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AN IMPROVED METHOD FOR DECARBOXYLATING INDOLE-2-CARBOXYLIC ACIDS AND ITS APPLICATION IN THE SYNTHESIS OF 7-AMINO-DL-TRYPTOPHAN

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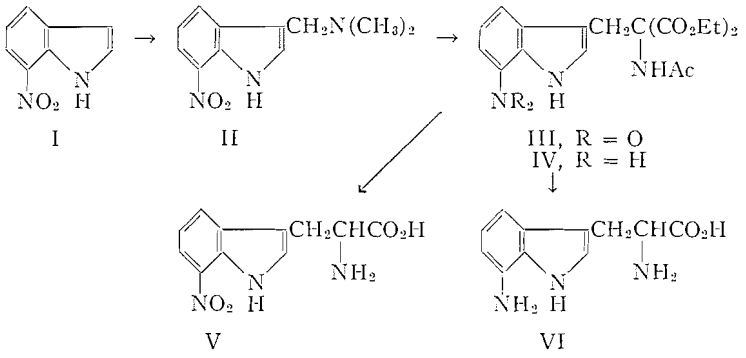
A projected synthesis of 7-bis(2-chloroethyl)amino-DL-tryptophan in these laboratories required the preparation of large quantities of 7-nitroindole (I). The general procedure of Parmerter *et al.* (1) for the preparation of I was very convenient except for the final step, the decarboxylation of 7-nitroindole-2-carboxylic acid in boiling quinoline. When



the decarboxylation was effected in refluxing N,N-dimethylacetamide employing as catalyst the copper salt of the acid, prepared by the method of Piers and Brown (2), the yield of I was higher and the isolation was much simpler than in the conventional quinoline procedure. The dimethylacetamide method of decarboxylation should be generally useful in the preparation of substituted indoles.

While this work was in progress, Da Settimo (3) and Hiremath and Siddappa (4) reported the synthesis of 7-nitro-DL-tryptophan (V), utilizing the same intermediates, the gramine (II) and the acetamidomalonate ester (III), that were used to prepare VI. Catalytic reduction of the diester (III) afforded a good yield of the crystalline amino-ester (IV), which was hydrolyzed directly to 7-amino-DL-tryptophan (VI) isolated as

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the hydrated dihydrochloride. Alternatively, 7-nitro-DL-tryptophan (V) (3) could be hydrogenated catalytically to the free base (VI), which was obtained as a crystalline solid and also converted to the dihydrochloride.

EXPERIMENTAL

7-Nitroindole (I)

A mixture of 4.0 g of 7-nitroindole-2-carboxylic acid (1), recrystallized from ethanol and *completely free* of inorganic salts, 0.4 g of the copper salt of 7-nitroindole-2-carboxylic acid, prepared by the method of Piers and Brown (2), and 20 ml of N,N-dimethylacetamide was refluxed, under nitrogen, until carbon dioxide evolution ceased (about 5 hours), then was poured onto 200 g of cracked ice. The yellow-green precipitate was washed and dried, then crystallized from 60 ml of boiling petroleum ether (60–110°) using Norit A, to afford 2.8 g (89%) of I, m.p. 96–97° (lit. (1) gives m.p. 95–96°).

7-Nitrogramine (II)

7-Nitrogramine (II) was prepared essentially as described by Da Settimo (3) although different physical constants were obtained. Thus, 7.0 g of 7-nitroindole (I) gave 11.2 g of crude II, m.p. 47–59°. Recrystallization of material by dissolving in 1 volume of hot methanol and adding 4 volumes of water gave the hydrate of II, m.p. 55–60°. Anal. Calc. for $C_{11}H_{13}N_3O_2.H_2O$: C, 55.7; H, 6.37; N, 17.7. Found: C, 55.7; H, 6.31; N, 17.9.

Alternatively, recrystallization from boiling toluene with azeotropic removal of any water gave the anhydrous compound, m.p. 91–92° (lit. (3, 4) give m.p. 69–71° and 79–80°, respectively). Anal. Calc. for $C_{11}H_{13}N_3O_2$: C, 60.3; H, 5.98; N, 19.2. Found: C, 60.4; H, 6.16; N, 18.8.

Ethyl α-Acetamido-α-carbethoxy-β-(7-amino-3-indolyl)propionate (IV)

A suspension of 3.0 g of ethyl α-acetamido-α-carbethoxy-β-(7-nitro-3-indolyl)propionate (III), prepared using the same procedure described by Da Settimo (3), 0.3 g of 5% palladium-on-charcoal, and 150 ml of absolute ethanol was treated with hydrogen at 25 p.s.i. and room temperature until the hydrogen uptake ceased (about 2 hours). The solution was filtered rapidly and the filtrate concentrated *in vacuo* to about 30 ml. The solution, after being chilled and scratched, deposited 2.3 g (82%) of crystalline product. The mother liquors were concentrated and treated with water, giving a second crop of crystals which raised the total crude yield to 95%. The analytical sample was recrystallized from ethanol and had m.p. 182–183°; $\lambda_{max\,(\mu)}^{Nujol}$ 2.90, 2.95, 3.10 (NH), 5.73 (ester C=O), 6.02 (amide C=O). Anal. Calc. for $C_{13}H_{23}N_3O_5$: C, 59.8; H, 6.42; N, 11.6. Found: C, 60.1; H, 6.62; N, 11.5.

7-Amino-DL-tryptophan (VI) and the Dihydrochloride

Method A

A stirred mixture of 0.13 g of 7-nitro-DL-tryptophan (3), 0.01 g of platinum oxide, and 50 ml of water was treated with hydrogen at atmospheric pressure until the theoretical amount of gas was absorbed (about 1 hour). The warm (50°) mixture was filtered rapidly and the filtrate was evaporated *in vacuo*, leaving a grey, crystalline powder which was dissolved in 20 ml of hot 60% aqueous ethanol. The solution was cooled, filtered through a thin layer of Norit A, and the filtrate concentrated *in vacuo*, affording 0.07 g (61%) of white crystals. The analytical sample, which slowly decomposed above 250°, was obtained by recrystallization from 3 ml of hot water; $\lambda_{max\,(\mu)}^{Nujol}$ 2.97 (NH), 3.6–4.0 and 4.75 ($NH_3\oplus$), 5.99 (NH_2), 7.04 ($CO_2\ominus$). Its paper chromatographic behavior in the isopropanol – 2 *N* hydrochloric acid system was identical with that of the dihydrochloride (see below). Anal. Calc. for $C_{11}H_{13}N_3O_2$: C, 60.3; H, 6.00; N, 19.2. Found: C, 59.8; H, 6.19; N, 18.9.

The dihydrochloride was obtained from the free base (VI) by dissolving it in a small volume of conc. hydrochloric acid. The chilled solution deposited crystals which were recrystallized from methanol–ether, affording a solid which decomposed slowly above 200°; $\lambda_{max\,(\mu)}^{Nujol}$ 3.08 (NH), 3.7–4.0 ($NH_3\oplus$), 5.69 (carboxyl C=O). The compound was homogeneous on paper chromatography (Whatman No. 1) in isopropyl alcohol – 2 *N* hydrochloric acid (65:35) with R_f 0.51, detected both by ninhydrin spray and ultraviolet examination. Anal. Calc. for $C_{11}H_{15}Cl_2N_3O_2.\frac{1}{4}H_2O$: C, 44.5; H, 5.27; Cl, 23.9; N, 14.2. Found: C, 44.7; H, 5.63; Cl, 24.0; N, 14.0.

Method B

A solution of 0.50 g of the aminoester (IV) in 4.0 ml of conc. hydrochloric acid was heated at reflux under nitrogen for 4 hours, then chilled. A crystalline solid, 0.26 g (65%), was collected and washed with acetone. The product was crystallized three times from methanol and ether, affording the analytical sample, which was identical with dihydrochloride prepared by method A (see above) according to infrared spectral and paper chromatographic comparison.

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THE INITIAL RATE OF DECOMPOSITION OF WATER VAPOR BY AN ELECTRICAL DISCHARGE[1]

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Gill and Townsend (1), in a mathematical analysis, based on classical kinetic theory, of the motions of free electrons in a high-frequency gas discharge, developed an expression which predicts that the transfer of energy from the field to the gas molecules will have a maximum value when the frequency of the electrical field (ν) is equal to the kinetic theory frequency of elastic gas–molecule collisions (f).

If the density of free electrons remains constant with pressure for a high-frequency discharge in water vapor and if dissociative excitation of water molecules is the main consequence of the electron–molecule collisions while no further destruction of water occurs during subsequent reactions then the rate of decomposition should exhibit a maximum at the pressure where $\nu = f$.

In this work, $\nu < f$, except at very low pressures, and hence the maximum in the rate dependence on pressure may not be observed. However, the rate of decomposition should decrease with increasing pressure.

EXPERIMENTAL

The reaction cell was a 250-ml rectangular volumetric flask upon opposite sides of which were deposited two rectangular (4 × 6 cm) indium electrodes. The distance between the electrodes was approximately 5.7 cm. One electrode was grounded and the other connected to a Tesla coil (standard leak tester). The power

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