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Visible Light- and Radiation-Induced Alkylation of Pyridine Ring with Alkanoic Acid. Effective Alkylation in the Presence of Iron(III) Sulfate

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Quinoline and 4-methylquinoline are efficiently alkylated with alkanoic acid in the presence of iron(III) sulfate upon visible light-irradiation. Iron(III) sulfate not only accelerates the photoreaction but also increases the yield of alkylation. Gamma-irradiation also brings about the alkylation. In the photo- and radiation-induced alkylation with alkanoic acid, alkyl radicals play important roles.

The utilization of solar light for organic syntheses is one of the challenging problems in photochemistry. The catalyses by transition metal ions and transition metal complexes which absorb solar light effectively are one of the promising fields for the chemical utilization of the solar light.

Many types of photoreactions catalyzed by metal salts or metal complexes have been studied,[1] including $TiCl_4$-catalyzed photochemical addition of alcohol to ketone[2] and $FeCl_3$-catalyzed photooxidation of olefins.[3] Sato et al. proposed a long range electron-transfer mechanism for the transition metal ion-catalyzed photooxidation.[4]

However, there have been a few attempts to use solar light for the metal salt- (or metal complex-) catalyzed photoreactions. The examples of the recent studies which have been done in aiming the effective uses of solar light are photochemical carbon dioxide fixation catalyzed by metal porphyrins[5] and photo-reduction of methyl viologen under the catalysis by ferrocene derivatives.[6,7]

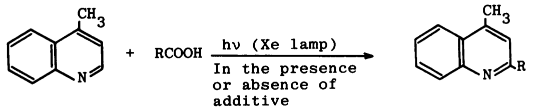
The generation of free radicals by solar light under the catalysis by transition metal salts and complexes is a useful reaction. Free radical species can play important roles in the chemistry of heteroaromatic compounds, because free radical species can attack electron-deficient heteroaromatic rings to give substitution products, while electrophiles which attack the normal aromatic rings to undergo substitution are not effective for the introduction of substituents in the electron-deficient heteroaromatic rings. One of the successful reactions of the category is the alkylation of the pyridine derivatives with alkanoic acids initiated by the thermal decomposition of peroxodisulfate under the catalysis by silver salt.[8]

The free radical species generated by gamma-irradiation, such as hydroxyalkyl radicals from alcohols, can be used for the alkylation of the pyridine ring.[9]

This paper describes the alkylation of the pyridine ring by alkyl radicals formed from alkanoic acids by the visible (or solar) light-irradiation under the catalysis by iron(III) sulfate or by γ-irradiation.[10] The iron(III)-catalyzed photoreaction is compared with the photoreactions catalyzed by TiO_2 and $EuCl_3$.

Results and Discussion

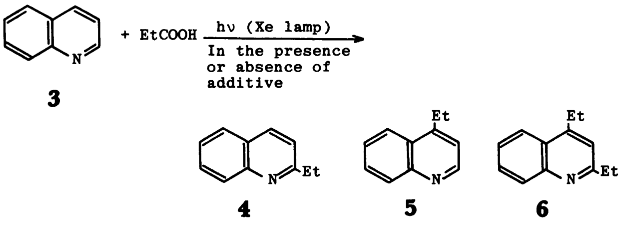
Visible Light-Induced Alkylation with Alkanoic Acid. The irradiation of 4-methylquinoline (**1**) in aqueous alkanoic acid solutions with a Xe lamp in the presence or absence of additives (sulfuric acid, metal salts, and titanium(IV) oxide) brings about alkylation at the 2-position of **1** (Table 1).



1 **2**

Although the photoalkylation with alkanoic acid occurs without any additives (the reaction in this case should be caused by the UV-light contained in the light emitted by a Xe lamp),[11] the reaction is the most effective in the acidic media in the presence of iron(III) sulfate. Iron(III) sulfate not only accelerates the photoreaction but also increases the yield of alkylation (yield=amount of product formed/amount of substrate reacted) either in the presence or absence of sulfuric acid. In particular, the effect of iron(III) sulfate is more remarkable in the presence of sulfuric acid than in its absence. In the reaction in the absence of iron(III), the addition of sulfuric acid inhibits the photoalkylation. The inhibition of photoreaction can be ascribed to the destruction of a hydrogen bond between quinoline and carboxylic acid. The addition of iron(III) sulfate in the acidic system results in the formation of the greater amount of the product than in the reaction in the absence of sulfuric acid and iron(III).

Europium chloride which has been reported to catalyze the photochemical hydroxymethylation of 1,3-dimethyluracil with methanol[12] inhibits the photoalkylation of 4-methylquinoline with alkanoic acid. Platinized titamium(IV) oxide promotes the photoalky-



4 **5** **6**

Table 1. Visible Light-Induced Alkylation of 4-Methylquinoline (**1**) with Alkanoic Acid (RCOOH). Light Source, 500 W Xe Lamp; Irradiation Time, 20 h; Irradiated Solution, 50 cm^3 Solution (Solvent: H_2O 80%-RCOOH 20% v/v) containing 1.0 mmol of **1**

R	$[H_2SO_4]$ mol dm^{-3}	Additive	Amount of additive g	Atmosphere	Amount of **1** reacted μmol	Amount of **2** formed μmol	Yield of **2**$^{a)}$ %
Me	—	$Fe_2(SO_4)_3$	0.36	Ar	190	19	10
	0.033	—	—	Ar	157	1	1
	0.033	$Fe_2(SO_4)_3$	0.36	Ar	189	60	32
	0.033	TiO_2-Pt	0.5	Ar	80	9	11
Et	—	—	—	Ar	140	79	56
	—	—	—	O_2	41	38	91
	—	$Fe_2(SO_4)_3$	0.36	Ar	165	126	76
	—	$Fe_2(SO_4)_3$	0.36	O_2	81	1	1
	0.033	—	—	Ar	203	16	8
	0.033	$Fe_2(SO_4)_3$	0.36	Ar	619	458	74
	0.033	$Fe_2(SO_4)_3$	0.36	O_2	96	1	1
	0.033	$EuCl_3 \cdot 6H_2O$	0.5	Ar	Trace	Trace	—
	0.033	TiO_2-Pt	0.5	Ar	96	35	36
	0.033	TiO_2-Pt	0.5	O_2	67	2	3
	0.033	TiO_2-Pt $AgNO_3$	0.5 0.2	Ar	82	78	95
	0.033	$AgNO_3$	0.2	Ar	13	8	62
n-Pr	0.033	—	—	Ar	101	21	21
	0.033	$Fe_2(SO_4)_3$	0.36	Ar	385	291	76
	0.033	TiO_2-Pt	0.5	Ar	117	17	15
i-Pr	0.033	—	—	Ar	147	20	14
	0.033	$Fe_2(SO_4)_3$	0.36	Ar	605	407	67
	0.033	TiO_2-Pt	0.2	Ar	159	52	32

a) Yield=Amount of product/Amount of substrate reacted.

Table 2. Visible Light-Induced Ethylation of Quinoline (**3**) with Propionic Acid. Reaction Conditions are the Same as Those for **1**

$[H_2SO_4]$ mol dm^{-3}	Additive	Amount of additive g	Amount of **3** reacted μmol	Amount of Product μmol and (Yield$^{a)}$ %) **4**	**5**	**6**	Amount of **5** / Amount of **4**
—	—		233	38 (16)	29 (12)	0 (0)	0.76
—	$Fe_2(SO_4)_3$	0.36	322	57 (18)	66 (20)	3 (1)	1.16
0.033	—		266	3 (1)	3 (1)	0 (0)	1
0.033	$Fe_2(SO_4)_3$	0.36	477	131 (27)	158 (33)	19 (4)	1.21
0.033	TiO_2-Pt	0.5	230	24 (11)	14 (6)	0 (0)	0.58
0.033	TiO_2-Pt $AgNO_3$	0.5 0.2	234	35 (15)	40 (17)	0 (0)	1.14
0.033	$AgNO_3$	0.2	115	4 (4)	4 (4)	0 (0)	1

a) Yield=Amount of product/Amount of substrate reacted.

lation much less efficiently than iron(III) sulfate.

The irradiation of quinoline (**3**) with propionic acid with the light from a Xe lamp causes the ethylation at the 2- and 4-position (Table 2).

The effects of iron(III) on the photoreaction of the quinoline-propionic acid system are similar to those of the 4-methylquinoline-propionic acid system. In iron(III) sulfate-catalyzed photochemical alkylation, alkyl radicals should play important roles. The reaction is inhibited by oxygen. Alkyl radicals would be produced by the excitation of a sort of complex between iron(III) and alkanoic acid (or alkanoate) which has an absorption band spreading over near ultraviolet-visible region. Brownish yellow color appears, when iron(III) sulfate and propionic acid are mixed in an aqueous sulfuric acid solution. The appearance of color is ascribed to the formation of a complex between iron(III) and propionic acid. No color develops, when iron(III) sulfate and 4-methylquinoline are mixed in an aqueous sulfuric acid solution. The alkyl radicals thus formed attack the electron-deficient protonated quinoline derivative.

Another role of iron(III) would be as an oxidant of the intermediate (**7**) and the reduction products of alkylquinoline, which are formed by the disproportionation of **7**. This contributes to the improvement of

Table 3. Gamma-Ray-Induced Alkylation of 4-Methylquinoline (**1**) with Alkanoic Acid (RCOOH). Radiation Source, Co-60 γ-Rays; Dose Rate 1.0×10^6 rad h^{-1}; Dose, 5×10^7 rad; Irradiated Solution, 10 cm^3 RCOOH Solution Containing 3 mmol of **1**

R	Atmosphere	Amount of **1** reacted	Amount of **2** formed	Yield of **2**[a)]	G(**2**)
		µmol	µmol	%	
Me	Ar	1220	447	37	0.82
Et	Ar	1500	489	33	0.95
	O_2	870	480	56	0.95
n-Pr	Ar	1440	372	26	0.74
i-Pr	Ar	1530	598	39	1.2

a) Yield=Amount of product/Amount of substrate reacted.

Table 4. Gamma-Ray-Induced Ethylation of Quinoline (**3**) with Propionic Acid. Reaction Conditions are the Same as Those for **1**

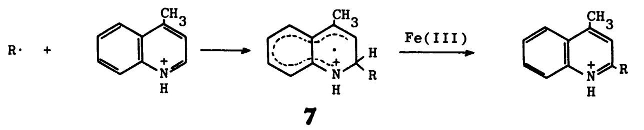
Atmosphere	Amount of **3** reacted	Amount of product µmol, (Yield[a)] %), and [G-value]			Amount of **5** / Amount of **4**
	µmol	**4**	**5**	**6**	
Ar	1480	278 (19) [0.60]	102 (7) [0.22]	46 (3) [0.10]	0.37
O_2	1020	240 (23) [0.52]	88 (9) [0.19]	18 (2) [0.04]	0.37

a) Yield=Amount of product/Amount of substrate reacted.

the yield of the alkylation.

$$RCOO\cdots\cdots Fe^{3+} \xrightarrow{h\nu} RCOO\cdot + Fe^{2+}$$

$$RCOO\cdot \longrightarrow R\cdot + CO_2$$



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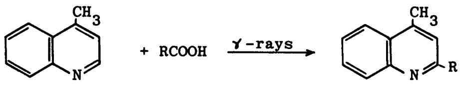
The excitation of the semiconducting titanium(IV) oxide generates electrons in the conduction band and holes. The holes undergo the oxidative decarboxylation of carboxylate to give an alkyl radical. The holes can also oxidize the intermediary formed radical **7** and/or the reduction products of quinoline and alkylquinolines. Therefore, the mechanism for the titanium(IV) oxide-catalyzed photoalkylation of the pyridine ring with alkanoic acid is similar to that for the iron(III)-catalyzed photoalkylation.

However, the TiO_2-catalyzed alkylation under the irradiation with a Xe lamp is inferior to the iron(III) sulfate-catalyzed reaction both with respect to the reaction rates and with respect to the yield of the alkylation. The low reaction rate is due to the low light absorption of titanium(IV) oxide in the visible region. The low yield for alkylation can be ascribed to the reduction of the substrate and the intermediate by the electron in the conduction band. The addition of Ag^+ which removes the electron in the conduction band of TiO_2 and/or oxidize the intermediate **7** improves the yield for alkylation (Table 1). In the semiconductor-catalyzed photo-cycloreversion and -valence isomerization, the promotion by oxygen has been reported.[13)] The promoting effect of oxygen is ascribed to the acceleration of the charge separation of a hole-electron pair and the increase in the lifetime of a hole due to the removal of electron from depletion layer. However, in the titanium(IV) oxide-catalyzed photoalkylation of pyridine ring with alkanoic acid, oxygen inhibits the reaction. In this case, oxygen would inhibit the reaction by trapping the alkyl radicals.

Radiation-Induced Alkylation with Alkanoic Acid. Gamma-irradiation of **1** and **3** in alkanoic acid also brings about the substitution of alkyl group derived from the decarboxylation of alkanoic acid for the hydrogen of the pyridine ring (Tables 3 and 4).



Methyl, ethyl, propyl, and isopropyl groups are introduced at the 2- and 4-positions of the pyridine ring in fairly good radiation-chemical yields (G-value=Number of molecules of product/100 eV of absorbed radiation energy).

Added sulfuric acid has only a small effect on the radiation-induced alkylation (Fig. 1). Oxygen retards the conversion of the substrate but increases the yield of the alkylation (Tables 3 and 4).

As it has been established that the main radiolysis product of alkanoic acid is carbon dioxide,[14)] the formation of alkyl radicals by the radiolysis of the alkanoic acid can be safely postulated. The key step of radiolytic alkylation with alkanoic acid should be the attack of the alkyl radicals to the pyridine ring. The isopropylation with isobutyric acid (2-methylpropanoic acid) which has a large G-value for decarboxylation ($G(CO_2)=14.4$[15)]) occurs in higher G-value than propyla-

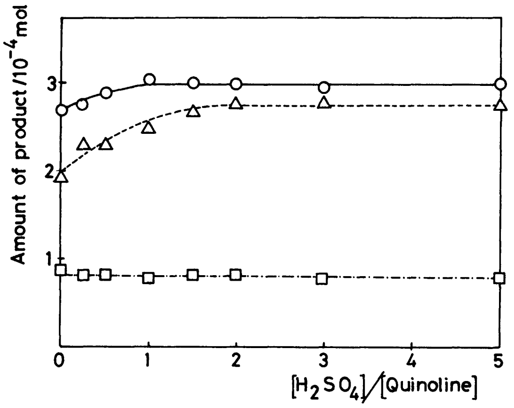
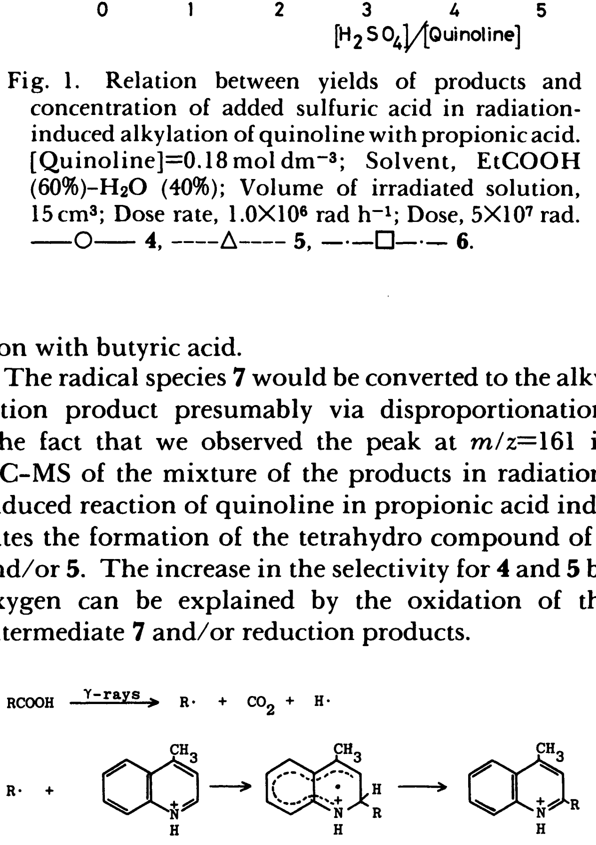


Fig. 1. Relation between yields of products and concentration of added sulfuric acid in radiation-induced alkylation of quinoline with propionic acid. [Quinoline]=0.18 mol dm^{-3}; Solvent, EtCOOH (60%)-H_2O (40%); Volume of irradiated solution, 15 cm^3; Dose rate, 1.0×10^6 rad h^{-1}; Dose, 5×10^7 rad. ——○—— **4**, ----△---- **5**, —·—□—·— **6**.

tion with butyric acid.

The radical species **7** would be converted to the alkylation product presumably via disproportionation. The fact that we observed the peak at m/z=161 in GC-MS of the mixture of the products in radiation-induced reaction of quinoline in propionic acid indicates the formation of the tetrahydro compound of **4** and/or **5**. The increase in the selectivity for **4** and **5** by oxygen can be explained by the oxidation of the intermediate **7** and/or reduction products.



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Experimental

Materials. Commercial quinoline (GR grade reagent of Tokyo Kasei Co.) and 4-methylquinoline (GR reagent of Wako Junyaku Co.) were used after the purification by distillation. Commercial GR grade reagents of acetic, propionic, butyric, and isobutyric acids (Wako Junyaku Co.) were used without further purification. Commercial europium(III) chloride 6 hydrate (made by Wako Junyaku Co.; 99.9% of purity), silver nitrate (EP grade reagent of Nisshin Kasei Co.), and iron(III) sulfate x hydrate (GR grade reagent of Wako Junyaku Co.) were used without further purification. The content of iron which was determined by the colorimetry with 1,10-phenanthroline was 72%.

Platinized titanium(IV) oxide was prepared by grinding 0.025 g of platinum black (Nippon Engelhard Co.) and 0.475 g of titanium(IV) oxide (P-25 made by Nippon Aerosil Co., a mixture of anatase and rutile) in a mortar according to Kawai and Sakata.[16]

Irradiation with a Xenon Lamp. Solutions (50 cm^3) of the substrate (0.02 mol dm^{-3}) and the additives in a mixed solvent of water and alkanoic acid (H_2O : RCOOH=4 : 1 v/v) were deaerated by bubbling Ar for 45 min before irradiation. The solutions were irradiated with a 500 W Xe lamp for 20 h under magnetical stirring.

For the irradiation under O_2 was bubbled oxygen gas through the solution for 45 min before irradiation.

Irradiation with γ-Rays. A solution containing the substrate (0.3 mol dm^{-3}) in alkanoic acid was deaerated by bubbling Ar (in some cases by oxygen) for 45 min before irradiation.

The solution was irradiated by Co-60 γ-rays at the irradiation facility of Japan Atomic Energy Research Institute in Takasaki at the dose of 5.0×10^7 rad (Dose rate, 1.0×10^6 rad h^{-1}).

For the dependence of the reaction on added sulfuric acid, solutions containing **3** (0.18 mol dm^{-3}) and sulfuric acid in a mixed solvent of H_2O (40%) and propionic acid (60%) were used.

Identification of Products. The identification of the alkylquinolines was described in our another paper.[9]

Quantitative Analysis of Photoproducts. The solution which was irradiated in the presence of sulfuric acid was neutralized with sodium carbonate. In the case of the irradiation in the presence of iron(III) sulfate, the formed precipitate of iron hydroxide was filtered off. The aqueous filtrate and the precipitate were extracted repeatedly with dichloromethane. After the removal of dichloromethane, the solvent was replaced by ethyl acetate and the solution was submitted to the gas-chromatographic analysis (column, 3 m column of PEG 20 M (10%); column temperature, 190 °C), using 3-pyridinecarbonitrile as an internal standard.

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