Evaporation of the solvent by a stream of air gave 0.462 g. (2.53 mmoles) of slightly yellow, crystalline 1,2,3,4-tetrahydrofluoren-1-one-1-C^{14}, m.p. 92–98°, representing a 46.5% yield for the two-step sequence. This product was sufficiently pure for the succeeding steps of the synthesis. Further crystallizations of unlabeled preparations from petroleum ether C gave white plates, m.p. 103–105°.

1-Fluorenol-1-C^{14}. 1,2,3,4-Tetrahydrofluoren-1-one-1-C^{14} (0.462 g., 2.53 mmoles) was mixed with 5 g. of sublimed fluorene and 0.241 g. of purified palladium black catalyst[16] in a 35-ml. round-bottom flask fitted with a reflux condenser. The mixture was heated under reflux by means of a Wood's metal bath for 4.5 hr. The cooled solid solution was dissolved in 40 ml. of ether and filtered through a layer of Celite into a 60-ml. centrifuge tube. The ether solution was extracted 3 times with 8-ml. portions of a 15% potassium hydroxide solution. The alkaline extract was warmed to remove any dissolved ether and was then filtered through a layer of Celite. The filtrate was acidified with concentrated hydrochloric acid and cooled. The precipitate was collected on a sintered glass funnel and dried to give 0.294 g. (1.61 mmoles) of crude 1-fluorenol-1-C^{14}, m.p. 115–119°, 64.5% yield. For the subsequent reaction further purification was not necessary. When desired, this could be accomplished by recrystallization from a large volume of hot water giving material melting at 120–121° with a resulting loss of 13% of 1-fluorenol. In large scale runs of this reaction, the materials were mixed in a ratio of 2.5 g. of palladium black catalyst, 5.0 g. of ketone and 25 g. of fluorene. With heating at the reflux temperature for 4 hr., the yield of crude 1-fluorenol was 64%. Following solution of the reaction mixture in ether, the catalyst may be recovered by filtration and reused for this reaction without purification.

2-Nitrofluorenol-1-C^{14}. 1-Fluorenol-1-C^{14} (0.294 g., 1.61 mmoles) was dissolved in 6.4 ml. of glacial acetic acid in a 25-ml. Erlenmeyer flask. The solution was stirred by a magnetic stirrer and cooled in an ice bath while a solution of 0.145 ml. (2.27 mmoles) of concentrated nitric acid in 0.145 ml. of water was added dropwise from a pipet. The pipet was washed with 1 ml. of glacial acetic acid and the wash liquid added to the reaction mixture. The flask was stoppered and the solution stirred at room temperature for 3.5 hr. The mixture was then cooled in ice. The yellow precipitate was collected on a sintered glass funnel, washed with 15 ml. of water and dried *in vacuo*. Addition of the wash water to the mother liquor caused precipitation of a second crop which was collected, washed with water, and dried. The first crop was purified by chromatography on a 1 × 18 cm. column of acid-washed, activated alumina using benzene as eluent and collecting only the leading yellow band. Crop 2 was purified in a like manner on the same column. Evaporation of the combined eluates by means of an air stream and infrared lamp gave 0.182 g. (0.80 mmole) of 2-nitro-1-fluorenol-1-C^{14}, m.p. 162–165°, 50% yield.

2-Amino-1-fluorenol-1-C^{14}. A solution of 2-nitro-1-fluorenol-1-C^{14} (0.182 g., 0.80 mmole) in 29 ml. of hot ethanol was prepared in a 50-ml. flask equipped with a reflux condenser and magnetic stirrer. Zinc dust (1.46 g.) was added and the mixture was stirred and heated under reflux while a solution of 0.4 g. of calcium chloride in 4.4 ml. of water was added dropwise. Stirring and heating were continued for 2.5 hr. at the end of which time the hot slurry was filtered through a layer of Celite into 1.6 ml. of concentrated hydrochloric acid. The zinc dust was washed with 5 ml. of ethanol. The combined filtrate and wash liquid were evaporated by means of an air stream and infrared lamp until there remained only a slurry of precipitated salts in a minimum volume of water. The salts were collected on a sintered glass funnel, washed with ether, and dried. The material was dissolved in 8 ml. of water, and the solution was filtered through a bed of Celite into 12 ml. of a 15% sodium acetate solution. The resulting suspension was cooled, and the precipitate was collected without delay. After washing with water, the product was dried *in vacuo* over calcium chloride to yield 0.0958 g. (0.49 mmole) of 2-amino-1-fluorenol-1-C^{14}, 60.5% yield.

N-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide. 2-Amino-1-fluorenol-1-C^{14} (0.0958 g., 0.49 mmole) was dissolved in 22.5 ml. of hot water containing 0.09 ml. of concentrated hydrochloric acid. The solution was filtered through a coarse sintered glass funnel and cooled to room temperature. Freshly distilled acetic anhydride (0.07 ml., 0.74 mmole) was added all at once with magnetic stirring. A solution of 0.09 g. (0.11 mmole) of sodium acetate in 4.9 ml. of water was added, and the reaction mixture was stirred and cooled in an ice bath for 15 min. The gray precipitate was collected and dried. An ethyl acetate solution of the product was percolated through a 0.6 × 15 cm. column of acid-washed, activated alumina. The eluate was evaporated to dryness *in vacuo* and the residue was recrystallized by being dissolved in 3 ml. hot ethanol which was then added to 15 ml. of water. A second pass through an alumina column using the same eluent followed by recrystallization gave pure, white N-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide, m.p. 210–212°. The yield was 0.0726 g. (0.30 mmole, 62.6%) and the specific radioactivity was 0.66 mC./mM.

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[16] Obtained from the Fisher Scientific Company, Chicago, Ill.

Convenient Syntheses of 3-Indolesuccinic and 3-Indolepropionic Acids

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In a recent publication[1] Noland and Hammer have shown that the dibasic acid obtained by the alkaline hydrolysis of maleyldiindole[2] is 3-indolesuccinic acid. The preparation of this acid from indole and diethyl diazosuccinate has been reported previously by Jackson and Manske.[3]

The facile preparation, in 95% yield, of 3-indolealdehyde[4] prompted us to use this compound as starting material for new and convenient syntheses of 3-indolesuccinic and 3-indolepropionic acids.

Compound I, prepared by a modification of a previously described procedure,[5] when treated with potassium cyanide in refluxing ethanol[6] gave rise to 3-indolesuccinonitrile (III). The dinitrile was readily hydrolyzed with aqueous base to give an al-

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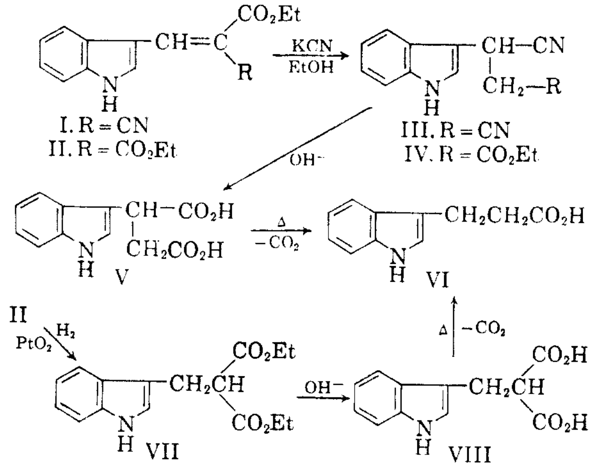

most quantitative yield of 3-indolesuccinic acid (V).

In an alternate synthesis 3-indolealdehyde was condensed with diethyl malonate in the presence of piperidine acetate,[7] and a good yield of ethyl 2-carbethoxy-3-(3-indolyl)acrylate (II) was obtained. This last compound, when treated with potassium cyanide in ethanol, yielded the cyanoester (IV), which on hydrolysis produced 3-indolesuccinic acid (V). This diacid was converted into 3-indolesuccinimide when heated with aqueous ammonia, or better with urea.

As reported by Jackson and Manske,[3] and later confirmed by Noland and Hammer,[1] 3-indolesuccinic acid is readily decarboxylated to 3-indolepropionic acid (VI) when heated above its melting point. A second convenient route to 3-indolepropionic acid was worked out according to the following sequence. Hydrogenation of compound II over platinum oxide gave diethyl 3-indolylmethylmalonate (VII),[8] which upon hydrolysis and subsquent decarboxylation led to 3-indolepropionic acid (VI).

EXPERIMENTAL[9]

Ethyl 2-cyano-3-(3-indolyl)acrylate (I).[5] A solution of 72.5 g. (0.5 mole) of 3-indolealdehyde,[4] 56.5 g. (0.5 mole) of ethyl cyanoacetate and 5 ml. of piperidine in 875 ml. of ethanol was heated at reflux for 10 min. and cooled, yielding 102.5 g. of bright yellow crystalline product melting at 164–165°. Evaporation of the filtrate yielded a second crop of 15 g., m.p. 162–164°; total yield 117.5 g. (98%); reported m.p. 165°.[5]

Ethyl 2-carbethoxy-3-(3-indolyl)acrylate (II). To a solution of 48 g. (0.3 mole) of diethyl malonate in 600 ml. of benzene there was added 43.5 g. (0.3 mole) of 3-indolealdehyde,[4] 6 ml. of piperidine, and 9 ml. of glacial acetic acid. The mixture was heated at reflux for 4 hr. while the theoretical amount (5.4 ml.) of water was collected in a Dean-Stark trap. After removal of the benzene under reduced pressure the residue was recrystallized from ethanol-water to yield 60 g. (70%) of pale yellow crystalline product having m.p. 99–100° (with shrinking at 92°).

Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96. Found: C, 67.04; H, 5.87. Infrared (KBr) (μ): 3.08 (NH); 5.82, 5.92 (ester).

3-Indolesuccinonitrile (III). A mixture of 96 g. (0.4 mole) of ethyl 2-cyano-3-(3-indolyl)-acrylate and 52 g. (0.8 mole) of potassium cyanide in 500 ml. of 90% ethyl alcohol was stirred and heated at reflux for 3 hr. After being cooled in ice the mixture was filtered and the solid washed with 80 ml. of 95% ethanol. The filtrate and washings were combined and concentrated under reduced pressure to one half of the original volume; the concentrated solution was heated to 65–70°, diluted with an equal volume of water, heated again to 65–70° and allowed to cool slowly overnight at 5–10°. The dark brown crystalline product was collected and dried; yield 59 g. of colored crystals melting at 113–116°. The crystalline solid was triturated with a small amount of cold ether, filtered, and recrystallized from 50% aqueous methanol, yielding 52 g. (66%) of colorless crystals melting at 117–118°.

Anal. Calcd. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.5. Found: C, 73.80; H, 4.65; N, 21.2. Infrared (KBr) (μ): 3.00 (NH); 4.45 (CN).

The picrate of 3-indolesuccinonitrile was prepared by adding a boiling solution of picric acid in ethanol to a boiling solution of the dinitrile in ethanol. The cooled solution was diluted with water until crystallization began. The yellow crystals were collected by filtration and recrystallized from ethanol; the pure yellow crystals melted at 117–118°.

Anal. Calcd. for: $C_{18}H_{12}N_6O_7$: C, 50.95; H, 2.85. Found: C, 51.50; H, 3.02.

Ethyl 3-cyano-3-(3-indolyl)propionate (IV). To a solution of 69 g. (0.24 mole) of ethyl 2-carbethoxy-3-(3-indolyl)-acrylate (II) in 300 ml. of 90% ethanol there was added 31 g. (0.48 mole) of potassium cyanide and the mixture was stirred at reflux for 2 hr. It was cooled, filtered, and the solid was washed with 25 ml. of 95% ethanol. The filtrate and washings were combined, diluted with 800 ml. of water and the resultant crystalline precipitate was collected and dried; yield 25.5 g. (61%) of IV having m.p. 108–110°. After successive recrystallizations from ethyl acetate and benzene the analytical sample had m.p. 110–111°.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82. Found: C, 69.82; H, 5.76. Infrared (KBr) (μ): 2.90 (NH); 4.45 (CN); 5.82 (ester).

3-Indolesuccinic acid (V). A suspension of 39 g. (0.2 mole) of III, or 48.4 g. (0.2 mole) of IV, in 330 ml. of 15% aqueous potassium hydroxide solution was heated at reflux for 3 hr. At the end of this period a clear solution was obtained and only a small amount of ammonia was being evolved. The resultant dark solution was treated with charcoal while still hot, filtered, cooled, and acidified to *p*H 2 with concentrated hydrochloric acid. The white crystalline product was collected, washed with cold water, and dried; yield 44.5 (95%), m.p. 197–200° (dec., with gas evolution). An analytical sample, recrystallized from water, melted at 204–205° (dec., gas evolution): reported m.p. 199°[3] and 195–197°.[1]

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.72; neut. equiv., 116.6. Found: C, 62.10; H, 4.88; neut. equiv. 116.7. Infrared (KBr) (μ): 2.92 (NH); 5.98 (C=O).

Diethyl 3-indolesuccinate was prepared in 93% yield from V, ethanol, and dry hydrogen chloride.and had m.p. 80–81°, a value in agreement with those previously reported.[1,3]

This diester was also prepared by saturating a chilled

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[7] Whereas ethyl cyanoacetate condensed readily with 3-indolealdehyde in the presence of piperidine, the same catalyst failed to bring about the condensation with diethyl malonate.

[8] (a) H. R. Snyder, C. W. Smith, and J. M. Stewart, *J. Am. Chem. Soc.*, **66**, 200 (1944). (*b*) D. I. Weisblat and D. A. Lyttle, *J. Am. Chem. Soc.*, **71**, 3079 (1949). (c) G. Stork and G. Singh, *J. Am. Chem. Soc.*, **73**, 4742 (1951).

[9] All melting points are uncorrected. Analyses by R. M. Downing, infrared by D. Evans.

solution of III or IV in ethanol with dry hydrogen chloride, diluting with water to the point of turbidity and storing for 24 hr. at 5–10°. This procedure yielded 88 to 90% of the desired material; m.p. 79–81°.

Dimethyl 3-indolesuccinate[2] was prepared either from the diacid or the dinitrile by treating them with dry hydrogen chloride in methanol. The dimethyl ester was obtained in yields of 85–95% and melted at 73–76° after recrystallization from a benzene-*n*-pentane mixture: reported m.p. 74°.[2]

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79. Found: C, 64.65; H, 6.06.

3-Indolesuccinimide. The following modification of the method used by Shaw[10] for the preparation of 3-indoleacetamides was employed. An intimate mixture of 35 g. (0.15 mole) of 3-indolesuccinic acid (V) and 70 g. (0.46 mole) of urea in a flask fitted with an air condenser was introduced into an oil bath at 160°. The bath temperature was raised to 185° during 30 min. and maintained at 180–190° for 2.5 hr. Brisk evolution of ammonia was evident during the first part of the final heating period. The hot melt was diluted to 250 ml. with water, cooled and filtered. The crude product was recrystallized from methanol with charcoaling, yielding 17 g. (53%) of white crystals of m.p. 197–198°. A mixed m.p. between this product and V gave considerable depression.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.29; H, 4.67; N, 13.1. Found: C, 67.33; H, 4.70; N, 12.8. Infrared (KBr) (μ): 2.92 (indole NH); 5.50, 5.65, 5.86, and 5.95 (C=O).

A small amount of 3-indolesuccinimide was also obtained by gradually heating a sample of 3-indolesuccinic acid (V) to 240° in concentrated ammonium hydroxide; it had m.p. 194–195°. The m.p. of a mixture of this material with that prepared from V and urea was not depressed.

Diethyl 3-indolylmethyl malonate (VII). Hydrogenation of a sample of II in ethanol over platinum oxide at 50 p.s.i. gave a 62% yield of diethyl 3-indolylmethylmalonate (VII)[8], m.p. 61–63° (recrystallized from benzene-*n*-pentane). An analytical sample was recrystallized from ethanol-water and had m.p. 63–65°; reported 62°.[8a,b]

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62. Found: C, 66.68; H, 6.76. Infrared (KBr) (μ): 2.97 (NH); 5.77 and 5.83 (C=O).

3-Indolylmethylmalonic acid (VIII). A 2.8-g. (0.01 mole) sample of diethyl 3-indolylmethylmalonate (VII) was heated under reflux for 1 hr. in 25 ml. of 15% potassium hydroxide solution. The solution was charcoaled, filtered, cooled, and acidified to *p*H 2 with concentrated hydrochloric acid to yield 1.6 g. (89%) of reddish 3-indolylmethylmalonic acid (VIII);[8] m.p. 182–184° (dec., with evolution of gas). An analytical sample, recrystallized from water, was still reddish; m.p. 185–187° (dec., gas evolution); reported 178° (dec.).[8a]

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.74. Found: C, 62.08; H, 4.94.

3-Indolepropionic acid (VI). Pyrolysis of a sample of 3-indolesuccinic acid (V) for 2–3 minutes at 205° gave a vigorous evolution of carbon dioxide; the residue was cooled and recrystallized from 20% ethanol (charcoal). The colorless crystals thus obtained melted at 133–134° either alone or upon admixture with an authentic sample of 3-indolepropionic acid.

3-Indolylmethylmalonic acid (VIII) was pyrolyzed at 190–200° to yield VI in a yield of 46%, m.p. 132–134° either alone or upon admixture with authentic VI.

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(10) E. Shaw, *J. Am. Chem. Soc.*, **77**, 4319 (1955).

Metalation of Polystyrene[1]

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This metalation of polystyrene was done in the hope of developing a method for introducing metal atoms on the alpha (to phenyl) carbon atoms of the chain. The reaction proved easier than expected. Under some conditions or in some fractions, 86 to 94% of the maximum possible amount of metalation on a chain was realized. The project was terminated before the fine conditions for control could be worked out, but the results deserve mention because they represent a new chemical attack at specific points on this polymer. The reaction also provides a new base for graft polymerization or chemical processes on polystyrene.

The reagent was potassium metal and sodium oxide[2] although the very recent experience[3] with amyl- and phenyl-potassium suggests that those reagents might be equally good or even better because they are finely divided and leave no inorganic residue other than potassium chloride or an alkoxide. Benzene was the medium, that solvent having been found satisfactory in a series of preliminary experiments with cumene, a low molecular weight pattern molecule. After a stipulated time the mixture was carbonated. Then the solid was digested with hot water to remove the carboxylate. Mineral acid precipitated the carboxylated polymer. The dried polymer was weighed, titrated with alkali to determine the neutralization equivalent, and mixed with potassium bromide for infrared measurements.

Metalation was about as easy as with cumene itself. Time was very important. At the end of three hours, under approximately comparable conditions, the weights of carboxylic acid were 0.7 and 0.5 gram for cumene and the polymer, respectively. The neutralization equivalent of the polymer carboxylate indicated that 94% of the available positions on the metalated chain had been occupied. In a longer time (15 hr.) the polymer took up 42% of the potassium, and 36% of the polymer was recovered as carboxylate (14.4 g.) for which 89% of the maximum possible metalation had taken place.

The potassium ion should be on the carbon alpha to the phenyl group because metalation of alkylaryl hydrocarbons by this reagent has occurred[2] only at that place. The absorption at 1700 cm.$^{-1}$ in the infrared (Fig. 1) accorded with this view. The position of absorption was similar to that found for other acids of that type. The intensity of absorption was very high, being much greater at

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(1) This work was performed as part of a research project sponsored by the National Science Foundation.

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