XXVI. STUDIES ON THE INTERACTION OF AMINO-COMPOUNDS AND CARBOHYDRATES.

II. THE PREPARATION OF GLUCOSE UREIDE.

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A CRYSTALLINE condensation product of glucose and urea was first described by Schoorl [1900, 1, 2; 1903]. So thorough did the last communication appear to be, that, apart from the synthesis of glucose ureide accomplished by Fischer [1914], the condensation of glucose and urea does not seem to have been further investigated.

As indicated in the previous paper [Hynd, 1926], it was found difficult to prepare pure glucose ureide in quantity by Schoorl's method and the author's experience is further corroborated by Hewitt [1913] and personal communications from several workers.

The object of the present paper is to show how, by a modification of the process, glucose ureide can be readily obtained in quantity in a pure condition.

PREPARATION OF GLUCOSE UREIDE BY SCHOORL'S METHOD.

Schoorl's instructions for the preparation of glucose ureide were rigidly followed, and as the method is quoted by Lippmann [1904], it will not be necessary to give details of the process. Working with 90 g. of glucose and the equivalent weight of urea (30 g.) there was obtained, in the first experiment, 26 g. of crude solid, which corresponded to 23·4 % of the theoretical yield. This material was isolated in three different crops of varying purity, weighing 12, 11 and 3 g. respectively. The first crop was readily recrystallised, about 10 g. of pure product being obtained. Attempts to purify the two other crops were quite unsuccessful, so that the total yield of recrystallised material was only 9 % of the theoretical.

In a similar experiment, 50 g. of crude solid material were obtained, corresponding to a 45 % yield; but great difficulty was experienced in purifying this material and the amount of recrystallised glucose ureide was only about 8 % of theory.

Scrutiny of Schoorl's original papers revealed the fact that his yields of pure material were of the same order.

MODIFIED METHOD OF PREPARING GLUCOSE UREIDE.

Formation of an additive compound of urea and glucose ureide.

27 g. glucose were dissolved in about 125 cc. water, 27 g. urea were added, and the resulting solution was filtered. To the clear filtrate 5.6 cc. 25 % sulphuric acid were added and after thorough mixing the rotation of the solution was determined in a 1 dm. tube. The mixture was then placed in a thermostat at 50°, polarimetric observations being made at intervals, some of which are recorded below:

Days	0	1	2	4	7	9
a	+9.05°	8.24°	2.67°	0.69°	0.40°	0.40°

The rotation thus became practically constant after heating at 50° for a week, and at the end of this time the solution was pale greenish yellow in colour, slightly acid to litmus and negative to congo red. As the sulphuric acid had been neutralised during the reaction, the use of barium carbonate was unnecessary, and though the mixture still reduced Fehling's solution vigorously, no attempt was made to eliminate the uncondensed glucose by means of yeast, but the solution, without further treatment, was evaporated under diminished pressure at 37° to a thin syrup. Crystallisation soon commenced and spread rapidly throughout the mass. After standing overnight in the cold, the white, sparkling crystals were drained at the pump, washed with a small amount of 90 % alcohol, and dried in a vacuum desiccator over sulphuric acid. The product thus obtained was practically pure *glucose ureide urea*, and the yield amounted to 31 g. or 73 % of the theoretical.

This preparation has been carried out with amounts of glucose varying from 9 to 180 g., and has always been successful. In the several experiments a total of 450 g. glucose has given 428 g. of the additive compound, which corresponds to a 61 % yield, but in the later experiments, as, for example, that described above, the yield has been somewhat better, so that on an average 66 % of the theoretical amount can be isolated. Other acids, for example phosphoric acid, can be used in place of sulphuric acid to bring about the condensation, but, as they have no special advantages, sulphuric acid is recommended.

Purification and physical properties of glucose ureide urea.

The crude glucose ureide urea was found to melt fairly sharply at about 167° to a colourless liquid, which on cooling resolidified. On raising the temperature above the melting-point, the liquid gradually became yellow, then brown and finally, at about 200°, decomposed with evolution of gas. The solubilities of the additive compound closely parallel those of glucose ureide. Thus it is readily soluble in water (though somewhat less than glucose ureide), very sparingly soluble in either ethyl or methyl alcohol, practically insoluble

in acetone, and quite insoluble in ether, chloroform, and non-hydroxy-solvents generally. Accordingly water was found to be the only suitable crystallising medium, and the use of this solvent has certain drawbacks, owing to the high solubility of glucose ureide urea even in cold water and the fact that on boiling an aqueous solution of the compound, decomposition occurs with evolution of ammonia. Details of the method adopted for the purification are, therefore, appended in the case of an experiment in which 30 g. of crude product were employed.

The solid material was dissolved by pouring over it its own weight (30 cc.) of boiling water. (Complete solution should take place and no filtration should be required, but, if necessary, the solution should first be made more dilute, and, after filtering, concentrated *in vacuo* at a temperature of not more than 40°.) The solution was then allowed to cool slowly, when a crop of crystals separated. These were removed by filtration, washed and dried in a vacuum desiccator. The 17 g. of recrystallised compound thus obtained melted at 170–172° and was evidently quite pure, as the melting-point remained unaltered after several recrystallisations. However, as only a little over 50 % of the material was isolated after each crystallisation from water, the weight of purified product after six recrystallisations was only 3 g., but the accumulated mother liquors on fractional evaporation *in vacuo* at 37° yielded a series of crops of crystals, the weights, melting-points, and specific rotations of which are given below:

Compound after six recrystallisations		Compound obtained from evaporation <i>in vacuo</i>			
		Crop 1	Crop 2	Crop 3	Crop 4
Wt.	3 g.	10.8 g.	6.5 g.	4.7 g.	3.5 g.
M.P.	171–172°	170–172°	170–171°	169–170°	167–169°
$[\alpha]_D$	–18.18°	–17.95°	–18.15°	–17.59°	
	(<i>c</i> = 2.5856)	(<i>c</i> = 3.636)	(<i>c</i> = 7.488)	(c = 2.3896)	

As a small fifth crop of less pure material, the melting-point and specific rotation of which were not determined, was obtained in addition to the 28.5 g. of crystalline material detailed above, the process was practically quantitative.

On microscopic examination the crystals were found to consist of stout prisms usually pointed at both ends, somewhat resembling triple phosphates and thus quite distinct in appearance from glucose ureide.

Analysis.

Very little loss of weight (a few mg.) resulted on heating the substance in a steam-oven, or at temperatures from 60 to 100° at 25 to 30 mm. Hg, and as, at the same time, slight browning of the material and lowering of the melting-point (165°) took place, the slight loss recorded was evidently due to decomposition and not to loss of water of crystallisation.

Accordingly, the glucose ureide urea was prepared for analysis by drying in a vacuum desiccator over sulphuric acid.

5 cc. of a 2.5856 % solution of the compound gave 18.16 cc. $N/10$ NH_3 (Kjeldahl).

0.1265 g. gave 0.0758 g. H_2O and 0.1564 g. CO_2 .

Found	C = 33.99 %	H = 6.66 %	N = 19.51 %
$(C_7H_{14}O_6N_2) \cdot (CH_4ON_2)$ requires	C = 34.04 %	H = 6.43 %	N = 19.81 %

INTERCONVERSION OF GLUCOSE UREIDE UREA AND GLUCOSE UREIDE.

(a) *Conversion of glucose ureide urea into glucose ureide.*

As already indicated, the additive compound of glucose ureide and urea is sufficiently stable to allow of its crystallisation from water provided the temperature is kept about 40° . The compound also remains unchanged after repeated grinding in a mortar with either alcohol or acetone. Thus 6 g. of the compound of melting-point 170° , after four such treatments with about 35 cc. absolute alcohol at a time, melted at 167° , and the united alcoholic extracts and washings on evaporation left only a film. The additive molecule of urea, however, is removed slowly by boiling alcohol.

Glucose ureide urea (70 g.), after 3 days' boiling with several fresh quantities (200 cc.) of absolute ethyl alcohol, was found to yield practically pure glucose ureide (55 g.) melting with decomposition about 200° . This material was recrystallised from water, as described for the additive compound, and the following were obtained:

No. of crop	1	2	3	4
Weight	6.3 g.	6.47 g.	39.9 g.	trace
Melting-point (with decomposition)	208°	207°	207°	205°

making a total of 52.67 g., which is practically a theoretical yield. Crops 1 and 2 crystallised slowly from the solution and consisted of colourless thick rhombic plates, whilst crop 3, which separated quickly from solution, was composed of fine needles. These variations in crystalline appearance do not seem to indicate the existence of different forms of glucose ureide, but depend entirely on the conditions under which crystallisation takes place, for, as shown above, all three crops of crystals had practically the same melting-point. Further, the specific rotation of the plate form was found to be -23.45° ($c = 2.1532$, $l = 2$); that of the needle form -23.27° ($c = 4.5556$, $l = 1$). These values are practically identical and agree with those quoted by Schoorl (-23.3°) and also by Fischer (-23.41°). No mutarotation was detected.

(b) *Conversion of glucose ureide into glucose ureide urea.*

By crystallising glucose ureide in presence of excess of urea the additive compound was found to be readily formed. Thus, when glucose ureide (12 g.) and urea (6 g.) were dissolved in the minimum quantity of hot water, and the resulting solution allowed to cool, the crystalline material which separated agreed in its properties with those already described for glucose ureide urea.

The reaction between glucose and urea, under the conditions described, no doubt proceeds further than is represented by the 60–70 % of glucose ureide isolated, so that the 30–40 % of syrupy residue contains, in addition to unchanged glucose, some glucose ureide. However, the reaction is not so simple as Schoorl imagined, for evidence has been obtained of the presence in this syrup of some other dextro-rotatory material, and its examination is at present receiving our attention.

SUMMARY.

(1) By the simple modification of using excess of urea in the preparation of glucose ureide, many of the difficulties of Schoorl's method are avoided, and the product is readily isolated as an additive compound (m.p. 170–171°), the conversion of which into glucose ureide (m.p. 207°) is quantitative.

(2) Whereas the yield of pure crystalline glucose ureide obtained by Schoorl's method is only about 10 % of the theoretical, a yield of 66 % can be readily obtained by the method now described.

(3) As the reaction product contains, in addition to the laevo-rotatory glucose ureide and unchanged glucose, some other dextro-rotatory material, the reaction cannot be a simple reversible one, as considered by Schoorl.

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