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Yasuyuki Suzuki : Syntheses of Methylpyridine Derivatives. I. Synthesis of 4-Substituted 3-Picolines.

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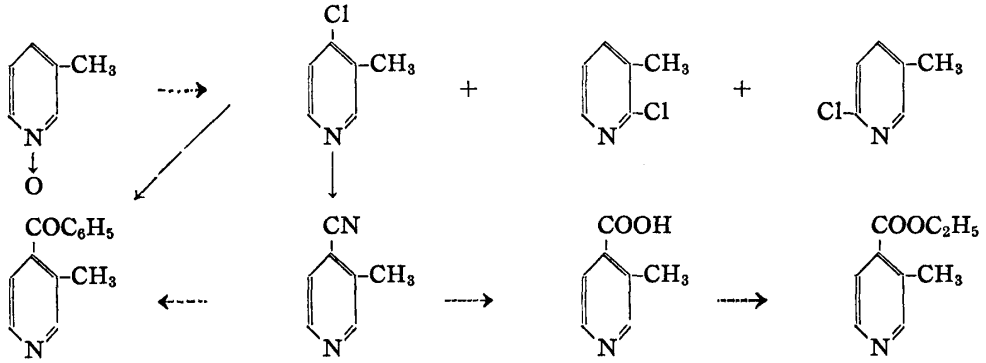
By heating 3-picoline 1-oxide with phosphoryl chloride for 3～5 hours, in accordance with the mothod of Kato,[1] 4-chloro-3-picoline was obtained in 35.5% yield. The fact that 2-chloro- and 6-chloro-3-picoline are formed during this reaction was confirmed by deriving the products to the corresponding hydroxy compounds.

This 4-chloro-3-picoline was heated with an equivalent amount of sodium sulfite to form sodium 3-picoline-4-sulfonate and fused with potassium cyanide, affording 4-cyano-3-picoline. The nitrile group in the 4-position was converted to a carboxyl, ethoxycarbonyl,[2] and benzoyl groups.



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Experimental

Reaction of 3-Picoline 1-Oxide and $POCl_3$—A mixture of 16.5 g. of 3-picoline 1-oxide hydrochloride, 30 cc. of $CHCl_3$, and 30 cc. of $POCl_3$ was refluxed for 5 hrs., cooled, and poured into ice water. The aqueous layer was rendered alkaline with Na_2CO_3 and submitted to steam distillation. The distillate was saturated with NaCl, extracted with ether, and ether was evaporated after drying over anhyd. Na_2SO_4. The ether residue was distilled under a reduced pressure and following fractions were obtained : (i) $b.p_{30}$ 77～80°(5.2 g., 35.5%), (ii) $b.p_{30}$ 81～87°(1.2 g., 8.3%), and (iii) $b.p_{30}$ 88～92°(2.0 g., 20.0%).

The picrate from 1 g. of fraction (i) was recrystallized from MeOH to yellow prisms, m.p. 152～153°. Yield, 2.24 g. (80.2% of (i)). This gave no depression of m.p. on admixture with 4-chloro-3-picoline picrate, obtained by deoxygenation of 4-chloro-3-picoline 1-oxide.[3～5]

Fractions (ii) and (iii) were combined and its 2 g. was derived to the hydroxy compound according to the method of Ochiai and Fujimoto.[6] Low-pressure distillation afforded 1.0 g. of $b.p_3$ 141～143° and 0.1 g. of $b.p_2$ 190～192°. Each of these was purified by chromatography through alumina and eluted with $CHCl_3$. The former afforded 0.46 g. of crystals, m.p. 139～141°(picrate, m.p. 158～160°), undepressed on admixture with 2-hydroxy-3-picoline and its picrate prepared according to the

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1) T. Kato : J. Pharm. Soc. Japan, **75**, 1236(1955).
2) O. Isler, *et al.* : Helv. Chim. Acta, **38**, 1033(1955).
3) W. Herz, L. Tsai : J. Am. Chem. Soc., **76**, 4184(1954).
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5) T. Itai, H. Ogura : J. Pharm. Soc. Japan, **75**, 292(1955).
6) E. Ochiai, M. Fujimoto : This Bulletin, **2**, 137(1954).

method of Seide.[7]

The fraction obtained by elution with $CHCl_3$ containing 1% MeOH afforded 0.3 g. of colorless prisms, m.p. 181~183° (*Anal.* Calcd. for C_6H_7ON: C, 66.0; H, 6.5. Found: C, 65.90; H, 6.07). The picrate recrystallized from MeOH as yellow rhomboprisms, m.p. 147~148° (*Anal.* Calcd. for $C_6H_7ON \cdot C_6H_3O_7N_3$: C, 42.6; H, 3.0. Found: C, 42.21; H, 3.02). The m.p. of this compound agrees with that of 6-hydroxy-3-picoline, reported by Bradlow and others,[8] and is depressed on admixture with 5-hydroxy-3-picoline, prepared according to the method of Matsumura, and 4-hydroxy compound described later, it seems certain that this is a 6-hydroxy compound.

The fraction of $b.p_2$ 190~192° was a unity and repeated recrystallization from acetone afforded colorless needles of m.p. 96~98°(sint. 90°), forming a picrate of m.p. 205~206°, neither showing depression of m.p. on admixture with 4-hydroxy-3-picoline and its picrate, prepared by the method of Clemo.[11] It follows, that the intitial fractions (ii) and (iii) were a mixture of 4-chloro-, 2-chloro-, and 6-chloro-3-picolines.

4-Cyano-3-picoline—Prepared according to the mothod of Ochiai and Suzuki[10] from 25.7 g. of 4-chloro-3-picoline. $b.p_{80}$ 130~132°. Recrystallization from petr. ether (b.p. 40~60°) afforded 10.2 g. (42.9%) of white needles, m.p. 50~52°. *Anal.* Calcd. for $C_7H_6N_2$: C, 71.2; H, 5.1. Found: C, 70.67; H, 4.83.

Picrate: Yellow needles (from MeOH), m.p. 154~156°. *Anal.* Calcd. for $C_7H_6N_2 \cdot C_6H_3O_7H_3$: C, 45.0; H, 2.6. Found: C, 44.91; H, 2.43

4-Benzoyl-3-picoline—To the Grignard reagent prepared from 17.3 g. of bromobenzene, 2.6 g. of Mg pieces, 50 cc. of dehyd. ether, and a minute amount of I_2, ether solution of 4.0 g. of 4-cyano-3-picoline was added dropwise under stirring and ice-chilling. After stirring the mixture for 30 mins. at room temperature, ether was evaporated, 50 cc. of dehyd. toluene was added, and the mixture refluxed for 2~3 hrs. On cooling, saturated NH_4Cl solution was added, toluene layer was separated, and extracted with 10% HCl. The acid extract was rendered alkaline with NaOH, extracted with ether, and ether was evaporated after drying over anhyd. Na_2SO_4. The ether residue was distilled under a reduced pressure and 4.38 g. (65.0%) of a fraction of $b.p_3$ 140~143° was obtained.

Picrate: Yellow needles (from MeOH), m.p. 178~180°. *Anal.* Calcd. for $C_{13}H_{11}ON \cdot C_6H_3O_7N_3$: C, 53.5; H, 3.3. Found: C, 53.17; H, 3.33.

3-Methylisonicotinic Acid—A mixture of 0.5 g. of 4-cyano-3-picoline, 0.75 g. of NaOH, and 30 cc. of 70% EtOH was refluxed on a water bath for 3 hrs., majority of EtOH was distilled off, and 10% HCl was added to the residue until of weakly acid reaction. This mixture was evaporated to dryness under a reduced pressure and the residue was extracted with hot EtOH. Recrystallization from EtOH afforded 0.3 g. (51.7%) of white prisms, m.p. 234~236°. *Anal.* Calcd. for $C_7H_7O_2N$: C, 61.3; H, 5.2. Found: C, 61.59; H, 5.17.

Ethyl 3-Methylisonicotinate—A mixture of 1.0 g. of 3-methylisonicotinic acid and 5 cc. of $SOCl_2$ was refluxed for 1 hr., excess of $SOCl_2$ was distilled off under a reduced pressure, and the residue was refluxed with 3 cc. of dehyd. EtOH for 2 hrs. After evaporation of EtOH, water was added to the residue, basified with Na_2CO_3, and extracted with ether. After drying over anhyd. Na_2SO_4, ether was evaporated and the residue was distilled in vacuo, affording 0.91 g. (75.5%) of a fraction of $b.p_{14}$ 116~117°.

Picrate: m.p. 138~140°(from MeOH). *Anal.* Calcd. for $C_9H_{11}O_2N \cdot C_6H_3O_7N_3$: C, 45.7; H, 3.6. Found: C, 45.39; H, 3.59.

Summary

3-Picoline 1-oxide was derived to 4-chloro-3-picoline by heating with phosphoryl chloride, and the chlorine at 4-position was substituted with nitrile, which was further converted to the carboxyl, ethoxycarbonyl, or benzoyl group.

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