VERSATILE PHOTOREARRANGEMENT OF PHOTOCYCLOADDUCTS FROM 5-FLUORO-1,3-DIMETHYLURACIL AND NAPHTHALENE

Kazue Ohkura,*a Hiromichi Akizawa,a Mikiko Kudo,a Tetsuya Ishihara,a Nobuhiro Oshima,a and Koh-ichi Seki*b

a Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan
E-mail: ohkura@hoku-iryo-u.ac.jp
b Central Institute of Radio Isotope Science, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060-0815, Japan

Abstract – Direct UV-irradiation of 5-fluoro-1,3-dimethyluracil (5-FDMU) and naphthalene (1) with a 500 W high-pressure mercury lamp in a degassed Pyrex tube (λ > 300 nm) predominantly afforded benzopyrimidobarrelene derivative (2) through 1,4-addition, while irradiation in the presence of piperylene in singlet excited states preferentially afforded naphthocyclobuta-pyrimidine derivative (3) via 1,2-addition. Upon 254 nm light-irradiation of 2 gave rise to the formation of benzopyrimidosemibullvalene (4) in fair yields. The reaction pathway for the formation of 4 is reasonably explained in the terms of di-π-methane rearrangement. Adduct 3 was newly converted to the corresponding barrelene derivative (2) by long-wave-length irradiation in the presence of a triplet sensitizer.

INTRODUCTION

In recent years, significant attention has been paid to the photocycloaddition of naphthalenes with alkenes as a useful procedure for constructing certain unique ring systems by way of 1,2-, 1,4-, 1,3-, 1,8-, and [4 + 4] additions. We previously reported that UV-irradiation of 5-fluoro-1,3-dimethyl-uracil (5-FDMU) and naphthalene (1) with a 500 W high-pressure mercury lamp in a degassed Pyrex tube (λ > 300 nm) predominantly afforded the 1,4-adduct, namely benzopyrimidobarrelene derivative (2) in high yield. A time course study of the photoreaction of an acetonirile solution of 5-FDMU and 1 under the same conditions showed that the 1,2-cycloadduct, naphthocyclobutapryrimidine derivative (3) is formed as the major product at the initial stage, which however, is quite labile to the UV-light used, to revert rapidly
back to 5-FDMU and 1, while the 1,4-adduct (2) was produced competitively with 3, though less effectively but insensitive to the light, to accumulate in the reaction mixture as the irradiation time is prolonged. The addition of the triplet quencher piperylene to the reaction mixture of 1 and 5-FDMU dramatically changed the mode of cycloaddition, resulting in the preferential formation of 3 through 1,2-addition. Thus, 1,4- and 1,2- adducts of the pyrimidine ring and naphthalene have been synthesized mode-selectively in fair yields upon long-wave-length irradiation by a high-pressure mercury lamp with a Pyrex filter ($\lambda > 300$ nm). Furthermore, we have obtained 1,3-cycloadducts, semibullvalene derivatives (4), by the UV-irradiation with a low-pressure mercury lamp ($\lambda = 254$ nm). The semibullvalenes were found to be secondary products derived from initially formed 1,4-adducts under UV-irradiation, although the precise reaction mechanism remained unclear. Thus, we have hitherto demonstrated a mode selective synthesis of three types of cycloadducts, 1,2-, 1,3-, albeit formally, and 1,4-adducts, by controlling the reaction conditions appropriately.

Although versatile photorearrangements of 1,4-adducts and 1,2-adducts of aromatic hydrocarbons with alkenes have extensively been explored, little is known about the photochemical behavior of heteroaromatic-fused barrelenes except pyrazinobarrelenes and benzoquinoxalinobarrelenes. Hence, our attention was focused to elucidate an aspect of the reciprocal valence isomerization of the adducts of 5-FDMU with naphthalene. In the present paper we describe the feature of the mutual conversion of the cycloadducts between 5-FDMU and 1.

RESULTS AND DISCUSSION

Photoisomerization of benzopyrimidobarrelene (2)

First, we examined photochemical behavior of 1,4-adduct (2). Upon UV-irradiation with a high-pressure
mercury lamp ($\lambda > 300$ nm), starting barrelene 2 was recovered unchanged, while irradiation of 2 in cyclohexane for 5 min with 254 nm light from a 60 W low-pressure mercury lamp gave rise to the formation of semibullvalene (4) in fair yields (40%), together with a trace amount of novel dehydrofluorinated semibullvalene derivative (5), and cyclo-reversionary products, 5-FDMU and 1, in 20% yield (Scheme 1).

Time course experiments of the present photolysis with $^1$H-NMR spectroscopy showed that prompt formation of 4 occurred first, while the formation of 5 was barely detectable at the initial stage (Figure 1).

The formation of 4 reached a maximum at 5 min. With the decrease of 4, formation of 5 rose. These results indicate that semibullvalene (4) may be converted to the dehydrofluorinated derivative (5) during the irradiation.

Indeed 4 gave semibullvalene 5 as a major product upon irradiation in cyclohexane with 254 nm light for 30 min (Scheme 2).
Photoisomerization of naphthocyclobutapyrimidine (3)

We then examined the photochemical behavior of 1,2-adduct (3). Direct irradiation of 3 with a high pressure mercury lamp (10 min) only restored the starting materials, 5-FDMU and 1, in high efficiency (63%). By contrast, the UV-irradiation of 3 in the presence of a triplet sensitizer, benzophenone, gave rise to the formation of benzopyrimidobarrelene (2) (10%), in competition with cyclo-reversion to the original 1 and 5-FDMU (55%) (Scheme 3).

The transformation from 1,2-adduct (3) to 1,4-adduct (2) can be explained by a mechanism involving biradical intermediate in the excited triplet state, as proposed by J. Aretz et al.14

Mechanistic studies for the formation of semibullvarene (4) from benzopyrimidobarrelene (2)

The formation of semibullvarene 4 from 2 can be accounted either in terms of di-\(\pi\)-methane rearrangement10 (pathway 1, participating atoms/bonds are denoted as a-b-c-d-e in Scheme 4), or by a mechanism involving a biradical intermediate (pathway 2 in Scheme 4). It would be readily clarified by carrying out the photoreaction with 8,12-dimethylbenzopyrimidobarrelene (6), whereby either 11a-fluoro-4a,10,11-trihydro-2,4,7,10-tetramethyl-5,10,11-metheno-5\(H\)-benzo[5,6]cyclohepta[1,2-\(d\)]pyrimidine-1,3-dione (7) via di-\(\pi\)-methane rearrangement, or 11a-fluoro-4a,10,11-trihydro-2,4,7,10-tetramethyl-5,10,11-metheno-5\(H\)-benzo[5,6]cyclohepta[1,2-\(d\)]pyrimidine-1,3-dione (8) through a biradical intermediate should be produced.
UV-Irradiation of 6 with a low-pressure mercury lamp resulted in the formation of 7 (18%) yield, clearly demonstrating that di-π-methane rearrangement is involved in the present photo-transformation. In this reaction a novel type semibullvalene, 4a-Fluoro-10,11,11a-trihydro-1,3,8,12-tetramethyl-5,10,11-metheno-5H-benzo[4,5]cyclohepta[1,2-d]pyrimidine-1,3-dione (9) was also produced through di-π-methane rearrangement shown in Scheme 5 (participating atoms/bonds are denoted as b-a-f-e-d) (14%). Although methyl groups on barrelene derivative may be influential on radical reactions, these results
exhibit significant participation of di-π-methane rearrangement in the reaction pathway for the formation of 4.

CONCLUSION
The present study clearly demonstrates the reciprocal photochemical valence isomerization of the cycloadducts of 5-FDMU and naphthalene. 1,4-adduct 2 which is intact to a long-wave-length light (λ > 300 nm), is readily converted into benzopyrimidosemibullvalene (4) with a short-wave-length light (λ = 254 nm). By contrast, 1,2-cycloadduct (3) is sensible to the light from a high-pressure mercury lamp (λ > 300 nm), to restore 5-FDMU and naphthalene through cyclo-reversion, whereas UV-irradiation with a high-pressure mercury lamp in the presence of a triplet sensitizer effected valence isomerization of 3 into 2. Thus, 1,2-, 1,3-, and 1,4-cycloadducts of 5-FDMU with naphthalene are shown to be produced mode-selectively.
From the viewpoint of photochemistry of aromatic- and heteroaromatic-fused cycloadducts, it is worthy of note that adducts 2 and 3 photo-isomerize with the fluoride atom remaining intact at the original position, while the photolysis of semibullvalene (4) gives pyrimidine-fused semibullvalene (5) via dehydrofluorination.

EXPERIMENTAL
NMR spectra were measured with a JEOL JNM-EA500 (500 MHz) spectrometer, and 1H-NMR chemical shifts were given on the δ (ppm) scale based on those of the solvent signals. MS spectra and high-resolution MS (HRMS) spectra were recorded with a LEOL JMS-HX110 (FAB). HPLC was conducted on a Shim-pac PREP-Sil (H) (25 cm x 20 mm i.d.) (silica gel), using a LC-10A apparatus (Shimadzu, Kyoto) with monitoring at 254 nm. UV-Irradiation was carried out externally with a 60 W low-pressure lamp (Eiko-sha, Osaka) in a quartz tube under argon (λ = 254 nm) or a 500 W high-pressure mercury lamp (Eiko-sha, Osaka) in a degassed Pyrex tube (λ > 300 nm) on a merry-go-round apparatus. Yields were determined using 1H-NMR spectroscopy with p-dinitrobenzene as an internal standard. Benzopyrimidobarrelene (2) was synthesized by the photoreaction of 5-FDMU and 1 in cyclohexane solution with a high-pressure mercury lamp (λ > 300 nm).6 Naphthocyclobutapyrimidine (3) was prepared by the similar photoreaction of 5-FDMU and 1 in the presence of piperylene.2
Photolysis of 2 in cyclohexane ----- A solution (0.051 mmol) of 2 in cyclohexane (70 mL) was put
portionwise (10 mL each) into 7 quartz tubes, and irradiated externally with a 60 W low-pressure lamp under an argon atmosphere at room temperature. The reaction mixture was concentrated in vacuo, and the residual oil was subjected to HPLC with 30% EtOAc in hexane.

11a-Fluoro-4a,10,11-trihydro-2,4-dimethyl-5,10,11-metheno-5H-benzo[5,6]cyclohepta[1,2-d]pyrimidine-1,3-dione (4): 1H-NMR(methanol-d4) δ:2.47(3H, s, N2-CH3), 2.48(1H, ddd, J= 6.3, 8.0, 18.3Hz, H-11), 2.74 (1H, dd, J= 6.3, 8.0 Hz, H-10), 3.07 (1H, ddd, J= 6.3, 6.3, 6.3 Hz, H-12), 3.14 (3H, s, N4-CH3), 4.07 (1H, ddd, J= 6.3, 6.3, 6.3 Hz, H-12), 4.44 (1H, ddd, J= 6.9, 30.4 Hz, H-4a), 6.85 (1H, d, J= 7.5 Hz, H-6), 7.02 (1H, ddd, J= 1.7, 6.3, 6.9 Hz, H-5), 7.12 (1H, ddd, J= 1.2, 7.5, 7.5 Hz, H-8), 7.22 (1H, d, J=7.5 Hz, H-9). NOE: H-11 with H-10 (19.7%), H-12 (3.6%); H-10 with H-12 (3.9%), H-9 (1.9%); H-12 with H-5 (3.6%), H-10 (2.4%); N4-CH3 with H-4a (2.3%), H-5 (1.3%), H-6 (1.1%); H-5 with H-4a (4.6%), H-6 (2.0%), H-12 (4.3%), N4- CH3 (2.0%). FAB-MS (m/z): [M + H]+ 287. HRFAB-MS (m/z): [M + H]+ Calcd for C16H16FN2O2, 287.1196; Found, 287.1204.

10,11-Dihydro-2,4-dimethyl-5,10,11-metheno-5H-benzo[5,6]cyclohepta[1,2-d]pyrimidine-1,3-dione (5): 1H-NMR(acetone-d6) δ:3.03 (1H, t, J= 6.9Hz, H-11), 3.08 (3H, s, N2-CH3), 3.15 (1H, dd, J= 6.3, 6.9Hz, H-10), 3.44 (1H, ddd, J= 6.3, 6.9, 6.9Hz, H-12), 3.58 (3H, s, N4-CH3), 4.71 (1H, d, J= 6.9 Hz, H-5), 7.11 (1H, dt, J= 1.2,7.5 Hz, H-7), 7.18 (1H, dt, J= 1.2, 7.5 Hz, H-8), 7.38 (1H, d, J= 7.5Hz, H-6), 7.40 (1H, d, J= 7.5Hz, H-9). NOE: H-11 with H-10 (1.0%), H-12 (1.8%). FAB-MS (m/z): [M + H]+ 267. HRFAB-MS (m/z): [M + H]+ Calcd for C16H15N2O2, 267.1133; Found, 267.1129.

**Photolysis of 4 in cyclohexane** ----- A solution (0.034 mmol) of 4 in cyclohexane (70 mL) was UV irradiated under the same conditions described above to afford 5 (28%) together with unreacted 4 (37%).

**Photolysis of 6 in cyclohexane** ----- A solution (0.027 mmol) of 2 in cyclohexane (50 mL) was put portionwise (10 mL each) into 5 quartz tubes, and irradiated externally with a 60 W low-pressure lamp under an argon atmosphere for 5 min at room temperature. The reaction mixture was concentrated in vacuo, and the residual oil was subjected to HPLC with 1% EtOAc in CH2Cl2 to give 7(18%) and 9 (14%), together with unreacted 6 (26%).

11a-Fluoro-4a,10,11-trihydro-2,4,7,10-tetramethyl-5,10,11-metheno-5H-benzo[5,6]cyclohepta[1,2-d]pyrimidine-1,3-dione (7): 1H-NMR(CDCl3) δ:1.54 (3H, s, C10-CH3), 2.25 (3H, s, C7-CH3), 2.38 (1H, dd, J= 6.3, 18.9Hz, H-11), 2.53 (3H, s, N2-CH3), 2.72 (1H, dd, J= 5.2, 6.3 Hz, H-12), 3.14 (3H, s, N4-CH3), 3.87(1H, dd, J= 5.2, 6.3 Hz, H-5), 4.16 (1H, dd, J= 6.3, 29.8 Hz, H-4a), 6.60 (1H, s, H-6), 6.98 (1H, d, J= 7.5 Hz, H-8), 7.08 (1H, d, J= 8.0Hz, H-9). NOE: C10-CH3 with H-11(1.6%), H-12 (1.0%), H-9 (1.4%);
H-4a with N^4-CH_3 (5.3%), H-5 (6.3%), H-12 (1.3%); H-5 with H-12 (5.6%), N^4-CH_3(2.8%), H-4a (7.1%), H-6 (3.1%); N^4-CH_3 with H-5 (1.4%), H-4a (2.4%), H-6 (1.6%). FAB-MS (m/z): [M + H]^+ 315. HRFAB-MS (m/z): [M + H]^+ Calcd for C_{18}H_{20}FN_2O_2, 315.1508; Found, 315.1510.

4a-Fluoro-10,11,11a-trihydro-1,3,8,12-tetramethyl-5,10,11-metheno-5H-benzo[4,5]cyclohepta[1,2-d]-pyrimidine-1,3-dione (9): ^1H-NMR(CDCl_3) δ : 1.67 (3H, s, C_{12}-CH_3), 2.13 (1H, dd, J= 6.3, 7.5 Hz, H-11) 2.26 (3H, s, C_{8}-CH_3), 2.41 (1H, d, J=7.5 Hz, H-10), 2.74 (3H, s, N^1-CH_3), 2.95 (3H, s, N^3-CH_3), 3.81(1H, dd, J= 2.9, 12.6 Hz, H-5), 4.28 (1H, ddd, J= 2.9, 6.3, 26.9 Hz, H-11a), 6.68 (1H, d, J= 7.5Hz, H-6), 6.81(1H, d, J=7.5Hz, H-7), 7.04 (1H, s, H-9). NOE: C_{12}-CH_3 with H -11 (1.6%), H-10 (1.6%), H-5 (2.3%); H-11 with C_{12}-CH_3 (2.4%), H-10 (7.3%), N^1-CH_3(2.8%), H-11a (8.8%); C_{8}-CH_3 with H-7 (2.1%), H-9 (2.2%); H-10 with C_{12}-CH_3(1.6%), H-11(7.3%), N^1-CH_3 (1.2%), H-9 (3.7%); H-5 with C_{12}-CH_3 (2.4%), H-6 (3.2%); H-11a with H-11(7.4%), N^1-CH_3 (3.5%); H-6 with N^3-CH_3(1.6%), H-5 (3.9%), H-7 (7.7%); H-9 with C_{8}-CH_3 (4.6%), H-10 (3.8%), N^1-CH_3 (1.4%). FAB-MS (m/z): [M + H]^+ 315. HRFAB-MS (m/z): [M + H]^+ Calcd for C_{18}H_{20}FN_2O_2, 315.1508; Found, 315.1512.

Photosensitization of 3 ----- An acetonitrile solution of 3 (0.025 M) was irradiated in the presence of benzophenone (0. 83 M) with a 500 W high-pressure mercury lamp in a degassed Pyrex tube to give 2 (10%) together with 5-FDMU (55%).

REFERENCES


