

**149. Takanobu Itai and Toshiaki Nakashima : Potential Anti-cancer Agents. VI.<sup>1)</sup> N-Oxidation of 3-Aminopyridazine Derivatives.**

(National Institute of Hygienic Sciences<sup>\*1)</sup>)

It was shown that 3,6-disubstituted 4-nitropyridazine 1-oxides had anti-cancer action,<sup>2)</sup> and an investigation of N-oxidation of 3-aminopyridazine derivatives were described in this paper.

Firstly, N-oxidation of (Ia) and (Ib) with phthalic monoperacid in ethereal solution was attempted. A reaction mixture of (Ia) turned dark, and no crystalline product was isolated. However, two portions of crystalline products were separated and purified from a mixture of (Ib) by chromatography to give colorless needles (A), m.p. 199~201°, in 82% yield, and colorless needles (B), m.p. 259°(decomp.) in 2% yield.

Nextly, 3-aminopyridazine derivatives<sup>3,4)</sup> (Ia-d) were oxidized to the corresponding N-oxides, by hydrogen peroxide-glacial acetic acid,<sup>5)</sup> as shown in Chart 1. Ethyl-6-chloro-3-pyridazinecarbamate (Id) was prepared from 3-amino-6-chloropyridazine (Ic)<sup>6)</sup> with ethyl chloroformate.

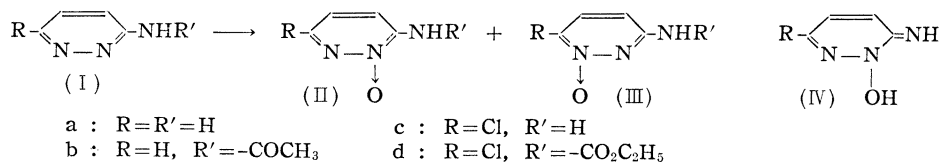


Chart 1.

In these cases, they gave only one isomer of N-oxides (IIa,c,d), except (Ib), which afforded two isomers, and were identical with (A) (yield 33%) and (B) (yield 10%).

On hydrolysis by warming with 10% NaOH, (A) was converted to (IIa), which could reversely be acetylated to (A) on warming with acetic anhydride.

(IIc) was dehalogenated by catalytic reduction to (IIa). (IId) was hydrolyzed to (IIa) with 10% NaOH through (IIc), followed by catalytic reduction.

The results suggested that N-oxidation of (Ia-d) occurred at least at a definite nitrogen which located at the same position in their rings, and (Ib) gave one more N-oxide.

With ferric chloride solution, (IIa,c) showed deep blue coloration which may be attributed to an iron salt of hydroxamic acid (IV), as shown in Chart 1, therefore it was presumed that N-oxides were located at the nitrogen of 2-position in their rings.

3-Aminopyridazine 1-oxide (IIIa) has been already synthesized in our laboratory<sup>6)</sup> by nitration of pyridazine 1-oxide according to the method of Ochiai and Kaneko,<sup>7)</sup> and by successive reduction. An elemental analysis of (B) was consistent with 3-acetamidopyridazine N-oxide, and an infrared spectrum of the hydrolyzed product was completely coincident with that of (IIIa). The hydrolyzed product of (B) did not show any deep blue

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1) Part V. T. Itai and S. Sako : This Bulletin, 10, 933 (1962).

2) *Idem* : *Ibid.*, 9, 149 (1961).

3) E. Steck *et al.* : J. Am. Chem. Soc., 76, 3225 (1954).

4) C. Grundman : Chem. Ber., 81, 1 (1948).

5) E. Ochiai : J. Org. Chem., 18, 534 (1953).

6) unpublished.

7) E. Ochiai, C. Kaneko : This Bulletin, 7, 267 (1959).

coloration with ferric chloride. As the result, it may be said that (B) and (IIIb) are 3-acetamidopyridazine 1-oxide, and (A) and (IIb) are 3-acetamidopyridazine 2-oxide. Accordingly, it was concluded that N-oxidation of (Ia,c,d) took place at 2-position in their rings.

The crystalline forms, melting points etc. of the N-oxides obtained were shown in Table I.

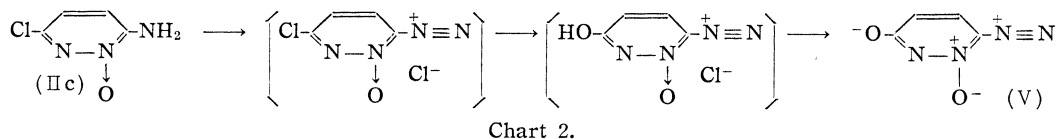
TABLE I.

Compound	Crystalline form	Solvent	Melting point(°C)	Yield(%)
(IIa)	needles	EtOH	210~211	43 <sup>a)</sup>
(IIb)	"	"	199~201	33, <sup>a)</sup> 82 <sup>b)</sup>
(IIIb)	"	MeOH	259(decomp.)	10, <sup>a)</sup> 2 <sup>b)</sup>
(IIc)	" (pale yellow)	EtOH	248( " )	91 <sup>a)</sup>
(IId)	scales	"	160~161	88 <sup>a)</sup>

*a)* H<sub>2</sub>O<sub>2</sub> and AcOH      *b)* phthalic monoperacid

As mentioned in the previous paper, it was considered that the reactivity of N-oxidation depended mainly on the basicity of nitrogen concerned and on the steric effect at the position. As the basicity of nitrogen at 2-position was strengthened by 3-amino group, N-oxidation of 3-aminopyridazine (Ia) and 3-acetamidopyridazine (Ib) took place at 2-position. This effect is not applicable to the alkoxy group, whose +M effect being smaller than amino group. When 6-position was vacant, N-oxidation occurred at 1-position, because of an absence of steric effect, and the basicity of nitrogen at 1-position was reduced by chlorine atom at 6, consequently, N-oxidation took place principally at 2-position, instead of 1-position. It might be presumable, that small amounts of isomers were yielded in each reaction, but that they could not be separated.

In order to prove the position of N-oxidation, (IIc) was further diazotized with either hydrochloric acid or sulfuric acid. Without regard to the acid used, both products were same in properties, which were lacking in acidic ions, explosive on heating, and coupled with 2-naphthol to give purple dye. The infrared spectra had strong absorptions at 2150 cm<sup>-1</sup> and 1638 cm<sup>-1</sup>(KBr), being attributable to N≡N and C=O. Referring to the report by LeFèvre,<sup>8)</sup> the structure (V), a resonance hybrid, was assigned to the diazotization products of (IIc). Supposed reaction process was described in Chart 2.



On boiling (V) in methanol, it gave colorless needles, which were identified as 3-hydroxypyridazine 1-oxide<sup>9)</sup> by infrared spectroscopy.

According to the method of Katrizky,<sup>10)</sup> ethyl-3-pyridazinecarbamate 2-oxide (IIe), obtained from the dehalogenation of (IId) by catalytic hydrogenation, was heated at about 115° to cyclize in to 2*H*-[1,2,4]oxadiazolo[2,3-*b*]pyridazin-2-one (VI). On the other hand, 2*H*-[1,2,4]oxadiazolo[2,3-*a*]pyridin-2-one (VII) was synthesized by Katrizky's method. When the infrared spectra of (VI), (VII) and their starting materials were compared, it was found that, a shift of the absorption bands for carbonyl group was to the similar degree, as shown in Table II, and the cyclization occurred expectedly.

8) R. T. W. LeFèvre *et al.*: J. Chem. Soc., 1954, 4686.

9) H. Igeta: This Bulletin, 7, 938 (1959).

10) A. R. Katrizky: J. Chem. Soc., 1956, 2063.

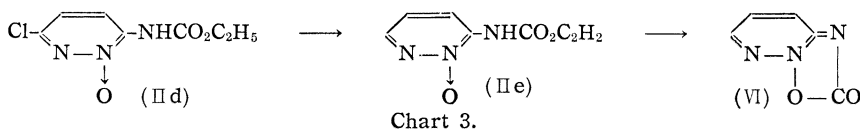


TABLE II. Absorption Band of Carbonyl Group. (KBr)

Ethyl-2-pyridinecarbamate 1-oxide	(VII)	(II e)	(VI)	} doublet
1735 $\text{cm}^{-1}$	1770 $\text{cm}^{-1}$	1735 $\text{cm}^{-1}$	1763 $\text{cm}^{-1}$ 1784	

### Experimental

**Ethyl-6-chloro-3-pyridazinecarbamate (Id)**—To a well-cooled mixture of 5 g. of (Ic) and 15 cc. of pyridine, 6.5 cc. of ethyl chloroformate was added dropwise. After standing overnight, the mixture was poured into ice-water and the product was collected, and recrystallized from EtOH to colorless plates, m.p. 189.5~190.5°, 5.9 g. (76%). *Anal.* Calcd. for  $\text{C}_7\text{H}_8\text{O}_2\text{N}_3\text{Cl}$ : C, 41.70; H, 4.00; N, 20.86. Found: C, 41.28; H, 3.90; N, 20.76.

**N-Oxidation of 3-Acetamidopyridazine (Ib) with Phthalic Monoperacid: Formation of 3-Acetamidopyridazine 2-Oxide (A) and 3-Acetamidopyridazine 1-Oxide (B)**—A suspension of 2.00 g. of (Ib) in 100 cc. of ethereal phthalic monoperacid solution (active oxygen, 7.15 mg./cc.) was allowed to stand for a week. The precipitates were filtered, extracted with each portions of 150 cc. of  $\text{Et}_2\text{O}$  five times. The residue was recrystallized from EtOH to give colorless needles, m.p. 197~199°, 0.98 g. The mother liquor was evaporated to dryness, and the residue was applied to the chromatography.

The  $\text{Et}_2\text{O}$  extracts were combined, and concentrated to dryness, and then the residue was repeatedly extracted with  $\text{CHCl}_3$  completely. The  $\text{CHCl}_3$  extracts were combined and to this the residue prepared above was dissolved. The solution was chromatographed through alumina column (1  $\times$  30 cm.), eluted with  $\text{CHCl}_3$  (ca. 300 cc.), and evaporated to dryness. Crystals, m.p. 197~199°, 0.85 g. These crystals were identical with the above-mentioned colorless needles recrystallized. Total amount 1.83 g. (82%). Recrystallization from EtOH gave colorless needles (A), m.p. 199~201° *Anal.* Calcd. for  $\text{C}_8\text{H}_7\text{O}_2\text{N}_3$ : C, 47.06; H, 4.60; N, 27.44. Found: C, 47.00; H, 4.24; N, 27.73.

It was eluted further with 100 cc. of 0.5% MemH containing  $\text{CHCl}_3$ . The effluent was evaporated to dryness, and gave crystals, m.p. 250° (decomp.), 0.05 g. (2%). Recrystallization from MeOH gave colorless needles (B), m.p. 259° (decomp.). *Anal.* Calcd. for  $\text{C}_8\text{H}_7\text{O}_2\text{N}_3$ : C, 47.06; H, 4.60; N, 27.44. Found: C, 47.27; H, 4.83; N, 27.65.

**N-Oxidation of 3-Acetamidopyridazine (Ib) with  $\text{H}_2\text{O}_2$ : Formation of 3-Acetamidopyridazine 2-Oxide (IIb) and 3-Acetamidopyridazine 1-Oxide (IIIb)**—To a solution of 2.00 g. of (Ib) in 15 cc. of AcOH, 1.5 cc. of 30%  $\text{H}_2\text{O}_2$  was added, and the solution was warmed at 65° for 45 min. After adding 1.5 cc. of 30%  $\text{H}_2\text{O}_2$ , the solution was warmed at the same temperature for 2 hr. still more, and then concentrated under reduced pressure. The residue was dissolved in a small quantity of  $\text{H}_2\text{O}$ , basified with  $\text{K}_2\text{CO}_3$ , and extracted with  $\text{CHCl}_3$  several times, which was dried over anhyd.  $\text{Na}_2\text{SO}_4$ . After evaporation of the solvent, it gave m.p. 199~201°, 0.74 g. (33%). This showed no depression of m.p. on admixture with (A), obtained in the above-mentioned experiment, and the IR spectra of the two samples were coincident.

The aqueous solution after extraction was evaporated to dryness under reduced pressure, and the residue was extracted with hot  $\text{CHCl}_3$  repeatedly. After distilling off the  $\text{CHCl}_3$  from the extract, the residue was recrystallized from MeOH to give colorless needles, m.p. 259° (decomp.), 0.23 g. (10%). This showed no depression of m.p. on admixture with (B), obtained in the above-mentioned experiment, and the IR spectra of the two samples were coincident.

**3-Aminopyridazine 2-Oxide (IIa)**—To a solution of 2.0 g. of (Ia) in 15 cc. of AcOH, was added 1.5 cc. of 30%  $\text{H}_2\text{O}_2$  and heated at 65° for 45 min. After adding 1.5 cc. of 30%  $\text{H}_2\text{O}_2$ , it was heated for 45 min. further, and then concentrated under reduced pressure. To this  $\text{H}_2\text{O}$  was added, and it was evaporated under reduced pressure again. After a repeated treatment, the residue was dried in a desiccator overnight. It was repeatedly extracted with  $\text{Me}_2\text{CO}$  and filtered. The  $\text{Me}_2\text{CO}$  insoluble substance was recrystallized from EtOH, giving crystals, 1.0 g. (43%), m.p. 200~205°, which were recrystallized again from EtOH to colorless needles, m.p. 210~211°. *Anal.* Calcd. for  $\text{C}_4\text{H}_5\text{ON}_3$ : C, 43.24; H, 4.54; N, 36.92. Found: C, 43.13; H, 4.24; N, 37.44.

$\text{Me}_2\text{CO}$  extracts were concentrated and the residue was extracted with  $\text{CHCl}_3$  several times. The  $\text{CHCl}_3$  insoluble substance was the starting material, 0.8 g. (40%). Evaporation of the extract gave 0.2 g. of dark red oily substance.

**3-Amino-6-chloropyridazine 2-Oxide (Ic)**—A mixture of 20.0 g. of (Ic), 150 cc. of glacial AcOH, and 15 cc. of 30% H<sub>2</sub>O<sub>2</sub> was heated at 65° for 45 min., 15 cc. of 30% H<sub>2</sub>O<sub>2</sub> was further added, and again heated at the same temperature for 2 hr. After standing overnight, crystals separated were collected. The mother liquor was concentrated to 10 cc., and crystals separated were collected. All of the crystals were combined and recrystallized from EtOH to yield 20.4 g. (91%) of yellow needles, m.p. 248°(decomp.). *Anal.* Calcd. for C<sub>4</sub>H<sub>4</sub>ON<sub>3</sub>Cl: C, 33.01; H, 2.77; N, 28.87. Found: C, 33.16; H, 2.61; N, 29.42.

**Ethyl-6-chloro-3-pyridazinecarbamate 2-Oxide (IId)**—A mixture of 5.7 g. of (Id), 30 cc. of glacial AcOH, and 5.5 cc. of 30% H<sub>2</sub>O<sub>2</sub> was heated at 70° for 8 hr. After the mixture was allowed to stand overnight, crystals separated were collected. The mother liquor was concentrated to 5 cc., and crystals separated were collected. Both of the crystals were recrystallized from EtOH to yield 5.4 g. (88%) of colorless plates, m.p. 160~161°. *Anal.* Calcd. for C<sub>7</sub>H<sub>8</sub>O<sub>3</sub>N<sub>3</sub>Cl: C, 38.63; H, 3.70; N, 19.31. Found: C, 38.27; H, 3.41; N, 19.65.

**Hydrolysis of 3-Acetamidopyridazine 2-Oxide (IIb): Formation of 3-Aminopyridazine 2-Oxide (IIa)**—A mixture of 1.00 g. of (IIb) and 5 cc. of 10% NaOH was warmed up to 50° for 30 min. After kept standing overnight, the mixture was neutralized with 10% HCl, and evaporated to dryness. The residue was extracted with dehydrated EtOH to remove NaCl by filtration, and the filtrate was concentrated to a small volume. After cooling, colorless needles deposited were collected. Yield, 0.53 g. (73%), m.p. 210~211°. This showed no depression of m.p. on admixture with (IIa), obtained in the above-mentioned experiment, and the IR spectra of the two samples were identical.

**Acetylation of 3-Aminopyridazine 2-Oxide (IIa): Formation of 3-Acetamidopyridazine 2-Oxide (IIb)**—A mixture of 1.0 g. of (IIa) and 10 cc. of Ac<sub>2</sub>O was warmed up to 50° for 30 min. After cooled, the product was filtered, and recrystallized from EtOH to give colorless needles (0.9 g. 65%) m.p. 199~201°. This showed no depression of m.p. on admixture with (IIb), obtained in the above-mentioned experiment, and the IR spectra of the two samples were coincident.

**Catalytic Hydrogenation of 3-Amino-6-chloropyridazine 2-Oxide (Ic): Formation of 3-Aminopyridazine 2-Oxide (IIa)**—A mixture of 3.00 g. of (Ic), 50 cc. of EtOH and 15 cc. of 10% NaOH was hydrogenated in the presence of Pd-C prepared from 0.3 g. of charcoal and 10 cc. of 1% PdCl<sub>2</sub> solution. After removal of the catalyst, the filtrate was neutralized with 10% HCl and evaporated to dryness. The residue was extracted with dehydrated EtOH to remove NaCl by filtration, and the filtrate was concentrated to a small volume. After cooling, the colorless needles deposited were collected, yielding 1.78 g. (78%) of m.p. 210~211°. This showed no depression of m.p. on admixture with (IIa), obtained in the above-mentioned experiment, and the IR spectra of the two samples were coincident.

**Hydrolysis of Ethyl-6-chloro-3-pyridazinecarbamate 2-Oxide (IId): Formation of 3-Amino-6-chloropyridazine 2-Oxide (Ic)**—A mixture of 200 mg. of (IId) and 3 cc. of 10% NaOH was warmed at 50° for 30 min. After standing overnight, the product was collected and recrystallized from EtOH to afford yellow needles (106 mg. 79%) m.p. 248°(decomp.). This showed no depression of m.p. on admixture with (Ic), obtained in the above-mentioned experiment, and the IR spectra of the two samples were identical.

**Hydrolysis of 3-Acetamidopyridazine 1-Oxide (IIIb): Formation of 3-Aminopyridazine 1-Oxide (IIIa)**—A mixture of 40 mg. of (IIIb) in 1 cc. of 5% NaOH was warmed at 50° for 30 min., allowed to stand at room temperature overnight, neutralized with 2N HCl, evaporated to dryness, and dried in a desiccator (KOH). It was extracted with 10 cc. each of hot AcOEt four times, and the extracts were decolorized with activated charcoal and condensed. After cooled, it gave colorless needles, m.p. 130~134°, 15 mg. (50%), no coloration was imparted with ferric chloride. Its IR spectrum coincided completely with 3-aminopyridazine 1-oxide.

**Reaction of 3-Amino-6-chloropyridazine 2-Oxide (Ic) with NaNO<sub>2</sub> in Acid: Formation of Dehydrated 6-Hydroxy-3-pyridazine Diazonium Hydroxide 2-Oxide (Inner Salt) (V)**—To a solution of 2.00 g. of (Ic) in 20 cc. of 50% H<sub>2</sub>SO<sub>4</sub>, while cooling at -2~0°, a saturated solution of 1 g. of NaNO<sub>2</sub> was added dropwise, and the solution was maintained at -10° for 2 hr. Crystals appeared were collected, dried in a desiccator (KOH), and washed with MeOH and dried in a similar manner. Weighing 0.97 g. (56%). Recrystallization from MeOH gave yellow needles, m.p. 174°(decomp.), explosive. *Anal.* Calcd. for C<sub>4</sub>H<sub>2</sub>O<sub>2</sub>N<sub>4</sub>: N, 40.57. Found: N, 40.40. C and H could not be analyzed from its explosibility.

**Coupling of (V) with 2-Naphthol**—When a suspension of (V) in H<sub>2</sub>O was added to an alkaline 2-naphthol solution, purple precipitates were produced, which were filtered, washed with H<sub>2</sub>O, dissolved in a large quantity of H<sub>2</sub>O on warming, and then filtered. After cooling, the filtrate was acidified with AcOH to deposit purple precipitates, which were filtered, washed and recrystallized from MeOH to give crystals m.p. 230°(decomp.). *Anal.* Calcd. for C<sub>14</sub>H<sub>10</sub>O<sub>3</sub>N<sub>4</sub>·½H<sub>2</sub>O: C, 57.73; H, 3.81; N, 19.24. Found: C, 57.22; H, 3.76; N, 19.25.

**Reaction of (V) with MeOH: Formation of 3-Pyridazinol 1-Oxide**—A solution of 300 mg. of (V)

in 30 cc. of MeOH was refluxed for 4 hr. After cooled, precipitates were filtered (174 mg, 58%). After removal of MeOH by distillation, the residue was recrystallized from Me<sub>2</sub>CO giving white needles, m.p. 198°(decomp.), 90 mg. (37%). The IR spectrum was identical with that of 3-pyridazinol-1-oxide.

**Ethyl-3-pyridazinecarbamate 2-Oxide (IIe)**—A mixture of 1.34 g. of (II d), 50 cc. of EtOH, and 1 cc. of 28% NH<sub>4</sub>OH, was hydrogenated with Pd-C, prepared from 0.2 g. of charcoal and 10 cc. of 1% PdCl<sub>2</sub> solution. After removal of the catalyst by filtration, the filtrate was neutralized with 10% HCl, and evaporated to dryness. The residue was extracted with CHCl<sub>3</sub>, and purified on Al<sub>2</sub>O<sub>3</sub> chromatography, yielding 1.10 g. (98%) of m.p. 84~85°, which was recrystallized from Et<sub>2</sub>O into colorless needles m.p. 84~85°. *Anal.* Calcd. for C<sub>7</sub>H<sub>9</sub>O<sub>3</sub>N<sub>3</sub>: C, 45.90; H, 4.95; N, 22.94. Found: C, 45.76; H, 4.75; N, 22.39.

**2H-[1,2,4]oxadiazolo[2,3-b]pyridazin-2-one (VI)**—Four hundred seventy milligrams of (IIe) was heated at 115±2° for 18 hr. The weight reduced was 61 mg. (52% to the calculated amount of 1 mole of EtOH). The residue was extracted with 10 cc. each of Et<sub>2</sub>O three times, and 240 mg. of the starting material was recovered from the extracts (51%). Further, the residue was extracted with 100 cc. each of Et<sub>2</sub>O five times on warming, filtered from white flocculents, and the filtrate was concentrated to about 50 cc. When cooled, white needles, m.p. 139.5~140°, 110 mg. (32%) were afforded. *Anal.* Calcd. for C<sub>5</sub>H<sub>5</sub>O<sub>2</sub>N<sub>3</sub>: C, 43.80; H, 2.25; N, 30.65. Found: C, 43.78; H, 2.52; N, 30.60.

The authors express their hearty gratitude to Dr. E. Ochiai, Professor Emelitus of the University of Tokyo, for his kind advice, and to Dr. T. Kariyone, Director of the Institute, for his encouragement. They are also indebted to Dr. I. Suzuki for his collaboration in a part of his experiments, to Dr. T. Ōba for infrared spectrometry, and to members of Faculty of Pharmaceutical Sciences, the University of Tokyo, and of Research Laboratory of Kowa Pharmaceutical Co. Ltd. for elemental analyses. This work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Health and Welfare.

### Summary

On N-oxidation of 3-aminopyridazine and its three derivatives, it was found that their main products were 2-oxides, and 3-acetamidopyridazine gave a small amount of 1-oxide, besides. Further, diazotization of 3-amino-6-chloropyridazine 2-oxide, and thermal cyclization of ethyl-3-pyridazinecarbamate 2-oxide were investigated for additional confirmation of the position of N-oxide.

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### 150. Zen-ichi Horii, Chuzo Iwata, and Yasumitsu Tamura : Studies on Ergot Alkaloids and Related Compounds. IV.\*<sup>2</sup> Preparation and Lithium Aluminum Hydride Reduction of Some Vinylogous Lactams.

(School of Pharmacy, Osaka University\*<sup>1</sup>)

In the course of works on syntheses of Clavine alkaloids,<sup>1)</sup> i. e., Agloclavine, Festuclavine, Pyroclavine, Costaclavine, etc., it was observed that condensation of 5-phthalimido-2-tetralone (Ic)<sup>2)</sup> with methy 2-methyl-3-methylaminopropionate<sup>3)</sup> according to the procedure of Nelson, Ladburg, and Hsi<sup>4)</sup> yielded a small amount of by-product besides

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\*<sup>2</sup> Part III : Yakugaku Zasshi, **82**, 706 (1962).

1) H. Auterhoff : Angew. Chem., **71**, 84 (1959).

2) L. L. McCorry, R. C. Terrell : J. Org. Chem., **24**, 131 (1959).

3) D. R. Howton : *Ibid.*, **10**, 277 (1945).

4) N. A. Nelson, J. E. Ladburg, R. S. P. Hsi : J. Am. Chem. Soc., **80**, 6633 (1958).

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### 150. Zen-ichi Horii, Chuzo Iwata, and Yasumitsu Tamura : Studies on Ergot Alkaloids and Related Compounds. IV.\*<sup>2</sup> Preparation and Lithium Aluminum Hydride Reduction of Some Vinylogous Lactams.

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In the course of works on syntheses of Clavine alkaloids,<sup>1)</sup> i. e., Agloclavine, Festuclavine, Pyroclavine, Costaclavine, etc., it was observed that condensation of 5-phthalimido-2-tetralone (Ic)<sup>2)</sup> with methy 2-methyl-3-methylaminopropionate<sup>3)</sup> according to the procedure of Nelson, Ladburg, and Hsi<sup>4)</sup> yielded a small amount of by-product besides

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\*<sup>2</sup> Part III : Yakugaku Zasshi, **82**, 706 (1962).

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