Reaction of p-chloro-, p-bromo- and p-iodotoluenes with potassium anilide. Potassium (5.6 g., 0.144 mole) was added to 250 ml. of refluxing aniline. The appropriate *p*-halotoluene (0.10 mole) was added, and the reaction mixture was heated under reflux for 15 min. Water was cautiously added to decompose the unreacted bases. Ether was added, the organic layer was washed several times with dilute hydrochloric acid, dried over anhydrous magnesium sulfate, and saturated with anhydrous hydrogen chloride. The precipitate was washed with ether, treated with water, extracted with ether, and flash distilled to remove high-boiling tarry materials. The compositions of the distillates were determined by comparison of their infrared spectra in carbon disulfide solution at 11.75–14.00 μ with those of synthetic mixtures of *m*- and *p*-tolylphenylamines.

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Synthesis of 1-Alkyltryptophans

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Considerable effort has been expended on the synthesis of tryptophan analogs for use in the study of enzyme inhibition. This note describes a new general method for the synthesis of 1-alkyltryptophans, in particular the 1-methyl and 1-ethyl derivatives. The only 1-alkyltryptophan previously described is 1-methyltryptophan. This was obtained from 1-methylindole-3-aldehyde *via* the azlactone[1,2] and from 1-methylindole *via* 1-methylgramine.[3] Our starting material was ethyl-α-acetylamino-α-carbethoxy-β-(3-indole)-propionate.[4] This indole derivative was alkylated on refluxing in an inert solvent with alkyl *p*-toluenesulfonates in the presence of potassium carbonate. Subsequent steps in the synthesis were analogous to those used by Snyder and Smith[4] for the synthesis of DL-tryptophan, namely basic hydrolysis to the malonic acid derivative, decarboxylation to the 1-alkyl-*N*-acetyltryptophan and finally deacetylation by refluxing with dilute hydrochloric acid.

The alkylation of indole using our conditions has led to both 1- and 3-alkyl derivatives[5,6] and since, in our reaction, there was also the possibility of alkylation of the actylamino group, the alkyltryptophans were decarboxylated in molten fluorene at 240–270°. The products were 1-alkyltryptamines, characterized as their phthalimides, hydrochlorides, and picrates. Furthermore, the infrared spectrum of our 1-methyltryptophan was quite different from the spectrum of the isomeric L-abrine [α-methylamino-β-(3-indole)propionic acid]. Our 1-methyltryptophan had a melting point of 250°–251° (dec.). Melting points previously reported for this compound were 289°,[1] 285°,[2] and 223–225°.[3] This variation may be due to partial solvation of the amino acid since a lower melting point was observed in the compound was not extensively dried *in vacuo* at 100°.

EXPERIMENTAL[7]

Ethyl-α-acetylamino-α-carbethoxy-β(3-N-methylindole)propionate (I). Ethyl-α-acetylamino-α-carbethoxy-β(3-indole)-propionate[4] (17.3 g., 0.05 mole) was refluxed in 200 ml. of dry xylene with methyl *p*-toluenesulfonate (10.0 g., 0.06 mole) and anhydrous potassium carbonate (15 g., 0.11 mole) for 5 hr. The mixture was filtered, the residue was washed with benzene, and the combined filtrates evaporated to dryness *in vacuo*. The residue was titurated with ether yielding crystals of I (12.6 g., 70% yield), m.p. 124°. Crystallization from ethanol afforded colorless rhombic crystals, m.p. 125–126°.

Anal. Calcd. for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71; N, 7.77. Found: C, 63.19; H, 6.70; N, 7.57.

The methylation was also carried out successfully in refluxing *o*-dichlorobenzene resulting in a 62% yield.

Ethyl-α-acetylamino-α-carbethoxy-β(3-N-ethylindole)propionate (II). This 1-ethyl derivative was prepared by substituting ethyl *p*-toluenesulfonate (12.0 g., 0.06 mole) for the methyl ester in the previous synthesis. The crude product (7.0 g., 54% yield), m.p. 107–108°, was crystallized from ethanol to yield short colorless prisms, m.p. 115–116°.

Anal. Calcd. for $C_{20}H_{26}N_2O_5$: C, 64.15; H, 7.00. Found: C, 64.10; H, 6.89.

α-Acetylamino-α-carboxy-β(3-N-methylindole)propionic acid (III). The ester I (18 g., 0.05 mole) was refluxed with 100 ml. of 10% sodium hydroxide solution for 4 hr. The cooled, filtered solution was acidified with concentrated hydrochloric acid. The malonic acid derivative (III) which separated was crystallized from 50% aqueous ethanol to yield colorless rhombic plates (14.1 g., 93% yield), m.p. 147–148°. The crystals became pink on exposure to air.

Anal. Calcd. for $C_{15}H_{16}N_2O_5$: C, 59.20; H, 5.30; N, 7.77. Found: C, 58.91; H, 5.56; N, 7.57.

α-Acetylamino-α-carboxy-β(3-N-ethylindole)propionic acid (IV). Hydrolysis of II as in the previous preparation yielded IV as colorless prisms (from ethanol) in 85% yield, melting at 128–129°.

Anal. Calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70. Found: C, 60.22; H, 5.94.

1-Methyl-N-acetyltryptophan (V). The malonic acid derivative III (7.6 g.) was heated in a nitrogen atmosphere at 180–190° for 15 min. The pale yellow glass which remained on cooling was crystallized from ethanol (charcoal) to yield large colorless prisms of V (5.6 g., 86% yield), m.p. 169.5–170.5° (lit.[3] 171–172°).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.58; H, 6.20. Found: C, 64.59; H, 6.44.

1-Ethyl-N-acetyltryptophan (VI). The decarboxylation of IV carried out as in the previous preparation yielded colorless plates of VI (from ethanol) in 82% yield, m.p. 185–187°.

(1) H. Wieland, W. Konz, and H. Mittasch, *Ann.*, **513**, 1 (1934).
(2) T. Matsuura, K. Matsui, and K. Ichihara, *Med. J. Osaka Univ.*, **4**, 449 (1954); *Chem. Abstr.*, **49**, 6222 (1955).
(3) H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, **70**, 3855 (1948).
(4) H. R. Snyder and C. W. Smith, *J. Am. Chem. Soc.*, **66**, 350 (1944).
(5) D. A. Shirley and P. A. Roussel, *J. Am. Chem. Soc.*, **75**, 375 (1953).
(6) H. Plieninger, *Ber.*, **87**, 127 (1954).
(7) Melting points are corrected. Microanalyses were performed by Miss Heather King of these laboratories.

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61. Found: C, 65.46; H, 6.56.

1-Methyltryptophan (VII). The acetyl derivative V (3.0 g.) was refluxed with 20 ml. of 2*N* hydrochloric acid for 2 hr. The solution was evaporated to dryness *in vacuo* and the residue redissolved in water. The 1-methyltryptophan crystallized (1.8 g., 72% yield) on addition of 1.5 g. of sodium acetate dissolved in a little water. Recrystallization from aqueous ethanol (charcoal) yielded colorless plates of VII, m.p. 250–251°.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.87; H, 6.59; N, 12.82.

The infrared spectrum of VII, determined as a suspension in potassium bromide, had prominent maxima at 1623, and 735 cm.$^{-1}$

The picrate of the amino acid was obtained on admixture of methanolic solutions of VII and picric acid. Crystallization from water gave fine orange-red needles of the hydrated picrate, m.p. 142–143° (with dec.).

Anal. Calcd. for $C_{12}H_{14}N_2O_2.C_6H_3N_3O_7.H_2O$: C, 46.45; H, 4.11. Found: C, 46.31; H, 4.10.

The amino acid hydrochloride was obtained by addition of ethanolic hydrogen chloride to VII, refluxing, and allowing to cool. Recrystallization from ethanol gave colorless needles of 1-methyltryptophan hydrochloride, m.p. 235–236° (dec.) (lit.[3] 239–242°).

Anal. Calcd. for $C_{12}H_{14}N_2O_2.HCl$: C, 56.59; H, 5.94. Found: C, 56.50; H, 6.01.

1-Ethyltryptophan (VIII). The acetyl derivative VI was refluxed with 2*N* hydrochloric acid for 2 hr. and then evaporated to dryness *in vacuo*. The residue was dissolved in water and brought to a *p*H of 6 by the addition of sodium hydroxide. The 1-ethyltryptophan immediately crystallized in small prisms, m.p. 234–235° (dec.). Crystallization from aqueous ethanol yielded colorless plates, m.p. 225–226° (dec.).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.07; H, 6.95; N, 11.89.

The picrate crystallized in short orange prisms from water as the monohydrate, m.p. 127–129° (dec.).

Anal. Calcd. for $C_{13}H_{16}N_2O_2.C_6H_3N_3O_7.H_2O$: C, 47.60; H, 4.42. Found: C, 47.61; H, 4.47.

Decarboxylation of the 1-alkylamino acids. (*a*) *1-Methyltryptamine.* 1-Methyltryptophan (1.0 g.) was added to molten fluorene (10 g.) heated on a metal bath at 270°. After 2–3 min. all evolution of carbon dioxide ceased and the mixture was cooled, diluted with benzene, and extracted with dilute hydrochloric acid. The aqueous extract was clarified by shaking with ether and then made basic with sodium hydroxide and extracted with ether. The dried ether extract was evaporated and the residue distilled (180°/0.1 mm.) to yield 1-methyltryptamine as a pale yellow oil (0.484 g., 64% yield). The picrate was obtained as yellow prismatic needles from ethanol, m.p. 183–184° (lit.[8] 180–181°). The hydrochloride was obtained as colorless plates from ether-ethanol, m.p. 205–206° (dec.) (lit.[3] 199–202°). The phthalimide was prepared by refluxing the amine with an equal weight of phthalic anhydride in acetic acid. Crystallization from the same solvent yielded pale yellow needles, m.p. 178–179° (lit.[3] 177–177.5°).

(*b*) *1-Ethyltryptamine.* The 1-ethyltryptophan was decarboxylated in molten fluorene at 240–250°. The amine was isolated as described in the previous preparation and was obtained as a pale yellow oil in 53% yield. The picrate was obtained as orange prisms from ethanol, m.p. 182.5–183° (lit[9] 180–181°). A large depression in melting point was observed on admixture with the picrate of N-ω-ethyltryptamine,[9] m.p. 186–187°. 1-Ethyltryptamine hydrochloride separated from a mixture of ethanol and ether in fine colorless needles, m.p. 193.5–194°.

Anal. Calcd. for $C_{12}H_{16}N_2.HCl$: C, 64.13; H, 7.63. Found: C, 64.20; H, 7.73.

1-Ethyltryptamine phthalimide was obtained as pale yellow prismatic needles from ethanol, m.p. 150–151°.

Anal. Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70. Found: C, 75.66; H, 5.78.

Paper chromatography of the amino acids. Chromatography was carried out on Whatman No. 1 paper using a mixture of 1-butanol (400 ml.), acetic acid (100 ml.), and water (250 ml.) as the developing solvent. The R_f values of tryptophan, 1-methyltryptophan, and 1-ethyltryptophan in this solvent were 0.63, 0.71, and 0.79, respectively. The amino acids appeared as brown spots on spraying with Millon reagent.

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(8) E. Späth and E. Lederer, *Ber.*, **63**, 2102 (1930).
(9) K. Eiter and O. Svierak, *Monatsh.*, **83**, 1453 (1952).

Anionic Exchange Resins as Catalysts in the Preparation of Fulvenes

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The preparation of fulvenes by the condensation of cyclopentadiene with aldehydes or ketones in the presence of bases, such as ammonia and the alcoholates or hydroxides of sodium and potassium,[1] has long been known.[2] Work in this laboratory has now demonstrated that ion exchange resins of either the high or medium base strength type also are capable of catalyzing this reaction, giving in many cases yields comparable to those obtained with more conventional catalysts. This system possesses an advantage in that the reaction time can be quite easily controlled simply by regulating the contact time of the reactants with the ion exchange resin. Thus it is possible to achieve some success in the preparation of sensitive monosubstituted fulvenes and of fulvene itself by simply stopping the condensation before the secondary, base-catalyzed reactions start. This also helps to avoid complications caused by the presence of a base during the isolation and purification of the product.

Several fulvenes were prepared using this method, including fulvene, methyl fulvene, ethyl fulvene, and dimethyl fulvene. Of these, only dimethyl fulvene was isolated. In spite of numerous attempts, the remainder of the fulvenes could not be purified due to their extreme instability. Attempts to react them with maleic anhydride in order to prepare their Diels-Alder adducts as derivatives were also unsuccessful because of both their thermal instability and the reactivity of the residual cyclopentadiene in this reaction. Thus it was necessary to depend on the intense color of the products and their characteristic ultraviolet absorption spectra for proof of their presence. This of course, makes it

(1) J. H. Day, *Chem. Revs.*, **53**, 167 (1953).
(2) J. Thiele and H. Balhorn, *Ann.*, **348**, 1 (1906).