[CONTRIBUTION FROM KOPPERS CO., INC., MULTIPLE FELLOWSHIP ON TAR SYNTHETICS, MELLON INSTITUTE]

OXIDATION OF CERTAIN METHYLPYRIDINES TO PYRIDINE CARBOXYLIC ACIDS

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Since several relatively pure methylpyridines are now commercially available from coal tar, and since there are many contradictions and few quantitative data in the older literature on the oxidation of the methylpyridines, it was considered worth while to establish satisfactory preparative conditions for certain pyridine carboxylic acids. Much of the early work was qualitative in nature and dealt mainly with the proof of structure of the pyridine carboxylic acids and of their parent methylpyridines.

EXPERIMENTAL

All melting and boiling points are corrected.

Methylpyridines. The methylpyridines (Table I), with the exception of 2-methyl-5-ethylpyridine, were products of Koppers Co., Inc., with minimal purity of 95%. The yield figures of the pyridine carboxylic acids obtained therefrom are conservative, because 100% purities were assumed for the methylpyridines in the yield calculations. The purity of 2-picoline was determined by analytical distillation; the purities of 3- and 4-picolines and of 2,6-lutidine were established by the cryoscopic method described by Freiser and Glowacki (1). 2-Methyl-5-ethylpyridine was synthesized by the reaction of paraldehyde with aqueous ammonia (2); the purity of the product was not established.

Apparatus. The oxidation apparatus was a 5-liter, 4-necked flask, with one of the necks elongated six inches and water-cooled to allow portion-wise addition of permanganate without loss of alkylpyridine by volatilization. The other three necks were equipped with thermometer, mercury-sealed stirrer, and large-capacity reflux condenser, respectively. The dehydration-extraction apparatus was a 5-liter flask provided with stirrer and water trap (Fig. 1) surmounted by an efficient reflux condenser.

Titration, isoelectric points, and isolation of pyridine carboxylic acids. Both colorimetric and electrometric (glass electrode) titrations were satisfactory. The isoelectric points of picolinic, nicotinic, isonicotinic, and 6-methylpicolinic acids were found to be 3.2, 3.4, 3.6, and 3.3, respectively. It was shown that the precipitation *p*H could be varied 0.3 on either side of the isoelectric point without affecting the yield of acid. Dipicolinic acid (2,6-dicarboxypyridine), a relatively strong acid, was precipitated from 1.5 *N* hydrochloric acid; isocinchomeronic acid (2,5-dicarboxypyridine) was isolated as the dimethyl ester and subsequently hydrolyzed to the free acid.

Recoverable non-oxidized base. Although non-oxidized base was not recycled in the laboratory runs, the amount of recoverable base was determined in order to calculate oxidation efficiency. Recovery was accomplished by distilling the alkaline oxidation filtrate until the distillate was base-free. About 8% of the base was recoverable in the oxidation of the picolines to mono-acids and of 2,6-lutidine and 2-methyl-5-ethylpyridine to di-acids; 20% of the base escaped oxidation in the preparation of 6-methylpicolinic acid from 2,6-lutidine.

Identification of non-oxidized base. Recovered base from the oxidation of the picolines was analyzed in order to check on degradation to pyridine or accumulation of impurity. The recovered base in the distillate was salted out by potassium hydroxide, separated, dried by potassium hydroxide, further dried by azeotroping its benzene solution and finally distilled. In all cases the recovered base (identified as picrate) was the same as the starting material.

Non-decarboxylation during preparation. Picolinic, nicotinic, isonicotinic, and dipicolinic acids were unchanged by boiling for six hours in alkaline solutions similar to that of the oxidation filtrate; also in water solution, and in 1.5 *N* and 5 *N* aqueous hydrochloric acids. Therefore, it is unnecessary to protect their boiling aqueous solutions by inert gas, as practised by Meyer and Tropsch (3), or to lower the boiling temperature by the use of reduced pressure. Three grams of isonicotinic acid (99.8% pure) was heated for 9 days

TABLE I

CONSTANTS OF METHYLPYRIDINES

COMPOUND	B.P. (°C.)	PRESSURE (MM.)	n_D^{20}	d_4^{20}	FR.P. (°C.)	PURITY %
2-Picoline	128.7–128.9	747	1.5002	0.946	−66.6	98
3-Picoline	143.1–143.3	745	1.5060	0.956	−19.8	96
4-Picoline	144.2–144.4	743	1.5050	0.953	1.5	96
2,6-Lutidine	142.8–143.0	743	1.4977	0.925	−8.1	96
2-Methyl-5-ethylpyridine	177.4–177.6	738	1.4970	0.918	—	—

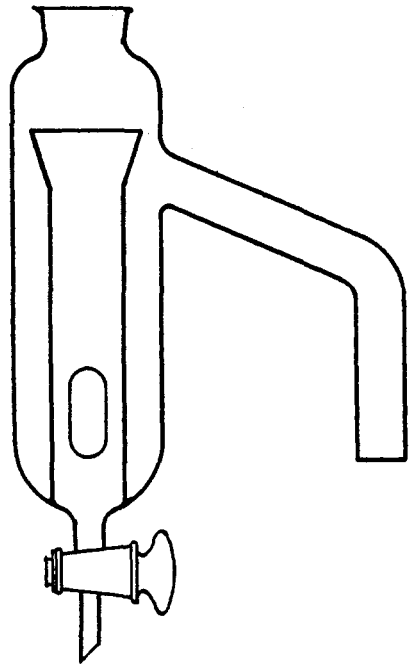

FIG. 1. WATER TRAP

at 110°; the weight loss was 0.1% per day, and the purity of the residual acid at the end of 9 days was 99.7%.

Picolinic acid (4–19) is very soluble in water (9 g. in 10 cc. of water at 9°). The present preparative method involves dehydrating the oxidation filtrate at its isoelectric point by azeotropic distillation with benzene and simultaneously extracting the picolinic acid. The solubility of picolinic acid in 1000 cc. of benzene at 15, 30, and 80° is 2, 4, and 41 g., respectively. Picolinic acid in boiling benzene (1% solution, boiled 20 hours) did not decompose. A similar experiment with a boiling xylene solution showed 36% decomposition of the acid.

(*A*) *Preparation.* Two hundred grams (2.15 moles) of 2-picoline and 2500 cc. of water were placed in the oxidation flask and 900 g. (5.7 moles) of crystalline potassium permanganate was added in ten portions during six hours. The first five additions were made at 70°, the last five at 85–90°. Each successive addition of permanganate, which was made only after the preceding amount had been consumed, was washed down the elongated neck with water (about 500 cc. total). After the last charge of permanganate had been decolorized, the hot reaction mixture was filtered by suction, and the manganese dioxide was washed on the filter with 1500 cc. of hot water in four portions, allowing each portion to soak into the cake without application of vacuum, finally sucking the cake dry before adding fresh wash water.

The combined filtrate-wash was concentrated to 700 cc. and the concentrate was set at *p*H 3.2 by adding about 265 cc. of concentrated hydrochloric acid. The solution was poured into the extraction flask and 3000 cc. of benzene was added. The flask was immersed in a water-bath at 90°, the reflux condenser was replaced by the water trap-condenser assembly, and the contents of the flask were stirred and boiled for about twelve hours until no more water collected in the trap. This dehydration-extraction produced a friable solid amenable to solvent extraction and was preferable to evaporating the water solution and subsequently extracting the solid with an organic solvent.

The hot benzene solution was filtered through a steam funnel and the filtrate was evaporated to dryness (5-liter flask in boiling water-bath). The air-dried residue of picolinic acid weighed 100 g. (38% yield). The residual solid in the extraction flask (picolinic acid

TABLE II

MELTING POINTS OF PICRATES OF RECOVERED PICOLINES

PICOLINES	AUTHENTIC PICOLINE PICRATES (A) M.P. (°C.)	PICRATES OF RECOVERED PICOLINES (B) M.P. (°C.)	MIXED PICRATES (A + B) M.P. (°C.)
2-Picoline	164–165	164–165	164–165
3-Picoline	147–149	146–148	146–148
4-Picoline	164–165	165–166	164–165

plus potassium chloride) was air-dried, screened to *ca.* 20 mesh, and re-extracted with 3000 cc. of benzene to give 66 g. of picolinic acid (25% yield); the combined yield was 166 g. (63%). (With 4.6 moles of permanganate instead of 5.7, the combined yield was 153 g.) The product titrated 99.8% pure and melted at 136.5–138°. Contrary to British patent 447,339 (1936) the picolinic acid contained little if any oxalic acid. The solubility of oxalic acid in boiling benzene (0.72 g. in 3000 cc.) fixed the maximal contamination at 1%, and mixed melting point determinations indicated that the contamination was less than 1%.

Four extraction residues were combined and the composite was twice extracted with benzene to give 32 g. and 12 g. of picolinic acid, respectively, raising the yield for a single oxidation to 177 g. (67% per-pass yield, 73% ultimate). The twice-extracted quadruple residue still contained 100 g. of picolinic acid. Therefore the ultimate oxidation efficiency was 83%. The picolinic acid in the residue can be concentrated by crystallization from water. For example, a residue containing 100 g. of picolinic acid and 1500 g. of potassium chloride was dissolved in 2800 cc. of boiling water, and the solution was cooled to 0°. Fifty per cent of the potassium chloride crystallized and the filtrate contained 99% of the picolinic acid.

(*B*) *Extraction by chloroform.* Boiling chloroform removed picolinic acid faster than benzene but yielded an impure product (*ca.* 93% pure) contaminated by potassium chloride. The solubility of picolinic acid in 1000 cc. of chloroform at 4, 33, and 64°, is 14, 31, and 81 g., respectively.

(*C*) *Liquid-liquid extraction.* Liquid-liquid extraction of aqueous picolinic acid at its

isoelectric point was fairly satisfactory. The efficiency of the extraction apparatus of Palkin, Murray, and Watkins (20) was raised by enlarging the extraction section and filling it with glass pearls to increase interfacial contact. Aqueous solutions (30 cc.) containing 9.3 g. of picolinic acid and an equivalent amount of potassium chloride (5.6 g.) were extracted at about 50° by benzene and chloroform (250 cc.). The recoveries of picolinic acid by benzene in 4, 11, and 35 hours were 23, 51, and 64%, respectively. The corresponding recoveries by chloroform in 4 and 11 hours were 83 and 89%, respectively. The 5.9 g. of picolinic acid extracted by benzene contained 0.05 g. of potassium chloride whereas the 8.3 g. of acid extracted by chloroform contained 1.2 g. of potassium chloride.

Nicotinic acid (*4–6, 8, 9, 15, 17, 21–25*). Two hundred grams (2.15 moles) of 3-picoline was oxidized in the same way as 2-picoline. The combined filtrate-wash was evaporated to 3000 cc. and the concentrate was set at *p*H 3.4 with about 260 cc. of concentrated hydrochloric acid. The mixture was heated to 95–100° to dissolve the voluminous precipitate and allowed to cool slowly to room temperature. The purpose of the slow cooling was to avoid contamination by potassium chloride. The nicotinic acid was washed with 50 cc. of cold water and air-dried. The filtrate was concentrated to 1300 cc., cooled at 5° overnight and filtered. The first crystal crop weighed 151 g. (air-dried 92% pure, pistol-dried 97.7% pure, 56% yield); the second crop weighed 61 g. (air-dried 83% pure, pistol-dried 91% pure, 21% yield). In all cases, air-drying took place at ordinary temperature and pressure, pistol-drying at reduced pressure (*ca.* 5 mm.) and 100°. The total per-pass yield of nicotinic acid was 77%; the ultimate yield was 83%. The solubility of nicotinic acid (crystallized from water, m.p. 234.5–235.5°, 99.6% pure) in 1000 cc. of water at 0, 40, 80, and 100°C, is 10, 26, 82, and 127 g., respectively.

Isonicotinic acid (*5, 6, 9, 18, 19, 22, 26–33*). 4-Picoline was processed as above, the precipitation *p*H being 3.6. Not all the precipitate dissolved when the mixture was heated to boiling. Slow cooling was employed as with nicotinic acid. The first crystal crop weighed 170 g. [air-dried 99.5% pure, pistol-dried 99.8% pure, m.p. 323–325° (dec.), 64% yield]. The second crystal crop weighed 17 g. (air-dried 94% pure, pistol-dried 94% pure, 6% yield). The total per-pass yield was 70%; the ultimate yield was 76%.

Crystallization of isonicotinic acid. Water is the best solvent for this purpose. The solubility of isonicotinic acid per 1000 cc. of water at 0, 40, 80, and 100° is 3, 9, 24, and 34 g., respectively. In water saturated with potassium chloride at 25° the solubility per 1000 cc. of solvent at 40, 68, and 100° is 8, 14, and 24 g., respectively.

Dipicolinic acid (*9, 10, 14, 15, 34–48*). 2,6-Lutidine (107 g., 1 mole) in 2500 cc. of water was oxidized by 838 g. of potassium permanganate (5.3 moles) added in ten portions during 17 hours. The concentrated filtrate-wash (2000 cc.) was made 1.5 normal with respect to hydrochloric acid by the addition of about 500 cc. of concentrated hydrochloric acid, heated to boiling to dissolve precipitated solid, allowed to cool slowly to room temperature, cooled overnight at 5° and filtered. The dipicolinic acid was washed with 50 cc. of cold water and air-dried. The filtrate was concentrated to 1200 cc., cooled at 5° overnight and filtered. The first crystal crop weighed 130 g. (air-dried 98% pure, pistol-dried 100% pure, 78% yield). The second crop was 8% pure (air-dried) and corresponded to an additional 6% yield; the impurity was potassium chloride. The total per-pass yield of dipicolinic acid was 84%; the ultimate yield was 92%. When 4.2 moles of permanganate was used instead of 5.3 moles, the per-pass yield was 57%, the first crop being 55% (air-dried 100% pure), the second crop 2% (air-dried 68% pure).

(*A*) *Method of precipitation.* It was essential that the acidified solution of dipicolinic acid be heated to boiling to dissolve all the solid, and that the hot solution be allowed to cool slowly, otherwise a gelatinous precipitate resulted which contained about 20% of potassium chloride. Potassium was determined as sulfate by ignition with sulfuric acid; chloride was determined as silver chloride, which was precipitated in 1.5 *N* nitric acid and filtered hot (*ca.* 65°).

Before the necessity of precipitation at high acidity was realized, the dipicolinic acid was usually contaminated with about 2.5% of potassium (negligible chloride) which cor-

responded to the presence of 7.8% of dipotassium dipicolinate or 13.2% of monopotassium dipicolinate. Pure dipicolinic acid could be obtained from this material by slow crystallization from water. The melting point of the acid was not much affected by this considerable salt contamination. The melting point of pure dipicolinic acid was 232–233° (dec., heating rate 1° per min.), whereas the melting point of impure dipicolinic acid containing 2.5% of potassium was 230–231° (dec.).

Dipicolinic acid can be recrystallized from 5 *N* hydrochloric acid, and the air-dried product is the free acid. The effect of hydrochloric acid normality on the solubility of dipicolinic acid is shown by solubility isotherms (Fig. 2). Relatively pure dipicolinic acid was sometimes obtained at *p*H 2.0, but the minimum acidity at which potassium-free acid was always obtained was *p*H 0.6.

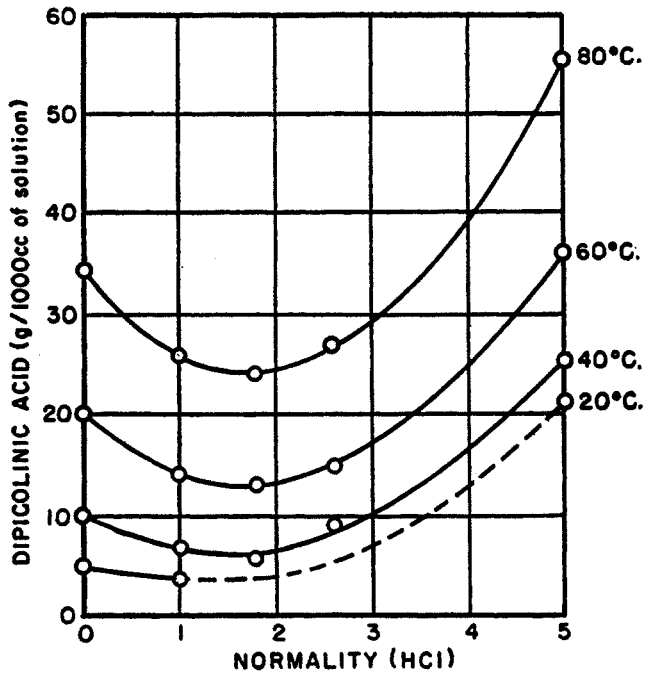

FIG. 2. SOLUBILITY ISOTHERMS OF DIPICOLINIC ACID

(*B*) *Potassium salts.* The calculated amount of potassium carbonate to form the monopotassium salt was added to an aqueous solution of dipicolinic acid. Short, thick crystals were obtained. This product was similar to one described by Pinner (9), who assigned the formula $C_7H_4NO_4K \cdot C_7H_5NO_4 \cdot 3H_2O$. Our air-dried product analyzed for $C_7H_4NO_4K \cdot C_7H_5NO_4 \cdot 2.5\ H_2O$.

Anal. Calc'd for $C_{14}H_{14}N_2O_{10.5}K$: K, 9.5; H_2O, 11.0.
Found: K, 9.4; H_2O, 10.8.

Fractional crystallization from water separated a product containing the theoretical amount of potassium for the monopotassium salt. The air-dried material was anhydrous.

Anal. Calc'd for $C_7H_4NO_4K$: K, 19.1. Found: K, 19.3.

6-Methylpicolinic acid (*9, 47, 49–54*). The oxidation was made as usual, except for temperature, starting with 107 g. (1 mole) of 2,6-lutidine and 335 g. (2.1 moles) of permanganate. The optimal temperature was 60–70° and the oxidation required 18 hours. Two methods of separating the mono- and di-acids were evaluated.

According to one method, the concentrated oxidation filtrate-wash (2500 cc.) was made 1.5 *N* with respect to hydrochloric acid whereupon dipicolinic acid crystallized on cooling. The mono-acid was subsequently recovered from the filtrate (set at *p*H 3.3) by dehydration-extraction with boiling benzene. The disadvantage of this method was the excessive quantity of potassium chloride produced by neutralizing the hydrochloric acid.

According to the other method, the oxidation filtrate-wash was concentrated to 500 cc., set at *p*H 3.3, and dehydrated-extracted by 1500 cc. of benzene. The mono-acid extracted by the dry benzene was free from di-acid. The solid in the extraction flask was extracted with 500 cc. of boiling 1.5 *N* hydrochloric acid, and dipicolinic acid crystallized from the solution on cooling.

These two methods of separation were based on the following solubility data. Dipicolinic acid is practically insoluble in boiling benzene (0.1 g. in 1000 cc.) and sparingly soluble in cold 1.5 *N* hydrochloric acid (Fig. 2), whereas the mono-acid is relatively soluble in benzene (9, 11, and 200 g. in 1000 cc. of benzene at 9, 20, and 80°, respectively), and very soluble in 1.5 *N* hydrochloric acid (8 g. per 10 cc. at 25°).

Using 60–70° as the oxidation temperature and the second method of separation, a 59% yield (80 g.) of 6-methylpicolinic acid and a 6% yield (10 g.) of dipicolinic acid was obtained. The former titrated 99% pure and melted at 126.5–128°.

Anal. Calc'd for $C_7H_7NO_2$: cc. of 0.1 *N* KOH, 20.7. Found: cc. of 0.1 *N* KOH, 20.6.

Upon exposure to air or crystallization from water, the anhydrous acid took on one molecule of water of crystallization and melted at 93.5–95°.

Anal. Calc'd for $C_7H_7NO_2 \cdot H_2O$: cc. of 0.1 *N* KOH, 17.5. Found: cc. of 0.1 *N* KOH, 17.6.

Isocinchomeronic acid (10, 36, 40, 41, 55–60). Numerous attempts were made to oxidize 2-methyl-5-ethylpyridine to the di-acid according to the procedure used for dipicolinic acid, but the results were erratic owing to the sluggishness with which the acid crystallized from the acidified concentrate of the oxidation filtrate, and the tenacity with which it retained potassium salt. An occasional 60% yield of acid (contaminated by 2% of potassium) was obtained by precipitating at *p*H 1 to *p*H 2.5. The finally accepted procedure was to make the dimethyl ester, from which potassium-free acid could be obtained. No attempt was made to develop procedures for preparing mono-acids from 2-methyl-5-ethylpyridine.

(*A*) *Dimethyl ester.* One mole of 2-methyl-5-ethylpyridine was oxidized by 7.9 moles of potassium permanganate in the usual manner. The combined filtrate-wash was concentrated and then dehydrated with benzene. The benzene was decanted, the dry solid was freed from benzene by evacuation, and to the solid was added a mixture of 700 g. of methyl alcohol and 910 g. of concentrated sulfuric acid. The solid-liquid mixture was refluxed in a water-bath for six hours with stirring, poured into cracked ice, and neutralized with aqueous sodium carbonate (about 900 g. of carbonate in 2500 cc. of water). The volume of solution was so chosen that solid dimethyl ester precipitated and sodium sulfate dissolved. The mixture was divided into two equal parts and each was vigorously stirred in a 5-liter flask with three portions of chloroform, 500 cc. the first time and 375 cc. the second and third times. The greater part of the chloroform solution separated after each extraction and the interfacial emulsion was broken by suction filtration. The combined extract (2500 cc.) was concentrated to about 400 cc. (*ca.* 65° liquid temperature), cooled in ice, and filtered. The small amount of mother liquor was allowed to evaporate at room temperature. The combined air-dried yield of the first and second crops (81.7 g. and 9.3 g., respectively) was 91 g. (46.5% yield). The crude ester melted at 161–163° and was 97% pure by saponification equivalent. Ester recrystallized from methanol melted at 162.5–163.5°. Its solubility in 1000 cc. of methanol at 3, 10, and 60° was 3, 10, and 40 g., respectively.

(*B*) *Hydrolysis of the dimethyl ester.* Dimethyl ester (19.5 g.) was refluxed for 4 hours with 100 cc. of 2 *N* hydrochloric acid; the mixture was cooled overnight at 5° and filtered to give 17.5 g. of isocinchomeronic acid (air-dried 93% pure, pistol-dried 99% pure, 95% yield). The anhydrous acid melted at 249–249.5° with decomposition [the 154° m.p. reported by

Meyer and Staffen (58) must be a typographical error]. Acid recrystallized from water and air-dried for a week contained 1.12 moles of water of crystallization, which it retained on subsequent exposure in an evacuated desiccator for 5 days (1 to 1.5 moles of water have been reported).

SUMMARY

Improved preparative directions are reported for picolinic, nicotinic, isonicotinic, dipicolinic, 6-methylpicolinic, and isocinchomeronic acids; also for dimethyl isocinchomeronate.

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