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A Synthesis of DL-Tryptophan from Acrolein[*1]

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DL-Tryptophan hydrantoin was obtained from phenylhydrazone of β-(hydanto-5-yl)-propionaldehyde acetal (5-(γ,γ-dialkoxypropyl)hydantoin) by Fischer's indole synthesis. β-(Hydanto-5-yl)propionaldehyde acetal was prepared by Bucherer's reaction from 1,1-diacetoxy-4,4-dialkoxybutane obtained by the hydroformylation of acrolein acetate. Attempts to crystallize β-(hydanto-5-yl)-propionaldehyde acetal from Bucherer's reaction solution were unsuccessful, but 5-alkoxy-1,3-dioxoperhydropyrro[1,2-*c*]imidazole was obtained by treating the solution with ion exchange resins in alcohol. It could be also converted to tryptophan hydantoin.

Tryptophan, an essential amino acid for human and animals, has been prepared by various synthetic routes since the first successful synthesis, by Ellinger, in 1907. The method using acrolein as the starting material was employed by Warner and Moe[1] and developed by Chibata and Yamada.[2] Namely, DL-tryptophan was obtained by the hydrolysis and decarboxylation of the indole derivative prepared from phenylhydrazone of γ-acetamido-γ,γ-dicarbethoxybutyraldehyde by Fischer's indole synthesis. The aldehyde was obtained by a Michael-type condensation between acrolein and ethyl acetamidomalonate. Of the hitherto reported methods, the synthetic route employed by Komachiya *et al.*[3] appears to be one of the most suitable routes for industrial synthesis. Tryptophan was obtained by the hydrolysis of β-(hydanto-5-ylmethyl)indole prepared from phenylhydrazone of β-(hydanto-5-yl)propionaldehyde by Fischer's indole synthesis. The aldehyde was formed by the catalytic hydrogenation of the 5-(β-cyanoethyl)-hydantoin obtained by Bucherer's reaction of β-cyanopropionaldehyde in aqueous acetic acid in the presence of a Raney nickel catalyst poisoned with lead. Considering these facts, it seemed possible to prepare DL-tryptophan from the 1,1-diacetoxy-4,4-dialkoxybutane obtained by the hydroformylation of acrolein acetate described in a previous paper.[4] The object of this paper is to describe this method.

The acetals of 4,4-diacyloxybutyraldehyde have two reactive groups. The diacetoxy group may be converted to the hydantoin group by Bucherer's reaction, while the acetal group may remain unchanged under these conditions, thus the acetals of 4,4-diacyloxybutyraldehyde can be converted to 5-(γ,γ-dialkoxypropyl)hydantoin. Therefore, the phenylhydrazone of this hydantoin derivative can be employed advantageously in the synthesis of DL-tryptophan.

Results and Discussion

In a previous paper,[4] it was reported that 1,1-diacetoxy-4,4-dialkoxybutane (I) was obtained by the hydroformylation of acrolein acetate. In the usual manner, 5-(γ,γ-dialkoxypropyl)hydantoin (II) was obtained from I by Bucherer's reaction. The reaction mixture in Bucherer's reaction was dried up, and attempts to crystallize II from the resultant syrup were unsuccessful. The alcohol solution of the syrup was then added to cation exchange resins and the mixture boiled for several hours. When the reaction solution was dried up, the residual oil crystallized spontaneously to colorless needles upon cooling. It has been shown by elementary analysis that this substance was not in agreement with II, but it was identified with the structure lost by one mole of alcohol from the formula of II. The infrared spectra of the substance showed that there was evidently a hydantoin ring, while the NMR spectra showed that one of the two NH functional groups of hydantoin ring has no hydrogen atom. Either the 1- or 3-position of hydantoin appeared to be substituted. Stucky[5] has shown that hydantoin in an aqueous or alcoholic alkaline solution underwent amido-imidol tautomerism involving the hydrogen of the 3-position; therefore, substitution in the 3-position was easily detected by the change in the ultraviolet absorption

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spectra. The substance not substituted in the 3-position of hydantoin indicates the absorption at wavelengths from 2000 to 2300 Å, while the 3-substituted substance does not show the absorption. The UV spectrum of the substance obtained from II is shown in Fig. 1.

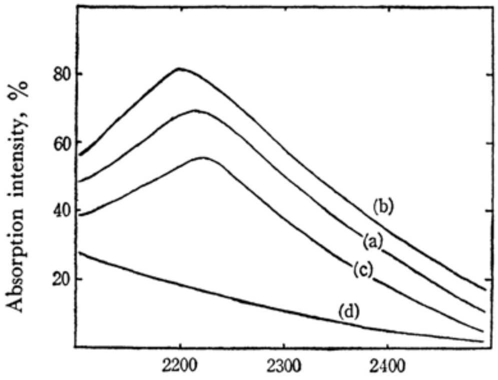


Fig. 1. The UV spectrum in 0.01 N aqueous sodium hydroxide solution.

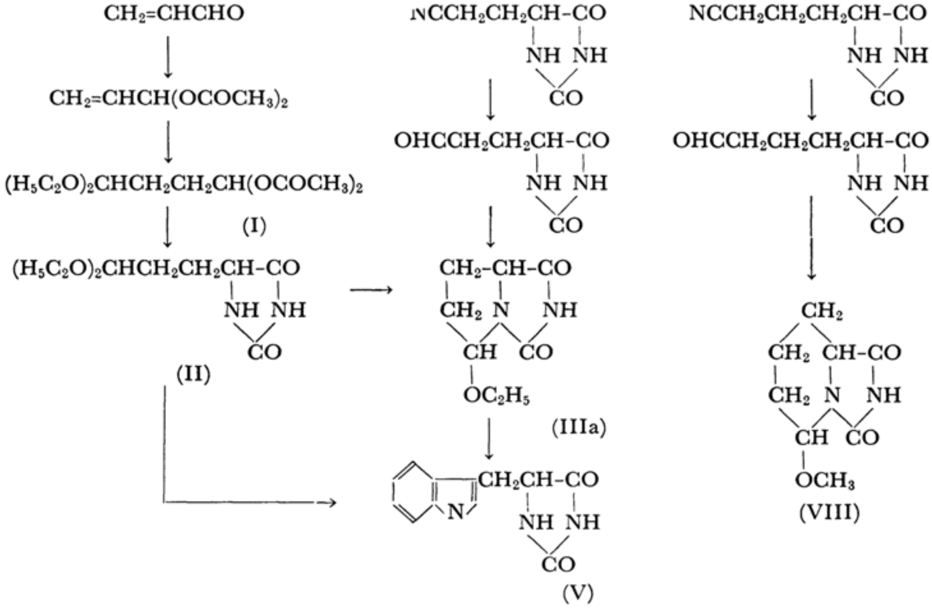
- (a) III λ_{max} 2205 Å $\varepsilon_{max}=9060$
- (b) Tryptophan hydantoin λ_{max} 2195 Å $\varepsilon_{max}=38650$
- (c) 5-Methylhydantoin λ_{max} 2210 Å $\varepsilon_{max}=6375$
- (d) 3-Cyanoethylhydantoin

It seemed likely that this substance was a hydantoin derivative which was substaituted not in the 3-position, but in the 1-position. In view of the above facts, the most reasonable structure of this substance was 5-alkoxy-1,3-dioxoperhydropyrro[1,2-*c*]imidazole (III). III could also be obtained by another route. Namely, 5-(β-cyanoethyl)-hydantoin was reduced to 5-(β-formylethyl)hydantoin according to the directions of Komachiya *et al.*[3]; this latter substance could be isolated as a crystalline semicarbazone derivative from the reaction mixture. When treated with ion exchange resins in alcohol as has been described above, this semicarbazone was converted to III. Similarly, the semicarbazone of 5-(γ-formylpropyl)-hydantoin obtained from 5-(γ-cyanopropyl) hydantoin was converted to 5-alkoxy-1,3-dioxoperhydropyrido[1,2-*c*]imidazole (VIII).

The phenylhydrazone of III was unstable to heat and light. It was converted to tryptophan hydantoin using the technique of Fischer's indole synthesis. This reaction could also be carried out without the isolation of the unstable phenylhydrazone. The procedure was simple, and satisfactory results were obtained. Instead of crystalline III, the syrup obtained from I by Bucherer's reaction could be employed for the Fischer's indole synthesis. Although the yield based on the starting material was low, the procedure has the advantage of simplicity. The results of these experiments are summarized in Scheme I.

Experimental[*2]

5-Alkoxy-1,3-dioxoperhydropyrro[1,2-*c*]imidazole (III) from β-(Hydanto-5-yl)propionaldehyde Semicarbazone (VI). *(1) 5-Ethoxy-1,3-dioxoperhydropyrro[1,2-c]imidazole (IIIa).* A mixture of 21.3 g



Scheme I

[*2] All melting points are uncorrected.

(0.1 mol) of β-(hydanto-5-yl)propionaldehyde semicarbazone (VI)[3] and 250 m*l* of dried cation exchange (H^+) resins (Diaion SK ♯1) in 400 m*l* of ethanol was heated with stirring for 3 hr at from 50 to 60°C. The resins were then filtered off and washed with ethanol. The removal of the ethanol by evaporation from the filtrate yielded 13.4 g (72.5%) of crude crystals; mp 102—104°C. Recrystallization from ethanol gave white needles; mp 119—120°C.

Found: C, 52.20; H, 6.63; N, 15.18%. Calcd for $C_8H_{12}O_3N_2$: C, 52.16; H, 6.57; N, 15.21%. Mol wt (Rast), 185.9, Calcd 184.2. The 2,4-dinitrophenylhydrazone prepared by the usual procedure decomposed at 216.5—217.5°C.

Found: C, 42.53; H, 3.75; N, 24.01%. Calcd for $C_{12}H_{12}O_6N_6$: C, 42.86; H, 3.60; N, 24.99%.

(2) 5-Methoxy-1,3-dioxoperhydropyrro[1,2-c]imidazole (IIIb). The method was identical with that described for (1), except that the ethanol was replaced with 500 m*l* of methanol. The crude product obtained weighed 13.8 g (81%). It was recrystallized from methanol to afford white crystals; mp 118—119°C.

Found: C, 49.42; H, 6.26; N, 16.42%. Calcd for $C_7H_{10}O_3N_2$: C, 49.40; H, 5.92; N, 16.46%.

γ-(Hydanto-5-yl)butyraldehyde Semicarbazone (VII) from 5-(γ-Cyanopropyl)hydantoin. To a mixture of 40 m*l* of water and 10 m*l* of methanol was added 4.2 g (0.025 mol) of 5-(γ-cyanopropyl)hydantoin, which had been obtained by Bucherer's reaction of γ-cyanobutyraldehyde. After the hydantoin had dissolved upon slight warming, these were added to the solution at room temperature 7.45 m*l* of glacial acetic acid, 0.058 g of lead acetate, and 1.05 g of Raney nickel which had been treated with sodium hydroxide in the usual manner. The reaction was run at room temperature under a hydrogen atmosphere in a shaking vessel. The hydrogen uptake was almost complete in about two hours. After the removal of the catalyst, 2.8 g (0.025 mol) of semicarbazide hydrochloride was added to the reaction mixture and it was stirred for half a day. The semicarbazone which crystallized when the mixture stood in an ice box overnight was filtered, washed with water, dried, and weighed; 3.7 g (65.8%), mp 198.5—199.5°C.

Found: C, 42.23; H, 6.20; N, 29.96%. Calcd for $C_8H_{13}O_3N_5$: C, 42.29; H, 5.77; N, 30.82%.

5-Methoxy-1,3-dioxoperhydropyrido[1,2-*c*]-imidazole (VIII) from γ-(Hydanto-5-yl)butyraldehyde Semicarbazone (VII). A mixture of 2.8 g (0.012 mol) of VII and 200 m*l* of dried cation exchange (H^+) resins in 300 m*l* of methanol was heated at from 50°C to 60°C for 3 hr with stirring. The resins were then filtered off and washed with methanol. After the methanol had been removed under reduced pressure, 1.8 g (79.2%) of a crude, powder-like product were obtained. Recrystallization from methanol gave white needles (mp 156—158°C).

Found: C, 52.46; H, 6.74; N, 15.05%. Calcd for $C_8H_{12}O_3N_2$: C, 52.16; H, 6.57; N, 15.21%. Mol wt (Rast), 183.4, Calcd 184.2. The NMR spectrum of this substance was measured in a $CDCl_3$ solution, with tetramethylsilane as the standard; these measurement showed that the ratio of the NH functional group to the CH functional group was 1 : 1. The UV spectrum indicated a maximum absorption at 2275 Å (ε_{max}= 6,840).

β-(Hydanto-5-yl)propionaldehydediethylacetal (II) from 1,1-diacetoxy-4,4-diethoxybutane (I). Into a mixture of 14.3 g (0.125 mol) of ammonium carbonate and 73.6 m*l* (0.11 mol as CN^- ion) of ammonium cyanide in an ammonia solution (1.5 mol per *l* as CN^- ion and 11 mol per *l* as NH_4^+ ion), 26.2 g (0.1 mol) of I were stirred at room temperature. The mixture was heated with stirring at from 50°C to 60°C for 3 hr, and then at from 60°C to 70°C for an additional hr. After the mixture had been dried up *in vacuo*, attempts to crystallize the resultant syrup were unsuccessful. The 2,4-dinitrophenylhydrazone was prepared by the usual procedure, which yielded red needles (74.5%). It decomposed at 217—218°C.

Found: C, 42.89; H, 3.87; N, 25.01%. Calcd for $C_{12}H_{12}O_6N_6$: C, 42.86; H, 3.60; N, 24.99%.

5-Ethoxy-1,3-dioxoperhydropyrro[1,2-*c*]imidazole (III) from II. By treating 0.05 mol of I by the method described above, II was obtained in a syrupy state. The syrup was added to 50 m*l* of cation exchange (H^+) resins in ethanol. The mixture was then heated at from 60°C to 70°C with stirring for 4 hr. After the resins had been removed and the ethanol evaporated, a white, crystalline substance was separated, dried, and weighed; 7.2 g (78.5% based on I, mp 116—117°C). Recrystallization from ethanol gave white needles; mp 119—120°C.

Found: C, 52.20; H, 6.66; N, 15.20%. Calcd for $C_6H_{12}O_3N_2$: C, 52.16; H, 6.57; N, 15.21%.

β-(Hydanto-5-yl)propionaldehyde Phenylhydrazone (IV). *(1) From 5-Ethoxy-1,3-dioxoperhydropyrro-[1,2-c]imidazole (IIIa).* A solution of 9.2 g (0.05 mol) of IIIa in 50 m*l* of water was refluxed for 1.5 hr. The solution was then cooled and added to a solution of 7.2 g (0.05 mol) of phenylhydrazine hydrochloride in 50 m*l* of water. The product which crystallized from the reaction mixture upon standing overnight in an ice box was filtered, washed, dried *in vacuo* at room temperature in a dark desiccator, and weighed; 10.5 g (82%).

Found: C, 58.16; H, 5.89; N, 22.23%. Calcd for $C_{12}H_{14}O_2N_4$: C, 58.52; H, 5.73; N, 22.75%.

(2) From II. The syrup of II was obtained by treating 0.025 mol of I by the method described above. Ethanol was added to the syrup, and it was evaporated again to remove the ammonia. A mixture of the syrup and diluted hydrochloric acid was refluxed for 1.5 hr. After cooling, the reaction mixture was poured into a solution of 3.6 g of phenylhydrazine hydrochloride in 40 m*l* of water; the crystals obtained on standing overnight in an ice box were filtered, washed, dried and weighed; 2.2 g (34.1% based on I). The infrared spectrum of the crystals was identical with that of the product described in the case of (1).

Tryptophan Hydantoin (V) from II. This method is a modification of the directions of Komachiya *et al.*[3] A syrup of II was afforded by treating 0.1 mol of I as above. To the syrup these were then added 2.5 m*l* of conc. hydrochloric acid, after which the mixture was diluted to 200 m*l* with water. A mixture of 1.25 m*l* of conc. hydrochloric acid and 13.9 g (0.096 mol) of phenylhydrazine hydrochloride was diluted to 200 m*l* with water. In a 1 *l*, four-necked, round-bottomed flask equipped with a reflux condenser, a sealed stirrer, a dropping funnel, and a thermometer, the solution of phenylhydrazine was placed. To the boiled solution in the flask, the solution of II was added, drop by drop, through the dropping funnel. After the addition, the mixture was refluxed while being stirred for 30 min. The flask was chilled to 80°C and then cooled with water to 20°C. After being allowed to stand at 20°C for 30 min, the crystals were filtered, washed, and dried. The yield was 10.3 g (45% based on I); mp 215°C.

Found: C, 63.03; H, 5.16; N, 18.37%. Calcd for $C_{12}H_{11}O_2N_3$: C, 62.87; H, 4.84; N, 18.33%.

In this case, a deposit of polymer was observed on the bottom of the flask. When the volume of conc. hydrochloric acid added to the syrup of II was increased to 7.5 m*l*, the yield of V was 14.2 g (62.1%), mp 212—213°C.

Found: C, 62.91; H, 5.25; N, 18.45%.

Tryptophan Hydantoin (V) from III. The reaction of 13.6 g (0.08 mol) of III in 200 m*l* of 0.1 N hydrochloric acid with 14.5 g (0.1 mol) of phenylhydrazine hydrochloride in 200 m*l* of 0.1 N hydrochloric acid was carried out in a manner similar to that used in the experiment described above. The first crop of crystals of tryptophan hydantoin (melting at 212—213°C) weighed 15.8 g (86.2%).

Found: C, 62.48; H, 5.36; N, 18.7%.

The second crop (1.3 g, melting at 207—208°C) was obtained by allowing the mother liquor to stand at room temperature. The total yield of tryptophan hydantoin was 93.2% based on III.

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