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PHOTOCHEMICAL SYNTHESIS AND CHARACTERIZATION OF THE TAUTOMERS OF 1,3,5,7,9- AND 1,3,6,8,10-PENTAMETHYLCYCLOOCTAPYRIMIDINE-2,4-DIONES

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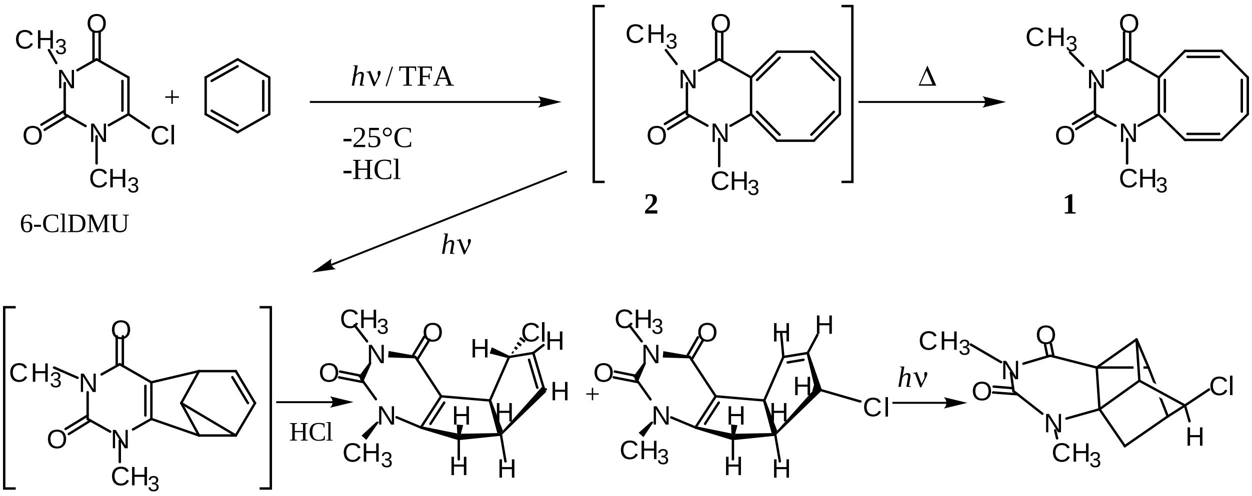
Abstract—UV-irradiation of 1,3,6,8,10- and 1,3,5,7,9-pentamethylcycloocta-pyrimidine-2,4-diones (**3**, **5**) effected bond-switching to produce their tautomeric isomers (**4**, **6**). Upon heated in the dark, the former (**4**) reverted to **3**, while the latter (**6**) transformed itself into cyclobutaquinazoline (**7**) through intramolecular Diels-Alder reaction.

Previously, we reported that photolysis of 6-chloro-1,3-dimethyluracil (6-ClDMU) in benzene[1] in the presence of trifluoroacetic acid (TFA) at room temperature produced 1,3-dimethylcyclooctapyrimidine-2,4-dione (**1**). In sharp contrast, the analogous photoreaction performed in frozen benzene at low temperature afforded the mixture of pentalenopyrimidines and the transannular derivative led through a [2 + 2] process.[2]

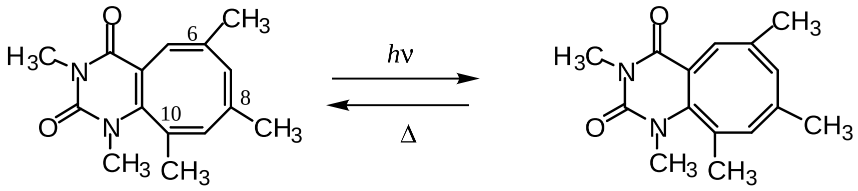


Scheme 1

This dramatic change in the product distributions was explained by invoking a tentative intermediate (**2**) that we refer to as the tautomer of **1**, whose thermochemical lability and photosensitivity would sway the successive reaction pathways (Scheme 1).[2,3] However, either the detection or the characterization of the postulated key intermediate (**2**) has not yet been performed.

On the way of our investigation on the photoproducts from 6-ClDMU and mesitylene by using HPLC, we accidentally experienced unexpected chromatographic behavior that one of the possible cycloadducts, 1,3,6,8,10-pentamethylcyclopyrimidine (**3**), was isolated from two independent fractions. From this, it was suspected that the tautomer (**4**) might have been produced in the photoreaction, which would restore to the starting **3**. In an expectation of gaining insight into the nature of the tautomeric isomer of cyclooctapyrimidine-2,4-diones, we have investigated the photochemistry of **3** and the 1,3,5,7,9-pentamethyl analogue (**5**), which is readily available from the TFA-catalyzed photoreaction of 6-ClDMU and mesitylene at low temperature.[4]

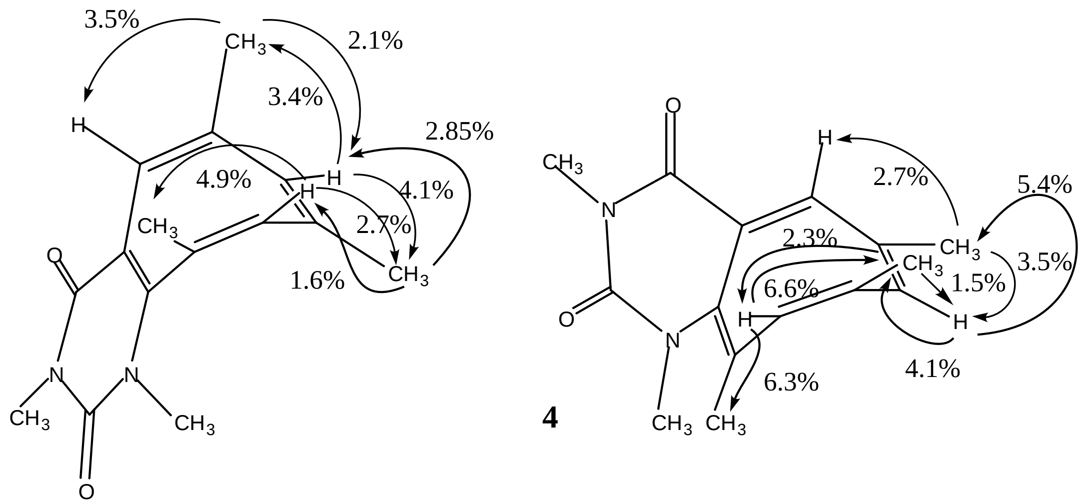
UV-irradiation (2 h) of **3** was carried out in benzene in a degassed Pyrex tube at ambient temperature.[5] The ^{1}H-NMR spectrum of the reaction mixture showed the formation of **4** in a ratio of **4**/**3** = 0.42.[6] Photoreaction at low temperature (-25°C) resulted in an analogous **4**/**3** ratio. Prolonged irradiation (4 h) of **3** was ineffective on the product ratio, or the formation of other valence isomer was not detected (Scheme 2).



3 **4**

Scheme 2

The structural assignment of **4**[7] was made essentially on the basis of the ^{1}H-NMR spectra and the NOE experiments. The ^{1}H-NMR spectrum (C_6D_6) of **4** showed three new singlet peaks at δ 5.16, 5.40, and 6.87 due to H-9, H-7, and H-5. The NOE experiments supported the structural assignment of **4**. In the expected conformation,[8] each hydrogen is closer to the adjacent methyl group through the C=C double bond than hydrogens to the neighboring methyl groups through the C-C single bonds. Indeed NOE different enhancements between 6-CH_3—7-H, and 8-CH_3—9-H are stronger than those between 5-H—6-CH_3, and



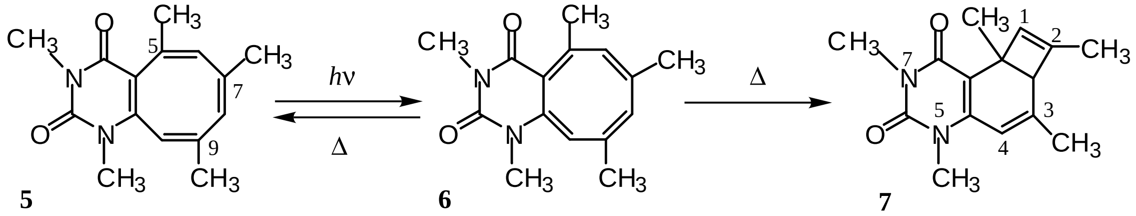
3 **4**

Figure 1. NOE Correlation for **3** and **4**

7-H—8-CH_3 (Figure 1). In contrast, **3**[9] showed stronger NOE enhancements between 5-H—6-CH_3, and 7-H—8-CH_3, and 9-H—10-CH_3 than between 6-CH_3—7-H, and 8-CH_3—9-H (Figure 1). These results led to the formulation of **4**.

Upon being allowed to stand in the dark at 25°C, **4** reverted to **3** with a half-life time of *ca*. 8 h. When **4** was heated at 60°C, it was restored to **3** quantitatively in 30 min.

Similarly the photolysis of the other 5,7,9-methylcyclooctapyrimidine derivative (**5**)[10] in toluene-d_8 at –25°C was found to form the tautomeric isomer (**6**) and reached the equilibrium of **6**/**5** = 0.21 in 10 min by using ^{1}H-NMR spectroscopy (Scheme 3).



Scheme 3

The structural assignment of **6**[11] was made analogously to that of **4** on the basis of the ^{1}H-NMR spectroscopy and the NOE experiments.

When the reaction mixture was kept in the dark at ambient temperature, 50% of **6** transformed itself to cyclobutaquinazoline (**7**)[12] through intramolecular Diels-Alder reaction. The rest reverted to **5** with a half-life time of *ca*. 30 min. Repeated irradiation (10 min x 6) and heating of a solution of **5** (60°C in the dark, 30 min) resulted in the 45% conversion of **5** into **7**. However, no formation of the further transformed product was observed during the irradiation period (Scheme 3).

Thus, in contrast to the tentative analogue (**2**) invoked in the reaction in frozen benzene, the tautomers (**4**, **6**) proved to be insusceptible to UV-light. However, these findings are consistent with the fact that the photoreaction with mesitylene conducted at low temperature furnished only **3** and **5** but no pentalenopyrimidine derivatives, even in a prolonged irradiation period (4 h). Photolysis of **1** failed to produce **2**.

Thus, the reasons for the differences in the photochemical behaviors between the tautomers (**4**, **6**) and tentative **2** remain unclear, the syntheses of the tautomers (**4** and **6**) would provide versatile information for elucidating the reaction mechanism lying in our continuing studies on the photoreaction of 6-ClDMU and benzenes[1-5, 13]

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2. K. Ohkura, Y. Noguchi, and K. Seki, *Chem. Lett.*, **1997**, 99.
3. K. Ohkura, Y. Noguchi, and K. Seki, *Heterocycles*, 1998, **47**, 429.

4. Photolysis of a 20 mmolar solution of 6-ClDMU in mesitylene in the presence of 2 equiv. molar TFA at low temperature (-25°C for 5 h) afforded **3** and **5** in 34.1 % and 19.4 % yields, respectively, K. Ohkura, K. Nishijima, A. Sakushima, and K. Seki, *Heterocycles*, in press.
5. UV-Irradiation was carried out externally with a 500 W high-pressure mercury lamp (Eiko-sha) in a degassed Pyrex tube or in an NMR sample tube.
6. Photo-induced bond switching in substituted cyclooctatetraenes has been reported; F. A. L. Anet and L. A. Bock, *J. Am. Chem. Soc.*,1968, **90**, 7130. See also Y. Hanzawa and L. Paquette, *Synthesis*, **1982**, 661.
7. **4** (pale yellow crystals): UV (cyclohexane) λ_{max} nm (e) 230 (22100).
8. Molecular orbital calculations by the PM3 method were performed with MOPAC on CAChe Work-system (Release 3.7) on a personal computer (Power Macintosh 8100/100AV) and the results were traced by using “CS ChemDraw ProI”.
9. **3**: ^{1}H-NMR (C_6D_6) δ: 1.32 (3H, d, J = 1.5 Hz, C10-CH_3), 1.49 (3H, dd, J = 0.7, 1.5 Hz, C8-CH_3), 1.67 (3H, dd, J = 0.7, 1.5 Hz, C6-CH_3), 2.82 (3H, s, N1-CH_3), 3.25 (3H, s, N3-CH_3), 5.43 (1H, *br* s, H-9), 5.45 (1H, *br* s, H-7), 6.32 (1H, q, J = 1.5 Hz, H-5). UV (cyclohexane) λ_{max} (ε) 225 (17200), 249 (10080), 296 nm (2400).
10. **5**: ^{1}H-NMR (toluene-d_6) δ: 1.52 (3H, s, C9-CH_3), 1.59 (3H, s, C7-CH_3), 2.16 (3H, s, C5-CH_3), 2.82 (3H, s, N1-CH_3), 3.20 (3H, s, N3-CH_3), 5.24 (1H, *br* s, H-10), 5.33 (1H, *br* s, H-8), 5.64(1H, *br* s, H-6).
11. **6**: ^{1}H-NMR (toluene-d_6) δ: 1.50 (3H, s, C9-CH_3), 1.57 (3H, s, C7-CH_3), 2.05 (3H, s, C5-CH_3), 2.90 (3H, s, N1-CH_3), 3.11 (3H, s, N3-CH_3), 4.92 (1H, s, H-10), 5.26 (1H, s, H-6), 5.36 (1H, s, H-8).
12. 2,3,5,7,8b-Pentamethylcyclobuta[*f*]quinazoline-6,8-dione (**7**): Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.57 (3H, s, 8b-CH_3), 1.72 (3H, t, J =1.5 Hz, 2-CH_3), 1.96 (3H, br s, 3-CH_3), 2.88 (1H, br s, H-2a), 3.33 (3H, s, N7-CH_3), 3.48 (3H, s, N5-CH_3), 6.07 (1H, br s, H-4), 6.18 (1H, br s, H-1). Ms m/z (%); 258 (M^+, 41), 243 (18), 218 (18). HRMS; Calcd for $C_{15}H_{18}N_2O_2$: 258.1368. Found: 258.1364.
13. K. Ohkura, N. Kanazashi, and K. Seki, *Chem. Lett.*, **1993**, 667; K. Ohkura, K Seki, Hajime Hiramatsu, K. Aoe, K. Okamura, T. Date, N. Kanazashi, and M. Terashima, *Heterocycles*, 1997, **44**, 467.