

Experimental

The NMR spectra were obtained in about 5% CHCl_3 solutions or 5% CS_2 solution using a Varian Associates DP 60 NMR spectrometer, operating at 60 Mc.p.s. Compounds studied were prepared by one of us (K. Y.), the detail of which has been already published.²⁾

The authors are indebted to Professor T. Okamoto of University of Tokyo for his advices and encouragement. Thanks are also indebted to Dr. Peter Beak of University of Illinois, U.S.A. for reviewing of this manuscript before publication. They are also grateful to Mr. H. Hotta of University of Tokyo for his helpful discussion and Dr. K. Nukada and Mr. T. Suzuki of the Government Chemical Industrial Research Institute of Tokyo for making an NMR spectrometer available for the present work.

Summary

The structures of N-methylorixidinine, N-methylisoorixidinine and N-methylorixidine have been verified by NMR analysis. In addition, the conformation of the substituents on dihydrofuran ring was discussed, based on the relationship between the dihedral angle and the spin coupling constant.

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22. Tatsuya Horie and Takeo Ueda : Studies on Pyridazine Derivatives. IV.¹⁾ N-Oxidation of 3-Aminopyridazine and Its Ring Substitutes.

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As pyridazine comprises two vicinal nitrogen atoms, there should exist two position isomers in any pyridazine N-monoxide derivatives having an unsymmetrical structure, in respect of the position of N-oxide group. Regarding N-oxidation of pyridazine derivatives, it is of interest to decide positions of N-oxide groups in resulting derivatives of pyridazine N-oxide.

Although many of heterocyclic N-oxide have been extensively investigated by a number of researchers, little is known as for pyridazine N-oxide. Itai²⁾, Igeta^{3,4)}, Kumagaya⁵⁾ and Nakagome^{6,7)} reported about N-oxidation of some pyridazine derivatives having substituent group at 3- or 3- and 6- positions on the ring such as alkoxy, chloro, methyl and phenyl. However, N-oxidation of 3-aminopyridazine derivatives has never been revealed in any literature up to date.

A number of compounds of 3-amino-6-substituted pyridazine were synthesized by the authors, as described in the previous report⁸⁾. Attempts were made on the N-oxidation

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1) Part III. T. Horie, T. Ueda : This Bulletin, **10**, 595(1962).

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

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

4) *Idem* : *Ibid.* **8**, 599 (1960).

5) M. Kumagaya : Nippon Kagaku Zasshi, **81**, 1148 (1960).

6) T. Nakagome : Yakugaku Zasshi, **82**, 244 (1962).

7) *Idem* : *Ibid.* **82**, 249 (1962).

8) Part I. T. Horie, T. Ueda : This Bulletin, **10**, 580(1962).

of these compounds and some interesting results were obtained regarding 3-aminopyridazine N-oxide and its ring-substitutes, as summarized in preceding paper⁹⁾.

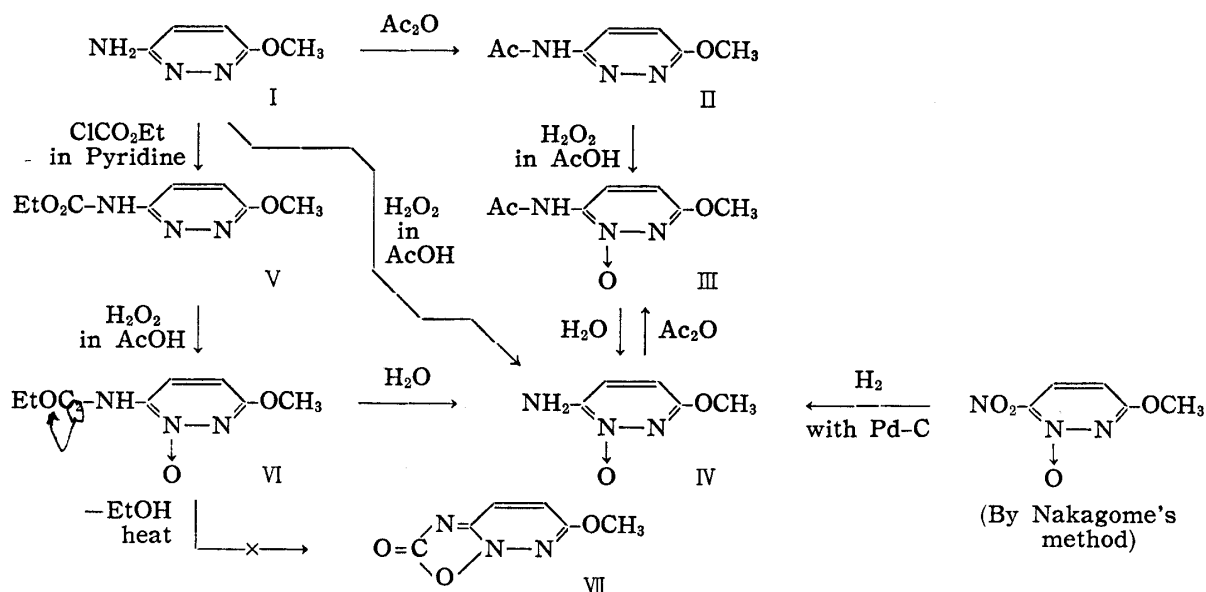
This paper describes the N-oxidation of 3-amino-6-substituted pyridazine and the decision of the position of N-oxide group in the resulting N-oxides.

N-Oxidation of 3-Amino-6-alkoxy-pyridazine

At first, the N-oxidation of 3-amino-6-methoxypyridazine and 3-acetamido-6-methoxypyridazine were examined to decide which the resulting N-oxides should be 1-oxide or 2-oxide.

According to the finding that 2-aminopyridine 1-oxide¹⁰⁾, 2-aminoquinoline 1-oxide¹¹⁾ etc. should be prepared by reacting acylaminoheterocyclane with hydrogen peroxide in acetic acid, followed by hydrolysing the resulting acylaminocyclane N-oxide, 3-acetamido-6-methoxypyridazine (II), prepared from the reaction between 3-amino-6-methoxypyridazine (I) and acetic anhydride, was reacted with a slight excess of hydrogen peroxide in acetic acid, and 3-acetamido-6-methoxypyridazine N-monoxide (III) was obtained in about 70% yield.

The hydrolysis of III with 10% hydrochloric acid afforded 3-amino-6-methoxypyridazine N-monoxide hydrochloride as colorless prisms of m.p. 208° (decomp.), and then, 3-amino-6-methoxypyridazine N-monoxide (IV) was obtained as white needles of m.p. 135°, by treating this hydrochloride with aqueous alkaline solution.



This monoxide IV was proved to be identical with the authentic sample of 3-amino-6-methoxypyridazine 2-oxide prepared according to the method of Nakagome¹²⁾. Therefore, it is evident from this identification that III and IV possess oxo group linked to the nitrogen atom of 2-position.

The ultraviolet absorption spectrum of III showed three maxima at 232 m μ , 269 m μ and 337 m μ . Each of other compounds of 3-acetamido-6-alkoxy-pyridazine N-monoxide, synthesized according to the similar method to that for IV, gave, also three absorption maxima at the quite similar wave lengths to those of IV, as shown in Table II.

9) T. Horie : *Yakugaku Zasshi*, **82**, 628 (1962).

10) R. Adams, S. Miyano : *J. Am. Chem. Soc.*, **76**, 2785 (1954).

11) H. Tanida : *Yakugaku Zasshi*, **79**, 1063 (1959).

12) T. Nakagome : *Ibid.* **81**, 554 (1961).

This finding indicates that all compounds of 3-acetamido-6-alkoxypyridazine N-monoxide belong to 2-oxide.

Moreover, it was found that IV was directly produced through the reaction between I and hydrogen peroxide in acetic acid.

At next, it has been found that ethyl 2-pyridinecarbamate 1-oxide¹³⁾, ethyl 2-quinolinecarbamate 1-oxide¹¹⁾ and ethyl 1-isoquinolinecarbamate¹¹⁾ 2-oxide easily lose one mole of ethanol from each molecule of the N-oxides to form the corresponding oxadiazolone derivatives. To examine whether this condensation holds true in the case of ethyl 6-methoxy-3-pyridazinecarbamate N-monoxide, the authors conducted the N-oxidation of ethyl 6-methoxy-3-pyridazinecarbamate.

Ethyl 6-methoxy-3-pyridazinecarbamate N-monoxide (VI) was exclusively obtained by oxidizing ethyl 6-methoxy-3-pyridazinecarbamate (V) with hydrogen peroxide in acetic acid in the similar manner to that for the oxidation of III. This monoxide (VI) gave 3-amino-6-methoxypyridazine 2-oxide (IV) after the hydrolysis with conc. hydrochloric acid. Therefore, it is evident that oxo group of VI should be attached to the nitrogen atom at 2-position. However, every effort to obtain the oxadiazolone derivative from (V) and VI, failed even in more drastic conditions than those for N-oxides of ethyl 2-pyridinecarbamate, ethyl 2-quinolinecarbamate and ethyl 1-isoquinolinecarbamate above cited.

In addition to the above finding, it was found that IV was converted into III by the acetylation with acetic anhydride, without any side reaction, and gave blue color with ferric chloride test-solution, just as known in 2-aminopyridine N-oxide derivatives.^{10,14)}

N-Oxidation of 3-Amino-6-chloropyridazine

It was found by the authors that the N-oxidation of 3-amino-6-chloropyridazine and 3-acetamido-6-chloropyridazine was somewhat different to that of I or II. As described above, 3-acetamido-6-methoxypyridazine (II) was found to be easily oxidized into the corresponding 2-oxide (III). In contrast to this finding, 3-acetamido-6-chloropyridazine (IX) was found to be, with difficulty, converted into the corresponding N-oxide by the oxidation with hydrogen peroxide in acetic acid. In this reaction, the greater part of X was recovered with a small amount of 3-amino-6-chloropyridazine N-monoxide (XI) from the reaction mixture. This fact suggested that 3-amino-6-chloropyridazine (VIII)

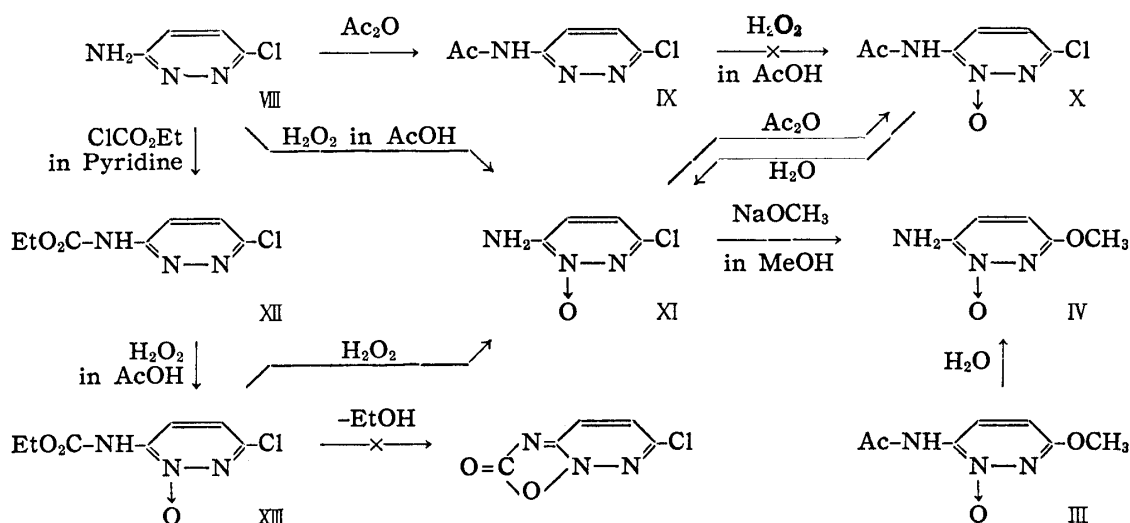


Chart 2.

13) A. R. Katritzky : J. Chem. Soc., 1956, 2063.

14) *Idem* : *Ibid.*, 1957, 191.

should be preferable to 3-acetamido-6-chloropyridazine (IX) to obtain XI. Hereupon, 3-amino-6-chloropyridazine was attempted to oxidize directly with hydrogen peroxide in acetic acid and expectedly, the objective compound XI was obtained in good yield.

The compound XI gave blue color with ferric chloride test solution, just as IV. This color reaction suggested that XI might belong to 2-oxide. Therefore, XI was converted into 3-amino-6-methoxypyridazine N-monoxide by the reaction with a slight excess of sodium methoxide in absolute methanol and the oxide was identical with the authentic sample of 3-amino-6-methoxypyridazine 2-oxide. This fact showed that XI should comprise oxo group at 2-position of pyridazine ring.

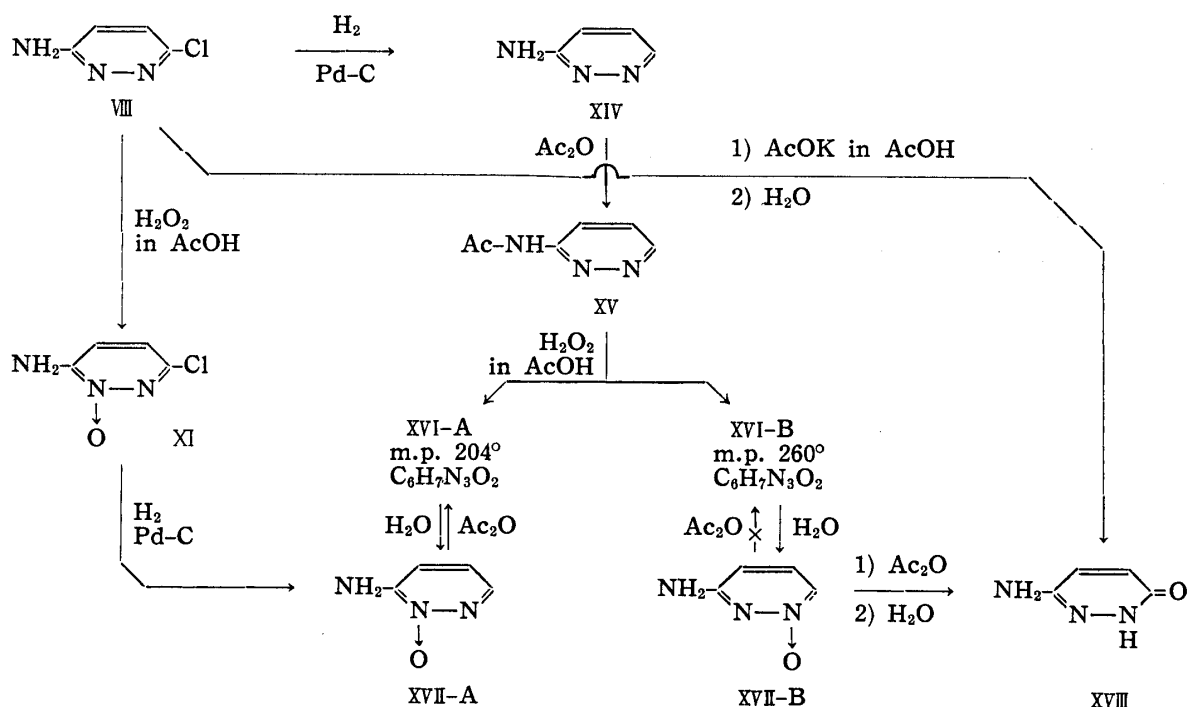
In connection with this finding, it was found that XI was converted into X by the acetylation with acetic anhydride and X was reversed by the hydrolysis with hydrochloric acid.

The infrared spectrum of X showed absorptions for acetamino group at 3270, 1703 and 1555 cm^{-1} , and for N-oxide at 1235 cm^{-1} . This finding denoted that the structure of X should be assigned to 3-acetamido-6-chloropyridazine 2-oxide.

The N-oxidation of ethyl 6-chloro-3-pyridazinecarbamate (XII) was conducted and ethyl 6-chloro-3-pyridazinecarbamate 2-oxide (VIII) was obtained from the reaction mixture, without the corresponding oxadiazolone.

N-Oxidation of 3-Acetamidopyridazine

It was found by the authors that the N-oxidation of 3-acetamidopyridazine is partially different to that of 3-acetamido-6-substituted pyridazine.



3-Aminopyridazine¹⁵⁾ (XIV) produced through the hydrogenation of 3-amino-6-chloropyridazine, was reacted with acetic anhydride and 3-acetamidopyridazine (XV) was obtained as the product in good yield. By oxidizing XV with hydrogen peroxide in acetic acid, colorless needles of m.p. 204° XVI-A as the main product and white prisms of m.p. 260° (decomp.), XVI-B as the minor product were isolated in about 50% total yield, after the

15) E. A. Steck : J. Am. Chem. Soc., 76, 3226 (1954).

repeated fractional recrystallization with methanol and water. The analytical data for XVI-A and XVI-B equally conformed for the formation of monoxide of XV having molecular formula of $C_6H_7N_3O_2$.

The deacetylation of XVI-A with aqueous sodium hydroxide solution afforded 3-aminopyridazine 2-oxide (XVII-A), which was identified with the authentic sample synthesized by the hydrogenation of 3-amino-6-chloropyridazine 2-oxide (XI).

However, the hydrolysis of XVI-B in the similar manner as that for XVI-A, gave a new product XVII-B of m.p. 141° , which was negative to ferric chloride test. The analytical datum of XVII-B was found to coincide with that of XVII-A. Therefore, it was assumable from the comparison of the data of the elementary analysis that there should exist an isomerism between XVI-A and XVI-B, as well as XVII-A and XVII-B.

Hereupon, it is considerable that 3-aminopyridazine N-monoxide should have two position isomers, 1-oxide and 2-oxide, in respect to the position of oxo group. Moreover, it is possible that 3-aminopyridazine 2-oxide could have two tautomeric structures, N-oxide form and N-hydroxy form as illustrated in Chart 4. Accordingly, 3-acetamidopyridazine 2-oxide, also, could have two tautomeric structures, acetamido form and acetoxy form as shown in Chart 4.

The authors conducted the decision of the structures of these four product as follows. If there exists a tautomerism between XVII-A and XVII-B, the unstable form should be converted into the other stable form by heating over its melting point. Such a mutual conversion by heating was not observed between the two compounds. At next, it was found that the acetylation of XVII-A differed to that of XVII-B. XVII-A was converted to the acetate XVI-A by acetylation with acetic anhydride, while XVII-B, to a hydrochloride by refluxing with acetic anhydride and hydrolyzing the resulting product with hydrochloric acid. The free base liberated from this hydrochloride was proved to be 6-amino-3(2*H*)-pyridazinone (XVIII), which was identified with the authentic sample prepared according to the method of the authors.⁹⁾ It is well known that oxo group in heterocyclic N-oxide is transferred to the vicinal carbon atom by the reaction with acetic anhydride.^{3,16,17)} This fact suggested that oxo group in XVII-B should be linked to the nitrogen atom at 1-position.

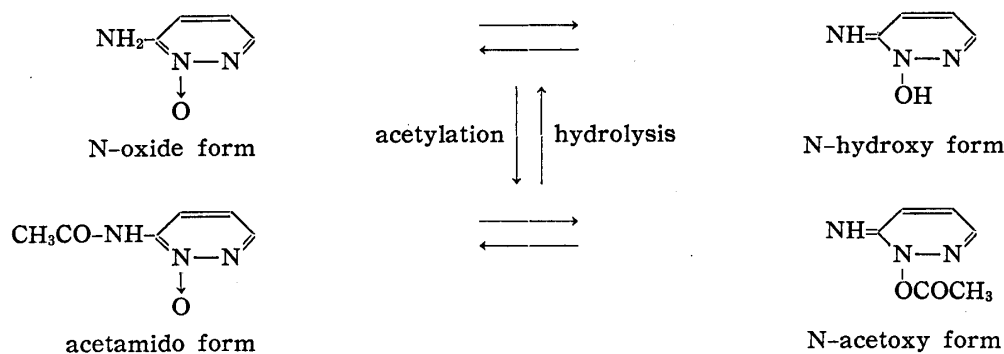


Chart 4. Tautomeric Isomers of 3-Aminopyridazine 2-Oxide and its Acetate

The inspection of the infrared absorption spectra supported that XVII-A and XVII-B should be 3-aminopyridazine 2-oxide and 3-aminopyridazine 1-oxide respectively, since XVII-A showed an absorption at 1235 cm^{-1} assigned to $N\rightarrow O$ and XVII-B, an absorption at 1275 cm^{-1} assigned to $N\rightarrow O$. Additionally, the acetate XVI-B was inferred to have the structure of 3-acetamidopyridazine 1-oxide, since the infrared spectrum of XVI-B showed an absorption at 1705 cm^{-1} and 1525 cm^{-1} assigned to $Ac-NH$, and an absorption at 1272

16) M. Katada : Yakugaku Zasshi, **67**, 51 (1947).

17) K. Igarashi : C. A., **48**, 738 (1954), Japan Pat. 7652 (1951).

cm^{-1} assigned to $\text{N}\rightarrow\text{O}$. On the other hand, the acetate XVI-A was presumed to be in form of N-acetoxy as illustrated in Chart 4, since the infrared spectrum of XVI-A did not show any absorption within the frequency range of amide II band and any strong absorption in the $1225\sim 1275\text{ cm}^{-1}$ range assigned to $\text{N}\rightarrow\text{O}$, but absorptions at 1717 cm^{-1} and 1217 cm^{-1} assigned to $\text{CH}_3\text{CO}-\text{O}-$ and absorptions at 3400 cm^{-1} and 1700 cm^{-1} assigned to $\text{NH}=\text{C}\langle$. This presumption suggests that acetyl entity of acetamino group might rearranged to N-oxide group in the course of the oxidation of XV or acetylation of XVII-A.

The ultraviolet absorption spectrum of 3-aminopyridazine 2-oxide (XVII-A) in ethanol showed three absorption maxima at $232\text{ m}\mu$, $260\text{ m}\mu$ and $348.5\text{ m}\mu$ and resembled to those of 3-amino-6-methoxypyridazine 2-oxide (IV) and 3-amino-6-chloropyridazine 2-oxide (XI), but differed from that of 3-aminopyridazine 1-oxide (XVII-B), which showed two absorption maxima at $256\text{ m}\mu$ and $340\text{ m}\mu$ in ethanol, as illustrated in Fig. 1.

As described above, it may be concluded that N-oxidation of 3-acetamidopyridazine gives a mixture of 2-oxide and 1-oxide, and the 2-oxide has a tautomeric N-acetoxy form, while N-oxidation of 3-amino- or 3-acylamino-6-substituted pyridazine affords exclusively 2-oxide.

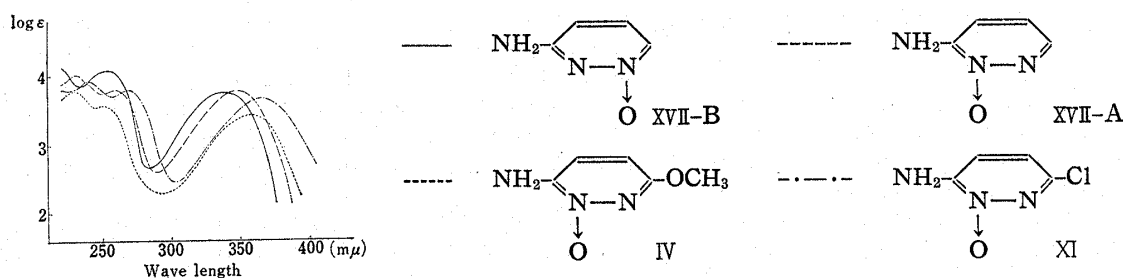


Fig. 1. Ultraviolet Absorption Spectra in Abs. EtOH

Experimental

General Method for the Synthesis of 3-Acetamido-6-alkoxypyridazine (II and its analogues)—To a solution of 0.1 mole. of crude 3-amino-6-alkoxypyridazine in ca. 50 cc. of hot AcOH was added dropwise ca. 20 cc of Ac_2O with shaking. After the reaction mixture was warmed on a steam bath for 3 hr., the volatiles were removed *in vacuo*. The residue was poured into ice- H_2O and basified with aq. NH_3 under cooling. The white precipitate was recrystallized from EtOH or dil. AcOH. Yield: ca. 80%.

The compounds synthesized are listed in Table I.

R	m.p. (°C)	Appearance	Recryst. solvent.	General Formula $\text{CH}_3\text{CO}-\text{NH}-\text{C}_4\text{H}_3\text{N}_2-\text{OR}$	Analysis (%)	
					Calcd. N	Found N
CH_3	222	white needles	EtOH	$\text{C}_7\text{H}_9\text{O}_2\text{N}_3$	25.14	25.38
C_2H_5	178	white needles	EtOH	$\text{C}_8\text{H}_{11}\text{O}_2\text{N}_3$	23.19	23.24
iso- C_3H_7	173	white needles	EtOH	$\text{C}_9\text{H}_{13}\text{O}_2\text{N}_3$	21.53	21.60
<i>n</i> - C_3H_7	153	white needles	EtOH	$\text{C}_9\text{H}_{13}\text{O}_2\text{N}_3$	21.53	21.77
<i>n</i> - C_4H_9	132	white needles	EtOH	$\text{C}_{10}\text{H}_{15}\text{O}_2\text{N}_3$	20.08	20.03
iso- C_5H_{11}	143	white needles	aq. MeOH	$\text{C}_{11}\text{H}_{17}\text{O}_2\text{N}_3$	18.82	18.86
<i>n</i> - C_5H_{11}	128	white needles	EtOH	$\text{C}_{11}\text{H}_{17}\text{O}_2\text{N}_3$	18.82	18.92
<i>n</i> - C_6H_{13}	132	white needles	aq. EtOH	$\text{C}_{12}\text{H}_{19}\text{O}_2\text{N}_3$	17.71	17.92
<i>n</i> - C_8H_{17}	128	white needles	aq. EtOH	$\text{C}_{14}\text{H}_{23}\text{O}_2\text{N}_3$	15.84	16.00
<i>n</i> - $\text{C}_{10}\text{H}_{21}$	122	white needles	EtOH	$\text{C}_{16}\text{H}_{27}\text{O}_2\text{N}_3$	14.32	14.31

3-Acetamido-6-chloropyridazine (IX)—It was prepared from 3-amino-6-chloropyridazine (VIII) by the reaction with Ac_2O , using the same method as described for 3-acetamido-6-alkoxy-pyridazine. Recrystallization from EtOH or AcOH gave white needles of m.p. 252~253° (decomp.). *Anal.* Calcd. for $\text{C}_6\text{H}_5\text{O}_2\text{N}_3\text{Cl}$ (IX): N, 24.56. Found: N, 24.39.

3-Acetamidopyridazine (XV)—It was prepared from 3-aminopyridazine (XIV) by the reaction with Ac_2O , using the same method as described above. Recrystallization from EtOH afforded white needles, m.p. 226°. *Anal.* Calcd. for $\text{C}_6\text{H}_7\text{ON}_3$ (XV): N, 30.65. Found: N, 30.51.

Ethyl 6-methoxy-3-pyridazinecarbamate (V)—To a solution of 12.5 g. of 3-amino-6-methoxy-pyridazine (I) in 100 cc. of dehyd. pyridine, the solution of 13 g. of ethyl chlorocarbonate in 30 cc. of Me_2CO was added dropwise with vigorous stirring. The reaction was carried out under cooling with cold H_2O . After the reaction mixture was kept at 50° for 1 hr., the solvents were evaporated *in vacuo* to leave an oil, which was poured into ice H_2O and the mixture was neutralized with AcOH. The precipitate was collected and recrystallized from 50% EtOH to white needles, m.p. 106~108°. Yield: 13 g. *Anal.* Calcd. for $\text{C}_8\text{H}_{11}\text{O}_3\text{N}_3$ (V): N, 21.32. Found: N, 21.59.

Ethyl 6-chloro-3-pyridazinecarbamate (XII)—To a suspension of 13 g. of pulverized 3-amino-6-chloropyridazine (VIII) in 100 cc. of dehyd. pyridine, a solution of 14 g. of ethyl chlorocarbonate in 30 cc. of Me_2CO was added dropwise, followed by a similar treatment as described for the synthesis of ethyl-6-methoxy-3-pyridazinecarbamate (V) to obtain colorless pillars of m.p. 201~202°. Yield: 14 g. *Anal.* Calcd. for $\text{C}_7\text{H}_8\text{O}_2\text{N}_3\text{Cl}$ (XII): N, 20.84. Found: N, 20.71.

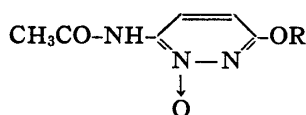
N-Oxidation of 3-Acetamido-6-methoxypyridazine (III)

Formation of 3-Acetamido-6-methoxypyridazine 2-Oxide (IV) and a Small Amount of 3-Amino-6-methoxypyridazine (V)—To a solution of 16.7 g. of (III) in 100 cc. of hot AcOH, 15 cc. of 30% H_2O_2 (corresponds to 1.3 moles.) was added portionwise under shaking. After the reaction mixture was warmed on a steam bath for 1 hr., it was allowed to stand overnight at a room temperature. The volatiles were removed *in vacuo* and the residue was poured into ice- H_2O . The resulting mixture was neutralized with aq. NH_3 and the deposited crude crystals were collected, recrystallized from EtOH to white needles of m.p. 216~217°. *Anal.* Calcd. for $\text{C}_7\text{H}_8\text{O}_3\text{N}_3$ (IV): C, 45.90; H, 4.95; N, 22.94. Found: C, 45.69; H, 4.88; N, 23.06. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 232 (4.11), 269 (3.98), 337 (3.65). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1697, 1535 ($\text{CH}_3\text{CO-NH-}$), 1253 ($\text{N}\rightarrow\text{O}$).

The basic filtrate of the crude product IV was concentrated to dryness and the residue was extracted with hot Me_2CO . After the extract was dried over anhyd. K_2CO_3 , the solvent was evaporated to leave a solid, which was recrystallized from Me_2CO and dried *in vacuo* to white needles of m.p. 134~135°. Yield: 1.6 g. *Anal.* Calcd. for $\text{C}_5\text{H}_7\text{O}_2\text{N}_3$ (V): N, 29.78. Found: N, 30.03. No depression was observed when mixed with an authentic sample of 3-amino-6-methoxypyridazine 2-oxide (IV).

The other nine of 3-acetamido-6-alkoxy-pyridazine 2-oxide were prepared from corresponding 3-acetamido-6-alkoxy-pyridazine by the reaction with H_2O_2 in AcOH, using the same method as described for N-oxidation of 3-acetamido-6-methoxypyridazine. The compounds synthesized are listed in Table II.

TABLE II. General Formula



R	m.p. (°C)	Appearance	Recryst. solvent	Formula	Analysis (%)		UV $\lambda_{\text{max}}^{\text{EtOH}}$ (m μ)
					Calcd. N	Found N	
C_2H_5	198	white needles	EtOH	$\text{C}_8\text{H}_{11}\text{O}_3\text{N}_3$	21.32	21.48	230, 270, 337
iso- C_3H_7	141	white needles	EtOH	$\text{C}_9\text{H}_{13}\text{O}_3\text{N}_3$	20.89	20.98	230, 270, 337
n- C_3H_7	125	white needles	EtOH	$\text{C}_9\text{H}_{13}\text{O}_3\text{N}_3$	20.89	20.78	230, 269, 337
n- C_4H_9	149	faint yellow needles	EtOH	$\text{C}_{10}\text{H}_{15}\text{O}_3\text{N}_3$	19.53	19.56	230, 268, 337
iso- C_5H_{11}	155	white needles	EtOH	$\text{C}_{11}\text{H}_{17}\text{O}_3\text{N}_3$	18.34	18.50	230, 268, 337
n- C_5H_{11}	144	white needles	EtOH	$\text{C}_{11}\text{H}_{17}\text{O}_3\text{N}_3$	18.34	18.12	230.5, 269, 337
n- C_6H_{13}	146	faint yellow needles	EtOH	$\text{C}_{12}\text{H}_{19}\text{O}_3\text{N}_3$	17.28	17.37	231, 270.5, 337.5
n- C_8H_{17}	131	white needles	EtOH	$\text{C}_{14}\text{H}_{23}\text{O}_3\text{N}_3$	16.34	16.19	231, 269, 337
n- $\text{C}_{10}\text{H}_{21}$	129	white needles	EtOH	$\text{C}_{16}\text{H}_{27}\text{O}_3\text{N}_3$	15.49	15.29	232, 269, 337

N-Oxidation of 3-Acetamidopyridazine (XV)

Formation of 3-Imino-2-acetoxy-2,3-dihydropyridazine (XVI-A) and 3-Acetamidopyridazine 1-Oxide (XVI-B)—16.7 g. of 3-acetamidopyridazine (XV) was dissolved into 80 cc. of AcOH on warming and the solution was added to 15 cc. of 30% H_2O_2 (corresponds to 1.3 moles.) all at once. The reaction mixture was warmed on a steam bath for 6 hr. and concentrated to a small volume *in vacuo* and then

made alkaline with dil. NH_3 under cooling. The deposited faint yellow precipitate was collected and purified by fractional recrystallization from MeOH.

5.2 g. of XVI-A was obtained as a easily soluble substance in MeOH. Recrystallization from MeOH gave white long needles of m.p. 203~204°. *Anal.* Calcd. for $\text{C}_6\text{H}_7\text{O}_2\text{N}_3$ (XVI-A): C, 47.05; H, 4.61; N, 27.44. Found: C, 46.96; H, 4.31; N, 27.25. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3400, 1700 (NH=C<); 1717, 1217 ($\text{CH}_3\text{CO-O-}$). No absorption for Ac-NH- and N→O.

1.8 g. of XVI-B, obtained as a hardly soluble substance in MeOH, was recrystallized from H_2O or AcOH+EtOH (1:1) to white fine prisms of m.p. 258~260° (decomp.). *Anal.* Calcd. for $\text{C}_6\text{H}_7\text{O}_2\text{N}_3$ (XVI-B): C, 47.05; H, 4.61; N, 27.44. Found: C, 47.46; H, 4.34; N, 27.39. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1705, 1525 ($\text{CH}_3\text{CO-NH-}$); 1270 (N→O).

Ethyl 3-Pyridazinecarbamate 2-Oxide (VI)—It was prepared from ethyl 6-methoxy-3-pyridazinecarbamate (V) by a similar procedure as described for N-oxidation of 3-acetamido-6-methoxypyridazine (III). Recrystallization from EtOH afforded white needles, m.p. 124~125°. *Anal.* Calcd. for $\text{C}_8\text{H}_{11}\text{O}_4\text{N}_3$ (VI): N, 21.32. Found: N, 21.59.

Ethyl 6-Chloro-3-pyridazinecarbamate 2-Oxide (XIII)—3.9 g. of ethyl 6-chloro-3-pyridazinecarbamate (XII) was boiled with 20 cc. of AcOH and 4.5 cc. of 30% H_2O_2 (corresponds to ca. 2 moles) for 3 hr. under reflux. After concentration *in vacuo*, the solid obtained was recrystallized from EtOH to colorless prisms of m.p. 161~162°. *Anal.* Calcd. for $\text{C}_7\text{H}_8\text{O}_3\text{N}_3\text{Cl}$ (XIII): N, 19.31. Found: N, 19.74.

3-Amino-6-methoxypyridazine 2-oxide (IV)

i) **From 3-Acetamido-6-methoxypyridazine 2-Oxide (III)**—A suspension of 9.5 g. of III in a mixture of 30 cc. of conc. HCl and 70 cc. of MeOH was boiled for 1 hr. under reflux. After the reaction mixture was treated with active charcoal, the volatiles were removed *in vacuo* to obtain a solid, which was recrystallized from MeOH to colorless long prisms of m.p. 207~208° (decomp.). Yield: 6.5 g. *Anal.* Calcd. for $\text{C}_6\text{H}_8\text{O}_2\text{N}_3\text{Cl}$ (IV·HCl): C, 33.80; H, 4.51; N, 23.66. Found: C, 33.70; H, 4.54; N, 23.38.

5.0 g. of IV·HCl obtained above, was dissolved into a small volume of aq. NH_3 and the solution was concentrated *in vacuo* to leave a solid residue, which was extracted with Me_2CO and after concentration of the extract crystals deposited. Recrystallization from Me_2CO , followed by drying over P_2O_5 *in vacuo* gave colorless needles of m.p. 134~135.5°. Yield: 2.8 g. *Anal.* Calcd. for $\text{C}_6\text{H}_7\text{O}_2\text{N}_3$ (IV): C, 42.55; H, 4.96; N, 29.78. Found: C, 42.49; H, 5.11; N, 29.53. No depression of melting point was observed when mixed with an authentic sample of 3-amino-6-methoxypyridazine 2-oxide, synthesized by the method of Nakagome. IV gave deep blue color with FeCl_3 test solution. UV $\lambda_{\text{max}}^{\text{EtOH}}$ $\text{m}\mu$ (log ϵ): 230 (3.42), 250 (3.23), 358 (3.18).

ii) **From Ethyl 6-Methoxy-3-pyridazinecarbamate 2-Oxide (VI)**—A suspension of 1.0 g. of VI in 10 cc. of conc. HCl was boiled for 4 hr. under reflux and concentrated *in vacuo* to afford crystals. Recrystallization from EtOH gave colorless prisms, m.p. 207~208° (decomp.), alone and on admixture with a sample of IV·HCl derived from III. *Anal.* Calcd. for $\text{C}_6\text{H}_8\text{O}_2\text{N}_3\text{Cl}$ (IV·HCl): N, 23.66. Found: N, 23.58.

iii) **From 3-Amino-6-methoxypyridazine (I)**—A solution of 2.5 g. of I in 20 cc. of AcOH was warmed on a steam bath with 3.0 cc. of 30% H_2O_2 for 2 hr. The reaction mixture was stood overnight at room temperature and concentrated *in vacuo* to leave an oil, which was crystallized by addition of a small amount of 28% NH_3 under cooling. The deposited crude crystals were collected and recrystallized from Me_2CO and dried over P_2O_5 *in vacuo* to obtain white prisms of m.p. 134~135°, which did not depress on admixture with a sample of IV prepared by the procedure i). Yield: 1.4 g.

iv) **From 3-Amino-6-chloropyridazine 2-Oxide (XI)**—To a solution of 2.0 g. of metallic Na in 100 cc. of abs. MeOH was added 10.0 g. of pulverized XI and the mixture was heated in an autoclave at 125~135° for 8 hr. After cooling, the precipitated NaCl was filtered off and the filtrate was concentrated to a small volume. The resulting mixture was acidified with conc. HCl and treated with active charcoal and then basified with 28% NH_3 again. After concentration *in vacuo*, the residual solid was extracted with Me_2CO . The extract was dried over anhyd. K_2CO_3 and concentrated to deposit crude crystals, which were recrystallized from Me_2CO , followed by drying over P_2O_5 *in vacuo* to give white needles of m.p. 134~135.5°, alone and on admixture with a sample of IV obtained by the procedure i). Yield: 5.6 g. (crude).

3-Amino-6-chloropyridazine 2-Oxide (XI)—A suspension of 6.5 g. of pulverized 3-amino-6-chloropyridazine (VIII) in 50 cc. of AcOH was boiled gently with 8.4 cc. of H_2O_2 (corresponds to 1.5 moles) on an oil bath for 3 hr. After cooling, the deposited crystals were collected, washed with cold H_2O and recrystallized from H_2O or AcOH to pale yellow needles of m.p. 253~255° (decomp.), giving deep violet color with FeCl_3 . Yield: 4.8 g. *Anal.* Calcd. for $\text{C}_6\text{H}_4\text{ON}_3\text{Cl}$ (XI): C, 32.99; H, 2.75; N, 28.87. Found: C, 32.65; H, 2.66; N, 28.96. UV $\lambda_{\text{max}}^{\text{EtOH}}$ $\text{m}\mu$ (log ϵ): 239 (3.68), 269 (3.42), 365 (3.28).

3-Aminopyridazine 2-Oxide (XVII-A)

i) **From 5-Imino-2-acetoxy-2,3-dihydropyridazine (XVI-A)**—A suspension of 1.5 g. of (XVI-A) in 10 cc. of EtOH was boiled with 6 cc. of 10% NaOH (corresponds to 1.5 moles) for 1 hr. under reflux.

When the reaction mixture was concentrated to about half volume, crude crystals deposited. Recrystallization from 50% EtOH afforded colorless dices, m.p. 214~215°, which did not depress on admixture with an authentic sample of 3-aminopyridazine 2-oxide (XVII-A) prepared by the procedure ii). Yield: 0.8 g.

ii) **From 3-Amino-6-chloropyridazine 2-Oxide (XI)**—A mixture of 7.3 g. of XI, 2.0 g of NaOH, 50 cc of water and 1.0 g. of 3% Pd-C was placed in a shaking flask and hydrogenated at atmospheric pressure. About 1250 cc. (corresponds to 1 mol.) of H₂ was absorbed. After the catalyst was filtered off, the filtrate was concentrated to deposit crystals, which were collected and washed with cold water. Recrystallization from 50% EtOH gave colorless dices, m.p. 214~215°, giving dark violet color with FeCl₃. Yield: 3.9 g. *Anal.* Calcd. for C₄H₅ON₃ (XVII-A): C, 43.24; H, 4.54; N, 37.83. Found: C, 42.85; H, 4.36; N, 37.88. UV $\lambda_{\max}^{\text{EtOH}}$ (log ϵ): 232 (4.02), 250 (3.75), 348.5 (3.77). IR $\nu_{\max}^{\text{Nujol}}$ 1238 cm⁻¹ (N→O).

3-Aminopyridazine 1-Oxide (XVII-B)—A suspension of 1.0 g. of 3-acetamidopyridazine 1-oxide (XVI-B) in 10 cc. of MeOH was boiled with 3 cc. of conc. HCl for 1 hr. under reflux. After the reaction mixture was concentrated *in vacuo*, the residue was basified with aq. NH₃ and concentrated again to dryness. The solid residue was repeatedly extracted with hot Me₂CO and the extract was dried over anhyd. K₂CO₃. The solvent was removed to leave crystals, which were recrystallized from Me₂CO and dried *in vacuum* desiccator to white needles of m.p. 140~141°, negative to FeCl₃ test. Yield: 0.42 g. *Anal.* Calcd. for C₄H₅ON₃ (XVII-B): C, 43.24; H, 4.54; N, 37.83. Found: C, 42.78; H, 4.70; N, 37.99. UV $\lambda_{\max}^{\text{EtOH}}$ m μ (log ϵ): 256 (4.06), 340 (3.76). IR $\nu_{\max}^{\text{Nujol}}$ 1276 cm⁻¹ (N→O).

The Treatment of 3-Amino-6-methoxypyridazine 2-Oxide (IV) with Ac₂O to form 3-Acetamido-6-methoxypyridazine 2-Oxide (III)—To a mixture of 1 cc. of Ac₂O and 1 cc. of AcOH was added 0.2 g. of IV. After the mixture was allowed to stand at a room temperature with occasional shaking for 6 hr., poured into ice water. The resulting precipitate was recrystallized from EtOH to give white long needles of m.p. 216~217°, alone and on admixture with an authentic sample of III synthesized by N-oxidation of II as described above. Yield: 0.12 g.

The Treatment of 3-Amino-6-chloropyridazine 2-Oxide (XI) with Ac₂O to form 3-Acetamido-6-chloropyridazine 2-Oxide (X)—To a mixture of 10 cc. of Ac₂O and 10 cc. of AcOH was added 2.0 g. of pulverized XI. After the reaction mixture was warmed on a steam bath with occasional shaking for 3 hr., the volatiles were removed *in vacuo* and the residue was poured into ice water to give a white precipitate, which was collected and recrystallized from MeOH, white fine needles of m.p. 202~203°. Yield: 1.8 g. *Anal.* Calcd. for C₆H₆O₂N₃Cl (X): C, 38.40; H, 3.20; N, 22.40. Found: C, 38.17; H, 3.10; N, 22.26. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 1703, 1555 (CH₃CO-NH-), 1235 (N→O).

The Treatment of 3-Aminopyridazine 2-Oxide (XVII-A) with Ac₂O to form 3-Imino-2-acetoxy-2,3-dihydropyridazine (XVI-A)—To a mixture of 0.5 cc. of Ac₂O and 5.0 cc. of Me₂CO was added 0.1 g. of XVII-A all at once. When the mixture was warmed for few min. and cooled, crystals deposited. Yield: ca. 0.1 g. Recrystallization from EtOH gave white long needles of m.p. 202~204°, alone and on admixture with an authentic sample of XVI-A obtained by the N-oxidation of XV as described above.

The Treatment of 3-Aminopyridazine 1-Oxide (XVII-B) with Ac₂O to form 6-Amino-3(2H)-pyridazinone (XVIII)—A solution of 0.05 g. of XVII-B in 1 cc. of Ac₂O was boiled for 3 hr. under reflux. After removing Ac₂O *in vacuo*, the oily residue was boiled with a mixture of 1 cc. of conc. HCl and 3 cc. of 75% EtOH for 1 hr. When volatiles were evaporated *in vacuo*, there was obtained a solid residue, which was recrystallized from EtOH to afford white needles of m.p. 240~245° (decomp.). This hydrochloride, supposed to be XVIII-HCl, was warmed with a small amount of aq. NH₃ and then cooled to deposit white needles, collected and recrystallized from EtOH. m.p. 225~227°, alone and on admixture with an authentic sample of 6-amino-3(2H)-pyridazinone XVIII prepared from VIII by the method of authors⁸⁾ as reported in previous paper. Yield: ca. 0.01 g. IR $\nu_{\max}^{\text{Nujol}}$ 1685 cm⁻¹ (cyclic amide).

Summary

It was found that N-oxidation of 3-acetamidopyridazine gave a mixture of 1-oxide and 2-oxide and the 2-oxide had a tautomeric N-acetoxy form, while N-oxidation of 3-acetamido-6-methoxypyridazine, 3-amino-6-methoxypyridazine and 3-amino-6-chloropyridazine afforded exclusively 2-oxide.

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