reaction.

CHCl₃-insoluble crystals (0.75 g.) were recrystallized from AcOEt to white prisms, m.p. 180~181°, neutral, equiv. 931.5. No depression of the melting point was observed on admixture with an authentic sample of succinic acid.

Summary

1) Octadecenoic acid obtained from the lipid of Pelleobagrus nudiceps was determined as CH₃(CH₃)₇-CH=CH(CH₂)₇-COOH by ozonolysis.

2) The structure of docosatetraenoic acid isolated from Pelleobagrus nudiceps and responsible for stimulation of the repair of tuberculous foci was proposed as

CH₃(CH₂)₇-CH=CH(CH₂)₇-CH=CH(CH₂)₇-CH=CH(CH₂)₇-COOH.

Two other structural possibilities of this acid, with the double bonds in 5, 6, 9-10, 12-13, 16-17, or 5-6 8-9, 12-13, 16-17 were not excluded as shown in the discussion.

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40. Noboru Takahayashi: Synthesis of Pyridazine Derivatives. VIII.*
Nucleophilic Substitution of 3,6-Dichloro-4-methylpyridazine.

(Pharmaceutical Faculty, University of Toyama)**

In the reaction of 3,6-dichloro-4-methylpyridazine (I) and hydrazine hydrate, it was reported by Kubota et al.¹ that the melting point of the resulting product was 193°. The author has, however, previously obtained a compound of m.p. 149° by the same reaction and the compound was converted to tetrazolo[4,5-b]pyridazine and s-triazolo- [4,3-b]pyridazine by the action of nitrous acid, formic acid, and acetic anhydride.² The methylation of monothiol compound, which was obtained from (I) and potassium hydrogen sulfide, produced 3-chloro-6-methylthio-4(or 5)-methylpyridazine, m.p. 103.5°, and the material was then oxidized.³

This paper deals with determination of the position of the methyl groups of those compounds.

The 4(or 5)-methylpyridazine derivatives were prepared by the method of Drucey.⁴ That is, methylglyoxal which was obtained by the oxidation of acetone with selenium dioxide was condensed with cyanacetohydrazide, and the resulting mixture of 5-methyl and 6-methyl compounds was separated by crystallization from chloroform and benzene. Each of those products was hydrolysed and decarboxylated, producing 5-methyl-3-pyridazinol (IIIb) and 6-methyl-3-pyridazinol (IIIc), respectively. (IIIc) was identical with the sample prepared from ethyl levulate and hydrazine hydrate by the method reported in the first paper of this series.⁵

Saponification of (I) by heating with 15% sodium hydroxide gave the mixture of (IIa) (needles, m.p. 148°, 75~80%) and (IIb) (leaflets, m.p. 227°, 15~20%). The latter was less soluble than the former in methanol and they could be separated by fractional recrystal-


** Okuda Toyama (高林 勝).


lization. When 50% methanol was used as a solvent, 60~65% of (IIa) and 30~35% of (IIb) were obtained.

Those two (II) compounds, on being converted into methylpyridazinols by catalytic reduction with Pd-C and chlorinated with phosphoryl chloride, changed into two chloromethylpyridazines. Among the above synthesized compounds, a methylpyridazinol has exactly the same melting point as that (IIIb) obtained by Druey's method, namely 152.5°, and the mixed melting point was also 152.5°. Their chlorinated products also were identical on admixture. These facts are summarized in Chart 2.

![Chemical structure and reactions](chart1)

**Chart 1.**

![Ultraviolet Absorption Spectra](fig1)

**Fig. 1.**

Ultraviolet Absorption Spectra (in EtOH)

Compounds derived from 3,6-Dichloro-4-methylpyridazine

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Melting Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-CH₃</td>
<td><img src="chart2" alt="Structure" /></td>
<td>m.p. 148°</td>
</tr>
<tr>
<td>5-CH₃</td>
<td><img src="chart2" alt="Structure" /></td>
<td>m.p. 227°</td>
</tr>
<tr>
<td></td>
<td><img src="chart2" alt="Structure" /></td>
<td>m.p. 46.5~47.5°</td>
</tr>
<tr>
<td></td>
<td><img src="chart2" alt="Structure" /></td>
<td>m.p. 134°</td>
</tr>
<tr>
<td></td>
<td><img src="chart2" alt="Structure" /></td>
<td>m.p. 152.5°</td>
</tr>
<tr>
<td></td>
<td><img src="chart2" alt="Structure" /></td>
<td>m.p. 139°</td>
</tr>
</tbody>
</table>

**Chart 2.**
Chart 3.

Fig. 2. Ultraviolet Absorption Spectra (in EtOH)

Chart 4.
In the reaction of (I) with excess of 80% hydrazine hydrate by heating on a steam bath, the monohydrazino compound (Va), m.p. 149⁰, was obtained in about 90% yield, but when methanol or benzene was used as a solvent, the compound (Vb), m.p. 193⁰, was produced in 70~85% yield and the yield of (Va) was only 10~25%. They were separated and recrystallized from methanol. By heating with conc. hydrochloric acid for 6 hours, (Vb) gave a substance, m.p. 227⁰, which was soluble in alkali and insoluble in acid. It was identified with (IIb) mentioned above. (Va) was also converted into (IIa) by the same treatment.

Preparation of the monoamino compounds was accomplished by heating (I) with ammonia saturated in methanol at 140⁰ in an autoclave for 8 hours. In this case, the products consisted of (Vla), m.p. 111~113⁰(10~15%), and (Vlb), m.p. 188⁰(about 80%), but when water was used as a solvent, (Vla) and (Vlb) were obtained in 40~45% and 50% respective yield. These two amino compounds were converted by the action of nitrous acid into the corresponding hydroxy compounds which were identical with (IIa) and (IIb), respectively.

6-Methylthio-4-methyl-3-pyridazinol (Vla), m.p. 104⁰, was prepared from (IIa) through the intermediate step of thiol compound. On the other hand, 3-chloro-4(or 5)-methyl-6-methylthiopyridazine, prepared from (I) by the same treatment, was converted into the compound (Vlb), m.p. 216⁰, by heating with 20% hydrochloric acid for 8 hours. This compound was assumed to be 6-methylthio-4(or 5)-methyl-3-pyridazinol from its analytical data and its properties of being positive to sulfur detection, negative to halogen detection, soluble in alkali, and insoluble in acid.

Considering the fact that (Vla) has a methyl group in 4-position, it was concluded that (Vlb), its starting material 3-methylthio-4(or 5)-methyl-6-chloropyridazine, and its derivatives must have their methyl group in 5-position.

Monomethoxy compound (X), m.p. 68⁰, was obtained by the reaction of (I) with sodium methoxide, and it was converted into methoxythiol compound (XI), m.p. 208⁰(decomp.), by the action of potassium hydrogen sulfide in a sealed tube. (XI) was methylated and the resulting methoxy-methylthio compound (IXa) melted at 58⁰, while the isomer (IXb), m.p. 100⁰, was obtained from 3-methylthio-4-methyl-6-chloropyridazine, m.p. 103.5⁰, described above. Therefore, it was concluded that (X), (XI), and (IXa) have their methyl group in the position ortho to their methoxy group.

Following Part III of this series, 3-hydrazino-4(or 5)-methyl-6-chloropyridazine (V) was treated with 80% formic acid, acetic anhydride, or nitrous acid. In each case, two kinds of a product were isolated, different in the position of the methyl group. Consequently, it became clear that the series of compounds which were reported in Part III were all 8-methyl compounds.

The author expresses his gratitude to Prof. T. Takahashi, University of Kyoto, for his encouragement and to Prof. D. Shiho, University of Toyama, for his advices in this work. The author is indebted to Miss T. Ishiguro for carrying out the elemental microanalyses.

Experimental

3-Hydrazino-4-methyl-6-chloropyridazine (Va) and 3-Hydrazino-5-methyl-6-chloropyridazine (Vb)—A mixture of 10 g. of 3,6-dichloro-4-methylpyridazine (I) and 10 cc. of 80% NH₂NH₂·H₂O was heated on a steam bath for 1 hr. After cooling, the crystals were collected and purified by crystallization from EtOH. The recrystallized substance (0.4 g.) obtained from comparatively dilute solution was colorless leaflets (Vb), m.p. 193⁰. After removal of (Vb), the solution was concentrated and (Va) was obtained as colorless leaflets, recrystallized from EtOH, m.p. 149⁰(8.9 g.). Anal. Calcd. for C₆H₄N₂Cl: C, 37.86; H, 4.45. Found (Va): C, 37.33; H, 4.24. (Vb): C, 38.02; H, 4.64.

3-Amino-4-methyl-6-chloropyridazine (Vla) and 3-Amino-5-methyl-6-chloropyridazine (Vlb)—A solution of (I) in 50 cc. of ethanolic ammonia (involving 3.5 g. of NH₃) was heated in an autoclave at 135~140⁰ for 8 hrs. A volatile portion was removed under reduced pressure and the residue
was extracted with AcOEt. The solution was chromatographed through an alumina column. From the early and later fractions, colorless needles (VIa), m.p. 111–113°, and colorless leaflets (VIIb), m.p. 188°, were respectively obtained. Their yield was 0.6 and 3.5 g.

b) A solution of 50 cc. of 28% NH₄OH and 5.0 g. of (I) was treated similarly as procedure a). The yield of (VIIa) and (VIIb) was 1.8 and 2.2 g., respectively.

4-Methyl-6-chloro-3-pyridazinol (IIa) and 5-Methyl-6-chloro-3-pyridazinol (IIb)—A mixture of 5.0 g. of (I) and 100 cc. of 15% NaOH was refluxed for 3 hrs. The solution was acidified with 50% AcOH with cooling. The resulting precipitate was separated and purified by crystallization from EtOH. The more soluble one was (IIa)(needles, m.p. 148°, 3.46 g.) and the less soluble one was (IIb)(leaflets, m.p. 227°, 0.72 g.). Anal. Calcd. for C₆H₄NO₂Cl: C, 41.54; H, 3.49. Found (IIa): C, 41.00; H, 3.59. Found (IIb): C, 41.53; H, 3.95.

b) To a solution of 50 cc. of MeOH and 5.0 g. of (I), 50 cc. of 30% NaOH solution was added and treated as described in procedure a). After the reaction was completed, MeOH was evaporated and the residual solution was acidified with 50% AcOH. The yield of (IIa) and (IIb) was 2.8 and 1.44 g., respectively.

c) (VIIa) and (VIIb) were heated strongly for 8 hrs. with conc. HCl to form the corresponding hydroxy compounds, (IIa) and (IIb), in poor yields. They were identical with those prepared by procedure a).

d) (VIIa) and (VIIb) were separately dissolved in conc. HCl and the solutions were treated with aqueous solution of NaNO₂ under stirring for 1 hr. at 0°, 0.5 hr. at room temperature. There was obtained the products (IIa) and (IIb) in good yields. These showed no depression of m.p. on mixing with authentic samples.

4-Methyl-3-pyridazinol (IIIa) and 5-Methyl-3-pyridazinol (IIIb)—A mixture containing 10 g. of (IIa), 300 cc. of MeOH, 5 cc. of 28% NH₄OH, and 2 g. of Pd-C was hydrogenated. After absorption of H₂ gas was completed, the catalyst and solvent were removed and the residue was extracted with AcOEt. After drying over anhyd. Na₂SO₄, the extract was distilled and the residue was recrystallized from MeOH and EtOH to give 7.1 g. of (IIIa) as colorless plates, m.p. 134°. U.V. λmax 230, 286 mp (log ε 3.29, 3.38).

A mixture of 2.0 g. of (IIb), 50 cc. of MeOH, 0.5 g. of Pd-C, and 1 cc. of 28% NH₄OH was similarly treated. Resulting compound (IIIb)(colorless plates, m.p. 152°, 1.4 g.) was identified on admixture with the sample obtained from 4-cyano-5-methyl-3-pyridazinol by Druey's method. U.V. λmax 230, 287 mp (log ε 3.38, 3.47). Anal. Calcd. for C₆H₄NO₂: C, 54.54; H, 5.49. Found (IIIa): C, 54.06; H, 6.13. (IIIb): C, 54.87; H, 5.44.

3-Chloro-4-methylpyridazine (IVa) and 3-Chloro-5-methylpyridazine (IVb)—(IIIa) was refluxed with 2.5 equiv. of POCl₃ for 0.5 hr. The excess POCl₃ was distilled off under a reduced pressure and the residual oil poured into ice with vigorous stirring. The solution was made alkaline with dil. NaOH and extracted with CHCl₃. The extract was dried, evaporated, and the residue was recrystallized from MeOH. (IVa) was obtained as colorless leaflets, m.p. 46.5→47.5°. (IVb) was obtained from (IIIb) by the same treatment as colorless leaflets, m.p. 139°.

6-Mercaptopyrrolopyridazine (VIIa)—A mixture of 3.0 g. of (IIa) and KHS solution prepared from 5.6 g. of KOH was heated in a sealed tube at 140° for 6 hrs. After volatile portion was removed, the residue was dissolved in Na₂CO₃ solution, decolorized, and acidified with 20% AcOH. The precipitate was recrystallized from MeOH. (VIIa) was obtained as slightly yellow needles, m.p. 187°(decomp.). Halogen detection test was negative.

4-Methyl-6-methylthio-3-pyridazinol (VIIia) and 3-Methoxy-4-methyl-6-methylthiopyridazine (IXa)—(VIIa) and (XI) were dissolved in MeOH solution of CH₂N₄Na(prepared from 1.1 equiv. Na), and one equiv. CH₃I was added. The mixture was refluxed for 1 hr., distilled, and the residue was extracted with AcOEt. The isolated product was recrystallized from ETOH and benzene. (IXa): Colorless needles, m.p. 104°. (IXa): Colorless leaflets, m.p. 58°. Anal. Calcd. for C₆H₄NO₂S (VIIa): C, 46.13; H, 5.16. Found: C, 46.01; H, 5.35. Anal. Calcd. for C₆H₄NO₂S (IXa): C, 49.39; H, 5.92 Found: C, 49.32; H, 6.24.

3-Methylthio-4-methyl-6-methoxypyrazidine (IXb)—This compound was prepared by the usual method from 3-methylthio-4-methyl-6-chloropyridazine and MeONa. Colorless leaflets, m.p. 109°. Anal. Calcd. for C₆H₄NO₂S: C, 49.39; H, 5.92. Found: C, 49.10; H, 6.22.

6-Chloro-7-methyl-s-triazolo(4,3-b)pyridazine (XIIb) and 6-Chloro-7,7-dimethyl-s-triazolo(4,3-b)pyridazine (XIVb)—A mixture of (IIb) and excess of 80% formic acid was heated for 1→2 hrs. on a water bath. (IIb) was also heated with Ac₂O. In the latter case, excess Ac₂O was decomposed with H₂O. The two solutions were made alkaline with 20% NaOH and extracted with benzene or AcOEt. Extracted residue was recrystallized from MeOH. (XIIb): Colorless, hexagonal plates, m.p. 158°. Anal. Calcd. for C₆H₄N₂Cl: C, 42.73; H, 2.99. Found: C, 42.61; H, 2.59. (XIVb): Colorless needles, m.p. 180°. Anal. Calcd. for C₆H₄N₂Cl: C, 46.04; H, 3.86. Found: C, 46.06; H, 3.86.

6-Hydrazino-8-methyl-s-triazolo(4,3-b)pyridazine (XIVa), 6-Hydrazino-7-methyl-s-triazolo(4,3-
b) pyridazine (XVb), 3,8-Dimethyl-6-hydrazino-s-triazolo[4,3-b]pyridazine (XVIa), and 3,7-Dimethyl-6-hydrazino-s-triazolo[4,3-b]pyridazine (XVIIb)—(XIIIa), (XIVb), (XIVa), and (XIVb) were respectively heated with excess of 80% N₂H₄·H₂O for 1 hr. After cooling, the crystals were collected and recrystallized from MeOH. All of them were colorless leaflets.

Summary

In the reaction of 3,6-dichloro-4-methylpyridazine (I) with hydrazine hydrate, ammonia, sodium hydroxide, sodium methoxide, or potassium hydrogen sulfide, mono-substituted compounds were obtained. The position of methyl group in those compounds and the relationship among them were cleared up. Examination was also made on whether substitution in (I) occurred in 3- or in 6-position according to the change of conditions.

6-Chloro-8-methyl-s-triazolo[4,3-b]pyridazine and 6-chloro-7-methyl-s-triazolo[4,3-b]pyridazine were prepared from 3-hydrazino-4-methyl-6-chloropyridazine and 3-hydrazino-5-methyl-6-chloropyridazine, and were derived to their 6-hydrazino derivatives.

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41. Ken'ichi Takeda and Katsumi Kotera: The Stereochemistry of Dihydrocoricine.¹

(Research Laboratory, Shionogi & Co., Ltd.*)

The structure of lycorine, the most abundantly and widely occurring member of alkaloids of the Amaryllidaceae, has been studied with great interest and discussed vigorously from the chemical as well as biogenetical standpoint for these several years. Although the structure of dihydrocoricine, obtained by the catalytic reduction of lycorine, has been firmly established as the formula (I),⁴ there still remained some problems to be solved conclusively on the stereochemistry of dihydrocoricine (I), such as the relationship of the two hydroxyl groups or B/C and C/D ring junctions.

In the present paper we wish to report the results of experiments on these problems. Dihydrocoricine monosylosylate, which was readily prepared by the action of tosyl chloride in pyridine at room temperature, afforded a substance, m.p. 148.5°, C₁₄H₁₄O₂N, when treated with 1% methanolic potassium hydroxide. The infrared spectrum of this substance indicated no hydroxyl nor carbonyl group. This substance gave monoaocetyl-dihydrocoricine with hot acetic acid, which on either acetylation or alkaline hydrolysis furnished diacetyldihydrocoricine (Ia) or dihydrocoricine (I), respectively. This monoaocetyl-dihydrocoricine was also obtained by the direct acetylation of dihydrocoricine with acetyl chloride in pyridine at 0° together with almost the same amount of diacetyldihydrocoricine. On the other hand, dihydrocoricine was directly obtained from the abovementioned substance with dilute sulfuric acid at 100°. It is clear from these facts that the substance, C₁₄H₁₄O₂N, is an epoxide (II). Although there are many studies on the

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1) The investigations described in this paper were outlined in a preliminary communication to the Chemistry & Industry, 1956, 347.