UDC 547.852.2.07

124. Takenari Nakagome: Synthesis of Pyridazine Derivatives. IX.[1] Nitration of 3,4-Dimethylpyridazine N-Oxide Derivatives.

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In the preceding work,[1] 3,4-dimethyl (Ia), 6-chloro-3,4-dimethyl (Ib), 6-methoxy-3,4-dimethylpyridazine 2-oxide (Ic) and 3,4-dimethylpyridazine 1-oxide (Id) were synthesized, and the structure of these N-oxides was confirmed. The present paper deals with nitration of these N-oxides with mixed acids.

As summarized in Table I and Fig. 1, nitration of Ia, Ib and Ic proceeded smoothly to form mono-nitro N-oxides (IIa, IIb and IIc) in good yields, whereas in case of Id much less satisfactory yield of IId was obtained, accompanied with a considerable amount of resinous product.

These mono-nitro compounds (IIa～IId) were catalytically hydrogenated in the presence of Raney-nickel[2] in methanol or palladized charcoal in dilute hydrochloric acid to yield the corresponding aminopyridazines (IIIa～IIId) in satisfactory yields.

Since in Ib and Ic only the 5-position, *para* to the N-oxide group is unsubstituted, the nitrated compounds (IIb, IIc) are reasonably assumed to be 5-nitro-6-chloro-3,4-dimethylpyridazine 2-oxide (IIb) and 5-nitro-6-methoxy-3,4-dimethylpyridazine 1-oxide (IIc).

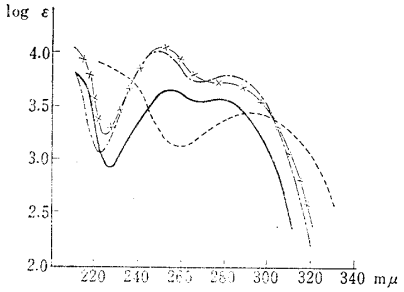

Fig. 1. Ultraviolet spectra
——— 5-amino-3,4-dimethylpyridazine (IIIa)
- - - - - - 6-amino-3,4-dimethylpyridazine (IIId)
—•—•— 3-methyl-4-aminopyridazine (IIIe)
—×—×— 3-methyl-5-aminopyridazine

Catalytic hydrogenation of IIa and IIb afforded one and the same amino compound (IIIa) which was not identical with the isomeric material (IIId) obtained from the nitrated compound (IId) of 3,4-dimethylpyridazine 1-oxide (Id) by catalytic reduction. Consequently, IIa, IId, IIIa and IIId must be 5-nitro-3,4-dimethylpyridazine 2-oxide, 6-nitro-3,4-dimethylpyridazine 1-oxide, 5-amino-3,4-dimethylpyridazine and 6-amino-3,4-dimethylpyridazine respectively, as represented in Chart 1.

Kano, *et al.*[3] reported that the ultraviolet absorption spectrum of 4-methyl-5-aminopyridazine typically differs from that of 3-amino-4-methylpyridazine. In this connection, ultraviolet spectra of IIIa and IIId were measured, together with those of 3-amino,[4] 4-amino-,[5] 3-methyl-5-amino-[3,6,14] and 3-methyl-4-aminopyridazine for comparison. 3-Amino-, 4-amino- and 3-methyl-5-aminopyridazine were prepared according to the

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1) Part VIII. T. Nakagome: This Bulletin, **11**, 721 (1963).
2) E. Hayashi, H. Yamanaka, K. Shimizu: *Ibid.*, **7**, 141 (1959).
3) H. Kano, M. Ogata, M. Watanabe: Presented at the Kinki branch meeting of the Pharmaceutical Society of Japan on March 19th, 1962.
4) E. A. Steck, R. P. Brundage, L. T. Fletcher: J. Am. Chem. Soc., **76**, 3225 (1954).
5) T. Kuraishi: Pharm. Bull. (Tokyo), **4**, 137 (1956).
6) Part IV. T. Nakagome: Yakugaku Zasshi, **82**, 253 (1962).

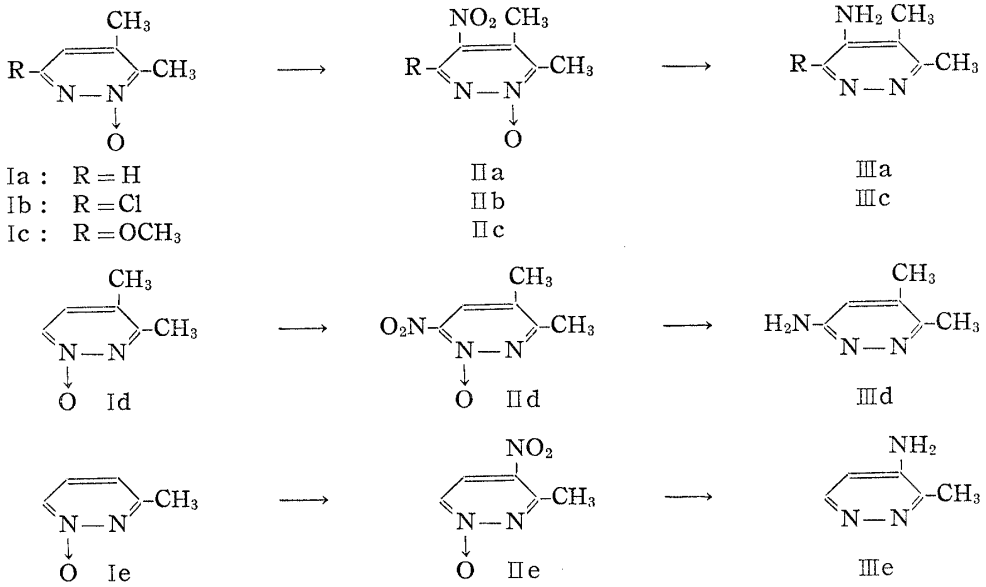
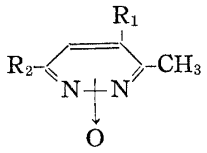


Chart 1.

Table I. Nitration of Pyridazine N-oxides



Starting material							Product	
Compd. No.	Substituent		N-oxide	HNO_3	Reaction temp.	Time	Compd. No.	Yield
	R_1	R_2		(mol.)	(°C)	(hr.)		(%)
Ia	CH_3	H	2-oxide	8	70	6	IIa	78
Ib	〃	Cl	〃	8	70	6	IIb[a]	66
Ic	〃	OCH_3	〃	2	room temp.	30	IIc[a]	86
Id	〃	H	1-oxide	10	50	9	IId	9
Ie	H	〃	〃	6	85～90	5	IIe	27
	〃	〃	2-oxide	6	85～90	5		65

a) Since (IIb) becomes purple and (IIc) becomes red when exposed to sunlight, they must be kept in the dark.

known procedure, while 3-methyl-4-aminopyridazine (IIIe), hitherto unknown compound, was prepared by nitration of 3-methylpyridazine 1-oxide (Ie)[3,7,8] with mixed acids, followed by catalytic hydrogenation over palladized charcoal in dilute hydrochloric acid. Nitration of Ie yielded only one product, 3-methyl-4-nitropyridazine (IIe) in 27% yield, much lower yield than in the case[6] of 3-methylpyridazine 2-oxide which gave 3-methyl-5-nitropyridazine 2-oxide in 65% yield under the same conditions, shown in Table I. Further examination of the reaction product failed to give any isomeric nitro compounds. The position of the nitro group in IIe was proved to be 4-position by reducing it to the amino compound (IIIe) which is different from any of the isomers as shown in Table II. Therefore, the amino compound (IIIe) must be 3-methyl-4-aminopyridazine.

As shown in Table II and Fig. 1, apparent differences are observed between the spectra of α-aminopyridazines and β-aminopyridazines. The former show a maximum at around 290～300 mμ, while maxima of the latter are present at around 250 and 280 mμ.

7) H. Kano, M. Ogata, H. Watanabe, I. Ishizuka : This Bulletin, **9**, 1017 (1961).
8) Part III. T. Nakagome : Yakugaku Zasshi, **82**, 249 (1962).

Table II.

Compd. (-pyridazine)	m.p. (°C)	m.p. of picrate (°C)	UV $\lambda_{max}^{95\%\,EtOH}$ mμ (log ε)		
4-Amino-			250 (4.13)	277	(3.67) [a]
			(252 (4.06)	281	(3.57)) [c]
3-Methyl-4-amino- (IIIe)	166~166.5	223~224 (decomp.)	249 (4.01)	280	(3.78)
3-Methyl-5-amino- [6]	162~163 [6]	222~223	251 (4.05)	276	(3.72) [a]
5-Amino-3,4-dimethyl- (IIIa)	196~197	239 (decomp.)	253 (3.64)	277	(3.56)
3-Amino-			234 (3.98)	302	(3.39)
			(234 (3.96)	301~302	(3.38)) [c]
6-Amino-3,4-dimethyl- (IIId)	222~223	228~229 (decomp.)	291 (3.44)		
3-Amino-methyl- [9]	225 [9]	220~221 [9]	(229 (3.87)	299	(3.30)) [b]

a) shoulder *b*) lit.,[9] measured in H_2O *c*) measured in EtOH[5]

It has been known that 3-methoxypyridazine 1-oxide undergoes nitration at 4- and 6-position with mixed acids, with the formation of 3-methoxy-6-nitropyridazine 1-oxide[12] and its deoxygenated 3-methoxy-6-nitropyridazine,[12] or 3-methoxy-4,6-dinitropyridazine 1-oxide,[11] depending on the conditions, in addition to 3-methoxy-4-nitropyridazine 1-oxide[11,12] as a principal product. It was also found[13] that 3-methoxy-4-methylpyridazine 1-oxide was smoothly nitrated at room temperature, giving 3-methoxy-4-methyl-6-nitropyridazine 1-oxide in a satisfactory yield. Now the replacement of the methoxyl group with the methyl group resulted in the decrease of electrophilic character of 6-position, and the yield of 6-nitro-3,4-dimethylpyridazine 1-oxide (IId) was only 9%, and 3-methylpyridazine 1-oxide (Ie) gave only the 4-nitro compound (IIe) even under more vigorous conditions.

Experimental*2

Nitration of 3,4-Dimethylpyridazine 2-Oxide (Ia)——A mixture of 5.0 g. of Ia, 16 cc. of conc. H_2SO_4 and 13.6 cc. of HNO_3 (d=1.51) was heated at 70° for 6 hr. After cool, the reaction mixture was poured on ice, extracted with $CHCl_3$. The $CHCl_3$ extract was washed with $NaHCO_3$ aqueous solution and dried over Na_2SO_4. After evaporation of $CHCl_3$, the residue was dissolved in benzene, passed through a Florisil column and the column was eluted with benzene. A yellow solution obtained was evaporated *in vacuo*, the residue was recrystallized from petr. benzin giving 5.3 g. (78%) of 6-nitro-3,4-dimethylpyridazine 2-oxide (IIa) as yellow leaflets, m.p. 94~96°. A further recrystallization from benzin raised the melting point to 97~97.5°. *Anal.* Calcd. for $C_6H_7O_3N_3$: C, 42.60; H, 4.17; N, 24.85. Found: C, 42.55; H, 4.27; N, 24.27. The aqueous mother liquor was neutralized with Na_2CO_3, extracted with $CHCl_3$. Evaporation of $CHCl_3$ left 0.5 g. of crude starting material.

Nitration of 6-Chloro-3,4-dimethylpyridazine 2-Oxide (Ib)——A mixture of 2.0 g. of Ib, 6.5 cc. of conc. H_2SO_4 and 5.2 cc. of HNO_3 (d=1.48) was heated at 70° for 6 hr. The reaction mixture was treated as for Ia and after passing through Florisil column, 2.3 g. (89%) of crude 5-nitro-6-chloro-3,4-dimethylpyridazine 2-oxide (IIb), m.p. 98~102°, was obtained, which was recrystallized from EtOH to yellow plates, m.p. 105~106°. Yield, 1.7 g. (66%). *Anal.* Calcd. for $C_6H_6O_3N_3Cl$: C, 35.36; H, 2.95; N, 20.62. Found: C, 35.35; H, 2.87; N, 20.85.

Nitration of 6-Methoxy-3,4-dimethylpyridazine 2-Oxide (Ic)——To a solution of 1.54 g. of Ic in 5 cc. of conc. H_2SO_4, 1 cc. of HNO_3 (d=1.48) was added with external cooling and the solution was allowed to stand for 1 day at room temperature. The mixture was poured on ice. Extraction with $CHCl_3$, removal of the solvent and recrystallization of the residue from EtOH gave 1.7 g. (86%) of yellow plates, melting at 105~106°. An additional recrystallization slightly raised the melting point to 106.5~107°. *Anal.*

*2 All melting points are uncorrected. Infrared and ultraviolet spectra were respectively measured with a Shimazu IR Infrared Spectrophotometer and a Shimazu RS-27 Recording Spectrophotometer.

9) W. G. Overend, L. F. Wiggins: J. Chem. Soc., **1947**, 239.
10) W. G. Overend, L. M. Turton: *Ibid.*, **1950**, 3500.
11) H. Igeta: This Bulletin, **7**, 938 (1959).
12) Part I. T. Nakagome: Yakugaku Zasshi, **81**, 554 (1961).
13) Part V. *Idem*: *Ibid.*, **82**, 1005 (1962).
14) Part VI. *Idem*: *Ibid.*, **82**, 1103 (1962).

Calcd. for $C_7H_9O_4N_3$: C, 42.21; H, 4.55; N, 21.10. Found : C, 42.34; H, 4.62; N, 21.09. No starting material was not recovered from aqueous mother liquor.

Nitration of 3,4-Dimethylpyridazine 1-Oxide (Id)——A mixture of 2.5 g. of Id, 15 cc. of conc. H_2SO_4 and 10 cc. of HNO_3 (d=1.48) was heated at 50° for 9 hr. After cool, the reaction mixture was poured on ice, extracted with $CHCl_3$. The $CHCl_3$ layer was washed with $NaHCO_3$ aqueous solution, and evaporated to dryness. The residue was dissolved in benzene, active alumina was added and filtered. The filtrate was poured on Florisil column, which was eluted with benzene. The initial fraction gave an oily substance which was not identified. The second fraction afforded yellow crystals, which were collected and recrystallized from benzene-petr. benzin to give 0.3 g. (9%) of 6-nitro-3,4-dimethylpyridazine 1-oxide (IId) as pale yellow plates, m.p. 97~98°, which depresses the melting point of IIa to 60~78°. *Anal.* Calcd. for $C_6H_7O_3N_3$: C, 42.60; H, 4.17; N, 24.85. Found : C, 42.51; H, 4.41; N, 25.19.

Nitration of 3-Methylpyridazine 1-Oxide (Ie)——To a solution of 1.9 g. of 3-methylpyridazine 1-oxide dissolved in 20 cc. of conc. H_2SO_4, 5.4 cc. of HNO_3 (d=1.49) was added and the solution was heated at 85~90° for 5 hr. The mixture was poured on ice, extracted with $CHCl_3$, and the extract was dried over Na_2SO_4. Removal of $CHCl_3$ and recrystallization of the residue from EtOH gave 0.73 g. (27%) of 3-methyl-4-nitropyridazine 1-oxide (IIe) as yellow needles, m.p. 72°. *Anal.* Calcd. for $C_5H_5O_3N_3$: C, 38.71; H, 3.25; N, 27.09. Found : C, 38.55; H, 3.55; N, 26.61.

5-Amino-3,4-dimethylpyridazine (IIIa)——(i) From IIa. A mixture of 3 g. of IIa, 2 cc. of AcOH, 50 cc. of MeOH and 3 cc. of Raney-Ni was hydrogenated at an atmospheric pressure. After about 4 hr., 4 moles of H_2 was uptaken. Following removal of the catalyst, the filtrate was neutralized with aqueous Na_2CO_3 and evaporated to dryness. The dried residue was repeatedly extracted with boiling AcOEt, which was filtered hot and the combined filtrate was evaporated. Recrystallization of the residue from MeCN afforded 1.8 g. (82%) of colorless prisms, m.p. 194~196°. An additional recrystallization raised the melting point to 196~197°. *Anal.* Calcd. for $C_6H_9N_3$: C, 58.51; H, 7.37; N, 34.12. Found : C, 58.49; H, 7.27; N, 34.16. Picrate : yellow prisms (EtOH), m.p. 239° (decomp.). *Anal.* Calcd. for $C_6H_9N_3 \cdot C_6H_3O_7N_3$: C, 40.91; H, 3.43; N, 23.86. Found : C, 40.91; H, 4.02; N, 23.77.

(ii) From IIb. A mixture of 0.5 g. of IIb, 10 cc. of 0.1N HCl, and Pd-catalyst prepared from 0.4 g. of charcoal and 20 cc. of 1% $PdCl_2$, was hydrogenated at an atmospheric pressure. The reaction was essentially complete within 1 hr. Treatment of the reaction mixture in the same manner as described above gave 0.25 g. (83.5%) of colorless prisms, m.p. 196~197°, undepressed on admixture with the material prepared from IIa as above. The picrate, precipitated from EtOH, m.p. 239° (decomp.), did not depress the melting point of the picrate of IIIa in (i).

5-Amino-6-methoxy-3,4-dimethylpyridazine (IIIc)——A mixture of 8 g. of IIc, 2 cc. of AcOH, 120 cc. of MeOH and Raney-Ni catalyst prepared from 5 g. of Ni-Al alloy (1:1) was subjected to hydrogenation as for IIa. After completion of 4 moles of H_2 uptake, the reaction mixture was worked up as for IIIa. When the AcOEt extract was concentrated to a small volume, colorless crystals separated out, which were collected, m.p. 182~183°. Yield, 5 g. (81%). A second recrystallization gave colorless prisms, m.p. 184°. *Anal.* Calcd. for $C_7H_{11}ON_3$: C, 54.88; H, 7.24; N, 27.43. Found : C, 54.40; H, 7.10; N, 27.21.

6-Amino-3,4-dimethylpyridazine (IIId)——A mixture of 0.6 g. of IIId, 20 cc. of 0.5N HCl and Pd-C prepared from 0.4 g. of charcoal and 20 cc. of 1% $PdCl_2$ solution, was hydrogenated at an atmospheric pressure. The same treatment of the reaction mixture as for IIIa and recrystallization of the product from AcOEt gave 0.25 g. (57%) of colorless plates, m.p. 222~223°. *Anal.* Calcd. for $C_6H_9N_3$: C, 58.51; H, 7.37; N, 34.12. Found : C, 58.83; H, 7.47; N, 33.85. Picrate : yellow needles, m.p. 228~229° (decomp.) (from MeOH).

3-Methyl-4-aminopyridazine (IIIe)——A mixture of 0.7 g. of IIe, 20 cc. of N HCl and Pd-C prepared from 0.4 g. of charcoal and 20 cc. of 1% $PdCl_2$ solution, was hydrogenated under atmospheric pressure. The reaction mixture worked up as above and concentration of the AcOEt extract afforded 0.44 g. (89%) of IIIe, m.p. 164~165°, which was recrystallized from AcOEt yielding colorless rhombs, m.p. 166~166.5°. The mixture with 3-methyl-5-aminopyridazine, m.p. 162~163°, melted at around 120°. *Anal.* Calcd. for $C_4H_7N_3$: C, 55.03; H, 6.47; N, 38.51. Found : C, 55.59; H, 6.57; N, 39.05. Picrate : m.p. 223~224° (decomp.), yellow needles (EtOH).

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Summary

Nitration of 3,4-dimethyl (Ia), 6-chloro-3,4-dimethyl (Ib), 6-methoxy-3,4-dimethyl-

pyridazine 2-oxide (Ic), 3,4-dimethyl (Id) and 3-methylpyridazine 1-oxide (Ie) was examined and it was proved that Ia, Ib, Ic and Ie afforded γ-nitropyridazine N-oxides (IIa～IIe), whereas Id in which γ-position was substituted gave α-nitro N-oxide (IId). All of these nitro derivatives were derived to aminopyridazines (IIIa～IIIe) by catalytic reduction over Raney-nickel in methanol or over palladium-charcoal in dilute hydrochloric acid. Ultraviolet spectra of several aminopyridazines are also given.

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125. Tomoharu Okuda, Makoto Suzuki, Tamotsu Furumai, and Hiroko Takahashi : Studies on Streptomyces Antibiotic, Cycloheximide. XVIII.[1] Isomerization Study of Cycloheximides and Thermal Degradation of Naramycin-B. Chemical Support of the Proposed Absolute Configuration of Cycloheximides.*1

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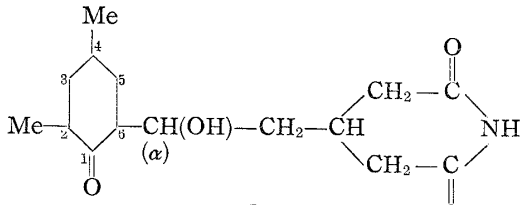
As evident from the plane structure (I) of cycloheximide which was elucidated by Kornfeld, *et al.*,[2] cycloheximide has four asymmetric centers in the molecule and, consequently, sixteen stereoisomers are possible to exist theoretically. Among these stereoisomers, three of them named as isocycloheximide,[3] Naramycin-B[4] and *α-epi*-isocycloheximide*3,5 were the main isomers found in a fermentation beer of a streptomyces or obtained by isomerizing cycloheximide or by synthesis.



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Studies on the elucidation of the absolute configuration of cycloheximide and its isomers began with Eisenbraun, *et al.*[6] who conformed the absolute configuration of (−)-2,4-dimethylcyclohexanone, an alkaline degradation product of cycloheximides, belonging to (2R:4R)-series. Thus, it was made evident that the absolute configuration of C-4 of cycloheximide and other isomers belongs to (S)-series. Lemin and Ford,[3] who successfully derived cycloheximide into isocycloheximide, suggested that a more

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*1 Preliminary accounts were published as a Communication to the Editor in this Bulletin, **10**, 639 (1962).
*2 Toda-machi, Kitaadachi-gun, Saitama-ken (奥田朝晴, 鈴木真言, 古米 保, 高橋裕子).
*3 A compound referred to as A_2 in J. Antibiotics, **14A**, 158 (1961).
1) Part XVII. T. Okuda, M. Suzuki : This Bulletin, **9**, 1014 (1961).
2) E.C. Kornfeld, R.G. Jones and T.V. Parke : J. Am. Chem. Soc., **71**, 150 (1949).
3) A.J. Lemin, J.H. Ford : J. Org. Chem., **25**, 344 (1960); U.S. Patents : No. 2,903,457 and 2,903,458 (1961).
4) Part II. T. Okuda, M. Suzuki, Y. Egawa, K. Ashino : This Bulletin **7**, 27 (1959).
5) Part XV. M. Suzuki, Y. Egawa, T. Okuda : This Bulletin, **11**, 582 (1963).
6) E.J. Eisenbraun, J. Osiecki, C. Djerassi : J. Am. Chem. Soc., **80**, 1261 (1958).