[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Synthesis of Indole-3-acetic Acids and 2-Carboxyindole-3-acetic Acids with Substituents in the Benzene Ring[1]

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A number of indole-3-acetic acids with substituents in the benzene ring have been prepared by the Fischer cyclization of corresponding succinaldehydic acid phenylhydrazones which were in turn prepared by the sequence of reactions: glutamic acid → succinaldehydic acid → succinaldehydic acid phenylhydrazone. The 4- and 6-chloroindole-3-acetic acids have also been synthesized by condensation of the corresponding indolylmagnesium iodide complexes with chloroacetonitrile and subsequent hydrolysis of the nitriles to the acids. Several of the corresponding substituted 2-carboxyindole-3-acetic acids have been obtained by cyclization of the substituted α-ketoglutaric acid phenylhydrazones resulting either as by-products from the preparation of the succinaldehydic acid phenylhydrazones or, in the form of their diethyl esters, by the Japp–Klingemann reaction between ethyl α-acetoglutarate and a phenyldiazonium salt.

The substituted indole-3-acetic acids are worthy of investigation as possible indoleacetic acid antagonists and as more difficultly catabolizable analogs of the phytohormone. The chloro derivatives are of special interest since preliminary Pea tests[2,3] have shown that the 5-chloro substituted 2-methylindole-3-acetic acid is more active than 2-methylindole-3-acetic acid itself.[4] The structures involved originally invited investigation because of the fact that substituents which have proved so critical in the phenoxyacetic acid series[5] had not been reported as having been incorporated into indoleacetic acid itself. Since so many other potential plant hormones have been synthesized, it seems likely that the chloroindoleacetic acids have not been recorded for lack of a feasible method of synthesis. At least one unsuccessful attempt at preparation from appropriate intermediates has been recorded.[6]

The methods found in the literature up until the present time for the synthesis of indole-3-acetic acid are reviewed in another paper[7] and will not be detailed here. Several of these, however, are applicable to the synthesis of substituted indole-3-acetic acids. They depend mainly upon Fischer ring closure of the proper succinaldehydic acid phenylhydrazone[6,8–12] or introduction of the acetic acid residue into the preformed indole ring.[13–20]

Accessibility of the substituted indole-3-acetic acids has been improved by the availability of succinaldehydic acid from inexpensive glutamic acid.[7,21] The aldoacid is conveniently isolated from the reaction mixture as the substituted phenylhydrazone, which can be cyclized to the corresponding indole-3-acetic acid. Since the substituted phenylhydrazines are available in relative profusion, in contrast to the corresponding derivatives of indole, this method is particularly attractive in the preparation of the indole-3-acetic acids substituted in the benzene ring. By use of this procedure the 4- and 2-chloro- and 2,4-dichlorophenylhydrazones[4] have been prepared and cyclized to the corresponding 5-, 7- and 5,7-dichloroindole-3-acetic acids. The *p*-tolyl- and *m*-chlorophenylhydrazones have also been cyclized. Cyclization of succinaldehydic acid *m*-chlorophenylhydrazone would be expected to give a mixture of the 4- and 6-chloroindole-3-acetic acids. Two products were obtained as expected. The principal product was an eutectic mixture of the 4- and 6-isomers, while the other product was a small amount of the 6-chloroindole-3-acetic acid. The identity of these products was established by synthesis of the 4- and 6-chloro isomers by unambiguous methods.

Use was made of the second general method for synthesizing indole-3-acetic acids. 4-Chloroindole was prepared by the method of Uhle,[22] and the 6-chloro isomer by an adaptation of the same method. After an unsuccessful attempt at the preparation of the 4-chloroindole-3-acetic acid through the 4-chlorogramine and cyanide by the method worked out by Snyder and Pilgrim[19] for the preparation of indole-3-acetic acid, both the 4- and 6-chloroindole-3-acetic acids were successfully synthesized by the method of Majima and Hoshino.[15] The 4- and 6-chloroindolylmagnesium iodide complexes were condensed with chloroacetonitrile and the resulting nitriles hydrolyzed to the corresponding indole-3-acetic acids.

The 6-chloroindole-3-acetic acid thus prepared was identical with the 6-chloroindole-3-acetic acid obtained from the cyclization of the succinaldehydic acid *m*-chlorophenylhydrazone. The identity of the 6-isomer is thus established. The identity of the eutectic mixture obtained from the cyclization of the *m*-chlorophenylhydrazone was clarified by Dr. A. I. Snow of this Chemistry Department by comparison of the powder X-ray diffraction patterns

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TABLE I

MELTING POINTS AND ANALYSES OF α-KETOGLUTARIC ACID PHENYLHYDRAZONES

α-Ketoglutaric acid phenylhydrazone derivative	M.p., °C., dec.	Neut. equiv. Calcd.	Neut. equiv. Found	Analyses Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
m-Chloro	182	135.3	135			10.30	10.44, 10.28
o-Chloro	191	135.3	136	13.1	13.3, 12.7		
2,4-Dichloro	223–224	152.6	155	23.2	22.6, 23.0	9.17	9.16, 9.15

of the two components and of the eutectic mixture, which was shown to consist of the 4- and 6-chloroindole-3-acetic acids with the latter present in larger amount.

In addition to the succinaldehydic acid formed from glutamic acid there is also formed as a by-product a small amount of α-ketoglutaric acid.[7] The α-ketoglutaric acid phenylhydrazones are precipitated along with the desired product, and cyclization of these by-products gives the substituted 2-carboxyindole-3-acetic acids. Compounds of this latter type, incidentally, have been converted to the corresponding indole-3-acetic acids.[6] The α-ketoglutaric acid phenylhydrazones were also obtained as their diethyl esters by the Japp–Klingemann reaction between ethyl α-acetoglutarate and a phenyldiazonium salt. By use of either one or both sources for the preparation of the intermediate α-ketoglutaric acid phenylhydrazones, several of the 2-carboxyindole-3-acetic acids have been prepared. The 5- and 7-methyl, 7-chloro and 5-bromo derivatives have been prepared from the corresponding α-ketoglutaric acid phenylhydrazones. An attempt to prepare the 5,7-dichloro-2-carboxyindole-3-acetic acid by ring closure of the α-ketoglutaric acid 2,4-dichlorophenylhydrazone was not successful.

Experimental[23]

Preparation of the Succinaldehydic Acid Phenylhydrazones.—These compounds were prepared by the method described earlier.[4] The principal products were separated from the α-ketoglutaric acid phenylhydrazones by extraction in hot benzene in which the latter are generally insoluble. This method of separation was not satisfactory, however, for the *p*-tolyl derivative. No attempt was made to purify the succinaldehydic phenylhydrazones further except in the case of the *m*-chloro, *p*-chloro and *p*-tolyl derivatives for which descriptions in the literature have not been found. The general procedure is illustrated in the preparation of succinaldehydic acid *m*-chlorophenylhydrazone. The *p*-chloro and *p*-tolyl derivatives could not be crystallized and were not obtained in a satisfactory condition for analysis.

Succinaldehydic Acid *m*-Chlorophenylhydrazone.—To a solution of 29.4 g. (0.2 mole) of glutamic acid in 400 ml. of 0.5 *N* sodium hydroxide was added 0.2 mole of freshly prepared sodium hypochlorite in 208 ml. of solution. The solution was warmed to 50° on the steam-bath until a negative test was obtained with starch–iodide paper, and then acidified by the addition of 70 ml. of 3 *N* HCl. Carbon dioxide was evolved during the acidification. The solution was maintained at 50° until the solution gave a negative test with starch–iodide paper (10 minutes). A solution of 17.1 g. (0.12 mole) of *m*-chlorophenylhydrazine dissolved in 50 ml. of 25% acetic acid was added. A thick oil separated immediately. Fifty ml. more of 3 *N* HCl was added and the stirring continued for two hours while the reaction mixture was allowed to cool to room temperature. The oil was extracted with three 200-ml. portions of ether. The combined ether extracts were dried over sodium sulfate and distilled. All volatile solvents were distilled off on the steam-bath by reducing the pressure with a water aspirator. Extraction of the oil with 200 ml. of benzene left 2.3 g. (0.0085 mole, 4.2% from glutamic acid), of crude α-ketoglutaric acid *m*-chlorophenylhydrazone melting 174° (dec.). Two recrystallizations from a water–ethanol mixture gave 2.8 g. of the pure phenylhydrazone, m.p. 182° (dec.). The analysis and m.p.'s of this and other α-ketoglutaric acid phenylhydrazones which were obtained by this same general method are summarized in Table I.

Concentration of the benzene extract to 25 ml. gave 13.1 g. of crystals m.p. 105°. Further concentration gave 11.2 g. of an oil which did not crystallize. An attempt to recrystallize the product, melting at 105°, from benzene gave 0.5 g. of crude α-ketoglutaric acid *m*-chlorophenylhydrazone, m.p. 173° (dec.), and 9.4 g. of the desired product m.p. 101–102°. Two recrystallizations from a water–ethanol mixture did not raise the m.p. All attempts to crystallize the oil fraction were unsuccessful. The yield, including the crude oil which was successfully used in a cyclization reaction, was 24.4 g. (54% based on the glutamic acid used).

Anal. Calcd. for $C_{10}H_{11}O_2N_2Cl$: neut. equiv., 226.6; N, 12.34. Found: neut. equiv., 226.2; N, 12.41, 12.50.

Cyclization of the Succinaldehydic Acid Phenylhydrazones.—All cyclizations were carried out with ethanolic sulfuric acid. It proved necessary to purify, by distillation under reduced pressure, the crude esters from the cyclization reaction before the saponification step. In numerous instances, omission of this fractionation resulted in no recoverable end-product. The saponification was conducted with an ethanolic solution of sodium hydroxide containing just enough water to dissolve the base. This point of procedure was also critical, since it made possible a separation of the 2-carboxyindole-3-acetic acids from the indole-3-acetic acids; the 2-carboxy derivatives form insoluble disodium salts. The separation worked well for the unsubstituted 2-carboxyindole-3-acetic acid and the 5-methyl-2-carboxyindole-3-acetic acid, but poorly for the halogenated analogs. The general procedure is illustrated in the cyclization of succinaldehydic acid *p*-chlorophenylhydrazone and of the *m*-chlorophenylhydrazone. The m.p.'s and analyses of the various derivatives of indole-3-acetic acid which were prepared by cyclization of the succinaldehydic acid phenylhydrazones, or from the corresponding indole through their nitriles, are summarized in Table II.

Cyclization of Succinaldehydic Acid *p*-Chlorophenylhydrazone.—A solution of 11.3 g. (0.050 mole) of crude succinaldehydic acid *p*-chlorophenylhydrazone, 30 ml. of concd. sulfuric acid, and 270 ml. of absolute ethanol was refluxed in a nitrogen atmosphere for five hours. The cooled solution was poured into 600 ml. of water and the oil which separated was extracted with five 200-ml. portions of ether. The combined ether extracts were dried over sodium sulfate containing a small amount of potassium carbonate to neutralize any acid in the ether. Distillation of the ether and alcohol left 10.1 g. of a dark red oil. This was transferred to a short-path distillation apparatus, made from a large test tube, and distilled. The product came over rapidly at a bath temperature of 210–220° at 0.2 mm. The distillate was a yellow oil weighing 5.8 g. The distillate was saponified by refluxing one hour with 60 ml. of 10% methanolic potassium hydroxide. One hundred ml. of water was added and the methanol distilled off under reduced pressure. The aqueous solution was extracted with two 40-ml. portions of ether, and the extract was discarded. Acidification of the aqueous solution gave a red oil which crystallized to sticky brown plates. Washing with chloroform gave dry crystals with m.p. 156–158°, wt. 2.52 g. (24%). The product was recrystallized from water (Norit A). The acid separated in beautiful white needles, m.p. 158–159.5°, wt. 2.04 g. The yield of pure 5-chloroindole-3-acetic acid was 19½%.

(23) Nitrogen was determined by the micro Dumas method and chlorine by a Parr bomb fusion followed by a Volhard titration. Unless otherwise noted the neutral equivalents were determined by titration, with a Beckman *p*H meter, of the acids in a 50% methanol solution. All m.p.'s are corrected.

TABLE II

YIELDS, MELTING POINTS AND ANALYSES OF INDOLE-3-ACETIC ACIDS

Indole-3-acetic acid derivative	M.p., °C.	Yield, %	Analyses: Neut. equiv. Calcd.	Neut. equiv. Found	Nitrogen, % Calcd.	Nitrogen, % Found	
5-Chloro	158–159.5 dec.	20[a]	209.6	210–212[b]	6.69	6.84	6.72
7-Chloro	164–165 dec.	13[a]	209.6	205	6.69	6.84	6.39
5,7-Dichloro	194–197 dec.	9[a]	244.1	249	5.73	5.74	5.64
5-Methyl	151–152[c]	31[a]					
4-Chloro	185–187 dec.	19[d]	209.6	210.5	6.69	6.85	6.78
6-Chloro	187–188 dec.	26[d]	209.6	.....	6.69	6.54	6.59
4- and 6-chloro eutectic mixture	158–159 dec.	16[a]	209.6	211	6.69	6.50	6.78

[a] Based on the succinaldehydic acid phenylhydrazone used in the cyclization reaction. [b] Phenolphthalein indicator. [c] F. Kögl and D. F. G. R. Kostermans, *Z. physiol. Chem.*, **235**, 201 (1935). [d] Based on the substituted indole used for the preparation of the intermediate nitrile.

Cyclization of Succinaldehydic Acid *m*-Chlorophenylhydrazone.—A solution of 7.2 g. (0.0317 mole) of pure succinaldehydic acid *m*-chlorophenylhydrazone, 21 ml. of concd. sulfuric acid and 200 ml. of absolute ethanol was refluxed in a nitrogen atmosphere for six hours. The cooled solution was poured into 1 l. of water and the oil which separated was extracted with three 150-ml. portions of ether. The combined ether extracts were washed with half-saturated sodium bicarbonate solution and dried over sodium sulfate. Distillation of the ether and alcohol left a dark oil, which was transferred to a molecular still. The ester came over at 140–150° at 0.05 mm. The distillate, 3.5 g. of a yellow oil, was saponified by refluxing for 40 minutes with 25 ml. of 10% ethanolic sodium hydroxide solution containing just enough water to dissolve the base. The alkaline solution was diluted with 50 ml. of water and distilled until the temperature of the vapor reached 98°. The cooled solution was extracted with a small amount of ether which was discarded. The aqueous solution was shaken with 0.2 g. of Norit A and filtered. Acidification of the filtrate precipitated an oil which crystallized on standing several hours. The sticky crystals were filtered off and dried. Extraction of the product with 5 ml. of chloroform left 1.6 g. (24%) of acid melting 151–160°. The crude acid was treated with a small amount of hot benzene, and an insoluble fraction was filtered off. This acid, wt. 0.4 g., was recrystallized from water. The product separated in plates m.p. 185–186° (dec.). A mixed m.p. of this compound with an authentic sample of 6-chloroindole-3-acetic acid showed no depression. Concentration of the benzene gave crystals (plates of an eutectic mixture of the 4- and 6-chloroindole-3-acetic acids, m.p. 154–159° (dec.). The melting point of this mixture was not depressed by either the 4- or 6-chloroindole-3-acetic acids.

Cyclization of 10 g. of the oily fraction gave 1.1 g. of crude crystals melting 144–150°. This product was worked up as above and the mother liquors of the two cyclizations were combined and treated in the usual manner. The total combined yield of pure and eutectic mixture from the two cyclizations was 2.6 g. (16%).

4-Chloroindole.—This compound was prepared from 2-nitro-6-chlorotoluene by the method described by Uhle.[22] The physical constants of the product obtained after careful vacuum fractionation with a 13-plate column were slightly different from those reported by Uhle. The constants recorded for the sample of 4-chloroindole prepared in this Laboratory were: b.p. 150° at 13 mm., $n^{20}D$ 1.6286, and d^{20}_{20} 1.259.

Anal. Calcd. for C_8H_6NCl: MR_D 42.4; Cl, 23.40. Found: MR_D 42.7; Cl, 23.25, 23.25.

4-Chlorogramine.—A solution of 8.0 g. (0.0528 mole) of 4-chloroindole, 4.3 g. (0.0515 mole) of 36% aqueous formaldehyde, 9.3 g. (0.0515 mole) of 25% aqueous dimethylamine, and 26 ml. of acetic acid was left standing at room temperature overnight. The acetic acid was distilled under diminished pressure. A small amount of tar separated when the solution was diluted with 75 ml. of water. The solution was decanted from the tar, shaken with 1 g. of Norit A. Alkalization of the filtrate with 1 *N* sodium hydroxide gave a white curdy precipitate which changed to a beautiful white crystalline solid on standing in the ice-box. These crystals were filtered off, washed with water and dried; yield 8.4 g. (78%, based on formaldehyde) of product m.p. 144–147°. A small amount was purified by recrystallization from acetone for analysis. The product melted 147–148.5° after the first and second recrystallizations. The m.p. varied slightly with the rate of heating. When heating was fairly rapid the m.p. was raised to 150–151°.

Anal. Calcd. for $C_{11}H_{13}N_2Cl$: Cl, 17.0. Found: Cl, 17.1, 17.1.

An attempt to convert the 4-chlorogramine to the 4-chloroindole-3-acetic acid by treatment with cyanide by the procedure described by Snyder and Pilgrim[19] for the preparation of indole-3-acetic acid from gramine gave only a small amount of crude acid. This could not readily be purified. A large amount of unidentified high melting solid, that could not be hydrolyzed to an acid, was also obtained.

6-Chloroindole-2-carboxylic Acid.—This intermediate was prepared from 2-nitro-4-chlorotoluene by the same sequence of reactions as used for the preparation of the 4-chloro isomer.[22] The yields were similar. The crude acid filtered from the reaction mixture melted 240–241° (dec.). Two recrystallizations from a water–ethanol mixture gave pure 6-chloroindole-2-carboxylic acid melting 242–244° (dec.).

Anal. Calcd. for $C_9H_6O_2NCl$: neut. equiv., 195.5; Cl, 18.15. Found: neut. equiv. (phenolphthalein indicator), 191.5, 193; Cl, 17.81, 17.80.

6-Chloroindole.—Five grams of cuprous chloride was dissolved in 60 ml. of technical grade quinoline and approximately 1 ml. of quinoline was distilled to remove all traces of water. After the solution had cooled to about 150°, 8.8 g. (0.045 mole) of 6-chloroindole-2-carboxylic acid was added. The flask was connected through a reflux condenser to a bubble counter and heated slowly in a Woods metal-bath until decarboxylation began. The evolution of CO_2 commenced at about 200°, but the bath temperature was maintained at 240° until the evolution of gas had ceased (3 hours). The solution was cooled and triturated with ether. Water was added and the mixture shaken vigorously. A large amount of solid was filtered off and washed alternately with dilute hydrochloric acid and ether. The ether–water mixture was made acid to congo red with concd. hydrochloric acid and the ether layer separated. The ether solution was washed twice with water and once with half-saturated sodium bicarbonate. After the ether solution had been dried over sodium sulfate and distilled there remained 7.2 g. of a black oil which solidified on cooling. The crude product was purified by vacuum distillation through a short Vigreux column. After 1 g. of forerun the product distilled at 90° at 0.3 mm. This gave 5.0 g. (73.5%) of crystals melting 83–86°. The m.p. of pure 6-chloroindole is 89–90°,[24] but this product was found to be suitable for the next synthesis.

6-Chloroindole-3-acetic Acid.—A solution of ethylmagnesium iodide was prepared in the conventional manner. To a solution of 5 g. (0.033 mole) of 6-chloroindole in 25 ml. of sodium-dried ether was added 35 ml. (0.033 mole) of the Grignard solution. The addition was carried out with cooling in an ice-bath and the solution was stirred at this temperature for one hour. A solution of 2.8 g. (0.037 mole) of chloroacetonitrile in 25 ml. of ether was added dropwise at the same temperature. The solution was stirred at 0° for 30 minutes and then at reflux temperature for 4 hours. The liquid was cooled in an ice-bath and a cold solution of 3 ml. of acetic acid in 50 ml. of water was

(24) H. N. Rydon and C. A. Long, *Nature*, **164**, 575 (1949).

added. Fifty ml. of benzene was added and the reaction mixture left standing overnight. The ether–benzene layer was separated and the water layer extracted with two 50-ml. portions of benzene. An estimated 1 g. of material which did not dissolve in either layer was discarded. The combined benzene–ether extracts were dried over sodium sulfate and distilled. The black viscous residue was transferred to a 50-ml. flask and vacuum distilled through a short vacuum-jacketed Claisen still head. Two grams of black oil distilled 160–180° at 0.2 mm. The distillate was saponified by refluxing 4 hours with 10 ml. of methanol and 20 ml. of 20% aqueous potassium hydroxide. The basic solution was triturated with 0.1 g. of Norit A and filtered through a layer of diatomaceous earth. The filtrate was extracted with two 40-ml. portions of ether which were discarded. Acidification of the aqueous layer with concd. hydrochloric acid gave a crystalline product (plates). The crystals were filtered off, washed copiously with water and air-dried. This gave 1.8 g. (26%) of acid melting 185–186° (dec.). One recrystallization from 300 ml. of water (Norit A) raised the m.p. to 187–188° (dec.).

Preparation of the 2-Carboxyindole-3-acetic Acids.—The 2-carboxyindole-3-acetic acids were prepared by cyclization of the α-ketoglutaric acid phenylhydrazones obtained as by-products from the preparation of the succinaldehydic acid phenylhydrazones or by cyclization of the crude esters obtained from ethyl α-acetoglutarate and a phenyldiazonium salt by the Japp–Klingemann reaction. The preparation of the 7-chloro and 5-bromo derivatives will suffice to illustrate both procedures. The results of other runs are summarized in Table III.

TABLE III

YIELDS, MELTING POINTS AND ANALYSES OF 2-CARBOXYINDOLE-3-ACETIC ACIDS

2-Carboxyindole-3-acetic acid derivative	M.p., °C., dec.	Yield, %	Neut. equiv. Calcd.	Neut. equiv. Found	Nitrogen, % Calcd.	Nitrogen, % Found
7-Chloro	253	31[a]	126.8	125	5.54	5.56, 5.72
5-Methyl	243	..[b]	116.6	117	6.01	6.01, 6.39, 5.83
7-Methyl	228-229	6[c]	116.6	113	6.01	6.1, 5.95
5-Bromo	247-248	13[c]	149.0	150, 152	4.69	4.48, 4.48

[a] Based on the α-ketoglutaric acid phenylhydrazone used in the cyclization reaction. [b] The acid was isolated from crude 5-methylindole-3-acetic acid after cyclization of crude succinaldehydic acid *p*-tolylhydrazone. [c] Based on the ethyl α-acetoglutarate used in the Japp–Klingemann reaction for the preparation of the ethyl α-ketoglutarate phenylhydrazone which was used in the cyclization reaction without purification.

7-Chloro-2-carboxyindole-3-acetic Acid.—One gram (0.0037 mole) of α-ketoglutaric acid *p*-chlorophenylhydrazone was refluxed 2.5 hours with 15 ml. of absolute ethanol and 3 ml. of concd. sulfuric acid. The cooled reaction mixture was poured into 50 ml. of water and the milky solution extracted with three 25-ml. portions of ether. The combined ether extracts were washed with half-saturated sodium bicarbonate solution and with water. Distillation of the wet ether extracts left a small amount of a dark oil, which was saponified by refluxing 30 minutes with a 15% ethanolic sodium hydroxide solution containing a small amount of water. Very little solid separated during the refluxing, but on standing overnight the disodium salt separated in plates. These were filtered off and washed copiously with ethanol. The salt was dissolved in water, treated with 0.2 g. of Norit A and filtered. Acidification of the filtrate gave 0.3 g. (31%) of crystals, m.p. 255° (dec.). A recrystallization from a water–ethanol mixture raised the m.p. to 256° (dec.). A second recrystallization from aqueous acetic acid did not raise the m.p. further. Neither solvent pair could be considered satisfactory as most of the solvent had to be distilled off to recover the acid in either case.

5-Bromo-2-carboxyindole-3-acetic Acid.—Ten grams (0.0435 mole) of ethyl α-acetoglutarate was dissolved in 42 ml. of 95% ethanol. The solution was cooled to −20° and 31 ml. of cold aqueous 20% sodium hydroxide was added. Immediately a solution of *p*-bromophenyldiazonium chloride, prepared from 8.6 g. (0.05 mole) of *p*-bromoaniline, 3.5 g. (0.05 mole) of sodium nitrite, 35 ml. of water and 12.5 ml. of concd. hydrochloric acid, was added. A yellow oil separated immediately. The suspension was stirred for five minutes and acidified by the addition of 25 ml. of concd. hydrochloric acid. The oil changed to bright red in color but showed no tendency to crystallize. The oil was extracted with 100 ml. of ether after the solution had been diluted with 200 ml. of water. Distillation of the wet ether extract left a dark oil which was used, without purification, in the cyclization reaction.

The crude ethyl α-ketoglutaric acid *p*-bromophenylhydrazone was refluxed for 5 hours in a nitrogen atmosphere with a solution of 20 ml. of concd. sulfuric acid in 180 ml. of absolute ethanol. The cooled solution was poured into 350 ml. of ice-water and the oil which separated was extracted with 150- and 75-ml. portions of ether. The combined ether extracts were washed with half-saturated sodium bicarbonate and distilled. After all the volatile solvents had been removed there remained 12.9 g. of a viscous red oil. The crude ester was saponified by refluxing 45 minutes with 60 ml. of a 10% ethanolic sodium hydroxide solution containing a small amount of water. After the solution had cooled the insoluble disodium salt was filtered off and washed copiously with absolute ethanol to remove a red color. The salt was dissolved in 50 ml. of water, boiled with 0.3 g. of Norit A and filtered. Acidification of the filtrate with 10% hydrochloric acid gave 5.6 g. of yellow crystals melting 157–165° (dec.). By concentration and acidification of the mother liquor from which the disodium salt was filtered 1.3 g. of crystals melting 211–216° (dec.) was obtained. After an unsuccessful attempt to recrystallize the crude products from an ethanol–water mixture the acid was precipitated as the disodium salt by dissolving in 40% sodium hydroxide and diluting the solution with absolute ethanol. The free acid was recovered from the salt as before. The acid was separated from a tarry contaminant by extracting the acid in a Soxhlet extractor overnight with water. The acid separated from the aqueous solution in beautiful needles when seeded. The crystals were filtered off, dried and washed with chloroform to remove a red color. This gave 1.7 g. (13%), of 5-bromo-2-carboxyindole-3-acetic acid melting 247–248° (dec.). A recrystallization from a dioxane–water mixture did not raise the m.p.

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