acylations, aldolizations and halogenations in the presence of acidic and basic reagents. Certain aspects of the theory of the reactions are considered.

DURHAM, N. C. RECEIVED SEPTEMBER 10, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

The Preparation of β,β-Trehalose Octaacetate

BY CHESTER M. MCCLOSKEY,[1] RONALD E. PYLE AND GEORGE H. COLEMAN

In connection with work in this Laboratory on the chromatographic separation of the azoyl derivatives of sugars, it was necessary to prepare β,β-trehalose. Since procedures previously reported did not prove satisfactory for preparing moderate quantities of this compound, modification of one of these methods was undertaken.

Fischer and Delbrück,[2] who discovered β,β-trehalose octaacetate, prepared it by the action of silver carbonate and a small amount of water upon an ether solution of tetraacetyl-α-D-glucosyl bromide, in a yield of about 1%; they also obtained it from the action of phosphorus pentoxide on a chloroform solution of 2,3,4,6-tetraacetyl-β-D-glucose in a yield of 2%.

In 1932 Schlubach and Schetelig[3] prepared β,β-trehalose octaacetate by the condensation of tetraacetyl-α-D-glucosyl bromide and 2,3,4,6-tetraacetyl-β-D-glucose in a chloroform solution with silver carbonate, calcium chloride and iodine. The reduction value of the crude reaction mixture was determined by Bertrand's method and the condensation was calculated as 50%, based on the reduction value of pure tetraacetyl glucose. The yield of crystalline product was not given.

The procedure of Schlubach and Schetelig was repeated several times in this Laboratory. The best yield of crystalline β,β-trehalose octaacetate was not more than 4%. The conditions described by these authors were duplicated as nearly as possible. However, it may be that some necessary precaution was omitted, since the reaction product showed a reduction value corresponding to only 18.8% condensation.

This preparation has been modified to conform more closely to the technique used by Kreider and Evans[4] in the Koenigs and Knorr synthesis. By effecting condensation in the presence of Drierite as drying agent, a 10% yield of crystalline product, m. p. 180.5–181.5° cor., has been obtained. The reduction value of the crude reaction product indicated a condensation of approximately 30%. The non-crystalline residues from which no more product could be obtained, still contained two-thirds of the original condensation product as shown by reduction values. This problem is being investigated further.

The use of iodine has been found essential for satisfactory condensation. Excessive amounts of glucosyl bromide and elevated temperatures did not produce appreciably higher yields.

In a series of several runs the percentage yields calculated from the reducing values varied from 30–40%. The actual yield of crystalline product did not, however, in any case exceed 10.5%. In one run in which only 4.5 g. of iodine was used the percentage yield calculated from the reducing value was 30%. The yield of crystalline material was only 3.4%.

Experimental Part

2,3,4,6-Tetraacetyl-α-D-glucosyl Bromide.—This compound was prepared by the method of Karjala and Link[5] or Redemann and Niemann[6] from pentaacetylglucose or its glucose equivalent. The crude reaction mixture prepared by this method from 120 g. of glucose pentaacetate was poured with rapid stirring into 1.5 liters of ice-water. The precipitate, which solidified, was filtered off and ground in a mortar in order to break up the lumps. It was then returned to the filter funnel and washed thoroughly with ice-water and sucked as dry as possible. The precipitate without further drying was dissolved in 300 ml. of ether. The aqueous layer was separated and the ether layer cooled in a freezing mixture. The crystals which formed were filtered off and the filtrate which had partially evaporated during the filtration was cooled as before. In this manner several crops of crystals were obtained. The crystallization of the last portion was facilitated by the addition of a little ligroin to the ether. The crystals were air dried a short time and then in a vacuum desiccator over phosphorus pentoxide. The product can be kept indefinitely without decomposition. The yield of product melting at 87–88° (uncor.) was 121 g. (96%).

2,3,4,6-Tetraacetyl-β-D-glucose was prepared by a modification of the method of Georg.[7] A solution of 125 ml. of anhydrous acetone and 82.2 g. of tetraacetylglucosyl bromide was cooled to 0° in an ice-bath and 2.3 ml. of water added. To the cold solution 46.5 g. of silver carbonate was added in small portions, with thorough shaking or stirring, during a period of fifteen minutes. After about thirty minutes more shaking the mixture was warmed to 50–60° and filtered. The silver salts were washed with 65 ml. of dry acetone, removed from the funnel and warmed in a flask with 65 ml. more acetone, filtered and washed again on the funnel. The combined filtrates were concentrated under reduced pressure and at room temperature. When most of the solution was filled with crystals the concentration was stopped and the mixture warmed until solution was complete. To this acetone solution an equal volume of absolute ether and a similar volume of ligroin were added. The solution so obtained was cooled in a freezing mixture with gentle stirring. The crystals of tetraacetate soon formed and after ten minutes in the ice-bath to ensure complete crystallization were filtered and air-dried. The

---

[1] Research Fellow of the Corn Products Refining Company.

[2] Fischer and Delbrück, *Ber.*, **42**, 2776 (1909).

[3] Schlubach and Schetelig, *Z. physiol. Chem.*, **213**, 83 (1932).

[4] Kreider and Evans, THIS JOURNAL, **58**, 797 (1936).

[5] Karjala and Link, *ibid.*, **62**, 917 (1940).

[6] Redemann and Niemann, "Organic Syntheses," Vol. 27, p. 1.

[7] Georg, *Helv. Chim. Acta*, **15**, 924 (1932).

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., $[\alpha]^{25}D$ −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).

IOWA CITY, IOWA RECEIVED SEPTEMBER 10, 1943

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

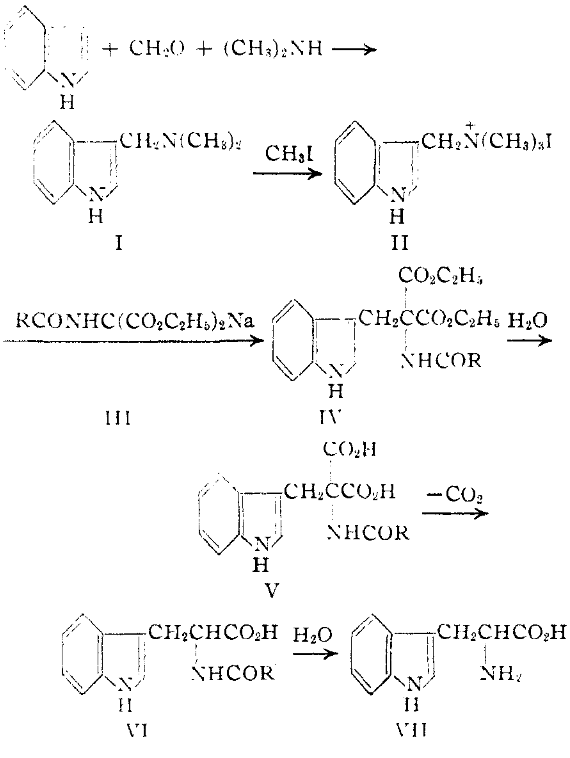
A Convenient Synthesis of *dl*-Tryptophan

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



---

(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).