tration of 100 p.p.m. Actidione, Pleocidin, and Trichomycin had moderate inhibitory effect, but others were not effective. In general, no marked specificity of an antibiotic for certain species of fungi was observed. Among 26 species of fungi tested, *Penicillium islandicum* was the most resistant against all antibiotics and *Byssoschlamys fulva* was the most susceptible. These fungi may be used as both extremes in screening antifungal substances.

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**Tsukasa Kuraishi**: 4,5-Substituted Pyrazidines. II.)*

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Although there have been many reports on the preparation of 4,5-substituted pyrazidines in recent years, substitution reaction of these compounds have not been thoroughly described yet even in the case of a simple nucleophilic or electrophilic reagents because simple pyridazine dererivatives are more inactive to usual reagents than pyridine dererivatives.

To extend the preceding studies on 4,5-substituted pyrazidines, some of substitution reaction of chloropyrazidines was examined.

The 4-substituted pyrazidines, such as 4-amino- and 4-methoxy-3,6-dichloropyridazine, were obtained by nucleophilic attacks at the chlorine atom in 4-position of 3,4,6-trichloropyrazidine. Similarly, 4-ethoxy- and 4-hydrazino-3,6-dichloropyrazidines were obtained. Both reactions occurred at room temperature and the separated 4-hydrazino- and 4-ethoxy-3,6-dichloropyrazidines were easily derived by catalytic reduction to 4-hydrazinopyrazidine hydrochloride and 4-ethoxypyrazidine, respectively.

4-Ethoxy-pyrazidine was led to 4-hydroxy-pyrazidine by refluxing in a sealed tube with an excess of anhydrous hydrobromic acid in glacial acetic acid at 120~125°C.

These facts indicate that the chlorine atom in 4- or 5-position is more reactive to

\[ \text{Cl} \quad \text{Cl} \quad \rightarrow \quad \text{C}_2\text{H}_5\text{O} \quad \text{N} \quad \rightarrow \quad \text{C}_2\text{H}_5\text{O} \quad \text{N} \quad \rightarrow \quad \text{OH} \]

\[ \text{N} \quad \text{N} \quad \rightarrow \quad \text{N} \]

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the anionoid reagents compared with that at 3- and 6- positions.

Recently, Druey et al. prepared 4-hydroxy-3,6-dichloropyridazine from 3,4,6-trichloropyridazine with ca. 40% yield by hydrolysis with 2N sodium hydroxide solution, and simultaneous formation of 3,4- or 3,5-dichloro-6-pyridazone in ca. 5% yield was reported.

Although attempt was made previously to obtain 4-hydroxy-3,6-dichloropyridazine from 3,4,6-trichloropyridazine with glacial acetic acid, the major product melting at 203~204°C (yield ca. 35%) was 3,4- or 3,5-dichloro-6-pyridazone because it was not led to 4-hydroxy-pyridazine but to 6-pyridazone by catalytic reduction.

Similar solvolysis occurred in 3,4,5-trichloro- and 3,6-dichloropyridazine. Thus, 4,5-dichloro-6-pyridazone and 3-chloro-6-pyridazone were obtained by heating the corresponding chloropyridazines with glacial acetic acid in respective yields of ca. 34% and 36%.

Actually, when chloropyridazines were heated with glacial acetic acid, hydrogen chloride liberated from the solution. The quantitative consideration of these reactions will be reported later.

The author expresses his gratitude to Prof. M. Yanai for his kind advices.

**Experimental**

4-Ethoxy-3,6-dichloropyridazine (II)—Ten grams of 3,4,6-trichloropyridazine (I) was dissolved in 50 cc. of dehyd. EtOH and 1.24 g. of Na in 26 cc. of dehyd. EtOH was added gradually under cooling. After standing the reaction mixture for 1 hr. at room temperature, EtOH was removed in vacuo, on a water bath and the residue was poured into water. The deposited crystals were recrystallized from hydr. EtOH with activated carbon to colorless needles, m.p. 115~116°C. Yield, 6.5 g. Anal. Calcd. for C\(_{6}\)H\(_4\)ONCl\(_2\)Cl: C, 37.30; H, 3.11. Found: C, 37.67; H, 2.95.

4-Ethoxy-5-pyridazine (III)—A mixture of 3.7 g. of (II), 1.55 g. of NaOH, 50 cc. of EtOH, and 1.4 g. Pd-C (8%\%) was placed in a shaking flask and hydrogenated at atmospheric pressure. After the catalyst was filtered off, solvent was removed and the residue was repeatedly extracted with CHCl\(_3\). The dried CHCl\(_3\) solution was freed from the solvent and the resulting residue was distilled under a reduced pressure. Yield, 1.5 g. Hygroscopic. b.p. 118~119°C. Picrate, m.p. 93~94°C. Anal. Calcd. for C\(_{6}\)H\(_4\)ON\(_2\)C\(_6\)H\(_4\)ON\(_2\): C, 40.80; H, 3.11. Found: C, 41.26; H, 2.97.

4-Hydroxy-5-pyridazine (IV)—A mixture of 6.5 g. of (III) and 16 cc. of glacial AcOH saturated with anhyd. HBr sealed in a glass tube was heated in an oil bath at 120~125°C for 3 hrs. After removal of the solvent, the residue was dissolved in a small amount of water and neutralized with anhyd. K\(_2\)CO\(_3\), but 4-hydroxy-pyridazine did not deposit on standing overnight in a refrigerator. The solution was acidified with AcOH, evaporated completely in vacuo, and the residue was extracted with hot dehyd. EtOH. Crude 4-hydroxy-pyridazine deposited from the solution on standing at room temperature and was recrystallized from MeOH. Yield 1.5 g. of m.p. 245~246°C.4

4-Hydrazone-3,6-dichloropyridazine (V)—Ten grams of (I) was dissolved in 30 cc. of EtOH and

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\*\* All m.p. are uncorrected.

4) Druey, et al. (loc. cit.) recorded m.p. 250~251°C for this compound.
3.4 g. of hydrazine hydrate (80%) was added with stirring. The reaction mixture became yellow. 4-Hydrazino-3,6-dichloropyridazine was deposited gradually by standing at room temperature. After the reaction mixture was warmed on a water bath for 30 mins. and cooled, the crystals were collected and recrystallized from EtOH. Yield, 3.6 g. of m.p. 195~196° (decomp.). Anal. Calcd. for C<sub>6</sub>H<sub>5</sub>N<sub>2</sub>C<sub>5</sub>: C, 26.81; H, 2.23; N, 30.28. Found: C, 27.03; H, 2.16; N, 30.44.

4-Hydrazinopyridazine Hydrochloride (VI)—A mixture of 2 g. of (V), 40 cc. EtOH, 10 cc. distilled water, and 0.8 g. Pd-C (ca. 8%) was hydrogenated at atmospheric pressure. After the calculated quantities of hydrogen were absorbed the catalyst was filtered off and washed with a small amount of water. The filtrate was evaporated in vacuo on a water bath and the residue was recrystallized from EtOH. Yield, 1.1 g. of needles, m.p. 240~242° (decomp.). Anal. Calcd. for C<sub>6</sub>H<sub>5</sub>N<sub>2</sub>ClHCl: C, 32.75; H, 4.71; N, 38.22. Found: C, 32.77; H, 4.63; N, 37.71.

Reaction of 3,4,6-Trichloropyridazine with Glacial Acetic Acid. Formation of 3,4- or 3,5-Dichloro-6-pyrazdine (VII)—Twenty grams of (I) was refluxed with 65 cc. of glacial AcOH for 1.5 hrs. After cool, the reaction mixture was poured into 300 cc. of water and deposited crystals were recrystallized from water. Yield, 6.3 g. of needles, m.p. 203~204°. Anal. Calcd. for C<sub>11</sub>H<sub>7</sub>Cl<sub>3</sub>N: C, 29.09; H, 1.21. Found: C, 30.14; H, 1.38.

Catalytic Reduction of (VII)—A mixture of 3 g. of (VII), 1.5 g. NaOH, 1.4 g. Pd-C (8%), and 50 cc. of distilled water was hydrogenated at atmospheric pressure. After filtration of the catalyst, the filtrate was neutralized with dil. HCl (1:1) and evaporated on a water bath using water aspiration. The residue was extracted with hot AcOEt and 6-pyrazdine (VIII), m.p. 96~99°, deposited on standing at room temperature. Yield, 0.6 g. The melting point becomes 70~71° as it forms a monohydrate in the air.

Reaction of 3,4,5-Trichloropyridazine with Glacial Acetic Acid. Formation of 4,5-Dichloro-6-pyridazine (X)—Eight grams of 3,4,5-trichloropyridazine (IX) was refluxed with 25 cc. of glacial AcOH for 1 hr. After cool, the reaction mixture was poured into 60 cc. of water and the deposited crystals were recrystallized from water. Yield, 2.5 g. of prisms, m.p. 199~200°. The mixed melting point with an authentic sample was not depressed.

Reaction of 3,6-Dichloropyridazine with Glacial Acetic Acid. Formation of 3-Chloro-6-pyridazine (XI)—Two grams of 3,6-dichloropyridazine (XI) was refluxed with 7 cc. of glacial AcOH for 1 hr. After cool, the mixture was poured into 30 cc. of water and 0.7 g. of crude 3-chloro-6-pyridazine, m.p. 95~96°, was obtained. It was recrystallized from AcOEt and dried in a vacuum desiccator. Yield, 0.62 g. of m.p. 138~139°.

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Norio Sugimoto and Hiroshi Kugita: Studies on the Syntheses of Hydrogenated Quinolines and Isoquinolines as Analgesics. XIV. Synthesis of 6-Hydroxy-4a,10-trimethylene-1,2,3,4,4a,9,10,10a-octahydrophenanthridine (Supplement).

( Osaka Research Laboratory, Gohei Tanabe & Co., Ltd.)

The synthesis of 6-hydroxy-4a,10-trimethylene-1,2,3,4,4a,9,10,10a-octahydrophenanthridine has been reported in earlier paper of this series and some considerations were made on the steric configuration of this compound this time.

The relationship between the configuration and synthetic method may be presented in the following manner, following past synthetic experiments.

The catalytic reduction of 2-(β-cyanoethyl)-2-(m-methoxyphenyl)cyclohexanone (I), prepared from 2-(m-methoxyphenyl)cyclohexanone and acrylonitrile, at high temperature and pressure, with Raney nickel as the catalyst, first effects reduction of the nitrile to form the amino ketone compound and this undergoes intramolecular condensation to the octahydroquinoline compound (II). The hydrogenation of this compound (II),

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