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A highly efficient intramolecular nitrene insertion was observed upon irradiation of 6-azidouridine derivatives. The  $N^6,2'$ -cyclo structure of the product was determined unequivocally by X-ray crystallography.

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Organic azides have been widely used as synthetic starting materials to construct nitrogen-containing heterocycles [1]. One of salient features of these molecules is the facile photochemical formation of a reactive species, nitrene, which can react with an unactivated carbon [2].

Although such photochemical property of 8-azidopurine nucleotides has been used to elucidate protein-nucleic acid interactions [3], this was not the case for the pyrimidine counterparts due to the inaccessibility.

We recently reported on the synthesis of 6-azidouridine from a 6-iodouridine derivative [4]. As a preliminary study, we examined photochemical reaction of 6-azidouridine derivatives, which is the subject of the present communication.

When 6-azido-2',3'-*O*-isopropylidene-5'-*O*-methoxymethyluridine (**1**) was irradiated in THF for 60 minutes at room temperature, a highly-crystalline product was obtained after silica gel column chromatography. Several characteristics in the  $^1\text{H-nmr}$  spectrum (400 MHz, in  $\text{DMSO-d}_6$ ) of this product are in order. 1) The H-1' appeared as a sharp singlet at  $\delta$  5.75. 2) Two well-separated deuterium oxide-exchangeable protons were observed at  $\delta$  9.12 and 10.45, respectively, suggesting the presence of  $N^6\text{-H}$  in addition to the  $N^3\text{-H}$ . 3) The methylene protons in the 5'-*O*-protecting group showed an AB-quartet [5]. 4) The difference in the chemical shift between the isopropylidene methyl signals was unusually small ( $\Delta\delta$  Me = 0.04 ppm), being influenc-

ed by either an anisotropic effect [6] or a steric compression in the sugar moiety.

Its mass spectrum ( $M^+\text{-Me}$ :  $m/z$  326) and the above  $^1\text{H-nmr}$  characteristics are best accommodated with the  $N^6,2'$ -cyclo structure **2**. The yield was 79%.

The structure of **2** was further confirmed by X-ray crystallography (Figure 1).

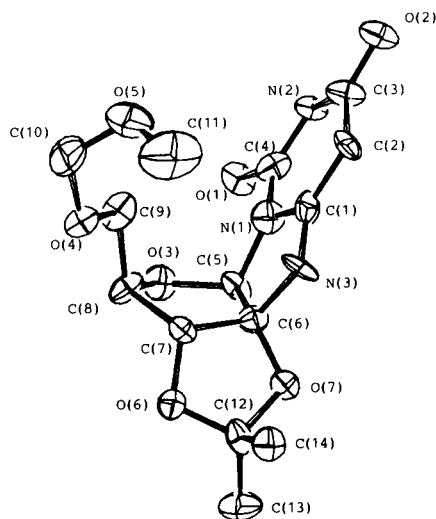
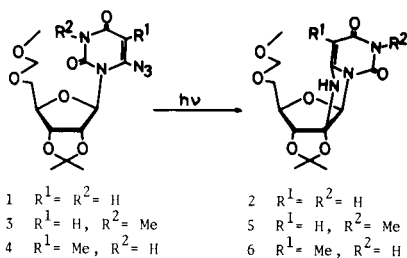


Figure 1. ORTEP drawing of  $N^6,2'$ -Cyclo-6-amino-2',3'-*O*-isopropylidene-5'-*O*-methoxymethyluridine (**2**).



Scheme 1

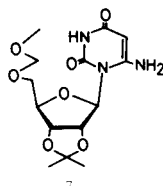
The observed crystal data are as follows: molecular formula  $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}_7$ , molecular weight 341, space group  $\text{P2}_12_12_1$ ,  $Z = 4$ ,  $a = 9.568(6)$ ,  $b = 24.738(10)$ ,  $c = 6.934(4)$  Å. The lattice constants and intensity data were obtained on a Philips PW 1100 diffractometer using graphite-monochromated  $\text{CuK}\alpha$  radiation by  $\theta$ - $2\theta$  scan method. A total of 896 reflections were measured within the  $2\theta$  angle of  $120^\circ$ . Intensity data were corrected for Lorentz and polarization factors, but no absorption correction was applied.

The crystal structure was determined by the direct

method using MULTAN [7] and refined by the block-diagonal least-squares using HBL5 IV [8]. The final R value was 0.102 including anisotropic thermal parameters for non-hydrogen atoms.

Similar photochemical reactions were carried out for the *N*<sup>3</sup>-methyl (**3**) and *C*<sup>5</sup>-methyl (**4**) derivatives to give the respective *N*<sup>6</sup>,2'-cyclized product **5** (60%) and **6** (86%).

It should be noted that, throughout these reactions, no trace amount of the corresponding 6-amino derivatives



was detected [9], showing a high efficiency of the intramolecular nitrene insertion. Such 6-aminouridine derivative **7** was obtained in 15% yield only when a THF solution of **1** was irradiated in the presence of triethylamine [10], but **2** was still the major product (45%).

The efficiency of this nitrene insertion may presumably be highly related to the suitable proximity of the base and sugar moieties. Further studies along this line are currently under investigation.

## EXPERIMENTAL

Melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. The <sup>1</sup>H-nmr were measured with an internal standard of TMS with either a JEOL JNM-FX 100 or a JEOL JNM-GX 400 nmr spectrometer. Mass spectra were taken on a JEOL JMS-D 300 spectrometer. Ultraviolet and infrared spectra were recorded on a Shimadzu UV-240 and a JASCO IRA-1 spectrophotometers, respectively. Column chromatography was carried out on silica gel (Wakogel<sup>®</sup> C-200). Tlc was performed on silica gel (precoated silica gel plates F<sub>254</sub>, Merck).

### 6-Azido-2',3'-*O*-isopropylidene-5'-*O*-methoxymethyluridine (**1**).

For the preparation and physical data of this compound: see reference [4].

### General Procedure for Photochemical Reactions of **1**, **3**, and **4**.

Irradiation of a 6-azidouridine derivative (200 mg) was carried out, with a Shigemi 250 W high-pressure mercury lamp equipped with a Pyrex filter, in dry THF (80 ml) under argon atmosphere for 60-70 minutes at room temperature. In the case of the formation of **7**, triethylamine (0.15 ml) was added to the above solution. After evaporation of the solvent, each product was isolated by silica gel column chromatography by using 4% ethanol in chloroform as an eluant.

### *N*<sup>6</sup>,2'-Cyclo-6-amino-2',3'-*O*-isopropylidene-5'-*O*-methoxymethyluridine (**2**).

This compound was crystallized from ethanol, mp > 290°; uv (methanol): λ max 261.5 nm (ε 26200); (methanol): λ min 231.5 nm (ε 3800); <sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>): δ 1.44 (s, 3H, isopropyl-Me), 1.48 (s, 3H, isopropyl-Me), 3.17 (s, 3H, CH<sub>2</sub>OCH<sub>3</sub>), 3.41 and 3.46 (each as dd, 2H, CH<sub>2</sub>-5'), 4.47 (q, 2H, CH<sub>2</sub>OCH<sub>3</sub>), 4.50 (t, 1H, H-4'), 4.57 (d, 1H, H-5), 4.58 (s, 1H, H-3'), 5.75 (s, 1H, H-1'), 9.12 (br, 1H, *N*<sup>6</sup>-H), 10.45 (br, 1H, *N*<sup>3</sup>-H); ms: (m/z) 326

(*M*<sup>+</sup>-Me).

*Anal.* Calcd. for C<sub>14</sub>H<sub>19</sub>N<sub>3</sub>O<sub>7</sub> (341.31): C, 49.25; H, 5.61; N, 12.31. Found: C, 49.26; H, 5.66; N, 12.10.

### 6-Azido-2',3'-*O*-isopropylidene-5'-*O*-methoxymethyl-3-methyluridine (**3**).

Treatment of a THF (40 ml) solution of 6-iodo-2',3'-*O*-isopropylidene-5'-*O*-methoxymethyluridine [**4**] (1.0 g) with an excess of diazomethane in ether gave a colorless oil after evaporation of the solvents. To this oil were added DMF (5 ml) and sodium azide (157 mg) and the mixture was stirred for 30 minutes at room temperature. Purification of the mixture through a silica gel column (1% ethanol in chloroform) gave **3** (798 mg, 95%), which was crystallized from methanol, mp 144-145°; ir (potassium bromide): ν 2155 cm<sup>-1</sup> (N<sub>3</sub>); uv (methanol): λ max 282.5 nm (ε 8200); (methanol): λ min 248 nm (ε 1700); <sup>1</sup>H-nmr (deuteriochloroform): δ 1.35 (s, 3H, isopropyl-Me), 1.56 (s, 3H, isopropyl-Me), 3.27 (s, 3H, *N*<sup>3</sup>-CH<sub>3</sub>), 3.36 (s, 3H, CH<sub>2</sub>OCH<sub>3</sub>), 3.71-3.78 (m, 2H, CH<sub>2</sub>-5'), 4.16-4.33 (m, 1H, H-4'), 4.65 (s, 2H, CH<sub>2</sub>OCH<sub>3</sub>), 4.87 (dd, 1H, H-3'), 5.15 (dd, 1H, H-2'), 5.56 (s, 1H, H-5), 6.14 (d, 1H, J = 1.0 Hz, H-1'); ms: (m/z) 368 (*M*-Me), 217 (*M*-B), 168 (B + 2).

*Anal.* Calcd. for C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>O<sub>7</sub> (383.36): C, 46.98; H, 5.53; N, 18.27. Found: C, 47.12; H, 5.52; N, 18.39.

### 6-Azido-2',3'-*O*-isopropylidene-5'-*O*-methoxymethyl-5-methyluridine (**4**).

A DMF (1.5 ml) solution of 6-iodo-2',3'-*O*-isopropylidene-5'-*O*-methoxymethyl-5-methyluridine [**11**] (200 mg, 0.43 mmole) was treated with sodium azide (31 mg, 0.47 mmole) for 30 minutes at room temperature. Purification of the mixture through a silica gel column (2% ethanol in chloroform) gave **4** (154 mg, 93%), which was crystallized from ethanol, mp 157-158°; ir (potassium bromide): ν 2160 cm<sup>-1</sup> (N<sub>3</sub>); uv (methanol): λ max 277.5 nm (ε 9000); (methanol): λ min 243 nm (ε 2900); <sup>1</sup>H-nmr (methanol-*d*<sub>4</sub>): δ 1.34 (s, 3H, isopropyl-Me), 1.53 (s, 3H, isopropyl-Me), 2.07 (s, 3H, 5-Me), 3.34 (s, 3H, CH<sub>2</sub>OCH<sub>3</sub>), 3.68-3.75 (m, 2H, CH<sub>2</sub>-5'), 4.06-4.17 (m, 1H, H-4'), 4.62 (s, 2H, CH<sub>2</sub>OCH<sub>3</sub>), 4.84 (m, 1H, H-3'), 5.20 (dd, 1H, H-2'), 6.29 (d, 1H, J = 1.5 Hz, H-1'); ms: (m/z) 368 (*M*-Me), 217 (*M*-B), 168 (B + 2).

*Anal.* Calcd. for C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>O<sub>7</sub> (383.36): C, 46.98; H, 5.53; N, 18.27. Found: C, 47.17; H, 5.54; N, 18.16.

### *N*<sup>6</sup>,2'-Cyclo-6-amino-2',3'-*O*-isopropylidene-5'-*O*-methoxymethyl-3-methyluridine (**5**).

This compound was crystallized from ethanol, mp 159-160°; uv (methanol): λ max 261.5 nm (ε 25500); (methanol): λ min 232 nm (ε 4000); <sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>): δ 1.45 (s, 3H, isopropyl-Me), 1.48 (s, 3H, isopropyl-Me), 3.03 (s, 3H, *N*<sup>3</sup>-Me), 3.11 (s, 3H, CH<sub>2</sub>OCH<sub>3</sub>), 3.41 and 3.45 (each as dd, 2H, CH<sub>2</sub>-5'), 4.45 (q, 2H, CH<sub>2</sub>OCH<sub>3</sub>), 4.51 (t, 1H, H-4'), 4.60 (s, 1H, H-3'), 4.73 (s, 1H, H-5), 5.80 (s, 1H, H-1'), 9.15 (br, 1H, *N*<sup>6</sup>-H); ms: (m/z) 355 (*M*<sup>+</sup>), 340 (*M*-Me).

*Anal.* Calcd. for C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>O<sub>7</sub> (355.34): C, 50.68; H, 5.96; N, 11.83. Found: C, 51.14; H, 6.17; N, 11.36.

### *N*<sup>6</sup>,2'-Cyclo-6-amino-2',3'-*O*-isopropylidene-5'-*O*-methoxymethyl-5-methyluridine (**6**).

This compound was crystallized from ethyl acetate, 248-249°; uv (methanol): λ max 270.5 nm (ε 25000); (methanol): λ min 238.5 nm (ε 4100); <sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>): δ 1.48 (s, 3H, isopropyl-Me), 1.49 (s, 3H, isopropyl-Me), 1.67 (s, 3H, 5-Me), 3.15 (s, 3H, CH<sub>2</sub>OCH<sub>3</sub>), 3.38 and 3.45 (each as dd, 2H, CH<sub>2</sub>-5'), 4.43 (q, 2H, CH<sub>2</sub>OCH<sub>3</sub>), 4.49 (t, 1H, H-4'), 4.59 (s, 1H, H-3'), 5.74 (s, 1H, H-1'), 8.67 (br, 1H, *N*<sup>6</sup>-H), 10.51 (br, 1H, *N*<sup>3</sup>-H); ms: (m/z) 355 (*M*<sup>+</sup>), 340 (*M*-Me).

*Anal.* Calcd. for C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>O<sub>7</sub> (355.34): C, 50.68; H, 5.96; N, 11.83. Found: C, 50.95; H, 5.97; N, 11.72.

### 6-Amino-2',3'-*O*-isopropylidene-5'-*O*-methoxymethyluridine (**7**).

This compound was crystallized from methanol, mp 255-256°; uv (methanol): λ max 269.5 nm (ε 22000); (methanol): λ min 234.5 nm (ε 1500); <sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>): δ 1.29 (s, 3H, isopropyl-Me), 1.50 (s, 3H, isopropyl-Me), 3.25 (s, 3H, CH<sub>2</sub>OCH<sub>3</sub>), 3.62 and 3.69 (each as dd, 2H, CH<sub>2</sub>-5'),

4.11 (dd, 1H, H-4'), 4.57 (s, 2H, CH<sub>2</sub>OCH<sub>3</sub>), 4.61 (d, 1H, H-5), 4.78 (dd, 1H, H-3'), 5.15 (dd, 1H, H-2'), 6.01 (d, 1H, J = 2.2 Hz, H-1'), 6.83 (br, 2H, NH<sub>2</sub>), 10.57 (br, 1H, NH); ms: (m/z) 343 (M<sup>+</sup>), 328 (M-Me), 217 (M-B), 127 (B + 1).

*Anal.* Calcd. for C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>7</sub> (343.33): C, 48.96; H, 6.17; N, 12.24. Found: C, 49.39; H, 6.22; N, 12.07.

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