Acetone-Sensitized Photocoupling of 5-Bromouridine to Tryptophan Derivatives via Electron-Transfer Process[1]

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Abstract: In connection with the photo-cross-linking of DNA containing bromouracil to proteins, photoreactions of 5-bromouracils with various indoles including tryptophan derivatives were investigated. It was shown that N^b-acetyltryptophan methyl ester (**2a**), a model for tryptophan in a protein, undergoes an efficient photocoupling to 2′,3′-*O*-isopropylidene-5-bromouridine (**1a**) or 5-bromo-1,3-dimethyluracil (**5**) on acetone sensitization in a highly regiospecific fashion. Involvement of the triplet state of **5** in the photocoupling reaction of **5** to **2a** was demonstrated by triplet sensitization and quenching experiments on direct photolysis. Solvent and substituent effects as well as the inhibitory effect of electron-transfer quenchers have suggested that the acetone-sensitized photocoupling of **5** to **2a** proceeds via an electron-transfer process. Synthetic applications of the photocoupling reaction were also described. For example, direct irradiation of **1a** with melatonin (**18**) gave the corresponding coupled product **19**, whereas acetone-sensitized irradiation of **1a** with N^b-*t*-Boc-tryptophylleucine benzyl ester (**20**) gave the coupled product **21**. Thus the photocoupling reaction provides a useful method for the synthesis of a new class of amino acid–nucleoside adducts.

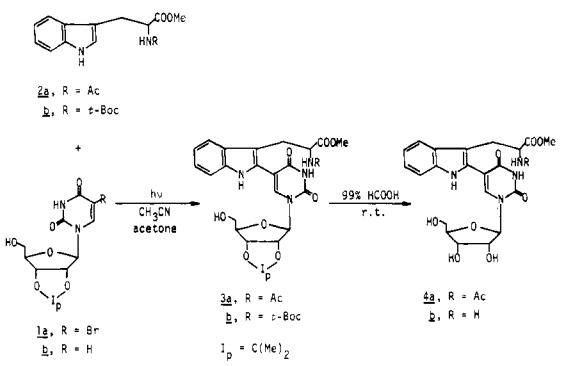
Introduction

Cross-linking of nucleic acids and proteins represents one of the reactions that can take place when bacterial or mammalian cells are irradiated with UV light. The importance of these cross-links in aging, carcinogenesis, and radiation biology has recently been reviewed.[2] The tendency of proteins and nucleic acids to form specific covalent adducts as a result of UV irradiation is also used as a probe for the investigation of the structure of native protein–nucleic acid complexes.[2,3] This approach utilizes photochemistry to "freeze" existing contact points in the complexes, thereby allowing the identification and chemical characterization of the interacting residues.

When thymine is replaced by 5-bromouracil (BrU) in DNA, the sensitivity of bacterial and mammalian cells to the killing by UV radiation is markedly increased.[4] At least three possible mechanisms responsible for this sensitizing effect have been suggested: (1) self-coupling of two BrU residues with the formation of 5-5′-diuracilyl linkages,[5] (2) induction of single-strand breaks in DNA;[4b,6] (3) enhancement in the rate of production of DNA–protein cross-links in cells.[7] The replacement of thymine in DNA by BrU is also used for investigating the contact position located in macromolecular complexes as a bifunctional bridging agent.[8] In spite of the importance of the cross-linking of DNA-containing BrU to various proteins, e.g., histone,[7b,9] RNA polymerase,[7b,10] and *lac* repressor,[7b,11] very little is known about the nature of the amino acid–nucleic acid adducts. Sulfhydryl compounds such as cysteine and glutathione have been reported to undergo photocoupling to BrU.[12] We have sought the possibility that aromatic amino acid residues in a protein may take part in the photo-cross-linking to DNA-containing BrU, since these aromatic amino acids can serve as light receptors and electron-rich aromatic systems are usually susceptible to photosubstitution with haloheteroarenes.[13] As a model for such cross-linking, we have investigated the photoreaction of 5-bromouracils with various aromatic amino acid derivatives and found that tryptophan derivatives undergo a specific photocoupling with 5-bromouracils in organic solution. The photocoupling reaction provides a useful method for the synthesis of 5-substituted uracils and uridines, a new class of amino acid–nucleoside adducts, which are of potential biological significance and otherwise difficultly accessible. In this paper we present the details of synthetic and mechanistic aspects of the photocoupling reactions.

Results and Discussion

Acetone-Sensitized Photocoupling of Protected 5-Bromouridine to Tryptophan Derivatives. Acetone-sensitized irradiation of 2′,3′-*O*-isopropylidene-5-bromouridine (**1a**) with Pyrex-filtered light in acetonitrile in the presence of N^b-acetyltryptophan methyl ester (**2a**), a model for tryptophan in a protein, provided a single photoproduct. No other products, except a minor amount of polymeric products derived from **2a**, were detected on TLC. Separation by preparative TLC yielded the coupled product **3a** in 70% yield (based on reacted **1a**). Spectral properties, including ^1H and ^{13}C NMR data, are in accordance with the assigned structure.[1a] In control runs, irradiation of a solution of **1a** and **2a** in the absence of acetone under the standard conditions did not produce **3a**. A similar coupled product, **3b**, has been obtained when N^b-*t*-Boc-tryptophan methyl ester (**2b**) was irradiated with **1a** in acetone–acetonitrile. Treatment of **3a** with 99% formic acid removed the isopropylidene group to give **4a**, whereas the acid treatment of **3b** allowed the removal of the *t*-Boc group simultaneously yielding **4b** (eq 1).



(1)

(1) Photoinduced Reactions. 120. Portions of this work were published in preliminary forms: (a) Saito, I.; Ito, S.; Matsuura, T. *J. Am. Chem. Soc.* **1978**, *100*, 2901; (b) Saito, I.; Ito, S.; Matsuura, T. *Tetrahedron Lett.* **1978**, 2585.

(2) (a) Smith, K. C., Ed. "Aging, Carcinogenesis and Radiation Biology; The Role of Nucleic Acid Addition Reactions"; Plenum Press: New York, 1976. (b) Kornhauser, A. *Photochem. Photobiol.* **1976**, 23, 457.

(3) Schimmel, P. R. *Acc. Chem. Res.* **1977**, 10, 411.

(4) For reviews, see: (a) Hutchinson, F. *Q. Rev. Biophys.* **1973**, *6*, 201; (b) Wang, S. Y. "Photochemistry and Photobiology of Nucleic Acids"; Wang, S. Y., Ed.; Academic Press: New York, 1976; Vol. 1, p 295.

(5) (a) Ishihara, H.; Wang, S. Y. *Nature (London)* **1966**, *210*, 1222. (b) Sasson, S.; Wang, S. Y. *Photochem. Photobiol.* **1977**, *26*, 357 and references therein.

(6) Hutchinson, F.; Hales, H. B. *J. Mol. Biol.* **1970**, *50*, 59.

(7) (a) Smith, K. C. *Photophysiology* **1964**, 3, 329. (b) Hélène, C., ref 2a, p 149. (c) Smith, K. C. "Photochemistry and Photobiology of Nucleic Acids"; Wang, S. Y., Ed.; Academic Press: New York, 1976; Vol. 2, p 187.

(8) (a) Bahl, C. P.; Wu, K.; Itakura, K.; Katagiri, N.; Narang, S. A. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 91. (b) Goeddel, D. V.; Yansura, D. G.; Caruther, M. H. *Ibid.* **1978**, *75*, 3578.

(9) Weintraub, H. *Cold Spring Harbor Symp. Quant. Biol.* **1973**, *37*, 247.

(10) Schmmel, P. R.; Budzik, G. P.; Lam, S. S. M.; Schoemaker, H. J. P., ref 2a, p 123.

(11) Lin, S. Y.; Riggs, A. D. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 947.

(12) Varghese, A. J. *Photochem. Photobiol.* **1974**, *20*, 461.

(13) (a) Allen, D. W.; Buckland, D. J.; Hutley, B. G.; Oades, A. C.; Turnar, J. B. *J. Chem. Soc., Perkin Trans. 2* **1977**, 621. (b) Matsuo, T.; Mihara, S.; Ueda, I. *Tetrahedron Lett.* **1976**, 4581.

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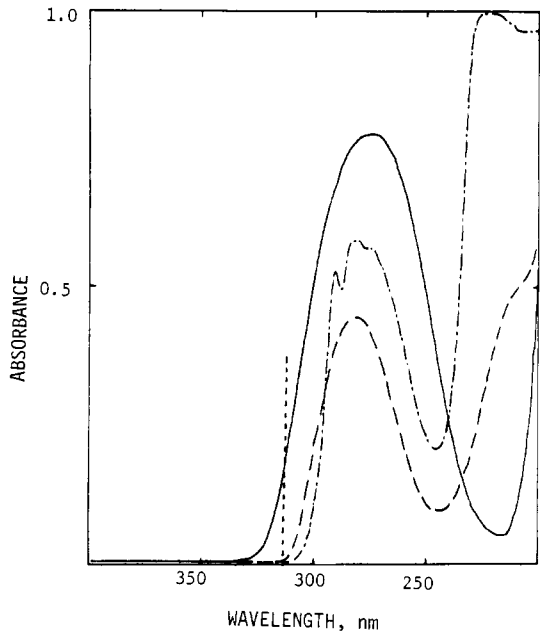
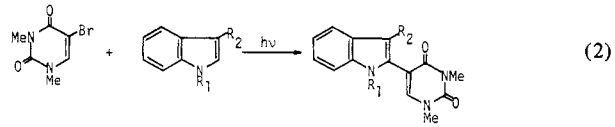


Figure 1. UV spectra of **2a** (-·-), **5** (---), and acetone (—) in acetonitrile: [**2a**] = 6.0×10^{-5} M; [**5**] = 2.8×10^{-5} M; [acetone] = 6.8×10^{-2} M.

Under conditions in which **1a** reacted smoothly with **2**, acetone-sensitized irradiation of **1** with *N*-acetyltyrosine methyl ester or *N*-acetylhistidine methyl ester never produced the corresponding coupled product, and the starting materials were recovered unchanged. Thus, the photocoupling reaction is specific for tryptophan. In order to get unprotected photoproducts directly, we have examined the photoreaction of 5-bromouridine with **2a** or L-tryptophan in aqueous acetone. However, the coupled product has not been observed in both cases. As will be reported in a forthcoming paper, the coupled product between free 5-bromouridine and L-tryptophan has only been obtained by the photoreaction in the aqueous frozen system.[14]

Acetone-Sensitized Photocoupling of 5-Bromo-1,3-dimethyluracil to Indoles. A Mechanistic Study. In order to gain a better insight into the mechanism of the photocoupling reaction, we have chosen a simple analogue, 5-bromo-1,3-dimethyluracil (**5**), in place of **1a**. Irradiation of **2a** (3×10^{-3} M) and **5** (1.4×10^{-3} M) in acetonitrile containing acetone (3.4 M) with Pyrex-filtered light gave rise to the coupled product **6** (67% isolated yield based on reacted **5**) as the sole isolable product except the polymeric products derived from **2a**. The same irradiation with 313-nm light through aqueous potassium chromate filter solution similarly produced **6**. Under the irradiation condition acetone absorbs more than 90% of the incident light at the 313-nm region as is evident from the UV spectra of Figure 1. The quantum yield for the formation of **6** under the standard condition was 0.018. Similarly, acetone-sensitized irradiation of **5** with excess 3-methylindole (**7**) afforded the corresponding coupled product **8** (64%) (eq 2).



(2)

5 **2a**, R_1 = H, R_2 = CH_2CHCO_2Me (NHAc) **6**, R_1 = H, R_2 = CH_2CHCO_2Me (NHAc)

7, R_1 = H, R_2 = Me **8**, R_1 = H, R_2 = Me

9, R_1 = R_2 = Me **10**, R_1 = R_2 = Me

12, R_1 = H, R_2 = $CH_2CH_2CO_2Me$ **13**, R_1 = H, R_2 = $CH_2CH_2CO_2Me$

A. Effect of Solvents and Sensitizers. Solvent effect on the coupling reaction between **2a** and **5** is summarized in Table I. As

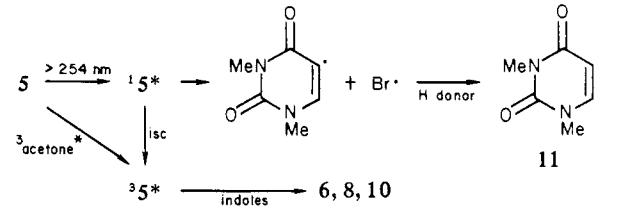
(14) Saito, I.; Ito, S.; Matsuura, T.; Hélène, C. *Photochem. Photobiol.*, in press.

Table I. Solvent Effect on the Photocoupling of 2a to 5[a]

solvent system	dielectric constant,[b] ϵ	yield of 6,[c] %
CH_3CN	37.5	0
CH_3CN-$(CH_3)_2CO$ (3:1)		67
$(CH_3)_2CO$	20.7	66
MeOH	32.7	0
CH_3CO_2Et-$(CH_3)_2CO$ (5:1)		71
CH_3CN-*t*-BuOH-$(CH_3)_2CO$ (10:5:3)		54
C_6H_6-$(CH_3)_2CO$ (3:1)		64
C_6H_6	2.3	0
CH_2Cl_2	0.893	0

[a] [**2a**] = 3 mM, [**5**] = 1.5 mM. Irradiation was made with a 100-W high-pressure mercury lamp through Pyrex filter at 20 °C for 10 h. [b] The values are cited from: Murov, S. L. "Handbook of Photochemistry", Marcel Dekker: New York, 1973; p 85. [c] Isolated yield based on consumed 5.

Scheme I



is evident in the table, acetone is essential for the coupling reaction as sensitizer. Solvent polarity does not seem to play an important role in the coupling reaction. We next examined the sensitizing effect of other sensitizers. Sensitization with acetophenone (E_T = 74 kcal/mol) and benzophenone (E_T = 69 kcal/mol), which are considered to have sufficient triplet energy to sensitize the indoles, e.g., **7** (E_T = 68 kcal/mol[15]) and tryptophan (E_T = 65 kcal/mol[16]), never produced the coupled products (**6**,**8**) and gave only polymeric products derived from the indoles together with the recovered **5**. These polymeric products are presumably derived from a 3-indolyl free radical resulting from hydrogen atom transfer from the NH-indoles by triplet ketones as has already been reported. In fact, acetone-sensitized irradiation of **5** and 1,3-dimethylindole (**9**), where the formation of 3-indolyl free radical is prohibited, led to the clean formation of the coupled product **10** (71%); only small amounts of polymeric products derived from **9** were observed. On sensitization with triphenylene (E_T = 66.5 kcal/mol), both **2a** and **5** were recovered unchanged even after prolonged irradiation. These results clearly indicate that the triplet states of indoles are not responsible for the photocoupling reactions. Unfortunately, triplet energies of **1a** and **5** are not known because these molecules do not measurably phosphoresce. However, in view of the estimated lowest triplet energy of 5-bromouracil (π,π^*, E_T = ca. 74 kcal/mol[17]), it seems reasonable that the triplet state of **5** formed by energy transfer from triplet acetone (E_T = 79–82 kcal/mol) is responsible for the photocoupling reaction.

B. Direct Irradiation. It has already been reported that direct irradiation of 5-bromouracil with 254-nm light gave rise to the debrominated product as the major product in aqueous solution.[4b,18,19] The reaction is believed to result from the homolytic cleavage of the C–Br bond via a short-lived excited state of BrU.[4b,20] In agreement with this observation, unsensitized irradiation of **2a** and **5** with 254-nm light in acetonitrile resulted in the formation of the debrominated product **11** (75%) as the

(15) Wilkinson, F.; Garner, A. *Photochem. Photobiol.* **1978**, *27*, 659.
(16) Bent, D. V.; Hayon, E. *J. Am. Chem. Soc.* **1975**, *97*, 2612.
(17) Rothman, W.; Kearns, D. R. *Photochem. Photobiol.* **1967**, *6*, 775.
(18) Campbell, J. M.; Schulte-Frohlinde, D.; von Sonntag, C. *Photochem. Photobiol.* **1974**, *20*, 465 and references therein.
(19) The direct photolysis in aqueous frozen system has been reported to give 5,5′-diuracilyl as the major product probably via a singlet excited state.[4b,5]
(20) (a) Danziger, R. M.; Hayon, E.; Langmuir, M. E. *J. Phys. Chem.* **1968**, *72*, 3842. (b) Langmuir, M. E.; Hayon, E. *J. Chem. Phys.* **1969**, *51*, 4893.

Table II. Effect of Substituents on the Acetone-Sensitized Photocoupling Reactions of 5 to Indoles[a]

indole	coupled product,[b] %
2a, R = CH_2CHCO_2Me (NHAc)	6 (67)
12, R = $CH_2CH_2CO_2Me$	nd[c]
14, R = CH_2CHCO_2Me (NH_2)	nd
15, R = CH_2CHCO_2H (NH-*t*-Boc)	nd
16, R = $CH_2CH_2NHCO_2Me$	nd
indole, R = H	nd

[a] In acetonitrile–acetone (3:1) at 20 °C. [b] Isolated yield based on consumed 5. [c] Not detected.

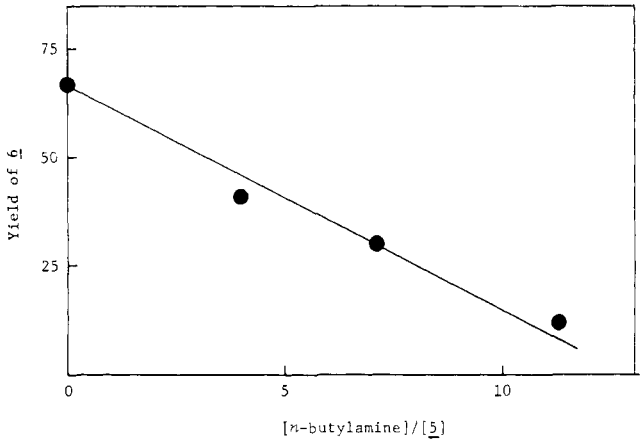
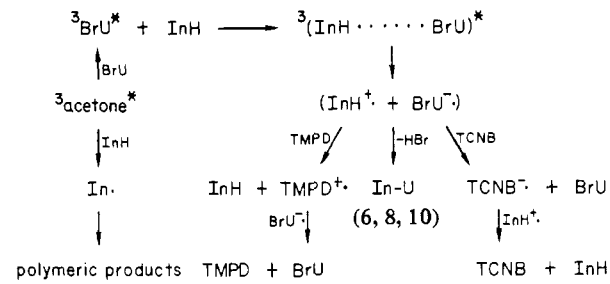


Figure 2. Dependence of the yield of **6** on the concentrations of *n*-butylamine. A mixture of **2a** (2.5 mM) and **5** (1.25 mM) in acetonitrile–acetone (3:1) was irradiated in the presence of different concentrations of *n*-butylamine.

major product together with a minor amount of **6** (15%), in sharp contrast to the finding that on acetone sensitization **6** was the sole product. Addition of 1,3-petadiene to the direct irradiation system inhibited the formation of the coupled product **6** but had no significant effect on the yield of **11**. The result suggests that on direct excitation at 254-nm light a short-lived excited state of **5**, probably a singlet excited state, undergoes homolytic cleavage of the C–Br bond, in competition with inefficient intersystem crossing to the triplet excited state of **5** as depicted in Scheme I, although the possibility that **6** is formed via a different route from the one in acetone-sensitized reaction is not rigorously ruled out. Nevertheless, the direct irradiation provides a less efficient but still useful method for the synthesis of the coupled products. As one of the examples, direct irradiation of **5** and methyl indole-3-propionate (**12**) with 254-nm light in acetonitrile afforded **13** (15%), in addition to **11** (60%). This method is particularly useful for indoles which are highly reactive to triplet acetone such as melatonin (vide infra).

C. Effect of Substituents. The photocoupling reaction is very sensitive to the functional groups of the indole side chains. Acetone-sensitized reaction with tryptophan derivatives having free amino or carboxyl groups such as **14** and **15** did not produce the coupled product (Table II). In order to know the effect of the primary amino group on the photocoupling reaction, we have examined the photoreaction of **2a** and **5** in the presence of varying amounts of *n*-butylamine. As shown in Figure 2, addition of 10 molar equiv of *n*-butylamine with respect to **5** quenched 90% of the coupling reaction. Addition of triethylamine (3 molar equiv to **5**) to the reaction system (**2a** and **5**) also inhibited the formation of **6** with the debrominated product **11** (46%) being formed as the major product instead.[21] The results suggest that a similar

Scheme II



type of efficient intramolecular quenching by the amino side chain is taking place in the case of **14**.

With regard to the inertness of **15**, we have examined the effect of propionic acid on the photocoupling reaction of **2a** to **5**. However, addition of even 30 molar equiv of propionic acid exhibited no appreciable inhibitory effect on the yield of **6**. N^b-Methoxycarbonyltryptamine (**16**) also gave none of the coupled product on acetone sensitization, despite its lower oxidation potential than that of **2a** (vide infra). The reason for the inertness of **15** and **16** toward the acetone-sensitized coupling is not clear.

Mechanistic Aspects. The fact that 1,3-dimethylindole (**9**) undergoes efficient photocoupling to **5** on acetone sensitization indicates that the NH group of the indole ring is not prerequisite for the coupling reaction, eliminating the possibility of the intervention of a 3-indolyl free radical (In· in Scheme II). The coupling reaction observed here is regiospecific with respect to the position of attack on the indole ring. The coupling occurred exclusively on the 2-position of the indoles in all cases; neither benzenoid ring nor 1- and 3-positions were attacked. Electrophilic substitution[22] usually occurs predominantly at the 3-position of indoles, whereas radical reactions,[23] including several photoinduced reactions,[24] proceed less selectively to give a mixture of 1-, 2-, 3-, 4-, and 6-substituted indoles. Such a preferential attack on the 2-position has often been observed in the reactions where electron-transfer processes are believed to be involved. Certain photoaddition,[13b] anodic cyanation,[25,26] and photosensitized electron-transfer cyanation,[26] all of which are suggested to involve electron-transfer processes, afford 2-substituted indoles predominantly. The calculated charge distribution for the cation radical of indole also indicates the highest positive charge on the 2-position.[26] These observations suggest that an electron-transfer process leading to a cation radical of indoles may play an important role in the present photocoupling reactions.

It has been demonstrated by laser flash photolysis that quenching of the triplet states of aromatic ketones such as acetophenone and xanthone by *N*-methylindole in a polar solvent such as ethanol results in an electron transfer from *N*-methylindole to triplet ketones to give the separated ions probably via a triplet charge-transfer complex.[27]

$$^3(\text{ArCOR})^* + N\text{-methylindole} \rightarrow {}^3(\text{CT complex})^* \rightarrow (\text{ArCOR})^{-\cdot} + (N\text{-methylindole})^{+\cdot}$$

However, such aromatic ketones cannot serve as the photosensitizer for the present photocoupling reactions. Thus, acetophenone-sensitized irradiation of *N*-methylindole or 1,3-dimethylindole (**9**) in the presence of **5** in acetonitrile afforded none of the coupled product; only complex mixtures of photoproducts

(21) Analogous photoreductions of haloarenes by triethylamine are well-known. For example, see: (a) Ohashi, M.; Tsujimoto, K.; Seki, K. *J. Chem. Soc., Chem. Commun.* **1973**, 384; (b) Kropp, P. J.; Poidexter, G. S.; Pienta, N. T.; Hamilton, D. C. *J. Am. Chem. Soc.* **1976**, *98*, 8135.

(22) Sundberg, R. J. "The Chemistry of Indoles"; Academic Press: New York, 1970, p 1.

(23) Hutton, J.; Waters, W. A. *J. Chem. Soc.* **1965**, 4253.

(24) (a) Somei, M.; Natsume, M. *Tetrahedron Lett.* **1973**, 2451. (b) Naruto, S.; Yonemitsu, O. *Ibid.* **1971**, 2297. (c) Yamasaki, K.; Matsuura, T.; Saito, I. *J. Chem. Soc., Chem. Commun.* **1974**, 944.

(25) Yoshida, K. *J. Am. Chem. Soc.* **1977**, *99*, 6111.

(26) Yoshida, K. *J. Am. Chem. Soc.* **1979**, *101*, 2116.

(27) Wilkinson, F.; Garner, A. *J. Chem. Soc., Faraday Trans. 2* **1977**, *73*, 222.

Table III. Inhibitory Effect of Electron-Transfer Quenchers on the Formation of 6 in the Acetone-Sensitized Photocoupling of 2a to 5[a]

quencher	E^{ox}, V vs. SCE	E^{red}, V vs. SCE	mole ratio (quencher/5)	relative yield of 6[b]
none				1.0
1,4-dimethoxybenzene	1.34[c]		1.0	1.0
1,2,4,5-tetramethoxybenzene	0.81[c]		1.0	1.0
N,N,N',N'-tetramethyl-*p*-phenylenediamine	0.36[d]		0.1	0.13
1,2,4,5-tetracyanobenzene		−0.64[e]	0.1	0.27

[a] [2a] = 3 mM, [5] = 1.5 mM. Irradiation was made with a 100-W high-pressure mercury lamp through Pyrex filter in acetonitrile–acetone (3:1) at 20 °C for 10 h. [b] Based on isolated yield. [c] Zweig, A.; Hodgson, W. G.; Jura, W. H. *J. Am. Chem. Soc.* **1964**, *86*, 4124. [d] Wawzonek, S.; Plaisance, T. H.; Smith, L. M., Jr.; Buchana, E. B., Jr. Preprints, Durham Symposium on Electroorganic Chemistry, Durham, North Carolina, 1968, p 247. [e] Farid, S.; Brown, K. A. *J. Chem. Soc., Chem. Commun.* **1976**, 564.

derived from *N*-methylindoles were obtained. The result clearly shows that the charge-transfer complex between triplet acetone and **9**, even if formed, plays no significant role in the formation of the coupled product **10**.

By the sensitized reaction and the quenching experiment on direct photolysis, we have already demonstrated an evidence which strongly supports the involvement of the triplet state of bromouracil **5** in the photocoupling reaction. With this in mind, we propose the following mechanism in which the triplet state of **5** (BrU) interacts with tryptophan derivative **2a** (InH) to give a triplet excited complex (Scheme II). It should be noted here that no ground-state charge-transfer interaction between **2a** and **5** was observed as evidenced by UV absorption spectra. The triplet exciplex, if formed, may dissociate into a radical ion pair in a polar solvent such as the solvent system containing acetone. The anion radical of **5** ($BrU^{-}\cdot$) thus formed would release Br anion yielding a 5-uracilyl radical, which combines with the cation radical of **2a** ($InH^{+}\cdot$) followed by deprotonation to produce the coupled product **6** (In–U). The coupling process may occur within a cage or between the "escaped" radical anion and cation.

In agreement with the proposed electron-transfer mechanism, compounds having low oxidation potentials such as *N,N,N',N'*-tetramethyl-*p*-phenylenediamine (TMPD), substantially (>85%) quench the formation of the coupled product **6** even at very low concentration (0.1 equiv to **5**) insufficient to react with the ground state and, presumably, the excited states of **5**, whereas 1,4-dimethoxy- and 1,2,4,5-tetramethoxybenzenes, which have higher or almost equal oxidation potentials compared to that of **2a** (E^{ox} = 0.82 V vs. SCE),[28] did not inhibit the formation of **6** even at higher concentrations (Table III). In view of the reduction potential of **5** (E^{red} = −0.90 V vs. SCE),[28] electron transfer from the anion radical of **5** ($BrU^{-}\cdot$) to 1,2,4,5-tetracyanobenzene (TCNB) is exothermic. Addition of TCNB (0.1 equiv to **5**) to the reaction system quenched the formation of **6** as expected. The inhibitory effect of these quenchers[29] can be explained in terms of a secondary electron-transfer reaction as depicted in Scheme II. However, addition of increasing amounts of quenchers (TMPD, TCNB) complicated the photoreactions, since 1:1 mixtures of TMPD–**5** and TCNB–**2a** pairs formed colored

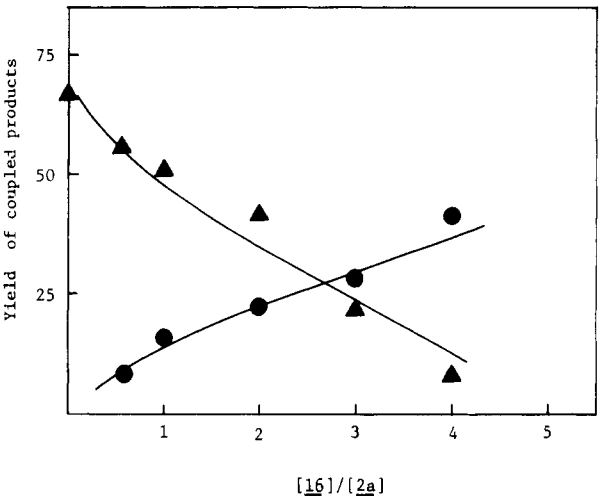


Figure 3. Dependence of the yields of **6** (▲) and **17** (●) on the concentrations of **16**. A mixture of **2a** (2.5 mM) and **5** (1.25 mM) in acetonitrile–acetone (3:1) was irradiated in the presence of different concentrations of **16**.

Scheme III

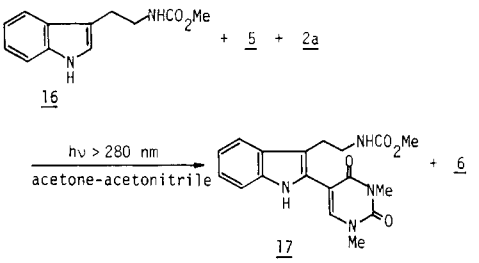
$$^{3}BrU^{*} \xrightarrow{2a} {}^{3}(BrU\cdots 2a)^{*} \longrightarrow (BrU^{-}\cdot + 2a^{+}\cdot) \longrightarrow 6$$

$$(BrU^{-}\cdot + 16^{+}\cdot) \longrightarrow 17$$

(16 and 2a)

charge-transfer complexes under the standard conditions. Such an electron-transfer type quenching by TMPD or TCNB may well occur with the dissociated radical ions, although one cannot neglect other possibilities such as quenching of the triplex exciplex or an exciplex substitution mechanism.[30]

Further support for the intervention of the electron-transfer process has been obtained in the photoreaction of N^{b}-methoxycarbonyltryptamine (**16**). Acetone-sensitized irradiation of **16** with **5** under similar conditions never gave the coupled product. However, in the presence of **2a** as an electron carrier, **16** reacted smoothly with **5** to yield the coupled product **17** at the expense of the coupled product between **5** and **2a**. Thus, the acetone-sensitized photolysis of an acetonitrile solution of a mixture of **5**, **2a**, and **16** (1:2:2) gave a mixture of coupled products **6** (42%) and **17** (22%) (eq 3). This competitive coupling reaction showed



(3)

a marked concentration dependency. As shown in Figure 3, the yield of **6** decreases with increasing concentrations of **16** accompanied by increased yield of **17**. Judging from the oxidation potentials[28] of **2a** (E^{ox} = 0.82 V vs. SCE) and **16** (E^{ox} = 0.75 V vs. SCE), these results may most reasonably be explained by assuming an electron-transfer process from the cation radical of **2a** to **16** as shown in Scheme III. A similar type of double electron-transfer process has already been observed in the photoreaction by using 2-methoxynaphthalene as an electron carrier in place of **2a**.[31]

There is growing evidence that triplet exciplexes are intermediates in many photochemical processes.[32,33] The intermediacy

(28) The E^{ox} and E^{red} values were determined by cyclic voltammetry in acetonitrile solution with tetrabutylammonium perchlorate supporting electrolyte. We are indebted to Professor T. Fujinaga and T. Hinoue (Department of Chemistry, Kyoto University) for CV measurements.

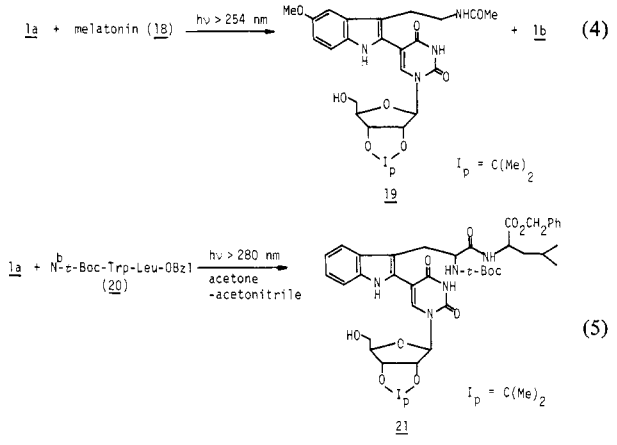
(29) Electron-transfer quenchers such as TCNB are frequently used for the support of electron-transfer process. For example, see: Brown-Wensley, K. A.; Mattes, S. L.; Farid, S. *J. Am. Chem. Soc.* **1978**, *100*, 4162.

(30) Ohta, H.; Creed, D.; Wine, R. H.; Caldwell, R. A.; Melton, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 2002.

(31) Ito, S.; Saito, I.; Matsuura, T. *Tetrahedron Lett.* **1979**, 4067.

of triplet exciplexes in photochemical systems has usually been supported by indirect evidence.[32] However, the direct characterization of triplet exciplexes or ion pairs derived from them has recently been reported in several systems.[27,33] The mechanism shown in Scheme II is proposed on the basis of only circumstantial evidences. In an effort to gain more direct evidence for the intervention of the electron-transfer process, many attempts have been made in order to detect the transient species, e.g., radical ions, formed during the acetone-sensitized photoreactions by microsecond flash photolysis.[34] These experiments, however, have been fruitless. Nevertheless, the results described here demonstrate that such an electron-transfer process via a triplet state can be successfully applicable to the synthesis of complex molecules. To our knowledge, only few examples are available with the electron-transfer type photoreactions via triplet excited states resulting in a synthetically useful reaction.[35]

Synthetic Application. From a synthetic point of view, considerable efforts have been made for the synthesis of nucleosides substituted by various functional groups at the pyrimidine C-5 position because of their potential biological activities.[36] Most of the methods consist of a nucleophilic displacement in 5-halogenopyrimidine nucleosides by heteroatom nucleophiles,[36] whereas there are only a few methods for forming carbon–carbon bonds at the C-5 position.[37] The present photocoupling reactions provide a convenient and useful method for the introduction of indolyl groups into the C-5 position of the uridine nucleus. As already shown, tryptophan and tryptamine derivatives were able to undergo such photocoupling reaction with 5-bromouracils on acetone sensitization. Melatonin (**18**) is also a biologically important compound. Under acetone-sensitized irradiation conditions, **18** is photolabile to decompose to dark polymeric products. However, direct irradiation of **18** with 254-nm light in the presence of **1a** in acetonitrile led to the formation of the coupled product **19** (13%) together with the debrominated product **1b** (35%). The acetone-sensitized photocoupling reaction can also be extended to a dipeptide containing tryptophan. Acetone-sensitized irradiation of N^b-*t*-Boc-tryptophylleucine benzyl ester (**20**) and **1a** in acetonitrile afforded **21** in 49% yield (eq 4 and 5).



(32) (a) Kocherar, I. E.; Wagner, P. G. *J. Am. Chem. Soc.* **1972**, *94*, 3859. (b) Cohen, S. G.; Parola, A. H.; Parsons, G. H., Jr. *Chem. Rev.* **1973**, *73*, 141. (c) Caldwell, R. A.; Sovocool, G. W.; Gajewski, R. P. *Ibid.* **1973**, *94*, 2549. (d) Parola, A. H.; Rose, A. W.; Cohen, S. G. *Ibid.* **1975**, *97*, 6202. (e) Gupta, A.; Hammond, G. S. *Ibid.* **1976**, *98*, 1215.

(33) (a) Roy, J. K.; Carroll, F. A.; Whitten, D. G. *J. Am. Chem. Soc.* **1974**, *96*, 6349. (b) Roth, H. D.; Manion Schilling, M. L. *Ibid.* **1979**, *101*, 1898. (c) Encinas, M. V.; Scaiano, J. C. *Ibid.* **1979**, *101*, 7740.

(34) We are indebted to Professor S. Kato (Osaka University) for flash photolysis experiments.

(35) (a) Creed, D.; Caldwell, R. A.; Ulrich, M. M. *J. Am. Chem. Soc.* **1978**, *100*, 5831. (b) Tsujimoto, Y.; Hayashi, M.; Miyamoto, T.; Odaira, Y.; Shirota, Y. *Chem. Lett.* **1979**, 613. For an example of electron-transfer type photosensitized reactions via singlet states, see: Maroulis, A. J.; Shigemitsu, Y.; Arnold, D. R. *J. Am. Chem. Soc.* **1978**, *100*, 535.

(36) Bardshaw, T. K.; Hutchinson, D. W. *Chem. Soc. Rev.* **1977**, *6*, 43.

(37) (a) Ruth, J. L.; Bergstrom, D. E. *J. Org. Chem.* **1978**, *43*, 2870 and references therein. (b) Arai, I.; Daves, G. D., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 288. (c) Saito, I.; Shimozono, K.; Matsuura, T. *J. Am. Chem. Soc.* **1980**, *102*, 3948.

Table IV. Fluorescence Spectra of Indole-Uracil Adducts[a]

compd	excitation wavelength, nm	emission max, nm
3a	350	461
3b	350	446
4a[b]	360	460
4b[b]	360	453
6	350	465
13	350	444
17	350	439
19	350	450
21	360	456

[a] In acetonitrile at 20 °C unless otherwise stated. [b] In water.

It is noteworthy that the absorption and fluorescence spectra of the coupled products have considerably red-shifted maxima compared to those of the starting materials. The 5-(2-indolyl)-uracil chromophor has an emission maximum at 450–460 nm on excitation at 350 nm (Table IV). Because of their unique fluorescence properties, the indole–uracil adducts may serve as a useful fluorescence probe for the study of nucleic acid-protein complexes.

Finally, we wish to point out that a similar coupling may probably take place between bromouracil-substituted DNA and tryptophan residues in a protein, since such a photocoupling reaction can occur in a mixed aggregate and is specific for tryptophan among other aromatic amino acids.[14]

Experimental Section

Melting points are uncorrected. Elemental analyses were performed at the Analytical Center of Kyoto University. Ultraviolet spectra were recorded with a Shimadzu UV-200 spectrophotometer. Fluorescence spectra were recorded with a Shimadzu RF-500 spectrometer. Proton magnetic resonance spectra were recorded with a Varian HA-100 or a Varian T-60 spectrometer, using Me_4Si as the internal reference. Carbon-13 magnetic resonance spectra were recorded with a Varian FT-80A spectrometer. Mass spectra were recorded with a JEOL-JMS-01SG-2 spectrometer. Irradiations were made with a 100-W high-pressure mercury lamp with the use of a Pyrex vessel fitted with a water-cooling jacket at ambient temperature under nitrogen atmosphere, unless otherwise stated. Preparative TLC was performed on a silica gel plate (Merck 60 PF_{254}).

Acetone-Sensitized Irradiation of 2′,3′-*O*-Isopropylidene-5-bromouridine (1a) and N^b-Acetyl-L-tryptophan Methyl Ester (2a). A solution of **1a**[38] (115 mg, 0.32 mmol) and **2a** (168 mg, 0.65 mmol) in acetonitrile–acetone (3:1, 200 mL) was irradiated under the standard conditions described above for 10 h. After removal of the solvent, the residue was purified by preparative TLC ($CHCl_3$–acetonitrile, 9:2) to give unreacted **1a** (67 mg), **2a** (65 mg), and **3a** (68 mg, 70% yield based on consumed **1a**).

N^b-Acetyl-2-[1,2,3,4-tetrahydro-1-[2,3-*O*-(1-methylethylidene)-β-D-ribofuranosyl]-2,4-dioxo-5-pyrimidinyl]-L-tryptophan methyl ester (**3a**): mp 158–162 °C dec (from methanol); UV (acetonitrile) 260 nm (log ε 4.07), 328 (3.72); ^1H NMR (acetone-d_6) δ 1.35 (s, 3 H), 1.55 (s, 3 H), 1.78 (s, 3 H), 3.24 (d, 2 H, J = 8.0 Hz), 3.59 (s, 3 H), 3.83 (d, 2 H, = J = 6.0 Hz), 3.76–4.13 (2 H, NH and OH), 4.25 (td, 1 H, J = 6.0, 3.0 Hz), 4.78 (td, 1 H, J = 8.6, 8.0 Hz), 4.98 (dd, 1 H, J = 14.0, 2.4 Hz), 5.02 (dd, 1 H, J = 14.0, 3.0 Hz), 6.12 (d, 1 H, J = 2.4 Hz), 6.95–7.64 (m, 4 H), 7.69 (br d, 1 H, J = 8.6 Hz, NH), 8.22 (s, 1 H), 10.25 (br s, 1 H, NH); ^{13}C NMR (acetone-d_6) δ 23.1 (q), 26.1 (q), 27.8 (t), 28.3 (q), 52.8 (q), 54.5 (d), 63.2 (t), 82.1 (d), 85.5 (d), 88.0 (d), 93.3 (d), 108.6 (s), 110.4 (s), 112.5 (d), 114.9 (s), 119.8 (d), 120.3 (d), 123.2 (d), 129.2 (s), 137.5 (s), 142.9 (d), 151.2 (s), 163.9 (s), 170.9 (s), 173.8 (s) (for assignment see ref 1a); mass spectrum (relative intensity), m/e 542 (M^+, 1.3), 486 (15), 475 (18), 436 (19), 375 (15), 362 (18), 306 (12), 275 (14), 256 (12), 240 (23), 232 (16), 225 (14), 215 (12), 174 (15), 173 (30), 163 (21), 151 (12), 144 (17), 133 (12), 126 (17), 113 (47), 82 (17), 73 (18), 69 (13), 65 (13), 59 (100), 55 (13), 51 (99); exact mass spectrum m/e 542.2012 (calculated for $C_{26}H_{30}N_4O_9$, 542.2003).

N^b-Acetyl-2-(1,2,3,4-tetrahydro-1-β-D-ribofuranosyl-2,4-dioxo-5-pyrymidinyl)-L-tryptophan Methyl Ester (4a). A solution of **3a** (544 mg,

(38) Ueda, T. *Chem. Pharm. Bull.* **1960**, 8, 455.

(39) (a) Moore, W. M.; Ketchum, M. *J. Am. Chem. Soc.* **1962**, *84*, 1388. (b) Wagner, P. G. *Ibid.* **1967**, *89*, 5898.

(40) We are indebted to Peptide Institute for Protein Research Foundation for a gift of **20**.

1 mmol) in 99% formic acid (100 mL) was stirred for 6.5 h at room temperature. Evaporation of the solvent gave the oily residue which was washed with methanol. Preparative TLC (dichloromethane–methanol–triethylamine, 40:3:2) of the residue gave **4a** (275 mg, 55%): mp 147–154 °C dec (from methanol–ether); UV (EtOH) 267 nm (log ε 4.03), 292 (3.91), 329 (3.61); ^{1}H NMR (Me_2SO-d_6) δ 1.75 (s, 3 H), 3.09 (d, 2 H, J = 7.6 Hz), 3.54 (s, 3 H), 3.63 (br s, 2 H), 3.80–4.36 (br, 2 H, OH), 3.93 (br d, 1 H, J = 4.2 Hz), 4.07 (dd, 1 H, J = 4.2, 4.8 Hz), 4.20 (dd, 1 H, J = 4.8, 5.0 Hz), 4.54 (td, 1 H, J = 7.6, 7.6 Hz), 5.01 (br, 1 H, NH), 5.37 (br, 1 H, OH), 5.93 (d, 1 H, J = 5.0 Hz), 6.95–7.62 (m, 4 H), 8.13 (s, 1 H), 8.22 (d, 1 H, NH, J = 7.6 Hz), 10.96 (br s, 1 H, NH); ^{13}C NMR (CD_3OD) δ 22.4 (q), 27.7 (t), 52.8 (q), 54.6 (d), 62.0 (t), 71.2 (d), 76.0 (d), 86.4 (d), 90.9 (d), 108.6 (s), 110.1 (s), 112.3 (d), 119.4 (d), 120.2 (d), 123.1 (d), 129.2 (s), 137.6 (s), 142.4 (d), 152.1 (s), 164.7 (s), 173.3 (s), 174.4 (s).

Anal. Calcd for $C_{23}H_{26}N_4O_9 \cdot 2H_2O$: C, 51.30; H, 5.20; N, 10.33. Found: C, 51.52; H, 5.40; N, 10.41.

Acetone-Senstitized Irradiation of 1a and N^b-t-Boc-Tryptophan Methyl Ester (2b). A solution of **1a** (123 mg, 0.34 mmol) and **2b** (223 mg, 0.7 mmol) in acetonitrile–acetone (3:1, 200 mL) was irradiated for 10 h. After removal of the solvent under vacuum, the residue was purified by preparative TLC (dichloromethane–methanol–triethylamine, 40:3:2) to give unreacted **1a** (50 mg), **2b** (32 mg), and **3b** (125 mg, 80% yield based on consumed **1a**).

N^b-t-Boc-2-[1,2,3,4-tetrahydro-1-[2,3-O-(1-methylethylidene)-β-D-ribofuranosyl]-2,4-dioxo-5-pyrimidinyl]-L-tryptophan methyl ester (**3b**): mp 129–132 °C dec (from methanol); UV (acetonitrile) 213 nm (log ε 4.36), 266 (3.99), 291 (3.85), 332 (3.61); ^{1}H NMR (acetone-d_6) δ 1.29 (s, 9 H), 1.35 (s, 3 H), 1.55 (s, 3 H), 3.31 (d, 2 H, J = 7.8 Hz), 3.52–3.94 (br s, 2 H, NH and OH), 3.61 (s, 3 H), 3.82 (m, d on addition of D_2O, 2 H, J = 3.6 Hz), 4.25 (td, 1 H, J = 3.0, 3.2 Hz), 4.57 (td, 1 H, J = 7.8, 7.8 Hz), 4.95 (dd, 1 H, J = 6.4, 3.0 Hz), 5.08 (dd, 1 H, J = 3.0, 6.4 Hz), 6.11 (d, 1 H, J = 3.0 Hz), 6.30 (br d, 1 H, J = 7.8 Hz), 6.99–7.70 (m, 4 H), 8.23 (s, 1 H), 10.20 (br s, 1 H, NH); ^{13}C NMR (Me_2SO-d_6) δ 26.9 (q), 27.5 (t), 28.8 (q), 29.8 (q), 53.0 (q), 55.5 (d), 62.1 (t), 79.9 (s), 81.1 (d), 84.8 (d), 86.9 (d), 93.9 (d), 101.8 (s), 107.5 (s), 111.4 (d), 113.9 (s), 118.2 (d), 119.2 (d), 122.1 (d), 126.3 (s), 126.8 (s), 133.8 (s), 142.8 (d), 150.9 (s), 161.1 (s), 165.1 (s), 171.6 (s); mass spectrum (relative intensity), m/e 600 (M^+, 3), 415 (4), 414 (11), 413 (26), 241 (79), 240 (63), 235 (22), 234 (23), 147 (51), 146 (61), 132 (17), 130 (31), 90 (33), 89 (21), 59 (31), 57 (82), 56 (100), 55 (82); exact mass spectrum m/e 600.2466 (calculated for $C_{29}H_{36}N_4O_{10}$, 600.2429).

2-(1,2,3,4-Tetrahydro-1-β-D-ribofuranosyl-2,4-dioxo-5-pyrimidinyl)-L-tryptophan Methyl Ester (4b). A solution of **3b** (1.04 g, 1.73 mmol) in 99% formic acid (170 mL) was stirred for 7 h at room temperature. After removal of formic acid under vacuum, the residue was purified by preparative TLC (dichloromethane–methanol–triethylamine, 40:3:2) to give **4b** (448 mg, 56%): mp 219–234 °C dec (from methanol–ether); UV (EtOH) 267.5 nm (log ε 3.66), 292 (3.55), 326 sh (3.32); ^{1}H NMR (Me_2SO-d_6) δ 3.06 (d, 2 H, J = 6.2 Hz), 3.52 (s, 3 H), 3.42–3.77 (br, 1 H), 3.59 (br s, 2 H), 3.89 (br d, 1 H, J = 3.8 Hz), 4.05 (dd, 1 H, J = 5.2, 3.8 Hz), 4.08 (m, 1 H), 4.20 (dd, 1 H, J = 5.2, 5.2 Hz), 4.46–5.62 (br, 5 H), 5.91 (d, 1 H, J = 5.2 Hz), 6.84–7.61 (m, 4 H), 8.22 (s, 1 H), 11.38 (br s, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 29.5 (t), 51.7 (q), 54.6 (d), 61.0 (t), 70.0 (d), 73.8 (d), 85.1 (d), 87.6 (d), 108.6 (s), 109.4 (s), 111.3 (d), 118.6 (d), 118.7 (d), 121.4 (d), 127.6 (s), 128.5 (s), 135.8 (s), 140.3 (d), 150.5 (s), 162.1 (s), 174.9 (s).

Anal. Calcd for $C_{21}H_{24}N_4O_8 \cdot 3H_2O$: C, 49.03; H, 5.84; N, 10.89. Found: C, 49.22; H, 5.94; N, 10.57.

Acetone-Sensitized Irradiation of 5-Bromo-1,3-dimethyluracil (5) and 2a. A solution of **2a** (164 mg, 0.63 mmol) and 5-bromo-1,3-dimethyluracil (**5**) (59 mg, 0.27 mmol) in acetonitrile–acetone (3:1, 200 mL) was irradiated for 10 h. Evaporation of the solvent followed by preparative TLC of the residue gave unreacted **2a** (70 mg), **5** (23 mg), and **6** (44 mg, 67% yield based on consumed **5**).

N^b-Acetyl-2-(1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-pyrimidinyl)-L-tryptophan methyl ester (**6**): mp 222–224 °C dec (from acetone); UV (CH_3CN) 264 nm (log ε 4.08), 288 (4.02), 337 (3.73); ^{1}H NMR ($CDCl_3$) δ 1.96 (s, 3 H), 3.32 (d, 2 H, J = 8.0 Hz), 3.36 (s, 3 H), 3.44 (s, 3 H), 3.62 (s, 3 H), 4.71 (td, 1 H, J = 8.0, 8.0 Hz), 6.64 (d, 1 H, J = 8.0 Hz, NH), 7.03–7.54 (m, 4 H), 8.09 (s, 1 H), 10.29 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 22.7 (q), 28.2 (t), 28.6 (q), 37.0 (q), 52.2 (d), 52.9 (q), 105.4 (s), 106.3 (s), 111.1 (d), 117.6 (d), 119.5 (d), 122.5 (d), 127.8 (s), 128.2 (s), 134.8 (s), 141.6 (d), 150.5 (s), 163.2 (s), 169.9 (s), 172.6 (s); mass spectrum (relative intensity), m/e 398 (M^+, 0.7), 361 (0.4), 350 (0.3), 343 (0.5), 269 (1), 267 (6), 200 (2), 180 (1), 130 (1), 129 (1), 120 (5), 118 (7), 87 (24), 85 (100), 83 (96), 81 (5), 57 (17), 48 (32), 46 (39), 42 (92); exact mass spectrum m/e 398.1592 (calculated for $C_{20}H_{22}N_4O_5$, 398.1590).

Acetone-Sensitized Irradiation of 3-Methylindole (7) and 5. A solution of **7** (418 mg, 3.2 mmol) and **5** (62 mg, 0.28 mmol) in acetonitrile–acetone (3:1, 200 mL) was irradiated for 10 h. After removal of the solvent, the residue was purified by preparative TLC ($CHCl_3$–acetonitrile, 9:1) to yield unreacted **7** (344 mg) and **8** (50 mg, 66% yield based on consumed **5**).

1,3-Dimethyl-5-(3-methyl-1H-indol-2-yl)uracil (**8**): mp 198–201 °C (from CH_3OH); UV (acetonitrile) 260 nm (log ε 3.95), 291 (3.98), 340 (3.72); ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3 H), 3.35 (s, 3 H), 3.38 (s, 3 H), 6.96–7.58 (m, 4 H), 7.94 (s, 1 H), 9.92 (br s, 1 H, NH); mass spectrum (relative intensity), m/e 169 (M^+, 42), 268 (20), 220 (21), 218 (23), 163 (10), 161 (8), 135 (12), 131 (10), 130 (14), 120 (14), 53 (18), 52 (13), 43 (18), 42 (100); exact mass spectrum m/e 269.1142 (calculated for $C_{15}H_{15}N_3O_2$, 269.1164).

Acetone-Sensitized Irradiation of 1,3-Dimethylindole (9) and 5. A solution of **9** (170 mg, 1.27 mmol) and **5** (59 mg, 0.27 mmol) in acetonitrile–acetone (3:1, 200 mL) was irradiated for 10 h. After removal of the solvent, the residue was purified by preparative TLC ($CHCl_3$–acetonitrile, 9:1) to give unreacted **5** (19 mg), **9** (129 mg), and **10** (37 mg, 71% yield based on reacted **5**).

1,3-Dimethyl-5-(1,3-dimethylindol-2-yl)uracil (**10**): mp 69–74 °C (from acetone–hexane); UV (acetonitrile) 230 nm (log ε 4.05), 284 (3.60), 326 (3.16); ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3 H), 3.33 (s, 3 H), 3.37 (s, 3 H), 3.51 (s, 3 H), 6.97–7.60 (m, 4 H), 7.23 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.3 (q), 28.1 (q), 30.5 (q), 37.0 (q), 105.3 s), 109.0 (s), 110.3 (d), 118.6 (d), 118.8 (d), 118.9 (d), 122.0 (s), 127.8 (s), 128.7 (s), 137.2 (d), 144.0 (s), 162.1 (s); mass spectrum (relative intensity), m/e 283 (M^+, 5), 220 (6), 218 (6), 145 (7), 144 (17), 86 (31), 84 (49), 49 (9), 47 (12), 43 (17), 42 (21), 32 (56), 28 (100); exact mass spectrum m/e 283.1345 (calculated for $C_{16}H_{17}N_3O_2$, 283.1320).

Direct Photolysis of 5 in the Presence of 2a. A solution of **2a** (180 mg, 0.69 mmol) and **5** (67 mg, 0.31 mmol) in acetonitrile (150 mL) was irradiated with a 10-W low-pressure mercury lamp through Vycor filter under nitrogen for 10 h. After removal of the solvent, the residue was purified by preparative TLC ($CHCl_3$–acetonitrile, 9:2) to yield unreacted **2a** (26 mg), **5** (9 mg), **6** (15 mg, 15% yield based on consumed **5**), and 1,3-dimethyluracil (**11**) (26 mg, 74% yield based on consumed **5**).

Direct Photolysis of 5 in the Presence of 2a and 1,3-Pentadiene. A solution of **2a** (175 mg, 0.68 mmol), **5** (77 mg, 0.35 mmol), and 1,3-pentadiene (7.01 g, 103 mmol) in acetonitrile (150 mL) was irradiated with a 10-W low-pressure mercury lamp through Vycor filter 10 h. After removal of the solvent, the residue was purified by preparative TLC ($CHCl_3$–acetonitrile, 9:2) to yield unreacted **2a** (26 mg), **5** (47 mg), and **11** (15 mg, 78% yield based on consumed **5**).

Direct Photolysis of 5 in the Presence of Methyl Indole-3-propionate (12). A solution of **12** (157 mg, 0.78 mmol) and **5** (73 mg, 0.34 mmol) in acetonitrile (150 mL) was irradiated with a low-pressure mercury lamp as described above for 10 h. After removal of the solvent, the residue was purified by preparative TLC ($CHCl_3$–acetonitrile, 9:1) to give unreacted **12** (107 mg), **5** (14 mg), **11** (38 mg, 60% yield based on consumed **5**), and **13** (13 mg, 15% yield based on consumed **5**).

Methyl 2-(1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-pyrimidinyl)-1H-indole-3-propionate (**13**): mp 59–60 °C (from methanol); UV (acetonitrile) 264 nm (log ε 4.00), 282 (4.01), 333 (3.74); ^{1}H NMR ($CDCl_3$) δ 2.67–3.32 (m, 4 H), 3.45 (s, 3 H), 3.57 (s, 3 H), 3.67 (s, 3 H), 7.01–7.66 (m, 4 H), 8.07 (s, 1 H), 9.87 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 28.1 (t), 33.9 (q), 34.2 (q), 37.2 (t), 51.6 (q), 105.3 (s), 110.8 (s), 111.1 (d), 118.1 (d), 119.4 (d), 122.3 (d), 126.7 (s), 135.3 (s), 135.3 (s), 139.7 (d), 141.2 (s), 163.1 (s), 174.0 (s); mass spectrum (relative intensity), m/e 341 (M^+, 100), 284 (28), 270 (41), 269 (23), 268 (100), 220 (97), 218 (90), 211 (24), 183 (39), 170 (61), 163 (38), 161 (29), 154 (28), 121 (22), 120 (20), 82 (30), 64 (23), 58 (34), 54 (33), 51 (69); exact mass spectrum m/e 341.1354 (calculated for $C_{18}H_{19}N_3O_4$, 341.1374).

Solvent Effect on the Formation of 6. Solutions of **2a** (3 mM) and **5** (1.5 mM) in various solvents were irradiated with a 100-W high-pressure pressure mercury lamp through Pyrex filter for 10 h. In each run the photoproduct (**6**) was isolated by preparative TLC as described before (Table I).

Sensitization. (A) With Acetophenone. A solution of **2a** (166 mg, 0.64 mmol), **5** (70 mg, 0.32 mmol) and acetophenone (7.35 g, 61.2 mmol) in acetonitrile (200 mL) was irradiated under the standard conditions for 10 h. After removal of the solvent, the residue was chromatographed on silica gel column ($CHCl_3$) to remove acetophenone. TLC analysis of the residue showed that it contains considerable amounts of polymeric products together with unreacted **2a** and **5**. Separation by preparative TLC ($CHCl_3$–acetonitrile, 9:2) gave only **2a** (61 mg) and **5** (65 mg).

Essentially the same results were obtained when **9** or N-methylindole was irradiated in the presence of **5** and acetophenone under the above conditions.

(B) With Benzophenone. A solution of **2a** (159 mg, 0.61 mmol), **5** (69 mg, 0.32 mmol), and benzophenone (5.03 g, 27.8 mmol) in acetonitrile (200 mL) was irradiated for 10 h. Similar workup followed by preparative TLC gave only **2a** (54 mg) and **5** (45 mg). **6** was not detected by TLC analysis.

(C) With Triphenylene. A solution of **2a** (163 mg, 0.63 mmol), **5** (65 mg, 0.3 mmol), and triphenylene (1.10 g, 48 mmol) in acetonitrile (200 mL) was irradiated for 10 h. After evaporation of the solvent, triphenylene was filtered off and the residue (530 mg) was purified by preparative TLC as described above. Only unreacted **2a** (156 mg) and **5** (34 mg) were obtained.

In the above sensitized reactions, concentrations of sensitizers were adjusted to such that more than 95% of the incident light was absorbed by the sensitizers.

Substituent Effect. (A) Methyl Indole-3-propionate (12). A solution of **5** (73 mg, 0.34 mmol) and **12** (157 mg, 0.78 mmol) in acetonitrile–acetone (3:1, 200 mL) was irradiated with a 100-W high-pressure mercury lamp (Pyrex filter) at 20 °C for 10 h. TLC analysis of the mixture showed none of the photoproducts. Preparative TLC ($CHCl_3$–acetonitrile, 9:1) of the reaction mixture gave unreacted **5** (65 mg) and **12** (125 mg).

(B) Tryptophan Methyl Ester (14). A solution of **5** (77 mg, 0.35 mmol) and **14** (151 mg, 0.69 mmol) in acetonitrile–acetone (3:1, 200 mL) was irradiated under the standard condition for 10 h. After removal of the solvent, the residue was purified by preparative TLC ($CHCl_3$–acetonitrile, 7:3) to give unreacted **5** (70 mg) and polymeric products (37 mg).

(C) N^b-*t*-Boc-tryptophan (15). A solution of **5** (68 mg, 0.31 mmol) and **15** (182 mg, 0.6 mmol) in acetonitrile–acetone (3:1, 200 mL) was irradiated for 10 h. A similar workup gave unreacted **5** (52 mg) and **15** (34 mg) together with considerable amounts of polymeric products.

(D) N^b-Methoxycarbonyltryptamine (16). A solution of **5** (64 mg, 0.29 mmol) and **16** (137 mg, 0.63 mmol) in acetonitrile–acetone (3:1, 200 mL) was irradiated for 10 h. A similar workup gave unreacted **5** (47 mg), **16** (84 mg), and polymeric products. The coupled product **17** could not be detected by careful TLC analyses.

(E) Indole. A solution of **5** (60 mg, 0.27 mmol) and indole (268 mg, 2.3 mmol) in acetonitrile–acetone (3:1, 200 mL) was irradiated for 10 h. A similar workup gave unreacted **5** (44 mg) and indole (260 mg).

Effect of Amines on the Formation of 6. (A) *n*-Butylamine. Solutions of **2a** (2.5 mM) and **5** (1.25 mM) in acetonitrile–acetone (3:1) containing varying amounts of *n*-butylamine were irradiated with a 100-W high-presure mercury lamp through Pyrex filter for 10 h under identical conditions. In each run the photoproduct **6** was isolated by preparative TLC. The results are shown in Figure 2.

(B) Triethylamine. A solution of **2a** (160 mg, 0.62 mM), **5** (65 mg, 0.3 mM), and triethylamine (82 mg, 0.9 mM) in acetonitrile–acetone (3:1, 200 mL) was irradiated for 10 h as described above. Evaporation of the solvent followed by preparative TLC of the residue gave **11** (12 mg, 46% based on consumed **5**), **2a** (101 mg), **and** 5 (24 mg).

Quantum Yield for the Formation of 6. Quantum yield measurement was carried out at 20 °C in a merry-go-round apparatus by using 0.1 M benzophenone–benzhydrol actinometry.[39] Potassium chromate (0.3 g/L) in 1% aqueous potassium carbonate was used to isolate the 313-nm region of the high-pressure mercury arc. Three solutions of **2a** (3×10^{-3} M) and 5 (1.4×10^{-3}M) in acetonitrile containing acetone (3.4 M) were prepared. Under the standard condition acetone absorbs more than 90% of the incident light. The actinometer and sample solutions were purged with nitrogen. The irradiation was stopped at less than 10% conversion of **5**. The sample solutions were assayed by Shimazu CS-900 TLC Scanner checked by UV spectroscopy by using precoated silica gel plates ($CHCl_3$–acetonitrile, 9:1). The error limit of this assay was ±20%.

Inhibitory Effect of Electron-Transfer Quenchers. A solution of **2a** (3 mM), **5** (1.5 mM) and a quencher (0.15 or 1.5 mM) in acetonitrile–acetone (3:1) was irradiated with a 100-W high-pressure mercury lamp through Pyrex filter at 20 °C for 10 h. In each run the photoproduct **6** was separated by preparative TLC (precoated silica gel plate, $CHCl_3$–acetonitrile, 9:2). In control runs a solution of **2a** and **5** without quencher was irradiated under the identical conditions for 10 h, and the photoproduct was assayed by the same method. The results are shown in Table III.

Acetone-Sensitized Photocoupling of 5 to N^b-Methoxycarbonyltryptamine (16) in the Presence of 2a as Electron Carrier. A solution of **2a** (151 mg, 0.58 mmol), **5** (64 mg, 0.29 mmol), and **16** (125 mg, 0.57 mmol) in acetone–acetonitrile (3:1, 200 mL) was irradiated with a 100-W high-pressure mercury lamp through Pyrex filter for 10 h. After removal of the solvent, the residue was purified by preparative TLC ($CHCl_3$–acetonitrile, 9:2) to give **2a** (88 mg), **5** (27 mg), **16** (21 mg), **6** (28 mg, 42% yield based on consumed **5**), and **17** (13 mg, 22% yield based on consumed **5**).

2-(1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-5-pyrimidinyl)-1*H*-3-(2-methoxycarbonylaminoethyl)indole (**17**): mp 163–168 °C dec (from acetone); UV (acetonitrile) 224 nm (log ε 4.33), 261 (3.98), 291 (3.95), 399 (3.71); ^{1}H NMR ($CDCl_3$) δ 2.97–3.21 (m, 2 H), 3.25–3.44 (m, 2 H), 3.44 (s, 3 H), 3.64 (s, 3 H), 3.68 (s, 3 H), 5.16 (br s, 1 H), 6.99–7.58 (m, 4 H), 8.20 (s, 1 H), 10.19 (s, 1 H, NH); ^{13}C NMR (acetone-d_6) δ 26.4, 30.1, 37.2, 42.1, 51.9, 105.5, 109.8, 112.0, 118.8, 119.7, 122.4, 128.8, 129.0, 136.6, 143.3, 151.6, 158.3, 163.5; mass spectrum (relative intensity), *m/e* 356 (M^+, 100), 269 (23), 268 (100), 211 (21), 188 (20), 183 (21), 172 (23), 170 (46), 168 (19), 154 (18), 146 (28), 145 (19), 142 (16), 130 (21), 120 (37), 115 (18); exact mass spectrum *m/e* 356.1520 (calculated for $C_{18}H_{20}N_4O_4$, 356.1483).

Solutions containing **2a** (2.9 mM), **5** (1.5 mM), and varying amounts of **16** in acetone–acetonitrile were prepared. Each solution was irradiated with a high-pressure mercury lamp under the identical conditions for 10 h. Photoproducts were separated by preparative TLC as described above. The results are shown in Figure 3.

Direct Photolysis of 1a in the Presence of Melatonin (18). A solution of **18** (111 mg, 0.48 mmol) and **1a** (91 mg, 0.25 mmol) in acetonitrile (150 mL) was irradiated by a 10-W low-pressure mercury lamp through Vycor filter for 10 h. Evaporation of the solvent followed by preparative TLC (dichloromethane–methanol–triethylamine, 40:3:2) of the residue gave **19** (13 mg, 13% yield based on consumed **1a**), the unreacted **1a** (19 mg), and $\mathbf{1}_b$ (6 mg).

5-[3-[2-(Acetylamino)ethyl]-5-methoxy-1*H*-indol-2-yl]-2′,3′-*O*-(1-methylethylidene)uridine (**19**): mp 108–113 °C dec (from CH_3OH); UV (acetonitrile) 219 nm (log ε 4.33), 274 (3.91), 307, (3.86), 330 (3.82); ^{1}H NMR (acetone-d_6) δ 1.36 (s, 3 H), 1.55 (s, 3 H), 1.86 (s, 3 H), 2.97 (t, 2 H, *J* = 7.8 Hz), 3.30–3.66 (m, t on addition of D_2O, 2 H, *J* = 7.8 Hz), 3.73–3.91 (br s, 2 H), 3.81 (s, 3 H), 4.23 (td, 1 H, *J* = 3.2, 3.4 Hz), 4.41–4.89 (br s, 3 H, OH and NH), 4.96 (dd, 1 H, *J* = 6.4, 3.2 Hz), 5.12 (dd, 1 H, *J* = 3.2, 6.4 Hz), 6.16 (d, 1 H, *J* = 3.2 Hz), 6.76 (dd, 1 H, *J* = 8.4, 2.4 Hz), 7.13 (d, 1 H, *J* = 2.4 Hz), 7.31 (d, 1 H, *J* = 8.4 Hz), 8.21 (s, 1 H), 10.09 (br s, 1 H, NH); ^{13}C NMR (Me_2SO-d_6) δ 22.7 (q), 25.3 (q), 27.2 (t), 29.0 (q), 40.3 (t), 55.5 (q), 61.4 (t), 80.7 (d), 83.8 (d), 86.5 (d), 91.3 (d), 100.4 (s), 107.2 (s), 110.6 (s), 111.6 (d), 111.9 (d), 113.1 (d), 127.7 (s), 128.1 (s), 131.0 (s), 140.9 (d), 150.0 (s), 153.2 (s), 161.2 (s), 169.3 (s); mass spectrum (relative intensity), *m/e* 514 (M^+, 6), 498 (5), 486 (4), 485 (7), 484 (6), 366 (5), 343 (26), 342 (28), 285 (24), 284 (79), 283 (66), 272 (30), 271 (82), 270 (100), 241 (7), 240 (8), 238 (10), 237 (15), 200 (8), 199 (7), 72 (12), 71 (40), 59 (20), 51 (38); exact mass spectrum *m/e* 514.2067 (calculated for $C_{25}H_{30}N_4O_8$, 514.2062).

Acetone-Sensitized Irradiation of 1a and N^b-*t*-Boc-tryptophylleucine Benzyl Ester (20). A solution of **20** (459 mg, 0.91 mmol) and **1a** (164 mg, 0.45 mmol) in acetonitrile–acetone (3:1, 200 mL) was irradiated with a 100-W high-pressure mercury lamp under the standard conditions for 14 h. After removal of the solvent, the residue was purified by preparative TLC ($CHCl_3$–acetonitrile, 9:3) to give unreacted **20** (216 mg), **1a** (77 mg) and **21** (146 mg, 49% yield based on consumed **1a**).

N^b-*t*-Boc-2-[1,2,3,4-tetrahydro-1-[2,3-*O*-(1-methylethylidene)-β-D-ribofuranosyl]-2,4-dioxo-5-pyrimidinyl]-L-tryptophylleucine benzyl ester (**21**): mp 172–174 °C dec (from acetone); UV (acetonitrile) 260 nm (log ε 4.49), 285 (4.41), 335 sh (4.15); ^{1}H NMR (CD_3OD) δ 0.84 (d, 3 H, *J* = 5.8 Hz), 0.88 (d, 3 H, *J* = 5.6 Hz), 1.30 (s, 9 H), 1.36 (s, 3 H), 1.54 (m, 1 H), 1.56 (s, 3 H), 3.12 (d, 2 H, *J* = 6.4 Hz), 3.21 (d, 2 H, *J* = 6.2 Hz), 3.78 (d, 2 H, *J* = 4.0 Hz), 4.24 (td, 1 H, *J* = 3.6, 4.0 Hz), 4.48 (t, 1 H, *J* = 6.4 Hz), 4.56 (t, 1 H, *J* = 6.2 Hz), 4.89 (dd, 1 H, *J* = 6.4, 3.6 Hz), 5.05 (s, 2 H), 5.09 (dd, 1 H, *J* = 2.6, 6.4 Hz), 6.4 (d, 1 H, *J* = 2.6 Hz), 6.92–745 (m, 3 H), 7.30 (s, 5 H), 7.58–7.78 (m, 1 H), 8.10 (s, 1 H); ^{13}C NMR (CD_3OD) δ 22.1 (q), 23.2 (q), 25.6 (q), 25.6 (d), 27.6 (t), 28.5 (q), 41.5 (t), 52.2 (d), 56.3 (d), 63.0 (t), 67.8 (t), 82.1 (d), 85.8 (d), 88.3 (d), 94.1 (d), 108.6 (s), 110.4 (s), 115.2 (s), 119.9 (d), 120.1 (d), 121.1 (d), 123.0 (d), 128.4 (s), 128.7 (d), 129.2 (d), 129.4 (s), 129.5 (d), 137.0 (s), 137.5 (s), 143.1 (d), 151.5 (s), 157.3 (s), 164.6 (s), 173.3 (s), 174.6 (s); exact mass spectrum *m/e* 789.3562 (calculated for $C_{41}H_{51}N_5O_{11}$, 789.3582).

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