

PHOTOCYCLOADDITION OF 2'-DEOXYRIBONUCLEOSIDE  
TO 2,3-DIMETHYL-2-BUTENE <sup>1</sup>

Naoki Haga, Ichiro Ishikawa, Masaya Kinumura, Hiroaki Takayanagi, and  
Haruo Ogura\*

School of Pharmaceutical Sciences, Kitasato University

5-9-1, Shirokane, Minato-ku, Tokyo 108, Japan

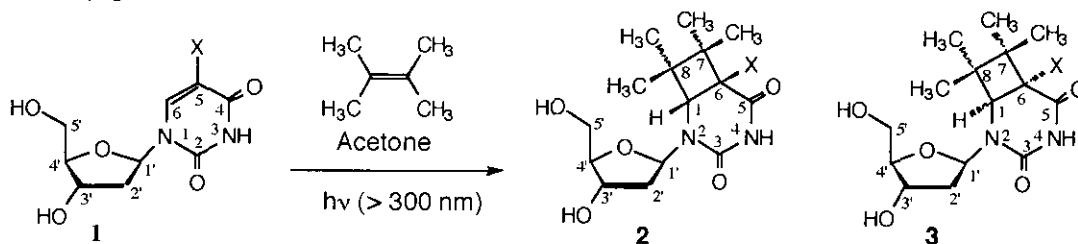
**Abstract**-Photosensitized cycloaddition of 2,3-dimethyl-2-butene to 2'-deoxyuridine, thymidine and 5-fluoro-2'-deoxyuridine by the uv irradiation in acetone have been studied. From the respective reactant, a pair of diastereomers which has a cyclobutane ring were formed. However in each reaction one of the two isomers could be isolated and purified by recrystallization.

Photodimerization of pyrimidine bases such as thymine and uracil <sup>2</sup> has been intensively studied because the photodimerization of thymine bases in the DNA double helix is responsible for the photo-deactivation of gene. Generally cycloaddition involving  $\alpha,\beta$ -unsaturated carbonyl compounds leads to the formation of a complex mixture. Swenton and Wexler, <sup>3-7</sup> however, have reported on the regioselective photoreaction of simple olefins with pyrimidine bases. To our knowledge, little attention has been paid to photoreactions of pyrimidine nucleosides with simple olefins except the work of Charlton and Lai,<sup>8</sup> presumably because cross-photocycloaddition furnishes an intractable mixture. It is very intriguing to examine the interaction of repair-enzymes with the cyclobutane adducts of this type. Our recent work <sup>9</sup> has revealed that two of photoadducts of cyclobutane-type could be isolated from uv-irradiated acetone solution containing uridine derivatives and 2,3-dimethyl-2-butene.

In this communication, we deal with the photocycloaddition of 2'-deoxyuridine (**1a**), thymidine (**1b**) and 5-fluoro-2'-deoxyuridine (**1c**) to 2,3-dimethyl-2-butene.

The near-uv irradiation ( $\lambda > 300$  nm) of 10 mM of 2'-deoxyuridines and 50 mM of 2,3-dimethyl-2-butene in acetone gave rise to two photoproducts, which account for more than 75% of the products, and we occasionally obtained a small amount of intractable products along with the starting material. Though these two products could not be cleanly separated by silica gel chromatography, the one of two, in every case, was found to be crystallized from methanol and ethyl acetate in a pure form on concentration of the eluate. On the basis of elemental analysis, FAB-ms, uv and nmr spectral properties, each pure product was unambiguously identified as the cyclobutane photoproducts which were formed by linking nucleosides to 2,3-dimethyl-2-butene at the positions 5 and 6 (Scheme 1)<sup>10-12</sup>. Furthermore, a X-ray crystallographic analysis confirmed the structures. A stereodiagram of the 2'-deoxyuridine photoproduct (**3a**) is shown in Figure 1. The absolute configuration of 1-C and 6-C was turned out to be *R*. Nmr spectrum of the mother liquor of the photoproducts of 2'-deoxyuridine exhibited very similar pattern to that of (**3a**), showing that it bears a 2-deoxyribose moiety, a 5,6-saturated pyrimidine ring and four methyl groups. Thus, another product was assigned as the (1*S*, 6*S*)-isomer (**2a**).

### Scheme 1



**Table I** Photocycloaddition of **1** to 2,3-Dimethyl-2-butene in acetone.<sup>a)</sup>

	X	time/h	yield (%)	<b>2</b> : <b>3</b>
<b>1a</b>	H	7.5	79	0.9:1.0
<b>1b</b>	CH <sub>3</sub>	8.0	86	2.7:1.0
<b>1c</b>	F	1.5	80	2.0:1.0

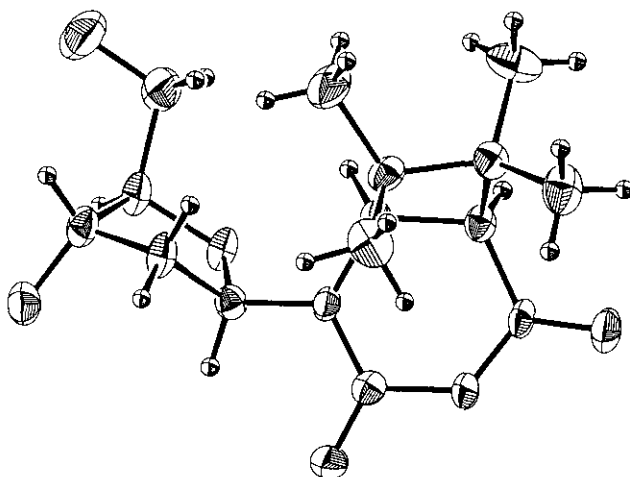
a) Irradiation was performed employing a 400 W high-pressure mercury lamp through a 2 mm Pyrex filter under nitrogen atmosphere.

Compound (**3a**) is characterized by the upfield chemical shift by 0.2 ppm of a signal owing to 2'-CH resonance, as compared to (**2a**). However the products obtained from the reaction mixture of (**1b**) and (**1c**) in

pure form failed to crystallize in a suitable form for X-ray diffraction. Nevertheless, on the basis of nmr property described above, we deduced their absolute configuration at positions 1 and 6 as *S*.

The reaction conditions and yields of the two cyclobutane photoproducts of (**1a**), (**1b**) and (**1c**) are given in Table I. The ratio of (**2**) to (**3**) was determined on the basis of the integration of anomeric proton in the nmr spectra.

Variation in the ratio of (**2**) to (**3**) may be a reflection of the substituent effect on regioselectivity. Further work is required for the elucidation of the detailed mechanism of this reaction. Complete separation of the two diastereomers employing 3', 5'-di-*O*-acetyl substrates and the measurement of quantum yield of the photoreaction are in progress. Results obtained from study on the interaction of the newly synthesized photoproduct with repair enzymes will be the subject of a separate paper.



**Figure 1** Stereoscopic View of (1*R*, 6*R*)-7,7,8,8-Tetramethyl-2-( $\beta$ -D-2'-deoxyribofuranosyl)-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione (**3a**)

## REFERENCES AND NOTES

- 1) The present paper is dedicated to professor Edward C. Taylor on the occasion of his 70th birthday.
- 2) For reviews, a) G. J. Fisher and H. E. Johns, '*Photochemistry and Photobiology of Nucleic Acid*', Vol. 1, ed. by S. Y. Wang, Academic Press, New York, 1976, pp. 225-294.  
b) J. Cadet, '*Bioorganic Photochemistry*', Vol. 1, ed. by H. Morrison, John Wiley & Sons, New York, 1990, pp. 1-272.

- 3) A. J. Wexler and J.S. Swenton, *J. Am. Chem. Soc.*, 1976, **98**, 1602.
- 4) A. J. Wexler, J. A. Hyatt, P. W. Raynold, C. Cottell, and J. S. Swenton, *J. Am. Chem. Soc.*, 1978, **100**, 512.
- 5) T. G. Savino, L. K. Chenard, and J. S. Swenton, *Tetrahedron Lett.*, 1983, **34**, 4055.
- 6) A. J. Wexler, R. J. Balchunis, and J. S. Swenton, *J. Org. Chem.*, 1984, **49**, 2733.
- 7) V. V. Kaminski, W. A. Wexler, R. J. Balchunia, and J. S. Swenton, *J. Org. Chem.*, 1984, **49**, 2738.
- 8) J. L. Charlton and H. K. Lai, *Can. J. Chem.* **54**, 1445.
- 9) I. Ishikawa, T. Itoh, H. Takayanagi, J. Ohshima, N. Kawahara, Y. Mizuno, and H. Ogura, *Chem. Pharm. Bull.*, 1992, **39**, 1922.
- 10) Nmr data of (1*R*, 6*R*)-7,7,8,8-tetramethyl-2-( $\beta$ -D-2'-deoxyribofuranosyl)-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione **3a**:  $\delta$  10.28 (s, 1H, 4-NH), 6.13 (dd, 1H, J = 8.0, 6.5, Hz, 1'-CH), 5.13 (d, 1H, J = 4.0 Hz, 3'-OH), 4.86 (t, 1H, J = 5.5, Hz, 5'-OH), 4.24 (d, 1H, J = 9.6 Hz, 1-CH), 4.17 (dddd, 1H, J = 5.2, 4.0, 3.2, 2.0 Hz, 3'-CH), 3.61 (dt, 1H, J = 4.0, 2.0 Hz, 4'-CH), 3.47 (dd, 2H, J = 5.5, 4.8 Hz, 5'-CH<sub>2</sub>), 2.81 (d, 1H, J = 9.6 Hz, 6-CH), 1.80 (dd, 1H, J = 8.0, 5.2 Hz, 2'-CH), 1.80 (dd, 1H, J = 6.5, 3.2 Hz, 2''-CH), 1.17, 0.97, 0.87, 0.86 (s, each 3H, CH<sub>3</sub>).
- 11) Nmr data of (1*S*, 6*S*)-6,7,7,8,8-pentamethyl-2-( $\beta$ -D-2'-deoxyribofuranosyl)-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione **2b**:  $\delta$  10.13 (s, 1H, 4-NH), 6.04 (dd, 1H, J = 8.8, 5.6 Hz, 1'-CH), 5.11 (d, 1H, J = 4.4 Hz, 3'-OH), 4.75 (t, 1H, J = 5.6 Hz, 5'-OH), 4.05 (dddd, 1H, J = 6.0, 4.4, 2.8, 2.6 Hz, 3'-CH), 3.64 (s, 1H, 1-CH), 3.62 (dt, 1H, J = 5.2, 2.6 Hz, 4'-CH), 3.43 (dd, 2H, J = 5.6, 5.2 Hz, 5'-CH<sub>2</sub>), 1.97 (ddd, 1H, J = 12.8, 8.8, 6.0 Hz, 2'-CH), 1.73 (ddd, 1H, J = 12.8, 5.6, 2.8 Hz, 2''-CH), 1.14, 1.04, 0.91, 0.86, 0.86 (s, each 3H, CH<sub>3</sub>).
- 12) Nmr data of (1*S*, 6*S*)-6-fluoro-7,7,8,8-tetramethyl-2-( $\beta$ -D-2'-deoxyribofuranosyl)-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione **2c**:  $\delta$  10.95 (s, 1H, 4-NH), 6.04 (dd, 1H, J = 8.8, 6.0 Hz, 1'-CH), 5.14 (br s, 1H, 3'-OH), 4.83 (br, 1H, 5'-OH), 4.28 (d, 1H, J = 22.6 Hz, 1-CH), 4.10 (m, 1H, 3'-CH), 3.67 (m, 1H, 4'-CH), 3.47 (m, 2H, 5'-CH<sub>2</sub>), 1.99 (ddd, 1H, J = 13.2, 8.8, 6.8 Hz, 2'-CH), 1.78 (ddd, 1H, J = 13.2, 6.0, 2.4 Hz, 2''-CH), 1.14 (d, 3H, J = 4.0 Hz, 7-CCH<sub>3</sub>), 1.05, 0.92, 0.81 (s, each 3H, 7,8,8-CCH<sub>3</sub>).

Received, 24th November, 1992