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# SYNTHESIS OF INDOLE DERIVATIVES. 5-INDOLECARBOXYLIC ACID

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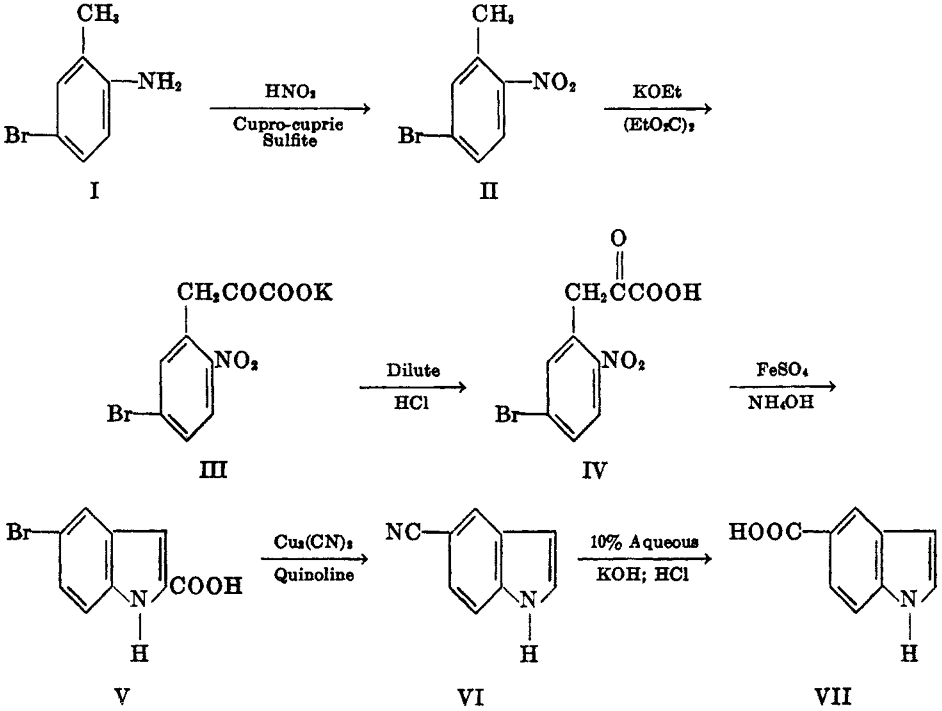
Of the various indolecarboxylic acids, only 5-indolecarboxylic acid has not yet been reported. During the course of synthesis of 7-indolecarboxylic acid (1), several intermediates were prepared which could be used in the synthesis of 5-indolecarboxylic acid in order to complete the series. The reaction sequence by which this compound was synthesized is indicated by formulas I–VII.



Bromination of acetylated *o*-toluidine and removal of the acetyl group by acid hydrolysis gave the starting material, 2-amino-5-bromotoluene (I), which by diazotization and treatment of the diazonium salt with a catalyst and nitrite was converted to 5-bromo-2-nitrotoluene (II). Condensation of the bromonitrotoluene with diethyl oxalate and hydrolysis of the resulting ester produced 5-bromo-2-nitrophenylpyruvic acid (IV) which was cyclized by treatment with ferrous hydroxide in ammonium hydroxide to form 5-bromo-2-indolecarboxylic

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acid[3] (V). Replacement of the bromo group with a cyano group and decarboxylation was accomplished by refluxing the bromoindolecarboxylic acid with a mixture of cuprous cyanide and quinoline. Hydrolysis of the cyanoindole[3] (VI) formed the 5-indolecarboxylic acid (VII).

Resistance of 4- and 6-bromo-2-indolecarboxylic acid to decarboxylation rereported by Barltrop and Taylor (2) was not encountered with the conversion of 5-bromo-2-indolecarboxylic acid to 5-cyanoindole. The latter conversion probably involves a mechanism similar to that involved in the cuprous bromide-catalyzed decarboxylation of 4- and 6-bromo-2-indolecarboxylic acid since substitution of cuprous chloride results in replacement of the 4- and 6-bromo groups to form 4- and 6-chloroindoles (3).

A spot of 5-indolecarboxylic acid on filter paper gave an $R_f$ value of 0.43 on ascending chromatographic development with a solvent consisting of isopropyl alcohol (8 parts), concentrated ammonium hydroxide (1 part), and water (1 part). The 5-indolecarboxylic acid gave a characteristic pink color on treatment with Ehrlich's reagent.

## EXPERIMENTAL[4, 5]

*2-Amino-5-bromotoluene* (I). *o*-Toluidine was acetylated with acetic anhydride. The acetyl derivative was brominated in acetic acid solution at 5°, and 2-amino-5-bromotoluene was obtained by hydrolysis of the brominated derivative with 20% hydrochloric acid as described by Ressy and Ortodocsu (4).

*5-Bromo-2-nitrotoluene* (II). 2-Amino-5-bromotoluene (14.4 g.) was dissolved with stirring in sulfuric acid (10 g. of concentrated sulfuric acid in 93 ml. of water). The solution was cooled to 0° and 7.5 g. of sodium nitrite in water was added slowly to the stirred solution. The reaction mixture containing the diazonium salt was poured slowly into a rapidly stirred mixture of 18.6 g. of cupro-cupric sulfite and 57 g. of sodium nitrite in 300 ml. of water. It was stirred for 3 hours at room temperature and then was steam-distilled. A yellow oil distilled over which rapidly solidified in the water. The mixture was cooled in the refrigerator overnight and then was filtered. The solid was dissolved in 95% ethanol, and was treated with charcoal in boiling ethanol. The mixture was filtered and water was added to the filtrate until the solution became cloudy and then it was cooled in a refrigerator. Crystals which deposited from the solution were recrystallized by the same procedure. The yield of product melting at 53–54° was 11 g. (64%). Geerling and Wibaut (5) report m.p. 53.0° for this product prepared by another method.

*5-Bromo-2-nitrophenylpyruvic acid* (IV). Potassium ethoxide was prepared by adding 6 ml. of absolute alcohol to a well stirred mixture of 2 g. of potassium in 30 ml. of absolute benzene. When the potassium had completely reacted, the excess solvents were distilled. After the addition of 60 ml. of absolute ether and 7.3 g. of diethyl oxalate, 10.8 g. of 5-bromo-2-nitrotoluene in ether was added dropwise. The reaction mixture was stirred at reflux temperature for 20 hours. At the end of 20 hours, the potassium salt (deep red in color) was collected and washed with absolute ether. The salt was shaken vigorously with four 100-ml. portions of water and the mixture was rapidly filtered. The combined aqueous solution (400 ml.) was heated to 70° for 3–5 minutes and cooled. Concentrated hydrochloric acid was added to the aqueous solution to give a 2% acid concentration. The solution was cooled and agitated in a water-ice bath. After 5–10 minutes, a yellow-brown precipitate appeared

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[3] In separate experiments, both 5-cyanoindole and 5-bromoindole-2-carboxylic acid inhibited growth of *Escherichia coli* at concentrations of approximately 200 $\gamma$ per ml. of inorganic salts-glucose medium.

[4] All melting points are corrected.

[5] Microanalyses by Dr. C. G. Skinner and Russell Claybrook.

which was separated by filtration, dried, then dissolved in chloroform, and treated with charcoal at the boiling point of the solvent. The solution was filtered and chilled in a refrigerator to obtain crystals. After recrystallization from chloroform, the pale yellow needles amounted to 6 g. (42%) and melted at 143–144°. This material gave a deep, blood-red color in normal sodium hydroxide and a deep green color with aqueous ferric chloride.

*Anal.* Calc'd for $C_9H_6BrNO_5$: C, 37.52; H, 2.10; N, 4.86.
Found: C, 37.47; H, 2.07; N, 4.93.

*5-Bromo-2-indolecarboxylic acid* (V). A solution of 4.7 g. of 5-bromo-2-nitrophenylpyruvic acid in 5% ammonium hydroxide was added to a suspension of ferrous hydroxide prepared from 31.2 g. of $FeSO_4 \cdot 7H_2O$ and 13.0 ml. of concentrated ammonium hydroxide in 114 ml. of water. The reaction mixture was maintained at its boiling point for 10 minutes. Ferric hydroxide (chocolate brown) which precipitated during the reaction was separated by filtration and was washed with 5% ammonium hydroxide until an aliquot no longer gave a precipitate on addition of 6 *N* hydrochloric acid. The filtrates then were acidified with 6 *N* hydrochloric acid. The precipitated product was removed by filtration, dried, dissolved in 95% ethanol and treated with charcoal. The mixture was heated to boiling and filtered. The solution was evaporated to a small volume and a small amount of water was added. The crystals separating were recrystallized by the same procedure. The yield of material decomposing at 275–280° was 2.7 g. (69%). This material gave a negative Kovac's test for indole.

*Anal.* Calc'd for $C_9H_6BrNO_2$: C, 45.03; H, 2.52; N, 5.84.
Found: C, 45.31; H, 2.32; N, 6.00.

*5-Cyanoindole* (VI). A mixture of 0.90 g. of 5-bromo-2-indolecarboxylic acid, 0.67 g. of cuprous cyanide, a small amount of potassium iodide and 10.5 g. of redistilled quinoline was maintained at reflux for 12 hours. The hot dark-brown solution was poured into a mixture of 10.0 ml. of concentrated hydrochloric acid and ice, and the well stirred mixture was filtered and the precipitate was discarded. The filtrate was extracted four times with 50-ml. portions of ether and the combined ether extracts were dried over sodium sulfate. Evaporation of the ether gave crude material which was dissolved with 95% ethanol and treated with charcoal at the boiling point of the solvent. The filtrate from the charcoal treatment was evaporated to a small volume and water was added to induce crystallization. On cooling, small needles appeared. The yield of material melting at 107–108°. was 0.184 g. (34%). This material gave a brilliant cherry-red color with Kovac's reagent. A mixture melting point of this material with 7-cyanoindole (m.p. 96°) was 63°.

*Anal.* Calc'd for $C_9H_6N_2$: C, 76.04; H, 4.25; N, 19.71.
Found: C, 75.50; H, 4.15; N, 19.88.

*5-Indolecarboxylic acid* (VII). 5-Cyanoindole (0.10 g.) was refluxed for 3 hours in 10 ml. of 10% aqueous potassium hydroxide in a test tube equipped with a cold finger. At the end of this time, the reaction mixture was boiled with charcoal, filtered, cooled and acidified. The precipitate was filtered, dissolved in 95% ethanol, and treated with charcoal in the boiling solvent. After filtration and evaporation to a small volume, water was added and the solution was re-evaporated to a small volume. On cooling, needles with a slight orange tinge formed. The yield of material was 0.055 g. (49%), melting at 208–209°. The compound was soluble in sodium hydroxide, insoluble in hydrochloric acid, and gave a brilliant cherry-red color with Kovac's reagent.

*Anal.* Calc'd for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69.
Found: C, 66.62; H, 4.42; N, 8.81.

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