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Photochemistry. VI.[1] Photo-induced Methylation of Pyridazines

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Irradiation of Pyridazine (Ia) in methanol containing 5% HCl, afforded 4-methylated and 4,5-dimethylated compounds. 3-Methylpyridazine (Ib) gave 4-methylated compound, along with 5-methylated and 4,5-dimethylated compounds. 3-Methoxypyridazine (Ic) afforded 4-methylated and 4,6-dimethylated compounds. 3,6-Dimethylpyridazine (Ie) gave 4-methylated and 4,5-dimethylated compounds. 3-Methoxy-6-methylpyridazine (If) gave 4-methylated compound as a sole product. 3-Methyl-6-chloropyridazine (Ig), 3,6-dichloropyridazine (Ih), and 3-phenyl-6-chloropyridazine (Ii) afforded 5-methylated and 4,5-dimethylated compounds, respectively. 3-Chloropyridazine (Id) did not give monomethylated, but 4,5-dimethylated compound in a low yield of 1—2%, presumably due to the unstability and the decomposition of the starting material.

Concerning the acid catalysed photo-induced alkylation of azaaromatic compounds, many reports have been published. Namely, Ochiai, *et al.*,[3] reported on the methylation of pyrimidines and condensed pyrimidines, and Stermitz, *et al.*,[4] on the alkylation of quinoline derivatives. Nozaki, *et al.*,[5] reported on the alkylation by organic carboxylic acid. In the previous papers, we have described that the irradiation of 3,6-dichloropyridazines in methanol containing HCl, afforded[6] methyl paraconates and dimethyl succinates, and the irradiation of 3-chloro-6-phenylpyridazine afforded[7] methyl 3-benzoylpropanoate, along with the methylated pyridazines in both cases.

These findings gave further impetus to the study of the photoinduced methylation of pyridazines and of the orientation of the methylation.

When pyridazines (Ia—i) were irradiated in methanol containing 5% HCl, with high pressure mercury lamp (400W) for 2—3 hr, the compounds (II), introduced one methyl group at 4- or 5-position, were obtained as main products in 20—40% yields. Further irradiation resulted in a decrease of the formation of II. The irradiation for 10—12 hr resulted in the formation of the compounds (III), introduced two methyl groups, as main products, accompanied by the decomposition product of the pyridazines in a small amount.

The prolonged irradiation time resulted in a decrease of the formation of the methylated pyridazines and an increase of the dedomposition product, discussions on which are excluded in the present paper.

In order to learn the positions and the facility of the methylation, the irradiation was carried out in a definite condition, which involve the irradiation time for 6 hr to afford both monomethylated (II) and di-methylated compounds (III). The results were shown in the Table I.

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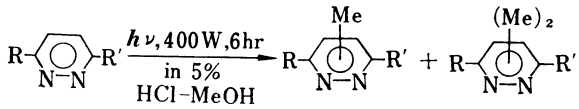

I II III

Chart 1

In the case of pyridazine (Ia) without substituent, the methylation at 4-position took place at first to give 4-methylpyridazine, followed by the methylation of 5-position to afford 4,5-dimethylpyridazine (IIIa). But any of 3-methylated compound was not obtained.

In the case of the symmetrically substituted pyridazines, 3,6-dimethylpyridazine (Ie) and 3,6-dichloropyridazine (Ih) afforded 4-methylated and 4,5-dimethylated compounds, similar to the case of Ia.

TABLE I

	I			II Yield %				III Yield %		
	R (3)	R′ (6)	*a*)	4-Me	*a*)	5-Me	*a*)	4.5-di-Me	*a*)	4,6-di-Me
a	H	H	8)	20—30	9)			8—10	10)	—
b	Me	H	11)	3— 5	12)	15—20	10)	15—17		—
c	OCH_3	H	13)	15—20	14)	—		—		5
d	Cl	H	15)	—		—		1— 2		—
e	Me	Me	16)	8—10	17)			10—15	17)	
f	OCH_3	Me	18)	45—50		—		—		
g	Me	Cl	19)	—		10—12	20)	45—50		
h	Cl	Cl	21)	28—30	22)			10	10)	
i	C_6H_5	Cl	23)	—	24)	5— 8	24)	10—13	24)	

a) references

As for the three kinds of 3-mono-substituted pyridazines, 3-methylpyridazine (Ib) afforded two kinds of the methylated compounds at 4- and 5-positions, followed by the formation of 4,5-dimethylated compound.

3-Methoxypyridazine (Ic) afforded 4-monomethylated compound and 4,6-dimethylated compound, in which 5-positions were not attacked.

3-Chloropyridazine (Id) did not give monomethylated, but 4,5-dimethylated compound in a low yield of 1—2%, presumably due to the unstability and the decomposition of the starting material.

In the case of pyridazines having different substituents at 3- and 6-positions, 3-methoxy-6-methylpyridazine (If) gave 4-methylated compound as a sole product in a considerable

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yield of 40—50%, and 5-methylated and 4,5-dimethylated compounds were not obtained. 3-Methyl-6-chloropyridazine (Ig) and 3-phenyl-6-chloropyridazine (Ii) gave 5-methylated and 4,5-dimethylated compounds.

From these findings, it is considered that in the cases of pyrimidines and quinolines, the methylation took place at the α-carbon atom to the nitrogen atom, whereas in the case of pyridazines the methylation did not take place at the α-positions, 3- and 6-positions, as were shown in the case of Ia, b, c.

Thus, it seems plausible that *o*-position to the chlorine group is easily methylated than that to the methyl and phenyl groups.

The starting materials (Ia—c) are the known substances and were prepared according to the literatures (Table I).

As for the products (II and III), the structures were inferred from elementary analyses, mass and nuclear magnetic resonance (NMR) spectra. Except for the following four kinds of compounds, the structures were confirmed in comparison with the samples synthesized by alternative routes written in the literatures and with the data given in the literatures.

6-Chloro-3,5-dimethylpyridazine (IIg) was hydrogenated with palladium-charcoal in the presence of ammonium hydroxide to give IIb. The structure of 3-methoxy-4,6-dimethylpyridazine (IIf=IIIc) was confirmed by the reaction of IIg with sodium methoxide in methanol to give the methoxy substituted compound of the chlorine group. 6-Chloro-3,4,5-trimethylpyridazine (IIIg) was hydrogenated in the same condition as for IIg to afford IIIb.

The structure of IIIb was also confirmed by the NMR spectral data shown in the Table II.

Table II. NMR Spectral Data

	3-Position		4-Position		5-Position		6-Position	
IIa	9.08 (s)	H	2.38	Me	7.27 (d)[a]	H	9.01 (d)[a]	H
IIIa	8.76 (s)	H	2.26	Me	2.26	Me	8.76 (s)	H
IIb-4	2.66	Me	7.17 (b)	H	2.32	Me	8.99 (b)	H
IIb-5	2.62	Me	2.27	Me	7.14 (d)[a]	H	8.83 (d)[a]	H
IIIb	2.64	Me	2.22	Me	2.27	Me	8.75 (s)	H
IIc	4.18	OMe	2.25	Me	7.20 (d)[b]	H	8.73 (d)	H
IIIc	4.05	OMe	2.14	Me	6.97 (b)	H	2.50	Me
IIId	—		2.37	Me	2.37	Me	8.83 (s)	H
IIe	2.60	Me	2.25	Me	7.01 (b)	H	2.60	Me
IIf	4.05	OMe	2.14	Me	6.97 (b)	H	2.50	Me
IIg	2.67	Me	7.27 (b)	H	2.40	Me	—	
IIIg	2.47	Me	2.19	Me	2.26	Me	—	
IIh	—		2.40	Me	7.27	H	—	
IIIh	—		2.37	Me	2.37	Me	—	
IIi	—		7.66 (b)	H	2.45	Me	—	
IIIi	—		2.28	Me	2.43	Me	—	

δ, 60 Mc in $CDCl_3$ with TMS as internal reference
a) J=4.8 cps *b*) J=6.0 cps

A general and facile synthetic method[25] of pyridazines comprises the reaction of 1,4-diketones with hydrazine. Consequently, for the preparation of the methylated pyridazines, the starting materials should be the methylated 1,4-diketones, which are tediously obtainable.

Thus, the photochemical syntheses of the methylated pyridazines by one step, just like present procedure, is believed to be very useful.

The ethylation and the propylation of the pyridazines were also proved to be successful in spite of the low yields, on which detailed investigations are now under way.

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Experimental

Irradiation of Pyridazines (Ia—i): Formation of Monomethylated Pyridazines (II) and Dimethylated Pyridazines (III)——General Method: A solution of 1 g of I dissolved in 300 ml of methanol containing 5% HCl was irradiated with high pressure mercury lamp (400 W, Nikko Sekiei Co., Ltd.) without filter for 6 hr at room temperature. The reaction mixture was evaporated to dryness *in vacuo* and the residue was made alkaline with $NaHCO_3$ solution, followed by extraction with CH_2Cl_2. The CH_2Cl_2 layer was dried on Na_2SO_4 and the solvent was removed *in vacuo*. The residue was separated by column chromatography on alumina to afford II and III. The chloro compounds were obtained from the eluates with benzene, and other compounds were obtained from those with *n*-hexane containing 5% ether.

Products II and III: Except for the following four kinds of compounds, the products were the known compounds and were confirmed with the samples synthesized by the methods described in the literatures shown in the Table I. Furthermore, their NMR spectral data also support the correctness of their structures (Table II).

3,4,5-Trimethylpyridazine (IIIb), mp 63—64° (from iso-Pr_2O), M^+ 122. *Anal.* Calcd. for $C_7H_{10}N_2$: C, 68.82; H, 8.28; N, 22.96. Found: C, 68.68; H, 8.31; N, 22.83.

3-Methoxy-4,6-dimethylpyridazine (IIf, IIIc), oil, picrate, mp 121—122° (from MeOH). *Anal.* Calcd. for $C_{13}H_{13}O_8N_5$: C, 42.51; H, 3.57; N, 19.07. Found: C, 42.77; H, 3.53; N, 18.89.

This compound was identical with the compound obtained from II (0.2 g) by the reaction with CH_3ONa (1.2 moles) in methanol.

6-Chloro-4,5-dimethylpyridazine (IIId), mp 63° (from *n*-hexane). *Anal.* Calcd. for $C_6H_7N_2Cl$: C, 50.39; H, 4.93; N, 19.59. Found: C, 50.11; H, 5.12; N, 19.56.

This compound (0.1 g), dissolved in 50 ml of CH_3OH and 3 ml of conc. NH_4OH solution, was hydrogenated with 5% Pd-C (0.2 g) and after removal of the catalyst and the solvent, the residue was extracted with CH_2Cl_2 and worked up as usual. The solid thus obtained was recrystallized from *n*-haxane to crystals, mp 53—55°, *ca.* 70%, identical with 4,5-dimethylpyridazine (IIIb).

6-Chloro-3,4,5-trimethylpyridazine (IIIg), mp 93—95° (from *n*-hexane). *Anal.* Calcd. for $C_7H_9N_2Cl$: C, 53.55; H, 5.78; N, 17.84. Found: C, 53.52; H, 5.80; N, 18.01.

This compound was hydrogenated in the same condition as described for IIId to give 3,4,5-trimethylpyridazine (IIIb).