4.409; mmoles $(C_4H_9)_3B$, 2.700, 4.240; m. at. H, 2.513, 3.970; at. H/mole $(C_4H_9)_3B$, 0.932, 0.936.

The concentrated solution of the salt slowly evolved butane, but the rate was too slow for quantitative recovery. At the same time, crystalline material separated. Butane was identified by its mol. wt.: wt. gas g., 0.0302, 0.1010; cc. (S.T.P.), 12.05, 38.57; mol. wt. found, 56.2, 58.7; calcd. for C_4H_{10}, mol. wt., 58.1. The weight of the dry product gave no clue as to its composition; an analysis for ethylamine gave 1.45 moles per mole of original borane.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

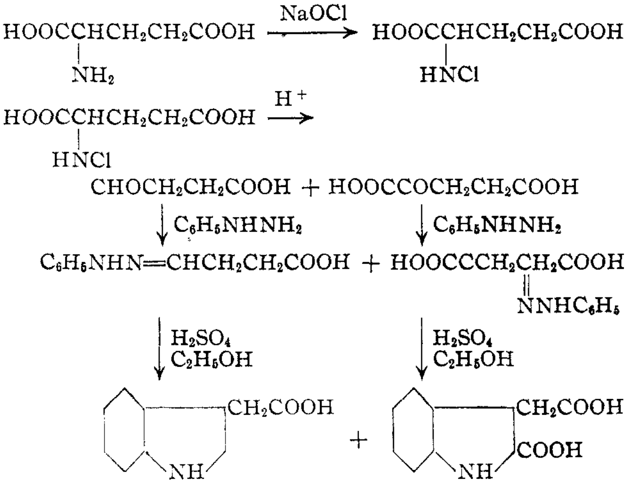
Synthesis of Indoleacetic Acid from Glutamic Acid and a Proposed Mechanism for the Conversion[1]

BY SIDNEY W. FOX AND MILON W. BULLOCK

An economical method for converting glutamic acid to indoleacetic acid, through the intermediate succinaldehydic acid phenylhydrazone, has been developed. α-Ketoglutaric acid has been found as a by-product in the preparation of the succinaldehydic acid. For the decomposition of the intermediate α-N-chloroaminoglutaric acid there is proposed a mechanism which explains the formation of all the products isolated from the reaction mixture.

Indoleacetic acid has been of interest in a large number of phytological applications which depend on its function as a growth hormone,[2-4] *heteroauxin*. Methods of preparation which might increase its general availability have been needed. The various syntheses of indoleacetic acid which may be found in the literature up until 1939 were critically reviewed by Harradence and Lions,[5] who stressed the inaccessibility of the starting materials. Since that time a number of other syntheses have been reported.[6-9] The methods which have been of most preparative value involve the introduction of the acetic acid residue into preformed indole by formaldehyde and hydrocyanic acid,[8] through gramine and cyanide,[9] by reaction of the indolylmagnesium iodide complex with chloroacetonitrile,[10] and by the reaction of indole with ethyl diazoacetate.[11] The principal other route to indoleacetic acid has been through succinaldehydic acid,[7,11,12] but this procedure has suffered from lengthy methods of preparation of the aldehyde. With the availability of glutamic acid[13] from large-scale manufacture however, it is possible to prepare succinaldehydic acid[14] rapidly, in quantity, and to convert it into the phenylhydrazone which serves as a convenient method of isolation. The precipitated oil can then be transformed into indoleacetic acid through the Fischer ring closure.

The synthesis of indoleacetic acid by this inexpensive conversion of glutamic acid has previously been noted,[15] but the conditions employed at the time did not give satisfactorily reproducible results.[16] This process, illustrated by the reactions below, has been brought under control with details that are presented in the Experimental section.



Although many of the reactions recorded in the above sequence have appeared individually in the literature, it was necessary in this Laboratory to introduce modifications and integration of steps in order to obtain product on a practical scale of operation.

In addition to the succinaldehydic acid formed in the decomposition of the α-N-chloroaminoglutaric acid, a small amount of α-ketoglutaric acid also results, as shown above. The resultant α-ketoglutaric acid phenylhydrazone accompanies the desired product and cyclization of the crude oil gives some of the 2-carboxyindole-3-acetic acid. These two products are easily separated.

Since α-keto acids are not decarboxylated under the conditions employed in the decomposition of the α-N-chloroaminoglutaric acid, the α-keto acid cannot be an intermediate in the formation of the half-aldehyde. To account for the products formed in the reaction mixture the following mechanism

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(1) Journal Paper No. J-1756 of the Iowa Agricultural Experiment Station, Ames, Iowa, Project No. 1110, Chemicals for Agricultural Utility. Also Paper V in a series, Amino Acid Conversion Products. Presented before the Division of Organic Chemistry at the American Chemical Society Meeting, September 8, 1950 at Chicago. From the Ph.D. thesis of Milon W. Bullock, 1950.

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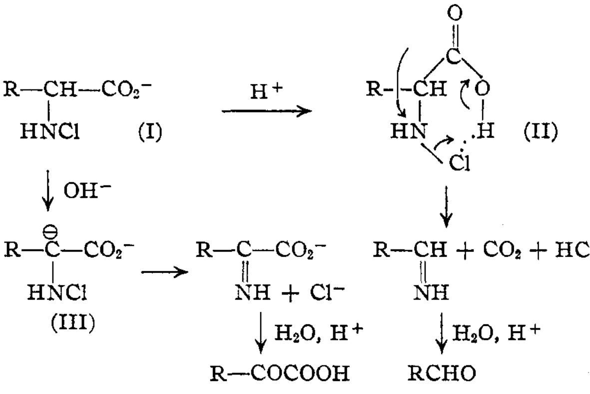
for the decomposition of α-N-chloroaminoacids is proposed



Acidification of the sodium salt of an α-N-chloroamino acid (I) gives the free acid which can form a six-membered chelated ring (II). If the electron shifts indicated by the arrows occur then the molecule can decompose to form three small stable molecules. Under the conditions of the reaction the imine hydrolyzes to form the aldehyde. The yield of the α-keto acid appears roughly to be proportional to the time elapsed between the formation and acidification of the α-N-chloroamino compound (I). This suggests that a proton is removed from the salt of the α-N-chloroamino acid to form the carbanion (III), which immediately or simultaneously stabilizes itself by the loss of a chloride ion. The imino compound may then be hydrolyzed. This proposal is in harmony with the original mechanism suggested by Langheld,[14] for the formation of aldehydes from α-amino acids.

Experimental

Succinaldehydic Acid Phenylhydrazone.—To 24.9 g. (0.20 mole) of glutamic acid (General Mills) in 400 ml. of 0.5 *N* sodium hydroxide solution, 200 ml. of fresh 1 *M* sodium hypochlorite solution[17] was added. The alkaline solution was stirred until it gave a negative test with starch–iodide paper, and acidified by the addition of 70 ml. of 3 *N* HCl which resulted in evolution of carbon dioxide. The solution was heated to 50° and maintained at that temperature until the starch–iodide test was negative (50 minutes). A solution of 22.0 g. (0.20 mole) of phenylhydrazine in 50 ml. of 25% acetic acid was added and the reaction mixture was heated for 20 minutes on the steam-bath. The reaction mixture was acidified to Congo red with hydrochloric acid, cooled, and extracted with 200 ml. of ether and with 100 ml. of ether. The combined ether extracts were extracted with 300 ml. of *N* NaOH. The basic solution was acidified with 10% hydrochloric acid. The phenylhydrazone was extracted with two 100-ml. portions of ether. The combined ether extracts were dried over sodium sulfate and distilled. The yield of crude succinaldehydic acid phenylhydrazone was 18 g. (47%). Other yields were in the range of 53–63%, determined as weighable crystalline *p*-nitrophenylhydrazone prepared from the aqueous solution. A 67% yield was obtained when Chloramine T was used instead of hypochlorite.[16]

Indoleacetic Acid.—Sixteen grams (0.083 mole) of crude succinaldehydic acid phenylhydrazone and a solution of 20 ml. of concentrated sulfuric acid in 180 ml. of absolute ethanol were refluxed five hours under nitrogen. The cooled solution was poured into 1 l. of water and the oil which separated was extracted with three 200-ml. portions of ether. The combined ether extracts were dried over sodium sulfate containing a small amount of potassium carbonate to neutralize any acid in the ether. Distillation of the ether and alcohol left 12.7 g. of an orange oil.

The crude ethyl indole-3-acetate was purified by vacuum distillation. The fraction distilling 160–180° at 0.2 mm., wt. 7.2 g., was collected as product. A second fraction distilling 180–220° at 0.2 mm. weighed 1.5 g. Saponification of this second fraction gave 0.85 g. of 2-carboxyindole-3-acetic acid, which melted 231–233° (dec.) after two recrystallizations from water.

Anal. Calcd. for $C_{11}H_9O_4N$: neut. equiv., 109.5; N, 6.40. Found: neut. equiv., 110 (potentiometric); N, 6.32, 6.34.

A mixed melting point with an authentic sample of 2-carboxyindole-3-acetic acid, m.p. 236° (dec.), prepared by the method of King and L'Ecuyer,[18] melted 235–236° (dec.).

The principal product was saponified by refluxing one hour with 100 ml. of 10% methanolic KOH. The solution was diluted with 200 ml. of water and distilled until the temperature of the vapor reached 99°. The alkaline solution was extracted once with 50 ml. of ether. Most of the ether was distilled out of the aqueous layer by reducing the pressure with an aspirator. Acidification of the aqueous solution with 10% HCl gave a light brown crystalline product. The crystals were filtered off, washed three times with water and air-dried in the filter. The product was washed with a small amount of chloroform, dried, and recrystallized from water (Norit A). This gave 1.82 g. of indoleacetic acid, m.p. 164–165° (dec.). A mixed melting point with an authentic sample of indoleacetic acid showed no depression. The mother liquors were combined and extracted with three 30-ml. portions of ether. The combined ether extracts were dried over sodium sulfate and distilled. The residue was extracted with 10 ml. of chloroform. The crystals were filtered off and washed with three 5-ml. portions of chloroform. This gave 1.47 g. of product, m.p. 155–160°. After one recrystallization from 20 ml. of water this product melted 165–167° (dec.), and weighed 1.21 g. The total yield of pure indoleacetic acid was 3.03 g. (21%).

The results of some other runs are summarized in Table I.

TABLE I

YIELDS OF INDOLEACETIC ACID IN SEVERAL RUNS

Run	Crude succinaldehydic acid phenylhydrazone, g.	Cyclization agent, H_2SO_4, ml.	EtOH, ml.	Yield of product Crude, %	Pure indoleacetic acid, %
1	28.0	70	700	34	28[a]
2	9.0	10	90	32	19[b]
3	8.2	10	90	32	24[b]

[a] The ester was distilled in a molecular still. [b] The ester was distilled through a short vacuum-jacketed Claisen still head.

Attempts to cyclize succinaldehydic acid phenylhydrazone with boron trifluoride without solvent, and with acetic acid as solvent, were not successful. An attempt to cyclize the ethyl ester of the succinaldehydic acid phenylhydrazone with boron trifluoride was also unsuccessful, as was an attempt to cyclize the acid with an hydrochloric acid solution saturated with zinc chloride. Since no starting material was isolated in any of the unsuccessful experiments, it is not known whether cyclization failed or whether the negative results were due to the difficulty of isolating the product from the reaction mixture. In none of these unsuccessful experiments, however, was the crude ester from the cyclization mixture purified by distillation before saponification.

AMES, IOWA RECEIVED OCTOBER 26, 1950

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(17) Prepared by the method of F. Raschig, *Ber.*, **40**, 4580 (1907). A commercial solution of sodium hypochlorite, "Chlorox," was found to be unsatisfactory.

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