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THERMODYNAMICALLY CONTROLLED PHOTOCYCLOADDITION OF 5-FLUORO-1,3-DIMETHYLURACIL TO NAPHTHALENES

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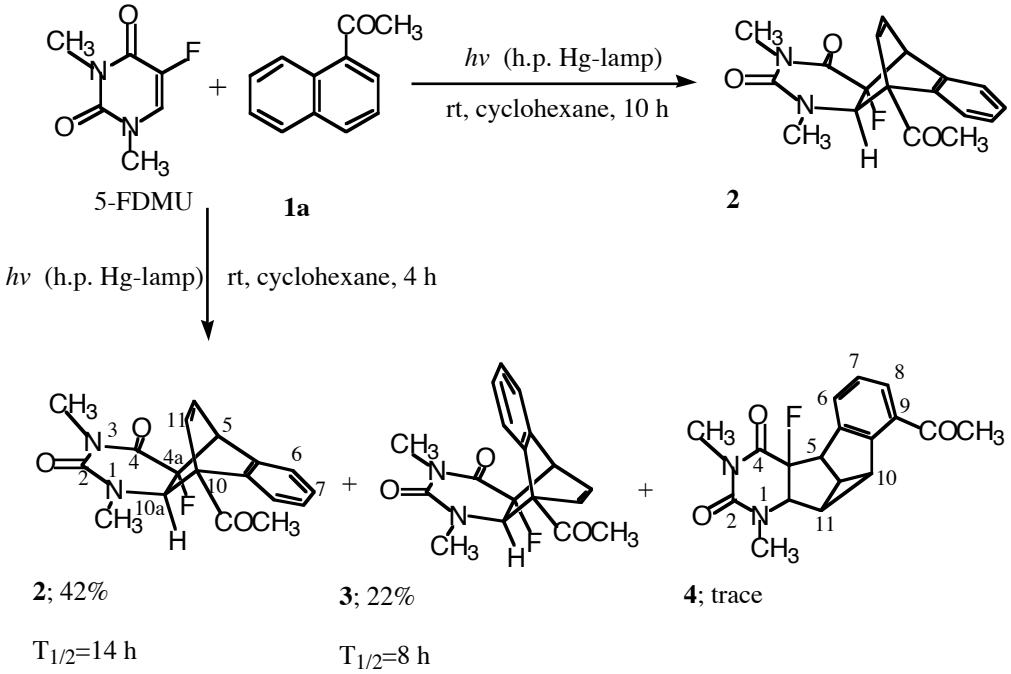
Abstract — UV-Irradiation of 5-fluoro-1,3-dimethyluracil (5-FDMU) and 1-acetonaphthone (**1a**) afforded *trans*-1,4-adduct, ethenobenzoquinazoline, (**2**) having an acetyl group at the C-10 bridgehead carbon, together with the *cis*-isomer (**3**). The *cis*-adduct (**3**) is more fragile than **2** in the dark at ambient temperature, and is more quickly converted back to the starting **1a** and 5-FDMU through cycloreversion. Thus, the *trans*-adduct (**2**) comes to the predominant product when irradiation is prolonged. Similar irradiation of 1-naphthonitrile afforded *cis*-ethenobenzoquinazoline-10-carbonitrile (**6**) and the *trans*-isomer (**7**) as the kinetically controlled cycloadducts together with *cis*-ethenobenzoquinazoline with a CN group on the benzene moiety (**5**) as thermodynamically controlled product.

Photocycloaddition reactions involving aromatic and heteroaromatic compounds have been recognized to give rise to the formation of a variety of complicated unique ring systems in one step, and hence these reactions have been studied extensively from both the synthetic and mechanistic point of view.[1] In the course of our continuing studies on the photochemical modification of the pyrimidine ring,[2] we have recently reported that UV-irradiation of a solution of 5-fluoro-1,3-dimethyluracil (5-FDMU) and naphthalene in protic media effected a substitution reaction to afford 5-(1-naphthyl)uracil as the major product. By contrast, when the solution was irradiated in aprotic media, 1,4-cycloaddition proceeded stereoselectively to give a *cis* -ethenobenzoquinazoline derivative in high yield.[3]

In an attempt to develop new aspects of this photocycloaddition, we have intended to apply the present photoreaction to reaction with naphthalenes having an electron-withdrawing group at C-1.[4] In the

present paper, we wish to report our findings that the photoreaction of 5-FDMU and 1-acetonaphthone (**1a**) provides the thermodynamically controlled adduct, *trans*-ethenobenzoquinazoline-2,4-dione(**2**).

A solution of 5-FDMU and 1-acetonaphthone (**1a**) in cyclohexane, when irradiated externally with a 500 W high-pressure mercury lamp in a degassed Pyrex tube (λ>300 nm) for 4 h, gave a *trans*-barrelene (10-acetyl-*trans*-ethenobenzoquinazoline, **2**) in 42% yield, wherein the ethylene bridge stands *trans* to the



Yields; based on 5-FDMU (40%) consumed.

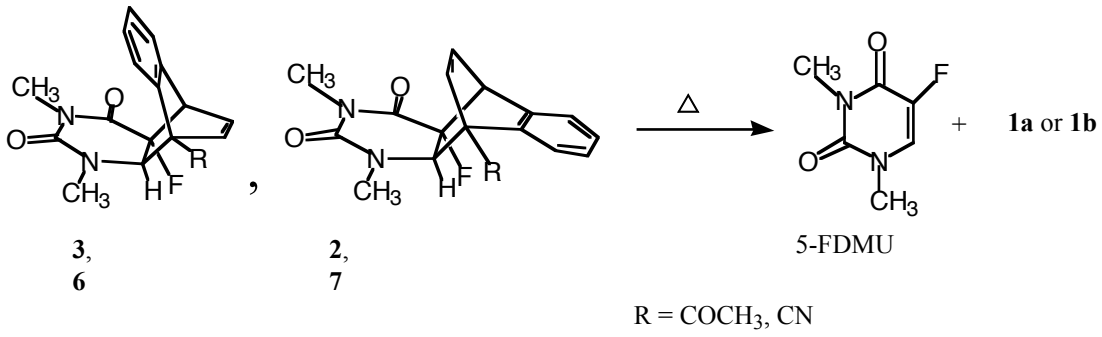
Scheme 1

corresponding 10a-H and 4a-F, as the major product and *cis*-isomer (**3**) in 22% yield as a minor product, together with a trace amount of a novel cycloadduct, 9-acetyl-1,3-dimethyl-5,6,11-methenobenzo[4,5]cyclohepta[2,1-*d*]pyrimidine-2,4-dione (**4**) (Scheme 1).

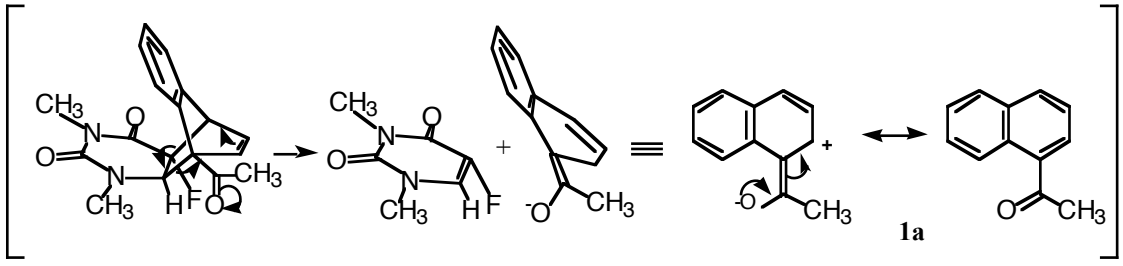
The stereochemistry of **2** was determined with the aid of NOE experiments. Irradiation of the H-10a proton significantly affected the H-9 aromatic proton (1.4%), as well as H-10 and N1-CH_3 (8.4%), indicating that the stereochemistry of **2** is *trans*, while stereoisomer (**3**) showed significant enhancement of signals at vinylic proton H-11 (1.0%), N1-CH_3 (7.6%), and C10-$COCH_3$ (2.8%) on irradiation of the H-10a proton, thus supporting the stereochemistry of **3** to be *cis*.

It is important to note that both of the adducts (**2** and **3**) bearing an acetyl group at the bridge-head, are fragile in the dark at ambient temperature, and are converted back to the starting **1a** and 5-FDMU through cycloreversion (Scheme 2). In addition, the half-life of **2** at 20°C is longer (14 h) than that of **3**

(8 h). This disparity between their thermolabilities should be responsible for the formation of the novel *trans*-isomer (**2**)[5] through a photochromic process. That is, the initially produced *cis*-isomer (**3**) as the kinetically controlled product, undergoes cycloreversion to the starting materials during irradiation, which are again subjected to cycloaddition, leading to the accumulation of the more stable component (**2**) in the reaction mixture. Short period-irradiation (1 h) of the reaction mixture produced approximately equal amounts of **2** and **3** with large amounts of unchanged 5-FDMU and **1a** (>90%), while prolonged irradiation (10 h) exclusively furnished the thermodynamically controlled *trans*-isomer (**2**) (Scheme 1), rationalizing the above explanation.



3, **6** , **2**, **7**



1a

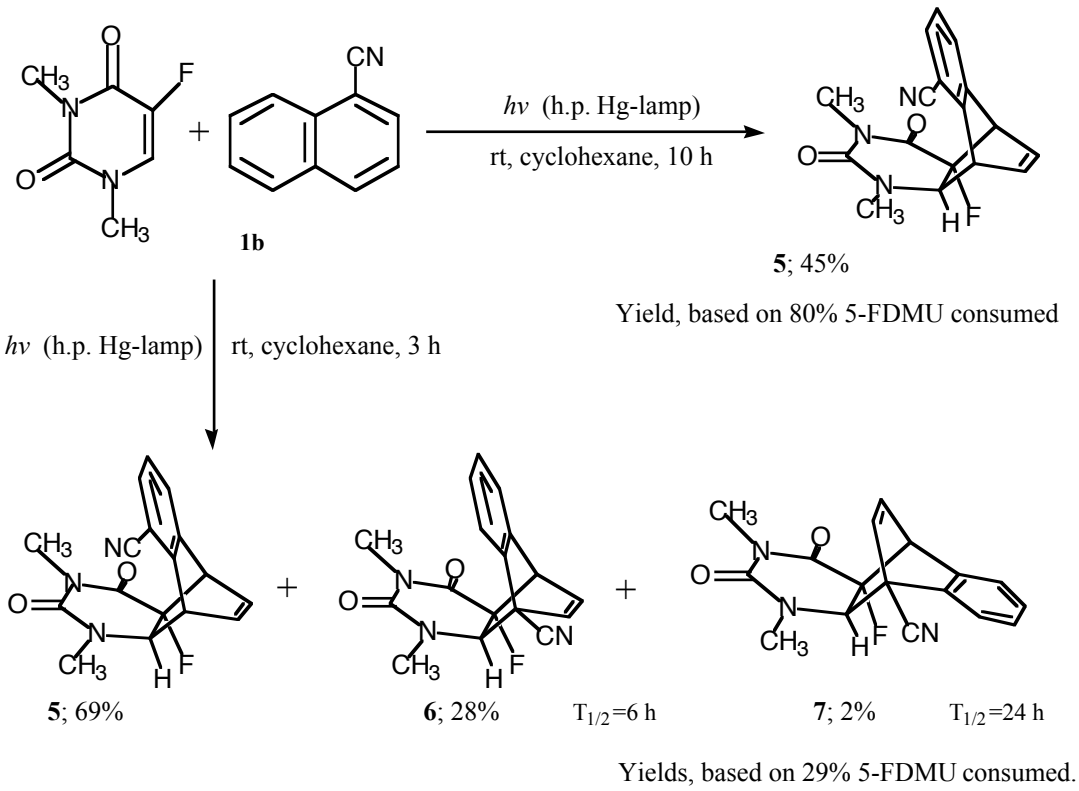
Scheme 2

MO calculations[6] showed that the heat of formation of the *trans*-isomer (-61.5 kcal) is lower than that of the *cis*-isomer (-31.5 kcal) by 30 kcal, suggesting that the *cis*-isomer is the kinetically controlled product, while the *trans*-isomer can be regarded as a thermodynamically controlled product.

Similar irradiation of a mixture of 5-FDMU and 1-naphthonitrile (**1b**) in cyclohexane for 3 h furnished *cis*-ethenobenzoquinazoline-9-carbonitrile (**5**) (69% yield), *cis*-ethenobenzoquinazoline-10-carbonitrile (**6**) (28% yield), and the *trans* isomer (**7**) *albeit* in low yield (2% yield) (Scheme 3). The adduct (**5**) is stable at room temperature, while the adducts having a CN group at the bridgehead are thermochemically unstable (Scheme 2). As expected, the half-life of **6** is appreciably shorter than that of

the *trans* isomer (**7**).

Prolonged irradiation (10 h), however, resulted in the formation of **5** as the major product (45 %), and the formation of **6** and **7** was not detected (Scheme 3). Presumably, the present reaction proceeded with less regioselectivity than with **1a**, resulting in the formation of thermally stable isomer (**5**), together with variable amounts of **6** and **7**. During prolonged irradiation times, **6** and **7** would presumably be converted into the stable **5** through cycloreversion.



Scheme 3

Thus, the present study provides the first synthesis of a *trans*-ethenobenzo[*f*]quinazoline derivative by introducing an acetyl group onto the naphthalene ring at the C-1 position.

EXPERIMENTAL

NMR spectra were measured with a JEOL JNM-EX400 (400 MHz) spectrometer, and ^{1}H-NMR chemical shifts are given on the δ (ppm) scale based on those of the signals of solvents; $CDCl_3$ (δ 7.26), C_6D_6 (δ 7.15). MS spectra and high-resolution MS (HRMS) spectra were recorded with 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-6A apparatus (Shimadzu, Kyoto) with monitoring at 254 nm. UV-Irradiation was carried out externally with a 500 W high-pressure mercury

(h. p. Hg) lamp (Eiko-sha, Osaka) in a degassed Pyrex tube (> 300 nm) on a merry-go-round apparatus. Yields are determined by means of ^{1}H-NMR spectroscopy with terephthalonitrile as an internal standard.

Photoreaction of 5-FDMU with naphthalenes (1a, 1b)----- An equivalent molar solution (1.5 mM) of 5-FDMU and a naphthalene in cyclohexane (160 mL) was put portion-wise (5 mL each) into 32 degassed Pyrex tubes, and irradiated externally at rt. The reaction mixture was concentrated *in vacuo*, and the residual oil was submitted to HPLC with 25% ethyl acetate in hexane.

10-Acetyl-4a-fluoro-4a,5,10,10a-tetrahydro-1,3-dimethyl-*trans*-5,10-ethenobenzo[*f*]quinazoline-2,4-dione (2): Colorless crystals; mp, not determined (decomposed at 20°C with a half-life of 14 h). ^{1}H-NMR ($CDCl_3$) □: 2.53 (3H, s, C^{10}-$COCH_3$), 2.93 (3H, s, N^1-CH_3), 3.11 (3H, d, *J*=0.5 Hz, N^3-CH_3), 3.86 (1H, d, *J*=28.9 Hz, H-10a), 4.57 (1H, br t, *J*=5.5, 6.4 Hz, H-5), 6.51 (1H, dd, *J*=7.9, 6.4 Hz, H-12), 6.90 (1H, d, *J*=7.9 Hz, H-11), 6.98 (1H, d, *J*=7.5 Hz, H-9),7.15~7.25 (2H, m, H-7-H-8), 7.37 (1H, d, *J*=7.7 Hz, H-6). NOE: H-10a with N^1-CH_3 (8.4%), H-9 (1.4%). FABMS *m/z* (%): 329 $(M+H)^+$, 309, 159. HRFABMS: Calcd for $C_{18}H_{18}N_2O_3F$: 329.1301. Found: 329.1311.

10-Acetyl-4a-fluoro-4a,5,10,10a-tetrahydro-1,3-dimethyl-*cis*-5,10-ethenobenzo[*f*]quinazoline-2,4-dione (3): Colorless crystals; mp, not determined (decomposed at 20°C with a half-life of 8 h). ^{1}H-NMR ($CDCl_3$) □: 2.60 (3H, s, N^4-CH_3), 2.61 (3H, s, C^{10}-$COCH_3$), 3.01 (3H, s, N^1-CH_3), 4.02 (1H, d, *J* =29.2 Hz, H-10a), 4.55 (1H, t, *J* =1.6, 6.0 Hz, H-5), 6.62 (1H, dd, *J* =1.6, 8.0 Hz, H-11), 6.86 (1H, dd, *J* =6.0, 8.0 Hz, H-12), 7.18 (1H, d, *J* =7.0 Hz, H-6), 7.20-7.28 (2H, m, H-7, H-8), 7.86 (1H, d, *J* =7.0 Hz, H-9). NOE: H-5 with H-6 (7.3%), H-12 (7.5%); H-10a with N^1-CH_3 (7.6%), C^{10}-$COCH_3$ (2.8%), H-11 (1.0%); C^{10}-$COCH_3$ with H-10a (7.4%), N^1-CH_3 (2.3%); H-12 with H-5 (10%), H-11 (6.3%); H-11 with C^{10}-$COCH_3$ (9.6%), H-12 (13.1%).

9-Acetyl-4a-fluoro-4a,10,11,11a-tetrahydro-5,10,11-metheno-1,3-dimethylbenzo[4,5]cyclohepta[1,2-*d*]pyrimidine-2,4-dione (4): Colorless prisms; mp 190-192°C. ^{1}H-NMR ($CDCl_3$) □: 2.61 (3H, s, C^9-$COCH_3$), 2.61 (1H, ddd, *J* =8.1, 6.0, 6.0 Hz, H-11), 2.75 (3H, s, N^1-CH_3), 2.95 (3H, s, N^3-CH_3), 3.40 (1H, ddd, *J* =6.6, 6.0, 5.1 Hz, H-12), 3.51 (1H, dd, *J* =8.1, 6.0 Hz, H-10), 4.11 (1H, ddd, *J* =11.8, 5.1, 2.9 Hz, H-5), 4.29 (1H, ddd, *J* =27.0, 6.0, 2.9 Hz, H-11a), 6.99 (1H, d, *J* =7.7 Hz, H-6), 7.14 (1H, t, *J* =7.7 Hz, H-8), 7.68 (1H, d, *J* =7.7 Hz, H-8). NOE: H-5 with H-6 (2.4%), H-12 (2.9%); H-6 with H-5 (1.5%), H-7 (9.0%): H-8 with H-7 (4.4%), C^9-$COCH_3$ (6.8%); H-10 with H-11 (7.6%) (9.6%), H-12 (3.3%): H-11 with H-10 (7.3%), H-11a (7.7%), H-12 (3.4%), N^1-CH_3 (2.1%): H-12 with H-5 (4.3%), H-10 (2.7%), H-11 (2.3%). FABMS *m/z* (%): 329 $(M+H)^+$. HRFABMS: Calcd for $C_{18}H_{18}N_2O_3F$: 329.1301. Found: 329.1309.

4a-Fluoro-4a,5,10,10a-tetrahydro-1,3-dimethyl-2,4-dioxo-*cis*-5,10-ethenobenzo[*f*]quinazoline-9-carbonitrile (5): Colorless prisms; mp 156-158°C. ^{1}H-NMR (C_6D_6) □: 2.26 (3H, d, *J*=0.7 Hz, N^3-CH_3), 2.75 (3H, s, N^1-CH_3), 3.01 (1H, dd, *J*=31.5, 2.6 Hz, H-10a), 4.28 (1H, ddd, *J*=6.4, 2.6, 1.2 Hz, H-10), 4.49 (1H, ddd, *J*=6.6, 6.0, 1.3 Hz, H-5), 5.95 (1H, ddd, *J*=7.4, 6.6, 1.2 Hz, H-11), 6.12 (1H, ddd, *J*=7.4, 6.4, 1.3 Hz, H-12), 6.32 (1H, t like, *J*=7.5, 7.8 Hz, H-7), 6.59 (1H, dd, *J*=7.8, 1.1 Hz, H-8), 6.67 (1H, dd, *J*=7.5, 1.1 Hz, H-6). NOE: H-10a with H-10

(7.0%), N^1-CH_3 (5.2%), H-11 (1.7%), H-12; H-11 with H-12 (6.1%), H-10 (7.3%), H-10a (1.9%). FABMS *m/z* (%): 312 $(M + H)^+$, 159. HRFABMS: Calcd for $C_{17}H_{15}N_2O_3F$: 312.1148. Found: 312.1119.

4a-Fluoro-4a,5,10,10a-tetrahydro-1,3-dimethy-2,4-dioxo-*cis*-5,10-ethenobenzo[*f*]quinazoline-10-carbonitrile (6): Colorless crystals; mp, not determined (decomposed at 20°C with a half-life of 6 h). ^{1}H-NMR ($CDCl_3$) □: 2.66 (3H, s, N^1-CH_3), 3.41 (3H, s, N^3-CH_3), 4.01 (1H, d, *J* =28.8 Hz, H-10a), 4.69 (1H, dt, *J* =1.6, 6.0 Hz, H-5), 6.78 (1H, dd, *J* =1.6, 7.6 Hz, H-11), 6.82 (1H, dd, *J* =6.0, 7.6 Hz, H-12), 7.24 (1H, dd, *J* =1.0, 7.5 Hz, H-6), 7.30 (1H, dt, *J* =1.0, 7.5 Hz, H-8), 7.35 (1H, dt, *J* =1.0, 7.5 Hz, H-7), 7.66 (1H, d, *J* =7.5 Hz, H-9). NOE: H-10a with N^1-CH_3 (9.1%), H-11 (5.5%), H-12 (1.0%); H-5 with H-6 (10.4%), H-12 (12.2%).

4a-Fluoro-4a,5,10,10a-tetrahydro-1,3-dimethy-2,4-dioxo-*trans*-5,10-ethenobenzo[*f*]quinazoline-10-carbonitrile (7): Colorless crystals; mp, not determined (decomposed at 20°C with a half-life of 24 h). ^{1}H-NMR ($CDCl_3$) □: 3.20 (3H, s, N^3-CH_3), 3.45 (3H, s, N^1-CH_3), 3.67 (1H, d, *J* =28.4 Hz, H-10a), 4.76 (1H, t, *J* =6.8 Hz, H-5), 6.56 (1H, dd, *J* =6.8, 7.2 Hz, H-12), 6.65 (1H, d, *J* =7.2 Hz, H-11), 7.35-7.45 (2H, m, H-7, H-8), 7.48 (1H, dd, *J* =12, 7.2 Hz, H-6), 7.7 (1H, d, *J* =7.4 Hz, H-9). NOE: H-5 with H-12 (10.6%), H-6 (9.1%); H-10a with N^1-CH_3 (8.9%); H-11 with H-12 (5.6%); N^1-CH_3 with H-10a (6.1%). FABMS *m/z* (%): 312 $(M + H)^+$. HRFABMS: Calcd for $C_{17}H_{15}N_2O_3F$: 312.1148. Found: 312.1159.

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5. Previously we have reported that photoreaction with 5-FDMU and naphthalene and its 2-substituted derivatives stereospecifically gave *cis*-ethenobenzoquinazolines in fair yields.[3]
6. MO calculation was performed by the AM1 method with MOPAC on CAChe Work-system (Release 3.7; Cache Scientific, Inc.).