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Multiple Paths for Photo-methylation and -methoxylation of Methyl 2-Pyridinecarboxylate in Methanol

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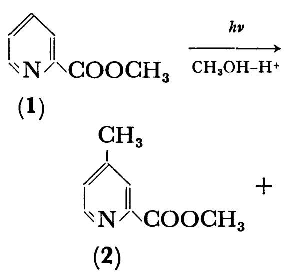
UV-irradiation of methyl 2-pyridinecarboxylate in methanol in the absence of added acid brings about methylation at the 5-position *via* the excitation of C=O of the ester group, while in the presence of added acid the 4-position of the pyridine ring is methylated. In the presence of sulfuric acid methoxylation *via* an excimer is dominant over methylation. In the presence of hydrochloric acid methylation *via* chlorine atoms becomes dominant.

Pyridinecarboxylic acids and their derivatives show a variety of photoreactions. In alcoholic solutions they undergo photochemical decarboxylation, alkylation, hydroxyalkylation, and alkoxylation.[1-4] The features of the photoreactions of the derivatives of pyridinecarboxylic acids are: 1) the photoreactivities are sensitive to the reaction conditions (the nature of the solvents, the concentration of the substrate, the added acids, the concentration of the added acid, and the additives), 2) the same products can be derived from the different excited states, and 3) the simultaneous contribution of several types of excited states.

Previously we reported the detailed analyses of the photoreactions of 3-pyridinecarboxylic ester in alcoholic solutions.[2] We report here the analysis of the photoreactions of 2-pyridinecarboxylic ester in alcohol.[5]

Results and Discussion

Similar to 3-pyridinecarboxylic ester, methyl 2-pyridinecarboxylate (**1**) undergoes the substitution of the ring hydrogen by alkyl or alkoxyl group derived from the solvent alcohol upon the UV-irradiation of **1** in the presence of sulfuric or hydrochloric acid.



The photo-methylation and -methoxylation of **1** are dependent on the reaction conditions: 1) concentration of the substrate, 2) added acid, and 3) additives.

In Figs. 1 and 2 are shown the dependencies of the photoreactions and the molar absorption coefficient of **1** on the concentration of the added acid at 10^{-3} mol dm^{-3} of **1**. The change in the molar absorption coefficient corresponds to the protonation and the deprotonation of the pyridine derivatives. The dependence of the efficiency of the photoreactions on the acid concentration correlates well with the dependence of the molar absorption coefficient on the acid concentration. This suggests that the photo-methylation and -methoxylation occur effectively, when the substrate is protonated.

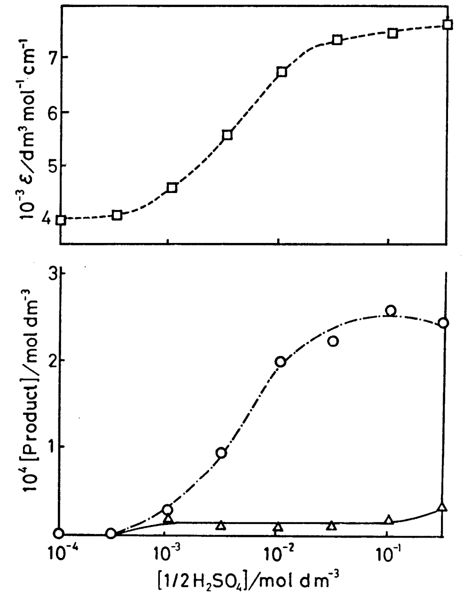


Fig. 1. Dependences of the photoreaction and the molar absorption coefficient of **1** upon the concentration of added H_2SO_4.
[**1**] = 1×10^{-3} mol dm^{-3}, irradiation time, 10 min.
—△—: Yield of **2**, ---○---: yield of **3**, ----□----: molar absorption coefficient.

In the photoreaction of **1** in methanol in the presence of H_2SO_4, the methoxylation at the 6-position is dominant and the methylation occurs in a low yield (Fig. 1). However, the methylation is promoted by hydrochloric acid, especially at its higher concentrations (Fig. 2). The addition of lithium chloride increases the yield for the methylation as is shown in Table 1. Analogous promotion of the methylation and depression of the methoxylation have been observed in the photoreaction of methyl 3-pyridinecarboxylate, for which a mechanism involving the electron transfer from chloride ion to the substrate has been proposed.[2] In the photoreaction of **1** in the presence of chloride ion, a similar mechanism should operate.

The most characteristic nature of the photo-methoxylation of **1** is its concentration dependence (Fig. 3). The concentration dependence suggests the participation of a dimer species of the substrate in the photo-methoxylation.

A mechanism involving an excimer can be postulated (Scheme 1). In this Scheme, **A** and **B** represent the products of other processes than the alkoxylation.

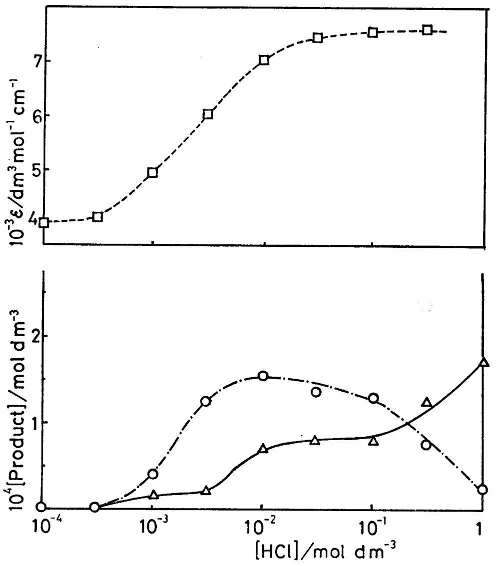


Fig. 2. Dependences of the photoreaction and the molar absorption coefficient of **1** upon the concentration of added HCl.
[**1**] = 1 × 10^{-3} mol dm^{-3}; irradiation time, 10 min.
—△—: Yield of **2**, ---○---: yield of **3**, ----□----: molar absorption coefficient.

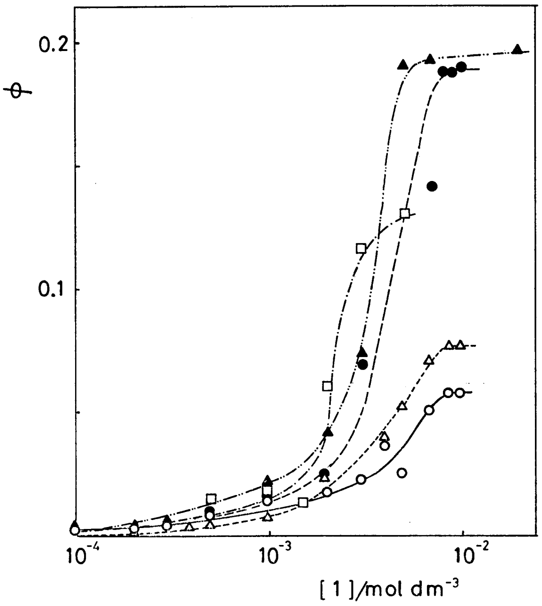


Fig. 3. Dependence of the quantum yield of photomethoxylation on the concentration of **1** at various temperatures.
[H_2SO_4] = 5 × 10^{-2} mol dm^{-3}.
—○—: at 11 °C, ----△----: at 17.5 °C, ---□---: at 27 °C, ---●---: at 32 °C, ····▲····: at 40 °C.

$$\mathbf{1} \xrightleftharpoons[k_{-1}]{h\nu} \mathbf{1}^*$$

$$\mathbf{1}^* + \mathbf{1} \xrightleftharpoons[k_{-2}]{k_2} (\mathbf{1}-\mathbf{1})^* \text{ (an excimer)}$$

$$(\mathbf{1}-\mathbf{1})^* + CH_3OH \xrightarrow{k_3} \mathbf{3}$$

$$(\mathbf{1}-\mathbf{1})^* \xrightarrow{k_4} 2\,\mathbf{1}$$

$$(\mathbf{1}-\mathbf{1})^* \xrightarrow{k_5} \mathbf{A}$$

$$\mathbf{1}^* \xrightarrow{k_6} \mathbf{B}$$

Scheme 1.

TABLE 1. EFFECT OF LITHIUM CHLORIDE ON THE PHOTOREACTION OF **1**
[**1**] = 1 × 10^{-3} mol dm^{-3}; irradiation time, 10 min.

[HCl] mol dm^{-3}	[LiCl] mol dm^{-3}	Alkoxylation [**3**] 10^{-5} mol dm^{-3}	Alkylation [**2**] 10^{-5} mol dm^{-3}
10^{-3}	—	3.6	1.9
10^{-3}	1	0.5	5.5
3 × 10^{-3}	—	23	5
3 × 10^{-3}	1	2	14

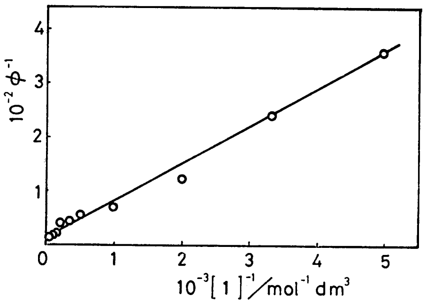


Fig. 4. Relation between the reciprocal of the quantum yields for the photomethoxylation at 40 °C and the reciprocal of the concentration of **1**.

The mechanism gives the following kinetic relationship:

$$1/\phi_3 = \frac{k_3[CH_3OH]+k_4+k_5}{k_3[CH_3OH]} + \frac{(k_{-1}+k_{-6})(k_{-2}+k_3[CH_3OH]+k_4+k_5)}{k_2k_3[CH_3OH]\,[\mathbf{1}]},$$

where ϕ_3 is the quantum yield of the methoxylation product *via* an excimer. The concentration of methanol is constant in the experimental conditions.

The plot of $1/\phi_3$ against $1/[\mathbf{1}]$ for the photo-methoxylation at 11 °C resulted in a straight line (Fig. 4) as predicted by the above equation and the mechanism *via* an excimer is thus kinetically supported.[6]

Since **1** is not fluorescent at any concentration even at the liquid nitrogen temperature, no direct evidence for the excimer has been obtained. However, the excimers of quinoline and isoquinoline have been established on the basis of the emission spectra.[7] These facts support the mechanism *via* an excimer.

The effects of additives for the photo-methylation are different from those for the photo-methoxylation. Because the additives absorb the 254 nm light competitively with the substrate, the effects of additives were analyzed by means of an index *A*, the relative quantum yield calculated on the basis of the light absorbed by the substrate,

$$A = Y/L$$

$$Y = \frac{\text{Yield in the presence of additive}}{\text{Yield in the absence of additive}}$$

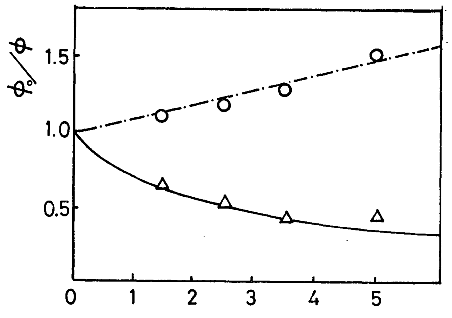


Fig. 5. Effect of benzene on the photoreaction of **1** in methanol acidified with H_2SO_4.
[**1**]$=1\times10^{-3}$ mol dm^{-3}, [H_2SO_4]$=5\times10^{-2}$ mol dm^{-3}.
—△—: **2**, ---○---: **3**.

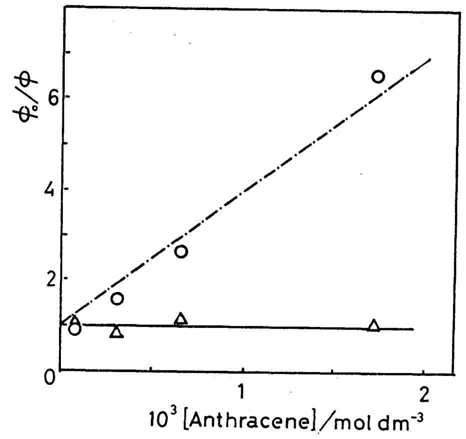


Fig. 6. Effect of anthracene on the photoreaction of **1** in methanol acidified with H_2SO_4.
[**1**]$=1\times10^{-3}$ mol dm^{-3}, [H_2SO_4]$=5\times10^{-2}$ mol dm^{-3}.
—△—: **2**, ---○---: **3**.

$$
\begin{aligned}
L &= \frac{\varepsilon_1 c_1}{\varepsilon_1 c_1 + \varepsilon_Q c_Q} \\
&= \{\text{Light absorbed by substrate } (\mathbf{1})\}/ \\
&\quad \{\text{Light absorbed by substrate } (\mathbf{1}) \\
&\quad + \text{Light absorbed by additive(Q)}\},
\end{aligned}
$$

where ε_1 and ε_Q are the molar absorption coefficients of the substrate and the additive at 254 nm, respectively. Symbols c_1 and c_Q are the concentrations of the substrate and the additive.

$A>1$ means that the additive promotes the reaction and $A<1$ means that the additive inhibits it. A^{-1} corresponds to ϕ_0/ϕ in the Stern-Volmer equation for the quenching experiment.

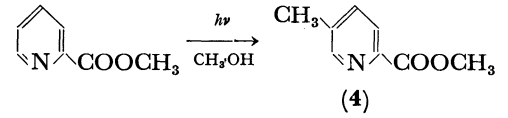
As is shown in Figs. 5 and 6, the methoxylation is inhibited to a smaller extent by benzene and to a larger extent by anthracene. Benzene, which has a high triplet energy value (E_T, 352 kJ mol^{-1}), is an inhibitor, although the effect is small. As reported earlier,[8] acetophenone has no effect on the photo-methoxylation. These facts suggest that the photo-methoxylation does not originate from a triplet state.

The additives may quench either an excited monomer or an excited dimer. The fact that the inhibition by anthracene was observed only for methoxylation and not for methylation suggests that the inhibition occurs not in the process of an excited monomer but in the process of an excited dimer.

The inhibition by benzene and anthracene can be explained by the electron transfer quenching by aromatic hydrocarbons:[9] anthracene with the lower ionization potential ($I_p=7.43$ eV[10]) causes greater inhibition ($k_q\tau=300$ dm^3 mol^{-1}) than benzene ($I_p=9.245$ eV,[10] $k_q\tau=10$ dm^3 mol^{-1}) with the higher ionization potential. (Here k_q is the rate constant for bimolecular quenching and τ is the lifetime of an excited species.) The results are similar to those reported by Caldwell *et al.*,[9] who investigated extensively the electron transfer quenching for excimers and exciplexes. Concerning the photo-methoxylation peculiar effects of additives were observed:[8] the photo-methoxylation is promoted specifically by 4-substituted pyridines. The promotion is explained by the exciplex formation between **1** and the 4-substituted pyridine.

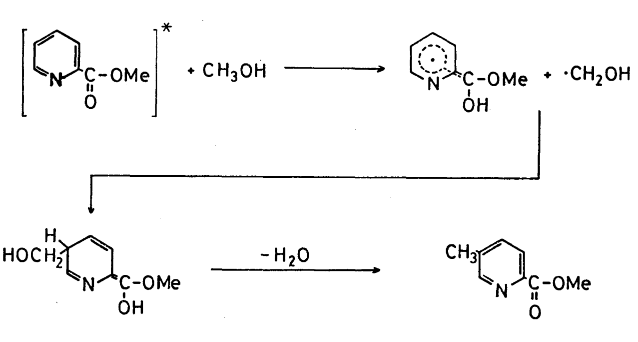
The photo-methylation at the 4-position in the presence of added acid is promoted by benzene. Anthracene has no effect on the reaction. However, a detailed study on the excited state responsible for the formation of **2** could not be done, because methylation is only a very minor reaction.

The UV-irradiation of **1** in methanol in the absence of added acid gives a methylation product. In this case methylation occurs at the 5-position and the efficiency for the methylation at the 5-position is much lower than that at the 4-position in the presence of acid.



(**4**)

With pyridine derivatives photoreactions occur normally at α- and γ-positions.[11] For the unusual alkylation at the β-position, the participation of the ester group should be taken into consideration. The hydrogen abstraction by the excited C=O of the ester group (or the electron transfer followed by proton transfer) has been reported for some aromatic esters.[12] Thus, the following mechanism is conceivable for the photo-methylation at the 5-position.



The effects of additives on the photo-methylation in the absence of added acids (Table 2) suggest that a triplet state is responsible for the methylation at the 5-position: the additives with higher triplet energies, benzene ($E_T=352$ kJ mol^{-1}) and naphthalene ($E_T=255$ kJ mol^{-1}), promote the photo-methylation, anthracene ($E_T=178$ kJ mol^{-1}) has no effect, and oxygen inhibits the reaction.

Table 2. Effects of additives on the formation of **4** in the absence of added acid

$[\mathbf{1}]=1\times10^{-3}$ mol dm^{-3}; irradiation time, 20 min.

Additive	[Additive] / mol dm^{-3}	L[a]	Y[a]	A[a]
Benzene	5.0×10^{-3}	0.87	1.05	1.21
	5.0×10^{-2}	0.40	0.87	2.18
Naphthalene	2.2×10^{-3}	0.84	1.10	1.31
	1.1×10^{-2}	0.50	2.41	4.82
Anthracene	3.9×10^{-5}	0.41	0.39	0.96
	1.6×10^{-4}	0.15	0.15	1.00
Oxygen	saturated	1.00	0.0	0.0

a) See text for the definition of L ,Y and A.

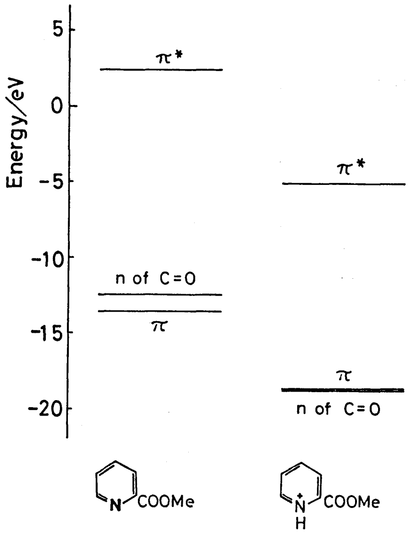


Fig. 7. Electronic state of **1**.

The participation of the n-π* state of the C=O in the ester group is supported by the consideration of the electronic states calculated by means of CNDO/2.[13] The results are shown in Fig. 7. For the free base form of **1**, the highest occupied orbital is assigned to the non-bonding orbital at C=O. On the other hand, for the pyridinium form π-orbital is the highest occupied orbital. This result can explain that the n-π* excited state is preferably formed in the irradiation of the free base form of **1**, whereas the π-π* excited state is populated in the photoreaction of the pyridinium form of **1**.

The photoreactions of methyl 2-pyridinecarboxylate, thus, can be summarized in Scheme 2.

Experimental

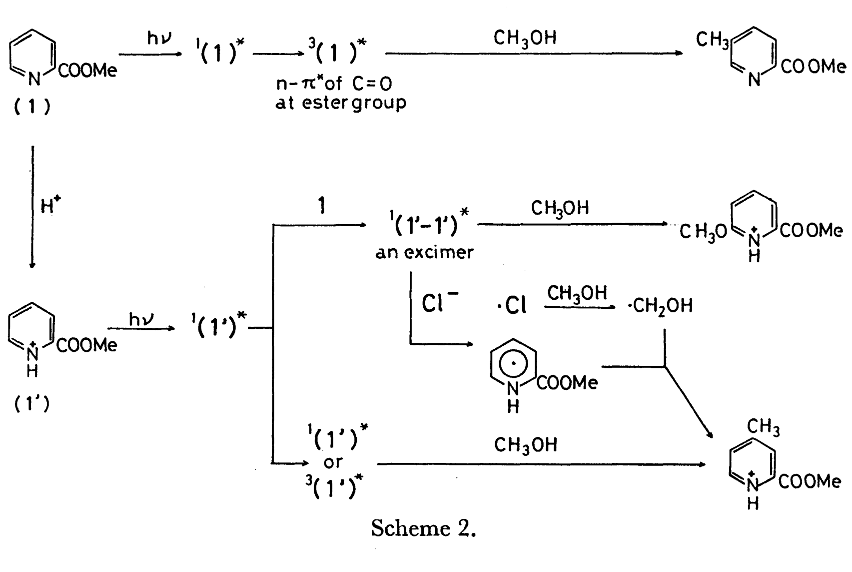
Materials. Commercial methyl 2-pyridinecarboxylate (**1**) (GR grade reagent of Tokyo Kasei Co.) was purified by vacuum distillation; bp 105—108 °C/7 mmHg. (1 mmHg≈133.322 Pa.) Anthracene (standard reagent for elementa analysis made by E. Merck Co.) was used for the quenching experiment.

UV-irradiation. The solutions of **1** containing mineral acid, and the additive if necessary, were deaerated by bubbling nitrogen or argon for 40 min before irradiation. The solutions were irradiated with a low pressure mercury lamp in a merry-go-round type irradiation apparatus which was set in a thermostat. Irradiation was carried out at 20 °C except in the experiment for temperature dependence.

Isolation and Identification of Products. After the irradiation the solution was concentrated under reduced pressure and neutralized with sodium hydrogencarbonate when the mineral acid was present. The products were extracted repeatedly with dichloromethane and were separated by means of TLC (plate, GF_{254} (Type 60) of E. Merck Co.; developing solvent, ethyl acetate–dichloromethane 1 : 1 v/v)

Methyl 4-methyl-2-pyridinecarboxylate (**2**), methyl 5-methyl-2-pyridinecarboxylate (**4**), and methyl 6-methoxy-2-pyridinecarboxylate (**3**) were identified by the accordance of their NMR spectra with those reported by Deady *et al.*[14]

Determination of the Yields of Products. The yields of the photoproducts were determined by the UV-spectrophotometric method or by the gas-chromatographic method. For the determination of the quantum yields for the photo-methoxylated product (data for Figs. 3 and 4) the spectrophotometric method was applied using the characteristic absorption of **3** at 287 nm. Actinometry was carried out by using potassium trioxalatoferrate(III). In other cases, the yields of the products were determined by means of GLC (column, 2 m column of PEG 20M (10%) on Celite 545 or 2 m column of Triton OS-15 (15%) on Uniport B; column temperature, 160—170 °C).



Scheme 2.

The authors are grategul to Professor L. W. Deady of La Trobe University in Australia for sending us the spectral data of pyridinecarboxylic acid derivatives.

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6) The following mechanism *via* the excitation of a dimer formed in the ground state could explain the concentration dependence in Fig. 3 qualitatively.

$$2\,\mathbf{1} \overset{K}{\rightleftharpoons} (\mathbf{1}-\mathbf{1})$$

$$(\mathbf{1}-\mathbf{1}) \xrightarrow{h\nu} (\mathbf{1}-\mathbf{1})^*$$

$$\mathbf{1} \underset{k_{-1}}{\overset{h\nu}{\rightleftharpoons}} \mathbf{1}^*$$

$$(\mathbf{1}-\mathbf{1})^* + \mathrm{CH_3OH} \xrightarrow{k_3} \mathbf{3}$$

$$(\mathbf{1}-\mathbf{1})^* \xrightarrow{k_4} 2\,\mathbf{1}$$

$$(\mathbf{1}-\mathbf{1})^* \xrightarrow{k_5} \mathbf{A} \text{ (Product of the side reaction from } (\mathbf{1}-\mathbf{1})^*\text{)}$$

$$\mathbf{1}^* \xrightarrow{k_6} \mathbf{B} \text{ (Product of the side reaction from } \mathbf{1}^*\text{)}$$

This mechanism, however, leads to the following expression for ϕ_3, the quantum yield of **3**:

$$1/\phi_3 = \left(\frac{k_3[\mathrm{CH_3OH}]+k_4+k_5}{4K\,k_3[\mathrm{CH_3OH}]}\right)\left\{\frac{1}{c}+4K+\left(\frac{1}{c^2}+8K\frac{1}{c}\right)^{1/2}\right\},$$

where $c=[\mathbf{1}]+[(\mathbf{1}-\mathbf{1})]$. This expression is based on the assumption that the molar absorption coefficient of (**1**—**1**) is twice that of **1**. Evidently the above mechanism is not compatible with the observed linear dependence of $1/\phi_3$ on $1/c$ (Fig. 4). The fact that the UV-spectra of **1** at higher concentrations, where photo-methoxylation occurs effectively, are identical with those at much lower concentrations is consitent with the view that (**1**—**1**) plays no important role.

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