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Photochemistry. II.[1] Formation of Methyl Paraconates and Dimethyl Succinates from Pyridazines

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Irradiation of 6-chloro-3(2H)pyridazones (I), maleic hydrazides (IV), and 3,6-dichloropyridazines (V and VI) in methanol containing HCl, afforded γ-lactones, methyl paraconates (II), and dimethyl succinates (III).

A shot time irradiation of 3,6-dichloropyridazines (V) resulted in the formation of methylated pyridazines (VI and VII), hydroxymethylated pyridazines (VIII), and methylated pyridazones (IX), along with the γ-lactones (II) and the succinates (III).

The mechanism of the formation of the γ-lactones and the succinates was also discussed.

We have been reporting a series of the novel photo-induced oxygenation reactions by pyridazine N-oxides.[3] Related to the study, we have investigated the photochemical reactions of the pyridazines themselves and have obtained interesting results as follows.

Irradiation of 6-chloro-3(2H)pyridazones (I), 3,6-(1H, 2H)pyridazinediones (IV), and 3,6-dichloropyridazines (V and VI) in methanol containing HCl, afforded γ-lactones, methyl paraconates, and dimethyl succinates, which were formed by the elimination of nitrogen molecules of pyridazines, in moderate yields.

After irradiation of I in methanol containing 5% HCl for 20 hr, the reaction mixture was evaporated *in vacuo* and the residue was extracted with ether. The ethereal extract was then passed through a column of alumina. Thus, from 6-chloro-3(2H)pyridazone (Ia), methyl paraconate (IIa, *ca.* 15%) and dimethyl succinate (IIIa, 5%) were obtained. From both of 4-methyl- and 5-methyl-6-chloro-3(2H)pyridazones (Ib and Ic), methyl β-methylparaconate (IIb) and dimethyl methylsuccinate (IIIb) were obtained in 15—20% and 3—5% yields, respectively.

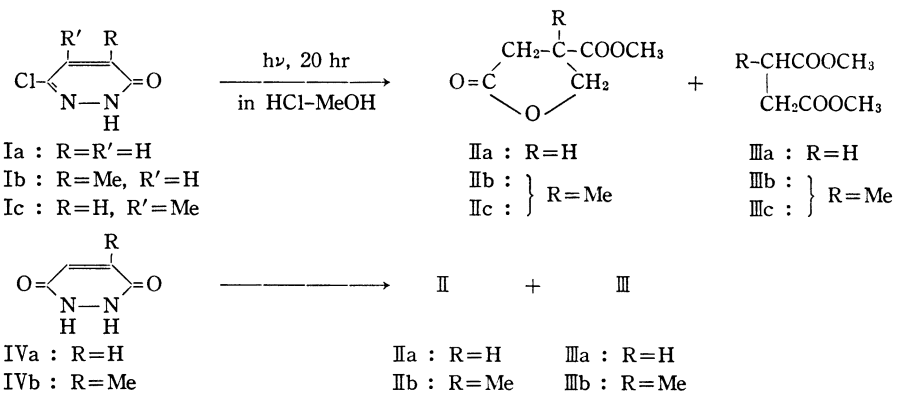

Chart 1

1) Part I: T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Letters*, **1970**, 3839.
2) Location: *Hatanodai, Shinagawa-ku, Tokyo.*
3) T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Letters*, **1969**, 2747; **1970**, 2213.

Similary, 3,6-dichloropyridazine (V) afforded two kinds of esters mentioned above, along with the compounds introduced one or two methyl groups. Namely, irradiation of V for 26—30 hr under a similar condition afforded three kinds of γ-lactone esters, methyl paraconate (IIa, 15%), its β-methyl dreivative (IIb, 7—8%), and α,β-dimethyl derivative (IIc, *ca.* 10%), and also two kinds of dimethyl succinates (IIIa, 12—13%, and IIIb, 1—2%). And 4-methyl-3,6-dichloropyridazine (VI) samely afforded two kinds of methyl paraconates (IIb, 12—15%, and IIc, 8—10%) and dimethyl methylsuccinate (IIIb, *ca.* 10%).

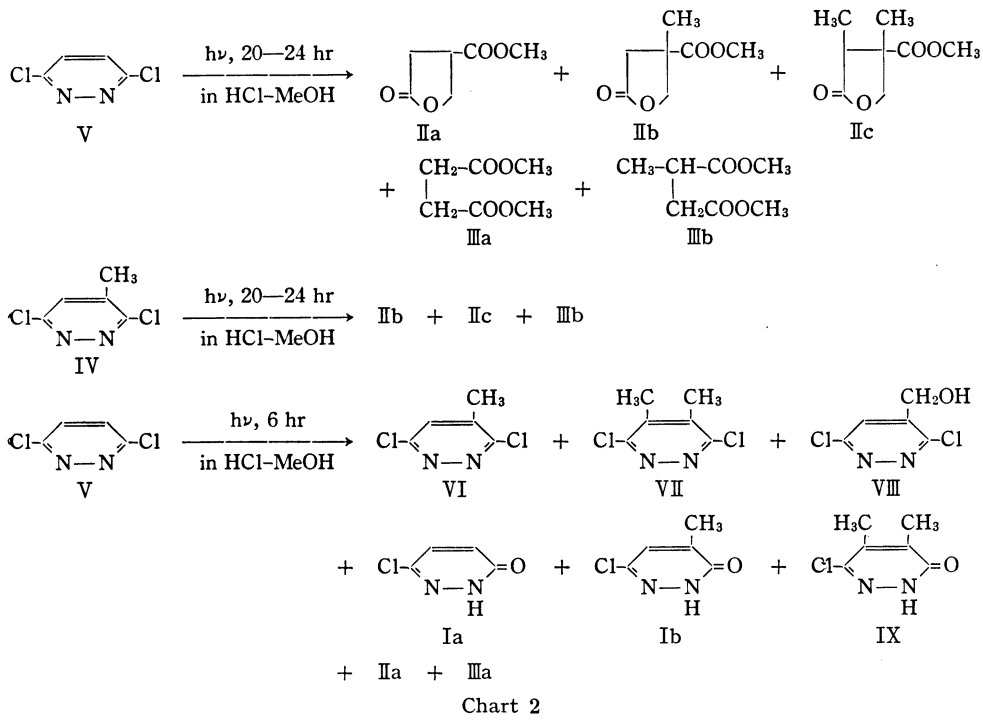

Chart 2

In place of the chloro compounds, irradiation of the bromo compounds, gave similar results in every case mentioned above.

The structure of IIa was confirmed in comparison with the sample prepared by an alternative route given by Piskov, *et al.*[4]

Its methyl derivatives (IIb and IIc) were determined in comparison with the spectral data (Table I). Namely, their infrared (IR) spectra showed the absorptions at around 1740 cm^{-1} due to the esters and at around 1785 cm^{-1} due to the γ-lactones. Besides, the nuclear magnetic resonance (NMR) spectra of them were reasonable for their structures.

In the NMR spectra of IIb and IIc, the signals of *cis*-protons to the methoxycarbonyl group are considered to be present at the lower field, and as a matter of fact, the Hα of IIc exhibited the signal at the lower field, 3.00 δ, so the methyl groups at α- and β-positions must be situated each other in the *cis* configuration.

As for the dimethyl succinates, the spectra of IIIa and IIIb exhibited the following patterns: IIIa, IR (liq.), 1742 cm^{-1}, NMR ($CDCl_3$,δ), 2.75 (4H, s), 3.83 (6H, s); IIIb, IR (liq.), 1740 cm^{-1}, NMR ($CDCl_3$, δ), 1.22 (3H, d, J=7.2 cps), 2.2—3.2 (3H, mc.), 3.79 (6H, s). And these spectral data were entirely coincident with those of the commercial samples.[5]

4) V.D. Piskov, *ZH. Obshch. Khim.*, **32**, 2047 (1962)
5) The authentic samples were obtained from Tokyo Chemical Industry Co. Ltd.

TABLE I. Spectral Data for the Compounds (II)

IR (liq.)		NMR ($CDCl_3$) δ			J=cps	
C=O,	cm^{-1}	Hα	Hβ	Hγ	C-CH_3	$COOCH_3$
IIa	1740	2.77 (d, J= 9.6)	3.50	4.45 (d, J=6.0)	—	3.76
	1785	2.97 (d, J= 7.0)	(multi.)[a]	4.46 (d, J=8.0)	—	
IIb	1740	2.38 (d, J=17.7)	—	4.05 (d, J=9.0)	1.46 (s)	3.77
	1785	3.07 (d, J=17.7)		4.55 (d, J=9.0)	1.31 (s)	
IIc	1735	3.00 (q, J= 7.2	—	4.03 (d, J=9.0)	1.31 (s)	3.77
	1785	and 15.0)		4.41 (d, J=9.0)	1.23 (d, J=7.2)	

a) Low field signals are hidden under methyl signal.

When they were irradiated in benzene or dichloromethane, they did not afford the esters. In methanol without HCl, I and IV did not give the esters, but 3,6-dichloropyridazines (V and VI) afforded the esters in small yields (below 3%). In the latter case, the presence of HCl was observed in the reaction mixture, presumably due to the hydrolysis of the starting materials.

3,6-Dichloropyridazines afforded mainly the compounds, to which one or two methyl groups were introduced.

Thus, a short time irradiation of V in methanol containing HCl, gave 4-methyl-3,6-dichloropyridazine (VI, *ca.* 20%) and 4,5-dimethyl-3,6-dichloropyridazine (VII,[6] 8—10%) as main products, and 4-hydroxymethyl-3,6-dichloropyridazine (VIII, 5—6%), 6-chloro-3(2H)pyridazone (Ia, 5%), 4-methyl-6-chloro-3(2H)pyridazone (Ib, 1%) and 4,5-dimethyl-6-chloro-3(2H)pyridazone (IX,[6] 2—3%) as minor products, of which the latter three were considered to be the hydrolysis products of the dichloropyridazines. In the case of this reaction, the esters (IIa and IIIa) were hardly obtained. But a prolonged time of irradiation resulted in a decreasement of the formation of pyridazines and pyridazones.

Consequently, irradiation of more than 20 hr resulted in the formation of the esters (II and III) as sole products in moderate yields, which were confirmed by gas–liquid chromatography (GLC).

Further irradiation of the reaction mixture resulted in the decomposition of II and III.

The acid catalysed photo-induced methylation of pyrimidines[7] and pyridines[8] has already been reported, but not yet on pyridazines. At present, the reactions of pyridazines under similar conditions are being investigated and the details on the methylation will be reported elsewhere.

Furthermore, the photo-induced hydroxymethylation in methanol has also been known in various cases,[9] involving that of pyridazines.[10] The methylation and the hydroxymethylation, described in the present paper, might be due to the similar mechanism to that of pyrimidines and pyridines.

Concerning the formation of the esters (II and III), the following mechanism can be proposed as the most reasonable one.

The photo-excited species (XI), derived from the pyridazone (X), is coupled with the hydroxy methyl radical due to methanol in the 5-position, followed by the intramolecular cyclization to give the γ-lactone ring. Then the elimination of hydrazine and the esterification reaction lead to the formation of γ-lactone ester (II).

6) R.H. Horning and E.D. Amstutz, *J. Org. Chem.*, **20**, 707 (1955).
7) M. Ochiai, E. Mizuta, Y. Asahi, and K. Morita, *Tetrahedron*, **24**, 5861 (1968).
8) E.F. Travecedo and V.I. Stenberg, *Chem. Commun.*, **1970**, 609.
9) P. Cerutti and H. Schmidt, *Helv. Chim. Acta*, **45**, 1992 (1962); **47**, 203 (1964); J. Nasielski, A. Kirsch-Demesmaeker, P. Kirsch, and P. Nasielski-Hinkens, *Chem. Commun.*, **1970**, 302.
10) M. Ogata and H. Kano, *Chem. Commun.*, **1967**, 1176.

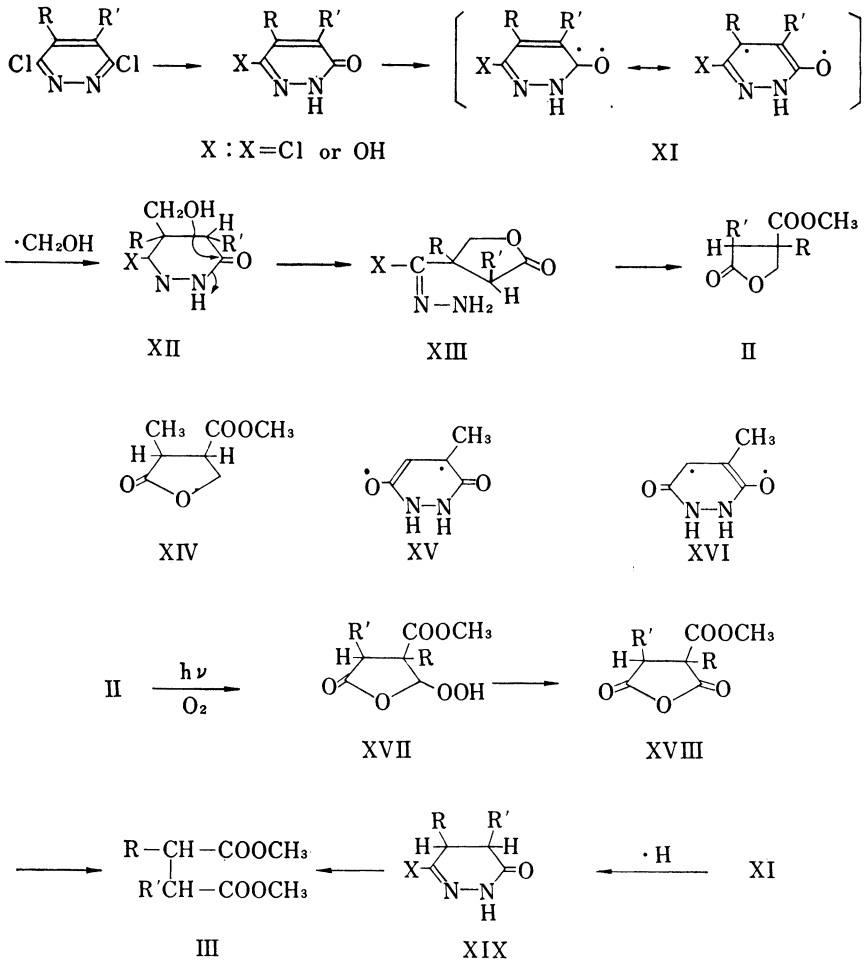

Chart 3

The fact that methyl α-methylparaconate (XIV) was not obtained from methyl maleic hydrazide (IVb), might be due to the greater stability of the radical (XV) than that of XVI. Moreover, the compound (XIV) was not obtained from Ib. These facts lead to the consideration that the photolysis proceeds after the hydrolysis to the dione is completed.

In the case of 3,6-dichloropyridazines (V), the methylation takes place at first to give 4-methyl-, 4,5-dimethyl compounds, and these methylated compounds and the starting materials are hydrolysed to the pyridazones, which are then submitted to the photolysis, following the mechanism mentioned above.

Two pathways are considered for the formation of dimethyl succinates (III). One is that methyl paraconates (II) are oxidised by photo-sensitised oxygenation to give the peroxide (XVII), which then is converted in to III, *via* XVIII. An alternative route is the photo-reduction of the excited species (XI) to form XIX, which then is converted into III.

Since the irradiation of III in methanol containing HCl, did not afford III, the reaction seems to proceed through the photo-reduction.

However, the presence of the pyridazones in the reaction mixture seems to play a role as the sensitizer, and so the pathway of the photo-sensitised oxygenation still can not be excluded at present. Detailed investigation on the mechanism is now underway.

Experimental

Irradiation of 6-Choloro-3(2H)pyridazones (Ia—Ic) and Maleic Hydrazides (IVa and IVb): Formation of Methyl Paraconates (IIa and IIb) and Dimethyl Succinates (IIIa and IIIb)——General Method: A solution of I or IV (5—10 g) dissolved in 300—400 ml of MeOH containing 5% HCl, was irradiated by high pressure mercury lamp without filter for about 20 hr at room temperature. The reaction mixture was evaporated *in vacuo*, and the residue was extracted with ether and dried on Na_2SO_4. The solvent was removed and the residue was purified by column chromatography on silica gel. From the eluate with *n*-hexane containing 10—15% ether, dimethyl succinate (IIIa) and its methyl derivative (IIIb) were obtained. The column was then eluted with *n*-hexane containing 20% ether, and from the eluate, methyl paraconate (IIa), its β-methyl derivative (IIb), and α,β-dimethyl derivative (IIc) were obtained successively. Each fraction of the eluates was checked by GLC (FID, Column: SE-30, 2% on Chromosorb W), and after removal of the solvent of the eluate, the residue was purified by distillation *in vacuo*. The samples thus obtained were examined by elementaly analyses, NMR-, and IR spectra (Table I).

i) Irradiation of 6-Chloro-3(2H)pyridazone (Ia): According to the general method, Ia (5 g) was allowed to react and the reaction mixture was treated by the procedure mentioned above to give two kinds of oils, dimethyl succinate (IIIa), 0.3 g, and methyl paraconate (IIa), 0.9 g. IIIa, bp_{10}75—80° (bath temp.), *Anal.* Calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.80. Found: C, 49.75; H, 6.91. IIa, bp_3 *ca.* 80° (bath temp.), *Anal.* Calcd. for $C_6H_8O_4$: C, 50.00; H, 5.60. Found: C, 49.75; H, 6.07.

IIIa and IIa were also confirmed respectively in comparison with NMR and IR spectral data of commercial sample and the compound synthesised by an alternative method given by Piskov, *et al.*

ii) Irradiation of 4-Methyl-6-chloro-3(2H)pyridazone (Ib): Ib (5 g) was allowed to react to give methyl methylsuccinate (IIIb), bp_{10}80—85° (bath temp.), 0.2 g and methyl β-methylparaconate (IIb), $bp_3$90° (bath temp.), 1.2 g. IIIb, *Anal.* Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.72; H, 7.81. IIb, *Anal.* Calcd. for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.41; H, 6.33.

iii) Irradiation of 5-Methyl-6-chloro-3(2H)pyridazone (Ic): Ic (5 g) was allowed to react to give IIIb, 0.35 g, and IIb, 1.1 g.

iv) Irradiation of Maleic Hydrazide (IVa): IVa (10 g) was allowed to react to afford the same products as was in the case of Ib, namely, IIIa, 1.25 g, and IIa, 1.9 g, were obtained.

v) Irradiation of Methylmaleic Hydrazide (IVb): IVb (5 g) was allowed to react to give the same products as was in the case of Ib and Ic, namely, IIIb, 0.35 g, and IIb, 1.4 g, were obtained.

Irradiation of 3,6-Dichloropyridazine (V)——i) Irradiation for 26 hr: V (8 g) was allowed to react a and the reaction mixture was treated by the procedure described for the general method. The products were dimethyl succinate (IIIa), 1.0 g, its methyl derivative (IIb), 0.7 g, and methyl *cis*-α,β-dimethylparaconate (IIc), $bp_3$100° (bath temp.), 0.9 g. IIc, *Anal.* Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.43; H, 6.88. In the case of this reaction, any of pyridazines and pyridazones was not obtained even by the treatment described below for ii.

ii) Irradiation for 6 hr: V (8 g) was allowed to react and the reaction mixture was evaporated *in vacuo*. The residue was extracted with ether. From the extract, 0.1 g of dimethyl succinate (IIIa) and methyl paraconate (IIa) were obtained, respectively. The substance insoluble in ether, was made alkaline with conc. ammonia followed by extraction with CH_2Cl_2. The CH_2Cl_2 layer was dried on Na_2SO_4 and evaporated. The residue (5 g) was purified by column chromatography on alumina. From the eluate with benzene, 4-methyl-3,6-dichloropyridazine (VI), mp 63—65° (from *n*-hexane), 1.7 g, was obtained at first. *Anal.* Calcd. for $C_5H_4N_2Cl_2$: C, 36.84; H, 2.47; N, 17.19. Found: C, 36.70; H, 2.46; N, 17.31. NMR (CCl_4, δ): 2.40 (3H, s), 7.27 (1H, s).

From the second fraction, 4,5-dimethyl-3,6-dichloropyridazine (VII), mp 115—116° (from *n*-hexane), 0.9 g, was obtazined. *Anal.* Calcd. for $C_6H_6N_2Cl_2$: C, 40.71; H, 3.42; N, 15.83. Found: C, 40.98; H, 3.50; N, 15.77. NMR (CCl_4, δ): 2.37 (s). The column was then eluted with CH_2Cl_2. From the eluate, 6-chloro-3(2H)pyridazone (Ia), mp 136—138° (from benzene), 0.5 g, 4-methyl-6-chloro-3(2H)pyridazone (Ib), mp 147—148° (from EtOH), 0.15 g, and 4,5-dimethyl-6-chloro-3(2H)pyridazone (IX), mp 200° (from AcOEt), 0.2 g, were obtained. IX, *Anal.* Calcd. for $C_6H_7ON_2Cl$: C, 45.47; H, 4.45; N, 17.67. Found: C, 45.44; H, 4.81; N, 17.47. NMR (DMSO-d_6, δ): 2.09 (3H, s).

Finally, the column was eluted with CH_2Cl_2 containing 5% MeOH. From the eluate, 4-hydroxymethyl-3,6-dichloropyridazine (VIII), mp 128—130° (from AcOEt), was obtained. *Anal.* Calcd. for $C_5H_4ON_2Cl_2$: C, 33.55; H, 2.25; N, 15.65. Found: C, 33.61; H, 2.29; N, 15.58. NMR (DMSO-d_6,δ): 4.55 (2H, d, J=0.6 cps), 7.79 (1H, s broad). Except for VIII, these compounds were known in the literatures and were confirmed in comparison with those synthesised by alternative routes.

Irradiation of 4-Methyl-3,6-dichloropyridazine (VI)——VI (5 g) was irradiated for 20 hr and the reaction mixture was treated by the procedure described for the general method. As the results, IIIb, 1.1 g, IIb, 0.6 g, and IIc, 0.9 g, were obtained. And in the case of this reaction, any of pyridazines and pyridazones was not obtained.