Table I. Urinary Metabolites after Administration of S-(2-Carboxypropyl)glutathione

Compound	Time after injection (hrs.)				
	Control	0～4	4～9	9～24	24～30
Fraction adsorbed on Amberlite IR-120 $CH_3-CH(COOH)-CH_2-S-CH_2-CH(COOH)-NH_2$	−	++	++	−	−
Fraction not adsorbed on Amberlite IR-120 $CH_3-CH(COOH)-CH_2-S-CH_2-CH(COOH)-NH(COCH_3)$	−	+	+	−	−

To isolate both the metabolites in a crystalline form, main part of each fraction obtained from the urine during the first 9 hours was treated with decolorizing charcoal to remove colored impurities and the resulting colorless solutions, after being evaporated to a small volume, were submited to paper chromatography in preparative scale, with the solvent system (a). By eluting each zone with water and recrystallizing the residual substance of the eluate from hydrous ethanol, 20 mg. of (II) and 5 mg. of (III) were obtained as fine needles from 80 ml. of the urine. Rf values of crystalline (II) and (III) so isolated were quite identical with those of synthesized samples of (II) and (III). On hydrolysis with 6*N* HCl, (III) gave (II), which in turn gave alanine and isobutyric acid on desulfurization with Raney-Ni. From these facts it is certain that (II) is S-(2-carboxypropyl)-cysteine and (III) is N-acetyl-S-(2-carboxypropyl)cysteine.

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Faculty of Pharmaceutical Sciences,
and Institute for Chemical Research,
University of Kyoto,
Yoshida-Konoe-cho,
Sakyo-ku, Kyoto.

Tomoji Suzuki (鈴木友二)
Michiyasu Sugii (杉井通泰)
Toshio Kakimoto (柿本年雄)

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Comm. N-Oxidation of 3-Aminopyridazine Derivatives

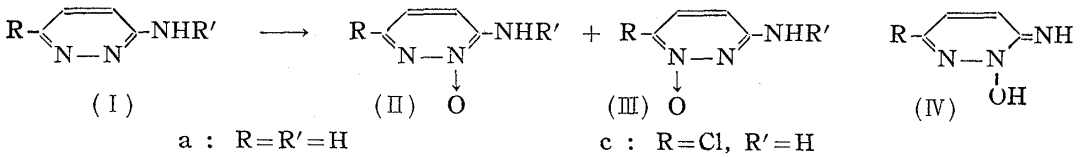
Following synthetic studies on 3,6-disubstituted 4-nitropyridazine 1-oxides,[1] N-oxidation of 3-aminopyridazine (Ia) and its derivatives was examined.

First, (Ia) and 3-acetamidopyridazine[2] (Ib) were oxidized with ether solution of monoperphthalic acid in a usual way. (Ia) gave no crystalline product but formed a resinous substance. From (Ib), 3-acetamidopyridazine 2-oxide (IIb) was obtained as colorless needles, m.p. 199～201°, and its 1-oxide (IIIb) as colorless needles, m.p. 259° (decomp.), in 82% and 2% yields respectively (*Anal.* Calcd. for $C_6H_7O_2N_3$: C, 47.06; H, 4.60; N, 27.44. Found (for (IIb)): C, 47.00; H, 4.24; N, 27.73. Found (for (IIIb)): C, 47.27; H, 4.83; N,

1) T. Itai, S. Sako: This Bulletin, **9**, 149 (1961).
2) C. Grundman: Chem. Ber., **81**, 1 (1948).

27.65).

Next, (Ia), (Ib), 3-amino-6-chloropyridazine[3] (Ic), and ethyl 6-chloro-3-pyridozinecarbamate (Id) were oxidized with hydrogen peroxide in glacial acetic acid,[4] and only



(I) (II) (III) (IV)

a : R=R′=H
b : R=H, R′=-COCH$_3$
c : R=Cl, R′=H
d : R=Cl, R′=-CO$_2$C$_2$H$_5$

Chart 1.

the corresponding 2-oxides were obtained from all, except from (Ib). The results are listed in Table I.

Table I.

Compound	Crystal form	Solvent	m.p. (°C)	Yield (%) (a)	Yield (%) (b)
(IIa)	needles	EtOH	210~211	43	
(IIb)	〃	〃	199~201	33	82
(IIIb)	〃	MeOH	259 (decomp.)	10	2
(IIc)	Pale yellow needles	EtOH	248 (decomp.)	91	
(IId)	Scales	〃	160~161	88	

(a) H_2O_2-AcOH. (b) Monoperphthalic acid.

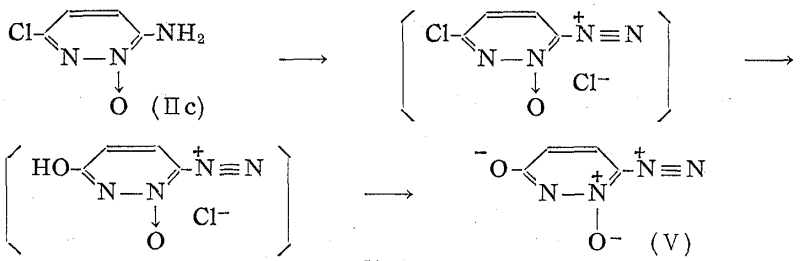
The position of these N-oxides was determined in the following way.

The product from hydrolysis of (IIb) was identical with (IIa), and (IIc) was catalytically dehalogenated to (IIa). (IId) was converted to (IIc) by hydrolysis. Accordingly, the N-oxide group in (IIa) to (IId) is in the same position.

On the other hand, the hydrolysis product of (IIIb) was proved identical with 3-aminopyridazine 1-oxide (IIIa), which had already been synthesized in this laboratory by nitration of pyridazine 1-oxide according to the method of Ochiai and Kaneko,[5] and by subsequent reduction, from comparing their infrared absorption spectra.

(IIa) and (IIc) developed deep blue color with ferric chloride solution. As (IIa) and (IIc) were able to form hydroxamic type (IV), the structure of 2-oxide was assigned to them.

When (IIc) was diazotized with sodium nitrite in mineral acid, 3-diazo-6-oxopyridazine 2-oxide (V), m.p. 174° (decomp.), was formed. Its infrared spectrum showed absorption bands at 2150 and 1638 cm^{-1}, attributable to N≡N and C=O, respectively. The analytical data of (V) (N) and its azo compound (C, H and N) with β-naphthol were coincident with their calculated values. When (V) was refluxed with methanol, its product was identical with 3-pyridazinol 1-oxide, synthesized by Igeta.[6]



(IIc) (V)

Chart 2.

3) E. Steck, *et al.*: J. Am. Chem. Soc., **76**, 3225 (1954).
4) E. Ochiai: J. Org. Chem., **18**, 534 (1953).
5) E. Ochiai, C. Kaneko: This Bulletin, **7**, 267 (1959).
6) H. Igeta: *Ibid.*, **7**, 938 (1959).
7) A. R. Katrizky: J. Chem. Soc., **1956**, 2063.

Katrizky[7] previously reported that 2-ethoxycarbonylaminopyridine 1-oxide was cyclized by heating to [1,2,4]oxadiazolo[2,3-*a*]pyridazine-2-one (Ⅶ), with fission of one mole of ethanol. When 3-ethoxycarbonylaminopyridazine 1-oxide (Ⅱe), m.p. 84～85°, was heated at 115°±2° for 18 hours, [1,2,4]oxadiazolo[2,3-*b*]pyridazine-2-one (Ⅵ), m.p. 139.5～140°, was produced. This structure was established from the analytical data and the fact that the infrared absorption bands for C=O in (Ⅱe) and in (Ⅵ) shifted in the same manner as that in the reaction of pyridine derivatives. These shifts are shown in Table Ⅱ.

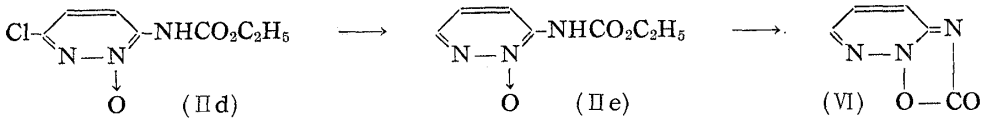


Chart 3.

Table Ⅱ. Absorption Bands of Carbonyl Groups (cm^{-1}) (KBr)

2-Ethoxycarbonylaminopyridine 1-oxide	(Ⅶ)	(Ⅱe)	(Ⅵ)
1735	1770	1735	1763, 1784 } doublet

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National Institute of Hygienic Sciences,
203-Tamagawa. Yoga 2-chome
Setagaya-ku, Tokyo.

Takanobu Itai (板井孝信)
Toshiaki Nakashima (中島利章)

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Comm.

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Über eine neue Nitrierung des Chinolin-1-oxydes mittels Metallnitrates

In der Fortsetzung der Versuche über die Nitrierung des Chinolin-1-oxydes (I) mittels Acylnitrates[1] haben wir nun bemerkt, dass man 3-Nitrochinolin 1-oxyd (Ⅱ) mit einer maximalen Ausbeute von ca. 50% erhalten kann, wenn man das Methosulfat von (I) in einer Lösung von Dimethylsulfoxyd mit 2 Molen irgendeines Metallnitrates, wie Kalium-, Barium- odor Bleinitrat u.s.w., auf 140° erhitzt. 6- bzw. 7-Methylchinolin 1-oxyd ergab das entsprechende 3-Nitroderivat von Schmp. 229～231° bzw. 214～217° (6-Methyl-3-nitrochinolin-1-oxyd : $C_{10}H_8O_3N_2$—Ber. : C, 58.82; H, 3.95; N, 13.72. Gef. : C, 58.78; H, 3.96; N, 13.65. 7-Methyl-3-nitrochinolin-1-oxyd : $C_{10}H_8O_3N_2$—Ber. : C, 58.82; H, 3.95; N, 13.72. Gef. : C, 58.93; H, 3.84; N, 13.66) wenn sein Methosulfat mit Kaliumnitrat ganz analog in Einwirkung gebracht wurde.

1) E. Ochiai, C. Kaneko : Diese Bulletin, 8, 284 (1960).