[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PRINCETON UNIVERSITY]

THE SYNTHESIS OF CERTAIN SUBSTITUTED INDOLEACETIC ACIDS[1]

STEPHEN P. FINDLAY AND GREGG DOUGHERTY

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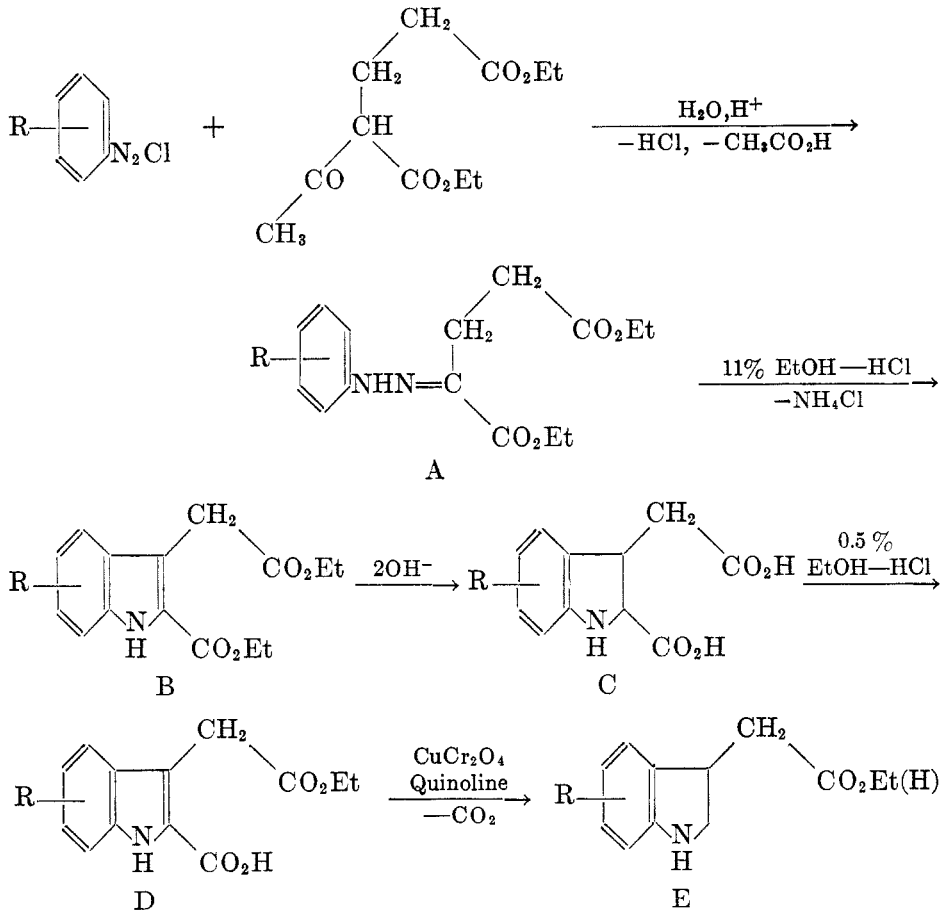
In connection with a study of the relation of structure to the plant growth regulating properties of organic compounds, several 3-indoleacetic acids substituted in the benzene ring have been prepared. The synthesis involved the application of the Japp-Klingemann reaction (1) for the formation of phenylhydrazones, the Fischer synthesis (2) for ring closure followed by hydrolysis of a diester, reesterification to a half ester, and decarboxylation.



R = OCH_3 or C_4H_4

[1] Abstracted from a dissertation submitted by Stephen P. Findlay to the Department of Chemistry, Princeton University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Through C, the scheme is essentially that employed by Manske and Robinson (3) to prepare β-(3-indolyl) propionic acid.

King and L'Ecuyer (4) and Tanaka (5) applied it to the preparation of unsubstituted indoleacetic acid, but the sequence in its entirety has not heretofore been applied to the rather sensitive and unstable nuclear substituted indole acids.

The compounds prepared were 5-, 6-, and 7-methoxyindoleacetic acids and 1- and 3-naphthazoleacetic acids. The 5-methoxy compound has been prepared previously by another method (6); the others do not appear in the literature and apparently have not been made before. In addition, the intermediate hydrazones necessary for the synthesis of 5,6-dimethoxyindoleacetic and three of the isomeric monochloroindoleacetic acids were obtained by the Japp-Klingemann reaction but some or all of the subsequent steps leading to the pure acids could not be carried out successfully.

Formation of the hydrazones. Although the formation of the hydrazones can take place under either acid or basic conditions, the monomethoxy compounds were obtained in higher yield in alkaline medium. The *o*-methoxy and ortho, meta, and para chlorophenylhydrazones of diethyl α-ketoglutarate were isolated as such; the others were used in the crude state for the subsequent cyclization process. It is worth noting that the hydrazones isolated were obtained initially as red or orange-red oils which could not be induced to crystallize. Treatment of the oils, however, with ethanolic hydrogen chloride produced the crystalline hydrazones accompanied by a distinct change of color. Furthermore, these crystals would not promote crystallization of the oils. This suggests that the initial step in the reaction was the formation of a diazo compound which was decomposed with rearrangement by strong acids.

The cyclization reaction. The literature contains accounts (7, 8) of the cyclization by alcoholic mineral acids of phenylhydrazones identical with or similar to some of those described here. In the cases of the methoxyphenylhydrazones the disposition has been to use 15–20% ethanolic HCl. It has been found in the present work that much better yields are obtained by the use of 8–11% acid. This concentration of acid was also sufficient to cyclize the naphthylhydrazones. On the other hand the conditions for cyclization of the chlorophenylhydrazones are considerably more vigorous than for most unsubstituted compounds. Ethanolic HCl alone or with zinc chloride had little effect. With *n*-butanolic mineral acids, cyclization occurred as indicated by the formation of ammonium salts, but no definite compounds could be isolated from the organic residue.

Miscellaneous observations. The indole diesters, B, with the exception of the 7-methoxy compound, were readily convertible to the corresponding diacid salts by refluxing with alcoholic alkali. The 7-methoxy compound was found to be unstable under the ordinary methods of saponification and was degraded largely to tarry material. However, the action of a dilute solution of potassium hydroxide in 99% ethanol at room temperature gave satisfactory results. The indole diacids were obtained as white microcrystalline substances which melted with decomposition above 200°.

The various indoleacetic acids were prepared by partial esterification of the corresponding 2-carboxy-3-indoleacetic acids, decarboxylation of the half ester so

obtained, and saponification. The decarboxylations proceeded rather smoothly in all cases but one, although, owing no doubt to the essential sensitivity of these compounds, the over-all yields were poor. The manner of preparation of the half esters, D, appears to exclude the possibility of obtaining 2-carboxyskatole as a final product. Indeed the 5- and 7-methoxy derivatives of 2-carboxyskatole are known and melt considerably higher than the isomeric indoleacetic acids. Where such isomers were also unknown, Ehrlich's reagent has been relied upon as a confirmatory diagnostic. It has been observed that when the 2-carboxyl group is removed, Ehrlich's reagent produces a color of heightened intensity (9).

EXPERIMENTAL

Copper-chromium oxide catalyst. This was prepared according to the directions of Connor, Folkers, and Adkins for the 39KAF modification using one-third quantities (10).

Ethyl β-bromopropionate. β-Bromopropionic acid was converted to the ethyl ester, b.p. 98°/49 mm., in 90% yield according to the directions of Kendall and McKenzie (11).

Ethyl α-acetoglutarate. Two moles (260 g.) of dry ethyl acetoacetate was added slowly to an ice-cold solution of sodium ethoxide made by dissolving one mole (23.0 g.) of sodium in 400 ml. of 99% ethanol. The mixture was warmed to 56–60° and 145 ml. (1.01 mole) of ethyl β-bromopropionate was added over a period of one and a half hours. The mixture was allowed to stand at room temperature for two days, refluxed for two hours on the steam-bath, cooled, and diluted with 200 ml. of dry ether. When most of the sodium bromide appeared to have separated it was removed and the ethanol, ether, and excess ethyl acetoacetate were fractionally distilled off and the product collected: 184 g. (80%), b.p. 140–142°/7 mm. The use of excess ethyl acetoacetate is a variation of procedures in the literature and had the effect of appreciably increasing the yield (12).

2-Carboxy-5-methoxy-3-indoleacetic acid. (a) *From the crude p-methoxyphenylhydrazone of diethyl α-ketoglutarate prepared in alkaline medium.* A diazonium chloride solution prepared from 2.5 g. of *p*-anisidine in 15 ml. of water was added to an ice-cold solution of 4.6 g. of diethyl α-acetoglutarate and 1.8 g. of sodium hydroxide in 33 ml. of 90% ethanol. The reaction mixture turned bright orange immediately, gradually deepened to blood red, and finally a red oil separated. After making slightly acid, the oil was extracted with ether and the extract washed with aqueous sodium chloride solution. The extract, dried several days over sodium sulfate, gave on removing the solvent a reddish brown oil which did not crystallize on standing.

Cyclization. The oil was taken up in 15 ml. of 11% ethanolic hydrogen chloride and refluxed gently thirty minutes on the steam-bath. Precipitation of ammonium chloride soon became noticeable. The mixture was cooled, poured into 50 ml. of water, and extracted with ether. After washing the extract with water and aqueous sodium bicarbonate, it was dried and the solvent removed.

Saponification. The residual oil was heated gently on the steam-bath for fifteen minutes with 1.6 g. of sodium hydroxide dissolved in 8 ml. of ethanol and 2 ml. of water. After dilution, the diacid was precipitated by acidification with 5 *N* hydrochloric acid: 2.9 g. (58%) of brown, granular material, m.p. 235–240°. One recrystallization from glacial acetic acid afforded 2.4 g. (48%) of tan microcrystalline material, m.p. 253.5–254.5° (decomp.): reported, 265° (decomp.) (7). This compound and related indole diacids underwent appreciable decomposition at elevated temperatures so that the melting point of a given sample depended in some measure upon the rate at which the compound was brought to the observed point of fusion.

(b) *From the p-methoxyphenylhydrazone prepared in acidic medium.* After preparing *p*-methoxybenzenediazonium chloride as above described, it was poured with shaking into a cold solution of 3.7 g. (0.045 mole) of sodium acetate in 33 ml. of 90% ethanol to which 4.6 g.

of the keto ester had been added just previously. The resulting clear brown solution soon became turbid and precipitated a dark brown oil, which was taken up in ether and washed with water, aqueous sodium bicarbonate, and aqueous sodium chloride. The brown oil obtained from the ether extract was cyclized and saponified as in the above case. The crude diacid, 1.9 g. (38%), m.p. 239–240°, on recrystallization from glacial acetic acid gave 1.6 g. (33%) of tan crystals, m.p. 257° (decomp.).

Attempted partial decarboxylation of 2-carboxy-5-methoxy-3-indoleacetic acid. This diacid could not be partially decarboxylated according to the procedure of King and L'Ecuyer, who removed the 2-carboxyl group of 2-carboxy-3-indoleacetic acid by heating the latter compound with copper powder in quinoline (4).

Ethyl 2-carboxy-5-methoxy-3-indoleacetate. A mixture of 25 ml. of 0.5% ethanolic hydrogen chloride and 2.5 g. of the diacid was refluxed two hours and most of the solvent removed under diminished pressure. The cold residue furnished 2.0 g. of crude product. Two crystallizations from aqueous ethanol provided pure material, m.p. 201.5–203.5° (decomp.).

Anal. Calc'd for $C_{14}H_{15}NO_5$: C, 60.61; H, 5.45.
Found: C, 60.56; H, 5.39.

This half ester was soluble in aqueous sodium bicarbonate, benzene, ether, and ethanol. With Ehrlich's reagent was obtained only a faint reaction.

5-Methoxy-3-indoleacetic acid. (a) *Decarboxylation of the half ester.* The half ester was conveniently decomposed by Tanaka's procedure. To 5 ml. of quinoline was added an intimate mixture of 0.50 g. of half ester and 90 mg. of catalyst 39KAF. This was heated in a Wood's metal-bath at 195–205°, the theoretical quantity of carbon dioxide being collected in a gas burette over toluene. The reaction mixture was digested with 50 ml. of ether, the catalyst filtered off, and the filtrate extracted with dilute hydrochloric acid and washed. After drying, the ether was removed, the residue saponified with an excess of ethanolic sodium hydroxide, and the product separating on acidification recrystallized twice from hot water: 0.10 g. of pure 5-methoxy-3-indoleacetic acid, m.p. 146° (decomp.): reported, 146–147° (decomp.) (6). It reacted with Ehrlich's reagent to give a violet color on warming and this was converted to a deep wine red by the addition of a trace of solid sodium nitrite.

Ethyl 2-carboethoxy-5-methoxy-3-indoleacetate. This was obtained from the cyclization residue which above was saponified without preliminary isolation of the diester. This compound, soluble in most of the common organic solvents, could be crystallized from benzene-ligroin or aqueous ethanol. The pure material crystallized from the latter solvent in pale yellow needles, m.p. 110–110.5°. It responded very faintly to Ehrlich's test.

Anal. Calc'd for $C_{19}H_{16}NO_5$: N, 4.60. Found: N, 4.79.

o-Methoxyphenylhydrazone of diethyl α-ketoglutrate. Although this compound may be prepared in both alkaline and acidic media, the yield in alkaline solution was found to be superior. Prepared from *o*-anisidine using the same quantities and procedure as for the *p*-methoxy isomer, it could be isolated or cyclized in the crude condition. In the former case, unlike the phenylhydrazone itself, the residual oil was observed to crystallize neither on long standing nor on seeding. However, treating with 10 ml. of cold 11% ethanolic hydrogen chloride converted the material, presumably a diazo compound, into the phenylhydrazone, which could be crystallized from methanol or aqueous ethanol. The pure material consisted of yellow aciculae, m.p. 81.5–82.5°.

Anal. Calc'd for $C_{16}H_{22}N_2O_5$: C, 59.61; H, 6.88; N, 8.69.
Found: C, 59.90, 59.63; H, 7.31, 6.95; N, 8.51, 8.52.

Saponification gave an acid which, after two recrystallizations from methanol, appeared as fine, brownish orange needles, m.p. 171.5° (decomp.): reported, 168° (decomp.)(7).

Ethyl 2-carboethoxy-7-methoxy-3-indoleacetate. Usually the *o*-methoxyphenylhydrazone was cyclized in the same manner as the *p*-methoxy isomer without prior purification. The cyclization product was always contaminated by large quantities of dark, viscous oil, the amounts of which increased with increasing strength of the alcoholic hydrogen chloride. It was found that the crude cyclization product, obtained in the same manner as the 5-methoxy analog from 0.02 mole of *o*-anisidine, could not be successfully saponified without

preliminary purification. In a typical experiment the crystalline material was freed of the oily impurities by drying on porous earthenware. Crystallization from ethanol gave 1.2 g. (20%) of material, m.p. 109.5–112.5°. Repeated recrystallization of the diester gave brown needles of pure material, m.p. 116°: reported, gray needles, m.p. 106° (7).

Anal. Calc'd for $C_{16}H_{19}NO_5$: N, 4.60. Found: N, 4.59.

Saponification to 2-carboxy-7-methoxy-3-indoleacetic acid. Considerable difficulty was encountered in transforming the 7-indole diester satisfactorily into the diacid. Heating a sample with a two-fold excess of 0.1 *N* ethanolic sodium hydroxide on the steam-bath for ten minutes caused extensive degradation, the amount of recoverable diacid being trivial. Results with longer heating time at 50° were no more encouraging. Partial saponification with 20% ethanolic potassium hydroxide at 25° or at higher temperatures gave starting material and a small amount of tan, crystalline material, m.p. 183°, which was not identified.

Finally, satisfactory results were obtained with potassium hydroxide dissolved in 99% ethanol. The pure ester (2.1 g.) was dissolved in 15 ml. of a 0.89 *N* solution of potassium hydroxide in 99% ethanol. After 48 hours in a stoppered flask at room temperature the voluminous, granular, pale yellow precipitate which had accumulated was collected and washed with 99% ethanol. The dried residue, aggregating 1.9 g., was dissolved in 10 ml. of warm water and, on acidifying the clear solution with 1 *N* hydrochloric acid, a yellow precipitate of 2-carboxy-7-methoxy-3-indoleacetic acid was obtained: 1.3 g., m.p. 213-214°. Recrystallization from methanol afforded 0.70 g. of tan crystals, m.p. 239–240° (decomp.): reported, 253° (decomp.) (7). This product was used in the next preparation without attempting further purification.

Ethyl 2-carboxy-7-methoxy-3-indoleacetate. The diacid (0.75 g.) was refluxed one hour with 3 ml. of 0.5% ethanolic hydrogen chloride. Since after four hours no crystals had separated from the cold solution, the solvent was removed at room temperature *in vacuo* over sulfuric acid and potassium hydroxide. The residue (0.82 g.) was crystallized from benzene: 0.70 g., m.p. 146.5–147°. A small sample recrystallized for analysis melted 147–148°. With Ehrlich's reagent this half ester gave a faint green color which changed to greenish yellow on addition of sodium nitrite. A satisfactory analysis was not obtained for this compound.

7-Methoxy-3-indoleacetic acid. A finely ground mixture of 0.60 g. of half ester and 80 mg. of catalyst 39KAF was added to 6 ml. of quinoline contained in a 10-ml. round-bottomed flask which was then connected to a gas burette and immersed in a Wood's metal-bath. Rapid evolution of carbon dioxide began about 210°. When the theoretical volume of gas had been collected, and this coincided with a marked falling-off of the carbon dioxide evolution, the mixture was cooled, stirred with a large volume of ether, filtered, and the filtrate washed with dilute hydrochloric acid, water, aqueous sodium bicarbonate, and aqueous sodium chloride.

After removing the solvent from the dried ethereal extract the dark, oily residue was saponified by mixing thoroughly with 1 ml. of 2 *N* absolute ethanolic potassium hydroxide and allowed to stand one hour. The mixture was diluted with 6 ml. of water and a small amount of oil which separated was removed by ether extraction. Acidification of the aqueous solution produced a heavy brown liquid which, on dissolution in ether and removal of the solvent, gave 0.29 g. of crude brown crystals. Two recrystallizations from hot water afforded about 0.1 g. of pure material, m.p. 127–127.5° (decomp.). With Ehrlich's reagent it furnished a pale blue color which was converted to a more intense reddish violet by the addition of solid sodium nitrite.

Anal. Calc'd for $C_{11}H_{11}NO_3$: C, 64.37; H, 5.40.
Found: C, 64.35; H, 5.40.

m-Anisidine. This was obtained by acetylation of *m*-aminophenol, methylation of the product and hydrolysis with hydrochloric acid (13).

Ethyl 2-carboethoxy-6-methoxy-3-indoleacetate. (a) *Preparation of the m-methoxyphenylhydrazone of diethyl α-ketoglutarate.* *m*-Anisidine (9.5 g., 0.077 mole), dissolved in 19 ml. of

concentrated hydrochloric acid and 8 ml. of water, was diazotized at about −5° with 5.3 g. (0.075 mole) of sodium nitrite in 15 ml. of water. When diazotization had been completed the solution was added with agitation to a mixture of 17.2 g. (0.31 mole) of potassium hydroxide in 70 g. of ice and water to which 17.7 g. (0.077 mole) of diethyl α-acetoglutarate had just been added. Then the reddish brown reaction mixture, after acidification with dilute hydrochloric acid, was extracted with ether and the extract washed and dried.

(b) *Cyclization.* The deep red oil remaining after removing all the solvent was cyclized by refluxing for one hour with 45 ml. of 15% ethanolic hydrogen chloride. The yield of product with 10% ethanolic acid was lower. After cooling, dilution with ether, washing, drying, and removal of the solvent the residual, dark viscous reaction product became semi-solid on standing. The crystalline material was advantageously separated from the liquid impurities by drying on porous earthenware: 7.4 g. (32%) of crude ester. Two crystallizations, one from methanol and one from ethanol, furnished 4.4 g. of pure material, m.p. 107.5–108.5°.

Anal. Calc'd for $C_{16}H_{19}NO_5$: C, 62.95; H, 6.25; N, 4.60.
Found: C, 62.75; H, 6.02; N, 4.65.

2-Carboxy-6-methoxy-3-indoleacetic acid. The 6-methoxyindole diester (3.0 g.) was saponified by refluxing 12 minutes on the steam-bath with 1.3 g. of sodium hydroxide in 15 ml. of 90% ethanol. After cooling, the white, solid salt which had separated was dissolved in 12 ml. of warm water, and acidified with dilute hydrochloric acid: 2.4 g., m.p. 217° (decomp.). Two recrystallizations from 50% acetic acid afforded pure material, m.p. 225° (decomp.): reported, 224–225° (8). Exposure to air or prolonged heating of its solutions caused the appearance of green decomposition products.

Anal. Calc'd for $C_{12}H_{11}NO_5$: N, 5.63. Found: N, 5.76.

Ethyl 2-carboxy-6-methoxy-3-indoleacetate. The diacid (1.8 g.) was refluxed with 5 ml. of 0.5 ml. of 0.5% ethanolic hydrogen chloride for thirty-five minutes. On cooling the green solution, crystalline material precipitated: 1.3 g., m.p. 171–172.5° (decomp.). Two crystallizations from aqueous ethanol gave pure material, m.p. 176°.

Anal. Calc'd for $C_{14}H_{15}NO_5$: N, 5.05.
Found: N, 5.16, 4.94.

6-Methoxy-3-indoleacetic acid. (a) *Decarboxylation.* An intimate mixture of 0.60 g. of half ester and 0.80 mg. of catalyst 39KAF was heated in 6 ml. of quinoline at 195–205° until the theoretical volume of carbon dioxide had been collected. The crude ester was obtained in the customary fashion.

(b) *Saponification.* The crude ester was dissolved in 1.0 ml. of a 2.3 *N* solution of potassium hydroxide in 99% ethanol and allowed to stand at room temperature one hour during which the mixture solidified. After warming three minutes on the steam-bath, the mixture was dissolved in 6 ml. of warm water and made just acid with 1 *N* hydrochloric acid. The precipitated material was collected and dried: 0.21 g. of dark red crystals, m.p. 157–158°. Two crystallizations from hot water furnished 0.10 g. of cinnamon-colored platelets, m.p. 163–164° (decomp.). In a preliminary preparation, this compound was obtained from hot water in apparently pure condition as bluish-green leaflets. Ehrlich's reagent in the cold produced a rather deep blue convertible to a more intense violet by addition of solid sodium nitrite.

Anal. Calc'd for $C_{11}H_{11}NO_3$: N, 6.83.
Found: N, 6.78, 6.88.

Veratrole. This diether, prepared from catechol, was obtained in 93 g. (74%) yield, b.p. 205–208°/760 mm. (14).

4-Nitroveratrole. Although this preparation was performed twice, the reported yield could not be attained (15). The crude, chocolate-colored material from the nitration of 25 g. of veratrole aggregated 28 g. (82%). Two crystallizations from aqueous ethanol provided 19 g. (55%) of pure material, m. 97.5°.

4-Aminoveratrole. 4-Nitroveratrole (11.0 g., 0.060 mole), dissolved in 200 ml. of ethanol, was catalytically hydrogenated at three atmospheres and room temperature using 0.120 g.

of platinum oxide. The solution of the unstable amine was separated from the catalyst, 50 ml. of benzene added, and the solvents removed through a fractionating column. The dark red residue was distilled in the presence of glass wool: 6.8 g. (74%) of yellowish orange crystals, b.p. 169°/18 mm.

Ethyl 2-carboethoxy-5,6-dimethoxy-3-indoleacetate. (a) *Preparation of the crude 3,4-dimethoxyphenylhydrazone.* 4-Aminoveratrole (6.3 g., 0.041 mole), dissolved in 20 ml. of 6 *N* hydrochloric acid and 20 ml. of water, was diazotized below 0° with 2.8 g. (0.040 mole) of sodium nitrite dissolved in 15 ml. of water. After ten minutes the dark brown solution was added with shaking to a cold solution of 7.4 g. (0.090 mole) of sodium acetate in 65 ml. of 90% ethanol to which 9.2 g. (0.040 mole) of diethyl α-acetoglutarate had just been added. After standing an hour in the cold the reaction mixture was extracted with a large volume of ether, and, after washing and removing the acids from solution, it was dried and the solvent removed, the last traces under diminished pressure.

(b) *Cyclization.* The residual, thick, red oil was refluxed with 42 ml. of 8% ethanolic hydrogen chloride for one-half hour and the cyclization product worked up in the customary manner. After separating from liquid impurities by drying on porous porcelain, the crude crystalline material amounted to 5.1 g. (38%), m.p. 122–124°. One crystallization furnished 4.5 g. (34%) of small pink aciculae. m.p. 126°. Recrystallization failed to improve the melting point. A trace of this ester in glacial acetic acid when treated with a drop of dilute nitric acid gave the brucine color reaction (7). Ehrlich's reagent produced a yellow shade which underwent a transition to green.

Anal. Calc'd for $C_{17}H_{21}NO_6$: C, 60.87; H, 6.31; N, 4.18.
Found: C, 61.05; H, 6.28; N, 4.51.

2-Carboxy-5,6-dimethoxy-3-indoleacetic acid. The pink diester was saponified by gently refluxing 2.0 g. with 15 ml. of 1.2 *N* methanolic sodium hydroxide for fifteen minutes. Addition of 10 ml. of warm water to the orange, alkaline solution followed by acidification and filtration resulted in 1.4 g. of crude material, m.p. 210–211° (decomp.). The filtrate possessed an odor reminiscent of grapefruit juice, this disappearing on addition of bicarbonate. Two crystallizations from glacial acetic acid afforded 0.8 g. of a powder melting indistinctly about 225° (decomp.). A satisfactory analysis for the compound was not obtained.

By-product of the saponification. On standing, the mother liquor from the recrystallization of the diacid acquired an inky opacity, and about 0.3 g. of finely divided material precipitated. Although its melting point and mixed melting point indicated that it was the impure diacid, esterification with 0.5% ethanolic hydrogen chloride resulted in a neutral compound, m.p. 138–141°, which was not obtained from the diacid under these conditions. With Ehrlich's reagent this ester furnished a moderately intense blue.

Anal. Calc'd for $C_{30}H_{36}N_2O_{11}$: C, 59.43; H, 5.99; N, 4.62.
Found: C, 59.54, 59.31; H, 6.02, 6.16; N, 4.52.

Ethyl 2-carboxy-5,6-dimethoxy-3-indoleacetate. The diacid (0.7 g.) was refluxed thirty minutes with 2 ml. of 0.5% ethanolic hydrogen chloride. During this interval the reaction mixture became deep blue. The crystals obtained from the cold solution by scratching aggregated 0.4 g., m.p. 192.5–193.5° (decomp.). Purified by recrystallization from methanol they melted at 195.5° (decomp.) and with Ehrlich's reagent gave a pale blue response converted to green when sodium nitrite was added. The partial saponification of ethyl 2-carboethoxy-5,6-dimethoxy-3-indoleacetate also furnished a small amount of this half ester.

Anal. Calc'd for $C_{15}H_{17}NO_6$: N, 4.56.
Found: N, 4.76, 4.73.

Decarboxylation experiments. The half ester (0.4 g.) intimately mixed with 50 mg. of catalyst 20KAF and 5 ml. of quinoline was submitted to decarboxylation. However, the evolution of gas was extremely sluggish and on working up the product in the customary manner an amount of crude crystalline material was obtained which made purification and identification impossible. With Ehrlich's reagent this gave a deep blue color. A repetition under slightly altered conditions was likewise unsuccessful.

Ethyl 2-carboethoxy-3-naphthazoleacetate. This diester, prepared in 39% yield from α-naphthylamine in the same manner as ethyl 2-carboethoxy-5,6-dimethoxy-3-indoleacetate, crystallized from benzene as pink needles, m.p. 167.5–168.5°. A pale yellowish green was obtained with Ehrlich's reagent.

Anal. Calc'd for $C_{19}H_{19}NO_4$: N, 4.31. Found: N, 4.56.

2-Carboxy-3-naphthazoleacetic acid. A mixture of 3.3 g. (0.010 mole) of diester, 5 ml. of 6 *N* aqueous sodium hydroxide, and 25 ml. of ethanol was refluxed twenty minutes on the steam-bath. After diluting with 25 ml. of water the warm solution was made just acid with hydrochloric acid and filtered. The residue after drying *in vacuo* over potassium hydroxide aggregated 2.7 g. (100%). One crystallization from glacial acetic acid afforded 2.1 g. (78%) of pink, lustrous platelets, m.p. 270° (decomp.). A second crop of 0.2 g. was obtained from the mother liquor. This compound, which formed supersaturated solutions in both ethanol and acetic acid, produced a faint blue color with Ehrlich's reagent and could not be satisfactorily analyzed for nitrogen. Of the five values obtained the last three were with the aid of potassium chlorate to oxidize the sample.

Anal. Calc'd for $C_{15}H_{11}NO_4$: N, 5.20.
Found: N, 4.06, 4.30, 4.33, 4.56, 4.47.

Ethyl 2-carboxy-3-naphthazoleacetate. To 12 ml. of 0.4% ethanolic hydrogen chloride was added 2.1 g. of the diacid, and the mixture refluxed on the steam-bath for one-half hour. On cooling, the product separated as small brown crystals: 1.7 g., m.p. 207.5–208.5°. A second crop amounted to 0.4 g. Recrystallization from ethanol did not improve the melting point. It gave a pale blue color with Ehrlich's reagent which became slowly more intense on warming.

Anal. Calc'd for $C_{17}H_{15}NO_4$: N, 4.71. Found: N, 4.60.

Decarboxylation to ethyl 3-naphthazoleacetate. (a) *Dry run.* A mixture of 0.20 g. of ethyl 2-carboxy-3-naphthazoleacetate and 40 mg. of catalyst 39KAF was ground in a mortar and heated at 220° and 1 mm. in a sublimation assembly immersed in a Wood's metal-bath. The crude material which collected on the cold finger aggregated 40 mg. Three recrystallizations from ethanol gave material melting 107.5° (softened at 101.5°). It gave with Ehrlich's reagent a pale blue in the cold, and this became quite deep on warming, acquiring an inky opacity upon addition of a trace of sodium nitrite.

(b) *Decarboxylation in quinoline.* An intimate mixture of 0.50 g. of half ester and 100 mg. of 39KAF was suspended in 6 ml. of quinoline was heated in a Wood's metal-bath at 195–205° for twenty minutes, when about 85% of the theoretical amount of carbon dioxide had been collected. After cooling, the reaction mixture was diluted with ether, filtered, and washed with dilute hydrochloric acid, water, aqueous sodium bicarbonate, and aqueous sodium chloride. The solution was dried over sodium sulfate, the solvent removed, and the brown crystalline residue distilled at 90–140° at 10^{-4} mm: 0.25 g. of crude material, m.p. 104.5–106.5°.

Anal. Calc'd for $C_{16}H_{15}NO_2$: N, 5.53. Found: 5.50.

3-Naphthazoleacetic acid. The ethyl ester (0.25 g.) was refluxed 15 minutes on the steam-bath with 1.5 ml. of 1.2 *N* methanolic sodium hydroxide. The reaction mixture was diluted with 2 ml. of water and acidified with dilute hydrochloric acid. The precipitated acid weighed 0.20 g., m.p. 189° (decomp.). Recrystallization from methanol and aqueous ethanol gave pure material, m.p. 194.5° (decomp.). With Ehrlich's reagent it gave a blue color greatly intensified by the addition of sodium nitrite.

Anal. Calc'd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92.
Found: C, 74.90; H, 4.83.

Ethyl 2-carboethoxy-1-naphthazoleacetate. This compound, obtained in 30% yield by the customary procedure, crystallized from benzene as tan needles: m.p. 149°.

Anal. Calc'd for $C_{19}H_{19}NO_4$: N, 4.31.
Found: N, 4.36, 4.46.

2-Carboxy-1-naphthazoleacetic acid. Prepared in the same fashion as the isomeric diacid, this compound crystallized from glacial acetic acid as minute crystals, m.p. 239–240° (de-

comp.). It presented the same analytical difficulties as the isomeric acid. The last three values for nitrogen were obtained using potassium chlorate.

Anal. Calc'd for $C_{15}H_{11}NO_4$: N, 5.20.
Found: N, 4.53, 4.29, 4.86, 4.62, 5.16.

Ethyl 2-carboxy-1-naphthazoleacetate. This compound, obtained in the same manner as isomeric half ester, melted at 219° and furnished a pale greenish blue with Ehrlich's reagent.

Anal. Calc'd for $C_{17}H_{15}NO_4$: N, 4.71. Found: N, 4.69.

Decarboxylation to ethyl 1-naphthazoleacetate. This ester, which can be prepared by either of the methods described for the isomeric compound, crystallized as lustrous brown platelets from ethanol: m.p. 160.5–162.5°.

Anal. Calc'd for $C_{16}H_{15}NO_2$: N, 5.53.
Found: N, 5.24, 5.26.

1-Naphthazoleacetic acid. Obtained by saponification of the ethyl ester and crystallization from hot water, this ester melted at 152–153° (decomp.). Ehrlich's reagent produced a pale blue response which was intensified on warming.

Anal. Calc'd for $C_{14}H_{11}NO_2$: C, 74.69; H, 4.92.
Found: C, 74.39; H, 5.01.

The isomeric monochlorophenylhydrazones of diethyl α-ketoglutarate. These compounds, prepared by the action of the appropriate diazotized amine on diethyl α-acetoglutarate, were obtained initially as reddish orange oils which were transformed to the crystalline phenylhydrazones by the action of ethanolic mineral acids. *m*-Chloroaniline was obtained by hydrogenation of *m*-nitrochlorobenzene at three atmospheres of hydrogen using a platinum oxide catalyst (16). The ortho, meta, and para isomers melted at 120°, 80.5°, and 57.5° respectively.

Anal. Calc'd for $C_{15}H_{19}ClN_2O_4$: Cl, 10.85.
Found: Cl, 10.76, 10.78 (*o*-isomer); 10.58 (*m*-isomer); 10.35, 10.23 (*p*-isomer).

Cyclization experiments. Boiling 14% butanolic sulfuric acid effected elimination of ammonium sulfate from the *m*-chlorophenylhydrazone. However, the organic material isolated could not be purified. Saponification furnished amorphous material soluble in alkali. Ethanolic hydrochloric acid containing zinc chloride and butanolic hydrochloric acid were less effective in producing cyclization.

SUMMARY

The preparation of 5-, 6-, and 7-methoxyindoleacetic acids and 1- and 3-naphthazoleacetic acids by the Japp-Klingemann method for phenylhydrazones, the Fischer indole synthesis, and subsequent transformation reactions is described.

It has been found that much better yields in the Fischer ring closure are obtained with approximately 10% ethanolic hydrochloric acid than with the much higher acid concentrations employed heretofore.

The three isomeric monochlorophenylhydrazones of diethyl α-ketoglutarate could not be successfully cyclized to crystalline indole derivatives.

PRINCETON, N. J.

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