The aqueous solution left after extraction of ether was acidified with HNO_3 and a few drops of 5% $AgNO_3$ solution was added by which white precipitate of silver cyanide formed.

Summary

Reactivity of cyano group in 4-position of 2, 6-dimethylpyrimidine-4-carbonitrile was examined. This compound behaves like ordinary nitriles in forming 4-acetyl compound with methylmagnesium bromide, 4-carboxylic acid ester with dehydrated alcohol and hydrogen chloride, and 4-acid amide with alkaline hydrogen peroxide. However, it showed specificity in undergoing substitution with methoxyl ion to form 4-methoxy compound. The ester or acid amide obtained by such reaction was reacted with hydrazine hydrate to afford 2,6-dimethylpyrimidine-4-carbohydrazide. Condensation with few other aldehydes was also carried out.

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125. **Tsukasa Kuraishi**: 4,5-Substituted Pyridazines. VII.[1] Synthesis and Acylation of 3,4-Dichloro-5-aminopyridazine.

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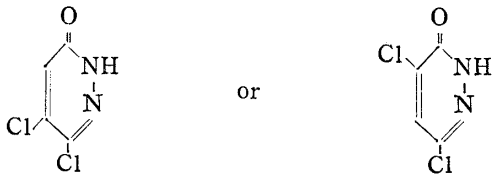
Previously, the author reported the preparation of two isomers of monoaminodichloropyridazines having m.p. 151° and 178°.[2]

Although they were led to 4-aminopyridazine by catalytic reduction, the structure of 4- or 5-amino-dichloropyridazine (VII and VIII) had not been established.

This paper is to report the synthesis of 3,4-dichloro-5-aminopyridazine (VIII) prepared by another route in connection with the structure of major product obtained from 3,4,6-trichloropyridazine (I) by heating with glacial acetic acid.[3]

In Part II of this series, preparation of 5,6- or 4,6-dichloro-3-pyridazinol (3,4- or 3,5-dichloro-6-pyridazone) (III) having m.p. 203~204° from the reaction of (I) with glacial acetic acid was described.



Replacement of the chlorine in 4- or 5-position of this compound (III) with an amino group yielded a product (IV) of m.p. 278~280°, which gave 3,6-dichloro-4-aminopyridazine (II) by chlorination with phosphoryl chloride in a sealed tube. Furthermore, catalytic reduction of (IV) presents a convenient method for preparing 5-amino-3-pyridazinol (V).[4] Accordingly, the structures of (III) and (IV) were confirmed as 5,6-dichloro-3-pyridazinol and 5-amino-6-chloro-3-pyridazinol, respectively.

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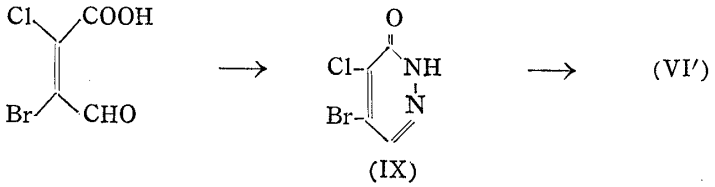
1) Part VI: This Bulletin, **6**, 551 (1958).
2) Part I: *Ibid.*, **4**, 497 (1956).
3) Part II: *Ibid.*, **5**, 376 (1957).
4) Part V: *Ibid.*, **6**, 331 (1958).

In 1952, Kuh[5] prepared 2-chloro-3-bromo-3-formylacrylic acid (mucobromochloric acid) from furfural by the action of bromine and gaseous chlorine. From this compound, 4-chloro-5-bromo-3-pyridazinol (IX) was obtained by condensation with hydrazine sulfate in the presence of sodium acetate by Grundmann's method.[6] In order to determine the structures of (VII) and (VIII), chlorination of (IX) with phosphoryl chloride was attempted. However, 3,4-dichloro-5-bromopyridazine was not obtained and only 3,4,5-trichloropyridazine was formed. When (IX) was heated with the excess of ethanolic ammonia solution a light yellow product (VI') having m.p.>300° was formed and was purified by repeated recrystallization from water.

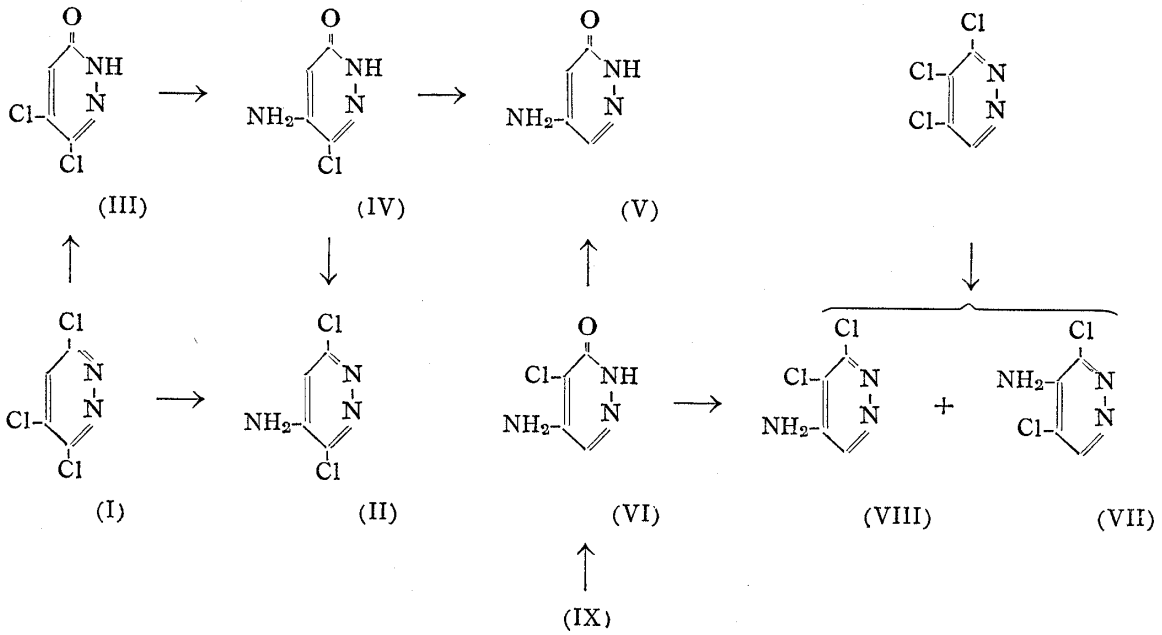


Microchemical analysis of this compound after three recrystallizations gave (1) C, 31.54; H, 2.24; and (2) C, 31.66; H, 2.01. A nearly satisfactory correspondence is considered with the structure of 4-chloro-5-amino-3-pyridazinol (VI), $C_4H_4ON_3Cl$, which requires C, 32.99; H, 2.75.

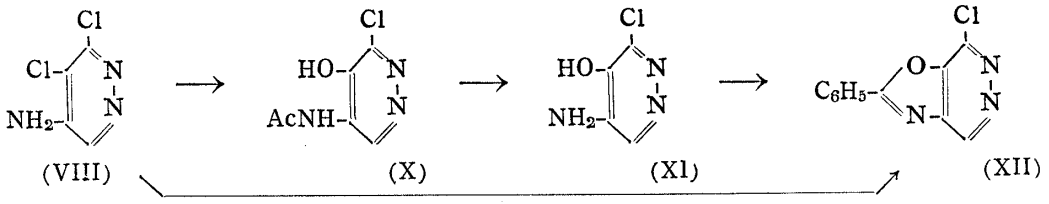
Although, 4-amino-5-bromo-3-pyridazinol may be expected as a by-product, the substance responsible could not be isolated from (VI') by fractional recrystallization.

The preparation of (VI) from 4,5-dichloro-3-pyridazinol was described in a preceding paper.[4] Actually, catalytic reduction of (VI') also gave (V), as in the case of (VI), and no other product was obtained. Ultraviolet absorption spectra of (VI) and (VI') are given in Fig. 1. The spectrum of (VI') was essentially identical with that of (VI).

3,4-Dichloro-5-aminopyridazine (VIII), m.p. 178°, was obtained from (VI) and (VI') by a similar method as in the case of (II), and showed no mixed m.p. depression with a sample obtained from 3,4,5-trichloropyridazine.



5) E. Kuh: U.S. Pat. 2,588,852 (American Cyanamid Co.) (C.A. **46**, 9587 (1952)).
6) C. Grundmann: Ber., **81**, 1 (1948).
7) T. Kuraishi: This Bulletin, **4**, 137 (1956).



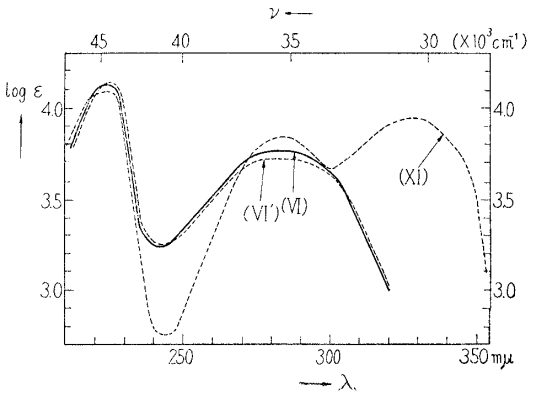


Fig. 1. Ultraviolet Absorption Spectra of (VI), (VI'), and (XI) (in EtOH)

Attempts to prepare the hydroxy compound of (VIII) failed to give the desired 3(or 4)-chloro-5-amino-hydroxypyridazine, by heating with diluted hydrochloric acid. However, when (VIII) was heated under reflux with acetic anhydride it furnished 3-chloro-4-hydroxy-5-acetamidopyridazine (X), m.p. 258° (decomp.). (X) was easily converted to the corresponding 3-chloro-4-hydroxy-5-aminopyridazine (XI). The position of the hydroxyl group was ascertained by preparing the acyl derivatives and then comparing ultraviolet absorption spectra with that of (VI) (Fig. 1).

On the other hand, acylation of (VIII) or (XI) with benzoyl chloride gave the same product and it was 2-phenyl-7-chloro-oxazolo[4,5-*d*]pyridazine (XII) from the elementary analysis

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Experimental[8]

5-Amino-6-chloro-3-pyridazinol (IV)—3.6 g. of 5,6-dichloro-3-pyridazinol (m.p. 203°), obtained by refluxing (I) with AcOH, was placed in a sealed tube with 80 cc. of dehyd. EtOH and saturated with dry NH_3. The mixture was heated in an oil bath at 150~160° for 20 hrs. After partial evaporation of the solvent, deposited crystals were collected and recrystallized from water. Yield, 2.1 g. of m.p. 278~280°. *Anal.* Calcd. for $C_4H_4ON_3Cl$: C, 32.99; H, 2.75; N, 28.86. Found: C, 32.72; H, 2.32; N, 28.47.

5-Amino-3-pyridazinol (V)—A mixture of 1.7 g. of (IV), 0.6 g. of NaOH, 1.2 g. of Pd-C (8%), and 40 cc. of distilled H_2O was hydrogenated under atmospheric pressure. After the catalyst was filtered off, the filtrate was neutralized with AcOH and evaporated on a water bath using water aspiration. The residue was washed with a small amount of water and recrystallized from water. Yield, 0.6 g. of m.p. 286~287°. This sample showed no depression of m.p. with an authentic sample described in a previous paper.[4]

3,4-Dichloro-5-aminopyridazine (VIII)—8.2 g. of (VI) or (VI') was heated in a sealed tube with 50 cc. of freshly distilled $POCl_3$ at 150~160° for 15 hrs. After removal of the excess of $POCl_3$ on a water bath *in vacuo*, the residue was dissolved in cooled water and filtered. The solution was made alkaline under cooling by the addition of conc. NaOH solution. After standing overnight, deposited crystals were collected, washed with water, and recrystallized from water. m.p. 178° and m.p. 176~178° on admixture with a specimen prepared from 3,4,5-trichloropyridazine. Yield, 4.5 g.

4-Chloro-5-bromo-3-pyridazinol (IX)—9.5 g. of 2-chloro-3-bromo-3-formylacrylic acid prepared by

8) All m.p.s are uncorrected.

the method of Kuh[5] was dissolved in a small amount of hot water and added to a hot aq. solution of the mixture of 5.8 g. of hydrazine sulfate and 9 g. of AcONa with stirring. Separated crystals (8 g.) were collected, washed with water, and recrystallized from water giving colorless prisms, m.p. 208°. *Anal.* Calcd. for $C_4H_2ON_2BrCl$: C, 22.90; H, 0.95; N, 13.36. Found: C, 23.03; H, 1.09; N, 13.16.

Reaction of (IX) with Saturated Ethanolic Ammonia Solution; Formation of 4-Chloro-5-amino-3-pyridazinol (VI′)—Five grams of (IX) was placed with 150 cc. of dehyd. EtOH in a sealed tube and saturated with dry NH_3 at 0° to 5°. The mixture was heated in an oil bath at 160~170° for 20 hrs., cooled, and the solution was evaporated to dryness on a water bath. The resulting residue was recrystallized from water with activated carbon. Yield, 2.9 g. of m.p.>300°.

3,6-Dichloro-4-aminopyridazine (II)—Two grams of (IV) was heated with 10 cc. of $POCl_3$ in a sealed tube at 150~160° for 8 hrs. and treated as in the case of (VIII). Crude product was recrystallized from water. Yield, 1.2 g. of m.p. 203°. The mixed m.p. with an authentic sample[4,7] was not depressed.

3-Chloro-4-hydroxy-5-acetamidopyridazine (X)—Two grams of (VIII) was heated under reflux with 15 cc. of Ac_2O for 30 mins. After standing at room temperature, deposited crystals were filtered, washed with MeOH, and recrystallized from EtOH. Yield, 0.9 g. of m.p. 258°(decomp.). *Anal.* Calcd. for $C_6H_6O_2N_3Cl$: C, 38.40; H, 3.20; N, 22.40. Found: C, 38.46; H, 2.89; N, 22.06.

3-Chloro-4-hydroxy-5-aminopyridazine (XI)—0.5 g. of (X) was heated with dil. HCl (10%) for 30 mins. After cool, the solution was neutralized with anhyd. K_2CO_3, the deposited crystals were collected, and recrystallized from water. Yield, 0.31 g. of m.p. 259°(decomp.). The mixed m.p. with (X) depressed to 240~242°. *Anal.* Calcd. for $C_4H_4ON_3Cl$: C, 32.99; H, 2.75; N, 28.86. Found: C, 33.38; H, 2.43; N, 28.53.

2-Phenyl-7-chloro-oxazolo[4,5-*d*]pyridazine (XII)—(i) 0.25 g. of (XI) was heated gently under reflux with 5 cc. of BzCl for 30 mins. After standing overnight in a refrigerator, separated crystals were filtered, washed with MeOH, and recrystallized from MeOH. Yield, 0.11 g. of m.p. 188°. This sample showed no m.p. depression on admixture with a specimen prepared from (VIII).

(ii) 0.4 g. of (VIII) was treated with 10 cc. of BzCl as described above. The reaction mixture became brown. Separated crystals were recrystallized from MeOH. m.p. 187~188°. *Anal.* Calcd. for $C_{11}H_6ON_3Cl$: C, 57.01; H, 2.59; N, 18.14. Found: C, 57.34; H, 2.32; N, 18.25.

Summary

1) The structures of 3,4-dichloro-5-aminopyridazine (VIII), m.p. 178,° and 5,6-dichloro-3-pyridazinol (III), m.p. 203~204°, were established. (VIII) was obtained from 4-chloro-5-amino-3-pyridazinol (VI) and was identical with the sample derived from 3,4,5-trichloropyridazine; (IV) was characterized as a convenient intermediate for preparing 5-amino-3-pyridazinol (V) and 3,6-dichloro-4-aminopyridazine (II).

2) Preparations of 5-amino-6-chloro-3-pyridazinol (IV), 3-chloro-4-hydroxy-5-aminopyridazine (XI), and 2-phenyl-7-chloro-oxazolo[4,5-*d*]pyridazine (XII) obtained from (VIII) and (XI) were reported.

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