Hammett σ-values are shown as the lower limit and the "dual" σ-values (3) as the upper limit. A value in between these two limits would seem to correlate the μ values for these groups.

There appears to be no simple relation of dipole moments of disubstituted benzenes with Taft's resonance and inductive parameters (7). The limited amount of data available do not permit any definite conclusions to be drawn. Similar correlations of the ultraviolet absorption spectra of substituted benzenes with reactivities have been made (5). However, the use of Taft's resonance parameters seems to be of greater significance here (6).

ACKNOWLEDGMENT

The authors wish to thank Professor Herbert C. Brown, Department of Chemistry, Purdue University, for his interest and encouragement.

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Received July 17, 1957.
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SYNTHESIS OF INDOLEACETIC ACIDS[1]

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In cold-run studies leading to a semimicro synthesis of 3-indoleacetic acid-C^{14} labeled in the benzene ring, the reaction sequence illustrated on the following page was investigated.

The method closely parallels that of Feofilaktov and Semenova (1, 2). Unfortunately, owing to the rather limited abstract information available to us, we were unable to confirm the excellent yields reported by the Russian workers. Only with several modifications were we able to obtain 3-indoleacetic acid in an over-all yield of 40% from aniline. These modifications, listed below, may be of general interest in the field of indole-acid synthesis.

The cyclization medium (absolute ethanol saturated with hydrogen chloride) was modified to include about 5%, by weight, of polyphosphoric acid. This raised the boiling point and ensured an anhydrous medium.

The phenylhydrazone of 2-ketoglutaric acid (IV) (2, 3, 5) was substituted for that of ethyl 2-keto-4-cyanobutyrate (1, 4, 6), eliminating several transfers.

The half-ester (VII), of a type reported by King and L'Ecuyer (5), was found to be more amenable to decarboxylation than was the diacid (VI).

The use of red cuprous oxide instead of copper powder, with quinoline, effected a much smoother decarboxylation at a lower temperature.

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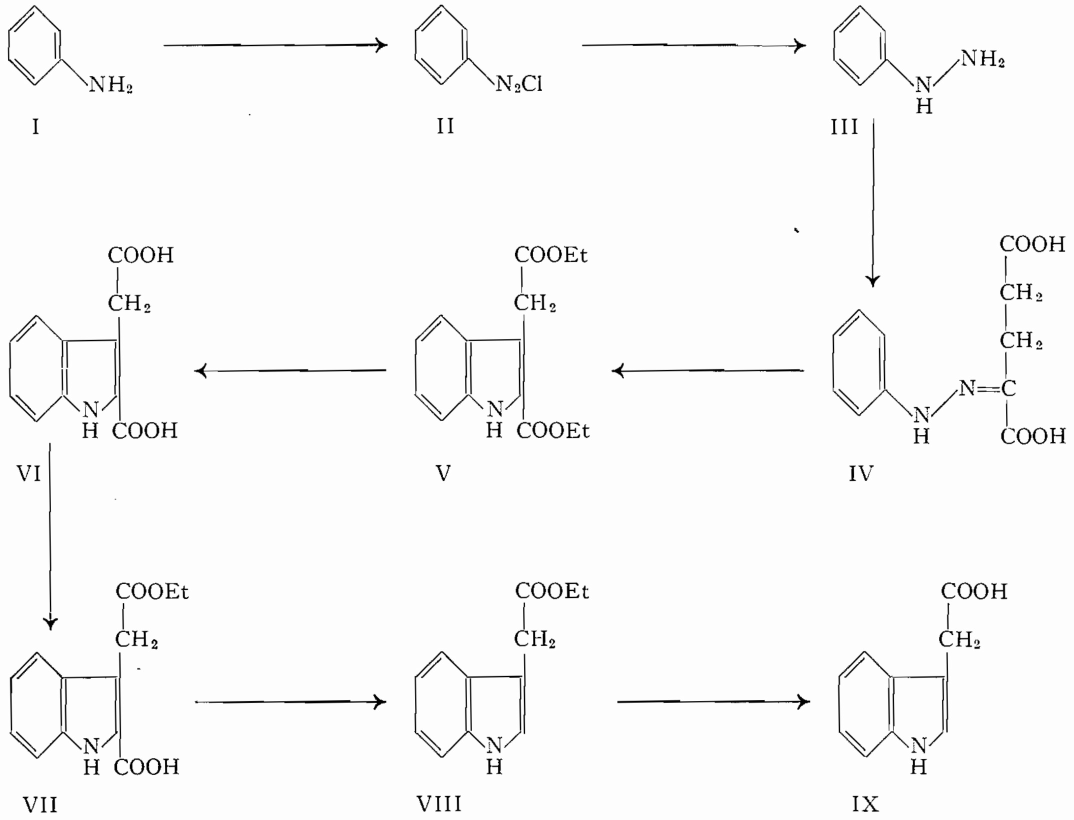
[1] *Issued as Paper No. 118, Science Service Laboratory.*



To aid in the extraction of the decarboxylated product (VIII) from the tarry residues, only 1 to 2 equivalents of quinoline was used, and the bulk of the decarboxylation medium consisted of diethylene glycol. This allowed the reaction mixture to be "quenched" in dilute HCl and extracted with ether, eliminating the necessity of a high vacuum distillation.

EXPERIMENTAL

Phenylhydrazine (III)

Using a weighed, 250 ml. (24/40) round-bottomed flask, 650 mg. (5 mM.) of aniline hydrochloride was dissolved in 15 ml. of 1 *M* HCl and diluted to 25 ml. with water. Diazotization was accomplished at 0° C. using 5 ml. of 1 *M* sodium nitrite. The cold diazonium salt solution was immediately treated with a freshly prepared solution of sodium bisulphite (prepared by saturating, with sulphur dioxide, a cooled solution of 960 mg. (24 mM.) of sodium hydroxide in 15 ml. of water) and warmed on the steam bath, under a watchglass, for 5 hours. Five milliliters of conc. HCl was then added dropwise and heating continued overnight, with a jet of dry nitrogen directed upon the surface of the solution to remove the water and dissolved gases.

2-Carboxy-3-indoleacetic Acid (VI)

The dry mixture of phenylhydrazine hydrochloride and sodium chloride was dissolved in 10 ml. of water and treated with 730 mg. (5 mM.) of 2-ketoglutaric acid dissolved in 5 ml. of water. The resulting clear solution was chilled in ice water with the formation of a yellow oil which crystallized when it was left standing overnight. The mother liquors were removed using a vacuum and "filter-stick" and, after being washed once with water, the yellow solid (IV) was dried *in vacuo* over calcium chloride. Weight, 1019 mg.; m.p. 158–159° with decomposition; yield 86% from aniline.

The cyclization medium consisted of 100 ml. of commercial "absolute" ethanol containing 5 g. of polyphosphoric acid and saturated, in the cold, with dry hydrogen chloride. This solution was poured on the dried phenylhydrazone, warmed to the boiling point, and again treated with HCl. The strongly acid solution was then heated under reflux for 3½ hours, with moisture excluded. The reflux condenser was then replaced by a still head and most of the ethanol was distilled away from the mixture. The residue, 20–30 ml., containing much precipitated ammonium chloride, was washed with stirring into 200 ml. of a crushed ice and water mixture and left standing overnight in the refrigerator. The resulting diester (V) was isolated by removal of the mother liquors with a filter-stick. After one washing with water the product was transferred, by means of a syringe pipette, with 25 ml. of 95% ethanol to a 60 ml. (19/22) round-bottomed flask. Potassium hydroxide (500 mg.) was added and the solution was warmed on the steam bath under a jet of nitrogen, keeping the volume constant by regular additions of water. When the alcohol was mostly replaced with water (3 hours), the flask was immersed in a boiling water bath and the evaporation continued for another hour. The aqueous solution was then cooled and, slowly with swirling, was acidified with phosphoric acid to pH 2. On standing overnight in the cold, the 2-carboxy-3-indoleacetic acid (VI) crystallized. The supernatant was removed with a filter-stick and the product washed once with cold water. It was dried thoroughly *in vacuo* over calcium chloride and weighed 700 mg. (64%, from aniline), and melted with decomposition at 235–236°.

Ethyl 2-Carboxy-3-indoleacetate (VII)

One milliliter of commercial "absolute" ethanol was cooled and saturated with dry hydrogen chloride. The solution was then diluted to 10 ml. with ethanol and poured on the dried diacid. The flask was stoppered and left at room temperature for 1 hour.

Two milliliters of concentrated ammonium hydroxide was diluted with water to 45 ml. This solution, cooled, was added all at once to the acidic, alcoholic solution of half-ester. The resulting clear, weakly alkaline solution was chilled in ice water and, while swirling, sufficient phosphoric acid was added dropwise to precipitate the half-ester at pH 2. After crystallization was complete the mother liquors were removed with a filter-stick and the product washed once with cold water. The flask and contents were dried *in vacuo* over calcium chloride. Wt. 765 mg. (62% from aniline), m.p. 175–176°.

Ethyl 3-Indoleacetate (VIII) and 3-Indoleacetic Acid (IX)

The half-ester (above) was dissolved in 12 ml. of diethylene glycol and the solution treated with 1 ml. of quinoline. Red cuprous oxide[2] (5–10 mg.) was added and the flask immersed in a hot oil bath. The bath temperature was raised rapidly to 200°, with stirring, and maintained there until vigorous gas evolution ceased (15 minutes). The mixture was then cooled and poured into 150 ml. of cold, dilute hydrochloric acid. The resulting mixture was extracted with ether, evaporated to an oil, and the latter taken up in 25 ml. of 95% ethanol and saponified with potassium hydroxide following the method outlined for the hydrolysis of the diester above.

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[2] *Prepared, with suitable particle size, by the action of glucose on hot Fehling's solution. The bright-red precipitate was washed three times with water, once with acetone, and dried. It may be kept indefinitely without losing its usefulness.*

The crude 3-indoleacetic acid was precipitated by acidification with phosphoric acid. It was isolated and sublimed at high vacuum. The yield was 350 mg. (40% from aniline), m.p. 169–170°.

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RECEIVED JULY 8, 1957.
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