solution was kept as anhydrous as possible since moisture interfered with the crystallization. The product so obtained melted at 133–135° (cor.). The yield was 56 g. (79%).

β,β-Trehalose Octaacetate.—In a 2-liter three-necked flask equipped with a mechanical stirrer, mercury seal, calcium chloride tube, and a 500-ml. dropping funnel, was placed 110 g. of 2,3,4,6-tetraacetyl-β-D-glucose, 180 g. of silver carbonate, 12 g. of iodine, 100 g. of powdered Drierite (previously dried for three hours at 500°), and 400 ml. of alcohol-free chloroform. The flask was covered with a dark cloth to prevent the entrance of light and stirred for thirty minutes. In 400 ml. of alcohol-free chloroform was dissolved 150 g. of 2,3,4,6-tetraacetyl-α-D-glucosyl bromide and the solution shaken with 50 g. of powdered Drierite for thirty minutes. At the end of the shaking, the solution of glucosyl bromide was decanted and added dropwise to the first mixture over a period of two hours. This was followed by a 100-ml. portion of chloroform used to wash the Drierite and the mixture was stirred for twelve hours. At the end of the stirring, the solid matter was filtered off and washed with 100 ml. of chloroform. The chloroform from the combined filtrate was removed by evaporation of the solution on a water-bath. The residue was dissolved in 900 ml. of benzene and the solution washed twice with 2 liters of water. Each washing was shaken for thirty minutes. Without drying, the benzene was removed from the solution by evaporation on a steam-bath and the residue dissolved in hot ethyl acetate. Ligroin was then added until the warm solution became turbid. Upon cooling, long needles of β,β-trehalose octaacetate formed. After three recrystallizations the melting point was constant at 180.5–181.5° cor., $[\alpha]^{25}\text{D}$ −18.4° (c = 3) in U. S. P. chloroform. The yield was 12.5 g. (6.5%). By working up the residues, 6.7 g. of additional product was obtained, giving a total yield of 19.2 g. (10%). Reduction values were determined by the method of Lane and Eynon[8] and expressed as the percentage of the reducing value of pure tetraacetylglucose. The residues from washing the benzene solutions of the product had reduction values approximately equal to pure tetraacetyl glucose. The reduction values of the residues from recrystallization indicated that some non-reducing material was still present.

Summary

A satisfactory method has been developed for the preparation of crystalline β,β-trehalose octaacetate from 2,3,4,6-tetraacetyl-α-D-glucosyl bromide and 2,3,4,6-tetraacetyl-β-D-glucose.

[8] Lane and Eynon, *J. Soc. Chem. Ind.*, **42**, 32T (1923).

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

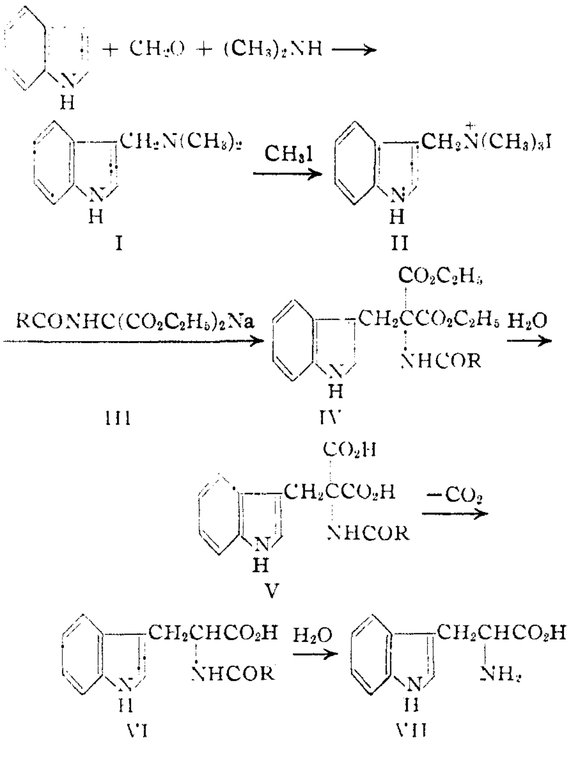
A Convenient Synthesis of *dl*-Tryptophan

BY H. R. SNYDER AND CURTIS W. SMITH

In an earlier work[1] it was discovered that quaternary salts containing a radical of the benzyl type can be used as carbon-alkylating agents. The methiodide of gramine (3-dimethylaminomethylindole, readily prepared from indole, formaldehyde and dimethylamine) was found particularly effective in the alkylation of active methylene compounds. This suggested that *dl*-tryptophan might be prepared by condensation of gramine methiodide with an alkali derivative of an acylaminomalonic ester. In view of the high yields previously obtained in reactions of gramine methiodide with malonic ester it seemed likely that the proposed synthesis would be much more practical than the earlier methods based on the condensation of indole-3-aldehyde with hippuric acid[2] or hydantoin.[3]

Gramine methiodide has been found to react smoothly with the sodium derivative of acetaminomalonic ester in the presence of dioxane. Ethyl α-acetamino-α-carbethoxy-β-(3-indole)-propionate (IV, R = CH_3) was obtained in yields of 63–70%. Saponification converted the ester to the acid (V, R = CH_3), and boiling a water suspension of the acid brought about decarboxylation. The resulting acetyltryptophan was converted to *dl*-tryptophan by alkaline hydrolysis. Two recrystallizations brought the product to analytical purity. The yield of *dl*-tryptophan, based on indole, was approximately 45%.

It is interesting to note that long boiling with 20% aqueous sodium hydroxide did not convert the substituted acetaminomalonic ester (IV) to the aminomalonic acid, but the acetyl group was



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[1] Snyder, Smith and Stewart, THIS JOURNAL, **66**, 200 (1944).

[2] Ellinger and Flamand, *Ber.*, **40**, 3031 (1907).

[3] Boyd and Robson, *Biochem. J.*, **29**, 2256 (1935).

removed easily after the decarboxylation of the acetaminomalonic acid (V).

Experimental

Ethyl Acetaminomalonate.—The isonitroso ester, prepared by a modification of the method of Redeman and Dunn,[4] was reduced and acetylated without isolation of any of the intermediates. A solution of 400 g. of malonic ester in 450 g. of glacial acetic acid, in a 3-liter three-necked flask, was cooled in an ice-bath. With stirring, a solution of 518 g. of sodium nitrite in 710 cc. of water was added over a period of one hour, the temperature of the mixture being kept below 20°. Gases which escaped were led to the hood. The mixture was stirred for four hours after the addition of sodium nitrite was completed. The reaction mixture was extracted with three 500-cc. portions of ether. The combined ether extracts were washed with three 250-cc. portions of 10% sodium carbonate and with two portions of water. The ether solution was dried over calcium chloride and the ether was removed by distillation under reduced pressure. The residual liquid was dissolved in 1000 cc. of absolute alcohol and 25 g. of Pd-charcoal catalyst (10% Pd) was added. The mixture was hydrogenated (1500 lb. pressure, room temperature, at start) and when absorption of hydrogen was complete the catalyst was removed by filtration. To the cooled filtrate was slowly added 204 g. of acetic anhydride, and the resulting solution was cooled in ice. When crystallization appeared complete the first crop (127 g.) of the product was collected. Concentration and cooling of the mother liquor produced additional crops, the total yield being 217 g. The first fraction was pure (m. p. 95–96°), but later crops required recrystallization.

Ethyl α-Acetamino-α-carbethoxy-β-(3-indole)-propionate (IV).—After 6.9 g. (0.30 mole) of sodium had been powdered in 100 cc. of dry xylene, most of the xylene was decanted. Then 500 cc. of dioxane which had been distilled from sodium and 68 g. (0.314 mole) of acetaminomalonic ester were added and the mixture was stirred for fourteen hours in an oil-bath at 92°. To the resulting light yellow suspension was added 101 g. (0.32 mole) of gramine methodide (II)[1] and the mixture was stirred in an oil-bath at approximately 108° for nineteen hours and then at 125° for three hours. The hot dioxane was separated from a brown pasty solid by filtration through a heated Büchner funnel. After standing overnight in a refrigerator (+5°) the solution had deposited 64.5 g. of the product (IV); m. p. 125–135°. A second fraction of 4.7 g. (m. p. 135–142°) was obtained by concentrating the mother liquor to one-fourth volume. A third fraction (6.4 g., m. p. 158°) was obtained by extracting the solid from the first filtration with 200 cc. of boiling 95% ethanol, diluting with 200 cc. of hot water, and cooling.

The two fractions of IV which had crystallized from dioxane (69.2 g.) were dissolved in 160 cc. of boiling 95% ethanol and 160 cc. of warm water was added to the solution. After standing overnight in a refrigerator at 5° the solution deposited 61.7 g. of IV; m. p., 156–8°. The total yield of IV, m. p. 156–8°,was thus 68.1 g. or 63%; other runs gave yields in the range 63–70%. An analytical sample of IV was prepared by recrystallization from *n*-butyl ether and then from 50% alcohol-water solution; m. p. 158°.

Anal. Calcd. for $C_{18}H_{22}N_2O_5$: C, 62.44; H, 6.40. Found: C, 62.42; H, 6.24.

α-Acetamino-α-carboxy-β-(3-indole)-propionic Acid (V).—The ester (IV) was saponified by refluxing 33.62 g. (0.097 mole) with 19.2 g. (0.48 mole) of sodium hydroxide in 192 cc. of water for four hours. After treatment with charcoal, the solution was cooled in an ice-bath and 50 cc. (0.6 mole) of cold concd. hydrochloric acid was added with cooling so that the temperature of the solution did not exceed 25°. The solution was cooled for four hours, and the light pink precipitate was filtered off and dried over calcium chloride in an evacuated desiccator for fourteen hours; the yield of crude material, containing some sodium chloride, was 32 g.; m. p. 136–139°. The acid could be purified by dissolving it in ten volumes of water (containing a trace of sodium hydrosulfite) at 50° and cooling. The analytical sample, after two recrystallizations from 20% ethanol, melted with decomposition at 144.5°.

Anal. Calcd. for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86. Found: C, 57.71; H, 5.02.

***dl*-Tryptophan (VII).**—A mixture of 28 g. of the crude malonic acid (V) and 120 cc. of water was heated under reflux for two and one-half hours. The N-acetyltryptophan (VI) produced was less soluble than the malonic acid and in some runs it partially crystallized from the solution as the reaction proceeded. After the decarboxylation was completed, 16 g. (0.4 mole) of sodium hydroxide in 40 cc. of water was added and the solution was refluxed for twenty hours. The alkaline solution was treated with charcoal and acidified with 24 g. (0.4 mole) of glacial acetic acid. A copious white precipitate formed immediately, but the solution was stored in the refrigerator for twelve hours before the solid was collected. It was dissolved in 200 cc. of water containing 5 g. of sodium hydroxide. After treatment with charcoal, 100 cc. of 95% ethanol was added to the solution. The solution was warmed to 70°, acidified with 7.5 cc. of glacial acetic acid, and allowed to cool slowly. The flat plates which separated from the solution were filtered off and washed with two 40-cc. portions of water, two 40-cc. portions of ethanol and two 30-cc. portions of ether; yield 14 g. (81% calculated on the basis of IV); m. p. 272–280° (dec.). An analytical sample, m. p. 275–282° (dec.), was prepared by two recrystallizations from 33% ethanol.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92. Found: C, 64.61; H, 5.90.

N-Acetyltryptophan (VI) was isolated from a similar run by allowing it to crystallize from the acidified solution after decarboxylation. For recrystallization, 11.7 g. of VI was dissolved in a solution of 100 cc. of water and 30 cc. of 95% ethanol, a few grains of sodium hydrosulfite were added, and the hot solution was treated with charcoal; yield, 8 g. (68.5%), m. p. 206° (lit.,[5] 206°). A sample recrystallized several times from very dilute ethanol was analyzed.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73. Found: C, 63.20; H, 5.61.

Summary

A convenient and economical synthesis of *dl*-tryptophan is described. Indole is converted to gramine (3-dimethylaminomethylindole) by condensation with formaldehyde and dimethylamine; the methiodide of gramine is condensed with the sodium derivative of ethyl acetaminomalonate to give ethyl α-acetamino-α-carbethoxy-β-(3-indole)-propionate; α-acetamino-α-carboxy-β-(3-indole)-propionic acid is obtained by saponification of the ester and is decarboxylated to acetyltryptophan by boiling in water; *dl*-tryptophan is obtained by alkaline hydrolysis of the acetyl derivative. The yield of tryptophan, based on indole, is about 45%.

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(4) Redeman and Dunn, *J. Biol. Chem.*, **130**, 341 (1939).

(5) Berg, Rose and Marvel, *ibid.*, **85**, 207 (1929–1930).