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Photochemistry. IV.[1] Photolyses of 3-Chloro- and 3-Hydroxy-6-phenylpyridazines in Methanol Containing Hydrogen Chloride

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Photolysis of 3-hydroxy-6-phenylpyridazine (III) in CH_3OH containing 5% HCl, afforded methyl 3-benzoylpropanoate (V) and methyl 2-methyl-3-benzoylpropanoate (VI), and three kinds of nitrogen free compounds. Similarly, 3-chloro-6-phenylpyridazine (IV) afforded V, methylated pyridazines (VII, VIII, IX, X, and XI), hydroxymethylated pyridazine (XI), and small amounts of nitrogen free compounds.

In a previous paper[3] we have reported that the photolyses of 3-hydroxy-6-chloropyridazines (I) and 3,6-dihydroxypyridazines (II) in methanol containing HCl, afforded methyl paraconates and dimethyl succinates. Namely, addition of the hydroxymethyl radical, formed from the solvent methanol, at 5-position, resulted in the attack of the oxygen atom of the hydroxymethyl group on the carbon atom at the 3-position, followed by the fission of the pyridazine ring and the elimination of nitrogen atoms to give methyl paraconates. On the other hand, addition of the hydrogen radicals at 4- and 5-positions resulted in the similar fission and elimination to form dimethyl succinates. Furthermore, both the chloro- and hydroxy-compounds afforded the same results, suggesting that during the reaction course hydrolysis of the chlorine group occurred to form the hydroxy compound of the type II.

Thus, we are interested in the photolyses of 3-hydroxy-6-phenylpyridazine[4] (III) and 3-chloro-6-phenylpyridazine[4] (IV), from which the 6-hydroxy compounds are not obtainable by hydrolysis.

III was irradiated by high pressure mercury lamp[5] (400W) without filter for 24 hr in methanol containing 5% HCl. The products were separated by column chromatography on silica gel, affording methyl 3-benzoylpropanoate (V) and methyl 2-methyl-3-benzoylpropanoate (VI) in the yields of 12% and 5%, respectively. Besides these two compounds, an oil was obtained and was proved to be a mixture of three compounds having no nitrogen atoms by gas and thin-layer chromatography, whose isolations and identifications were not yet performed. The alkaline hydrolysis of V afforded 3-benzoylpropanoic acid,[6] methylation of which reproduced V.

The ester (VI) was proved to have one more methyl group than the compound (V) from elementary analysis, molecular weight determination, infrared (IR) and nuclear magnetic resonance (NMR) spectra. The position of the methyl group was determined by the NMR spectrum.

Similarly, 3-chloro-6-phenylpyridazine (IV) was irradiated and the products were separated by column chromatography on alumina. As the nitrogen free compound, the ester (V) was obtained in *ca.* 5% yield. Furthermore, five kinds of pyridazines were obtained, *i.e.* 3-chloro-

1) Part III: T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Letters*, **1971**, 2579.
2) Location: *Hatanodai, Shinagawa-ku, Tokyo.*
3) T. Tsuchiya, H. Arai, and H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **19**, 1108 (1971).
4) S. Gabriel and J. Colman, *Ber.*, **32**, 395 (1899).
5) High pressure mercury lamp (Nikko Sekiei Co., Japan) was used as a light source.
6) The authentic sample was obtained from Tokyo Chemical Industry Co., Ltd. Japan.

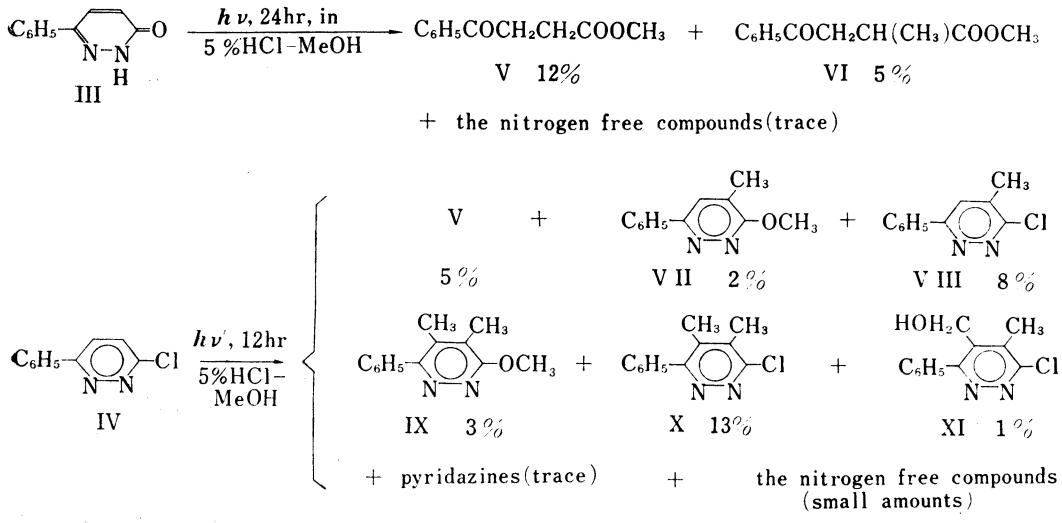

Chart 1

4-methyl-6-phenylpyridazine (VIII), mp 144—145° (8%), 3-methoxy-4-methyl-6-phenylpyridazine[7] (VII), mp 55—56° (2%), 3-chloro-4,5-dimethyl-6-phenylpyridazine (X), mp 166° (13%), 3-methoxy-4,5-dimethyl-6-phenylpyridazine (IX), mp 77—78° (3%), and 3-chloro-4-methyl-5-hydroxymethyl-6-phenylpyridazine (XI), mp 180° (1%).

Besides these six kinds of compounds, a couple of pyridazines and the nitrogen free compounds were obtained, but their isolations and identifications were not yet carried out on account of small amount.

Of the pyridazines, the compound (VII) is the known compound,[7] whose physical data well agree with those written in the literature.

The reaction of the chloro compound (VIII) with sodium methoxide in methanol afforded the methoxy compound (VII), and irradiation of VII and VIII in methanol containing HCl, afforded IX and X, respectively. The methanolysis of the chloro compound (X) afforded IX. Thus, the structures of these three kinds of compounds were confirmed.

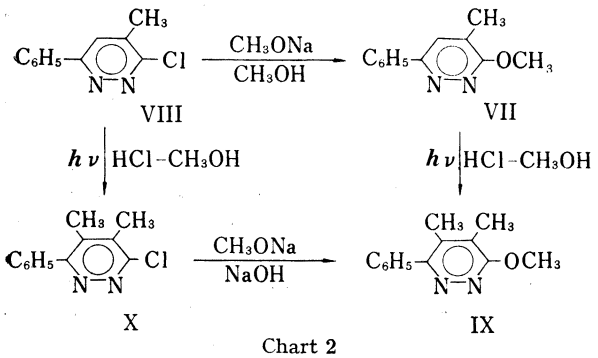

Chart 2

The positions of the methyl and the hydroxymethyl groups of XI were inferred from the NMR spectral data as follows. In the case of 3-chloro compounds (VIII and X), the signals of 4- and 5-CH_3 groups appeared at around 2.43 δ and 2.2—2.3 δ, respectively, and the signal of the methyl group of XI appeared at 2.52 δ, whose value was reasonable to be assigned to that of the 4-position, in spite of consideration of the influence of the hydroxymethyl group at the adjacent carbon atom. Thus, the structure of XI was inferred to be the 4-methyl-5-hydroxymethyl compound.

7) I. Crossland, *Acta Chem. Scand.*, **20**, 258 (1966).

Table I. NMR Spectral Data[a] (δ)

V	2.60 (2H, t, α-H), 3.16 (2H, t, β-H), 3.58 (3H, s,-$COOCH_3$), 7.25—7.55 (3H, mc, *meta*- and *para*-H of phenyl), 7.75—8.05 (2H, mc, *ortho*-H)
VI	1.22 (3H, d, α-CH_3), 2.7—3.5 (1H, mc, α-H), 3.08 (2H, t, β-H), 3.57 (3H, s, -$COOCH_3$), 7.15—7.50 (3H, mc, *meta*- and *para*-H), 7.75—8.05 (2H, mc, *ortho*-H)
VII	2.28 (3H, s, 4-CH_3), 4.17 (3H, s, -OCH_3), 7.56 (1H, broad, 5-H), 7.35—7.7 (3H, mc, *meta*- and *para*-H), 7.85—8.1 (2H, mc, *ortho*-H)
VIII	2.45 (3H, s, 4-CH_3), 7.66 (1H, broad, 5-H), 7.3—7.6 (3H, mc, *meta*- and *para*-H), 7.8—8.1 (2H, mc, *ortho*-H)
IX	2.20 (6H, s, 4- and 5-CH_3), 4.12 (3H, s, -OCH_3), 7.40 (5H, s, phenyl protons)
X	2.28 (3H, s, 5-CH_3), 2.43 (3H, s, 4-CH_3), 7.42 (5H, s, phenyl protons)
XI[b]	2.52 (3H, s, 4-CH_3), 4.43 (2H, d, -CH_2-), 5.47 (1H, t, -OH, erased by D_2O), 7.4—7.6 (5H, mc, phenyl protons)

a) 60 MC in $CDCl_3$ with TMS as internal reference b) in DMSO-d_6

There have been many reports[8] on such acid catalyzed photoinduced methylation and hydroxymethylation, including our report[9] on pyridazines, in which the reaction mechanism was proposed. Similarly, the present reaction seems to proceed through the same mechanism.

Concerning the formation of methyl 3-benzoylpropanoate the following mechanism can be proposed as the most reasonable. The 3-chloro compound (XII) was hydrolyzed to form the keto compound (XIII), which was then converted into the photo-excited species (XIV). Reduction of XIV gives XV, followed by the fission of the ring and the elimination of hydrazine to form methyl 3-benzoylpropanoate (XVII).

The pathway of the formation of VI from III, is considered that after photo-induced methylation at 4-position has occurred, then the reaction proceeds forward. In the case of IV, before the formation of the keto compound, the methylation takes place considerably. Thus, 4-methyl compound (VIII) and 4,5-dimethyl compound (X) seem to produce the nitrogen free compounds mentioned above *via* the keto compounds (XIII). Their isolations and identifications are now under way.

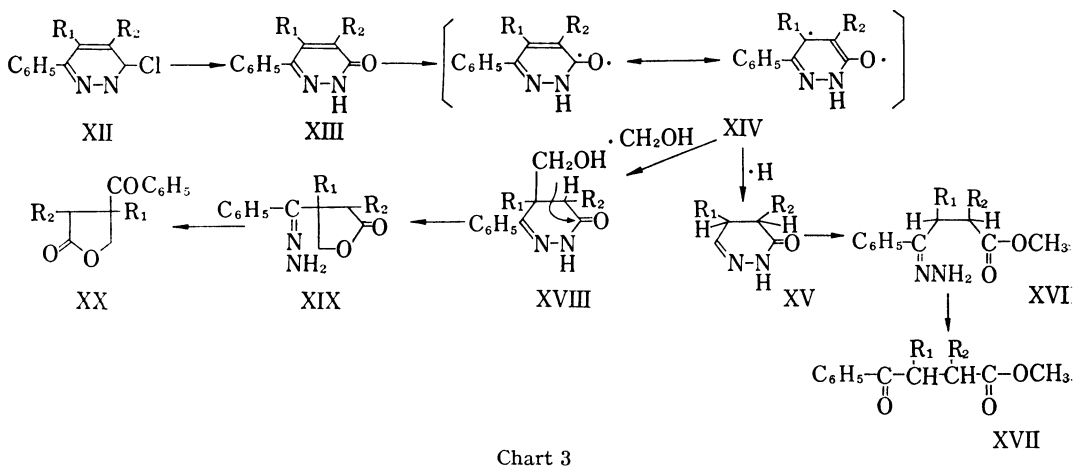

Chart 3

8) M. Ochiai, F. Mizuta, Y. Asahi, and K. Morita, *Tetrahedron*, **24**, 5861 (1968); F.R. Stermitz, C.C. Wei, and C.M. O'Donnell, *J. Am. Chem. Soc.*, **92**, 2745 (1970); H. Nozaki, M. Kato, R. Noyori, and M. Kawanishi, *Tetrahedron Letters*, **1967**, 4259.

9) T. Tsuchiya, H. Arai, and H. Igeta, Presented at the Meeting of Kanto Branch, Pharmaceutical Society of Japan, Tokyo, November 1970; T. Tsuchiya, H. Arai, and H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **19**, 1108 (1971).

3,6-Dihydroxy compound (II) and 3,6-dichloro- and 3-hydroxy-6-chloro compounds, the latter two of which are easily converted into II by hydrolysis, turn to the excited species (XIV), to which the hydroxymethyl radical, formed from the solvent, attacks at 5-position, followed by the intramolecular cyclization to form γ-lactone ring and subsequently by the hydrolysis of the hydrazone to give 3-benzoyl-γ-lactone (XX). Thus, examination of the mixture mentioned above by IR spectra showed a weak absorption at 1780 cm^{-1}, indicating the formation of the lactone in trace.

But, it seems to be due to the effect of the phenyl group at 6-position that the reaction pathway from XVIII to XX hardly proceeds.

Experimental

Irradiation of 3-Hydroxy-6-phenylpyridazine (III)——A solution of III (3 g) dissolved in 300 ml of CH_3OH containing 5% HCl, was irradiated by high pressure mercury lamp (400 W) without filter for 12 hr at room temperature. The solvent was removed *in vacuo* and the residue was neutralized with 5% $NaHCO_3$ solution and extracted with CH_2Cl_2 and dried on Na_2SO_4. After removal of the solvent, the residue was separated by column chromatography on silica gel. From the eluate with *n*-hexane containing 3% ether, methyl 3-benzoylpropanoate (V), *ca.* 400 mg, bp 140—150° (bath temp.), C=O (liq.): 1745 cm^{-1} (-$COOCH_3$), 1695 cm^{-1} (-COC_6H_5), was obtained. *Anal.* Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.70; H, 6.59.

From the second eluate, methyl 2-methyl-3-benzoylpropanoate (VI), 180 mg, bp 150—160° (bath temp.), C=O (liq.); 1745 cm^{-1}, 1695 cm^{-1}, was obtained. *Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.41; H, 6.89.

Irradiation of 3-Chloro-6-phenylpyridazine (IV)——The compound (IV, 3 g) was irradiated under the same condition as described for III. The products were separated by column chromatography on alumina and eluted with benzene.

From the first eluate, methyl 3-benzoylpropanoate (V), 150 mg, was obtained, which was confirmed in coparison with the sample obtained in the case of III.

From the second eluate, 3-methoxy-4-methylpyridazine (VII), 70 mg, mp 55—56° (from *n*-hexane), was obtained. *Anal.* Calcd. for $C_{12}H_{12}ON_2$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.06; H, 6.06; N, 13.95.

From the third eluate, 3-chloro-4-methyl-6-phenylpyridazine (VIII), 260 mg, mp 144—145° (from *n*-hexane), was obtained. *Anal.* Calcd. for $C_{11}H_9N_2Cl$: C, 64.44; H, 4.43; N, 13.67. Found: C, 64.32; H, 4.30; N, 13.40.

From the fourth eluate, 3-methoxy-4,5-dimethyl-6-phenylpyridazine (IX), *ca.* 100 mg, mp 77—78° (from iso-Pr_2O), was obtained. *Anal.* Calcd. for $C_{13}H_{14}ON_2$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.49; H, 6.19; N, 13.32.

From the fifth eluate, 3-chloro-4,5-dimethyl-6-phenylpyridazine (X), 420 mg, mp 166° (from *n*-hexane), was obtained. *Anal.* Calcd. for $C_{12}H_{11}N_2Cl$: C, 65.81; H, 5.06; N, 12.79. Found: C, 65.50; H, 5.34; N, 12.51.

Then, the column was eluted with CH_2Cl_2, giving 3-chloro-4-hydroxymethyl-5-methyl-6-phenylpyridazine (XI), 40 mg, mp 180° (from AcOEt). *Anal.* Calcd. for $C_{12}H_{11}ON_2Cl$: C, 61.33; H, 4.72; N, 11.92. Found: C, 61.01; H, 4.52; N, 11.72.