4. Yasuyuki Suzuki: Syntheses of Methylpyridine Derivatives. II.11
Synthesis of 2-Cyanomethylpyridines.

(Kowa Chemical Laboratories*)

Substitution of the halogen in 2- or 4-position of pyridine ring with nitrile has been attempted by many workers and the substitution of bromine in 2-bromopyridine,23 4-bromo-2-methylpyridine,39 and 4-bromo-3-ethyl-6-methylpyridine9 with nitrile by heating with cuprous cyanide was concluded successfully, but the substitution of a chlorine has been rare.

A few years ago, Ochiai and Suzuki9 reported the substitution of chlorine in 4-position of pyridine ring with nitrile by heating with aqueous solution of sodium sulfite to derive it to the sodium sulfonate, and heating it with potassium cyanide to fusion. The present paper describes the introduction of a nitrile into 2-position of the pyridine ring by a similar reaction.

Seven kinds of 2-chloropyridines used were 2-chloro-, 2-chloro-6-methyl-, 2-chloro-5-methyl-, 2-chloro-4-methyl-, 2-chloro-3-methyl-, 2-chloro-4,6-dimethyl-, and 2-chloro-3-ethyl-6-methyl-pyridines, and were prepared from the corresponding methylpyridines through methylaminopyridines by the method of Seide.6) 2-Chloro-5-methylpyridine was prepared by heating 2-hydroxy-5-methylpyridine11 with phosphoryl chloride.

A mixture of each of the chloropyridines and calculated amount of sodium sulfite in water was heated in an autoclave at 150~210°C for 10 hours and, without isolating the corresponding sodium 2-pyridinesulfonate thereby formed, the product was mixed with potassium cyanide, heated over an open flame, and the objective 2-cyanopyridines were obtained in 35~60% yield. The majority of 2-cyanopyridines formed colorless prismatic crystals of low melting point, recrystallizable from a mixture of petroleum ether and ether. The yield was generally poor compared to that of 4-cyanopyridines. The boiling and melting points and yield of 2-cyanopyridines are given in the accompanying table.

<table>
<thead>
<tr>
<th>2-Chloro-R-pyridine</th>
<th>2-Cyanor-R-pyridine</th>
<th>b.p./mm. Hg</th>
<th>m.p.(°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>H</td>
<td>R</td>
<td>H</td>
<td>114~116/24</td>
</tr>
<tr>
<td>6-methyl</td>
<td>6-methyl</td>
<td>135~136/38</td>
<td>72~74</td>
<td>39.0</td>
</tr>
<tr>
<td>5-methyl</td>
<td>5-methyl</td>
<td>135~138/28</td>
<td>88~89</td>
<td>39.1</td>
</tr>
<tr>
<td>4-methyl</td>
<td>4-methyl</td>
<td>145~148/38</td>
<td>87~88</td>
<td>59.0</td>
</tr>
<tr>
<td>3-methyl</td>
<td>3-methyl</td>
<td>139~142/38</td>
<td>51~52</td>
<td>32.6</td>
</tr>
<tr>
<td>4,6-dimethyl</td>
<td>4,6-dimethyl</td>
<td>125~130/16</td>
<td>49.7</td>
<td></td>
</tr>
<tr>
<td>3-ethyl-6-methyl</td>
<td>3-ethyl-6-methyl</td>
<td>145~151/32</td>
<td>107~110/17</td>
<td>60.6</td>
</tr>
</tbody>
</table>

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4) T.B. Lee and G.A. Swan (J. Chem. Soc., 1956, 771) heated 4-bromo-3-ethyl-6-methylpyridine with CuCN and KCN in EtOH in an autoclave and, without isolating the 4-cyano compound, heated this with H2SO4 and EtOH, to obtain ethyl 3-ethyl-6-methyl-4-pyridinecarboxylate.
4-Chloro-3-ethyl-6-methylpyridine also afforded the corresponding 4-cyano compound in 60% yield by the same reaction. This 4-chloro-3-ethyl-6-methylpyridine was obtained by the treatment of 3-ethyl-4-nitro-6-methylpyridine 1-oxide, a nitration product of 3-ethyl-6-methylpyridine 1-oxide, with acetyl chloride and then with phosphorus trichloride.

The writer is deeply grateful to Prof. Eiji Ochiai of the University of Tokyo for his unfailing guidance throughout the course of this work.

**Experimental**

4-Chloro-3-ethyl-6-methylpyridine—To a solution of 9.1 g. of 3-ethyl-4-nitro-6-methylpyridine 1-oxide dissolved in 30 cc. CHCl₃, 17.8 cc. of AcCl was added dropwise under stirring while chilling in ice, the mixture was stirred for 30 mins. at 50°, and 8.8 cc. of PCl₃ was added dropwise while chilling in ice, the mixture was stirred for 30 mins. at room temperature, and warmed to 60~70° for 1 hr. on a water bath. When cool, the mixture was poured into 100 cc. of ice water, the aqueous layer was separated, and CHCl₃ layer was washed with 20 cc. of water. The washing was combined with the aqueous layer, washed with 30 cc. of ether, rendered alkaline with Na₂CO₃, and submitted to steam distillation. The distillate was saturated with K₂CO₃ and extracted with ether. After drying over anhyd. Na₂SO₄, the ether was evaporated and the residue was distilled under a reduced pressure, affording 5.27 g. (67.8%) of a colorless liquid, b.ps 92~95°.

Picrate: Yellow needles (from EtOH), m.p. 135~135.5°. **Anal.** Calcd. for C₉H₇NOCl·C₆H₆O₃N₂: C, 43.7%; H, 3.4; N, 14.6. Found: C, 43.67; H, 3.28; N, 14.15.

2-Cyanopyridine—A mixture of 5.7 g. of 2-chloropyridine, 6.4 g. of Na₂SO₄, and 70 cc. of water was heated in an autoclave at 150~160° for 10 hrs. Extraction of the reaction mixture with ether yielded 1.14 g. of the recovered starting material. The aqueous solution was treated with activated carbon, evaporated to dryness under a reduced pressure, and thoroughly mixed with 6.4 g. of KCN. This mixture was filled in a glass tube and heated over a low, direct flame. The yellow, oily distillate obtained was dissolved in ether, dried over anhyd. Na₂SO₄, and ether evaporated. The low-pressure distillation of the residue afforded 2.08 g. (49.7%) of a slightly yellow liquid, b.ps 114~116° (reported3 b.ps 118~120°).

2-Cyan-6-methylpyridine—A mixture of 8.0 g. of 2-chloro-6-methylpyridine, 8.0 g. of Na₂SO₄, and 80 cc. of water was heated in an autoclave at 170~180° for 10 hrs. Extraction of the reaction mixture with ether yielded 4.0 g. of the recovered starting material. The aqueous solution was evaporated to dryness under a reduced pressure, the residue was mixed thoroughly with 4.3 g. of KCN, filled in a glass tube, and heated over a low, direct flame. The yellow, oily distillate crystallized immediately and this was dissolved in ether, dried over anhyd. Na₂SO₄, and ether evaporated. The residue was distilled under a reduced pressure and the fraction of b.ps 135~136° was recrystallized from petr. ether–ether mixture to 1.44 g. (39.0%) of colorless prisms, m.p. 69~71°. **Anal.** Calcd. for C₉H₇N₂: C, 71.2; H, 5.1; N, 23.7. Found: C, 71.20; H, 5.21; N, 23.60.

2-Cyan-5-methylpyridine—A mixture of 2.5 g. of 2-chloro-5-methylpyridine, 2.5 g. of Na₂SO₄, and 25 cc. of water was heated in an autoclave at 200~210° for 10 hrs. Treated as in the foregoing cases, 0.8 g. of the starting material was recovered and fusion with 2.0 g. of KCN afforded a fraction of b.ps 135~138°, which recrystallized from petr. ether–ether mixture to 0.58 g. (36.8%) of colorless prisms, m.p. 72~74°. **Anal.** Calcd. for C₉H₇N₂: C, 71.2; H, 5.1; N, 23.7. Found: C, 71.19; H, 5.05; N, 23.54.

2-Cyan-4-methylpyridine—A mixture of 6.0 g. of 2-chloro-4-methylpyridine, 6.0 g. of Na₂SO₄, and 60 cc. of water was heated in an autoclave at 180~190° for 10 hrs. Extraction of the reaction mixture yielded 2.9 g. of the recovered material. The evaporation residue from the aqueous solution was fused with 3.3 g. of KCN and treated as in the foregoing cases, affording a fraction of b.ps 145~148°, which crystallized to 1.12 g. (39.1%) of colorless prisms, m.p. 88~89°. **Anal.** Calcd. for C₉H₇N₂: C, 71.2; H, 5.1; N, 23.7. Found: C, 71.21; H, 5.15; N, 24.14.

2-Cyan-3-methylpyridine—A mixture of 12.8 g. of 2-chloro-3-methylpyridine, 12.8 g. of Na₂SO₄, and 130 cc. of water was heated in an autoclave at 170~180° for 10 hrs. Treated as in the foregoing cases, 7.9 g. of the starting material was recovered and fusion of the residue from the aqueous solution with 5.3 g. of KCN afforded a fraction of b.ps 139~142°, which crystallized to 2.68 g. (59.0%) of colorless prisms, m.p. 87~88°. **Anal.** Calcd. for C₉H₇N₂: C, 71.2; H, 5.1; N, 23.7. Found: C, 71.44; H, 5.22; N, 23.52.

2-Cyan-4,6-dimethylpyridine—A mixture of 19.8 g. of 2-chloro-2,4-dimethylpyridine, 18 g. of Na₂SO₄, and 180 cc. of water was heated in an autoclave at 200~210° for 10 hrs. Treated as in the foregoing cases, 1.6 g. of the starting material was recovered and fusion of the residue from the

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aqueous solution with 16.6 g. of KCN afforded a fraction of b.p. 125~130°, which crystallized to 5.52 g. (32.6%) of colorless needles, m.p. 51~52°. Anal. Calcd. for C₅H₆N₂: C, 72.7; H, 6.1; N, 21.2. Found: C, 72.36; H, 5.95; N, 20.86.

2-Cyano-3-ethyl-6-methylpyridine—A mixture of 7.2 g. of 2-chloro-3-ethyl-6-methylpyridine 6.0 g. of Na₂SO₃ and 80 cc. of water was heated in an autoclave at 210~220° for 10 hrs. Treatment as in the foregoing cases afforded 4.5 g. of the recovered material and fusion of the residue with 2.3 g. of KCN afforded 1.26 g. (49.7%) of a colorless liquid, b.p. 145~151°. Anal. Calcd. for C₆H₄N₂: C, 73.9; H, 6.9; N, 19.2. Found: C, 73.5; H, 7.21; N, 18.97.

4-Cyano-3-ethyl-6-methylpyridine—A mixture of 4.7 g. of 4-chloro-3-ethyl-6-methylpyridine, 3.9 g. of Na₂SO₃, and 40 cc. of water was heated in an autoclave at 180~200° for 3 hrs. Treated as in the foregoing cases, 1.75 g. of the starting material was recovered and fusion with 3.3 g. of KCN afforded 1.68 g. (60.6%) of colorless liquid, b.p. 107~110°.

Picrate: Yellow needles (from EtOH), m.p. 123~124°. Anal. Calcd. for C₁₂H₁₆N₄·C₂H₅O₂N₅: C, 48.0; H, 3.5; N, 18.7. Found: C, 48.00; H, 3.41; N, 18.78.

**Summary**

Methylpyridines possessing chlorine in 2(or 4)-position were derived to the corresponding 2(or 4)-cyano-methylpyridines by heating with sodium sulfite in water in an autoclave at 150~220° for 10 hours and heating the sodium sulfonate thereby obtained with potassium or sodium cyanide to fusion.

(Received October 19, 1956)

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5. Jun Hasegawa : Studies on Tablets. III.¹

*Weight Variation of Compressed Tablets.*

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Weight variation is the most important point in the evaluation of compressed tablets and many investigators have reported the deviation in weight of compressed tablets, but most of them discussed the matter from the standpoint of consumers⁵ or the survey⁶⁻⁸ on a marketed tablets. A tablet consists of many ingredients and is compressed through many manufacturing processes, so that deviation of tablet weight is affected by many factors. Some of them may be as follows: (1) Diameter of punch (diameter of tablet), (2) depth of die cavity,⁶ (3) particle size of granules to be compressed (granulated sieve mesh), (4) fluidity of granules⁷ (kind and amount of lubricant added), (5) properties of ingredients (physical and micromeritical characters of powder), (6) speed of compression, and (7) tabletting machine used (single punch or rotary type).

When manufacturing tablets in a hospital pharmacy, it is very important to solve such practical problems and only a few reports⁸⁻⁹ on these points have been seen.

The object of this study is to learn in a relatively short period the effect of (1) tablet

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¹ Hongo, Tokyo (巻谷川 浩).
9) Dansk Tidskr. Farm., 2, 151(1928) (C.A., 22, 4203(1928)).