Photooxidation of 1,4-Dihyropyridines

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1,4-Dihydropyridines were successfully photooxidized to corresponding pyridines under suitable conditions. The substituents of the dihydropyridines, reaction mediums, and atmospheres affect the course of the reactions. When diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**1a**), diethyl 1,4-dihydropyridine-3,5-dicarboxylate (**1b**), 2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridine (**1c**), and 3,5-diacetyl-1,4-dihydropyridine (**1d**) were irradiated by a super high pressure mercury lamp with filter in ethanol under air or oxygen, corresponding pyridines, diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**2a**), diethyl pyridine-3,5-dicarboxylate (**2b**), 2,6-dimethyl-3,5-diacethylpyridine (**2c**), and 3,5-diacetylpyridine (**2d**) were formed in good yields. Irradiation of **1a**, **1c**, and **1d** in acetonitrile afforded **2a**, **2c**, and **2d** irrespective of their atomosphere, oxygen or nitrogen. On the other hand, photolysis of **1b** by the same lamp and filter in ethanol or acetonitrile in an atmosphere of nitrogen resulted in the formation of photodimer (**3**) which on irradiation by low pressure mercury lamp in acetonitrile dissociated to **1b** followed by photooxidation giving **2b**. Diethyl 1-acetyl-1,4-dihydropyridine-3,5-dicarbolxyate (**4e**) and 1,3,5-triacetyl-1,4-dihydropyridine (**4f**) afforded **2b** and **2d** in fairly good yields when the photolyses were carried out in an atmosphere of air in ethanol or acetonitrile.

The pyridine nucleotides, with their reduced forms, play a role in biological oxidation-reduction process and in biological hydroxylation of substrates by molecular oxygen.[1,2] For the chemical models of the process, the non-photochemical reaction of 1,4-dihydropyridine derivatives with a variety of hydrogen acceptor compounds has been widely investigated.[1,3]

Recently, Abelson, *et al.*[4] have examined the photolysis of reduced nicotinamide-adenine dinucleotide (NADH) and have speculated as to biological significance of the photoproducts. There are few reports, however, of the photochemical reactions of 1,4-dihydropyridines and NADH.[5-7] Eisner *et al.*[8] have demonstrated that on irradiation with medium pressure mercury lamp through a Pyrex filter in an atmosphere of nitrogen, diethyl 1,4-dihydropyridine-3,5-dicarboxylate in *t*-butyl alcohol afforded photodimer as a main product.

In the course of the investigation on the reactions coupled to oxidation-reduction systems, it was found that on irradiation of 1,4-dihydropyridines (**1**) under appropriate conditions the corresponding pyridines were formed in good yields.[9]

Irradiation of 1,4-Dihydropyridines in Ethanol under Oxygen Atmosphere. When diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**1a**) in ethanol was irradiated under air, the oxidized product, diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**2a**) was formed as indicated by UV spectrum and thin layer chromatography (tlc) (Fig. 1). As shown in Fig. 1, isosbestic points were observed at 219 mμ, 265 mμ, and 300 mμ. Under similar conditions (ethanol, irradiation under air), diethyl 1,4-dihydropyridine-3,5-dicarboxylate (**1b**) and 2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridine (**1c**) gave diethyl pyridine-3,5-dicarboxylate (**2b**) and 2,6-dimethyl-3,5-diacetylpyridine (**2c**), respectively (Fig. 2, 3).

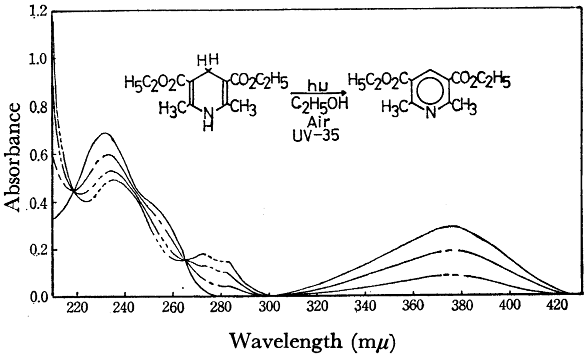

Fig. 1. Photolysis of diethyl 2,6-dimethyl-1, 4-dihydropyridine-3,5-dicarboxylate (**1a**). —— Before irradiation, —— after 15 min, —— after 40 min, ——— after 130 min.

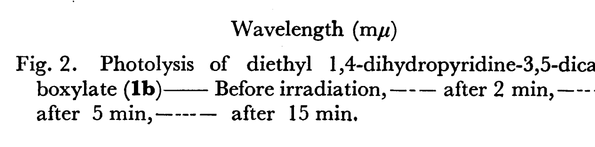

Fig. 2. Photolysis of diethyl 1,4-dihydropyridine-3,5-dicarboxylate (**1b**)—— Before irradiation,—— after 2 min,—— after 5 min,—— after 15 min.

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[1] T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 2; W. A. Benjamin, Inc. New York (1966), p. 301.

[2] M. Florkin and E. H. Stotz (Ed.), "Comprehensive Biochemistry," Vol. 14, Elsevier Publishing Co. Amsterdam (1966).

[3] K. A. Schellenberg and F. H. Westheimer, *J. Org. Chem.*, **30**, 1859 (1965) and refs. cited therein; E.A. Braude, J. Hannah, and R. Linstead, *J. Chem. Soc.*, **1960**, 3249, 3257.

[4] D. Abelson, E. Parthé, K. W. Lee, and A. Boyle, *Biochem. J.*, **96**, 840 (1965).

[5] J. A. Berson and E. Brown, *J. Chem. Soc.*, **77**, 447 (1955).

[6] J. L. Kurz, R. F. Hutton, and F. H. Westheimer, *ibid.*, **83**, 584 (1961).

[7] A. A. Krasnovskii and G. P. Brin, *Ul'trafiolet Izluch*, No. 4, **50** (1966); *Chem. Abstr.*, **68**, 35938 (1968).

[8] U. Eisner, J. R. Williams, B. W. Matthews, and H. Ziffer, *Tetrahedron*, **26**, 899 (1970).

[9] Unless otherwise stated, the photolyses were carried out in a quartz vessel by use of super high pressure mercury lamp with Toshiba UV-31 or UV-35 filter.

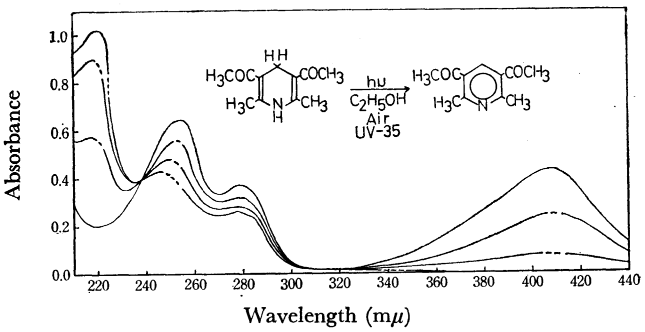
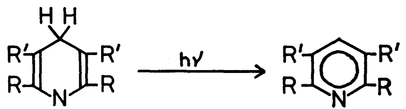


Fig. 3. Photolysis of 2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridine(**1c**).—— Before irradiation,——— after 20 min,——— after 60 min,-------- after 120 min.

When oxygen was bubbled throughout the reaction, practically same results were obtained except that strong absorption intensity due to charge-transfer interaction between oxygen and ethanol[10] were observed in the short wavelength region.



1 **2**

a: R=CH_3, R′=$COOC_2H_5$ **b**: R=H, R′=$COOC_2H_5$
c: R=CH_3, R′=$COCH_3$ **d**: R=H, R′=$COCH_3$

When 3,5-diacetyl-1,4-dihydropyridine (**1d**) in ethanol was irradiated in an atmosphere of oxygen, a new absorption maximum was appeared at 313 mμ as decrease of a maximum at 397 mμ of **1d**. Further irradiation caused a decrease of the new peak and 3,5-diacetylpyridine (**2d**) was simultaneously formed (Fig. 4). The appearance of the absorption maximum at 313 mμ may be attributed to the formation of an intermediate.

Irradiation of 1,4-Dihydropyridines in Ethanol under Nitrogen Atmosphere. Similar to the results obtained by Eisner *et al.*,[8] the irradiation of **1b** or **1c** in ethanol under nitrogen atmosphere resulted in the formation of a photodimer (**3**, λ_{max} 279 mμ) or 3-acetyl-2,6-dimethyl-5-α-hydroxyethylpyridine, respectively. The photodimer was isolated in an 81% yield. Under similar conditions, **1d** gave a new product (λ_{max} 298 mμ) which we presumed to be corresponding dimer as judged by its UV spectrum (Fig. 5). The attempt to isolate and confirm the structure of the compound was not made.

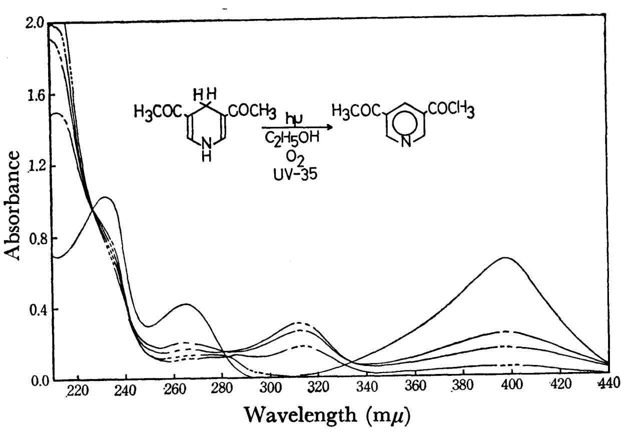


Fig. 4. Photolysis of 3,5-diacetyl-1,4-dihydropyridine (**1d**). —— Before irradiation,——— after 10 min,——— after 20 min, -------- after 40 min,-------- after 460 min.

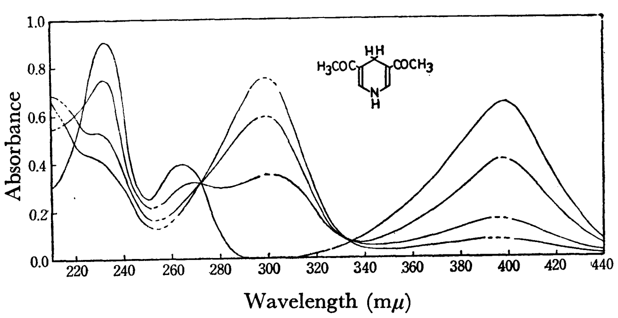


Fig. 5. Photolysis of 3,5-diacetyl-1,4-dihydropyridine (**1d**) in ethanol under an atomosphere of nitrogen using 100W immersion lamp.—— Before irradiation,——— after 70 hr,——— after 150 hr,-------- after 300 hr. A new peak at 298 mμ may due the formation of photodimer.

Photolysis of **1a** under similar conditions showed little spectral change; irradiation for 12 hr resulted in a decrease in the absorption maximum no less than 17% of the initial extinction.

Irradiation of 1,4-Dihydropyridines in Acetonitrile under Nitrogen or Oxygen. When acetonitrile was used as the solvent in the above experiments, **1a**, **1c**, and **1d** were oxidized to **2a**, **2c**, and **2d** irrespective of their atmosphere, nitrogen or oxygen. On irradiation of **1d** in acetonitrile under nitrogen atmosphere, **2d** was isolated in a 74% yield. Irradiation of **1b** under oxygen led to the formation of **2b**, while irradiation of **1b** under nitrogen led to dimerization to **3** which was isolated in a 74% yield.

It was noteworthy that when a solution of **3** in acetonitrile was irradiated without filter under an atmosphere of nitrogen, the solution fluoresced a blue color and new absorption maxima were appeared at 372 mμ and 220 mμ. Further irradiation caused disappearance of the peak at 372 mμ and **2b** was formed as indicated by UV spectrum (Fig. 6). This result suggests that the **3** is rather stable toward ultraviolet light of wavelength

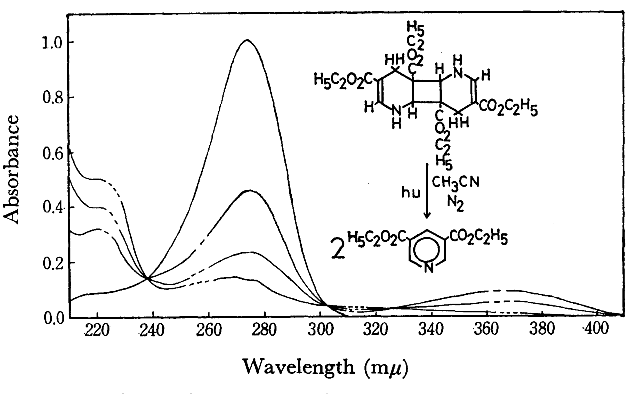


Fig. 6. Photolysis of tetraethyl 1,5,8,8bβ-tetrahydrocyclobuta [1,2-*b*:3,4-*b*′] dipyridine-3, 4aβ 7, 8aβ(4*H*, 4*b*β*H*) tetracarboxylate.—— Before irradiation,——— after 8 min,——— after 23 min,-------- after 75 min.

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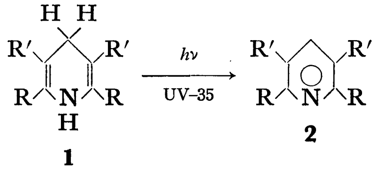
10) H. Tsubomura and R. S. Mulliken, *J. Amer. Chem. Soc.*, **82**, 5966 (1960).

TABLE 1. PHOTOLYSIS OF 1,4-DIHYDROPYRIDINES



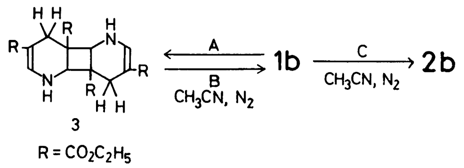
a: R=CH_3 R'=$COOC_2H_5$
b: R=H R'=$COOC_2H_5$
c: R=CH_3 R'=$COCH_3$
d: R=H R'=$COCH_3$

Atmosphere		Solvent							
		Ethanol				Acetonitrile			
		1a	**1b**	**1c**	**1d**	**1a**	**1b**	**1c**	**1d**
O_2	Concentration of **1** $\times 10^5$ mol/l	4.33	6.71	5.53	6.82	4.69	6.70	5.34	7.04
	Product	**2a**	**2b**	**2c**	**2d**	**2a**	**2b**	**2c**	**2d**
N_2	Concentration of **1** $\times 10^5$ mol/l	4.30	4.52 $\times 10^3$	5.53	1.04 $\times 10^3$	4.35	1.73 $\times 10^3$	5.41	5.00 $\times 10^2$
	Product	a)	**3**	b)	c)	**2a**	**3**	**2c**	**2d**

a) The rate of the formation of **2a** was very slow.
b) 3-Acetyl-2, 6-dimethyl-5-α-hydroxyethylpyridine; λ_{max} 282, 243 mμ (lit[8]) λ_{max} 280, 240 mμ)
c) Presumably corresponding photodimer

above 310 mμ, whereas the **3** dissociated to **1b** followed by oxidation to **2b** by ultraviolet light of wavelength below 310 mμ. This assumption was proved by a separate experiment in which **1b** was oxidized to **2b** on irradiation with low pressure mercury lamp.

Contrary to the photolysis of the **3** in acetonitrile, the irradiation of the **3** in ethanol resulted in the formation of only a small amount of **2b** along with many side products as indicated by tlc.[11]



3
R = $CO_2C_2H_5$

A: high pressure Hg lamp with UV-35 filter
B: high pressure Hg lamp without filter
C: low pressure Hg lamp without filter

These results are summarized in Table 1.

Photolysis of 1-Substituted-1,4-dihydropyridines. Loev and Snader[12] have demonstrated that in the nitrous acid oxidation of 1,4-dihydropyridines, the most likely mechanism is that involves initial attack at 1-position. Thus, 1-methyl, 1-benzyl, and 1-acetyl-1,4-dihydropyridines were irradiated in order to investigate the influence of the substituents at 1-position.

When diethyl 1,2,6-trimethyl-1,4-dihydropyridine-3, 5-dicarboxylate (**4a**), diethyl 1-methyl-1,4-dihydropyridine-3,5-dicarboxylate (**4b**), 1-methyl-3,5-diacetyl-1,4-dihydropyridine (**4c**), and 1-benzyl-3,5-diacetyl-1,4-dihydropyridine (**4d**) were irradiated and the reaction mixtures were monitored by tlc, only small amounts of the corresponding pyridines were formed along with many side products under the conditions examined (in ethanol or acetonitrile; under an atmosphere of nitrogen or oxygen). Although the possibilities of the formation of 1-alkylpyridinium salts could not be excluded, further attempts to isolate and determine the structures of the products were not be made.

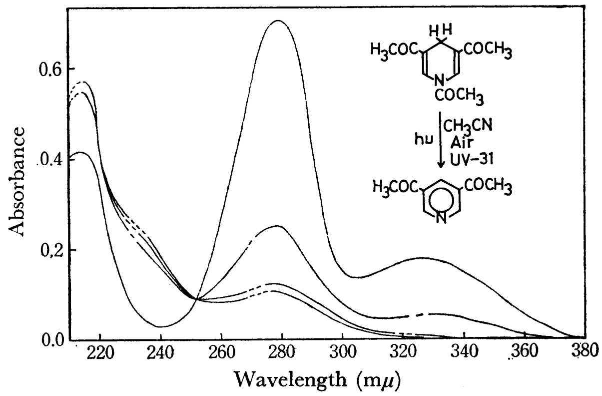
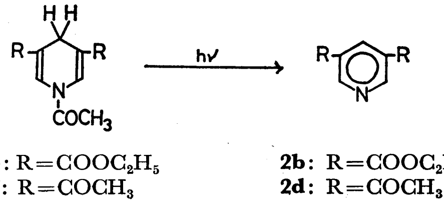


Fig. 7. Photolysis of 1,3,5-triacetyl-1,4-dihydropyridine (**4f**). —— Before irradiation,—— after 10 min,—— after 25 min, ------ after 45 min.

Contrary to the cases of 1-alkyl-1,4-dihydropyridines diethyl 1-acetyl-1,4-dihydropyridine-3,5-dicarboxylate (**4e**) and 1,3,5-triacetyl-1,4-dihydropyridine (**4f**) afforded corresponding pyridines in fairly good yields when the photolyses were carried out in an atmosphere of air in ethanol or acetonitrile (Fig. 7). While **4e** is stable in ethanol at room temperature, **4f** decomposed to 3,5-diacetyl-1,4-dihydropyridine during blowing oxygen or nitrogen through the reaction vessel before irradiation. This result suggests that **4f** is an active acylating reagent. The use of 1-acyl and 1-phosphoryl-1,4-dihydropyridines for the acylation and phosphorylation of active hydrogen compounds are now under investigation.



4e: R=$COOC_2H_5$ **2b**: R=$COOC_2H_5$
4f: R=$COCH_3$ **2d**: R=$COCH_3$

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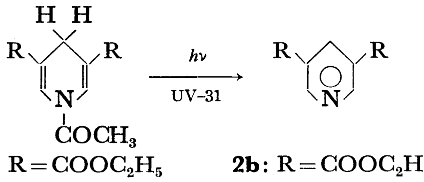
[11] The photolysis was carried out by means of super high pressure mercury lamp without filter under an atmosphere of nitrogen or oxygen.

[12] B. Loev and K. M. Snader, *J. Org. Chem.*, **30**, 1914 (1965).

Being irradiated under nitrogen atmosphere, **4e** and **4f** gave no expected pyridines, **2b** and **2d** but many side products were formed as indicated by tlc irrespective of their solvents, ethanol or acetonitrile. The results are summarized in Table 2.

Table 2. Photolysis of 1-acetyl-1,4-dihydropyridines



4e: R=$COOC_2H_5$ **2b**: R=$COOC_2H_5$

4f: R=$COCH_3$ **2d**: R=$COCH_3$

Atmosphere		Solvent and Reactant			
		Ethanol		Acetonitrile	
		4e	**4f**	**4e**	**4f**
O_2	Concentration of **4** $\times 10^5$ mol/l	3.55	4.07	3.62	3.44
	Product	**2b**	a)	**2b**	**2d**
Air	Concentration of **4** $\times 10^5$ mol/l	3.55	4.12	3.43	3.44
	Product	**2b**	**2d**	**2b**	**2d**
N_2	Concentration of **4** $\times 10^5$ mol/l	3.54	4.24	3.43	4.89
	Product	b)	a)	b)	b)

a) **4f** decomposed to 3,5-diacetyl-1,4-dihydropyridine during the oxygen was bubbled through the reaction vessel before irradiation.

b) Only small amount of the corresponding pyridines were formed along with many side products.

The results reported in this paper indicate that the photooxidation of 1,4-dihydropyridines to pyridines depends on the atmosphere and solvents used and under certain conditions, corresponding pyridines were formed in good yields. As have been pointed out by Eisner *et al.*[8] the substituents at 2,6-position also affect the course of the reaction. 1,4-Dihydropyridines without substituents at 2,6-positions such as diethyl 1,4-dihydropyridine-3,5-dicarboxylate afforded corresponding dimers on irradiation with ultraviolet light of wavelength above 310 mμ (N_2, in ethanol or acetonitrile). While, photolysis by means of ultraviolet light of short wavelength, **1b** was oxidized to diethyl pyridine-3,5-dicarboxylate (**2b**; N_2, in acetonitrile).

Further investigation on the photoreduction of various classes of substrates by means of 1,4-dihydropyridines are in progress.

Experimental

The UV spectra were obtained with a Hitachi EPS-3T spectrometer. The IR spectra were taken at Nippon Bunko IR-G spectrometer (KBr disk). The thin layer chromatograms were prepared on silica gel PF_{254} (Merck) and developed with chloroform, ethyl acetate or acetonitrile.

Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**1a**),[13] diethyl 1,4-dihydropyridine-3,5-dicarboxylate (**1b**),[14] 2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridine (**1c**),[15] 3,5-diacetyl-1,4-dihydropyridine (**1d**),[16] diethyl 1,2,6-trimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4a**),[14] diethyl 1-methyl-1,4-dihydropyridine-3,5-dicarboxylate (**4b**),[14] 1-methyl-3,5-diacetyl-1,4-dihydropyridine (**4c**),[14] and 1,3,5-triacetyl-1,4-dihydropyridine (**4f**),[17] were prepared by known procedures. Acetonitrile was purified by distilling from phosphorus pentoxide.[18] Ethanol was dried and purified by known procedure.[19]

Preparation of 1-Benzyl-3,5-diacetyl-1,4-dihydropyridine (4d). 3,5-diacetyl-1,4-dihydropyridine (0.0696 g) and sodium hydride (0.0683 g) in dimethoxyethane (8 ml) were stirred for 30 min at room temperature. Benzyl chloride (0.5 ml) was added and stirring was continued for an additional 5 hr. The solution was filtered through a hyflo-super-cel and the filtrate was evaporated to dryness under reduced pressure. After two crystallization from ethyl acetate, the dihydropyridine was obtained yellow crystals, mp 159—160°C. Found: C, 74.43; H, 6.51%. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.61%.

Preparation of Diethyl 1-Acetyl-1,4-dihydro-3,5-dicarboxylate (4e). Under nitrogen atmosphere, diethyl 1,4-dihydropyridine-3,5-dicarboxylate (0.5 g) and sodium hydride (0.6 g) in dimethoxyethane (50 ml) were stirred for 30 min at room temperature. Acetyl chloride (6 ml) was added and stirring was continued for an additional 2 hr. The mixture was filtered through a hyflo-super-cel and the filtrate was evaporated to dryness under reduced pressure. After recrystallization from acetonitrile, the dihydropyridine was obtained as white crystals, mp 113—114°C. Found: C, 59.68; H, 6.44%. Calcd for $C_{13}H_{17}NO_5$; C, 58.42; H, 6.41%.

General Photolysis Procedures. A solution of 1,4-dihydropyridine (**1**) in ethanol or acetonitrile in a quartz vessel (5 cm × 5 cm diameter) was irradiated by super high pressure mercury lamp (Ushio Electric Co., Type SH-250) with UV-35 (Toshiba Electric Co., opaque below 325 mμ, 50% transmission at 350 mμ, 80% transmission above 400 mμ) or UV-31 filter (opaque below 250 mμ, 50% transmission at 310 mμ, 90% transmission above 350 mμ). Nitrogen or oxygen was bubbled throughout the reaction and aliquots of 4 ml were removed after appropriate time intervals followed by spectrophotometric measurement.

When the photolyses were carried out in air, the solutions were placed in an absorption spectrum quartz cell of optical path 1.0 cm and irradiated through the filter.

The pyridines produced were identified by comparison of R_f values of tlc with those of authentic samples after the reaction mixtures were concentrated to a small volume.

For the preparative scale experiments, the reactions were carried out in a three necked flask using a 100 W high pressure immersion lamp (Osawa, Type NY-2).

Photolysis of 3,5-Diacetyl-1,4-dihydropyridine (1d) in Acetonitrile under an Atmosphere of Nitrogen. A solution of **1d** (0.330 g) in acetonitrile (400 ml) was stirred for 21 hr while irradiating with a 100 W high pressure immersion mercury lamp. Nitrogen was bubbled throughout the reaction. After the solution was evaporated to dryness under reduced pressure, the residue

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[13] A. Singer and S. M. McElvain, "Organic Syntheses," Coll. Vol. II, p. 214 (1948).

[14] P. J. Brignell, U. Eisner, and P. G. Farrell, *J. Chem. Soc. B*, **1966**, 1083.

[15] M. Scholtz, *Ber.*, **30**, 2295 (1897).

[16] J. Kuthan and E. Janeckova, *Coll. Czechoslov. Chem. Commun.*, **31**, 2618 (1966).

[17] F. Micheel and H. Dralle, *Ann.*, **760**, 57 (1963).

[18] A. Weissberger and E. S. Proskauer (First Ed.); J. A. Riddick and E. E. Toops, Jr. (Second Ed.), "Technique of Organic Chemistry" Vol. VII, "Organic Solvents," Interscience Publisher, Inc., New York (1955).

[19] L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath & Company, Boston (1955).

was extracted with *n*-hexane. The extract was evaporated to give 3,5-diacetylpyridine in 74.2% (0.242 g) yield, mp 67—68°C. The melting point and IR spectrum were identical to those of an authentic sample.

*Photolysis of Diethyl 1,4-Dihydropyridine-3,5-dicarboxylate (**1b**) in Ethanol under an Atmosphere of Nitrogen.* A solution of **1b** (0.77 g) in ethanol (77 m*l*) placed in a quartz vessel (5 cm × 5 cm diameter) was irradiated with super high pressure mercury lamp through UV-35 filter for about 60 hr. A stream of nitrogen was bubbled throughout the reaction. After removal of the solvent *in vacuo*, there was obtained pale green crystals which was recrystallized from ethyl acetate to give an 81% (0.62 g) of photodimer (**3**) as a white crystals, mp 226—228°C. The melting point, elemental analysis, UV, IR, and NMR spectra were identical to those of tetraethyl 1,5,8,8b*β*-tetrahydrocyclobuta[1,2-*b*: 3,4-*b*′]dipyridine-3,4a*β*,7,8a*β*(4*H*,4b*βH*)tetracarboxylate.[8]

We thank Professor N. Hata and Mr. Y. Kamura for their helpful advices.