

On the Isomerism of Hydroxyurea

II. Preparation of the Isomers

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An improved method of preparation of the alleged isomers has been devised. They are obtained in almost equal amounts and the combined yield is 30-50 %.

Reported methods of preparation of the two known isomers of hydroxyurea* are based on the ionic reaction



Dresler and Stein¹, the discoverers of the higher melting isomer, on mixing concentrated aqueous solutions of potassium cyanate and hydroxylammonium sulphate observed an immediate rise of temperature and evolution of ammonia. The reaction products were urea and various other substances but no hydroxyurea. When, however, the process was conducted at low temperature, the decomposition was repressed, and the reaction (1) appeared to be favoured. Dresler and Stein, by repeated fractional precipitations, succeeded in isolating minute quantities of a substance analyzing as hydroxyurea and melting at 128-130°. Their compound, as we now know, was an impure specimen of the higher melting isomer.

During their process of isolation the reaction mixture was exposed to room temperature for a considerable time, and finally heat was applied during the evaporation of the solvent. For these reasons Dresler and Stein failed to notice the thermolabile lower melting isomer. This was first prepared by Francesconi and Parrozzani² by letting *solid* potassium cyanate and hydroxylammonium chloride react in test tubes at low temperature. The reaction mixture was treated with dry acetic ester, in which both isomers are tolerably soluble. Upon evaporation of the solvent the lower melting isomer was isolated from

* In a paper, which has appeared after the present one had been delivered for publication, C. Runti and R. Deghenghi report that hydroxyurea, m.p. 140°, can be obtained in 63 % yield, when ethyl urethan is treated with excess of hydroxylamine. (*Annali Triestini* 23 (1953) 5).

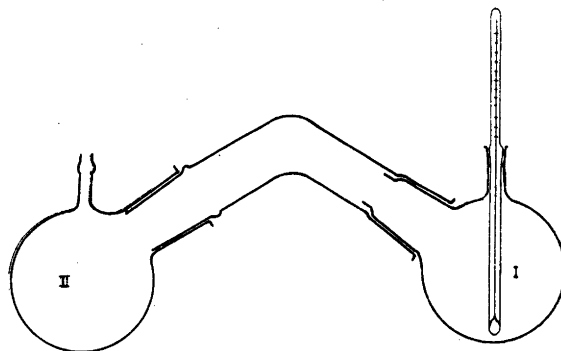


Fig. 1. Freeze-drying apparatus for removal of the solvent.

the extract by means of dry ether. The reaction in solid phase seems rather irrational. Attempts by the present author to reproduce this way of preparation gave extremely small yields and proved that a certain amount of moisture was necessary to initiate the reaction. Most of the material was decomposed.

Conduché³ obtained a solution of the lower melting isomer, probably containing some of the higher melting isomer as well, by slowly mixing aqueous solutions of the reactants at low temperature. He did not isolate the crystalline material as such but employed the solution for preparation of derivatives.

The above material and a number of preliminary experiments by the present author seem to indicate that the isomers are formed simultaneously by the reaction (1) in aqueous solution, when the heat of reaction is removed. Kinetic measurements⁴ showed that the reaction is sufficiently rapid at 0° C for preparative purposes, so that the small yields are not due to incomplete reaction. It was further established that no decomposition involving formation of ions took place within 20 h in dilute aqueous solution at 0° C. It is therefore reasonable to assume that the unsatisfactory yields are due to a pronounced lability of the isomers or of some intermediates in aqueous solution at higher temperatures. For this reason it was decided not only to conduct the reaction but also to remove the solvent, water, at low temperature. A kind of primitive freeze-drying technique was used as described below in the experimental section. Upon complete removal of the solvent the lower melting isomer was extracted by means of dry ether. From the remaining mixture of potassium chloride and the higher melting isomer the latter was isolated by means of absolute ethanol.

The crystalline isomers were obtained in almost equal proportions and in overall yields varying from 30–50 % of the theoretical. They corresponded to the descriptions given in the literature.

EXPERIMENTAL

Materials. The hydroxylammonium chloride and potassium cyanate were identical with those described in the preceding paper⁴.

Procedure. The 100 ml flask I was removed from the rest of the apparatus shown in Fig. 1 and used as reaction vessel. It was equipped with a mechanical stirrer and placed

in a freezing mixture of salt and ice. A solution of 13.9 g (0.2 mole) hydroxylammonium chloride in 30 ml water was placed in the flask. When the temperature had reached -5°C , a freshly prepared solution of 16.2 g (0.2 mole) potassium cyanate in 30 ml water was slowly run into the flask with stirring, the temperature being kept below -5°C throughout the reaction (about 1 h).

The time t_a required for the bimolecular reaction to proceed to a degree a is $t_a = \frac{1}{k \cdot c_0} \cdot \frac{a}{1-a}$. In the present preparation the initial concentration of the reactants is $c_0 = 3.33$ moles/l, the rate constant for this unit of concentration and using the minute as time unit has previously⁴ been determined as $k = 8$ at 0°C . Inserting these values we get $t_{0.999} = 37$ min. as the time required for 99.9 % of the starting materials to be transformed into hydroxyurea, which is satisfactory for the preparative purpose.

The reaction mixture was therefore left for another hour at 0°C , and should now contain much less than 0.1 % of the starting materials. The flask was then reconnected with flask II as in Fig. 1, the ground glass joints being carefully lubricated with high-vacuum grease. Flask II was cooled in a mixture of solid carbon dioxide and acetone; the system was evacuated with an oil rotary pump, yielding a residual pressure less than 0.01 mm Hg. Gentle heat was applied to flask I (an electrically heated mercury-bath was found useful) so as to provide for a rapid sublimation of the ice from the reaction mixture into flask II. By this primitive freeze drying technique the solvent was removed in less than half an hour, without exposing the hydroxyureas to temperatures higher than 0°C . In the later stages, when the evaporation became insufficient to keep the temperature down, flask II was surrounded by a water bath at 0° . The final drying was effectuated by replacing flask II by another flask containing phosphorus oxide, and the temperature of the reaction mixture was only allowed to rise to 20° after removal of the last traces of water.

The reaction mixture was immediately extracted with 200 ml boiling anhydrous ether, in which the lower melting isomer is slightly soluble. The ether was decanted and the lower melting isomer obtained as colorless plates on cooling to -10° . Two batches of 200 ml ether were used alternately for extraction. After five to eight extractions no more crystalline material could be obtained. The remanence was extracted with 100 ml absolute ethanol at 40°C for 1 min. Colorless rosettes of the higher melting isomer were obtained on cooling. The mother liquor was used for two more extractions. The yields are given below.

It is of utmost importance that all equipment is dry, and that the solvents are absolutely anhydrous. Extractions must be carried out rapidly and heating of the compounds in contact with solvents must be reduced to the shortest possible time. Even with these precautions loss of material in form of gaseous destruction products cannot be quite avoided, as indicated by a smell of ammonia, which has been noticed in nearly all stages of the isolation and particularly in less successful experiments. The lability of the substances is also clearly shown in Table 1, representing the one experiment, which gave the highest yields.

Table 1. Preparation of hydroxyurea.

Reactants		Products					
			calculated	obtained			
				freeze-dried mixture	after fractionation		
KOCN	0.2 mole = 16.2 g	hydroxyurea 72°	} 15.2 g	} 28.7 g	} 3.3 g		
HONH ₂ Cl	0.2 mole = 13.9 g	hydroxyurea 140°				} 14.9 g	} 14.5 g
		KCl†					
30.1 g			30.1 g	28.7 g	22.0 g		
Loss of material during reaction and freeze-drying			1.4 g	6.7 g			
Loss of material during isolation							

Nothing is known about the proportions in which the two isomers are formed, but taking into account the greater lability of the lower melting isomer, it appears to be 1 : 1.

Characterization. The identity of the above substances with the hydroxyureas described in the literature was proved by their melting points, or rather destruction points. In an electrically heated melting-point apparatus, essentially as described by F. Halstrøm⁵, 71° C was observed for the lower melting isomer (lit. 70–72° C³) and 140° C for the higher melting one (lit. 130° C³; 139° C²; about 141° C³.) Details of the behaviour of the substances when heated under the microscope will be presented in a subsequent paper together with other physical properties. Determination of nitrogen by the "micro-Kjeldahl" method⁶ gave the following equivalent weights. Lower melting isomer 49.0, 45.5, 55.4, 50.5, 49.7, and 49.8. Higher melting isomer 49.5. Calculated for CH₄O₂N₂ 38.0. The reason for the irreproducible and much too high results probably is that some of the nitrogen content is lost in elementary form during the destruction. The average value, about 50, does not, however, correspond to any stoichiometric fraction of the nitrogen content.

The author is greatly indebted to the head of this laboratory, professor H. Baggesgaard Rasmussen for the kind interest he has shown my work. My thanks are due to Dr. Tso Yueh Huang for valuable assistance.

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Received June 9, 1953.