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Multiple Paths for Photo-alkylation and -alkoxylation of 3-Pyridinecarboxylic Ester in Alcohol. Simultaneous Contribution of Several Kinds of Excited States

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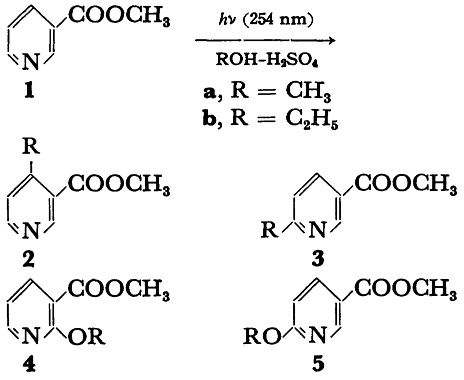
UV-irradiation of methyl 3-pyridinecarboxylate (**1**) in acidic alcoholic solutions brings about the alkoxylation and alkylation at the pyridine ring. Photoalkylation occurs in several paths: 1) alkylation initiated by the triplet π-π^* state, 2) alkylation initiated by the triplet n-π^* state of the carbonyl moiety of the ester group, 3) alkylation initiated by an exciplex between a free base form of **1** and a pyridinium form of **1**, and 4) alkylation promoted by chloride ions. Photoalkoxylation originates from a singlet excited state of **1**. In the photoreactions of **1** in strongly acidic methanolic solutions acidified with H_2SO_4, three kinds of excited states (two kinds of triplet states for alkylation and a singlet state for alkoxylation) contribute simultaneously.

Photochemical reactions of azaaromatic compounds with alcohols have been extensively investigated.[1] Previously we reported alkylation and alkoxylation in the photoreactions of pyridinecarboxylic acid derivatives.[2] Stermitz *et al.* explained the photoalkylation at α- and γ-positions of the pyridine ring according to the mechanism of hydrogen abstraction by excited protonated pyridines from alcohol, followed by the geminate radicals and dehydration.[3] Castellano *et al.* proposed a mechanism for photoalkylation *via* the monophotonic hydrogen abstraction by n-π^* state-pyridine in neutral alcoholic solutions, and *via* biphotonic electron transfer in alcoholic solutions acidified with HCl.[4] In the latter case they did not detect the formation of Cl atoms. We report here that the photoalkylation and photoalkoxylation of 3-pyridinecarboxylic ester in alcohol proceed in several different pathways.[5] The 3-pyridinecarboxylic ester–alcohol system is a very interesting system in which several excited states of the same multiplicity contribute simultaneously. β,γ-Unsaturated ketone is another system in which $^3(\pi$-$\pi^*)$ and $^3(\text{n}$-$\pi^*)$ contribute simultaneously.[6]

Results and Discussion

The UV-irradiation of methyl 3-pyridinecarboxylate (**1**) in alcohols in the presence of mineral acids brings about two types of substitution by the groups derived from the solvent alcohols: alkylation and alkoxylation. The substitution occurs at the α- and γ-positions of the pyridine ring. In the methanolic solutions acidified with sulfuric acid, two alkylation products (**2a** and **3a**) and two alkoxylation products (**4a** and **5a**) are formed by the irradiation with 254 nm light.



The yields of the products are linear with the irradiation time, as exemplified by the photoreaction under the conditions of $[\mathbf{1}] = 1\times10^{-2}$ mol dm^{-3} and $[H_2SO_4] = 5\times10^{-2}$ mol dm^{-3} (Fig. 1).

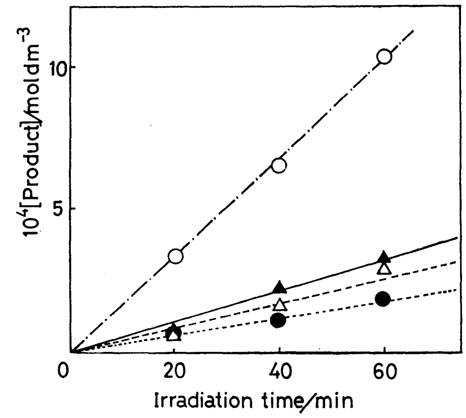


Fig. 1. Relation between the product yield and the irradiation time. Irradiated with 254 nm light in methanol.
$[\mathbf{1}] = 1\times10^{-2}$ mol dm^{-3}; $[H_2SO_4] = 5\times10^{-2}$ mol dm^{-3}.
---△---: **2a**, —▲—: **3a**, -·-○-·-: **4a**, ···●···: **5a**.

The photo-alkylation and -alkoxylation of 3-pyridinecarboxylic ester are dependent upon the reaction conditions: 1) the concentration of the substrate, 2) the mineral acid added, 3) the concentration of the added acid, 4) the nature of the solvent alcohol, and 5) additives.

Figure 2 shows the dependences of photoreactions on the concentrations of sulfuric acid at 1×10^{-3}, 3×10^{-3}, and 1×10^{-2} mol dm^{-3} concentrations of methyl 3-pyridinecarboxylate.

As is seen typically in Figs. 2—3, the acidity dependence of the photoreactions of **1** is complex, with photoalkylation and -alkoxylation competing. The region where photoalkylation is effective is divided into two parts.

In the higher acidity region (Region B), alkylation and alkoxylation are comparable. The peak of alkyla-

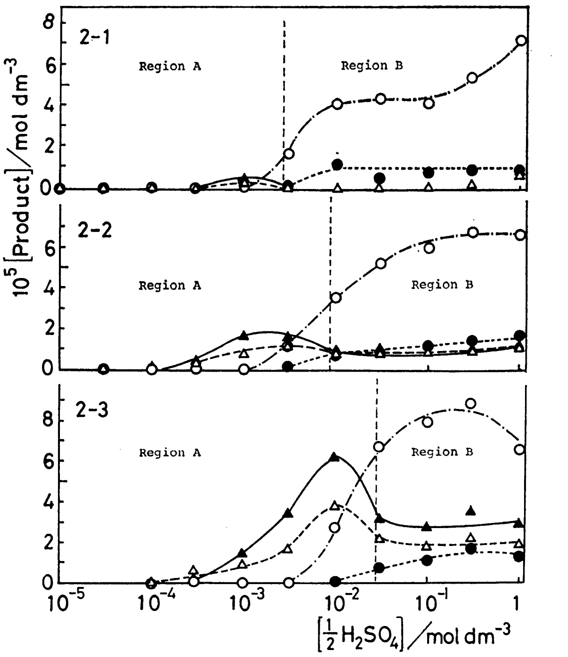


Fig. 2. Dependence of the photoreactions of **1** on the concentration of H_2SO_4 (irradiation time, 60 min). 2-1: [**1**]$=1\times10^{-3}$ mol dm^{-3}, 2-2: [**1**]$=3\times10^{-3}$ mol dm^{-3}, 2-3: [**1**]$=1\times10^{-2}$ mol dm^{-3}, ---△---: **2a**, —▲—: **3a**, -·-○-·-: **4a**, ···●···: **5a**.

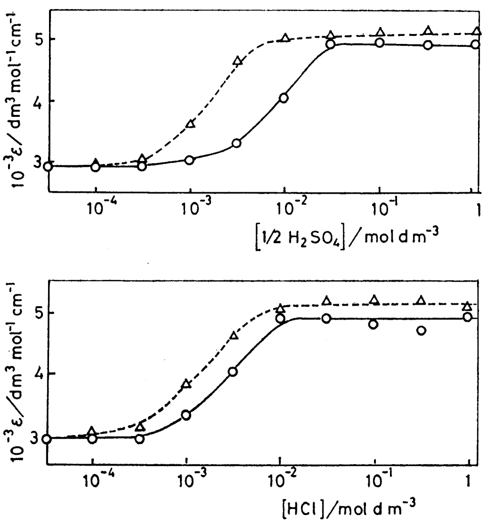


Fig. 3. Relation between the molar absorption coefficients of **1** and the concentration of mineral acids. --△--: [**1**]$=10^{-3}$ mol dm^{-3}, —○—: [**1**]$=3\times10^{-3}$ mol dm^{-3}.

tion in the lower acidity region (Region A) moves depending on the concentration of the substrate (**1**). As the concentration of **1** becomes lower, the acid concentration which gives the peak becomes lower and the peak height goes down.

The acidity dependence of the molar absorption coefficient of **1** in methanol (Fig. 3) indicates that **1** exists in the pyridinium form in Region B. In Region A the pyridinium form and the free base-form of **1** coexist.

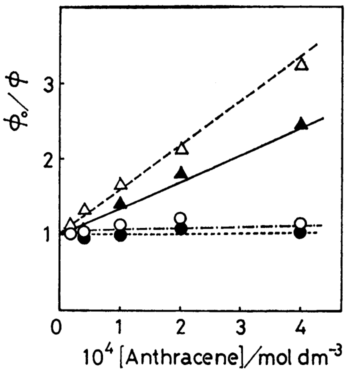


Fig. 4. Effect of anthracene on the photoreactions of **1**. [**1**]$=1\times10^{-2}$ mol dm^{-3}; [H_2SO_4]$=5\times10^{-2}$ mol dm^{-3}, --△--: **2a**. —▲—: **3a**, -·-○-·-: **4a**, ···●···: **5a**.

The excited states responsible for the photo-alkylation and -alkoxylation in the higher acidity region were assigned by the effects of additives, solvents, and temperature.

Figure 4 shows Stern-Volmer plots for the quenching by anthracene, a triplet quencher ($E_T=176$ kJ mol^{-1}). Because anthracene absorbs the light of 254 nm competitively with the substrate, the quantum yields are normalized on the basis of the light absorbed by the substrate by the following formula:

$$\phi_0/\phi = \mathrm{L/Y},$$

$$\mathrm{Y} = \frac{\text{Yield in the presence of quencher}}{\text{Yield in the absence of quencher}},$$

$$\mathrm{L} = \frac{\text{Light absorbed by the substrate}}{\text{Light absorbed by the substrate} + \text{Light absorbed by the quencher}}.$$

The Stern-Volmer plots indicate that the alkylation and the alkoxylation originate from triplet and singlet exited states, respectively. Furthermore, the different dependences of anthracene on the two alkylation reactions suggest that the product alkylated at α- and γ-positions originate from the triplet excited states of different character.

This view is supported by the temperature dependence of the photoreactions. Figure 5 is the plot of ln(relative

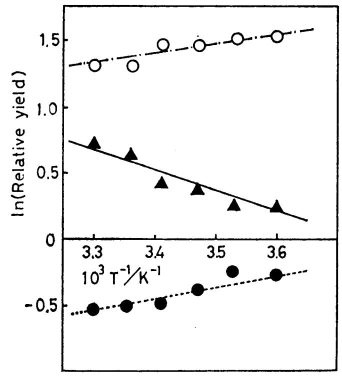


Fig. 5. Temperature dependence of photoreactions of **1**. Relative yield = yield of product/yield of **2a**. —▲—: **3a**, -·-○-·-: **4a**, ···●···: **5a**.

Table 1. Effects of additives on the photoalkylation and alkoxylation of **1**
$[\mathbf{1}]=1\times10^{-2}$ mol dm^{-3}; Irradiation time, 50 min.

Additive	$\frac{[\text{Additive}]}{\text{mol dm}^{-3}}$	$[H_2SO_4]=5\times10^{-3}$ mol dm^{-3} 10^5 [Product]/mol dm^{-3}				$[H_2SO_4]=5\times10^{-2}$ mol dm^{-3} 10^5[Product]/mol dm^{-3}			
		Alkylation		Alkoxylation		Alkylation		Alkoxylation	
		2a	**3a**	**4a**	**5a**	**2a**	**3a**	**4a**	**5a**
—	—	3.7	6.1	2.7	0.5	1.8	2.7	7.9	1.1
Benzene	10^{-1}	1.6	3.3	0.0	0.0	3.1	5.8	6.6	1.1
Naphthalene	10^{-2}	0.9	5.4	0.0	0.0	2.7	9.3	6.6	0.5
Anisole	10^{-2}	1.8	3.3	0.0	0.0	1.3	1.8	6.5	1.0
Oxygen						0.0	0.0	1.4	0.5

Table 2. Dependence of photoreactions of **1** on alcohol
$[\mathbf{1}]=2\times10^{-2}$ mol dm^{-3}.
$[H_2SO_4]=1.5\times10^{-1}$ mol dm^{-3}.

Alcohol	Yield of product/%[a)]			
	Alkylation		Alkoxylation	
	2	**3**	**4**	**5**
Methanol	7.1	9.5	8.8	3.8
Ethanol	0.0	31.6	2.0	0.7

a) Yields are based on the quantity of **1** consumed. Analysis was done by means of TLC and NMR.

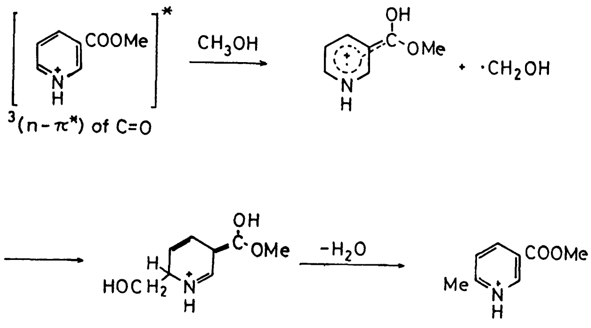
yield) *vs.* the reciprocal of temperature; the slope of the plot gives the difference in the activation energies between a given reaction and the standard reaction (in this case the formation of **2a**).

The plots for the two alkoxylation reactions have the same temperature dependence, whereas the photoalkylations at α- and γ-positions differ in temperature dependence.

The effects of benzene, naphthalene, and anisole (Table 1) (small effects on the photoalkoxylation, large effects on the photoalkylation, and different effects on the two alkylation reactions) also support the view.

The results obtained in the irradiation in ethanol are compared with those in methanol (Table 2). The irradiation in ethanol depresses the alkoxylation, but the change in the ratio of the isomers is small. Alkylation becomes dominant and the product ethylated at the 6-position is selectively formed. The solvent effect indicates that the triplet states responsible for the alkylation at the 6-position and the 4-position are of n-π^* and π-π^* character, respectively.

As the photoreactions occur in acidic solutions, the n-π^* state should not be the excitation of the electrons at N atom, because the lone pair electrons are donated to a proton. However, the excitation of the lone pair electrons located at O atom of the ester C=O is possible. In the UV-irradiation of 2-pyridinecarboxylic ester in methanol, methylation occurs at the 5-position.[5)] This indicates the participation of the excited C=O moiety in the alkylation. The hydrogen abstraction by the excited C=O of the ester group (or the electron transfer followed by the proton transfer) has been reported for some aromatic esters.[7)] These facts suggest that the excitation of the ester C=O can contribute to the photoreactions of 3-pyridinecarboxylic ester. If the excitation of a non-bonding electron of C=O is taken into account, the alkylation at the 6-position can be explained as is shown in Scheme 1.



Scheme 1.

The alkylation at the 4-position can be explained by the reaction of π-π^* state through the mechanism proposed by Stermitz *et al.*[3)]

The results of quenching, solvent effects, and temperature dependence show that the two alkoxylation products are due to the same excited state. Alkoxylation occurs presumably *via* the nucleophilic attack of alcohol to the polar, singlet excited-state substrate.

The fact that, in Region A, pyridinium and free base forms of **1** coexist suggest that the alkylation in Region A is brought about by the cooperation of the pyridinium and free base forms.

The effects of benzene, naphthalene, and anisole on the photoalkylation in Region A are different from those in Region B (Table 1). This also suggests that the mechanism for alkylation reactions in Regions A and B are different.

We propose two mechanisms for alkylation in Region A: *via* an excited complex between the excited pyridinium and the ground-state free base and *via* that between the excited free base and the ground-state pyridinium; these are shown in Scheme 2.

In the Scheme, Py and PyH$^+$ stand for the free base and pyridinium forms of 3-pyridinecarboxylic esters, respectively. *K* is the equilibrium constant and *k*'s are the rate constants of the corresponding reactions, and ε_A and ε_B are the molar absorption coefficients of the pyridinium and free base forms of **1** at the wavelength

Mechanism A

$$\mathrm{Py} + \mathrm{H^+} \overset{K}{\rightleftharpoons} \mathrm{PyH^+}$$

$$\mathrm{PyH^+} \underset{k_{-2}}{\overset{h\nu,\, k_2}{\rightleftharpoons}} (\mathrm{PyH^+})^* \qquad k_2 = \frac{I\,\varepsilon_A[\mathrm{PyH^+}]}{\varepsilon_A[\mathrm{PyH^+}] + \varepsilon_B[\mathrm{Py}]}$$

$$(\mathrm{PyH^+})^* + \mathrm{Py} \xrightarrow{k_3} (\mathrm{PyHPy^+})^*$$

$$(\mathrm{PyHPy^+})^* \xrightarrow{k_4} \mathrm{PyH^+} + \mathrm{Py}$$

$$(\mathrm{PyHPy^+})^* \xrightarrow{k_5} \longrightarrow \text{Alkylation product}$$

Mechanism B

$$\mathrm{Py} + \mathrm{H^+} \overset{K}{\rightleftharpoons} \mathrm{PyH^+}$$

$$\mathrm{Py} \underset{k'_{-2}}{\overset{h\nu,\, k_2'}{\rightleftharpoons}} \mathrm{Py}^* \qquad k_2' = \frac{I\,\varepsilon_B[\mathrm{Py}]}{\varepsilon_A[\mathrm{PyH^+}] + \varepsilon_B[\mathrm{Py}]}$$

$$\mathrm{Py}^* + \mathrm{PyH^+} \xrightarrow{k_3'} (\mathrm{PyHPy^+})^*$$

$$(\mathrm{PyHPy^+})^* \xrightarrow{k_4'} \mathrm{PyH^+} + \mathrm{Py}$$

$$(\mathrm{PyHPy^+})^* \xrightarrow{k_5'} \longrightarrow \text{Alkylation product}$$

Scheme 2.

of the irradiating light (intensity, I).

The mechanisms A and B can explain a) the appearance of the peak for the alkylation at an acid concentration and b) the fact that the peak height (maximum quantum yield) increases with the increase in the substrate concentration.

According to mechanism A, the quantum yield of the product (ϕ) is:

$$\phi = \frac{k_3 k_5}{k_4 + k_5}\,\frac{c}{k_{-2}(1+K[\mathrm{H^+}]) + k_3 c}\,\frac{K[\mathrm{H^+}]}{K[\mathrm{H^+}] + \varepsilon_B/\varepsilon_A},$$

where $c=[\mathrm{Py}]+[\mathrm{PyH^+}]$.

The quantum yield of the photoreaction reaches the maximum at $[\mathrm{H^+}]_{\mathrm{max}}$:

$$[\mathrm{H^+}]_{\mathrm{max}} = \frac{1}{K}\sqrt{\frac{\varepsilon_B k_3}{\varepsilon_A k_{-2}}\left(c + \frac{k_{-2}}{k_3}\right)}.$$

The maximum quantum yield, ϕ_{max}, at $[\mathrm{H^+}]_{\mathrm{max}}$ is

$$\phi_{\mathrm{max}} = \frac{\dfrac{k_3 c}{k_{-2}}}{\left\{2\sqrt{\dfrac{\varepsilon_B}{\varepsilon_A}\left(1+\dfrac{k_3 c}{k_{-2}}\right)} + \left(1+\dfrac{\varepsilon_B}{\varepsilon_A}\right) + \dfrac{k_3 c}{k_{-2}}\right\}\left(1+\dfrac{k_4}{k_5}\right)}.$$

The ϕ_{max} value thus obtained is 0 at $c=0$ and increases monotonously with c to reach the limiting value of $(1+k_4/k_5)^{-1}$. A similar conclusion can be deduced from mechanism B.

Mechanisms A and B can explain qualitatively the results shown in Fig. 2, where the vertical axis is expressed in the concentrations of the products formed after 60 minutes' irradiation. The values are proportional to the quantum yields for the products. No direct evidence for the participation of an excited complex is obtained, because methyl 3-pyridinecarboxylate is not fluorescent under any conditions. At present we have no experimental results from which we decide which mechanism actually operates.

Dependences of the photoreactions on the concentration of hydrochloric acid are shown in Fig. 6. The presence of hydrochloric acid depresses the alkoxylation

TABLE 3. EFFECT OF LITHIUM CHLORIDE ON THE PHOTOREACTION OF **1**. Irradiation time, 10 min.

[1] mol dm^{-3}	[HCl] mol dm^{-3}	[LiCl] mol dm^{-3}	[Alkylation product] 10^{-5} mol dm^{-3}		[Alkoxylation product] 10^{-5} mol dm^{-3}	
			2a	**3a**	**4a**	**5a**
1×10^{-3}	1×10^{-2}	—	1.8	2.2	3.7	0.5
1×10^{-3}	1×10^{-2}	1	3.4	4.5	0.9	—
1×10^{-2}	1×10^{-2}	—	11.8	17.3	5.2	0.3
1×10^{-2}	1×10^{-2}	1	14.4	20.4	—	—

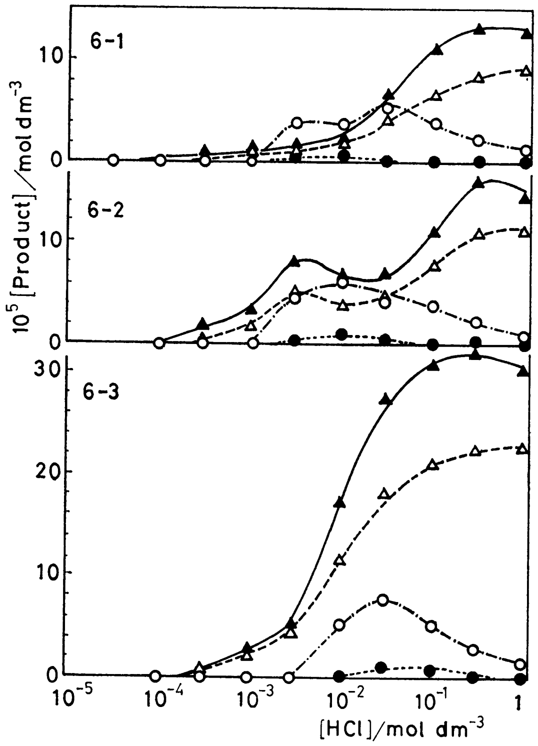


Fig. 6. Dependence of the photoreactions of **1** on the concentration of HCl (irradiation time, 60 min).
6-1: [**1**]$=1\times10^{-3}$ mol dm^{-3}, 6-2: [**1**]$=3\times10^{-3}$ mol dm^{-3}, 6-3: [**1**]$=1\times10^{-2}$ mol dm^{-3},
---△---: **2a**, —▲—: **3a**, -·-○-·-: **4a**, ···●···: **5a**.

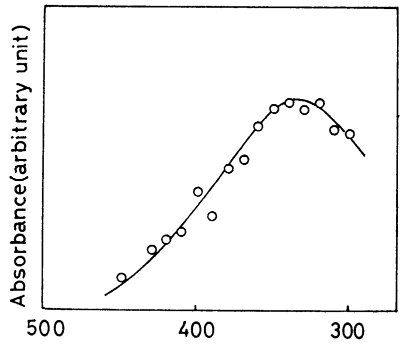
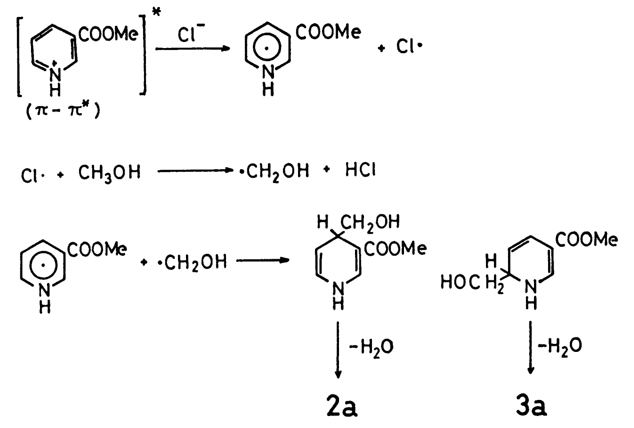


Fig. 7. Absorption spectrum in the flash photolysis of the 3-pyridinecarboxylic acid–HCl–H_2O system. Spectrum of 2 μs after the flash. [3-Pyridinecarboxylic acid]$=5\times10^{-4}$ mol dm^{-3}, [HCl]$=1$ mol dm^{-3}.



Scheme 3.

and instead promotes the alkylation. The inhibition of alkoxylation and the promotion of alkylation are remarkable in the higher concentration region of hydrochloric acid.

The promotion of alkylation by hydrochloric acid can be attributed to the participation of chloride ions; the addition of lithium chloride promotes the alkylation and depresses the alkoxylation (Table 3).

As the mechanism for the promotion of alkylation by chloride ions, two paths are conceivable: the acceleration of intersystem crossing by the external heavy atom effect and/or a reaction involving chloride ions. At present we can not conclude which mechanism operates. However, the results of the flash photolysis favor the latter mechanism.

In the microsecond flash photolysis of aqueous 3-pyridinecarboxylic acid acidified with hydrochloric acid (photolyzing light, emission from Ar; duration of a flash, 4 μs; energy of a flash, 10 J), a transient absorption was observed at λ_{max}=340 nm, which is similar to that of $Cl_2^{\cdot-}$ reported by Anbar and Thomas.[8]

The promotion of alkylation by chloride ions thus can be explained by a mechanism *via* chlorine atoms formed in the electron transfer from chloride ions to the excited pyridinium, which should undergo electrophilic alkoxylation in the absence of chloride ions. The alkylation of 3-pyridinecarboxylic ester *via* chlorine atoms should proceed as in Scheme 3.

The photoreactions of 3-pyridinecarboxylic ester in the region of higher concentration of acids are summarized in Scheme 4.

Experimental

Materials. Commercial methyl 3-pyridinecraboxylate (GR grade reagent of Tokyo Kasei Co.) was purified by vacuum distillation. Mp, 36—37 °C. Anthracene (standard reagent for elemental analysis made by E. Merck Co.) was used for the quenching experiment.

UV-irradiation. Methanolic or ethanolic solutions containing methyl 3-pyridinecarboxylate (10^{-3} — 10^{-2} mol dm^{-3}), sulfuric acid or hydrochloric acid (10^{-5} — 1 mol dm^{-3}), and the additive in the quenching experiment were deaerated by bubbling nitrogen or argon for 30 min before irradiation. The solutions were irradiated with a low pressure mercury lamp in a merry-go-round type irradiation apparatus normally at 32 °C.

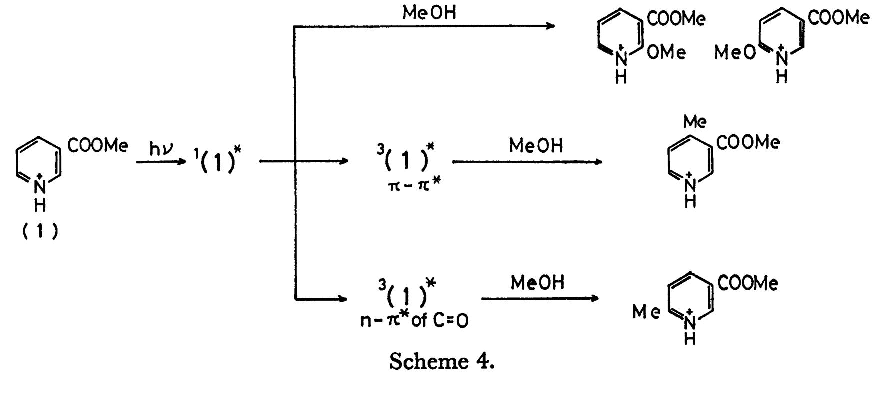
Isolation and Identification of Products. After the irradiation the solution was concentrated under reduced pressure. The solution was neutralized with sodium hydrogencarbonate and the products were extracted repeatedly with dichloromethane. The products were separated by means of thin-layer chromatography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

Methyl 2-methoxy-3-pyridinecarboxylate (**4a**), liquid (lit,[9] 28—29 °C), IR, 2980, 2950, 2850 (C–H), 1732 (ester C=O), 1270, 1130, 1082 (C–O–C), and 790 cm^{-1} (bending of C–H in the pyridine ring); NMR($CDCl_3$) δ=8.27 (1H, dd, J=5.1 and 2.5 Hz, H at the 6-position), 8.09 (1H, dd, J=7.9 and 2.5 Hz, H at the 4-position), 6.92 (1H, q, J=7.9 and 5.1 Hz, H at the 5-position), 4.09 (3H, s, OCH_3), and 3.91 (3H, s, $COOCH_3$).

Methyl 6-methoxy-3-pyridinecarboxylate (**5a**) was identified by the accordance of its NMR spectra with those obtained by Deady *et al.*[10]

Methylation products (the products methylated at 4- and 6-positions) could not be isolated by means of TLC. Methyl 6-methyl-3-pyridinecarboxylate (**3a**), one of the methylation products, was identified by the accordance of NMR and GLC with those of the authentic sample synthesized by the method of Graf.[11] The other component in the mixture was identified NMR-spectroscopically. The following NMR spectra were ascribed to methyl 4-methyl-3-pyridinecarboxylate (**2a**). NMR($CDCl_3$) δ=9.10 (1H, s, H at the 2-position), 8.52 (1H, d, J=6.0 Hz, H at the 6-position), 7.15 (1H (1H, d, J=6.0 Hz, H at the 5-position), 3.9 ($COOCH_3$), and 2.6 (CH_3).

The corresponding ethylation and ethoxylation products were identified by comparing their NMR and IR spectra with those of the corresponding methylation and methoxylation products.



Scheme 4.

Determation of the Yields of Products. After the irradiation the reaction mixture was concentrated under reduced pressure and was neutralized with sodium hydrogencarbonate. The products were extracted with dichloromethane and were analyzed by means of GLC (column, 3 m column of PEG 20M (10%) on Celite 545; column temperature, 165 °C) with a Shimadzu gas-chromatograph Model GC-6A. The gas-chromatographic sensitivy of each compound was determined by using the solution of the known concentration. For **2a**, which could not be obtained in pure form, the same sensitivity as for **3a** was presumed.

Flash Photolysis. The experimental detail of the flash photolysis has been described elsewhere.[12)]

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