Carbonation of 3-Pyridinols

F. Mutterer and C. D. Weis

Dyestuffs and Chemicals Department, CIBA-GEIGY Corp., Basel, Switzerland

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Procedures are described for the high pressure carbonation of substituted 3-pyridinols, yielding the corresponding pyridine carboxylic acids. Treatment of *o*-aminohydroxypyridinecarboxylic acid with cyanogen and with phosgene, respectively, gave access to oxazolo[4,5-*b*]pyridine derivatives. The synthesis of 3-amino-6-methyl-2-pyridinecarboxylic acid was accomplished by heating 3-hydroxy-6-methyl-2-pyridinecarboxylic acid in liquid ammonia.

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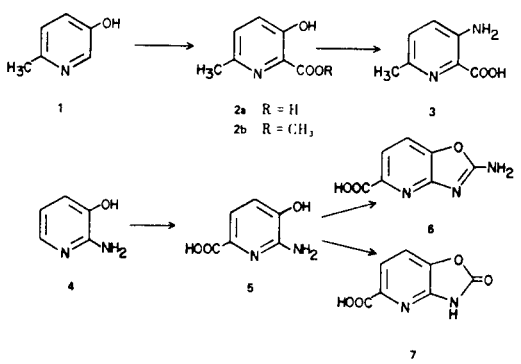
The carbonation of the pyridine nucleus has been less extensively studied than carbonation in the aromatic series. Thus, the 2-, 3-, and 4-pyridinols were converted into the hydroxypyridinecarboxylic acids under Kolbe-Schmidt reaction conditions in 22-52% yield (1). A later report described the carbonation of 2-methyl-3-pyridinol yielding 5-hydroxy-6-methyl-2-pyridinecarboxylic acid (2).

The now readily accessible series of substituted 3-pyridinols which were prepared starting from 2-furane aldehyde (3,4) led us to investigate the carbonation of the 3-pyridinols **1** and **4**, respectively, under Kolbe-Schmidt reaction conditions.

Heating the dry potassium salt of **1** and **4**, respectively, to 220° under a pressure of 860 psi (60 atmospheres) of carbon dioxide yielded the pyridine carboxylic acids **2a** and **5** in 72% and 70%, respectively (Scheme 1). It is essential that great care be taken to use only rigorously dried potassium salts of **1** or **4**, as otherwise the yields of carboxylic acids decrease drastically.

Scheme 1



The potassium salt of **4** was diluted with quartz sand, since the solidified product obtained could otherwise only be removed from the autoclave with considerable difficulty.

The amino acid **3** could be readily obtained by heating **2a** in liquid ammonia to 200° while **5** under similar conditions yielded only tar like material. The picolinic acid **2a** was hitherto only accessible by a multiple step reaction sequence (5), while the amino acids **3** and **5** were unknown.

Esterfication of the carboxylic acid **2a** was accomplished with methanol and thionyl chloride while other methods failed to give the ester **2b**. Treatment of **5** with cyanogen bromide and with phosgene, yielded the oxazolo[4,5-*b*]pyridine derivatives **6** and **7**, respectively (6).

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded in potassium bromide discs and the nmr spectra were recorded at 100 MHz.

3-Hydroxy-6-methyl-2-pyridinecarboxylic Acid (**2a**).

2-Methyl-5-hydroxypyridine (218 g., 2 moles) was dissolved in 1 liter of 2 *N* aqueous potassium hydroxide solution. The solution was evaporated to dryness under reduced pressure, 500 ml. of benzene was added and the solution again evaporated to dryness and the procedure repeated. The crude potassium salt was first dried at 90° under vacuum, ground in a mixer to a dust-like material and finally dried over phosphorus pentoxide at 90° and 12 torr for a period of 24 hours, yielding 279 g. (93.5%). The potassium salt was thoroughly mixed with 365 g. (2.64 moles) of fused potassium carbonate, placed in a 2.5 liter autoclave, pressured with 55-60 atmospheres of carbon dioxide, and then heated to 225° for a period of 4 hours. The resulting product was dissolved in 4.6 liters of boiling water and filtered from insoluble

material. The filtrate was adjusted to *p*H 2 with concentrated sulfuric acid, sodium hydroxide solution added to *p*H 3-4, and the crystals filtered from the cold solution at 10°. They were slightly contaminated with potassium sulfate and were, therefore, recrystallized from 3 liters of water in the presence of 15 g. of decolorizing carbon, yielding 207.5 g. (72%) of pure acid, m.p. 237° (5), ir cm^{-1}: 3413, 2899, 1667, 1608, 1538, 871, 810, 805.

Anal. Calcd. for $C_7H_7NO_3$: C, 54.89; H, 4.60; N, 9.14. Found: C, 54.91; H, 4.54; N, 9.11.

3-Hydroxy-6-methyl-2-pyridinecarboxylic Acid Methyl Ester (**2b**).

To a suspension of 23 g. (0.15 mole) of 3-hydroxy-6-methyl-2-pyridinecarboxylic acid in 400 ml. of methanol was added dropwise 70 g. (0.59 mole) of thionyl chloride. The solution was heated to 40° for 12 hours and then refluxed for an additional 12 hours. The excess methanol was distilled off, and the remaining oil dissolved in 50 ml. of water and neutralized with 2 *N* sodium bicarbonate. The crystals were filtered and washed with a few ml. of water. The crude material was dissolved in benzene, filtered from insoluble material and the filtrate evaporated to dryness yielding 15.5 g. (62%) of product, which was purified by sublimation at 90°/0.1 mm, m.p. 83-84°; ir cm^{-1}: 1675, 1592 (pyridine); nmr (deuteriochloroform): 10.5 OH; 7.32 (s) H-4 and H-5; (due to accidental coincidence of the chemical shifts of H-4 and H-5 in deuteriochloroform only one single peak is observed); 4.10 (s); $COOCH_3$; 2.58 (s) CH_3.

Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.41; H, 5.41; N, 8.44.

2-Amino-6-methyl-2-pyridinecarboxylic Acid (**3**).

3-Hydroxy-6-methyl-2-pyridine carboxylic acid (153 g., 1 mole) and 500 ml. (17 moles) of liquid ammonia were placed in a 1 liter stainless steel autoclave and heated to 200° for a period of 5 hours. Excess ammonia was evaporated and the residue dried under vacuum at 60° yielding 141 g. (92.2%). Recrystallization from methanol-water yielded white crystals, m.p. 157-158°; ir cm^{-1}: 3425, 3175, 1669, 1605, 1563, 1471; nmr (acetone-d_6): 12.24 (s, COOH); 7.35 (d) H-4; 7.23 (d) H-5; 2.44 (s) CH_3.

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41, Found: C, 55,38; H, 5.46; N, 18.42.

2-Amino-3-hydroxy-6-pyridinecarboxylic Acid (**5**).

2-Amino-3-hydroxypyridine (110 g., 1 mole) was dissolved in a solution of 56 g. (1 mole) of potassium hydroxide in 500 ml. of water. The solution was evaporated to dryness under reduced pressure, the residual solid dissolved in ethanol, 200 ml. of benzene added and both solvents distilled off. The same volume of benzene was again added and the procedure repeated. Drying was completed at 120° in a vacuum oven. A mixture of 148 g. (1 mole) of potassium salt, 193 g. (1.4 moles) of fused potassium carbonate and 800 g. of quartz sand was thoroughly ground in a mechanical mixer for 2 hours and dried at 120° in a vacuum oven. It was then placed in an autoclave, pressured with 60 atmospheres of carbon dioxide and heated at 220° for 4 hours. The reaction mixture was slurried in 2 liters of boiling water and filtered from insoluble material. The filtrate was heated with 140 g. of decolorizing carbon, filtered and reduced in vacuum to 1.2 liters and adjusted to *p*H 2.8-3.0 with 245 ml. of concentrated hydrochloric acid. The precipitate was filtered after 24 hours, washed with water and dried, yielding 107 g. (70%) of product, m.p. 223-224°. A sample of 10 g. was recrystallized from 1740 ml. of water yielding 7.5 g., m.p. 224°. Titration in water with 0.1 *N* tetramethylammonium hydroxide gave a p*K* 5.29; ir cm^{-1}: 3401, 3226, 3030, 2564 (broad), 1692, 1661, 1565, 1393, 1269, 781; nmr (sodium deuteroxide): 7.43 (d, H-4), 6.73 (d, H-5), J = 8. An analytical sample was dried at 130°/12 torr for a period of 40 hours.

Anal. Calcd. for $C_5H_6N_2O_3$: C, 46.76; H, 3.93; N, 18.18. Found: C, 46.49; H, 3.93; N, 17.85.

2-Aminooxazolo[4,5-*b*]pyridine-2(3*H*)one-7-carboxylic Acid (**6**).

Into a stirred suspension of 30.8 g. (0.2 mole) of **5** in 800 ml. of dimethoxyethane was introduced a current of phosgene (100 g., 1 mole) over a period of 30 minutes. A solution of 15 g. (0.15 mole) of triethylamine in 40 ml. of dimethoxyethane was then added dropwise over the same period of time. After 4 hours the solution was again saturated with phosgene and stirred for a further 24 hours. The crystals were filtered from the solution and the filtrate evaporated to dryness. The residual oil was heated with 30 ml. of water, the pale yellow precipitate collected by filtration and washed with water, yielding 29.8 g. (82.8%) of product. An analytical sample was obtained by crystallization from water, m.p. 275° dec., ir cm^{-1}: 3448, 3144, 1818, 1718, 1639, 1631.

Anal. Calcd. for $C_7H_4N_2O_4$: C, 46.67; H, 2.23; N, 15.55. Found: C, 46.62; H, 2.24; N, 15.48.

Oxazolo[4,5-*b*]pyridine-7-carboxylic Acid (**7**).

To a solution of 7.7 g. (0.05 mole) of **5** in 75 ml. of 2 *N* aqueous sodium hydroxide solution was added 10.6 g. (0.2 mole) of cyanogen bromide. The resulting solution was stirred for 24 hours, neutralized by adding dilute hydrochloric acid, and the precipitate (6.5 g., 72.5%) filtered off and washed with water. An analytical sample was obtained by recrystallization from dimethylformamide-water, and the very slowly precipitating crystals collected after standing for 2 days at room temperature, m.p. 270° dec.; ir cm^{-1}: 3225, 2874, 1709, 1605.

Anal. Calcd. for $C_7H_5N_3O_3$: C, 46.93; H, 2.81; N, 23.45. Found: C, 46.83; H, 3.00; N, 23.75.

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