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PHOTOCHEMISTRY OF 9,10-DIHYDRO-1,3,5,7-TETRAMETHYL-9-METHYLENECYLOOCTAPYRIMIDINE-2,4-DIONE: SYNTHESIS OF NOVEL RING SYSTEMS THROUGH ELECTROCYCLIC REACTIONS [1]

Kazue Ohkura, Ken-ichi Nishijima, Akiyo Sakushima, and Koh-ichi Seki*
Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan

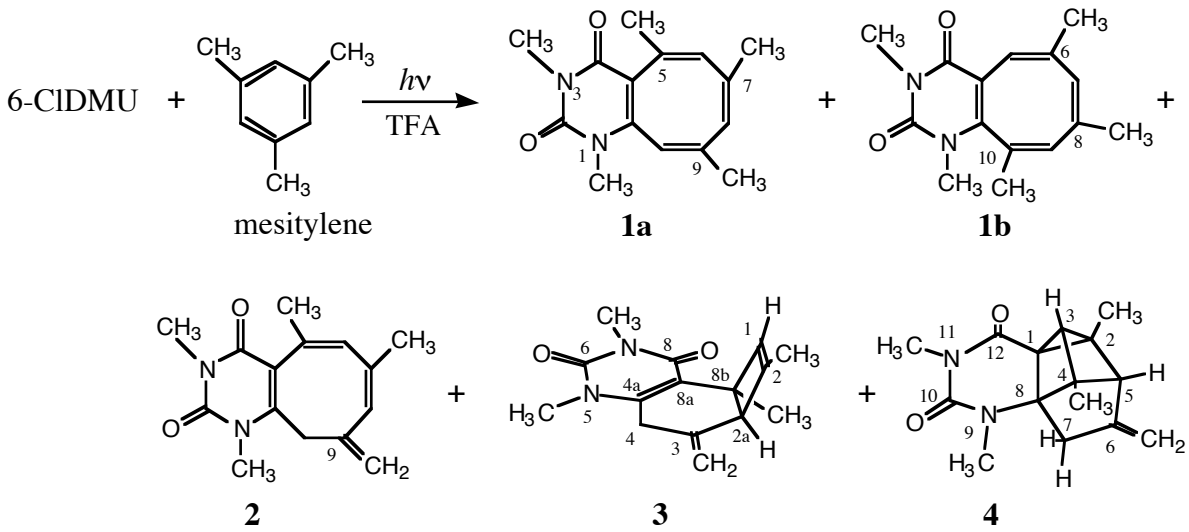
Abstract - Photolysis of 1,3,5,7,9-pentamethylcyclooctapyrimidine-2,4-dione (**1a**) prepared by the photoreaction of 6-chloro-1,3-dimethyluracil with mesitylene in the presence of TFA at low temperature resulted in the formation of the 9-*exo*-methylene derivative (**2**), which was further converted into a novel cyclopropa-pentalenopyrimidine (**5**) and a cyclobutaquinazoline (**3**) through [4 + 2] and [2 + 2] electrocyclic reactions, respectively. The latter (**3**) was ultimately transformed into the 9,11-diazapentacyclo[6.4.0.0^{1,3}.0^{2,5}.0^{4,8}]dodecane-2,4-dione derivative (**4**).

During the course of our studies on the acid-catalyzed photoreaction of pyrimidine bases with substituted benzenes, we have reported that photolysis of 6-chloro-1,3-dimethyluracil (6-ClDMU) in benzene[2] and substituted benzenes[3] in the presence of trifluoroacetic acid (TFA) effected *ortho*-cycloaddition to give cyclooctapyrimidine-2,4-diones in fair yields. Similar photoreaction with *p*- and *m*-xylenes gave rise to the formation of 9,11-diazapentacyclododecanes consisting of a [6.4.0^{1,3}.0^{2,5}.0^{4,8}] system and a [6.4.0^{1,3}.0^{2,6}.0^{4,8}] system, as well as cyclooctapyrimidines.[4] In order to explore the general feature of this photoreaction, we have extended our work to mesitylene.

In the present paper, we describe our findings that the photoreaction gave various cycloadducts, including a pentacyclo[6.4.0^{1,3}.0^{2,5}.0^{4,8}]dodecane analogue (**4**) and a novel tetracyclic compound (**5**). In addition, these cycloadducts were found to be led from the initially produced 9-methylcyclooctapyrimidine derivative (**1a**), by way of the successive photochemical transformation, wherein 9-methylene-cyclooctapyrimidine (**2**) would play a key role.

One-hour irradiation[5] of 6-ClDMU in mesitylene in the presence of TFA[6] yielded a complex mixture of products. After separation by HPLC, the following cycloadducts were obtained, together with recovered

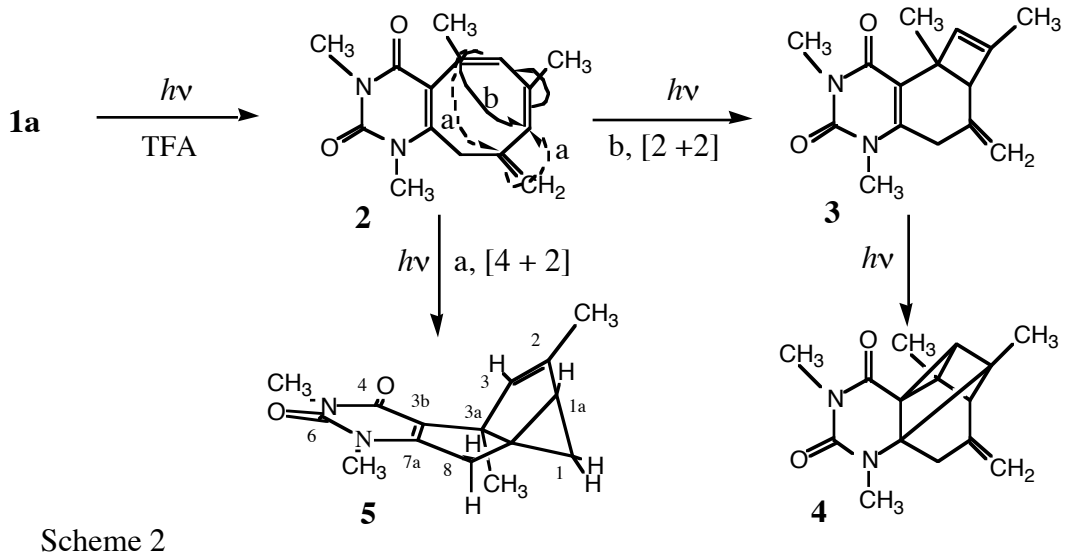
6-ClDMU (91 %); 9-methyl cyclooctapyrimidine (**1a**)[7] (0.3 %), the 10-methyl derivative (**1b**)[8] (5.3 %), the 9-methylene derivative (**2**)[9] (1.3 %), cyclobutaquinazoline (**3**)[10] (0.4 %), and pentacyclododecane (**4**)[11] (0.3 %) (Scheme 1).



Scheme 1

From the substituted position of the methylene group, it is supposed that **2**, **3**, and **4** may be derived from **1a**, while **1b** is unsusceptible to the photoisomerization under the present conditions. In fact, when the reaction was performed under prolonged irradiation (3 h), the yield of **1b** increased (7.2 %), while that of **1a** was not increased (0.2 %). Instead, a novel cycloadduct (**5**)[12] consisting of a cyclopropapentalene system was obtained (0.3 %), together with **2**, **3**, and **4** in increased yields (2.2, 0.6, and 0.4 %) (recovered 6-ClDMU, 83.2%). In order to obtain more insight into the reaction mechanism, the present photoreaction was carried out at low temperature (-25°C for 5 h), to give **1a** (19.4 %) and **1b** (34.1 %) in fair yields. Irradiation of **1a** in the presence of TFA at room temperature for 1 h afforded **2** quantitatively. Subsequent irradiation of **2** in benzene-d_6 in an NMR tube at room temperature for 30 min effected the cyclization to give **3** (26 %) and **5** (9 %) together with unreacted **2** (65 %) (NMR yields). Successive irradiation (90 min) of the resulting mixture gave rise to the formation of **4** (22% yield), as well as **5** in increased yield (65 %) (NMR yields), whereas the yield of **3** was reduced into 13%. These findings support the above basis that **3**, **4**, and **5** are the products from the common precursor (**2**). Photo-excitation of **2** effects the rearrangement into either cyclobuta[*f*]quinazoline (**3**) *via* the [2 + 2] electrocyclic reaction, or tetracyclic derivative (**5**) through the [4 + 2] process (Scheme2). The former is responsible for the formation of **4** through the second [2 + 2] combination. Presumably the present [4 + 2] process may be regarded as analogous to that found in the photo-transformation of vitamin D_3 into suprasterol I[13] and II.[14] Thus, the present work provides the synthesis of a tetracyclic compound consisting of a novel ring

system (**5**) through an uncommon [4 + 2] electrocyclic reaction.[15] In addition, the reaction pathway leading to the 9,11-diazapentacyclo-[6.4.0^{1,3}.0^{2,5}.0^{4,8}]dodecane derivative (**4**) was clearly demonstrated.



Scheme 2

REFERENCES

1. Presented at the 17th International Congress of Heterocyclic Chemistry, Vienna, Austria, August 1999.
2. K. Seki, N. Kanazashi, and K. Ohkura, *Heterocycles*, 1991, **32**, 229.
3. K. Ohkura, N. Kanazashi, and K. Seki, *Chem. Pharm. Bull.*, 1993, **41**, 239.
4. K. Ohkura, K. Seki, H. Hiramatsu, K. Aoe, and M. Terashima, *Heterocycles*, 1997, **44**, 467.
5. UV-Irradiation was carried out externally with a 500 W high-pressure mercury (h.p.Hg) lamp (Eiko-sha) in a degassed Pyrex tube at room temperature (20 ± 5 °C).
6. Spectroscopic studies on the effects of the added TFA to 6-ClDMU have been reported; see ref. 3 and 4.
7. 1,3,5,7,9-Pentamethylcyclooctapyrimidine-2,4-dione (**1a**): mp 113-114 °C. ^{1}H-NMR (C_6D_6) δ: 1.47 (3H, s, C9-CH_3), 1.59 (3H, s, C7-CH_3), 2.19 (3H, s, C5-CH_3), 2.79 (3H, s, N1-CH_3), 3.24 (3H, s, N3-CH_3), 5.19 (1H, *br* s, H-10), 5.33 (1H, *br* s, H-8), 5.67 (1H, *br* s, H-6). MS *m/z* (%): 258 (M^+, 100), 243 (61). HRMS*:* Calcd for $C_{15}H_{18}N_2O_2$: 258.1368. Found: 258.1369.
8. 1,3,6,8,10-Pentamethylcyclooctapyrimidine-2,4-dione (**1b**): mp 123-125 °C (recrystallized from 2-propanol). ^{1}H-NMR (acetone-d_6) δ: 1.77 (3H, dd, *J* = 0.7, 1.5 Hz, C6-CH_3), 1.80 (3H, dd, *J* = 0.7, 1.5 Hz, C8-CH_3), 1.93 (3H, d, *J* = 1.5 Hz, C10-CH_3), 3.20 (3H, s, N3-CH_3), 3.27 (3H, s, N1-CH_3), 5.63 (1H, *br* s, H-7), 5.92 (1H, q, *J* = 1.5 Hz, H-5), 6.05 (1H, *br* s, H-9). MS *m/z* (%): 258 (M^+, 100), 243 (49). HRMS; Calcd for $C_{15}H_{18}N_2O_2$: 258.1368. Found: 258.1357.
9. 9,10-Dihydro-1,2,5,7-tetramethyl-9-methylenecyclooctapyrimidine-2,4-dione (**2**): mp 142-144 °C (re-crystallized from 2-propanol). ^{1}H-NMR ($CDCl_3$) δ: 1.79 (3H, s, C7-CH_3), 2.09(3H, s, C5-CH_3), 3.27 (1H, d, *J* = 13.6 Hz, H10-a), 3.34 (3H, s, N3-CH_3), 3.54 (3H, s, N1-CH_3), 4.05 (1H, d, *J* = 13.6Hz, H10-b), 5.00 (1H, s, C9=CHa), 5.10 (1H, s, C9=CHb), 5.82 (1H, s, H-6), 6.00 (1H, s, H-8). MS *m/z* (%): 258 (M^+, 100), 243 (77). HRMS: Calcd for $C_{15}H_{18}N_2O_2$: 258.1368. Found: 258.1368.

10. 2a,3,4,8b-Tetrahydro-2,5,7,8b-tetramethyl-3-methylenecyclobuta[*f*]quinazoline-6,8-dione (**3**): Colorless oil. ^{1}H-NMR (C_6D_6) δ: 1.56 (3H, t -like, C2-CH_3), 1.76 (3H, s, C8b-CH_3), 2.45 (1H, d, *J* = 20.0 Hz, H4-b), 2.53 (1H, d, *J* = 20.0 Hz, H4-a), 2.59 (3H, s, N5-CH_3), 2.64 (1H, *br* s, H-2a), 3.30 (3H, s, N11-CH_3), 4.67 (1H, *br* s, C6=CHb), 4.82 (1H, *br* s, C6=CHa), 6.44 (1H, *br* s, H-3). MS *m*/*z* (%): 258 (M^+, 92), 243 (90), 91 (100).
11. 2,4,9,11-Tetramethyl-6-methylene-9,11-diazapentacyclo[6.4.0^{1,3}.0^{2,5}.0^{4,8}]dodecane-10,12-dione (**4**): mp 109-111 °C (recrystallized from ether). ^{1}H-NMR (C_6D_6) δ: 0.56 (3H, s, C4-CH_3), 1.62 (3H, s, C2-CH_3), 1.89 (1H, dt, *J* = 2.2, 17.0 Hz, H-7a), 2.00 (1H, dt, *J* = 2.55, 17.0 Hz, H-7b), 2.46 (1H, s, H-5), 2.59 (3H, s, N9-CH_3), 2.64 (1H, s, H-3), 3.33 (3H, s, N11-CH_3), 4.62 (1H, *br* s, C6=CHa), 4.75 (1H, *br* s, C6=CHb). MS *m*/*z* (%): 258 (M^+, 28), 243 (100). HRMS*:* Calcd for $C_{15}H_{18}N_2O_2$: 258.1368. Found: 258.1346.
12. 1a,2,3,3a,8,8a-Hexahydro-2,3a,5,7-tetramethyl-1*H*-cyclopropa[6,6a]pentaleno[2.3-*d*]pyrimidine-4,6-dione (**5**): Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.58 (1H, t-like, *J* = 3.5 Hz, H1-b), 1.05 (1H, dd, *J* = 4.9, 7.9 Hz, H1-a), 1.24 (3H, s, 3a-CH_3), 1.48 (1H, dd, *J* = 3.5, 7.9 Hz, H-1a), 1.73 (3H, d, *J* = 1.5 Hz, 2-CH_3), 2.60 (1H, d, *J* = 17.2 Hz, 8H-b), 3.27 (1H, d, *J* = 17.2 Hz, 8H-a), 3.33 (1H, s, 5-CH_3), 3.34 (3H, s, 7-CH_3), 5.41 (1H, *br* s, H-3). HRMS: Calcd for $C_{15}H_{18}N_2O_2$: 258.1368. Found: 258.1367.

13. W. G. Dauben, I. Bell, T. W. Hutton, G. F. Law, A. Rheiner Jr., and H. Urscheler, *J. Am. Chem. Soc*., 1958, **80**, 4116.
14. W. G. Dauben and B. Baumann, *Tetrahedron Lett*., **1961**, 565; C. P. Saunderson and D. C. Hodgkin, *ibid*., **1961**, 573.
15. Les Règles,"De Woodward Hoffmann", ed. by N. T. Anh, Ediscience S. A., Paris, 1970. Japanese edition, translated by I. Mita, Tokyo Kagaku Dojin Inc., Tokyo, 1975, Chap. 7.