Summary

(1) ACh dose-response curve in the presence of various concentrations of antagonist was traced fully and it was suggested experimentaly that the curve moved parallel by the atropine-like action and its maximum response was depressed non-competitively by the papaverine-like action.

(2) It was made possible to discriminate precisely the atropine-like action as competitive antagonism to a low concentration of ACh 4×10^{-8} g./cc. and the papaverine-like action as non-competitive antagonism to a high concentration of ACh (1.11×10^{-4} g./cc.).

(3) The potency ratios in relaxing the contraction due to the high concentration of ACh was almost the same as the ratios against $BaCl_2$.

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102. **Tsukasa Kuraishi**: 4,5-Substituted Pyridazines. III.[1] Oxidation and Solvolysis of 4-Methyl-3,6-dichloropyridazine.

(*Pharmaceutical Faculty, University of Nagasaki**)

In connection with the synthesis of 4,5-substituted pyridazines, which was reported in the previous papers, the oxidation and solvolysis of 4-methyl-3,6-dichloropyridazine (I) were studied and this paper describes the oxidation of the methyl group in the 4-position of some pyridazine compounds.

Very recently, Takabayashi[2] reported the synthsis of 4-methyl-6-chloro-3-pyridazinol (IIIa) and 5-methyl-6-chloro-3-pyridazinol (IIIb) by heating (I) with sodium hydroxide solution, using hydrous and 50% methanol solution, and the isomers were separated by fractional recrystallization from methanol or ethanol.

Previously, the writer[1] carried out the solvolysis of 3,6-dichloro-, 3,4,6-trichloro-, and 3,4,5-trichloropyridazines with glacial acetic acid and in the present paper, reports the result of the same experiment (I) performed by the same method.

By oxidation with excess of potassium dichromate in conc. sulfuric acid, (I) was easily converted to 4-carboxy-6-chloro-3-pyridazinol (II), which recrystallized from water as a monohydrate.

Catalytic reduction of (II) with palladium-charcoal yielded 4-carboxy-3-pyridazinol (IV) which was identical with the sample derived from 4-cyano-3-pyridazinol (V) by Druey's method.[3]

On the other hand, when (I) was refluxed with glacial acetic acid for one hour, (IIIa) and (IIIb) were formed and were separated by pouring the mixture into five volumes of water. (IIIb) deposited on standing at room temperature and (IIIa) was obtained from the filtrate by evaporation to dryness *in vacuo*. Each of these products was purified by recrystallization from water.

Oxidation of (IIIa) and (IIIb) by similar procedure respectively gave in poor yields

* Schowa-machi, Nagasaki (倉石 典).

1) Part II: This Bulletin, **5**, 376(1957).
2) N. Takabayashi: *Ibid.*, **5**, 229(1957).
3) P. Schmidt, J. Druey: Helv. Chim. Acta, **37**, 134(1954).

(II) and 5-carboxy-6-chloro-3-pyridazinol (IX). Esterification of (II) with dehyd. ethanol containing a few drops of sulfuric acid by heating on a water bath for five hours gave a mixture of 4-ethoxycarbonyl-6-chloro-3-pyridazinol (VI) and the unchanged material (II).

4-Hydrazinocarbonyl (VII) and 4-carbamoyl (VIII) compounds were obtained in a good yield from (VI) by the usual method.

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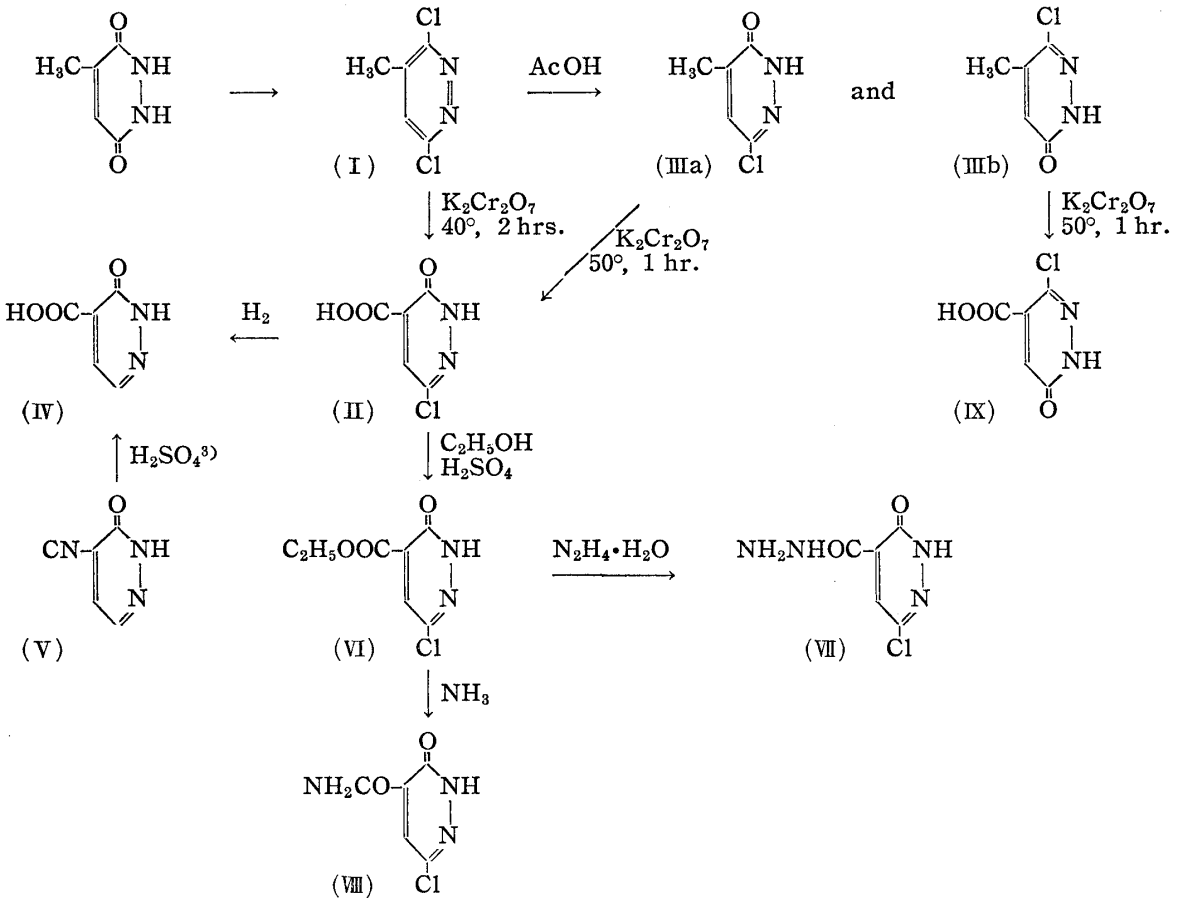

Experimental

(All m.p.s are uncorrected)

4-Methyl-3,6-dichloropyridazine (I)—Forty grams of 4-methyl-3,6-pyridazinediol, prepared from citraconic anhydride and hydrazine sulfate by the method of Spoerri, *et al.*,[4] was refluxed with 150 cc. of $POCl_3$ in an oil bath for 4 hrs. After removal of the excess $POCl_3$, the residue was poured onto crushed ice, and extracted with Et_2O. Yield, 37 g. $b.p_{21}$ 149~151°.

4-Carboxy-6-chloro-3-pyridazinol (II)—1) To a solution of 13 g. of (I) dissolved in 80 cc. of conc. H_2SO_4, 28 g. of finely powdered $K_2Cr_2O_7$ was added gradually under vigorous stirring, keeping the temperature below 40° and the stirring was continued at this temperature for further 2 hrs. Then, the viscous dark green liquid was poured onto crushed ice and extracted repeatedly with Et_2O. Et_2O solution was dried over anhyd. Na_2SO_4, freed from the solvent, and the residue was recrystallized from water. Yield, 10 g. m.p. 209~210°. *Anal.* Calcd. for $C_5H_3O_3N_2Cl \cdot H_2O$: C, 31.16; H, 2.59. Found: C, 31.04; H, 2.63.

The anhydrate was obtained by drying at 110° for 3 hrs. in high vacuum. m.p. 216°.

2) To a solution of 1.5 g. of (IIIa) in 30 cc. of conc. H_2SO_4, 3.6 g. of finely powdered $K_2Cr_2O_7$ was added slowly under stirring, the temperature being kept at 35~40°. When the addition was completed, the oxidation was still not perfect, as indicated by the yellowish green coloration. Thereafter, the

4) R. H. Mijjoni, P. E. Spoerri: J. Am. Chem. Soc., **76**, 2201(1954).

reaction mixture was stirred at 50° for further 1 hr. The resulting liquid was cooled, poured gradually onto crushed ice, and extracted with Et_2O, which was dried over anhyd. Na_2SO_4, evaporated, and the residue was recrystallized from water giving light yellow leaflets, m.p. 207~209°. The mixed melting point with a sample of (II) was undepressed. Yield, 0.4 g.

4-Carboxy-3-pyridazinol (IV)—A mixture of 5 g. of (II), 1.05 g. NaOH, 1.6 g. of Pd-C (7%), and 30 cc. of distilled water was placed in a shaking flask and hydrogenated under atmospheric pressure. The filtrate was acidified with HCl (1:1) and evaporated to dryness on a water bath, *in vacuo*. The residue was extracted with $CHCl_3$ and acetone on a water bath for 20 mins. After filtration and removal of the solvent, the residue was recrystallized from EtOH or water, m.p. 196~197°, and m.p. 197~198° on admixture with an authentic sample prepared from 4-cyano-3-pyridazinol (V) by the method of Druey *et al.*[3] Yield, 1.0 g.

4-Methyl-6-chloro-3-pyridazinol (IIIa) and 5-Methyl-6-chloro-3-pyridazinol (IIIb)—Five grams of (I) was refluxed with 20 cc. of glacial AcOH for 1 hr. After standing at room temperature for several hrs., deposited crystals were filtered and recrystallized from water, giving white leaflets (IIIb), m.p. 225°. Yield, 1.0 g. The filtrate was evaporated *in vacuo* to dryness on a water bath and the residue was recrystallized from water to thin needles (IIIa), m.p. 149~151°. Yield, 2.7 g. *Anal.* Calcd. for $C_5H_5ON_2Cl$: C, 41.54; H, 3.49. Found (IIIa): C, 41.28; H, 3.41. Found (IIIb): C, 41.16; H, 3.40.

4-Ethoxycarbonyl-6-chloro-3-pyridazinol (VI)—Five grams of (II) (anhydrate) was heated with 30 cc. of dehyd. EtOH containing few drops of conc. H_2SO_4 on a water bath for 5 hrs. The excess of EtOH was removed and the residue was treated with water and extracted with Et_2O. The ethereal solution was washed with 50 cc. of 5% K_2CO_3 solution to remove the unchanged material, washed, dried over anhyd. Na_2SO_4, and freed from solvent. The residue was recrystallized from water, m.p. 152.5°. Yield, 1.9~2.3 g. *Anal.* Calcd. for $C_7H_7O_3N_2Cl$: C, 41.48; H, 3.46. Found: C, 41.06; H, 3.53.

4-Carbamoyl-6-chloro-3-pyridazinol (VIII)—0.7 g. of (VI) was suspended in 25 cc. of EtOH, saturated with. NH_3 under ice-cooling, and the reaction mixture was allowed to stand with a good stopper for 48 hrs. in a refrigerator. The deposited crystals were recrystallized from water, m.p. 253°. Yield, 0.47 g. *Anal.* Calcd. for $C_5H_4O_2N_3Cl$: C, 34.63; H, 2.31. Found: C, 34.72; H, 2.37.

3-Hydroxy-6-chloro-4-pyridazinecarbohydrazide (VII)—0.1 g. of hydrazine hydrate (80%) was added to a solution of 0.2 g. of (VI) in 15 cc. EtOH and the mixture heated on a water bath for 2 hrs. After cool, deposited crystals were weighed (0.15 g.) and recrystallized from EtOH. m.p. 236~237°(decomp.). *Anal.* Calcd. for $C_5H_5O_2N_4Cl$: C, 31.83; H, 2.65. Found: C, 31.97; H, 2.62.

5-Carboxy-6-chloro-3-pyridazinol (IX)—Three grams of (IIIb) was dissolved in 30 cc. of conc. H_2SO_4, and 7.3 g. of finely powdered $K_2Cr_2O_7$ was added slowly and treated as described in method of (II) 2). White prismatic crystals separated after pouring the reaction mixture onto crushed ice, filtered, washed with water, and recrystallized from water, m.p. 245°(decomp.). Yield, 1.3 g. *Anal.* Calcd. for $C_5H_3O_3N_2Cl$: C, 34.39; H, 1.72. Found: C, 34.36; H, 1.87.

Summary

1) 4-Methyl-6-chloro-3-pyridazinol (IIIa) and 5-methyl-6-chloro-3-pyridazinol (IIIb) were obtained from 4-methyl-3,6-dichloropyridazine (I) by refluxing with glacial acetic acid.

2) 4-Carboxy-6-chloro-3-pyridazinol (II) was formed from 4-methyl-3,6-dichloropyridazine (I) and 4-methyl-6-chloro-3-pyridazinol (IIIa) by oxidation with potassium dichromate in conc. sulfuric acid and it was led to ester (VI), hydrazide (VII), and amide (VIII) derivatives.

3) 5-Carboxy-6-chloro-3-pyridazinol (IX) was also obtained by similar procedure from 5-methyl-6-chloro-3-pyridazinol (IIIb).

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