with α-resorcillic acid monomethyl ether.[4]

From the mother liquor of the benzene extracts colorless needles separated out after cooling, which showed m.p. 158~162° (decomp.) on recrystallization from benzene. A mixed fusion with *p*-orsellinic acid (m.p. 171~172°) melted at 161~166° and the IR spectra of both specimens in Nujol were almost identical. Methylation of the acid with CH_2N_2 for a short time gave colorless needles from MeOH-water, m.p. 97~98°. A mixed fusion with methyl *p*-orsellinate showed no depression of m.p.

Treatment of Compound G with Methanolic Potassium Hydroxide——Compound G (0.2 g.) was refluxed with MeOH-KOH (10%, 10 cc.) for 30 min. Dilution with water and acidification with HCl afforded precipitate, which was collected and dried; yield, 0.15 g. It darkened around 280° and did not show any definite m.p. The properties were identical with those of 3-methyl-1,6-dihydroxy-8-xanthonecarboxylic acid.[4]

The sublimation under reduced pressure gave colorless product, m.p. over 300°, which was proved to be identical with 1,6-dihydroxy-3-methylxanthone[7] by IR spectrum.

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Summary

Compound G, a metabolite of *Oospora sulphurea-ochracea* v. Beyma, was shown to be desmethylsulochrin (I, R^1:R^2:R^4:H, R^3:CH_3).

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Takanobu Itai and Shigeru Sako: Potential Anti-cancer Agents. IV.[1] 3-Substituted 6-Chloropyridazine 1-Oxides.

(*National Institute of Hygienic Sciences*[*1])

In Part III of this series, the N-oxidation of pyridazine derivatives was reported.[1] N. Takabayashi[2] oxidized 3-methoxy-6-chloropyridazine to its N-oxide, but the position of the N-oxide was not yet determined. H. Igeta[3] obtained 3-methoxypyridazine 1-oxide by oxidation of 3-methoxypyridazine, and M. Kumagai[4] published a paper on the N-oxidation of 3-methylpyridazine and its derivatives, bearing an ethoxy or a phenyl group at the 6-position of the molecule. The position of the oxide was not made clear in the former two cases, but it was shown to be the 2-position in the latter case. Although N. Takabayashi[2] and H. V. Euler *et al.*[5] failed to gain 3,6-dichloropyridazine N-oxide (II) from 3,6-dichloropyridazine (I) with hydrogen peroxide in glacial acetic acid, they obtained 6-chloro-3(2*H*)-pyridazinone due to hydrolysis. H. Igeta[6] obtained 3-chloropyridazine 1-oxide by oxidation of 3-chloropyridazine with perbenzoic acid.

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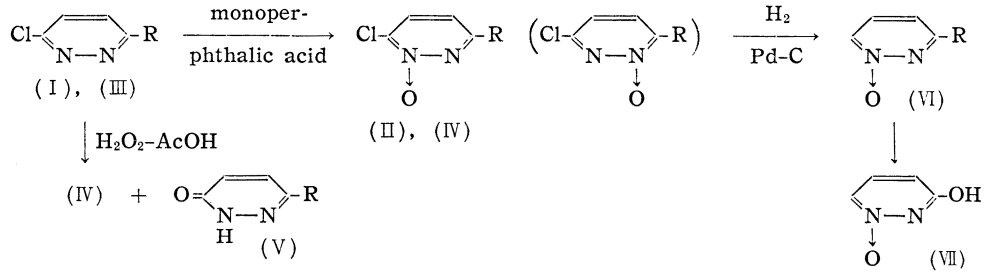
1) Part III. T. Itai, S. Sako: This Bulletin, **9**, 149 (1961).
2) N. Takabayashi: Yakugaku Zasshi, **76**, 1293 (1956).
3) H. Igeta: This Bulletin, **7**, 938 (1959).
4) M. Kumagai: Nippon Kagaku Zasshi, **81**, 1148 (1960).
5) H. V. Euler, H. Hasselquist, O. Heidenberger: C. A., **54**, 12156b (1960); Arkiv. Kemi., **14**, 419 (1959).
6) H. Igeta: This Bulletin, **8**, 559 (1960).

We have now had occasion to study the oxidation of (I) and 3-alkoxy-6-chloropyridazines (III). (I), when allowed to react with monoperphthalic acid, was led to its oxide (II). With the same reagent, however, (III) gave the N-oxides (IV), but considerable amounts of the starting materials were recovered. With hydrogen peroxide in glacial acetic acid, N-oxides (IV) were produced in poor yield, and in this case, 6-alkoxy-3(2*H*)-pyridazinones (V) were obtained as by-products, together with the starting materials. These results are summarized in Table I.



(I), (III) (II), (IV) (VI) (IV) + (V) (VII)

(I), (II): R=Cl (III)～(VI) a: R=$-OCH_3$
b: R=$-OC_2H_5$
c: R=$-OC_3H_7$ (*n*)

TABLE I.

Starting material	Oxidizing agent	Recovery (%)	(IV) Crystals	(IV) m.p. (°C)	(IV) Yield (%)	(V) m.p. (°C)	(V) Yield (%)
(I) Cl-	A	54	prisms	118～120	9		
(IIIa)CH_3O-	A	little	scales	159～161	32		
	B	little	scales	159～161	14	164～166	35*
(IIIb)C_2H_5O-	A	65	needles	115～116	16		
	B	30	needles	115～116	13	175～176	14
(IIIc)C_3H_7O-	A	little	scales	83～84	26		
	B	66	scales	83～84	9	118～119	10

A: monoperphthalic acid, B: H_2O_2-glacial AcOH, * unpurified material.

(II), when allowed to react with sodium ethoxide at about 50°, was converted into 3,6-diethoxypyridazine 1-oxide, which was shown to be identical with an authentic sample[1] prepared from 3,6-diethoxypyridazine.

(IV) was dehalogenated to 3-alkoxypyridazine N-oxides (VI) by catalytic hydrogenation with palladium-charcoal as a catalyst (see Table II). 3-Methoxypyridazine N-oxide (VIa),

TABLE II.

(VI)	R	Crystals	m.p. (°C)	Yield (%)
a	CH_3O-	plates	78～80	38
b	C_2H_5O-	prisms	73～75	64
c	C_3H_7O-	prisms	61～63	37

so obtained, was found to be identical with 3-methoxypyridazine 1-oxide prepared by the method described by H. Igeta.[3] In order to determine the position of the N-oxide, 3-ethoxypyridazine N-oxide (VIb) was hydrolyzed with sodium hydroxide solution to the deethylated N-oxide (VII). (VII) was found to be identical with 3-hydroxypyridazine 1-oxide[3] prepared from (VIa), by direct infrared spectra comparison and the mixed melting point determination. These results indicate that the N-oxidation took place at the 1-position of their rings.

3,6-Dimethoxy-, diethoxy- and dipropoxy-pyridazines were easily oxidized to their

N-oxides,[1,7] but oxidation of (I) was rather difficult. Considering from these results, in the N-oxidation of (IIIa), which bears a rather small group, methoxyl, it was expected that 3-methoxy-6-chloropyridazine 2-oxide was obtained as a main product. However, after repeated purification of the reaction product by chromatography through an alumina column, 3-methoxy-6-chloropyridazine 1-oxide was isolated as a main product, and in addition, 6-methoxy-3(2*H*)-pyridazinone (Va) was obtained together with the starting material. In this case the expected 3-methoxy-6-chloropyridazine 2-oxide was not isolated.

Experimental

3,6-Dichloropyridazine 1-Oxide (II)——To a solution of 480 mg. of (I) in 5 cc. of Et_2O, 40 cc. of an ethereal solution of monoperphthalic acid (7 mg. of active O_2 per cc.) was added, and the mixture was allowed to stand for 4 days at room temperature. The Et_2O was then evaporated, the residue was basified with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and the $CHCl_3$ was evaporated. The residue was dissolved in ligroin-benzene, passed through an alumina column, and eluted with benzene. 260 mg. (54%) of (I) was recovered from the initial 60 cc. of the eluate. Subsequent eluate fractions, after evaporation of the solvent, yielded a crystalline residue which melted at 110~119°. Recrystallization from ligroin-benzene finished colorless prisms, m.p. 118~120°. Yield, 50 mg., 9.4%. *Anal.* Calcd. for $C_4H_2ON_2Cl_2$: C, 29.12; H, 1.22; N, 16.98. Found: C, 29.47; H, 1.27; N, 16.70.

General Procedure for N-Oxidation of 3-Alkoxy-6-chloropyridazines (III) with Monoperphthalic Acid——To a solution of (III) (ca. 0.003 mole) in 5~10 volumes of Et_2O, an ethereal solution of monoperphthalic acid (6 mg. of active O per cc., ca. 0.01 mole) was added, and the mixture was treated as described above. The extract was dissolved in benzene, passed through an alumina layer, and eluted with benzene-$CHCl_3$. (III) was recovered from the first eluted fraction. From the second fraction, (IV) was obtained, as colorless needles or scales, after recrystallization from benzene or ligroin.

3-Methoxy-6-chloropyridazine 1-oxide (IVa), m.p. 159~161°. Yield, 32%. *Anal.* Calcd. for $C_5H_5O_2N_2Cl$: C, 37.40; H, 3.14; N, 17.45. Found: C, 37.42; H2.94; N, 17.05.

3-Ethoxy-6-chloropyridazine 1-oxide (IVb), m.p. 115~116°. Yield, 16%. *Anal.* Calcd. for $C_6H_7O_2N_2Cl$: C, 41.27; H, 4.04; N, 16.05. Found: C, 41.37; H, 4.01; N, 16.38. 3-Ethoxy-6-chloropyridazine (IIIb) was recovered in 65% yield.

3-Propoxy-6-chloropyridazine 1-oxide (IVc), m.p. 83~84°. Yield, 26%. *Anal.* Calcd. for $C_7H_9O_2N_2Cl$: C, 44.57; H, 5.19; N, 14.85. Found: C, 44.50; H, 4.67; N, 14.25.

N-Oxidation of 3-Alkoxy-6-chloropyridazines (III) with Hydrogen Peroxide in Glacial Acetic Acid——(III) was dissolved in 7~10 volumes of glacial AcOH, 1 volume of 30% H_2O_2 was added, and the mixture was warmed on a water bath at 70° for 3 hr. Further 1 volume of 30% H_2O_2 was added, and the mixture was warmed at the same temperature for 5~10 hr. The AcOH was distilled off under reduced pressure, a small amount of water was added to the residue and the solvents were again distilled. The residue was basified with $NaHCO_3$, extracted with $CHCl_3$, and the N-oxide was isolated by the procedure described above. After chromatography, the third eluate fraction, on evaporation of the solvent, left a crystalline residue, which was recrystallized from benzene to give (V). The N-oxide so obtained showed no depression on admixture with the corresponding sample obtained by oxidation with monoperphthalic acid.

(IVa). Yield, 14%.

(IVb). Yield, 13%. 6-Ethoxy-3(2*H*)-pyridazinone (Vb) was obtained as colorless needles, m.p. 175~176°, in 14% yield. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.17; H, 5.73; N, 20.33. IR ν_{max}^{KBr} cm^{-1}: 3,180 (NH), 1,660 (CONH). (IIIb) was recovered in 30% yield.

(IVc). Yield, 9.4%. 6-Propoxy-3(2*H*)-pyridazinone (Vc) was obtained as colorless needles, m.p. 118~119°, in 10% yield. *Anal.* Calcd. for $C_7H_{10}O_2N_2$: N, 18.17. Found: N, 17.91. IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 1660 (CONH). (IIIc) was recovered in 66% yield.

Reaction of (II) with Sodium Ethoxide (Formation of 3,6-Diethoxypyridazine 1-Oxide)——To a solution of 112 mg. of (II) in 5 cc. of EtOH, excess of EtONa (about 40 mg. of Na was dissolved in 3 cc. of EtOH) was added. The mixture was warmed at about 50° and left at room temperature for 30 min. The solvent was distilled off under reduced pressure, a small amount of H_2O was added to the residue, and the mixture extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and the $CHCl_3$ was evaporated. The residue was crystallized from ligroin to colorless

7) T. Itai, H. Igeta: Yakugaku Zasshi, **75**, 966 (1955).

plates, m.p. 72~73°. Yield, 75 mg., 60%. The m.p. of this N-oxide was undepressed when mixed with the sample[1] prepared from 3,6-diethoxypyridazine, and these N-oxides gave identical IR spectra.

Catalytic Hydrogenation of 3-Alkoxy-6-chloropyridazine 1-Oxide (IV) (Formation of 3-Alkoxypyridazine 1-Oxide (VI))——To a solution of 200 mg. of (IV) in 50 cc. of EtOH, 1cc. of 28 % NH_4OH and 0.1 g of 6% Pd-C were added. The mixture was hydrogenated at atmospheric pressure and room temperature. The reduction ceased after one equivalent of H_2 had been absorbed. The catalyst was filtered off, and the EtOH was evaporated from the filtrate. The residue was extracted with hot benzene and crystallized from ligroin-benzene.

3-Methoxypyridazine 1-oxide (VIa). Colorless plates, m.p. 78~80°. Yield, 38%. Admixture with 3-methoxypyridazine 1-oxide prepared from 3-methoxypyridazine by the method described by H. Igeta[3] showed no depression of m.p., and their IR spectra were also identical. *Anal.* Calcd. for $C_5H_6O_2N_2$: C, 47.62;H 4.80; N 22.22. Found : C, 48.14; H, 4.62; N, 23.03.

3-Ethoxypyridazine 1-oxide (VIb). Colorless prisms, m.p. 73~75°. Yield, 64%. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found : C, 51.67; H, 5.73; N, 19.90.

3-Propoxypyridazine 1-oxide (VIc). Colorless prisms, m.p. 61~63° Yield, 37%. *Anal.* Calcd. for $C_7H_{10}O_2N_2$: N, 18.17. Found : N, 18.46.

Hydrolysis of 3-Ethoxypyridazine 1-Oxide (VIb) : Formation of 3-Pyridazinol 1-Oxide (VII)——90 mg. of (VIb) was hydrolyzed by the same procedure as described by H. Igeta[3] for hydrolysis of 3-methoxypyridazine 1-oxide. Colorless prisms, m.p. 198~200°. Yield, 34 mg., 47%. The m.p. of this N-oxide was undepressed when mixed with 3-pyridazinol 1-oxide prepared from 3-methoxypyridazine 1-oxide, and these N-oxides exhibited identical IR spectra.

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Summary

When 3,6-dichloropyridazine and 3-alkoxy-6-chloropyridazines were oxidized with monoperphthalic acid or hydrogen peroxide-glacial acetic acid, the corresponding N-oxides were produced. With the latter reagent, however, 6-substituted-3(2*H*)-pyridazinones gave rise to byproducts. The N-oxidation of 3-alkoxy-6-chloropyridazines was shown to take place at the 1-position of the molecules. By catalytic dehalogenation, several 3-alkoxypyridazine 1-oxides were also prepared.

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