guidances and encouragements. Thanks are also to Dr. Y. Matsui, Dr. K. Tori for discussions on the analysis of infrared and nuclear magnetic resonance spectra, and to Mr. M. Takasuka and Mr. K. Aono for infrared and nuclear magnetic resonance spectral measurements, and to the members of the Analysis Room of this Laboratory for elemental analysis.

Summary

The reaction of methylpyridazine N-oxides with amyl nitrite in the presence of sodium amide in liquid ammonia afforded the corresponding *syn*-aldoximes. These *syn*-aldoximes were isomerized to *anti*-aldoximes with hydrochloric acid or heating alone except the case of some aldoximes. The configuration of the aldoximes was confirmed by the infrared and nuclear magnetic resonance spectra.

(Received July 12, 1963)

[Chem. Pharm. Bull. 11 (12) 1522 ~ 1527]

UDC 547.852.2.07

236. **Masaru Ogata** : Pyridazines. VII.[*1] Synthesis of Cyanopyridazines.

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There are two reports on the synthesis of cyanopyridazines. Schmidt, *et al.*[1] obtained 4-cyano-3(2*H*)-pyridazinone derivatives, and recently Robba[2] obtained 3-cyano- and 4-cyano-pyridazines from the corresponding amides. Several methods are known for the direct introduction of cyano group into heteroaromatic ring.

In this paper, application of two of these methods, the reaction of benzoylchloride and potassium cyanide on N-oxides (method A)[3] and the reaction of potassium cyanide on quarternary salt of N-oxides (method B)[4] on pyridazine series is described.

With pyridazine 1-oxide (I), these reaction (method A and B) failed to obtain the objective compound, giving oily product. The method A on 3-chloropyridazine 1-oxide (II)[5] resulted in the recovery of the starting material, but the method B afforded the

Table I. 3-Cyanopyridazines

Compd. No.	Solvent of recrystn.	m.p. (°C)	Yield (%)	
			Method A	Method B
III	benzene-petr. benzin	94~95	~0	34.6
VI	〃	90~91	~2	35.0
X	〃	94~95	28.4	72.2
XII	〃	93~94	10.0	68.5
XIV	EtOH	184.5~5.5	41.6	57.1

[*1] Part VI. This Bulletin, **11**, 1517 (1963).

[*2] Fukushima-ku, Osaka (尾形 秀).

[1] P. Schmidt, J. Druey: Helv. Chim. Acta, **37**, 134 (1954).

[2] Max Robba: Ann. Chim. (Paris), **5**, 351 (1960); C. A., **56**, 5961 (1962).

[3] A. Reissert: Ber., **38**, 1603, 3415 (1905).

[4] T. Okamoto, H. Tani: This Bulletin, **7**, 130, 925 (1959); F. Felly, E.M. Bears: J. Am. Chem. Soc., **81**, 4004 (1959).

[5] H. Igeta, This Bulletin, **8**, 559 (1960).

3-chloro-6-cyanopyridazine (III) in 34.6% yield. With 3-methyl,[6] 3-methoxy,[7] 3-benzyloxy[8] and 6-phenylpyridazine 1-oxide (V, IX, XI, XIII), the method A afforded cyanopyridazine (VI, X, XII, XIV) in low yield, while the method B afforded the cyanopyridazines in considerable yield as are shown in Table I.

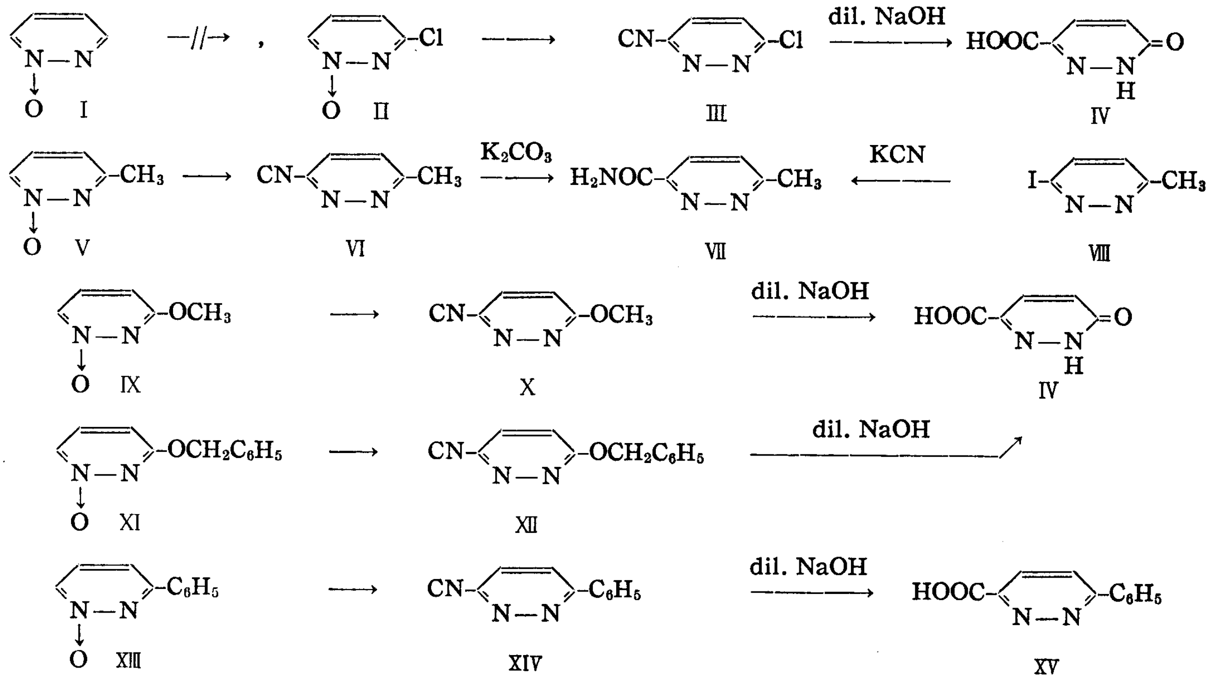

Chart 1.

The hydrolysis of these cyano compounds (III, X, XII) with dil. sodium hydroxide afforded known 6-oxo-1,6-dihydro-3-pyridazine carboxylic acid (IV).[9] From these fact, the position of cyano group in III, X, and XII was confirmed to be 6-position. The hydrolysis of VI with dil. potassium carbonate afforded amide (VII), which was identical with VII derived from VIII and potassium cyanide. Accordingly, IV was formulated as 3-methyl-6-cyanopyridazine. The hydrolysis of cyano compound (XIV) with dil. sodium hydroxide gave carboxy compound (XV), which was identical with authentic 3-phenyl-

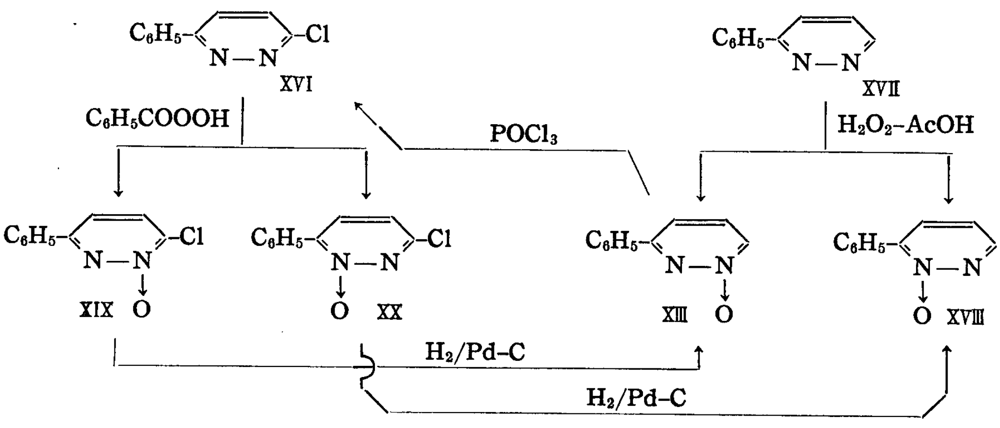

Chart 2.

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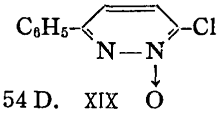
6) M. Ogata, H. Kano, H. Watanabe, I. Ishizuka : This Bulletin, **9**, 1017 (1961).
7) H. Igeta : *Ibid.*, **7**, 938 (1959).
8) T. Nakagome : Yakugaku Zasshi, **82**, 244 (1962).
9) R.F. Homer, Hilda Gregory, W.F. Overend, L.F. Wiggius : J. Chem. Soc., **1948**, 2185.

6-pyridazinecarboxylic acid,[10] therefore XIV was formulated as 3-phenyl-6-cyanopyridazine.

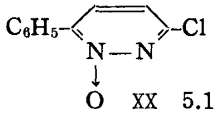
The synthesis and/proof of 3-phenylpyridazine 1-oxide (XIII) used in the above-mentioned reaction were carried out by the following method.

Heating of 3-phenylpyridazine (XVII)[11] with hydrogen peroxide in acetic acid, gave XIII and its isomer (XVIII). The ratio of XIII to XVIII isolated was about 100:1. 3-Phenyl-6-chloropyridazine[11] (XVI) was oxidized with perbenzoic acid in chloroform solution to give two 3-phenyl-6-chloropyridazine N-oxide (XIX, XX), the ratio XIX to XX isolated was about 3:1. Catalytic hydrogenation of XIX and XX with palladium-carbon in hydrous methanolic ammonia solution gave 3-phenylpyridazine N-oxides, XIII and XVIII respectively. When XIII was treated with phosphoryl chloride, XVI was obtained. This result is in fovour of 3-phenylpyridazine 1-oxide for XIII. Further evidences for these structure were obtained by dipole moments studies as follows.

The dipole moments of 3-phenyl-6-chloropyridazine N-oxide (XIX, XX) were measured in order to determine the position of N-O groups, and the observed value are shown in following.



5.54 D. XIX



XX 5.19 D.

In the previous paper,[12] the moment of pyridazine N-oxide is observed 5.21 D., the direction of which makes an angle of 10°10′ with a y axis (Chart 3).

The molecular moment of 3-phenyl-6-chloropyridazine N-oxide may be considered approximately as the resultant of the moments of pyridazine N-oxide and C-Cl bond, the moment of phenyl group being neglect in this case, because the phenyl group can be reasonably expected to afford only a little effect on their moments. When chlorine atom is attached at 6-position, the resultant moment of 1-oxide is expected to be larger than that of 2-oxide as illustrated in Chart 4.

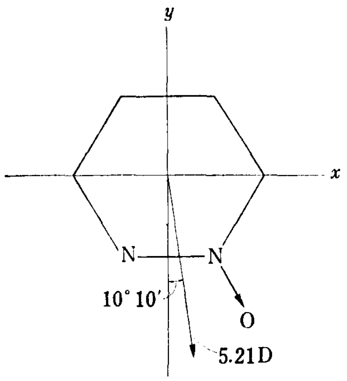


Chart 3.

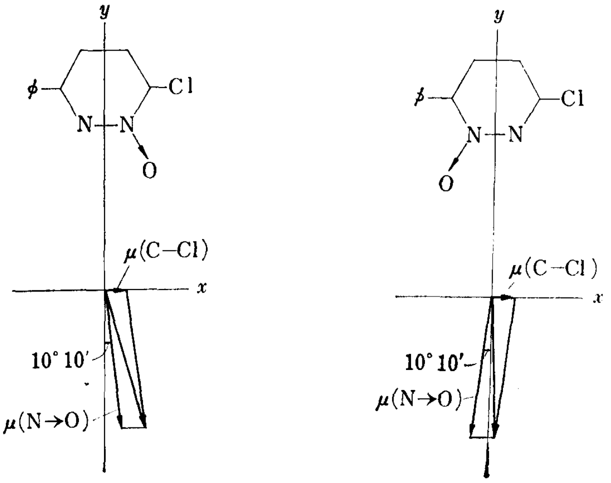


Chart 4.

Comparing the observed moments with the expectation on the order of their magnitude, one can unequivocally assign the N-oxide having the larger moment 5.54 D. to 1-oxide and the smaller moment 5.19 D. to 2-oxide.

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10) M. Kumagai : Nippon Kagaku Zasshi, 81, 489 (1960).
11) S. Gabriel, J. Colman : Ber., 32, 395 (1899).
12) H. Watanabe, M. Ogata, H. Kano : This Bulletin, **11**, 39 (1963)

By catalytic hydrogenation, XIX is converted to XIII and XX is to XVIII. Consequently, XIII is formulated as 3-phenylpyridazine 1-oxide and XVIII is 3-phenylpyridazine 2-oxide.

Experimental*[3]

3-Chloro-6-cyanopyridazine (III)——Method B: A mixture of 1.1 g. of II and 1.1 g. of dimethyl sulfate was heated on a water bath for 4 hr. After cool, to this salt in 18 ml. of dioxane, 8 ml. of H_2O and KCN solution (830 mg. of KCN in 2 ml. of H_2O) was added dropwise with stirring at 0～5°. The reaction mixture was stirred for another 30 min, at room temperature and extracted with $CHCl_3$. After evaporation of the solvent, the crude product was dissolved in benzene and chromatographed on alumina and the column was eluted with benzene. The residue from the fraction eluted with benzene was recrystallized from benzene-petr. benzin to colorless needles, m.p. 93～95°. Yield, 410 mg. Repeated recrystallization from benzene-petr. benzin gave colorless needles, m.p. 94～95°. *Anal.* Calcd. for $C_5H_2N_3Cl$: C, 43.01; H, 1.44; N, 30.01. Found: C, 43.04; H, 1.49; N, 30.02.

Formation of 6-Oxo-1,6-dihydro-3-pyridazinecarboxylic Acid (IV) from III——A mixture of 100 mg. of III, 2 ml. of 10% NaOH and 0.2 ml. of EtOH was warmed on a water bath for 40 min. After evaporation of EtOH, the solution was acidified with 6*N* HCl, and the deposited crystals were collected, m.p. 258° (decomp.). Yield, 40 mg. This was identified with an authentic sample prepared according to the method of Homer, *et al.*[5] by comparison of their IR spectra.

3-Methyl-6-cyanopyridazine (VI)——i) Method A: To a solution of 820 mg. of V and 1.0 g. of KCN dissolved in 10 ml. of H_2O, cooled in ice-water, 2.0 g. of BzCl was added dropwise with vigorous stirring. A reddish brown resinous oil began to separate out as the reaction progressed under stirring. After two hours, the reaction mixture was extracted with Et_2O. The Et_2O layer was washed with 10% NaOH solution and H_2O, dried over anhyd. Na_2SO_4. Et_2O was evaporated and the oily residue was washed with benzene, and recrystallized from benzene to colorless needles (VII), m.p. 204°. Yield, 7 mg. *Anal.* Calcd. for $C_6H_7ON_3$: C, 52.54; H, 5.15; N, 30.64. Found: C, 52.77; H, 5.34; N, 30.15. The benzene soluble fraction was chromatographed on alumina and the column was eluted with benzene. The residue from the fraction eluted with benzene was recrystallized from benzene-petr. benzin to colorless crystalls (VI), m.p. 81～87.5°. Yield, 5 mg. Repeated recrystallization from benzene-petr. benzin gave colorless needles, m.p. 90～91°. *Anal.* Calcd. for $C_6H_5N_3$: C, 60.49; H, 4.23; N, 35.28. Found: C, 60.90; H, 4.51; N, 35.00.

ii) Method B: Treatment of 2.2 g. of V, 2.6 g. of dimethylsulfate, 18 ml. of dioxane, 8 ml. of H_2O and KCN solution (1.94 g. of KCN in 4 ml. of H_2O) by the same procedure as for II afforded 840 mg. (35.0%) of colorless prisms, m.p. 86～90.5°. Repeated recrystallization from benzene-petr. benzin gave colorless prisms, m.p. 90～91°. This was identical with VI derived from V using method A by comparison of their IR spectra.

3-Methyl-6-pyridazine Carboxamide (VII)——i) From VI: A mixture of 100 mg. of VI, 200 mg. of K_2CO_3, 2 ml. of H_2O and 2 ml. of MeOH was warmed on a water bath for 5 min. After evaporation of MeOH, the solution was extracted with $CHCl_3$, and $CHCl_3$ was evaporated. The residue was recrystallized from benzene to colorless needles, m.p. 204～205°. Yield, 75 mg. This was identical with VII obtained in method A by comparison of their IR spectra.

ii) From VIII: A mixture of 1.8 g. of VIII, 3 g. of KCN, 6 ml. of H_2O and 6 ml. of EtOH was refluxed for 5 hr. After evaporation of EtOH, the solution was extracted with $CHCl_3$, and $CHCl_3$ was evaporated. The residue was recrystallized from benzene to colorless needles, m.p. 198°. Yield, 20 mg. This was identical with VII derived from VI by comparison of their IR spectra.

3-Methyl-6-iodopyridazine (VIII)——A mixture of 1.4 g. of 3-methyl-6-chloropyridazine and 4 ml. of conc. HI was heated at 120° for 2 hr. After cool, the mixture was neutralized with 10% NaOH and extracted with $CHCl_3$. The $CHCl_3$ was evaporated, and the residue was recrystallized from petr. benzin to colorless scales, m.p. 88～89°. Yield, 1.2 g. Repeated recrystallization from petr. benzin gave colorless scales, m.p. 90.5°. *Anal.* Calcd. for $C_5H_5N_2I$: C, 27.28; H, 2.28; N, 12.73. Found: C, 27.50; H, 2.43; N, 12.39.

3-Methoxy-6-cyanopyridazine (X)——i) Method A: Treatment of 2.0 g. of IX, 2.0 g. of KCN, 10 ml. of H_2O and 4.5 g. of BzCl by the same procedure as for V afforded 640 mg. (28.4%) of colorless needles, m.p. 91～92.5°. Repeated recrystallization from benzene-petr. benzin gave colorless needles, m.p. 94～95°. *Anal.* Calcd. for $C_6H_5ON_3$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.49; H, 3.90; N, 30.27.

ii) Method B: Treatment of 2.5 g. of IX, 2.8 g. of dimethylsulfate, 18 ml. of dioxane, 8 ml. of H_2O and KCN solution (1.94 g. of KCN in 4 ml. of H_2O) by the same method as for II afforded 1.95 g. (72.2%) of colorless needles, m.p. 89.5～92°. Repeated recrystallization from benzene-petr. benzin gave

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*[3] Melting points were determined on a Kofler-Block "Monoscope IV" and are uncorrected.

colorless needles, m.p. 94~95°. This was identified with X derived from IX using method A by comparison of their IR spectra.

Formation of 6-Oxo-1,6-dihydro-3-pyridazinecarboxylic Acid (IV) from X——A mixture of 250 mg. of X and 3 ml. of 10% NaOH was warmed on a water bath for 30 min. The solution was acidified with 6*N* HCl, and the deposited crystals were collected, m.p. 258°(decomp.). Yield, 100 mg. This was identified with an authentic sample[9] by comparisom of their IR spectra.

3-Benzyloxy-6-cyanopyridazine (XII)——i) Method A: Treatment of 2.0 g. of XI, 1.3 g. of KCN, 10 ml. of H_2O and 2.8 g. of BzCl by the same procedure as for V afforded 210 mg. (10.0%) of colorless needles, m.p. 92~94°. Repeated recrystallization from benzene-petr. benzin gave colorless needles, m.p. 93~94°. *Anal.* Calcd. for $C_{12}H_9ON_3$: C, 68.23; H, 4.30; N, 19.90. Found: C, 68.46; H, 4.43; N, 19.72.

ii) Method B: Treatment of 1.6 g. of XI, 1.1 g. of dimethylsulfate, 18 ml. of dioxane, 8 ml. of H_2O and KCN solution (780 mg. of KCN in 2 ml. of H_2O) by the same procedure as for II afforded 1.15 g. (68.5%) of colorless needles, m.p. 85~90°. Repeated recrystallization from benzene-petr. benzin gave colorless needles, m.p. 93~94°. This was identified with XII derived from XI using method A by comparison of their IR spectra.

Formation of 6-Oxo-1,6-dihydro-3-pyridazinecarboxylic Acid (IV) from XII——A mixture of 400 mg. of XII, 2 ml. of EtOH and 5 ml. of 10% NaOH was warmed on a water bath for 40 min. After evaporation of EtOH, the solution was acidified with 6*N* HCl, and the deposited crystals were collected, m.p. 258°(decomp.). Yield, 260 mg. This was identified with an authentic sample[9] by comparison of their IR spectra.

3-Phenyl-6-cyanopyridazine (XIV)——i) Method A: Treatment of 0.5 g. of XIII, 0.5 g. of KCN, 10 ml. of H_2O and 1.1 g. of BzCl by the same procedure as for V afforded 220 mg. (41.6%) of pale yellow scales, m.p. 178~181°. Repeated recrystallization from EtOH gave colorless scales, m.p. 184.5~185.5°. *Anal.* Calcd. for $C_{11}H_7N_3$: C, 72.91; H, 3.89; N, 23.19. Found: C, 72.88; H, 4.01; N, 23.10.

ii) Method B: Treatment of 860 mg. of XIII, 700 mg. of dimethylsulfate, 9 ml. of dioxane, 4 ml. of H_2O and KCN solution (490 mg. of KCN in 1 ml. of H_2O) by the same procedure as for II afforded 520 mg. (57.1%) of colorless scales, m.p. 180~183°. Repeated recrystallization from EtOH gave colorless scales, m.p. 184~185°. This was identified with XIV derived from XIII using method A by comparison of their IR spectra.

Formation of 3-Phenyl-6-pyridazinecarboxylic Acid (XV) from VI——A mixture of 80 mg. of XIV, 2 ml. of 10% NaOH and 1 ml. of EtOH was warmed on a water bath for 1 hr. After evaporation of EtOH, the solution was acidified with 6*N* HCl, and the deposited crystals were collected (colorless scales), m.p. 180~181°(decomp.). Yield, 90 mg. Recrystallization from hot water did not alter the melting point. *Anal.* Calcd. for $C_{11}H_8O_2N_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.58; H, 4.03; N, 13.64.

3-Phenyl-6-chloropyridazine 1-Oxide (XIX) and 2-Oxide (XX)——A mixture of 0.9 g. of XVI and *ca.* 3.5% perbenzoic acid-$CHCl_3$ solution was allowed to stand for 2 days at room temperature and $CHCl_3$ was removed under reduced pressure. H_2O was added to the residue, neutralized with $NaHCO_3$, and then extracted with $CHCl_3$. $CHCl_3$ was evaporated. The residue was chromatographed on alumina, and the column was eluted with benzene. The initial fraction of eluate gave 30 mg. of starting material, the residue from the further fraction eluted with benzene was recrystallized from benzene to colorless needles (XX), m.p. 157.5~158.5°. Yield, 50 mg. *Anal.* Calcd. for $C_{10}H_7ON_2Cl$: C, 57.97; H, 3.38; N, 13.52. Found: C, 58.06; H, 3.49; N, 13.25. The residue from the fraction eluted with $CHCl_3$ was recrystallized from EtOH to colorless needles (XIX), m.p. 151~151.5°. Yield, 170 mg. *Anal.* Calcd. for $C_{10}H_7ON_2Cl$: C, 57.97; H, 3.38; N, 13.52. Found: C. 57.70; H. 3.57; N, 13.19.

3-Phenylpyridazine 1-Oxide (XIII) and 2-Oxide (XVIII)——A mixture of 1.4 g. of XVII, 20 ml. of AcOH and 5 ml. of 30% H_2O_2 was heated at 60° for 3 hr., further 5 ml. of 30% H_2O_2 was added, and again heated at the same temperature for 3 hr. To this solution, H_2O was added, AcOH was evaporated under a reduced pressure, and this procedure was repeated. After neutralization of the residue with Na_2CO_3, the solution was extracted with $CHCl_3$, the $CHCl_3$ layer was evaporated. The residue was recrystallized from benzene to give 960 mg. of colorless needles (XIII), m.p. 112~113°. *Anal.* Calcd. for $C_{10}H_8ON_2$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.88; H, 4.73; N, 16.19. The filtrate was chromatographed on alumina, and the column was eluted with benzene. The initial fraction was collected and benzene was evaporated. The residue was recrystallized from benzene to give 15 mg. of colorless scales (XVIII), m.p. 131.5~132°. *Anal.* Calcd. for $C_{10}H_8ON_2$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.95; H, 4.78; N, 16.10. And then, the column was eluted with $CHCl_3$, the residue from the fraction eluted with $CHCl_3$ was recrystallized from benzene to give 160 mg. of pale yellow needles (XIII), m.p. 110~111.5°. Repeated recrystallization from benzene gave colorless needles, m.p. 112~113°.

Catalytic Reduction of 3-Phenyl-6-chloropyridazine 1-Oxide (XIX): Formation of 3-Phenylpyridazine 1-Oxide (XIII)——A mixture of 90 mg. of XIX, 2 ml. of MeOH, 0.5 ml. of 28% NH_4OH and 30 mg. of 10% Pd-C was subjected to hydrogenation. The catalyst was filtered, and MeOH was evaporated. The residue was added to H_2O, extracted with $CHCl_3$, and $CHCl_3$ was evaporated. The residue was recrystallized from benzene-petr. benzin to colorless needles, m.p. 112~113°. Yield, 30 mg. This was identical with XIII derived from XVII by comparison of their IR spectra.

Catalytic Reduction of 3-Phenyl-6-chloropyridazine 2-Oxide (XX): Formation of 3-phenylpyridazine 2-Oxide (XVIII)——A mixture of 70 mg. of XX, 2 ml. of MeOH, 0.5 ml. of 28% NH_4OH and 50 mg. of 10% Pd-C was subjected to hydrogenation. When the reaction mixture was treated in the same way as described above, 15 mg. of XVIII as colorless scales, m.p. 131~132° was obtained. This was identified with XVIII derived from XVII by comparison of their IR spectra.

3-Phenyl-6-chloropyridazine (XVI)——To a solution of 0.5 g. of XIII dissolved in 10 ml. of $CHCl_3$, 1.0 g. of $POCl_3$ was added, the mixture refluxed for 2 hr. The solvent was removed *in vacuo*. The residue was neutralized with Na_2CO_3, and extracted with $CHCl_3$. $CHCl_3$ was distilled and the residue was recrystallized from EtOH to colorless scales, m.p. 158~160°. Yield, 10 mg. This was identified with XVI by comparison of their IR spectra.

The author expresses his gratitude to Prof. Emeritus E. Ochiai of the University of Tokyo, Dr. K. Takeda, Director of this laboratory, and to Dr. H. Kano of this laboratory, for their helpful guidances and encouragements. He also thanks Dr. T. Itai of National Institute of Hygienic Sciences for providing the valuable suggestion. Thanks are also to Dr. H. Watanabe, Dr. T. Yoshizaki, Dr. Y. Matsui, and Mr. M. Takasuka for dipole moment and infrared spectral measurements, and to the members of the Analysis Room of this laboratory for elemental analysis.

Summary

3-Chloro, 3-methyl, 3-methoxy, 3-benzyloxy, and 3-phenyl-6-cyanopyridazine (III, VI, X, XII, XIV) was synthesized from 3-chloro, 3-methyl, 3-methoxy, 3-benzyloxy, and 3-phenylpyridazine 1-oxide (II, V, IX, XI, XIII).

(Received July 12, 1963)

[Chem. Pharm. Bull. 11 (12) 1527 ~ 1539]

UDC 547.852.7.07 : 543.422.25[539.143.43]

237. Masaru Ogata, Hideo Kano, and Kazuo Tori: Pyridazines. VIII.[*1] Syntheses and Nuclear Magnetic Resonance Spectra of Cinnoline N-Oxides.[*2]

(*Shionogi Research Laboratory, Shionogi & Co., Ltd.*[*3])

Several investigations have been made on the syntheses of benzodiazine N-oxides such as quinoxaline N-oxides,[1] quinazoline N-oxides,[2] and phthalazine N-oxides.[3] Study of cinnoline N-oxides, however, has been limited to synthesis of 4-arylcinnoline N-oxides,[4] and the position of their N-O groups has not been determined.

This paper describes synthetic and structural studies of cinnoline N-oxides, including nitration of 3-methoxycinnoline 1-oxide. Furthermore, nuclear magnetic resonance (NMR) spectra of cinnoline N-oxides are investigated.

Cinnoline (I) was readily converted into its isomeric N-oxides on treatment with hydrogen peroxide in acetic acid. The product was chromatographed on alumina to separate

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[*1] Part VII This Bulletin, **11**, 1522 (1963).

[*2] Preliminary reports of this work were published as "Communication to the Editor" in this Bulletin, **10**, 1123 (1962); **11**, 681 (1963).

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