4.62 (1H, dd, $J_{A,B}$ 12.0, $J_{A,2'}$ 4.1, H_A-1'), 4.37 (1H, dd, $J_{A,B}$ 11.1, $J_{A,2'}$ 9.6, H_A-3'), 4.29 (1H, dd, $J_{B,A}$ 12.0, $J_{B,2'}$ 2.7, H_B-1'), 4.17 (1H, dd, $J_{B,A}$ 11.1, $J_{B,2'}$ 3.0, H_B3'), 2.73 (3H, s, CH_3 of NAc), 2.06 (3H, dd , $J_{Me,6}$ 1.1, CH_3-5), 2.03 (3H, s, CH_3 of OAc). Anal. calc. for $C_{12}H_{15}N_3O_4$ (265.26): C 54.33, H 5.70, N 15.84. Found: C 54.41, H 5.72, N 15.69.

Acknowledgement: This work was supported by the Ministry of Science and Technology, Republic of Croatia, project no. 009807.

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Received 12/8/99
Accepted 7/17/00