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PHOTOCHEMICAL RING OPENING OF THYMIDINE AND THYMINE IN THE PRESENCE OF PRIMARY AMINES[1]

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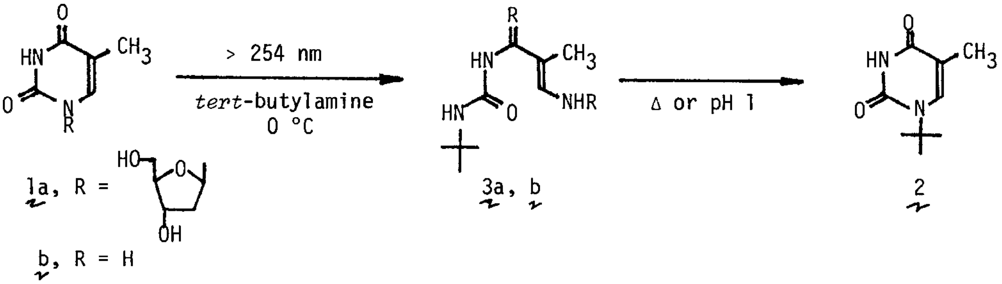
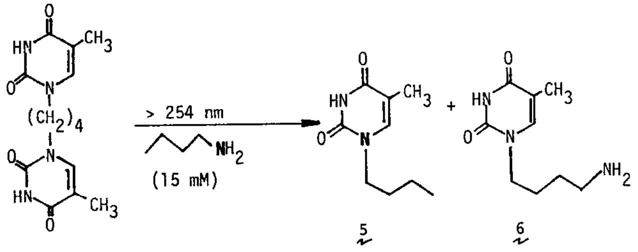
Summary: Irradiation of thymidine or thymine in the presence of tert-butylamine at 0 °C provided ring-opened photoadduct 3 which on heating at 70 °C gave 1-tert-butylthymine (2) quantitatively. Synthetic application of this photoexchange reaction with amines has been described.

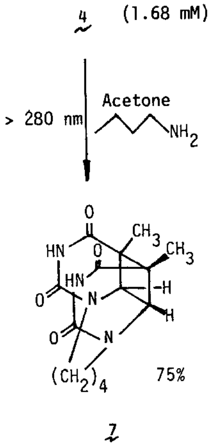
Considerable interest has been displayed in the development of base-specific reactions with nucleic acid components as a means of modifying or sequencing DNA.[2] In a previous paper we have reported that primary alkylamines, including lysine, react photochemically with thymine in DNA to produce N(1)-substituted thymines.[3] This type of photoreaction can induce a specific cleavage of thymines from DNA chains without acid hydrolysis.[3] This paper discloses our results on the isolation and characterization of the intermediates and some synthetic applications of this novel type of photoreaction.

As we reported earlier, irradiation of thymidine (1a) in the presence of *tert*-butylamine with 254-nm light in aqueous solvent at ambient temperature (∿35 °C) gave 1-*tert*-butylthymine (2) in 43% isolated yield.[3] However, when a solution (pH 11.5) of 1a (10 mM) and *tert*-butylamine (0.1 M) in distilled water was irradiated at lower temperature (0 ∿ 5 °C),[4] ring-opened photoadduct 3a[5] was obtained in 70% isolated yield. Brief heating of 3a in water at 70 °C immediately produced 2 in quantitative yield.[6] Alternatively, acidification of the aqueous solution of 3a to pH 1 gave 2 (95%). These observations clearly demonstrate that 3a is the precursor of 2. A similar type of photoproduct 3b[5] (50%) has been obtained when thymine (1b, 10 mM) and *tert*-butylamine (0.1 M) was irradiated in water (pH 11.6) at 0 °C under the specified conditions.[7] Upon warming at 70 °C 3b was quantitatively converted into 2.

Direct irradiation of dinucleotide analog 4[8] (1.7 mM) in the presence of *n*-butylamine (15







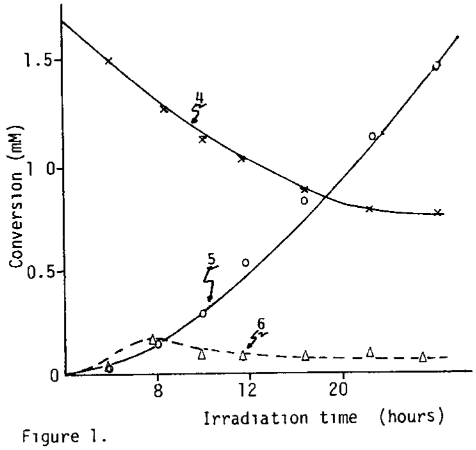
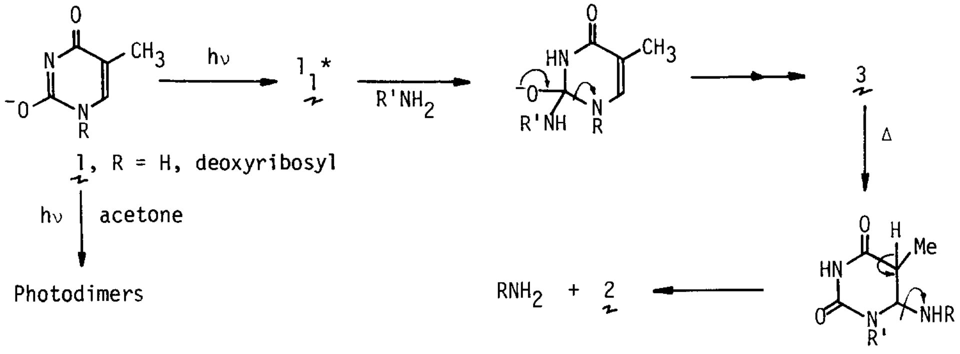


Figure 1.

mM) in water (pH 11.3) with 254-nm light at room temperature provided 5 and 6[8] with the ratio being dependent upon irradiation time (Fig. 1), due to the further reaction of the photoproduct 6. In contrast, acetone-sensitized irradiation of 4 with *n*-butylamine in water at same pH gave only *cis-syn* cycloadduct 7 as reported by Leonard *et al.*,[9] indicating that the triplet state of 4 is not responsible for this photoaddition reaction.

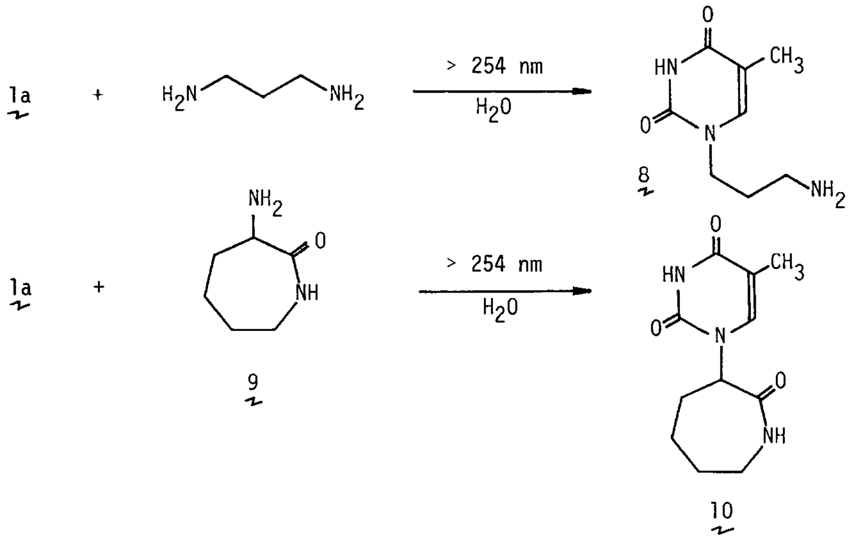
This type of photoreactions with primary amines proceeded only in aqueous solvents at alkaline pH (> pH 8), suggesting that the photoexcited species of a partially ionized form of 1 (1a, pK_a 9.8) is involved in the photoaddition reaction.[3] These experimental results may most reasonably be explained by the mechanism shown in Scheme 1. Nucleophilic attack of the amino group on C_2 of the photoexcited 1a followed by ring opening would furnish 3, although we previously proposed a nucleophilic attack on C_6.[3] Nucleophilic attack on C_6 is a well

Scheme 1



documented process in ground- and excited states of pyrimidine bases,[10] whereas there is only few precedent for the nucleophilic attack on C_2.[11]

This remarkable photoexchange reaction may be employed for the synthesis of a variety of N(1)-substituted thymines. For example, irradiation[4] of 1a (5 mM) and 1,3-diaminopropane (15 mM) in water (pH 11.6) gave 8[8] (56%), whereas irradiation of 1a (5 mM) with amino lactam 9[12] (15 mM) in water (pH 10) gave 10[5] (49%).



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REFERENCES AND NOTES

1. Photoinduced Reactions 133.
2. For example, see A. M. Maxam and W. Gilbert, *Proc. Natl. Acad. Sic., USA*, **74**, 560 (1977).
3. I. Saito, H. Sugiyama, S. Ito, N. Furukawa, and T. Matsuura, *J. Am. Chem. Soc.*, **103**, 1598 (1981).
4. Irradiation was done with a low-pressure mercury lamp (10 W) through Vycor filter (> 250 nm) under nitrogen atmosphere for 24 h. Photoproduct was isolated by preparative HPLC (reverse phase Nucleosil 7 C_{18} column, 1 : 1 MeOH-H_2O). Yield was based on consumed **1a**.
5. All new compounds exhibited consistent spectral data (^1H and ^{13}C NMR, UV) and elemental analyses. Selected spectral data follow. **3a**; ^1H NMR ($CDCl_3$) δ 1.37 (s, 9 H), 1.68 (s, 3 H), 2.02 (m, 2 H), 3.40 - 4.40 (m, 6 H, on addition of D_2O 4 H), 4.70 (m, 1 H, anomeric H), 6.04 (dd, 1 H, J = 12, 8 Hz, NH), 7.35 (d, J = 12 Hz, 1 H), 7.94 (br s, 1 H, NH), 8.88 (br s, 1 H, NH); UV (H_2O) 291 nm (log ε, 4.38). **3b**; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H), 1.70 (s, 3 H), 4.30 (br d, 2 H, J = 10 Hz, NH_2), 7.48 (t, 1 H, J = 10 Hz), 7.88 (br s, 1 H, NH), 8.87 (br s, 1 H, NH); UV (H_2O) 293 nm (log ε, 4.23). **10**; mp > 300 °C; ^1H NMR (DMSO-d_6) δ 1.45 - 2.10 (m, 6 H), 1.79 (d, 3 H, J = 1 Hz), 3.05 - 3.25 (m, 2 H), 5.16 (m, 1 H), 7.40 (d, 1 H, J = 1 Hz), 7.60 - 8.10 (br, 2 H, NH).
6. G. Shaw, R. N. Warrener, M. H. Maguire and R. K. Ralph, *J. Chem. Soc.*, **1958**, 2294.
7. In this case (Z)-isomer of **3b** has also been isolated as a minor product (10%). In aqueous solution (Z)-isomer gradually isomerizes to **3b**.
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10. For example, see (a) T. K. Bradshaw and D. W. Hutchinson, *Chem. Soc. Rev.*, **6**, 43 (1977); (b) W. A. Summers, C. Enwall, J. G. Burr and R. L. Letsinger, *Photochem. Photobiol.*, **17**, 295 (1973).
11. Recently, Nakanishi *et al.* [H. Komura, K. Nakanishi, B. W. Potvin, H. J. Stern and R. S. Krooth, *J. Am. Chem. Soc.*, **102**, 1208 (1980)] have proposed the attack of ribose 5-phosphate anion on C_2 carbonyl of the monoanion of barbituric acid for unusual spontaneous reaction between barbituric acid and D-ribose 5-phosphate in water.
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