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INTERNAL PHOTODIMERIZATION OF SOME PYRIMIDINE-6-AZAPYRIMIDINE DINUCLEOTIDE ANALOGUES

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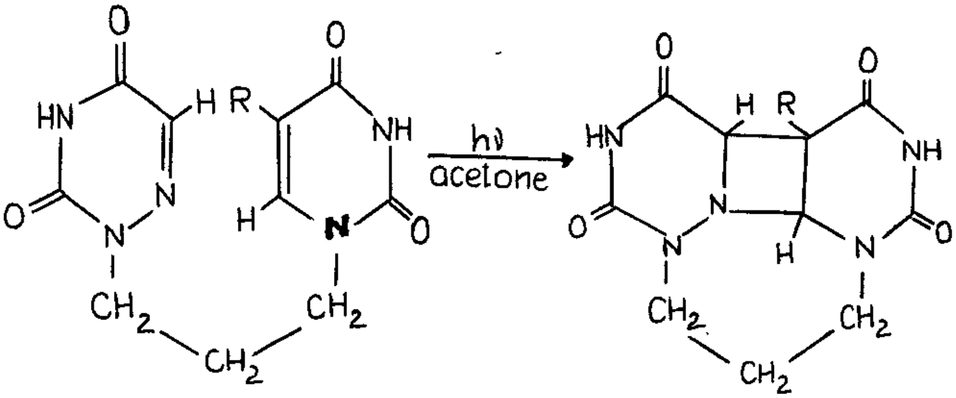
Abstract - The UV irradiation of dinucleotide analogues in which 6-azauracil moiety was connected with trimethylene chain to uracil and thymine led to internal photodimers containing azacyclobutane ring. The geometry of these photodimers has been discussed on the basis of NMR data.

The internal photodimerization of dinucleotide analogues in which pyrimidine bases were connected with polymethylene spacers has been already well elaborated[1,2,3]. So far, relatively little is known on the photochemical behaviour of 6-aza-analogues of pyrimidine although they have a great importance in photochemotherapy[4]. According to calculations the excited-state properties of the 6-aza-analogues of uracil and thymine should closely resemble those of the parent carbon systems[5]. In practice there has been observed the anomalous unreactivity of these aza-systems[6,7], while 1,3-dimethyl-6-azauracil and thymine underwent the acetone-sensitized cycloaddition with ethylene, tetramethylene, isobutylene, ethyl vinyl ether, vinyl acetate and isopropenyl acetate[8,9]. Suprisingly smooth photoaddition of dibromomaleimides with 1,3-dimethyl-6-aza-uracil was also reported[10].

In the recent communication we report the internal photodimerization of dinucleotide analogues in which the uracil and thymine are connected with 6-azauracil with trimethylene chain[11] /Scheme 1/.

Scheme 1



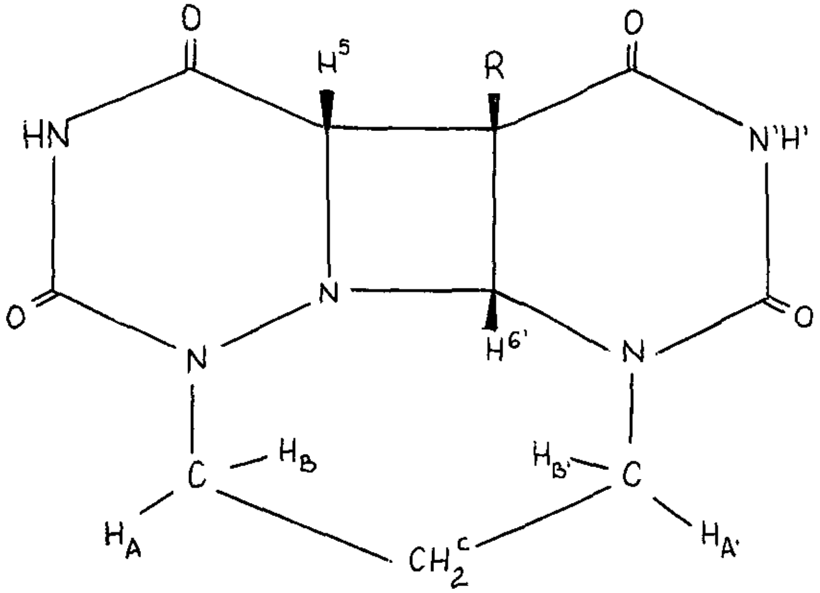
1a R = H
1b R = CH_3

2a R = H
2b R = CH_3

RESULTS AND DISCUSSION

The long-wave UV irradiation of acetone solutions of 1a and 1b led to internal photodimers 2a and 2b which were isolated in high yields. The disappearance of UV absorption at $\lambda = 270$ nm and photoreversibility of these compounds strongly support the formation of aza-cyclobutane ring. These internal photodimers are not stable in aqueous solutions and are slowly decomposed to the substrates. Similarly to 1,1′-trimethylene-bis-/5-alkyl/-uracils analogues the internal photodimerization of 1a and 1b led only to one photoproduct and no traces of other photoisomers could have been observed. While the configuration of numerous 1,1′-trimethylene-bis-/5-alkyl/-uracil photodimers has been unequivocally proved as being cis-syn[1,3,12], the geometry of photodimers obtained from analogues containing 6-azauracil moiety deserves special consideration.

The inspection of Dreiding models of possible isomers of photodimers in question led us to the conclusion that only cis-syn and trans-syn isomers could be formed. The cis-anti and trans-anti isomers cannot be synthesized on account of the length of three carbon atoms polymethylene chain. The structure of photodimers is also supported by the stacking effect which is comparable with formerly known polymethylene-bis-pyrimidines[13]. On the base of this assumption the base-base stacking effect should favor the formation of cis-syn isomer.



<u>2a</u> R = H.
<u>2b</u> R = CH_3

	R	H^5	$H^{6'}$	H_A, $H_{A'}$	H_B, $H_{B'}$	H^c	NH N'H'
<u>2a</u>	5.27,m /dd?/	6.00,d, $J_{H^5H^R}$=3.5Hz	6.38,d $J_{H^{6'}H^R}$=4.0Hz	4.18,dd $J_{H_AH_B}$=-11.5Hz $J_{H_AH^c}$=$J_{H_{A'}H^c}$= =3.3Hz	3.13,d $J_{H_{A'}H_{B'}}$=-11.5Hz $J_{H_BH^c}$=$J_{H_{B'}H^c}$= =0 Hz	1.6-1.9 m	10.29 s 10.24 s
<u>2b</u>	1.66,s	4.52,s	4.91,s	4.17,dt $J_{H_AH_B}$=-12.0Hz $J_{H_AH^c}$=$J_{H_{A'}H^c}$= =3.5Hz	2.84,3.10,dt $J_{H_AH_B}$=-12.0Hz $J_{H_BH^c}$=$J_{H_{B'}H^c}$= =3.5Hz	1.6-1.9 m	10.23 s 10.11 s

Table 1. ^{1}H-NMR data of 6-azaUra{1/CH_2/$_3$ 1'}Ura <u>2a</u> and 6-azaUra{1/CH_2/$_3$ 1'}Thy <u>2b</u>. Chemical shifts in ppm, samples in DMSO-d_6 with TMS as internal reference.

The ^1H-NMR spectra of obtained photodimers and their comparison with previously reported photodimers of polymethylene-bis-pyrimidines suggested that synthesized products have cis-syn structure.

The ^1H-NMR data are collected in Table 1.

In case of 6-azaUra[1/$CH_2/_3$ 1]Ura 2a the signals of hydrogens attached to the azacyclobutane ring are significantly shifted low field /about 1.5 ppm/ in comparison with 6-azaUra[1/$CH_2/_3$ 1′]Thy 2b. This phenomenon can be explained by the steric effect caused by the presence of methyl group. The steric hindrance seems to be responsible for additional strain in azacyclobutane ring and because of it ^1H-NMR signals of H^5 and $H^{6'}$ are shifted upfield. On the other hand the stereochemistry of polymethylene chain is almost identical in these two compounds according to the NMR data.

The ^1H-NMR spectrum of two N-/methylene groups showed to be AA′BB′ pattern. In case of 6-azaUra[1/$CH_2/_3$ 1′]Ura 2a the chemical shifts of H_A - $H_{A'}$ and H_B - $H_{B'}$ are almost identical whereas in 6-azaUra[1/$CH_2/_3$ 1′]Thy 2b they differ slightly depending where they are attached /to 6-azauracil or thymine moiety/. The coupling constant $^3J_{H_BH^c} = {}^3J_{H_{B'}H^c} = 0$ Hz in the 6-azaUra[1/$CH_2/_3$ 1′]Ura 2a showed that the two middle-chain methylene protons do not couple to one of non-equivalent protons of N-CH_AH_B /or N-$CH_{A'}H_{B'}$ / whereas they split the signal of H_A and $H_{A'}$ with $^3J_{H_AH^c} = {}^3J_{H_{A'}H^c} = 3.5$ Hz. This can be explained on the basis of Karplus theory that dihedral angles $H_B - C - C - H^c$ and $H_{B'} - C - C - H^c$ are about 90° respectively, what makes understandable that coupling constant is close to be 0 Hz [14].

In 6-azaUra[1/$CH_2/_3$ 1′]Thy 2b protons H_A, $H_{A'}$, H_B and $H_{B'}$ couple to middle chain methylene group giving complex pattern of splittings with $^3J_{H_AH^c} \cong {}^3J_{H_{A'}H^c} \cong {}^3J_{H_BH^c} \cong {}^3J_{H_{B'}H^c} \cong 3.5$ Hz. The geminal coupling constants in both compounds $^2J_{H_AH_B} = {}^2J_{H_{A'}H_{B'}} = 11.5$-$12.0$ Hz indicate that the angle between $H_A - C - H_B$ corresponds to typical tetrahedral structure[15]. The obtained so far spectroscopic data strongly support the cis-syn geometry for the obtained photodimers with azacyclobutane rings.

EXPERIMENTAL

The synthetical procedure and physico chemical properties of photoproducts.

The acetone 1.25 x 10^{-3}M and 5.7 x 10^{-3}M solutions of 1a and 1b were irradiated for 15 min in cylindrical reactor with immersed high pressure Mercury lamp with cylindrical Pyrex filter. During the irradiation the argon was let through the solution. After that time no traces of the substrates could have been detected by TLC on Merck silica gel plates 60 F_{254} using chloroform - methanol /15:1, v:v/ as eluent. Also the UV spectrum of the irradiated samples showed only end absorption at 270 nm. The irradiated solutions were evaporated to dryness. The white residue was washed with methanol and ether and dried in vacuo.

Photoproduct 2a 6-azaUra[1/CH_2/$_3$ 1′]Ura: Yield 79%, mp 210°C with decomp.

IR major peaks /cm^{-1}/: 3080, 2860, 1710, 1650, 1480, 1420, 1370, 1350, 1330, 1280, 1230, 1180, 1150, 1130, 1080, 1020, 970, 950 /in KBr pellets/

MS /M^+/ 265 /40%/ 82 /100%/

Elemental analysis for $C_{10}H_{11}N_5O_4$:

Found /calcd./ %: C 45.20 /45.28/, H 4.16 /4.18/, N 26.35 /26.40/

Photoproduct 2b 6-azaUra[1/CH_2/$_3$ 1′]Thy: Yield 95%, mp 165°C with decomp.

IR major peaks /cm^{-1}/: 3200, 3060, 2840, 1760, 1700, 1670, 1490, 1400, 1380, 1360, 1310, 1280, 1260, 1210, 1170, 1130, 1040, 980, 930 /in KBr pellets/

MS /M^+/ 279 /64%/, 56 /100%/

Elemental analysis for $C_{11}H_{13}N_5O_4$:

Found /calcd./ %: C 47.14 /47.30/, H 4.68 /4.69/, N 25.00 /25.08/

Reversals with ultraviolet light.

Aqueous 8.0 x 10^{-5}M solutions of 2a or 2b photoproducts irradiated with Original Hanau low pressure Mercury lamp for 5 min showed the increase of absorption at λ = 270 nm to approximately 45% of the absorption value of the substrates used for photodimerization. The slow increase of absorption at λ = 270 nm was also observed when aqueous solutions of 2a and 2b were storaged at ambient temperature.

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