1-INDOLEACETIC ACID[1]

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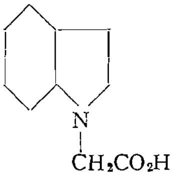
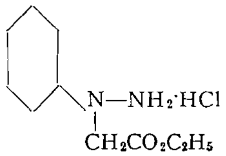
ABSTRACT

1-Indoleacetic acid, 3-methyl-1-indoleacetic acid, and several of their derivatives were formed from phenylhydrazineacetic ester, and their structures were determined in three different ways. Several of the new compounds exhibited plant growth regulating activity.

In this paper it is shown that 1-indoleacetic acid (I) and some of its derivatives may be formed from asymmetrical phenylhydrazineacetic ester hydrochloride (II) by conventional methods, and that some of these derivatives exhibit plant growth regulating activity to an interesting degree. The problem was suggested to us several years ago by Dr. R. H. Manske.



I



II

Phenylhydrazineacetic ester hydrochloride (II) was made from phenylglycine by the method of Harries (6) and also from phenylhydrazine and chloroacetic acid by the method of Busch (2). The former method gave a product of unambiguous structure, but the latter method was much more convenient. Two new demonstrations of the identity of the products made by the two methods are described in the experimental part and are desirable because of the previous confusion regarding the structure of the substance made by the second method (2, 6, 14).

Condensation of phenylhydrazineacetic ester hydrochloride (II) with ethyl pyruvate in alcoholic hydrogen chloride gave excellent yields of the diethyl ester of 2-carboxy-1-indoleacetic acid (III*a*). The ester was easily saponified to give the free acid (III*b*), which readily formed the anhydride, the acid amide (IV*a*?), and the half ester (IV*b*). Decarboxylations of the half esters of 2-carboxy-3-indoleacetic acids by heating them either alone or in quinoline in the presence of a copper chromium oxide catalyst have been performed by King and L'Ecuyer (10), by Tanaka (16), and by Findlay and Dougherty (4), but large amounts of tar were formed when their methods were applied to the half ester IV*b*. It was thought that dilution of the reaction mixture with

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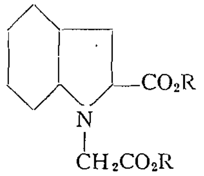
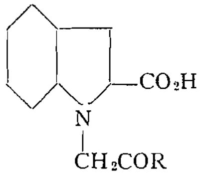
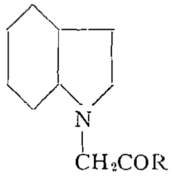
large amounts of quinoline should favor the decarboxylation in competition with the formation of tar, since the former reaction should be unimolecular and the latter at least bimolecular in IV*b*. Dilution did suppress the formation of tar but another interesting complication arose. The quinoline contained small amounts of aniline and in the decarboxylations carried out in large volumes of quinoline, some anilide of 1-indoleacetic acid (V*b*) was formed as well as the expected ester (V*a*). The formation of the anilide was not unwelcome since it was a highly crystalline and stable derivative of the rather unstable free acid (I) and since it proved to be highly active as a plant growth regulator. Hydrolysis of either the ester (V*a*) or the anilide (V*b*) gave the desired 1-indoleacetic acid (I) as small, shining needles of melting point 179°C. It was a rather unstable substance, difficult to purify.



III*a*: R = C_2H_5
III*b*: R = H

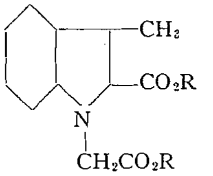


IV*a*: R = NH_2
IV*b*: R = OC_2H_5

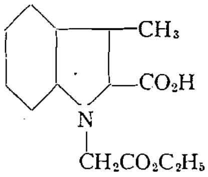


V*a*: R = OC_2H_5
V*b*: R = NHPh

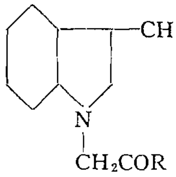
Phenylhydrazineacetic ester hydrochloride (II) and the methyl ester of α-ketobutyric acid were smoothly converted in ethanolic hydrogen chloride to the *diethyl* ester of 2-carboxy-3-methyl-1-indoleacetic acid (VI*a*), which was readily hydrolyzed to give the free acid (VI*b*). Conversion of the latter to its half ester (VII) occurred easily, and when VII was heated in quinoline with copper chromium oxide, a mixture of the ethyl ester (VIII*a*) and the anilide (VIII*b*) of 3-methyl-1-indoleacetic acid was formed. Tar formation during the decarboxylation was much less than in the decarboxylation of IV*b*, as was expected since the reactive 3-position was occupied in VII but not in IV*b*. Hydrolysis of the ester (VIII*a*) gave the free 3-methyl-1-indoleacetic acid as white crystals of melting point 179°C., somewhat more stable than those of 1-indoleacetic acid.



VI*a*: R = C_2H_5
VI*b*: R = H

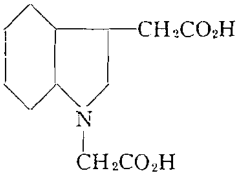


VII

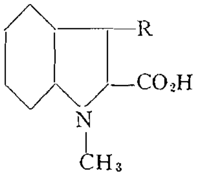


VIII*a*: R = OC_2H_5
VIII*b*: R = NHPh
VIII*c*: R = OH

The 3-methyl-1-indoleacetic acid (VIII*c*) prepared in this way proved to be identical with that made by Jackson and Manske (8) from 1,3-indolediacetic acid (IX), a rather conclusive proof of the structures suggested in the present paper for the monocarboxylic acids and their derivatives and for the dicarboxylic acids and their diethyl esters. These structures were confirmed in two other ways. Decarboxylation of the dicarboxylic acids III*b* and VI*b* could lead either to the acids I and VIII*c*, or to the acids X*a* and X*b*, respectively, depending on which carboxyl group was lost. The acids X*a* (5) and X*b* (9) are known; both melt at 212°C. rather than at 179°C. as do both of the monocarboxylic acids obtained in the present work, so that structures I and VIII*c* were confirmed. The fact that the compounds thought to be III*b*, IV*b*, VI*a*, VI*b*, and VII gave negative tests with Ehrlich's reagent, while the compounds thought to be I, V*a*, V*b*, VIII*a*, VIII*b*, and VIII*c* all gave strongly positive tests with the reagent also confirmed the structures suggested for them, since the intensified color given by the second set of compounds was evidence that they had lost a carboxyl group in the 2-position (4). The structures of the half esters of the dicarboxylic acids were given as IV*b* and VII because of their decarboxylation to V*a* and VIII*a* respectively. This method of proof has been accepted by several authors (4, 10, 16) but is perhaps not absolutely conclusive because of the drastic conditions used in the decarboxylations. Finally, the structure of the half amide of 2-carboxy-1-indoleacetic acid was thought to be IV*a* because of its analogy to the half esters (IV*b* and VII) and to the anilides (V*b* and VIII*b*).



IX



X*a*: R = H
X*b*: R = CH_3

Some of the new indole derivatives were compared with 3-indoleacetic acid in their ability to produce cell elongation in young tomato plants, as suggested by Zimmerman (17). Our tests were not sufficiently accurate or extensive to make quantitative comparisons advisable, but they did establish the fact that some of the compounds, notably the anilide of 1-indoleacetic acid, were highly active as plant growth regulators. This observation was of considerable interest because of the geometrical similarity of the compounds to the very active 3-indoleacetic acid.

EXPERIMENTAL

Melting points are corrected unless otherwise stated.

asymm-Phenylhydrazineacetic Ester Hydrochloride

(*a*) *By Harries' Method* (6)

N-phenylglycine (12) was esterified in 50% yield with ethanol and hydrogen chloride (15) or in 64% yield with ethanol and sulphuric acid, and the ester was quantitatively converted to its N-nitroso derivative as described by

Harries (6). Less zinc dust and alcohol (7) than suggested by Harries were used in the reduction of the nitroso compound, but our yields were much lower than his. The crude phenylhydrazineacetic ester was obtained from the reduction as a red syrup; attempts to purify it by Harries' method failed, but a method like that of Busch (2) succeeded. The red syrup was dissolved in absolute ethanol and the solution was saturated with dry hydrogen chloride. After the mixture had been thoroughly chilled, the slightly pink needles which formed were recovered, washed with alcohol and with ether, and dried first in the air and then *in vacuo* over sulphuric acid. The yield was 18% and the melting point of the crystals was 194.8-195.7°C. with decomposition. In other experiments one of us obtained yields of 20% and 23%. Harries reported a yield of 55%, and a melting point of 195-196°C.

(*b*) *By Busch's Method* (2)

Crude *asymm*-phenylhydrazineacetic acid was made according to Busch's directions in a yield of 83%, but the product soon turned to a gum and its subsequent reactions failed. In another run, the crude acid was *immediately* recrystallized from 60% alcohol to give a heavy crop of light yellow needles in a yield of 46%. This product was stable. The once-recrystallized acid (37.7 gm.) was suspended in absolute ethanol (240 cc.), the mixture was thoroughly saturated with hydrogen chloride, and then heated under reflux for 30 min. Yellow needles separated from the cooled reaction mixture and were recovered, washed with ethanol, and rigorously dried; yield 33.4 gm. or 64%, m.p. 192.6-194.6°C. with decomposition, mixed m.p. with the ester hydrochloride prepared by Harries' method 193.0-195.1°C.

Ethyl Ester of 2-Carbethoxy-1-indoleacetic Acid

Phenylhydrazineacetic ester hydrochloride (prepared by Busch's method as above, 30.0 gm.), methyl pyruvate (3) (once distilled, 13.2 gm.), and absolute ethanol (200 cc.) were mixed and saturated with dry hydrogen chloride. The mixture was then heated under reflux for 60 min., cooled slightly, and filtered to remove ammonium chloride; the filtrate was then evaporated under reduced pressure to give a partly-oily, partly-crystalline residue which was thoroughly extracted with ether. The insoluble crystalline residue weighed 4.2 gm. Evaporation of the ethereal extract gave the crude diethyl ester as a dark red syrup in a yield of 92%, based on methyl pyruvate. A small portion of this syrup was fractionally distilled three times to give the following fractions: (1) 1.565 gm., b.p. 120-150°C. at 0.2 to 0.3 mm. (2) 2.308 gm., b.p. 150-155°C. at 0.2 mm. (3) 2.120 gm., b.p. 155°C. at 0.2 mm. Fractions (2) and (3) were pale yellow, viscous oils which slowly crystallized to form long yellow needles. Calc. for $C_{15}H_{17}O_4N$: C, 65.42%; H, 6.23%. Found for fraction (2): C, 65.90, 65.70%; H, 6.25, 6.16%. Greenish-yellow and light red shades were produced by this substance in Ehrlich's test.

2-Carboxy-1-indoleacetic Acid

The crude diethyl ester of this acid (66.7 gm.) was saponified by heating it under reflux for four hours with sodium hydroxide (39.2 gm.) and water (490 cc.). The cooled mixture was extracted with ether; the aqueous layer was filtered from a small precipitate and then cautiously acidified with concentrated hydrochloric acid, ice being added to keep the temperature down. A light brown precipitate was formed, and was recovered, washed with water, and dried in the air; yield 37.6 gm. or 71%. When the product was taken up in hot alcohol, boiled with charcoal for some time and filtered, and the filtrate treated with several volumes of hot benzene and cooled, sand-colored crystals were recovered in a yield of 25 gm., and further amounts were recovered from the mother liquor. A small portion of this product was further recrystallized twice from water with charcoal and once from benzene–ethanol with charcoal to give the analytical sample of small, white, but not well-shaped, crystals, m.p. 232.8-234.4°C. with decomposition. Calc. for $C_{11}H_9O_4N$: C, 60.27%; H, 4.14%. Found: C, 60.72, 60.33%; H, 4.20, 4.42%. When *asymm*-phenylhydrazineacetic ester hydrochloride made by Harries' method was similarly condensed with almost the theoretical amount of ethyl pyruvate (kindly given to us by Dr. Kulka, Ref. 11), the same diacid was formed on saponifying the intermediate ester, since after purification the acid melted at 234.9-236.0°C., with decomposition, and the analyses were approximately correct. The yield of the crude acid, based on ethyl pyruvate, was 84%. 2-Carboxy-1-indoleacetic acid from either source gave an almost completely negative test with Ehrlich's reagent.

Anhydride of 2-Carboxy-1-indoleacetic Acid

Once-recrystallized 2-carboxy-1-indoleacetic acid (2.02 gm.) and copper chromium oxide catalyst (1) (0.042 gm.) were heated together in a sublimation tube at 0.05 to 0.17 mm. pressure and 178-245°C. The sublimate was powdered and thoroughly extracted with cold aqueous sodium bicarbonate and the insoluble residue (0.32 gm.) was collected, washed, and dried. In a similar experiment, the insoluble sublimate weighed 0.38 gm. The two preparations were recrystallized together from a mixture of isopropyl ether and acetic anhydride. In a third experiment, the same amounts of reactants were used, but the conditions were more drastic. The pressure was held at 200 mm. until the external temperature reached 215°C.; the pressure was then adjusted to 12 mm. and the bath temperature kept at 230-235°C. for 15 min. and up to 245°C. for 10 min. Gas was evolved during this period. The bicarbonate-insoluble sublimate weighed only 0.29 gm. A small portion of it was found to be insoluble in cold caustic solution but soluble in warm caustic solution, from which crystals could then be precipitated by acidification. The rest of the insoluble sublimate from the third experiment was recrystallized from acetic anhydride but much darkening of the material occurred. All of the bicarbonate-insoluble crystals from the three experiments were now united and very cautiously sublimed at a pressure of 0.0005 to 0.005 mm. The sublimate was very thoroughly extracted with aqueous bicarbonate, washed, carefully dried, and recrystallized from a mixture of isopropyl ether (60 cc.) and acetic anhydride (19 cc.), care being taken not to prolong the heating period. The well-formed, light yellow needles were recovered, washed with isopropyl ether, and rigorously dried. Calc. for $C_{11}H_7O_3N$: C, 65.67%;

H, 3.48%. Found: C, 66.26, 66.11, 66.07, 66.15%; H, 3.67, 3.62, 3.85, 3.71%. The crystals had a melting point of 230.5-231.0°C. (uncorr.) with decomposition; their corrected melting point is estimated to be about 237-238°C. from their melting point relative to that of the diacid on the same thermometer. Unchanged diacid was recovered in yields of 48% and 52% in the first two experiments, respectively, but only in low yield in the third.

Acid Amide of 2-Carboxy-1-indoleacetic Acid

Once-crystallized 2-carboxy-1-indoleacetic acid (2.22 gm.) was treated with concentrated ammonium hydroxide (5 cc.) and water (8 cc.) and the mixture was rapidly evaporated to dryness. When the thoroughly dried residue was sublimed at 95-230°C., the pressure of sublimation rose from 0.004 to 0.3 mm. and then fell again to 0.003 mm., showing that gas was evolved. The crystalline residue and sublimate were then treated exactly as before, being even more rigorously dried before sublimation. The sublimate was dissolved in ammonium hydroxide and filtered from a scanty precipitate which was discarded. Acidification of the filtrate gave a solid which was extracted for 30 min. with boiling ethanol (25 cc.); the insoluble material was kept. Evaporation of the alcoholic extract gave a solid which was again treated with ammonium hydroxide, sublimed at a pressure above 0.2 mm., and worked up as before. The alcohol-insoluble material was kept, and the alcohol-soluble material again treated as before, the sublimation being performed at a higher pressure (above 0.2 mm.) and performed more slowly. The combined lots of material insoluble in ethanol but soluble in ammonium hydroxide were recrystallized from ethanol (140 cc.), recovered, dissolved in dilute ammonia, treated with charcoal in the cold, recovered by acidification, and once again treated with ammonia and charcoal as before. The glistening white crystals after thorough washing and drying melted at 272.0-273.6°C. with decomposition. Calc. for $C_{11}H_{10}O_3N_2$: C, 60.55%; H, 4.59%. Found: C, 60.75, 61.20, 60.39%; H, 4.53, 4.40, 4.57%.

Acid Ethyl Ester of 2-Carboxy-1-indoleacetic Acid

Once-recrystallized 2-carboxy-1-indoleacetic acid (33.3 gm.) and absolute ethanol (81 cc.) were warmed to 65°C. and treated with a vigorous stream of hydrogen chloride gas. The crystal cake which formed in about two minutes was broken up; the mixture was warmed to 80°C. and was saturated with hydrogen chloride. Water was added and the mixture was cooled and filtered. The turbid, greasy filtrate was discarded; after being washed and dried the recovered solid weighed 32.0 gm., a yield of 85%. After four recrystallizations from ethanol with charcoal, the material was pure, m.p. 200.5-201.5°C. Calc. for $C_{13}H_{13}O_4N$: C, 63.15%; H, 5.30%. Found: C, 63.37, 62.94%; H, 5.34, 5.57%. The test with Ehrlich's reagent was practically negative.

Anilide of 1-Indoleacetic Acid

Twice-recrystallized acid ethyl ester of 2-carboxy-1-indoleacetic acid, which had been formed from phenylhydrazineacetic ester made by Busch's method, was used. The acid ester (7.0 gm.), quinoline (a redistilled sample of Naugatuck's synthetic material, containing a little aniline, 97 cc.), and copper chromium oxide catalyst (1) (0.18 gm.) were heated together on an oil bath in an atmosphere of nitrogen. The bath was held at 190°C. for 80 min., at 195-197°C. for 10 min., and at 205°C. for 20 min., then heated briefly to 209°C. The catalyst was removed by filtration; the filtrate was cautiously acidified with dilute hydrochloric acid, ice being added to keep the temperature low. Ether (150 cc.) was added during the acidification. The mixture was filtered and repeatedly extracted with ether; the combined ethereal extracts were washed with dilute hydrochloric acid, with sodium carbonate solution, and finally with water. Evaporation of the ethereal extracts left a brown, gummy residue which was distilled in a Von Braun retort heated in an air bath. Two fractions were obtained: (*a*) an oil which distilled at a bath temperature of 100-130°C. and a pressure of 0.07 to 0.08 mm., yield 2.0 gm., (*b*) crystals which distilled at a bath temperature above 130°C., yield 2.2 gm., m.p. 177.3-178.4°C. A portion (0.48 gm.) of the crystalline fraction was twice recrystallized from dilute ethanol to give the pure anilide of 1-indoleacetic acid as white needles, m.p. 180.3-181.0°C. Calc. for $C_{16}H_{14}ON_2$: C, 76.80%; H, 5.60%. Found: C, 76.81, 76.83%; H, 5.78, 5.80%. Ehrlich's test was positive, several shades of red being produced.

Attempts to decarboxylate the acid ester by heat alone failed, and experiments in which the catalyst was omitted led to very unsatisfactory results.

1-Indoleacetic Acid

(1) The oily fraction of the distillate described just above was heated under reflux for three hours with potassium hydroxide (1.30 gm.), water (2.5 cc.), and ethanol (11 cc.). The solution was concentrated and then made distinctly acid in the cold. White crystals which rapidly began to turn brown were recovered in a yield of 1.58 gm. or 92%. Some ordinary methods of purification failed, but the following procedure was satisfactory. The crude crystals (1.58 gm.) were taken up in ether (75 cc.); the solution was filtered, and the filtrate was allowed to stand in contact with charcoal for two days at room temperature before being filtered again. The filtrate was then evaporated to small volume and treated with five volumes of petroleum ether to give white, fluffy crystals, which turned pink on standing, in a yield of 1.05 gm., m.p. 174.7-175.7°C. Three more similar treatments with charcoal in ether, lasting one day each time, followed by recovery in the same way as before, gave white but not very well formed needles of m.p. 176.3-177.3°C. A final recrystallization from benzene gave the analytical sample, m.p. 178.4-179.4°C., as small, shining needles. Calc. for $C_{10}H_9O_2N$: C, 68.56%; H, 5.18%. Found: C, 68.17, 68.22%; H, 5.34%, 4.96%. Ehrlich's test was strongly positive: a few milligrams of the compound were dissolved in alcohol and treated with an alcoholic solution of *p*-dimethylaminobenzaldehyde to give a yellow solution. Addition of a few drops of concentrated hydrochloric acid gave a medium red color which changed to a ruby red when the mixture was heated. Cooling did not alter the color but the addition of sodium nitrite gave a very dark red solution not changed by heating or cooling.

(2) The crude anilide of 1-indoleacetic acid (obtained in the second fraction

of the distillate described in the previous section, 1.32 gm.) was heated under reflux for three hours with potassium hydroxide (0.70 gm.), water (1.2 cc.), and ethanol (6.0 cc.). Two products were eventually isolated in the usual way: a basic oil which was identified as aniline by converting it to benzenesulphonanilide, m.p. 109-110°C. (uncorr.), and acidic crystals, m.p. 174.7-176.3°C., mixed m.p. with 1-indoleacetic acid 174.7-176.8°C., which were therefore not quite pure 1-indoleacetic acid. This experiment confirmed the constitution of the anilide of 1-indoleacetic acid.

Pyrolysis of 2-Carboxy-1-indoleacetic Acid

Pyrolysis of the diacid at very low pressures in the presence of a catalyst led only to the partial conversion of the acid to its anhydride, as already described. Pyrolysis of the diacid alone at ordinary pressure produced a tar which yielded no pure products, as well as very small amounts of an oily distillate thought to be N-methylindole and of a crystalline sublimate thought to be crude 1-indoleacetic acid. When 2-carboxy-1-indoleacetic acid (1.50 gm.) was heated with quinoline (7.2 cc.) and copper chromium oxide catalyst (0.043 gm.), some impure 1-indoleacetic acid was obtained, but considerable amounts of tar were formed as well. Better results were obtained when the diacid (3.48 gm.) was heated with quinoline (54 cc.) and copper chromium oxide catalyst (0.101 gm.), since very little tar was formed and 1-indoleacetic acid was recovered by the method already described; after three years it had a melting point of 176.3-177.8°C. This acid was not analyzed, but the pyrolyses of the diacid in quinoline also yielded neutral crystals of m.p. 181.0-182.0°C. and mixed m.p. with the anilide of 1-indoleacetic acid already described, 180.0-181.5°C. Calc. for $C_{16}H_{14}ON_2$: C, 76.80%; H. 5.60; N, 11.20%. Found: C, 76.22, 75.94, 77.17%; H, 5.57, 5.61, 5.64%; N, 11.03, 10.98%. Since the anilide made in the experiments of this section had been formed from phenylhydrazineacetic ester made by Harries' method, the mixed melting point with the anilide described previously was confirmation also of the identity of the phenylhydrazineacetic esters made by the method of Harries (6) and of Busch (2).

2-Carboxy-3-methyl-1-indoleacetic Acid, Diethyl Ester

α-Ketobutyric acid was formed in excellent yield from crotonic acid by the method of Pfister, Robinson, and Tishler (13), and then converted to its methyl ester in 51% yield by the elegant general method of Clinton and Laskowski (3). Crude phenylhydrazineacetic ester hydrochloride (made by Busch's method, 36.0 gm.), methyl α-ketobutyrate (b.p. 66-69.5°C. at 26 mm., 18.0 gm.), and absolute ethanol (240 cc.) were then mixed, saturated with dry hydrogen chloride, heated under reflux for one hour, cooled slightly, and filtered; the precipitated ammonium chloride weighed 6.0 gm. The filtrate deposited a heavy crop of crystals on standing, and a further crop was obtained by evaporating the mother liquors. Extraction of the combined crystal crops with ether gave the crude diethyl ester as very light brown crystals (soluble in ether) in a yield of 38.3 gm. or 86% based on methyl α-ketobutyrate. When a small sample was thrice recrystallized from ethanol, charcoal being used twice, white, well-formed needles of m.p. 80.0°C. (uncorr.) were obtained. Calc. for $C_{16}H_{19}O_4N$: C, 66.42%; H, 6.62%. Found: C, 66.88, 66.54%; H, 6.40, 6.57%. The material gave a practically negative test with Ehrlich's reagent.

2-Carboxy-3-methyl-1-indoleacetic Acid

The crude diethyl ester (36.3 gm.) was saponified in the usual way with aqueous alcoholic sodium hydroxide, and the crude dicarboxylic acid was obtained in 93% yield. When a small portion was recrystallized twice from benzene–ethanol and twice from dilute ethanol with charcoal, pure 2-carboxy-3-methyl-1-indoleacetic acid was obtained in well-formed, shining crystals of m.p. 236.5-237.6°C. with decomposition. Calc. for $C_{12}H_{11}O_4N$: C, 61.80%; H, 4.75%. Found: C, 61.67, 61.43%; H, 4.81, 4.90%. The test with Ehrlich's reagent was practically negative.

Acid Ethyl Ester of 2-Carboxy-3-methyl-1-indoleacetic Acid

The crude acid obtained as above (22.1 gm.) was mixed with absolute ethanol (50 cc.), warmed to 65°C., and treated with dry hydrogen chloride. The crystal cake was then broken up, treated with an additional 10 cc. of absolute ethanol, warmed to 80°C., and saturated with hydrogen chloride. Deep blue crystals having an extremely foul odor were recovered from the red, turbid, diluted alcoholic medium, and dried to give 21.8 gm. (88%) of the crude half ester. Three recrystallizations of the product from ethanol with charcoal gave colorless but not well-formed crystals which had a sweet odor. One more recrystallization of a small portion of these crystals from a large amount of ethanol gave the analytical sample of m.p. 195.7-196.7°C. Calc. for $C_{14}H_{15}O_4N$: C, 64.34%; H, 5.79%. Found: C, 64.88, 64.62, 64.81%; H, 5.79, 5.88, 5.64%. The test with Ehrlich's reagent was negative.

Decarboxylation of the Acid Ethyl Ester of 2-Carboxy-3-methyl-1-indoleacetic Acid

The half ester described above (thrice crystallized, 7.0 gm.), quinoline (Naugatuck's redistilled, 31.0 cc.), and copper chromium oxide catalyst (0.17 gm.) were heated together at a bath temperature of 180-190°C. for 80 min., at 190-200°C. for 10 min., and at 200-204°C. for 15 min. The mixture was then filtered, cooled, treated with ether, and acidified in the cold with dilute hydrochloric acid, again filtered, and then thoroughly extracted with ether. Very little tar was produced in the reaction. After the combined ethereal extracts had been washed with dilute hydrochloric acid, with sodium carbonate solution, and with water, they were evaporated to leave a semisolid, brown residue which was distilled at 0.06 mm. pressure in a von Braun retort. The following fractions were obtained: (1) distilled at a bath temperature of 95-110°C., an oil; (2) bath temperature 110-116°C., yield 1.585 gm., an oil; (3) bath temperature 116-165°C., an oil; the total yield of the first three fractions was 4.376 gm.; (4) bath temperature 165-250°C., yield 0.486 gm., a solid; (5) tarry residue, 0.19 gm.

The crystalline fraction (4) (0.486 gm.), together with 0.129 gm. of distilled crystals from a similar run, was recrystallized from hot ethanol (30 cc.) to give 0.346 gm. of crystals of m.p. 219.7-223°C. Evaporation of the mother liquor yielded a brown gum, so that this fraction of the distillate was not homogeneous. Two more recrystallizations of the crystals from ethanol gave very white crystals of m.p. 221.9°-222.4°C. whose analysis showed them to be the anilide of 3-methyl-1-indoleacetic acid. Calc. for $C_{17}H_{16}ON_2$: C, 77.25%; H, 6.10%. Found: C, 77.34%; H, 6.33%. Light amber and pink shades were produced with this material in Ehrlich's test.

The oily fraction (2) of the distillate (1.585 gm.) was redistilled, and the oily central fraction distilling at a bath temperature of 112-115°C. at 0.06 mm. was collected and analyzed. Calc. for $C_{13}H_{15}O_2N$: C, 71.86%; H, 6.96%. Found: C, 72.03, 72.34%; H, 7.19, 7.13%, showing it to be ethyl 3-methyl-1-indoleacetate. Ehrlich's test on the material produced successively deep pink, light red, brown, and purple shades.

3-Methyl-1-indoleacetic Acid

(1) The crude ethyl ester of this acid (3.72 gm. from the first three fractions of the distillate described in the previous section, together with 1.50 gm. from a similar experiment) was saponified in aqueous alcoholic potassium hydroxide and the product was recovered in the usual way. The crude acid was obtained in a yield of 2.624 gm. or 58%, m.p. 175.2-177.8°C. with slight decomposition. It had a foul odor and turned light brown when dried but was noticeably more stable than 1-indoleacetic acid. The crude acid was dissolved in ether, treated for several hours with two successive portions of charcoal, separated from the charcoal, and precipitated with petroleum ether. Two further recrystallizations of the product from benzene gave very white crystals of m.p. 178.9-179.9°C. Calc. for $C_{11}H_{11}O_2N$: C, 69.82%; H, 5.86%. Found: C, 69.68, 69.90%; H, 6.02, 5.83%. Red, amber, and violet shades were obtained with this material in Ehrlich's test.

(2) Crude 1,3-indoleacetic acid (m.p. 232°C., 0.658 gm.), kindly given to us by Dr. R. H. Manske, was melted at atmospheric pressure and immediately distilled at 0.5 mm. pressure. The distillate was purified in the usual way, but unfortunately its melting point could not be raised above 174-176°C. In microscopic appearance and in odor it was identical with the 3-methyl-1-indoleacetic acid made by method (1) and on admixture with the latter (which after several months also melted a few degrees below its true melting point) it caused no depression of the melting point. Jackson and Manske (8) obtained a melting point of 178°C. for the acid made in this way.

Biological Tests (17)

Young tomato plants were purchased on the Kingston market and grown under vertical light until they were 8 to 12 in. high. Each plant was then photographed, treated on the upper sides of the leaf petiole and on one side of the adjacent stem with a solution of an analytically pure indole derivative (15 mgm.) in lanolin (1 gm.), and kept in darkness at night and under vertical light by day. The plants were photographed at intervals and the change in the angle between petiole and stalk was measured on the photographs. Under these conditions, the well-known growth regulator 3-indoleacetic acid produced marked induced cell elongation in 24 hr., with little further change occurring after five days. The anilide of 1-indoleacetic acid had an effect about two-thirds as great, but produced it equally quickly. Smaller and more slowly induced elongations were given by the half esters of 2-carboxy-1-indoleacetic acid and of 2-carboxy-3-methyl-1-indoleacetic acid, and by the diethyl ester of 2-carboxy-3-methyl-1-indoleacetic acid, while the elongation produced by the diethyl ester of 2-carboxy-1-indoleacetic acid was slight. The plants treated with 1-indoleacetic acid, 3-methyl-1-indoleacetic acid, 2-carboxy-1-indoleacetic acid, and 2-carboxy-3-methyl-1-indoleacetic acid all withered and turned brown after about one day; during this time slight cell elongation occurred with the first and fourth of these acids but not with the other two.

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