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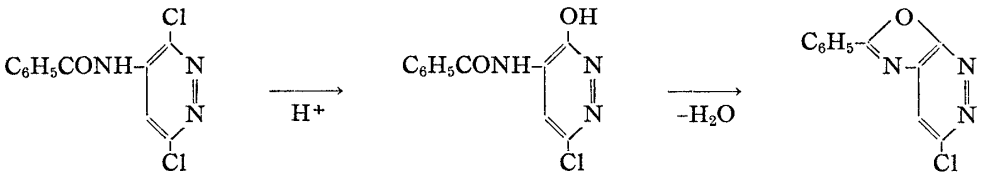
## 57. Tsukasa Kuraishi : 4,5-Substituted Pyridazines. V.*
## Acylation of 4-Amino-3,6-dichloropyridazine.


(*Pharmaceutical Faculty, University of Nagasaki***)


In the first paper of this series,[1] synthesis of 4-amino-3,6-dichloropyridazine (I) was reported briefly as a key intermediate for the preparation of 4-aminopyridazine. Synthetic studies of simple pyridazine derivatives have advanced in recent years. As a part of work on the chemistry of simple pyridazine compounds, this paper describes the acylation of (I) and the synthesis of 4-amino-3-pyridazinol (VI) derived from it. (I) was prepared from 3,4,6-trichloropyridazine by the action of ethanolic ammonia solution in a sealed tube at 120~130°. In some cases, however, 4-ethoxy-3,6-dichloropyridazine (II)[2] was produced as an impurity, especially when a small amount of the solvent was used, at low temperatures, the yield of (I) being poor. For example, (II) was obtained in 38~40% yield from 3,4,6-trichloropyridazine upon standing with ethanolic ammonia solution in a refrigerator for one week.

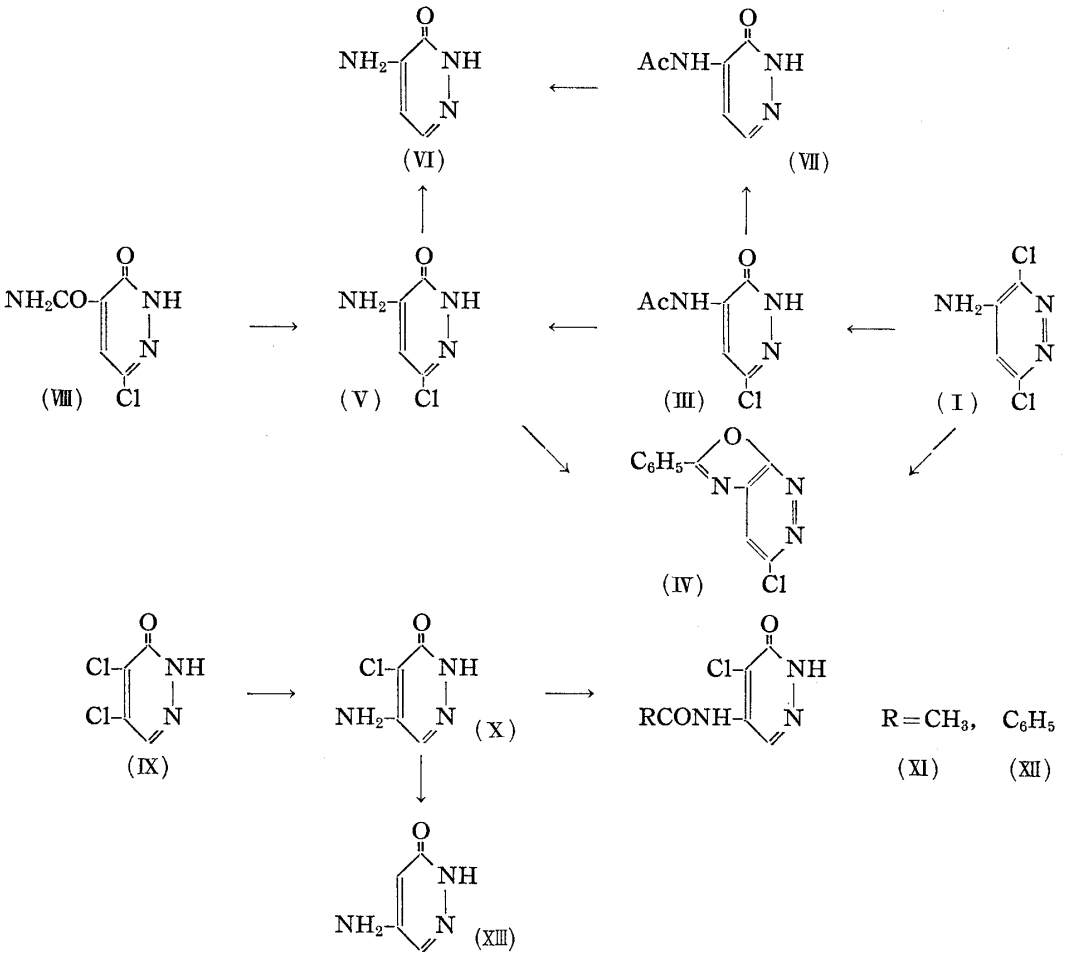
Separation of (I) was effected by fractional recrystallization from water or organic solvent. Acetylation of (I) with excess of acetic anhydride was attempted by heating on a water bath for one hour but the starting material was recovered. The product obtained by refluxing for 2 hours was a monoacetamido-chloro-3-pyridazinol (III). After deacetylation with dilute hydrochloric acid, it was purified by recrystallization from water. This compound (V) was identified with an authentic sample prepared from 4-carbamoyl-6-chloro-3-pyridazinol (VIII)[3] by the Hofmann reaction. Therefore, the structure of the compound (V) is undoubtedly 4-amino-6-chloro-3-pyridazinol. Dehalogenation of (V) using palladium-charcoal as a catalyst in the presence of sodium hydroxide in water gave 4-amino-3-pyridazinol (VI) melting at 228~229°. The reaction of (I) with excess of benzoyl chloride produced an alkali-insoluble compound, and the same product was obtained from (V) by a similar treatment. From analytical data, this substance was considered to be 2-phenyl-6-chloro-oxazolo[5,4-*c*]pyridazine (IV). Cyclization to the oxazolopyridazine ring would have occurred in the free hydroxyl compound as the intermediate.




* Part IV : This Bulletin, **6**, 234(1958).
** Showa-machi, Nagasaki (倉石 典).
1) T. Kuraishi : This Bulletin, **4**, 137(1956).
2) Part II : *Ibid.*, **5**, 376(1957).
3) Part III : *Ibid.*, **5**, 587(1957).

The reaction of this cyclization to oxazolo ring was applied to the product (X) of m.p. above 300°, obtained from the reaction of 4,5-dichloro-3-pyridazinol (IX)[4] with ethanolic ammonia solution.

In this case, however, corresponding product was not obtained and only a monoacyl compound formed in a low yield. Catalytic reduction of (X) yielded 5-amino-3-pyridazinol (XIII), m.p. 286~287°, which showed depression on admixture with (VI).

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## Experimental*

**4-Acetamido-6-chloro-3-pyridazinol (III)**—Three grams of (I) was refluxed with 30 cc. of $Ac_2O$ for 2 hrs. After cool, the solution was poured into water, the deposited crystals were collected, washed with water and EtOH, and recrystallized from EtOH. Yield 1.5 g. of m.p. 255~256°. *Anal.* Calcd. for $C_6H_6O_2N_3Cl$: C, 38.40; H, 3.20. Found: C, 38.77; H, 3.20.

**4-Amino-6-chloro-3-pyridazinol (V)**—i) A suspension of 0.3 g. of (VIII) and 0.4 g. of NaOH in 3 g. of water was cooled in ice water and 0.3 g. of $Br_2$ was added dropwise into the flask under stirring. After a clear solution was obtained, the flask was allowed to stand at room temperature for 20 mins. and warmed on a water bath for 10 mins. The solution was then cooled and neutralized with AcOH. The deposited crystals were collected, washed with water, and recrystallized from water. Yield, 0.2 g. of m.p. 285°. *Anal.* Calcd. for $C_4H_4ON_3Cl$: C, 32.99; H, 2.75. Found: C, 33.07; H, 2.68.

ii) A solution of 1.5 g. of (III) in 20 cc. of dil. HCl (1:3) was refluxed for 1 hr. After cool, the sepa-

4) Part I: *Ibid.*, 4, 497(1956).

* All melting points are uncorrected.

rated crystals (1.1 g.) were recrystallized from water. m.p. 284~285°. This sample showed no depression on admixture with a sample prepared from (Ⅷ) described above.

**4-Amino-3-pyridazinol (VI)**—i) A mixture of 1 g. of (V), 0.4 g. of NaOH, 70 cc. of distilled water, and Pd-C, prepared from 1 g. of charcoal and 20 cc. of $PdCl_2$ solution (1%), was hydrogenated at atmospheric pressure. After 1.1 moles of $H_2$ was absorbed, the catalyst was removed by filtration and the filtrate neutralized with AcOH. The solution was concentrated on a water bath using water aspiration. After cool, the deposited crystals were collected and recrystallized from water. Yield, 0.3 g. of m.p. 228~229°. *Anal.* Calcd. for $C_4H_5ON_3$: C, 43.26; H, 4.51; N, 37.83. Found: C, 42.82; H, 4.41; N, 38.62.

ii) A mixture of 0.6 g. of (Ⅶ) and 10 cc. of HCl (8%) was refluxed for 1.5 hrs., cooled, and neutralized with $Na_2CO_3$. The deposited crystals were collected and recrystallized from water or MeOH. m.p. 229~230°. It was identified by mixed m.p. with an authentic sample obtained from (V) mentioned above.

**2-Phenyl-6-chloro-oxazolo[5,4-*c*]pyridazine (IV)**—i) A mixture of 0.5 g. of (V) and 12 cc. of BzCl was gently refluxed for 30 mins. After cooling by standing at room temperature, 0.4 g. of yellow precipitate deposited from the clear solution which was collected, washed with EtOH, and recrystallized from EtOH. m.p. 208°. *Anal.* Calcd. for $C_{11}H_6ON_3Cl$: C, 56.95; H, 2.59; N, 18.13. Found. C, 56.95; H, 2.73; N, 17.80.

ii) 0.5 g. of (I) was treated as in i) and 0.2 g. of crystals, m.p. 208°, was obtained after recrystallization from EtOH. A mixed melting point of this sample with the one obtained from (V) was not depressed.

**5-Amino-4-chloro-3-pyridazinol (X)**—A mixture of 3 g. of (IX) and excess of dehyd. EtOH saturated with dry $NH_3$ placed in a sealed tube was heated at 150~160°(oil bath temp.) for 10 hrs. After cool, the solution was evaporated to dryness on a water bath and the residue was recrystallized from water giving 1.9 g. of colorless thin needles, m.p. >300°. *Anal.* Calcd. for $C_4H_4ON_3Cl$: C, 32.99; H, 2.76. Found: C, 33.42; H, 2.71.

**5-Acetamido-4-chloro-3-pyridazinol (XI)**—1 g. of crude (X) was refluxed with 10 cc. of $Ac_2O$ for 2 hrs. The excess of $Ac_2O$ was removed under reduced pressure, the residue was added to a small amount of water, and neutralized with $K_2CO_3$. After standing overnight, crude product was collected and recrystallized from MeOH with activated carbon. Yield, 0.6 g. of m.p. 277~279°. *Anal.* Calcd. for $C_6H_6O_2N_3Cl$: C, 38.40; H, 3.20. Found: C, 38.04; H, 3.02.

**5-Benzamido-4-chloro-3-pyridazinol (XII)**—A mixture of 0.3 g. of crude (X) and 10 cc. of BzCl was refluxed for 30 mins. After standing overnight, the deposited crystals were collected, washed with EtOH, and recrystallized from EtOH to needles, m.p. 244°. *Anal.* Calcd. for $C_{11}H_8O_2N_3Cl$: C, 52.90; H, 3.20. Found: C, 52.53; H, 3.10.

**4-Acetamido-3-pyridazinol (VII)**—1.65 g. of (Ⅲ) was reduced using 0.1 g. of Pd-C (10%) in the presence of 3% NaOH solution. After the calculated volume of $H_2$ was absorbed, the catalyst was filtered off and the filtrate was acidified with AcOH. The deposited crystals were collected and recrystallized from water. m.p. 272°. *Anal.* Calcd. for $C_6H_7O_2N_3$: C, 47.06; H, 4.57; N, 27.45. Found: C, 47.29; H, 4.43; N, 27.53.

**5-Amino-3-pyridazinol (XIII)**—A mixture of 1 g. of (X), 2.2 moles of aqueous NaOH solution (5%), and 0.1 g. of Pd-C (10%) was treated as in the case of the reduction of (V). The reduction was slow, but an additional 0.2 g. of catalyst aided completion. Recrystallized from water. m.p. 286~287°. A mixed m.p. with the specimen of (VI) was depressed to 203~205°. *Anal.* Calcd. for $C_4H_5ON_3$: C, 43.26; H, 4.50; N, 37.83. Found: C, 42.95; H, 4.38; N, 38.02.

## Summary

2-Phenyl-6-chloro-oxazolo[5,4-*c*]pyridazine (IV) was prepared by heating 4-amino-3,6-dichloropyridazine (I) or 4-amino-6-chloro-3-pyridazinol (V) with excess of benzoyl chloride. The synthesis of 4-amino-3-pyridazinol (VI), 5-amino-4-chloro-3-pyridazinol (X), 5-acylamido-4-chloro-3-pyridazinol (XI and XII), and 5-amino-3-pyridazinol (XIII) was also described.

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