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THE INFLUENCE OF ALKYL SUBSTITUENTS ON INTERNAL PHOTODIMERIZATION OF PYRIMIDINE-6-AZAPYRIMIDINE DINUCLEOTIDE ANALOGUES

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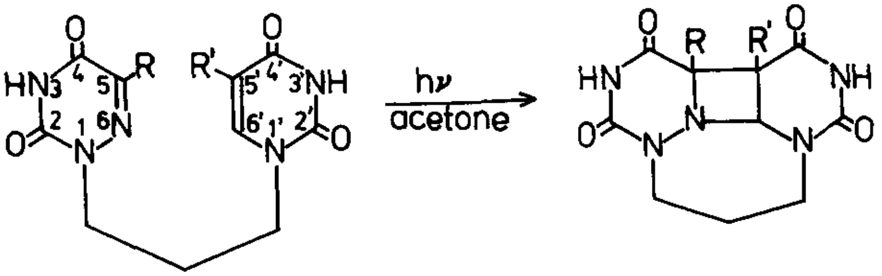
Abstract - The new internal photodimers of dinucleotide analogues in which 5-alkyl derivatives of uracil and 6-azauracil are connected with trimethylene chain have been obtained. The structure is discussed on the basis of spectroscopic data.

In the recent communication[1] we described the formation of cis-syn internal photodimers during UV irradiation of dinucleotide analogues in which uracil or thymine was connected with 6-azauracil with a trimethylene bridge. The unusual properties of some protons at the azacyclobutane ring - according to ^{1}H-NMR spectra - inspired us to examine the influence of alkyl substituents in 5,5′-positions on the formation of such internal photodimers.



1a R = H R′= C_2H_5
1b R = H R′= C_3H_7
1c R = CH_3 R′= H

2a R = H R′= C_2H_5
2b R = H R′= C_3H_7
2c R = CH_3 R′= H

In order to reach some quantitative data on unbonding base-base interaction in compounds 1a, 1b and 1c the hypochromism values[2] have been calculated and compared with the proper pyrimidine-pyrimidine counterparts. The obtained results are presented in the Table 1.

Compound	% H
Ura(1 $(CH_2)_3$ 1)Ura [2]	1.2
Ura(1 $(CH_2)_3$ 1)6-azaUra	-1.2
Thy(1 $(CH_2)_3$ 1)Ura [3]	2.6
Thy(1 $(CH_2)_3$ 1)6-azaUra	0.3
5-EtUra(1 $(CH_2)_3$ 1)Ura [3]	4.5
5-EtUra(1 $(CH_2)_3$ 1)6-azaUra	0.6
Thy(1 $(CH_2)_3$ 1)Thy [2]	7.0
Thy(1 $(CH_2)_3$ 1)6-azaThy	5.1

Table 1. Values of hypochromism % H of some dinucleotide analogues.

It is evident from the data given in the Table 1 that the hypochromism of the analogues having 6-azauracil moiety is lower than their uracil counterparts. Nevertheless the differences are too small to be responsible of the different behaviour of these two series under UV irradiation in aqueous solution. The short time irradiation of compounds 1a, 1b and 1c in aqueous solution with $\lambda > 290$ nm led exclusively to photohydrates, whereas the same experiments carried out with pyrimidine-pyrimidine analogues gave as a result cyclobutane type photodimers[2,3]. The prolongation of the irradiation resulted in complicated mixture of productd as shown by TLC. Quite different results were obtained when acetone was used as solvent and sensitizer. The irradiation of compounds 1a, 1b and 1c in acetone with $\lambda > 290$ nm for 15 min gave exclusively the azacyclobutane photodimers 2a, 2b and 2c in high yields. The obtained photodimers showed only end UV absorption at $\lambda = 270$ nm as shown in the Figure 1. The photodimers 2a, 2b and 2c are unstable in aqueous solution and they decompose gradually to 1a, 1b and 1c,respectively /within 4 days 2a, 2b and 2c stored in water solution at room temperature completely reverses to 1a, 1b and 1c, respectively/. The short time irradiation of photodimers

2a, 2b and 2c with λ = 254 nm reverses the dimerization what is visualized by appearance of UV absorption at 270 nm /similarly to pyrimidine-pyrimidine analogues [2,3]/.

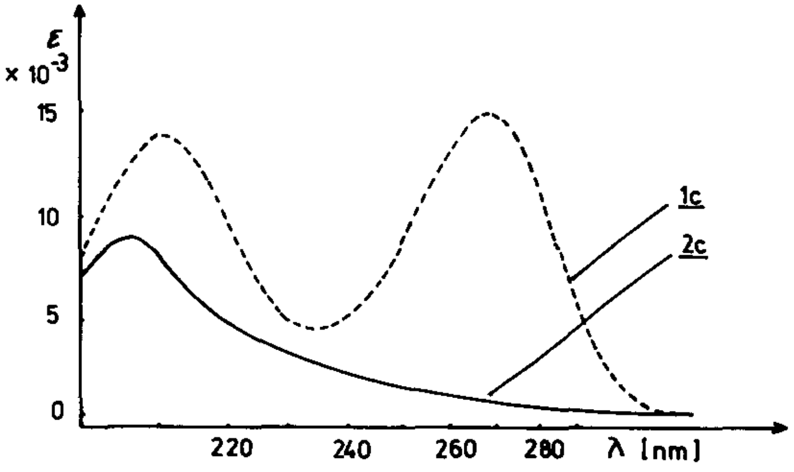
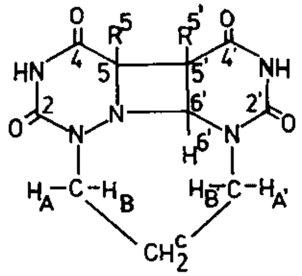


Figure 1. UV spectra of compounds 1c and 2c in water.

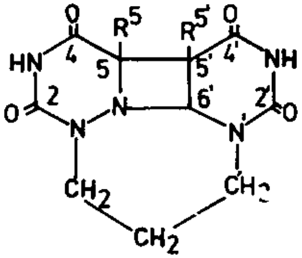
The ^{1}H-NMR and ^{13}C-NMR spectra of known internal photodimers and newly obtained in 6-azauracils series showed their close similarity. Obtained results simply suggested that these compounds should have the cis-syn geometry. The NMR data are collected in Table 2 and Table 3.

The chemical shifts of $H^{6'}$ and H^{5} in all reported compounds are almost identical. Also geometry of seven-member diazacycloheptane ring on the basis of NMR data seems to be identical. The very complex pattern of splittings of CH_2^c signals and also suprisingle of H_B and $H_{B'}$ need some additional comment. This complicated picture of splittings may be probably attributed to second order splitting pattern or internal isomerization. In case of cis-syn geometry of obtained photodimers the expected internal isomerization is due to the possibility of equilibrium between two relatively stable rotamers.



	R^5	$R^{5'}$	$H^{6'}$	H_A , $H_{A'}$	H_B , $H_{B'}$	H^C
Thy[1(CH$_2$)$_3$ 1]6-azaUra [4]	4.97,s	1.92,s	5.13,s	4.66,dt, $^2J_{H_AH_B}$=14 Hz $^3J_{H_AH^C}$=3.5Hz	3.0,/dt?/ complex mult.	1.6-1.9 complex mult.
2a	4.95,s	C$\underline{H}_3$,1.05,t, ^3J=7.5Hz	5.22,s	4.64,dt, $^2J_{H_AH_B}$=14 Hz $^3J_{H_AH^C}$=3.5Hz	3.0,/dt?/ complex mult.	1.9-2.8 complex mult.
2b	4.95,s	C$\underline{H}_3$,0.86,t, ^3J=7.5Hz	5.23,s	4.68,dt, $^2J_{H_AH_B}$=14 Hz $^3J_{H_AH^C}$=3.5Hz	3.0,/dt?/ complex mult.	1.6-2.7 complex mult.
2c	1.94,s	4.10,d, ^3J=7.5Hz	5.25,d ^3J=7.5Hz	4.56,dt, $^2J_{H_AH_B}$=14 Hz $^3J_{H_AH^C}$=4.0Hz	3.0,/dt?/ complex mult.	1.6-2.7 complex mult.

Table 2. ^{1}H-NMR spectra of some dinucleotide analogues /all spectra in PyH-d$_6$, in ppm downfield from TMS/



	R^5	$R^{5'}$	$\underline{C}^{6'}$	$\underline{C}^5$	$\underline{C}^{5'}$	N-$\underline{C}$	N-$\underline{C}'$	C-$\underline{C}$-C	$C^2,C^{2'}$	$C^4,C^{4'}$
Ura[1(CH$_2$)$_3$1]6-azaUra	-	-	77.0	55.3	47.5	45.3	43.3	20.9	151.6 151.3	168.7 167.6
Thy[1(CH$_2$)$_3$1]6-azaUra	-	21.7	81.2	66.3	45.5	46.6	46.6	23.1	150.6 149.8	166.6 165.7
2a	-	8.1 27.7	78.3	64.5	48.3	46.7	46.7	23.1	150.3 149.5	165.7 165.5
2b	-	13.8 16.9 36.9	78.7	64.9	47.8	46.8	46.8	23.1	150.2 149.4	165.8 165.4
2c	reverses to 1c within time of NMR spectrum performance									

Table 3. ^{13}C-NMR spectra of some dinucleotide analogues /all spectra in DMSO-d$_6$, in ppm downfield from TMS/

In both rotamers the pattern of N-CH_2 groups can be described as AA'BB', but only one pair of protons is effected by the stereoisomerization whereas another pair is not influenced by these changes. To prove such suggestion we run out the ^{1}H-NMR spectra in elevated temerature / up to 75°C/, where the complex pattern of splittings simplified. The hypothesis of existence of equilibrium between two rotamers is supported by ^{13}C-NMR spectra. The additional set of signals, especially in carbonyl region, C^6 and $C^{6'}$, and N-C-C-C-N appeared when spectra have been run at room temperature. The low solubility of 2a, 2b and 2c in solvents suitable for low temperature NMR study makes such experiments impossible to run. Such conclusions support strongly our predictions concerning cis-syn configuration of obtained photodimers. In case of trans-syn geometry this rotameric equilibrium does not occur. The anti configuration is not taken for the consideration because of length of trimethylene chain.

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