175 ml. of heptane and 20 ml. of ethanol at 150° and 1900 p.s.i. using 10 g. of Raney nickel gave 23 g. (44%) of 1-methyl-4-phenylpiperidine (V), b.p. 114–119° (8 mm.) (lit.[6] b.p. 120–122° (10 mm.)); picrate, m.p. 239–240° (lit.[6] m.p. 239–240°).

Anal. Calcd. for $C_{18}H_{20}N_4O_7$: C, 53.46; H, 4.99; N, 13.86. Found: C, 53.46; H, 5.34; N, 13.90.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (VI).—A mixture of 191 g. (1.0 mole) of 1-methyl-4-phenyl-4-piperidinol (III), 144 g. (8.0 moles) of water and 150 g. (1.5 moles) of concentrated hydrochloric acid was stirred at 95° for 7 hr., allowed to stand overnight, poured into 500 ml. of water and made basic with excess 50% sodium hydroxide solution. The amine was taken up in toluene, dried and distilled to give 142 g. (82%) of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (VI), b.p. 85–105° (0.6 mm.). Redistillation gave a center cut of 56 g., b.p. 99–100° (1.3 mm.), which crystallized and melted at 40–42° after recrystallization from heptane.

Anal. Calcd. for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09. Found: C, 82.64; H, 8.64; N, 7.76.

The hydrochloride melted at 247–249° after recrystallization from acetone (lit.[7] m.p. 248–250°).

Anal. Calcd. for $C_{12}H_{16}NCl$: Cl, 16.9. Found: Cl, 16.8.

(6) F. Bergel, J. W. Haworth, A. L. Morrison and H. Rinderknecht, *J. Chem. Soc.*, 261 (1944).

(7) S. M. McElvain and J. C. Safranski, Jr., THIS JOURNAL, **72**, 3134 (1950).

PHILADELPHIA, PENNSYLVANIA

[FROM THE BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS, AND THE CLAYTON FOUNDATION FOR RESEARCH]

Synthesis of 7-Indolecarboxylic Acid[1]

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3-Chloro-2-nitrotoluene (VI) was condensed with diethyl oxalate in the presence of potassium ethoxide, and the product was hydrolyzed to form 3-chloro-2-nitrophenylpyruvic acid (VIII). Reductive cyclization of this compound with ferrous sulfate in dilute ammonium hydroxide yielded 7-chloro-2-indolecarboxylic acid (IX). Conversion of IX to 7-cyanoindole (X) was accomplished by means of cuprous cyanide in quinoline. Hydrolysis of the nitrile led to the desired product, 7-indolecarboxylic acid (XI). 7-Indolecarboxylic acid is inactive in replacing anthranilic acid in supporting growth of *Lactobacillus arabinosus* 17-5 and mutant strains of *Neurospora* requiring anthranilic acid or indole for growth.

The inhibitory effect of 5-methyltryptophan on growth of *Lactobacillus plantarum* 8293 is prevented competitively by anthranilic acid, but both indole and tryptophan at relatively low concentrations reverse the toxicity of the methyltryptophan non-competitively.[3] Among possible explanations for these results, including the possibility that 5-methyltryptophan inhibits the conversion of anthranilic acid to indole, one alternative explanation was considered in which the biological conversion of anthranilic acid to tryptophan might have been preceded by intermediate formation of 7-indolecarboxylic acid and 7-carboxytryptophan, the decarboxylation of which might have been inhibited by 5-methyltryptophan. The carboxyl group of anthranilic acid is known to be lost during its biological conversion to tryptophan.[4] Accordingly, 7-indolecarboxylic acid was synthesized in the present investigation but was found to be inactive in replacing anthranilic acid or indole in supporting growth of several organisms.

Several procedures including the Fischer method were unsuccessful in preparation of indoles from *o*-substituted anilines such as anthranilonitrile; however, the Reissert method of cyclization was successful with 3-chloro-2-nitrophenylpyruvic acid which could be converted to 7-chloro-2-indolecarboxylic acid and finally to 7-cyanoindole and 7-indolecarboxylic acid by a sequence of reactions analogous to the steps used in the synthesis of 4-indolecarboxylic acid by Uhle[5] and 6-indolecarboxylic acid by Kermack.[6] The various reactions including the preparation of 3-chloro-2-nitrophenylpyruvic acid as well as its conversion to 7-indolecarboxylic acid were carried out in the sequence as indicated.

To prepare the appropriate intermediates, sodium 4-amino-*m*-toluenesulfonate (I) was converted to the 2-amino-3-chlorotoluene (V) by acetylation, chlorination and hydrolysis of the acetylsulfonic acid groups as indicated by the sequence of compounds I to V[7]; and the aminochlorotoluene was converted by diazotization and replacement reactions to 3-chloro-2-nitrotoluene (VI) as previously reported.[8]

The condensation of 3-chloro-2-nitrotoluene (VI) with diethyl oxalate to form 3-chloro-2-nitrophenylpyruvic acid (VII) was effected by a procedure similar to that reported for the conversion of 2-nitro-4-(1-pentenyl)-toluene to 2-nitro-4-(1-pentenyl)-phenylpyruvic acid.[9] Ring closure of the chloronitrophenylpyruvate (VII) was accomplished by the standard procedure of reductive cyclization with ferrous sulfate in dilute ammonium hydroxide, and the resulting 7-chloro-2-indolecarboxylic acid

(1) From part of a thesis submitted by Herbert Singer to the Graduate School, The University of Texas, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1955.

(2) Rosalie B. Hite Fellow, 1954–1955.

(3) E. Beerstecher, Jr., and W. Shive, unpublished work; E. Beerstecher, Jr., Ph.D. Thesis, University of Texas, June, 1948.

(4) J. F. Nyc, *J. Biol. Chem.*, **179**, 783 (1949).

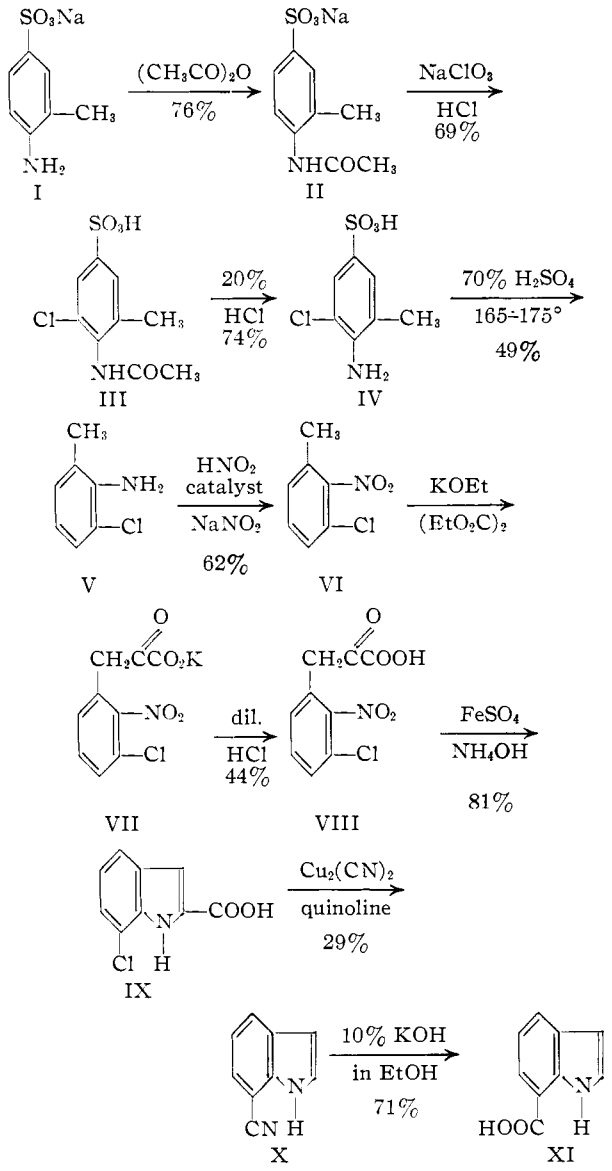
(5) F. C. Uhle, THIS JOURNAL, **71**, 761 (1949).

(6) W. O. Kermack, *J. Chem. Soc.*, **125**, 2285 (1924).

(7) An indication that 2-amino-3-chlorotoluene could be prepared as indicated appeared in early patent literature but preparative procedures and properties of the compounds were not reported (German Patent 217,370, Jan. 10, 1911; *Frdl.*, **10**, 932 (1910)).

(8) This conversion has been previously reported in patent literature (A. Sieglitz and K. Steger (to I. G. Farbenind. A-G) German Patent 638,486, Oct. 26, 1936; *Frdl.*, **23**, 191 (1940), but the product was characterized only by boiling point under reduced pressure and no analytical data was reported. Other methods of synthesis of 3-chloro-2-nitrotoluene have been reported (K. Brand and H. Zoller, *Ber.*, **40**, 3324 (1907); J. B. Cohen and H. J. Hodsman, *J. Chem. Soc.*, **91**, 970 (1907); L. A. Elson, C. S. Gibson and J. D. A. Johnson, *ibid.*, 2735 (1929); J. P. Wibaut, *Rec. trav. chim.*, **32**, 292 (1913); H. Burton and J. Kenner, *J. Chem. Soc.*, **119**, 1052 (1921)).

(9) H. R. Snyder and H. R. Beilfuss, THIS JOURNAL, **75**, 4921 (1953).



(IX) was heated with cuprous cyanide to replace the chloro by a cyano group and remove the carboxyl group. The specificity of introduction of the cyano group into the position occupied by a halogen has been demonstrated previously.[5,10] Hydrolysis of the resulting 7-cyanoindole (X) gave the desired 7-indolecarboxylic acid (XI) which melted at 198–199° in contrast to the melting points of the two other known benzene-substituted indolecarboxylic acids, 4-indolecarboxylic acid (213–214°)[5] and 6-indolecarboxylic acid (243–244°).[6]

An ascending chromatogram of 7-indolecarboxylic acid using a mixture of isopropyl alcohol (8 parts), concentrated ammonia (1 part) and water (1 part) as a solvent gave an R_f value of 0.61. Sprayed with Ehrlich reagent (2% soln. of *p*-dimethylaminobenzaldehyde in 1.2 *N* hydrochloric acid) a spot of 7-indolecarboxylic acid on paper chromatographs gave a characteristic pink colored product. Paper chromatographs of products elaborated in the media of various mutant strains of *Neurospora* requiring indole or tryptophan for growth did not show any detectable amounts of this compound; also, 7-indolecarboxylic acid did not replace anthranilic acid in promoting growth of *Lactobacillus arabinosus* 17-5 and did not have growth-promoting activity for mutant strains of *Neurospora* requiring anthranilic acid or indole for growth. Thus, the conversion of anthranilic acid to indole does not appear to involve initial formation of the indole ring with subsequent loss of the carboxyl unless conjugated intermediates are involved. Since this work was completed an analog of anthranilic acid, 4-methylanthranilic acid, has been shown[11] to give 6-methylindole in an *E. coli* auxotroph indicating that the point of closure of the indole ring is the position of the carboxyl which is lost in the process.[4]

(10) Braun, U. S. Dept. of Commerce, Office of Technical Services, PB 626 (1946).

Experimental[12,13]

4-Acetamido-*m*-toluenesulfonic Acid (Sodium Salt).—4-Amino-*m*-toluenesulfonic acid (sodium salt, Eastman Kodak Co. technical), 90 g., was dissolved in 300 ml. of water and treated with charcoal at 100° for a few minutes. The solution was filtered and cooled to 50°. Acetic anhydride, 51 g., was added rapidly to the well-stirred solution so that the temperature did not rise above 65° during the addition of the anhydride. After standing for 1 hour at 50°, the solution was evaporated to near dryness on a water-bath. The solid precipitating from the concentrated solution was filtered and dried in a büchner funnel and then washed with small amounts of absolute alcohol and air-dried. The yield of crude acetylated material was 82 g. (76% of the theoretical yield).

4-Acetamido-5-chloro-*m*-toluenesulfonic Acid.—The acetylated salt, 50 g., was dissolved in 200 ml. of water and warmed to dissolve all the material. To this solution, 180 ml. of concentrated hydrochloric acid was added with rapid stirring. The temperature of the solution was regulated to exactly 40°, with addition of approximately 50 ml. of water. A solution of 8.4 g. of sodium chlorate in 30 ml. of water was added dropwise. The temperature rose to 45–47° but was not allowed to go higher. With the complete addition of the chlorate solution, the solution was stirred for two hours longer during which time a white crystalline material precipitated. The mixture was kept overnight in the refrigerator and then filtered. The crystals dried at 90–100° amounted to 36 g. (69%). For analysis, the product was decolorized with charcoal in boiling water and recrystallized by concentrating the solution to a small volume and passing hydrogen chloride into the solution. The white crystals were filtered on a sintered glass filter and dried in a vacuum desiccator. This dihydrate was dried at 130° for 3 hours to give the anhydrous material which did not melt up to 300°.

Anal. Calcd. for $C_9H_{10}ClNO_4S$: C, 40.99; H, 3.82; N, 5.31; neut. equiv., 263.7. Found: C, 40.90; H, 4.16; N, 5.65; neut. equiv., dihydrate, 300.0; anhydrous, 263.1.

4-Amino-5-chloro-*m*-toluenesulfonic Acid.—To 400 ml. of 20% hydrochloric acid was added 20 g. of 4-acetamido-5-chloro-*m*-toluenesulfonic acid. The solution was refluxed for three-quarters of an hour and then cooled to obtain a precipitate which after filtration and drying at 90–100° amounted to 12.5 g. (74.5%). Material for analysis was decolorized with charcoal in boiling water, and the solution was filtered and evaporated to a small volume. Long white needles which formed on standing at room temperature overnight were dried in a vacuum desiccator. The crystals, a monohydrate, gave on drying at 130° for 3 hours anhydrous material which did not melt up to 300°.

Anal. Calcd. for $C_7H_8ClNO_3S$: C, 37.93; H, 3.64; N, 6.32; neut. equiv., 221.7. Found: C, 38.09; H, 3.40;

(11) C. Yanofsky, *Science*, **121**, 138 (1955).

(12) All melting points are corrected.

(13) Microanalyses by J. Russell Claybrook, Alice Brown, Richard Thompson and Ted Brooks.

N, 6.49; neut. equiv., monohydrate, 239.0; anhydrous, 221.0.

2-Amino-3-chlorotoluene.—In a 3-necked 200-ml. flask, equipped with an exit tube for a condenser and an entrance tube for steam, 25 g. of 4-amino-5-chloro-*m*-toluenesulfonic acid and 125 ml. of 70% sulfuric acid was heated in an oil-bath. When the temperature of the material in the flask reached 175°, steam was passed cautiously into this mixture, and the reaction mixture was maintained at 170° for 24 hours. At the end of this time, the solution was cooled and poured into water. The resulting solution was neutralized with sodium carbonate until it was basic to litmus, and the reaction product was then steam distilled. To the distillate was added 25 g. of sodium chloride per each 100 ml. of distillate, and the solution extracted with four 50-ml. portions of ether. The combined ether extracts were dried over sodium sulfate. The ether was removed by distillation and the residue was fractionally distilled under reduced pressure to obtain the product boiling at 96.9° (10 mm.), $n^{25}D$ 1.5755. The yield amounted to 7.8 g. (49%).

Anal. Calcd. for C_7H_8ClN: C, 59.37; H, 5.69; N, 9.89; MR_D, 40.09. Found: C, 58.93; H, 5.63; N, 10.20; MR_D, 39.93.

2-Acetamido-3-chlorotoluene.—To two drops of 2-amino-3-chlorotoluene was added 7 drops of acetic anhydride and the mixture heated for 5 minutes. The reaction mixture was cooled and diluted with 3 ml. of water. The derivative crystallized upon cooling and melted at 163°. Bamberger[14] reports a melting point of 165° and Silvester and Wynne[15] report 163° for this product.

3-Chloro-2-nitrotoluene.—Cupric acetate·H_2O, 77 g., was dissolved in a liter of water at 85°. Sulfur dioxide was passed into the solution with stirring for 45 minutes at a temperature of 85°. The solution containing the dark red precipitate was allowed to cool, and the precipitate of cupro-cupric sulfite[16] was filtered and air-dried.

To 93 ml. of water was added 12 g. of concentrated sulfuric acid and 16.5 g. of 2-amino-3-chlorotoluene. The reaction mixture was cooled to 0° and with stirring was treated with an aqueous solution of 9 g. of sodium nitrite. The diazonium solution 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. The mixture was stirred for 2 hours at room temperature and then steam distilled. The product separated as an oil which solidified on standing in a refrigerator overnight. The water was decanted, and the solid material was dissolved in ether and dried over sodium sulfate. Fractional distillation gave material boiling at 107–108° (9.5 mm.), $n^{25}D$ 1.5382. The yield amounted to 12.35 g. (61.7%).

Anal. Calcd. for $C_7H_6ClNO_2$: C, 49.00; H, 3.52; N, 8.16; MR_D, 41.99. Found: C, 49.19; H, 3.32; N, 8.45; MR_D, 41.67.

3-Chloro-2-nitrophenylpyruvic Acid.—To a well-stirred mixture of 30 ml. of anhydrous benzene and 2 g. of potassium, 6 ml. of absolute alcohol was added slowly. When the potassium had reacted completely, the excess solvents were removed by distillation. After the addition of 60 ml. of absolute ether and 7.3 g. of diethyl oxalate to the potassium ethoxide, 8.6 g. of 3-chloro-2-nitrotoluene was added dropwise. The reaction mixture was stirred and refluxed. After 4 hours, a red salt began to precipitate on the walls and bottom of the flask and, after 20 hours, the potassium salt was collected by filtration, extracted with absolute ether and dissolved in 160 ml. of water. The ether was washed with three 20-ml. portions of water and combined with the aqueous solution of the solid. The combined aqueous solutions were heated to approximately 70° for 3 to 5 minutes, cooled and extracted twice with ether and the ether added to the ether extract of the original solid in order to recover starting material. To obtain the product, concentrated hydrochloric acid was then added to the aqueous solution to give a 2% acid concentration. The substituted phenylpyruvic acid was extracted from the acidic solution with ether. The ether extract was washed with water and dried over sodium sulfate. Removal of the ether on a steam-bath gave the solid product which was purified by leaching several times with warm chloroform. The chloroform solution contained some of the product along with impurities. The yield of purified material (pale yellow crystals) was 4 g. (44%), m.p. 161–162°. This material gives a deep, blood-red color in normal sodium hydroxide and gives a deep green color with aqueous ferric chloride.

Recovery of the reactant from the ether filtrates was accomplished by extraction of the ether solution with 1 *N* sodium hydroxide until the red color was no longer extractable. The ether solution was dried over sodium sulfate, and excess ether removed on a steam-bath. The starting material was recovered to the extent of 2.2 g. (crude). In order to re-use this material it was steam distilled.

Anal. Calcd. for $C_9H_6ClNO_5$: C, 44.37; H, 2.48; N, 5.75; neut. equiv., 243.6. Found: C, 44.39; H, 2.21; N, 6.03; neut. equiv., 244.0.

7-Chloro-2-indolecarboxylic Acid.—A solution of 4. g. of 3-chloro-2-nitrophenylpyruvic acid in 5% ammonium hydroxide was added to a suspension of ferrous hydroxide prepared from 31.2 g. of $FeSO_4·7H_2O$ and 13 ml. of concentrated ammonium hydroxide in 114 ml. of water, and the mixture was maintained at the boiling point for 10 minutes. Ferric hydroxide (chocolate brown) was separated by filtration, washed with 5% ammonium hydroxide until an aliquot no longer gave a precipitate on addition of 6 *N* hydrochloric acid. The filtrate and washings were then acidified with 6 *N* hydrochloric acid. The precipitate was filtered, dried, treated in boiling 95% ethanol with charcoal. The filtrate from the charcoal treatment was evaporated to a small volume and water was added. White needles precipitated. Recrystallization for alcohol–water gave 2.6 g. (81%) of material melting at 236–238°. This material gave a negative Kovac test for indole (Ehrlich reagent using isoamyl alcohol as solvent).

Anal. Calcd. for $C_9H_6ClNO_2$: C, 55.26; H, 3.09; N, 7.16; neut. equiv., 196.6. Found: C, 55.28; H, 2.88; N, 7.47; neut. equiv., 195.5.

7-Cyanoindole.—A mixture of 0.750 g. of 7-chloro-2-indolecarboxylic acid, 0.67 g. of cuprous cyanide, a small amount of potassium iodide and 7.0 g. of redistilled quinoline was maintained at reflux for 12 hours. The hot dark brown solution was poured with stirring into a mixture of 5 ml. of concentrated hydrochloric acid and ice. The precipitate was removed by filtration and washed with water. The product in the filtrates was obtained by extractions with ether. The combined ether extracts were washed with dilute hydrochloric acid and then with water. The ether solutions were dried over sodium sulfate and then evaporated to obtain crystalline material. The crystalline material was decolorized with charcoal in boiling 95% ethanol. The ethanol solution was then evaporated to a small volume and water added. On cooling, white silky needles appeared. These were finally recrystalllized from hot water. Yield of material melting at 96° was 0.158 g. (29%). This material gave a brilliant cherry red color with Kovac reagent.

Anal. Calcd. for $C_9H_6N_2$: C, 76.04; H, 4.25; N, 19.71. Found: C, 75.68; H, 4.32; N, 19.72.

7-Indolecarboxylic Acid.—7-Cyanoindole, 42 mg., was dissolved in 5 ml. of 10% ethanolic potassium hydroxide (95% ethanol). A small amount of water was added to the mixture which was refluxed for 24 hours. At the end of this time, the solution was evaporated to remove alcohol and a small amount of water was added. The solution was then acidified with dilute hydrochloric acid. Upon standing in the refrigerator, the solution gave an orange-yellow precipitate. The precipitate was dissolved in ethanol and decolorized with charcoal. Evaporation of the alcohol and recrystallization from dilute ethanol gave on standing overnight in a refrigerator colorless crystals, 34 mg. (71%), melting at 198–199°. The product was soluble in sodium hydroxide, insoluble in hydrochloric acid and gave a brilliant cherry-red color with Kovac reagent.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.93; H, 4.17; N, 8.93.

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(14) E. Bamberger, *Ann.*, **443**, 205 (1925).

(15) W. A. Silvester and W. P. Wynne, *J. Chem. Soc.*, 691 (1936).

(16) Gmelin-Krant, *Handbuch der Anorganischen Chemie*, Auflage VII, Bd V, S825.