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Alkylation of thymine with 1,2-dibromoethane

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Abstract—Alkylation of thymine with 1,2-dibromoethane depends strongly on the reaction conditions. Various alkyl derivatives may be produced, including *N*-1- or *N*-3-monosubstituted alkylthymines and products of their cyclisation, as well higher molecular weight products resulting from intermolecular substitution of *N*-1- and *N*-3-mono- and *N*-1,*N*-3-dialkylthymines. We have identified two cyclic products **5** and **6** and the dialkylated derivative **7**, for which detailed structural analyses have been performed.

1. Introduction

There are numerous reports in the chemical literature concerning the synthesis of *N*-1-(2-aminoethyl)thymine (**1**).[1] Direct aminoethylation of thymine with aziridine, performed in aqueous solution provides **1**, although the predominant product of this reaction is *N*-1,*N*-3-di(2-aminoethyl)thymine accompanied by minute amounts of *N*-3-(2-aminoethyl)thymine (**2**). Isolation of pure **1**, **2** or the product of bis-alkylation from this reaction mixture is a tedious process, since *N*-aminoalkylation competes with polymerisation of aziridine.[1] An alternative approach to **1** involves reaction of thymine with 1,2-dibromoethane providing *N*-1- and *N*-3-(2-bromoethyl)thymines (**3** and **4**) with subsequent substitution of the terminal bromine with azide ion followed by reduction to the desired **1** or **2**. According to a recently published procedure, compound **3** was obtained in 44% yield by the reaction of 2,4-(bis-trimethylsilyloxy)-5-methylpyrimidine with 1,2-dibromoethane as the solvent at 100°C.[2] Interestingly, in another report, the reaction of thymine with 1,2-dibromoethane was described as an efficient route to **3** (yield 65%). This reaction was performed in DMF solution at ambient temperature, using 4 molar equivalents of 1,2-dibromoethane, in the presence of K_2CO_3.[3] Comparison of the physical properties of compounds **3** presented in both reports revealed essential differences in melting points, solubilities and spectral characteristics. Due to our interest in finding an effective synthesis of **1** and **2** we reinvestigated both the above procedures. The results of our findings are presented below.

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2. Results

Reaction of 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine with 1,2-dibromoethane as solvent, in the presence of sodium iodide at 100°C for 24 h, provided a mixture of DMSO soluble compounds, which were crystallised from ethanol. Low solubility in organic solvents and difficulties in chromatographic separation of this crystalline material prompted us to investigate the chemical composition of the products by means of mass spectrometry and ^{1}H NMR (DMSO-*d6*). Fig. 1 represents a mass spectrum of this mixture recorded under conditions of chemical ionisation (positive mode) and reveals a low content of the desired **3** (*m/z* 233) and the presence of polycondensation products. Such conclusions are supported by the ^{1}H NMR spectrum, which contains at least six resonances, of nearly equal intensity, characteristic for thymine 6-H protons. Formation of polycondensation products, namely *N*-1,*N*-1′-(alkanediyl)-bis-thymines, by treatment of thymine with $Br(CH_2)_nBr$ (n=3–10) in the presence of *t*-BuOK in DMF, has been described by Itahara.[4] However, with 1,2-dibromoethane, the reaction gave a cyclic derivative **5** (Fig. 2). Indeed, in the above-mentioned mass spectrum (Fig. 1), in addition to the high molecular mass peaks, we observed a low-intensity peak of *m/z* 153, which corresponds to molecular ion of compound **5**. Since the mixture of products obtained in this reaction of 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine with 1,2-dibromoethane was not of any synthetic value, the structures of the individual components of the mixture were not investigated in detail.

To avoid formation of intermolecular alkylation products we used less drastic conditions for the alkylation of thymine using 1,2-dibromoethane (4 equiv.) as reagent in DMF as solvent.[3] The reaction was carried out in the presence of

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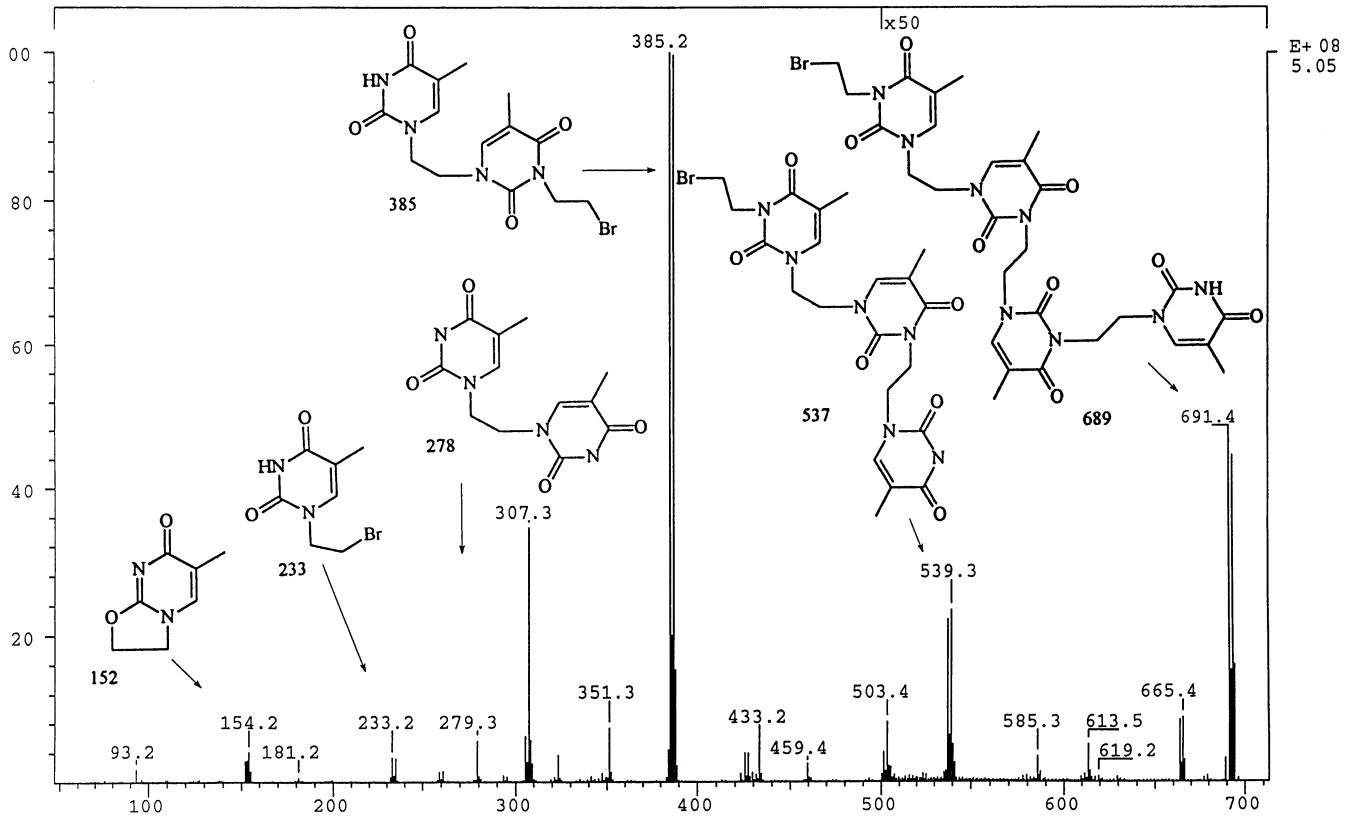


Figure 1. Mass spectrum of products obtained by reaction of 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine with 1,2-dibromoethane in the presence of sodium iodide at 100°C for 24 h.

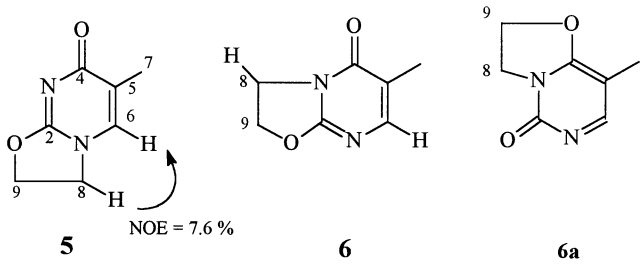
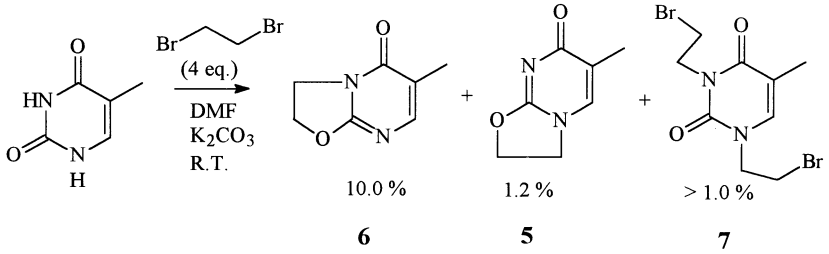


Figure 2. Possible cyclic structures of thymidine derivatives obtained by alkylation of thymine with 1,2-dibromoethane.

K_2CO_3 at room temperature. After 48 h more than 60% of thymine was still present in the reaction mixture. Prolongation of the reaction time did not improve the product/substrate ratio. Three products were isolated by silica gel column chromatography (Scheme 1), in addition to a small amount (less than 1%) of high molecular weight material resulting from intermolecular substitution. The predominant product was isolated in ca. 10% yield and the two minor products with yields of 1.2% and less than 1%. Only the most hydrophobic compound, the lowest yielding product, contained bromine. Spectroscopic analysis revealed that this compound was the *N*-1,*N*-3-bis-alkyl-derivative **7**. The two remaining products did not contain bromine. The lack of imino protons in the ^{1}H NMR spectrum, and of bromine isotope peaks in the MS (*m/z* 153), indicated their cyclic structure. It was important to distinguish between the *N*-1 and *N*-3 substituted isomers. By analysis of the ^{1}H and ^{13}C NMR data we identified the lower yield product as the *N*-1/*O*-2 cyclic derivative **5**, already described in the literature.[4] NOE correlations between H-8 and H-6 of compound **5** confirmed the *N*-1 substitution (Fig. 2). X-ray analysis (details included in Experimental) of compound **5** confirmed unequivocally its *N*-1/*O*-2 cyclic structure (Fig. 3a,b, Tables 1–3).



Scheme 1.

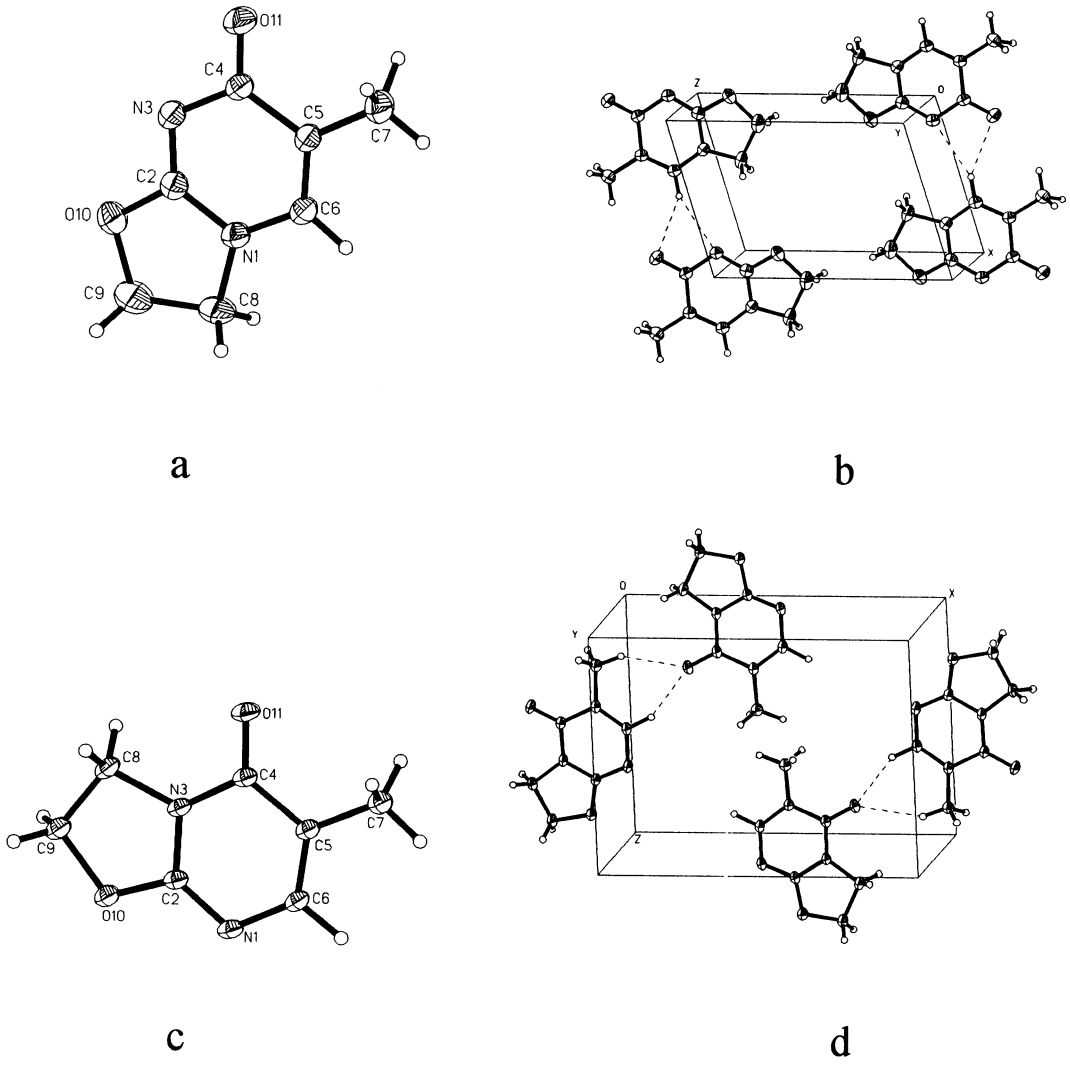


Figure 3. (a) Thermal ellipsoidal view with the atom numbering scheme and (b) crystal packing diagram for compound **5**. Ellipsoids are shown with 50% probability, (c) thermal ellipsoidal view with the atom numbering scheme and (d) crystal packing diagram for compound **6**. Ellipsoids are shown with 50% probability.

The main product (10% yield) could be either *N*-3/*O*-2 (**6**) or *N*-3/*O*-4 (**6a**) cyclic derivative (Fig. 2). Simple spectral analysis by means of the ^{1}H and ^{13}C NMR data did not give us any clear answer and no appropriate NOEs were observed. The chemical shift of *C*-6 (δ 151.0 ppm) was considerably deshielded relative to the corresponding carbon of the heterocyclic ring of compound **5** (δ 134 ppm) indicating a change in the nature of the conjugated system. The structure of the main reaction product was determined by X-ray analysis (Fig. 3c,d, Tables 1–3). It occurred that the investigated compound is the *N*-3/*O*-2 cyclic derivative **6**.

To test usefulness of a GIAO (B3PW91/6-311G**) method[5] for molecular modelling of the three possible cyclic ethylenethymine structures, *N*-1/*O*-2 (**5**), *N*-3/*O*-2 (**6**) and *N*-3/*O*-4 (**6a**) (Fig. 2) we performed calculations using shielding parameters of ^{13}C NMR spectroscopy. All calculations were run on a Silicon Graphics Challenge computer by means of standard methods and functions routinely implemented in the Gaussian package.[5] Optimisation geometry was done on the level of HF/6-31G*. Table 4 contains the experimentally determined ^{13}C chemical shifts of both isolated cyclic compounds and the calculated shielding parameters σ_{iso} of the three possible cyclic structures **5**, **6** and **6a**. The ***a*** data correspond to the lower yield product **5** and the ***b*** data to the higher yield product **6**. Correlation of experimental chemical shifts with calculated shielding parameters gave six possible solutions (supplementary data). Comparison of the correlation coefficients R^2 for every possible combination (Table 5) remains in agreement with X-ray results.

The calculation method GIAO also allowed the determination of the theoretical dipole moment for all of the structures under investigation. Compound **5** has a much higher theoretical dipole moment (μ=8.73 D) than compound **6** (μ=2.63 D). These data explain the much higher polarity of compound **5** relative to compound **6**, which results in their very different mobility on silica gel thin layer chromatography. R_f values of 0.14 and 0.53 were observed for compound **5** and **6**, respectively on TLC in methanol/chloroform 9/1, v/v.

Table 1. Crystal data and experimental details of X-ray analysis of **5** and **6**

	Compound **5**	Compound **6**
Molecular formula	$C_7H_8N_2O_2$	$C_7H_8N_2O_2$
Formula weight	152.15	152.15
Crystallographic system	monoclinic	Orthorhombic
Space group	$P2_1/m$	Pnma
a (Å)	6.0657(7)	11.6628(11)
b (Å)	6.5481(9)	6.5670(7)
c (Å)	8.8844(12)	8.7710(8)
α (°)	90.00	90.00
β (°)	106.424(11)	90.00
γ (°)	90.00	90.00
V (Å^3)	338.48(8)	671.77(11)
Z	2	4
D_c (g/cm^3)	1.493	1.504
μ [cm^{-1}]	1.12	1.13
Crystal dimensions (mm)	0.25×0.35×0.40	0.30×0.30×0.70
Maximum 2θ (°)	60.14	61.86
Radiation, λ (Å)	MoKα, 0.71073	MoKα, 0.71073
Scan mode	ω	ω
hkl ranges:		
h=	−6 8	−15 15
k=	−8 8	−8 8
l=	−12 11	−10 11
No. of reflections: unique	939	966
with $I>0\sigma(I)$	939	966
obs. with $I>2\sigma(I)$	789	904
No. of parameters refined	86	86
Largest diff. Peak (eÅ^{-3})	0.346	0.315
Largest diff. Hole (eÅ^{-3})	−0.238	−0.267
shift/esd max	0.000	0.000
R_{obs}	0.0420	0.0411
wR_{obs}	0.1188	0.1091
S_{obs}	1.113	1.117
R_{int}	0.0168	0.0372

Table 2. Bond lengths (Å) for non-hydrogen atoms

		Compound **5**	Compound **6**
N1	C2	1.352(2)	1.296(2)
N1	C6	1.371(2)	1.390(2)
Nx[a]	C8	1.455(2)	1.461(2)
C2	N3	1.295(2)	1.359(2)
C2	O10	1.337(2)	1.338(2)
N3	C4	1.390(2)	1.393(2)
C4	O11	1.242(2)	1.230(2)
C4	C5	1.459(2)	1.450(2)
C5	C6	1.350(2)	1.363(2)
C5	C7	1.495(2)	1.496(2)
C8	C9	1.502(3)	1.527(2)
C9	O10	1.454(2)	1.467(2)

[a] Nx=N1 for Compound **5**, Nx=N3 for compound **6**

Table 3. Bond angles (°) for non-hydrogen atoms

			Compound **5**	Compound **6**
C2	N1	C6	118.72(12)	113.39(11)
C2	Nx[a]	C8	111.73(14)	111.91(12)
C6	Nx[a]	C8	129.55(13)	125.63(10)
Ny[b]	C2	O10	121.95(13)	122.31(12)
N1	C2	N3	126.73(14)	126.20(13)
O10	C2	Nx[a]	111.32(13)	111.49(11)
C2	N3	C4	116.83(12)	122.46(10)
O11	C4	N3	119.22(13)	120.00(11)
O11	C4	C5	121.63(14)	126.52(13)
N3	C4	C5	119.14(12)	113.48(11)
C6	C5	C4	118.94(14)	118.51(13)
C6	C5	C7	122.94(13)	124.03(12)
C4	C5	C7	118.12(13)	117.46(12)
C5	C6	N1	119.64(13)	125.95(12)
Nx[a]	C8	C9	101.44(13)	101.39(10)
O10	C9	C8	107.16(13)	106.36(11)
C2	O10	C9	108.35(13)	108.85(10)

[a] Nx=N1 for Compound **5**, Nx=N3 for compound **6**
[b] Ny=N3 for Compound **5**, Ny=N1 for compound **6**

Table 4. Experimental ^{13}C chemical shift parameters of cyclic products ***a*** and ***b*** and theoretical shielding parameters calculated for a three possible cyclic structures

Carbon number	δ [ppm]		σ_{iso} [ppm]		
	a	***b***	*N*-1/*O*-2	*N*-3/*O*-2	*N*-3/*O*-4
2	160.6	158.0	28.9	29.8	36.7
4	171.7	161.5	22.4	28.8	25.4
5	115.7	116.9	61.4	66.9	97.1
6	134.4	151.0	58.1	34.3	19.1
7	13.6	12.4	170.6	173.0	176.5
8	46.2	42.4	140.1	144.6	142.5
9	66.6	66.1	123.6	122.8	120.4

Table 5. Correlation coefficients R^2 calculated for both isolated cyclic products and their possible cyclic structures (*N*-1/*O*-2, *N*-3/*O*-2 and *N*-3/*O*-4)

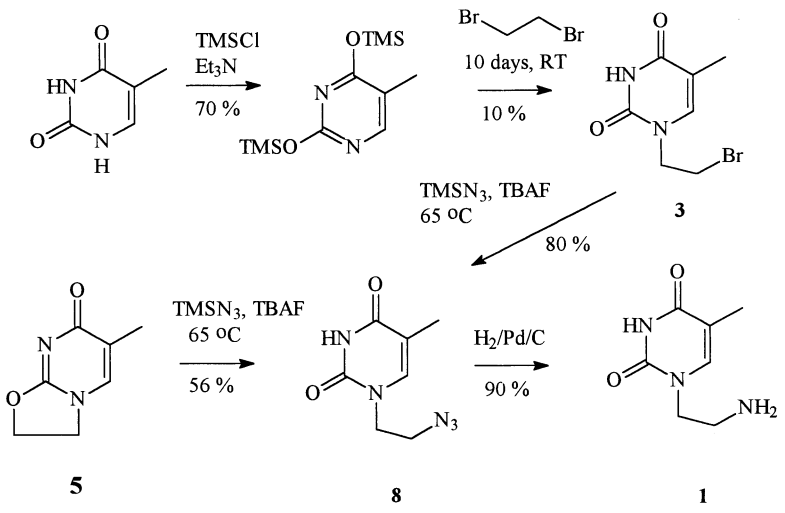
Compound	Possible cyclic structure		
	N-1/*O*-2	*N*-3/*O*-2	*N*-3/*O*-4
a	**0.9918**	0.9740	0.9155
b	0.9733	**0.9986**	0.9552

The desired *N*-1-(2-bromoethyl)thymine **3** was finally obtained by alkylation of 2,4-bis-(trimethylsilyloxy)-5-methylpyrimidine with 1,2-dibromoethane under mild conditions (ambient temperature, 10 days).[6] The yield of the reaction was very modest (10%) and much unreacted substrate remained. However we did not observe formation of the *N*-3-alkylation product **4** or any other cyclic or higher substituted products. The spectral data of compound **3** were identical to those described earlier in the literature.[2,4]

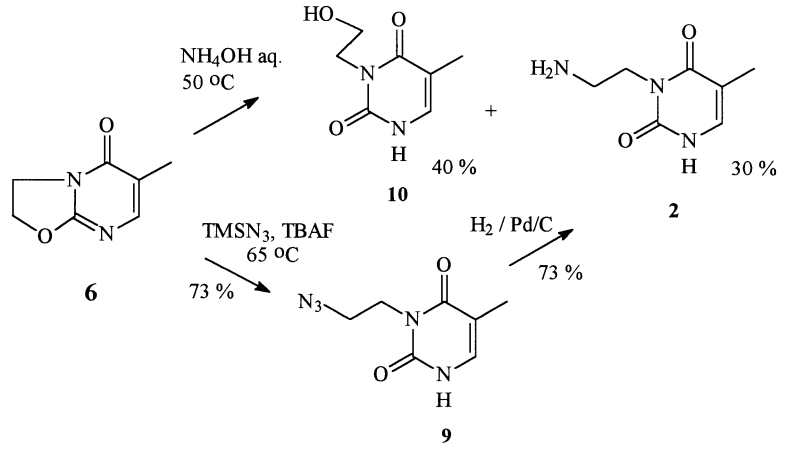
Reaction of compound **3** or the cyclic oxazolopyrimidine **5** with trimethylsilylazide in the presence of fluoride ions[7] gave a good yield (70–85%) of azide **8**. Catalytic reduction of compound **8** resulted in the formation of the desired *N*-1-(2-aminoethyl)thymine **1** (Scheme 2). An analogous transformation of the cyclic derivative **6** gave the *N*-3-(2-aminoethyl)thymine **2** (Scheme 3). On the other hand, heating compound **6** with aqueous ammonium hydroxide gave predominantly *N*-3-(2-hydroxyethyl)thymine **10** (40%) in addition to the amine **2**, obtained in 30% yield. This *N*-3-hydroxyethyl-derivative **10** was not identified in a direct hydroxyalkylation of thymine, performed with an equimolar amount of ethylene carbonate in the presence of a catalytic amount of sodium hydroxide.[8] *N*-1-(2-Hydroxyethyl)-thymine (70%) and a small amount of the *N*-1,*N*-3-bis-alkylated derivative were the only identified products.

3. Discussion

In general, *N*-alkylation of pyrimidine bases gives predominantly *N*-1-monosubstituted and *N*-1,*N*-3-bis-substituted



Scheme 2.



Scheme 3.

derivatives rather than *N*-3 or acid-labile *O*-alkyl derivatives.[9] The regioselectivity of this reaction is determined by the acidity of the two ionisable protons of the heterocyclic ring. The acidity of the *N*-1 proton is much higher (p*K*a=9.43 for uracil, and 9.86 for thymine) than that of the *N*-3 proton (p*K*a>13 for uracil,[10] 13.96 for thymine[11]). Despite the large difference in the p*K*a values of the protons it is not possible to obtain the *N*-1 product selectively, since *N*-1 substitution of the pyrimidine ring generates a significant increase in the acidity of the *N*-3 proton (p*K*a=9.71 for an *N*-1 substituted uracil[12,13]). The ratio of *N*-1-mono- to *N*-1,*N*-3-bis-substituted products depends on the reaction conditions, mostly on the molar ratio of the heterocyclic base and the alkylating agent.[9,14] When dibromoalkanes [$Br(CH_2)_nBr$ (n=3–10)] were used as alkylating agents, formation of polycondensation products namely *N*-1,*N*-1′-(alkanediyl)bis-thymines was observed.[4] However, alkylation of thymine with 1,2-dibromoethane in the presence of *t*-BuOK resulted in the formation of the cyclic derivative **5**.[4] We isolated such a *N*-1/*O*-2 cyclic derivative **5** as a minor reaction product only when 1,2-dibromoethane was used in four-fold excess over thymine, and the reaction was carried out in the presence of potassium carbonate. In such conditions, however, the main reaction product was *N*-3/*O*-2 cyclic derivative **6**. Formation of such *N*-3/*O*-2 cyclic derivatives most probably occurs via an alkylation of *N*-3 nitrogen atom with 1,2-dibromoethane followed by subsequent nucleophilic substitution of the second bromine by the oxygen atom at position 2 of the heterocyclic ring. Such nucleophilic substitution by the oxygen *O*-2 is rather surprising, since it is well known that the oxygen atom *O*-4 of the nucleobase ring is more electronegative than oxygen *O*-2[15] and thus one would expect formation of an *N*-3/*O*-4 cyclic derivative **6a** rather than an *N*-3/*O*-2 isomer **6**. In none of the performed reactions we were able to isolate *N*-3-(2-bromoethyl)thymine **4**, the product of selective substitution at *N*-3 position and the precursor of cyclic derivative **6**. Alkylation at ambient temperature without catalyst resulted in monoalkylation of thymine at position *N*-1 (product **3**), although the yield of this reaction was rather low. A small amount of polycondensation product was present in all the reactions, while a considerable amount of substrate was always left. When the alkylation reaction was performed under drastic conditions (100°C, without solvent) we observed, as expected, the formation of polyalkylated products rather than monosubstituted thymines.

4. Conclusions

In summary, the outcome of the alkylation of thymine with 1,2-dibromoethane depends strongly on the reaction conditions. Various alkyl derivatives may be produced, including *N*-1- or *N*-3-monosubstituted alkylthymines and products of their cyclisation, as well higher molecular weight products resulting from intermolecular substitution of *N*-1- and *N*-3-mono- and *N*-1,*N*-3-dialkylthymines. We have identified two cyclic products **5** and **6** and the dialkylated derivative **7**, for which detailed structural analyses have been performed.

5. Experimental

5.1. Alkylation of thymine

Procedure A: 1,2-Dibromoethane (35.52 g, 189 mmol) was added to a suspension of thymine (6 g, 47.6 mmol) and anhydrous potassium carbonate (16.32 g, 124 mmol) in anhydrous DMF (100 mL). The mixture was kept at room temperature for 48 h, then the solid was filtered off and the solvent was evaporated under reduced pressure. The reaction products were separated by flash column chromatography on silica gel 60G in gradient of methanol in chloroform.

Compound **5** (2,3-dihydro-6-methyl-7H-oxazolo[3,2-a]-pyrimidin-7-one) (0.09 g, 1.2%): R_f=0.14 ($CHCl_3$/MeOH, 9/1), mp 285–289°C,[4] ^{1}H NMR (200 MHz, DMSO-*d6*, ppm): 7.63 (q, *J*=1.2 Hz, 1H, H-6), 4.64 (t, *J*=8.45 Hz, 2H, CH_2O), 4.18 (t, *J*=8.45 Hz, 2H, CH_2N), 1.77 (d, *J*=1.2 Hz, 3H, CH_3), FAB MS 153 $[M+1]^+$, IR (KBr, cm^{-1}): 3049, 2922, 1667, 1611, 1550, 1504, 1377, 880.

Compound **6** (2,3-dihydro-6-methyl-5H-oxazolo[2,3-a]-pyrimidin-5-one) (0.70 g, 10.0%): R_f=0.53 ($CHCl_3$/MeOH, 9/1), R_f=0.15 (ethyl acetate), mp>390°C, ^{1}H NMR (200 MHz, DMSO-*d6*, ppm): 7.57 (q, *J*=1.1 Hz, 1H, H-6), 4.67 (t, *J*=8.45 Hz, 2H, CH_2O), 4.29 (t, *J*=8.45 Hz, 2H, CH_2N), 1.86 (d, *J*=1.1 Hz, 3H, CH_3); HR MS for $C_7H_8O_2N_2$: $[M]^+$ 152.05858 (calc.), 152.05731 (exp.); IR (KBr, cm^{-1}): 2922, 1663, 1611, 1561, 1437, 1358, 1256, 1000, 766.

Compound **7** (0.118 g, 0.9%): R_f=0.53 ($CHCl_3$/MeOH, 9/1), R_f=0.52 (ethyl acetate), ^{1}H NMR (200 MHz, $CDCl_3$, ppm): 7.05 (q, *J*=1.2 Hz, 1H, H-6), 4.03 (t, *J*=6.0 Hz, 2H, CH_2), 3.58 (t, *J*=6.0 Hz, 2H, CH_2), 1.84 (d, *J*=1.2 Hz, 3H, CH_3); HR MS for $C_9H_{13}O_2N_2Br_2$(79): 338.93437 (calc.) 338.93372 (exp.), for $C_9H_{13}O_2N_2Br$(79)Br(81): 340.93233 (calc.), 340.93126 (exp.).

Procedure B: A solution of 2,4-bis(trimethylsilyloxyl)-5-methylpyrimidine[16] (9.0 g, 33.3 mmol) in 1,2-dibromoethane (115 mL) was stirred for 10 days at room temperature. Then water (300 mL) was added to the reaction mixture and the products were extracted with chloroform (3×300 mL). After removal of solvents, the residue was poured onto the silica gel column. The product was eluted with gradient of methanol in chloroform. Bromide **3** (0.78 g, 10%) was obtained as a white solid. R_f=0.59 ($CHCl_3$/MeOH, 9/1), mp 197–200°C, (199–200°C,[2] 200–202°C,[4] 164–165°C[3]), ^{1}H NMR (200 MHz, DMSO-*d6*, ppm): 11.33 (br s, 1H, NH), 7.55 (q, *J*=1.1 Hz, 1H, H-6), 4.02 (t, *J*=12.6 Hz, 2H, CH_2N, 3.69 (t, *J*=12.6 Hz, 2H, CH_2Br), 1.75 (d, *J*=1.1 Hz, 3H, CH_3), FAB MS 233 $[M+1]^+$, 235 $[M+3]^+$.

5.1.1. *N*-1-(2-azidoethyl)thymine 8. To a solution of bromide **3** (520 mg, 2.24 mmol) in anhydrous THF (20 mL), azidotrimethylsilane (0.6 mL) and tetrabutylammonium fluoride (4.5 mL) were added. The reaction mixture was stirred at 65°C for 3 h. After removal of the solvent, the residue was crystallised from ethanol. The product **8** was obtained as a white solid (320 mg, 80%). Mp 152–155°C, R_f=0.61 (ethyl acetate), ^{1}H NMR (200 MHz, $CDCl_3$, ppm): 7.02 (s, 1H, H-6), 3.82 (br q, 2H, CH_2), 3.67 (br q, 2H, CH_2), 1.94 (s, 3H, CH_3), IR (KBr, cm^{-1}): 2122; HR MS for $C_7H_9N_5O_2$: $[M+H]^+$ 196.08345 (calc.), 196.08407 (exp.). Synthesis of azide **8** was performed analogously as described above starting from cyclic compound **5** (76 mg, 0.5 mmol). The product was obtained as a white solid (55 mg, 56%).

5.1.2. *N*-3-(2-azidoethyl)thymine 9. Synthesis of azide **9** was performed analogously as described above starting from cyclic compound **6** (340 mg, 2.23 mmol). The product was obtained as a white solid (320 mg, 73%). Mp 119–120°C, R_f=0.75 (ethyl acetate), ^{1}H NMR (200 MHz, CD_3OD, ppm): 7.24 (q, *J*=1.1 Hz, 1H, H-6), 4.15 (t, *J*=6.2 Hz, 2H, CH_2), 3.50 (t, *J*=6.2 Hz, 2H, CH_2), 1.88 (d, *J*=1.1 Hz, 3H, CH_3); IR (KBr, cm^{-1}): 2110, 2088; HR MS for $C_7H_9N_5O_2$: $[M+H]^+$ 196.08345 (calc.), 196.08269 (exp.).

5.1.3. *N*-1-(2-aminoethyl)thymine 1. 10% Pd/C (20 mg) was added to the solution of azide **8** (300 mg, 1.54 mmol) in methanol (10 mL) and hydrogen was bubbled through the reaction mixture for 2.5 h (TLC control). The reaction mixture was filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography in gradient of methanol in chloroform. Amine **1** was obtained as a white solid (230 mg, 90%). Mp 180–185°C; R_f=0.08 (2×$CHCl_3$/MeOH, 8/2); ^{1}H NMR (200 MHz, CD_3OD): 7.40 (q, *J*=1.2 Hz, 1H, H-6), 3.76 (t, *J*=6.28 Hz, 2H, CH_2), 2.89 (t, *J*=6.28 Hz, 2H, CH_2), 1.87 (d, *J*=1.2 Hz, 3H, CH_3); FAB MS 170 $[M+1]^+$, 168 $[M-1]^-$; IR (KBr, cm^{-1}): 3342, 3289, 3054, 2960, 1705, 1660, 1481, 1358, 1046, 760.

5.1.4. *N*-3-(2-aminoethyl)thymine 2. Synthesis of amine **2** was performed analogously as described above starting from azide **9** (340 mg, 2.23 mmol). The product was obtained as a white foam (320 mg, 73%). R_f=0.16 (2×$CHCl_3$/MeOH, 8/2), ^{1}H NMR (200 MHz, CD_3OD, ppm): 7.23 (q, *J*=1.2 Hz, 1H, H-6), 4.05 (t, *J*=6.4 Hz, 2H, CH_2), 2.93 (t, *J*=6.4 Hz, 2H, CH_2), 1.88 (d, *J*=1.2 Hz, 3H, CH_3); HR MS for $C_7H_{11}N_3O_2$: $[M+H]^+$ 170.09295 (calc.), 170.09392 (exp.); IR (KBr, cm^{-1}): 3343, 3281, 3058, 2895, 1703, 1637, 1343, 1000, 770.

5.1.5. *N*-3-(2-hydroxyethyl)thymine 10 and *N*-3-(2-aminoethyl)thymine 2. Cyclic derivative **6** (390 mg, 2.56 mmol) was treated with aqueous ammonium hydroxide

(20 mL) at 50°C for 16 h (TLC). After removal of solvent the mixture was separated by flash column chromatography on silica gel with a gradient of methanol in chloroform. Hydroxy-derivative **10** (R_f=0.36 in $CHCl_3$/MeOH, 9/1) was isolated as a fast eluting product (170 mg, 40%) and amine **2** as a slow eluting product (120 mg, 30%). **10**: Mp 170–175°C, ^{1}H NMR (200 MHz, DMSO-*d6*, ppm): 10.83 (d, *J*=5.5 Hz, 1H, NH), 7.28 (dq, *J*=1.2 Hz, *J*=5.5, 1H, H-6), 4.72 (t, *J*=5.8 Hz, 1H, OH), 3.85 (t, *J*=6.7 Hz, 2H, CH_2), 3.46 (dt, *J*=6.7 Hz, *J*=5.8 Hz, 2H, CH_2), 1.76 (d, *J*=1.2 Hz, 3H, CH_3); HR MS for $C_7H_{10}N_2O_3$: $[M+H]^+$ 171.07697 (calc.), 171.07693 (exp.); IR (KBr, cm^{-1}): 3423, 3221, 3075, 1712, 1637, 1449, 1216, 1084, 767.

5.2. X-Ray analysis

Crystal and molecular structures of **5** and **6** were determined using data collected at low temperature on a KM4 diffractometer (KUMA Diffraction Instruments GmbH) with graphite monochromatized MoKα radiation. Compound **5** crystallises from ethanol in monoclinic system, in space group $P2_1/m$ with the unit cell consisting of 2 molecules. Compound **6** crystallises from chloroform in orthorhombic system, in space group Pnma with the unit cell consisting of 4 molecules. Crystal data and experimental details are shown in Table 1. The lattice constants were refined by least-squares fit of 2138 reflections in the θ range 3.64°–30.07° for **5** and 3731 reflections in the θ range 3.88°–30.93° for **6**. For **5** and **6**, respectively, a total of 939 and 966 independent reflections with $I \geq 0$ were used to solve the structure by direct methods and to refine it by full matrix least-squares using F^2.[17,18] Hydrogen atoms were found on a difference Fourier map and refined isotropically. Anisotropic thermal parameters were refined for all non-hydrogen atoms. The final refinement of **5** converged to R=0.0420 for 86 refined parameters and 789 observed reflections with $I \geq 2\sigma(I)$. The final refinement of **6** converged to R=0.0411 for 86 refined parameters and 904 observed reflections with $I \geq 2\sigma(I)$. Data processing was carried out with the KM4CCD software, structure solution SHELXS[17] and structure refinement SHELXL.[18]

The authors have deposited all crystallographic data for these structures with the Cambridge Crystallographic Data Centre[19] under CCDC 156329 and 156330 deposition numbers for compounds **5** and **6**, respectively.

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