

On the Isomerism of Hydroxyurea

III. Some Physical Properties of the Isomers

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In Part II of this series an improved method was described for the preparation of the alleged isomers.

The present paper is chiefly devoted to an examination of the products in the solid state.

Crystal form, approximate solubilities and stability of the solids are discussed. The common empirical formula $\text{CH}_4\text{O}_2\text{N}_2$ has been confirmed. The homogeneity of the two products was tested by microthermal analysis and X-ray powder diagrams. The isomers had entirely different X-ray patterns and none of them was contaminated with the other one to an extent detectable by this method.

It has been demonstrated that the lower melting isomer is not detectably converted to the higher melting one on heating in the solid phase.

Whereas all samples of the lower melting hydroxyurea showed the same diffraction pattern, two different patterns were found for the higher melting isomer. This is probably due to polymorphism.

Comparison of the X-ray pattern of the freeze-dried reaction mixture with those of the pure components suggests that the lower melting isomer is the primary product formed by the reaction between hydroxylammonium ion and cyanate ion.

A parallel investigation of the analogous process leading to methoxyurea showed that this compound does not display a similar isomerism, even under favourable conditions. Methoxyurea was found to be monomorphous.

CRYSTAL FORM AND HABIT

At room temperature both hydroxyureas are colourless crystalline substances without any characteristic taste or smell.

The lower melting isomer, isolated as described in a previous paper¹, crystallizes from anhydrous ether solution as rhombical plates. Well developed single crystals up to 0.5 mm were best obtained from the first batches of ether when the solvent was evaporated in a round-bottomed flask connected directly to a water pump. The heat of evaporation was supplied by infra-red radiation in such a way that the temperature was held below 10° C.

It proved less easy to obtain well-developed single crystals of the higher melting isomer. When crystallized from ethanol, ethanol + ether or dioxane it usually formed crystal aggregates, often rosettes or compact spheres of a size up to 0.5 mm or more. A typical crystal form, irregular hexagonal plates, was found in microsublimates (*vide infra*). A similar crystal form has been reported by Dresler and Stein² who obtained "mikroskopischen rhombischen Blättchen mit abgestumpften spitzen Winkeln" on addition of ether to an alcoholic solution.

SOLUBILITY

Both substances are very soluble in water and insoluble in benzene at 20° C. Boiling absolute ethanol dissolves approximately 3 % of the higher melting isomer; at 0° C the solubility is less than 0.2 %. Even a small content of water in the solvent raises the solubility considerably. The lower melting hydroxyurea is more soluble in ethanol than the higher melting one.

Boiling anhydrous ether dissolves approximately 0.2 % of the lower melting isomer; at -10° the substance is practically insoluble. The higher melting isomer is insoluble in anhydrous ether at the boiling point.

Boiling anhydrous dioxane dissolves approximately 1.5 % of the higher melting hydroxyurea. The solubility at 20° C is *ca.* 0.2 %. The lower melting isomer shows a higher solubility.

STABILITY IN THE SOLID STATE

The higher melting isomer is relatively stable. Pure samples can be stored at room temperature for at least several weeks before a slow decomposition sets in. On the other hand a sample, which had been stored in a sealed tube for 6 months, had acquired a moist appearance, and the tube exploded violently owing to gas pressure when an attempt was made to open it.

The lower melting isomer is more labile. Pure specimens stored at room temperature in a dry atmosphere usually begin to smell from ammonia after 1—2 days. Impure specimens sometimes decompose within hours.

At low temperatures both isomers show a satisfactory stability for practical work. The lower melting hydroxyurea has been stored at -15° C over phosphorus oxide for 1 week without detectable drop in melting point. All investigations in this and the following papers were carried out within one week from the date of the preparation and applying the above storage conditions.

The spontaneous decomposition process has been investigated in some detail in older literature. Carbon dioxide, ammonia, nitrogen and urea were among the decomposition products found by Dresler and Stein² on heating the higher melting isomer to the melting point 130°, and Francesconi and Parrozzani³ obtained the same products when decomposing the lower melting isomer at 100° C.

MICROTHERMAL EXAMINATION

Freshly isolated, pure and dry specimens of the isomers were examined in a polarising microscope equipped with an electrical hot stage, essentially as designed by F. Halstrøm⁴. The magnification was 50 : 1.

The lower melting hydroxyurea appeared as well-developed rhombical plates, displaying beautiful interference colours between crossed nicols. On heating with a rate of $2^\circ/\text{min}$ no changes whatsoever were observed until a temperature of $68\text{--}70^\circ$, at which the crystals began to sinter, and gas bubbles appeared in their interior. At 71°C the half-melted substance decomposed rapidly with a brisk effervescens, at $72\text{--}73^\circ\text{C}$ all crystalline material had disappeared and the object appeared black between crossed nicols. The general behaviour and decomposition temperature correspond to that given in previous literature³. The main object of the investigation was to find out, whether the "isomers" were possibly two forms of one and the same polymorphic substance. There were no indications of such relationship, but unfortunately the lability of both hydroxyureas at and above their melting points prohibited a detailed microthermal analysis. Every attempt to seed one substance with crystals of the other one at appropriate temperatures resulted in immediate decomposition.

When the lower melting hydroxyurea was quickly heated to just under the destruction temperature — about 65° — and this temperature was maintained for some time, a microsublimate was slowly deposited on the cover slip. It was both in appearance and melting point identical with the bulk. Higher melting crystals have never been observed during these experiments. It seems justified to conclude, therefore, that the lower melting hydroxyurea is not transformed into the higher melting isomer (m.p. 140°) simply on heating the solid. The transformation reported³ earlier must therefore be confined to solutions. Transformation in solid phase is further disproved by X-ray methods (*vide infra*).

The sample of the higher melting hydroxyurea consisted of crystal aggregates with poorly developed crystal form. They showed typical anisotropy between crossed nicols. On heating at a rate of $2^\circ/\text{min}$ no visible changes occurred until the crystals began to sinter at approximately 135° with a slight evolution of gas. At 140° the last trace of crystalline material disappeared (crossed nicol field) and there was a rapid decomposition accompanied by evolution of gas. The decomposition temperatures reported in the literature^{2,3,5,6}, vary from 128 to 141°C . The absolute values are for both isomers strongly dependent on the rate of heating.

When the higher melting isomer was heated on a slide to 125°C and this temperature was maintained for some time a microsublimate was deposited on the cover slip. It consisted of hexagonal plates which showed the same decomposition temperature as the main crop.

The two hydroxyureas thus behave similarly when heated under the microscope, the only difference being that the sublimation and decomposition occur at different temperatures.

X-RAY POWDER DIAGRAMS

In an attempt to throw further light on the formation, homogeneity and interconversions of the isomers some X-ray powder diagrams were taken.

The radiation, Cr- K_α ; $\lambda = 2.2896 \text{ \AA}$, was supplied by a self-rectifying Machlett tube with a chromium target. A vanadium pentoxide filter was used. The diffraction pattern was recorded photographically in a 19 cm

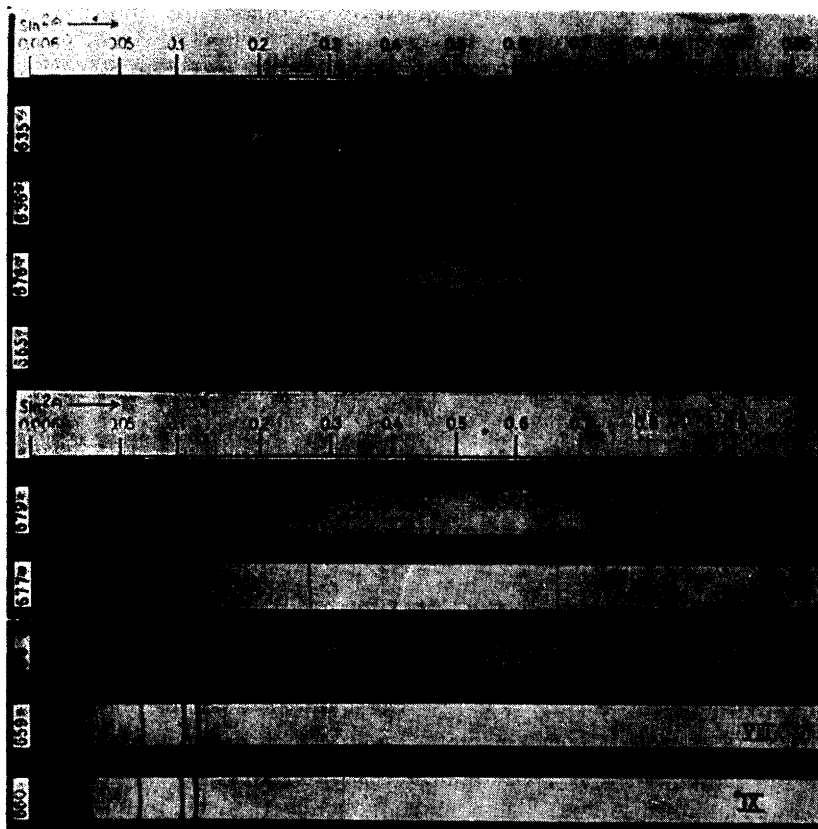


Fig. 1. For explanation see the text and Table 1.

Bradley camera, and the general technique was as previously described by one of us⁷. The time of exposure was *ca.* 6 hours and the temperature was 21—23° C.

The patterns are reproduced in Fig. 1. Detailed analyses, carried out as previously described⁷ are given in Table 1. The positions of the various lines in the pattern are described by the term $\sin^2 \theta$, in which θ is the glancing angle. The relative intensities (I) of the diffraction lines are estimated by visual examination and described as follows: s+, s, s— (strong), m+, m, m— (medium), w+, w, w— (weak), ? doubtful. Identity of any two patterns with respect to position and relative intensity of the lines may be taken as an indication that the corresponding substances are chemically and crystallographically identical. From non-identity of patterns it is not possible to decide, without thorough investigation, whether the substances differ in chemical structure or only in crystal lattice.

In Fig. 1, *I* is reproduced the pattern of the lower melting isomer, first crop of crystals obtained on cooling the first batch of ether used for extraction (ref. 1, p. 940); *II* represents the pattern of the last crop from the same prepa-

Table 1. Analysis of the characteristic X-ray diffraction patterns. (Roman numerals correspond to those in Fig. 1.)

II Hydroxyurea, lower melting isomer
III Hydroxyurea, higher melting isomer, from ethanol
IV Hydroxyurea, higher melting isomer, sublimate
V Freeze-dried reaction mixture, containing *II*, *IV* (?) and *VI*
VI Potassium chloride
VIII Methoxyurea

<i>II</i>		<i>III</i>		<i>IV</i>		<i>V</i>		<i>VI</i>		<i>VIII</i>	
<i>I</i>	Sin ² θ	<i>I</i>	Sin ² θ	<i>I</i>	Sin ² θ	<i>I</i>	Sin ² θ	<i>I</i>	Sin ² θ	<i>I</i>	Sin ² θ
.0655	m+	.0297	w	.0679*	w	.0656	w-	.1333	m+	.0269	m+
.0872	m+	.0683*	w+	.0777	m	.0777	w-	.2664	m	.0313	m
.0961	w	.0853*	m+	.0814	w-	.0872	w-	.3982	w	.0511	w
.1023	w	.1050	w	.0856*	m-	.1023	?	.5305	w	.0533	w
.1157	m+	.1143	w	.0937	m-	.1153	w-	.6633	m-	.0691	m
.1233	m+	.1221*	m+	.1015	m	.1231	w	.7954	m-	.0910	w
.1337	m	.1320	m	.1220*	m	.1295	w-			.1026	w
.1558	m	.1462	m	.1287	m+	.1330	m+			.1087	m+
.1604	m-	.1566*	w	.1364	w	.1562	w-			.1235	m+
.1738	m	.1662	m	.1479	w+	.1740	?			.1318	m
.1886	w	.1928	w	.1566*	m	.2653	m			.1391	w
.2290	w+	.2046*	w+	.1687	w+	.3979	w			.1545	w+
.2343	w-	.2181*	w	.2053*	w	.5305	w-			.1679	m-
.2402	w	.2270	w+	.2129	w+	.6626	m-			.1762	w+
.2630	w+	.2445	w	.2186*	w+	.7950	m-			.2010	w
.2761	w	.2660*	w+	.2235	m-					.2100	m
.2945	w	.3111*	w	.2312	w+					.2332	m-
.3019	w	.3299	w-	.2427	w+					.2413	m-
.3194	w+	.3402	w	.2655*	w-					.2492	m-
.3339	w+	.3500	w	.2967	w-					.2572	w+
.3487	w	.3703	w	.3116*	w+					.2644	m-
.3595	w	.4209	w-	.3220	w					.2747	w+
.3889	w-	.4889	w+	.3513	w					.2864	m-
.3992	w	.5354	w-	.3832	w					.2934	w+
.4626	w+	.5642	w-	.4855	w					.3201	w+
.4941	m-			.5171	w+					.3438	w
.5213	w			.5338	w					.3532	w
.5299	?									.3683	w+
.5543	w									.3840	w
.5886	w-									.3897	w+
.6601	w-									.3948	w+
.6685	w-									.4371	w
										.4697	w
										.4807	w
										.4915	w
										.5163	w
										.5279	w
										.5569	w
										.5713	?
										.6175	w
										.6469	w+

ration, obtained on concentration of the mother liquor. The patterns are identical, which is a reasonable proof of the homogeneity of the ether-soluble fraction. The melting points were also identical.

The pattern of the higher melting isomer, crystallized from ethanol is reproduced in *III*. It is entirely different from that of the lower melting hydroxyurea.

The higher melting hydroxyurea (pattern *III*) could be sublimated in quantity at 115° C and 1 mm Hg in Eder's apparatus⁸. The sublimate, about one third, showed the normal decomposition temperature, 135—140°, of the higher melting isomer, but the X-ray diffraction pattern (*IV*), was different from *III*. The possibility could not *a priori* be excluded that the higher melting isomer in fact consisted of two or more closely related chemical species. The difficulties in obtaining well-developed single crystals could be a result of such inhomogeneity. Since sublimation usually implies some purification it might be expected that the sublimate (*IV*) represented one compound or crystal modification and the original substance (pattern *III*) were a mixture of this and a different species. On inspection of the data in Table 1, *III* and *IV* it is seen that a certain number of lines in pattern *IV* (marked with an asterisk) actually reappear in pattern *III*. The $\sin^2 \theta$ values as well as the relative intensities of corresponding lines fit fairly well. A serious objection, however, is that several of the most intense lines (*m* and *m+*) of pattern *IV* are lacking in pattern *III*. It is therefore most reasonable to conclude that *III* and *IV* correspond to two pure modifications of the higher melting isomer, or alternatively that *IV* represents a new isomer.

It is important that pattern *III* does not contain any lines attributable to the lower melting isomer (*II*). This means that the higher melting hydroxyurea

Table 2. Origin of the lines in the pattern of the reaction mixture, *V*.

Reaction mixture <i>V</i>		KCl <i>VI</i>		Hydroxyurea lower m. p. higher m. p.			
<i>V</i>		<i>VI</i>		<i>II</i>		<i>IV</i>	
$\sin^2 \theta$	I	$\sin^2 \theta$	I	$\sin^2 \theta$	I	$\sin^2 \theta$	I
.0656	w—			.0655	m+		
.0777	w—					.0777	m
.0872	w—			.0872	m+		
.1023	?					.1015	m
.1153	w—			.1157	m+		
.1231	w			.1233	m+		
.1295	w—					.1287	m+
.1330	m+	.1333	m+				
.1562	w—			.1558	m		
.1740	?			.1738	m		
.2653	m	.2664	m				
.3979	w	.3982	w				
.5305	w—	.5305	w				
.6626	m—	.6633	m—				
.7950	m—	.7954	m—				

is not contaminated with the lower melting isomer. The X-ray powder method is, however, not very sensitive. Less than *ca.* 10% impurity cannot usually be traced in the patterns of the present type of compounds. The efficiency of the method of separation¹ has, however, been demonstrated by other means, as will be reported in a following paper.

In Fig. 1, *V* is reproduced the pattern of the freeze-dried reaction mixture (ref. 1, p. 940) recorded immediately after the solvent had been removed. Besides the intense lines of potassium chloride (*cf.* the pure potassium chloride pattern, *VI*) it exhibits the major lines of the lower melting hydroxyurea (*I—II*), whereas it is less easy to discern those of the higher melting isomer (*III* or *IV*). The origin of the various lines in *V* is more clearly seen from Table 2, in which the relevant data have been extracted. All the lines of potassium chloride are easily recognizable. Six of the most intense lines of the lower melting hydroxyurea reappear in the mixed pattern as weak lines, whereas only two, perhaps three of the lines appertaining to the higher melting isomer can be detected in *V*. These lines represent the strongest lines in pattern *IV* of the *sublimate*, whereas there are no common lines with the higher melting hydroxyurea crystallized *from ethanol*, pattern *III*. Although somewhat surprising this is probably an incident, which is readily understood, if the relationship between *III* and *IV* is assumed to be a case of polymorphism. A probable conclusion from Table 2 is that the hydroxyurea formed primarily by the reaction of hydroxylammonium chloride with potassium cyanate in aqueous solution under the given mild conditions¹ is the *lower* melting isomer. During the process of isolation this is partially transformed into the higher melting one, so that the ultimate ratio becomes about 1 : 1 (*cf.* ref. 1, p. 940).

Fig. 1, *VII* shows the pattern of the lower melting isomer, the sample having previously been heated to 50° C for 3 hours. The pattern is identical with *I* and *II*, which confirms that the lower melting hydroxyurea is not appreciably, if at all, transformed into the higher melting isomer on heating the solid, in accordance with the observation, that it could be sublimated unaltered (*I—II*). The rearrangement reported by others is therefore confined to solutions.

A parallel investigation of methoxyurea, which only exists as one chemical individual, showed that the substance is probably monomorphous. Powder diagrams of a sample crystallized from ethanol and of a sublimate are reproduced in Fig. 1, *VIII* and *IX*. It is evident that they are identical.

EXPERIMENTAL

Materials. The preparation of the *hydroxyureas* has been described in a previous paper¹. Analyses:

Lower melting isomer (CH ₄ O ₂ N ₂):	Calc.	C 15.79	H 5.31	N 36.68
	Found	» 16.12	» 5.20	» 36.34
Higher melting isomer (CH ₄ O ₂ N ₂):	Calc.	N 36.86		
	Found	» 36.3		

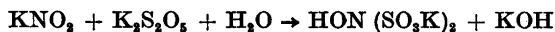
Molecular weights in aqueous solution were determined by cryoscopy, using the conventional Beckmann apparatus.

Results:

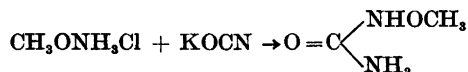
	Thermom. reading		
Water	2.708	2.709	} Depression 0.629° C M. w. 76.8 (calc. 76.0)
	2.709		
	2.708		
	2.710		
Higher melting hydroxyurea 0.762 g dissolved in 29.2 g water.	2.078	2.080	
	2.081		
	2.083		
	2.080		
Water	2.104	2.101	} Depression 0.619° C M. w. 78.5 (calc. 76.0)
	2.100		
	2.099		
	2.101		
Lower melting hydroxyurea 0.767 g dissolved in 29.2 g water	2.718	2.720	
	2.722		
	2.720		
	2.719		

The results are in accordance with those obtained by Francesconi and Parrozzani⁸. They clearly indicate that the hydroxyureas exist as monomers in aqueous solution and are only little dissociated. The same conclusion was previously drawn from conductivity measurements⁹.

Methoxyurea was synthesized in the following way. Potassium hydroxylamine disulphonate was first prepared according to Raschig's method¹⁰.



In the original procedure sodium hydrosulphite and sodium nitrite were used and the less soluble potassium salt of the sulphonic acid was precipitated by adding large quantities of potassium acetate. It was found more convenient to use directly potassium salts as starting materials, taking 1 mole (222 g) potassium pyrosulphite (corresponding to 2 moles potassium hydrosulphite) and 1 mole potassium nitrite. The yield of potassium hydroxylamine disulphonate was 240 g or 89 %. This compound was used for the preparation of O-methyl hydroxylammonium chloride by methylation followed by hydrolysis according to Traube¹¹. The yield was recrystallized from ethanol and had m.p. 151° C (lit. 151° C¹¹). Finally methoxyurea was obtained by a process analogous to that leading to hydroxyurea



By following the experimental conditions of Traube, who first prepared this substance, methoxyurea was obtained in good yield, m.p. 84° C, both from absolute ethanol and from benzene. Contrary to the hydroxyureas, methoxyurea is quite stable at the melting point.

A particular preparation of methoxyurea was carried out, using the "mild" conditions of reaction and isolation which were found to favour the yield of the labile, lower melting hydroxyurea. The product was carefully investigated for possible occurrence of isomers, but only one chemical individual could be isolated.

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