U. D. C. 547.821.41.07

4. **Yasuyuki Suzuki**: Syntheses of Methylpyridine Derivatives. II.[1] Synthesis of 2-Cyanomethylpyridines.

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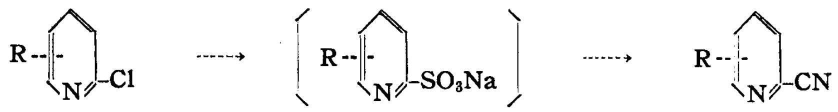
Substitution of the halogen in 2- or 4-position of pyridine ring with nitrile has been attempted by many workers and the substitution of bromine in 2-bromopyridine,[2] 4-bromo-2-methylpyridine,[3] and 4-bromo-3-ethyl-6-methylpyridine[4] with nitrile by heating with cuprous cyanide was concluded successfully,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

A few years ago, Ochiai and Suzuki[5] 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-dimetyl-, 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-methylpyridine[1] 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° 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.



2-Chloro-R-pyridine R	2-Cyano-R-pyridine R	b.p./mm. Hg	m.p.(°C)	Yield (%)
H	H	114~116/24	—	49.7
6-methyl	6-methyl	135~136/38	69~71	39.0
5-methyl	5-methyl	135~138/28	72~74	36.8
4-methyl	4-methyl	145~148/38	88~89	39.1
3-methyl	3-methyl	139~142/38	87~88	59.0
4,6-dimethyl	4,6-dimethyl	125~130/16	51~52	32.6
3-ethyl-6-methyl	3-ethyl-6-methyl	145~151/32	—	49.7
4-Chloro-3-ethyl-6-methylpyridine	4-Cyano-3-ethyl-6-methylpyridine	107~110/17	—	60.6

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[1] Part I: This Bulletin, **5**, (1957).

[2] L. C. Craig: J. Am. Chem. Soc., **56**, 231(1934).

[3] E. Ochiai, I. Suzuki: This Bulletin, **2**, 147(1954).

[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 H_2SO_4 and EtOH, to obtain ethyl 3-ethyl-6-methyl-4-pyridinecarboxylate.

[5] E. Ochial, Y. Suzuki: This Bulletin, **2**, 247(1954).

[6] O. Seide: Chem. Zentr., III, 1022(1923); Ber., **57**, 791, 1802(1924).

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,[4,7] 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. $CHCl_3$, 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 PCl_3 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 $CHCl_3$ 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 Na_2CO_3, and submitted to steam distillation. The distillate was saturated with K_2CO_3 and extracted with ether. After drying over anhyd. Na_2SO_4, the ether was evaporated and the residue was distilled under a reduced pressure, affording 5.27 g. (67.8%) of a colorless liquid, b.p$_{20}$ 92~95°.

Picrate: Yellow needles (from EtOH), m.p. 133~134.5°. *Anal.* Calcd. for $C_8H_{10}NCl \cdot C_6H_3O_7N_3$: 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 Na_2SO_3, 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. Na_2SO_4, and ether evaporated. The low-pressure distillation of the residue afforded 2.08 g. (49.7%) of a slightly yellow liquid, b.p$_{24}$ 114~116° (reported[2]) b.p$_{25}$ 118~120°).

2-Cyano-6-methylpyridine—A mixture of 8.0 g. of 2-chloro-6-methylpyridine, 8.0 g. of Na_2SO_3, 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. Na_2SO_4, and ether evaporated. The residue was distilled under a reduced pressure and the fraction of b.p$_{38}$ 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 $C_7H_6N_2$: C, 71.2; H, 5.1; N, 23.7. Found: C, 71.20; H, 5.21; N, 23.60.

2-Cyano-5-methylpyridine—A mixture of 2.5 g. of 2-chloro-5-methylpyridine, 2.5 g. of Na_2SO_3, 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.p$_{28}$ 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 $C_7H_6N_2$: C, 71.2; H, 5.1; N, 23.7. Found: C, 71.19; H, 5.05; N, 23.54.

2-Cyano-4-methylpyridine—A mixture of 6.0 g. of 2-chloro-4-methylpyridine, 6.0 g. of Na_2SO_3, 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.p$_{38}$ 145~148°, which crystallized to 1.12 g. (39.1%) of colorless prisms, m.p. 88~89°. *Anal.* Calcd. for $C_7H_6N_2$: C, 71.2; H, 5.1; N, 23.7. Found: C, 71.21; H, 5.15; N, 24.14.

2-Cyano-3-methylpyridine—A mixture of 12.8 g. of 2-chloro-3-methylpyridine, 12.8 g. of Na_2SO_3, 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.p$_{38}$ 139~142°, which crystallized to 2.68 g. (59.0%) of colorless prisms, m.p. 87~88°. *Anal.* Calcd. for $C_7H_6N_2$: C, 71.2; H, 5.1; N, 23.7. Found: C, 71.44; H, 5.22; N, 23.52.

2-Cyano-4,6-dimethylpyridine—A mixture of 19.8 g. of 2-chloro-2,4-dimethylpyridine, 18 g. of Na_2SO_3, 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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7) J. A. Berson, T. Cohen: J. Org. Chem., **20**, 1461(1955).

aqueous solution with 16.6 g. of KCN afforded a fraction of b.p$_{16}$ 125$\sim$130°, which crystallized to 5.52 g. (32.6%) of colorless needles, m.p. 51$\sim$52°. *Anal.* Calcd. for $C_8H_8N_2$: 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 Na_2SO_3, and 80 cc. of water was heated in an autoclave at 210$\sim$220° for 10 hrs. Treatment as in the foregoing cases afforded 4.5 g. of the recovered material and fusion of the residue with 2.3 g. of KCN afforded 1.26 g. (49.7%) of a colorless liquid, b.p$_{32}$ 145$\sim$151°. *Anal.* Calcd. for $C_9H_{10}N_2$: C, 73.9; H, 6.9; N, 19.2. Found : C, 73.53, 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 Na_2SO_3, and 40 cc. of water was heated in an autoclave at 180$\sim$200° for 3 hrs. Treated as in the foregoing cases, 1.75 g. of the starting material was recovered and fusion with 3.3 g. of KCN afforded 1.68 g. (60.6%) of colorless liquid, b.p$_{17}$ 107$\sim$110°.

Picrate : Yellow needles (from EtOH), m.p. 123$\sim$124°. *Anal.* Calcd. for $C_9H_{10}N_2 \cdot C_6H_3O_7N_3$: 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$\sim$220° for 10 hours and heating the sodium sulfonate thereby obtained with potassium or sodium cyanide to fusion.

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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 consumers[2] or the survey[3~5] 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 granules[7] (kind and amount of lubricant added), (5) properties of ingredients (physical and micromeritical charactors 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 reports[8,9] 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] Part II. J. Pharm. Soc. Japan, **75**, 480(1950).

[2] J. F. Liverseege : Pharm. J., **116**, 232.

[3] Pharm. Acta Helv., **30**, 131(1955).

[4] Schweiz. Apoth. Ztg., **66**, 489(1928) (C. A., **23**, 4776(1929)).

[5] M. Aoki, T. Fukuda : Japan. J. Pharm. & Chem., **26**, 184(1954).

[6] K. Asahina : J. Pharm. Soc. Japan, **76**, 47(1956).

[7] A. M. Raff, *et al.* : J. Am. Pharm. Assoc., **44**, 290(1955).

[8] A. S. Arambulo, *et al.* : *Ibid.*, **42**, 690, 692(1953).

[9] Dansk Tidskr. Farm., **2**, 151(1928) (C. A., **22**, 4203(1928)).