[Contribution from the Research Division, Electrochemicals Department of E. I. du Pont de Nemours and Company]

THE TRIMERIZATION OF GLYCOLONITRILE

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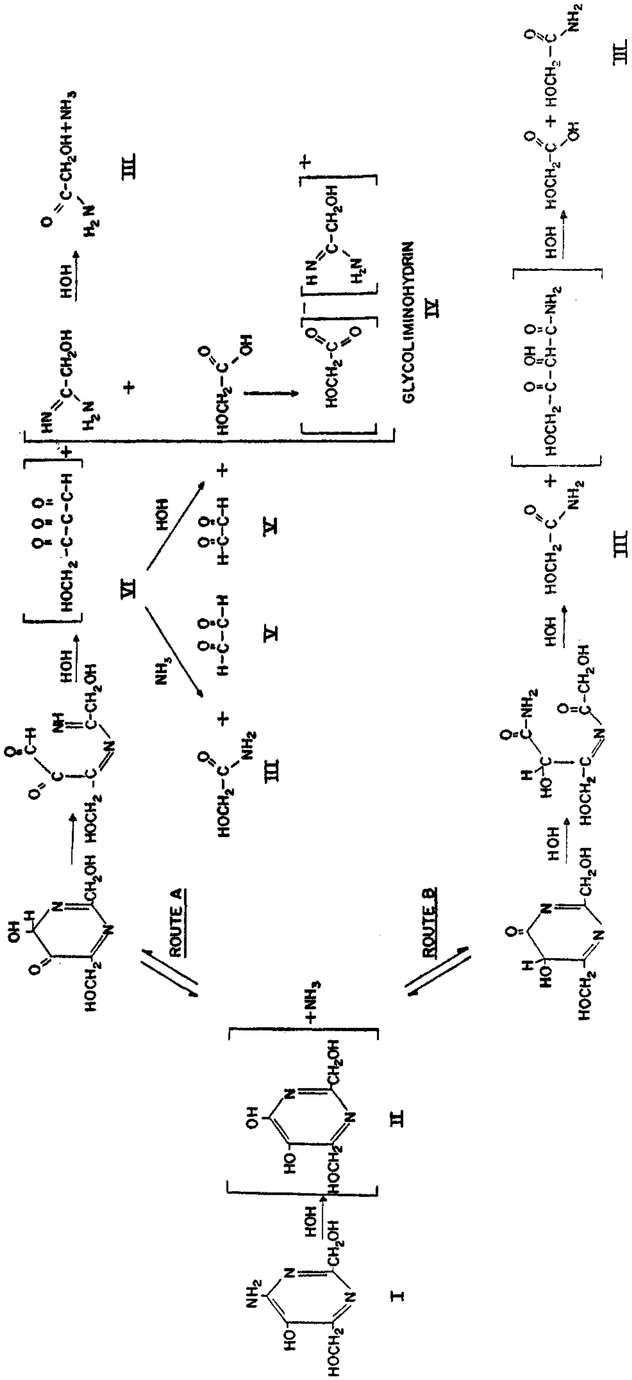
This paper describes the base-catalyzed trimerization of glycolonitrile and characterization of the trimer as 4-amino-5-hydroxy-2,6-di(hydroxymethyl)-pyrimidine (I).

A survey of the literature (1–4) reveals that nitriles having hydrogen atoms on the *alpha* carbon atom will trimerize in the presence of basic catalysts to aminopyrimidines. The reaction generally entails treating the nitrile with sodium or sodium alkoxide in an appropriate solvent at 100 to 150° for 2 to 3 hours. Yields range from 27 to 66%. Reynolds (4) has recently presented a mechanism for this type condensation. He also cites conditions for dimerization to β-iminonitriles.

It was reported by Jacobson (5) that passing a stream of air through a sample of glycolonitrile, made basic with aqueous caustic resulted in the formation of a trimer which was tentatively identified as 2,4,6-tri(hydroxymethyl)-1,3,5-triazine. We have found that the trimerization of glycolonitrile takes place on adjusting its acidity to *p*H 8 with 10% sodium hydroxide and allowing it to stand at 0° for several hours. The white, crystalline trimer separates in 30 to 50% yield and melts in the vicinity of 95°. It is insoluble in a wide variety of organic solvents but dissolves with decomposition in hot water, hot ethanol, or aqueous caustic. In the latter instances ammonia evolution is detected. These peculiar solubility characteristics prevent recrystallization of the trimer and considerably limit the reactions in which it can participate.

The ease of hydrolysis to form ammonia as noted above, led to a consideration of other structures for the trimer. Analytical data indicated that the compound was 4-amino-5-hydroxy-2,6-di(hydroxymethyl)pyrimidine (I). A Van Slyke amino determination indicated one free amino group. Also, the neutralization equivalent was found to be 177.9 (Theory, 171.2). Reaction with acetic anhydride gave a compound satisfying the analysis for the triacetate or the N-acetyl diacetate of I. The latter is favored since no labile 4-amino group could be detected.

More conclusive evidence in support of I was obtained from its hydrolytic degradation to glycolamide, glycoliminohydrin, and glyoxal. The trimer was dissolved in water and placed over phosphoric anhydride in a vacuum desiccator for several days. On separating the constituents of the brown residue two compounds were readily identified, namely glycolamide (III) and glycoliminohydrin (IV), the glycolamidine salt of glycolic acid. The brown polymeric material remaining was believed to be glyoxal polymer. The formation of glyoxal was confirmed by isolating the dimedone derivative of glyoxal (V) from a subsequent hydrolysis. The isolation of glyoxal from such a mild hydrolysis is most significant since, from a number of possible structures for the trimer I is the only structure that would be expected to yield glyoxal.


I
HOH
II
+NH₃
ROUTE A
ROUTE B
HOH
III
VI
NH₃
V
HOH
GLYCOLIMINOHYDRIN
IV
HOH
III
HOH
HOH
III
III

It may be assumed that I is readily cleaved to II as shown in the diagram. This ease of cleavage of the 4-amino group of I may be compared with the ready replacement of the amino group in the 4 and/or 6 position of 5-nitroso pyrimidines by hydroxyl on short boiling with dilute acid as observed by Taylor and Cain (6). The tautomeric forms of II readily react with water to undergo cleavage as shown by routes A and B. Since no glycolic acid or ammonium glycolate were isolated from the degradation it may be that route A predominates to the exclusion of route B. Glycolamide could result from hydrolysis of glycolamidine and ammonolysis of the unstable intermediate VI. The high yield of the dimedone derivative, based on a one-route hydrolysis, does not constitute proof of the "one-route" thesis as the derivative was obtained under non-equilibrium conditions. It is interesting to note that McCasland and Tarbell (7) have synthesized 2-hydroxymethyl pyrimidines by condensing glycolamidine with α-keto esters.

EXPERIMENTAL

Purification of glycolonitrile. Glycolonitrile, Rohm & Haas, 70% aqueous solution was distilled through a 37-mm. Vigreux column. The water-clear anhydrous material boiling at 65° (4 mm.), and having n_D^{17} 1.4117 was collected. About 5–10 drops of 85% phosphoric acid were used to stabilize 500 cc. of the anhydrous glycolonitrile. These were always added to the receiver prior to distilling. The pot temperature was not allowed to exceed 90°.

Trimerization of glycolonirtile. Aqueous sodium hydroxide solution (10%) was added to acid-stabilized glycolonitrile (11.4 g., 0.2 mole) to *p*H 8.0. Approximately 1 cc. was required. The solution was placed in a refrigerator at 0 to 10°, and on standing overnight crystals formed on the bottom of the flask. The solid was broken up, filtered, and the filtrate returned to the refrigerator. A second batch of crystals precipitated on short standing. These were collected, combined with the first, triturated in dry acetone, filtered, and air dried. Yield, 5.4 g. (47%); m.p. 90–95°.

Anal. Calc'd for $C_6H_9N_3O_3$: C, 42.1; H, 5.3; N, 24.6.
Found: C, 42.2; H, 5.1; N, 24.3.
Previous work (5): C, 41.8; H, 5.2; N, 24.4.

Van Slyke amino nitrogen determination. A 0.8281 g. sample of the trimer was dissolved in water and made up to 100 cc. A 10-cc. sample of this was treated with sodium nitrite and acetic acid, and from the volume of nitrogen collected the trimer was found to contain 7.85% "active" nitrogen. The calculated value was 8.18%.

Determination of neutralization equivalent. A sample of the trimer weighing 0.2641 g. was dissolved in water and titrated immediately with 14.82 ml. of a 0.1002 *N* hydrochloric acid solution to a Methyl Orange end point. The mean of three determinations was 177.9 grams/equivalent.

4-Acetamido-2,6-diacetoxymethyl-5-hydroxypyrimidine. To a slurry of 8.6 g. (0.05 mole) of I and 50 cc. of acetone was added 15.3 g. (0.15 mole) acetic anhydride dropwise with stirring. When the mixture was heated to 40° the solid dissolved and the solution became orange-red. The solution was stirred and maintained at 40° for two hours, and then allowed to stand overnight. The solvent was stripped off and unreacted acetic anhydride and acetic acid totaling 7.9 g. were collected. The dark residue was taken up in dioxane and filtered through a 20-cc. column of activated alumina. The faintly yellow filtrate was evaporated and the solid tan residue was shaken with benzene. The product was collected and washed twice with benzene; it formed white crystals, m.p. 114–116°. The solid was recrystallized twice from benzene and yielded a total of 1.0 g. of material, m.p. 115–117°.

Anal. Calc'd for $C_{12}H_{16}N_3O_6$: C, 48.5; H, 5.05; N, 14.14.
Found: C, 48.5; H, 4.27; N, 14.20.

Neutral hydrolysis of the trimer. A weighed sample of the trimer was dissolved in water and the solution was placed in a vacuum desiccator over phosphoric anhydride for five days. The dark brown residue was taken up in methanol and the undissolved tan crystals were collected. When the brown filtrate was treated with ether, an oil precipitated out. The ether was decanted and evaporated; the residue crystallized in the form of needles which were recrystallized three times from dioxane. The melting point of the product, alone and when mixed with authentic glycolamide, was 112–114°.

Anal. Calc'd for $C_2H_5NO_2$: C, 32.00; H, 6.66; N, 18.66.
Found: C, 32.51; H, 6.20; N, 17.99.

The tan crystals above were dissolved in hot methanol, filtered, and the hot filtrate was diluted with ether. The precipitated solid and solution were cooled and filtered. The light tan solid, after having been recrystallized twice from methanol, had m.p. 163.2-165.0°. Hantzsch and Voegelen (8) list 162–163° as the melting point of glycoliminohydrin while Rule (9) gives 166 to 168° for this material which he showed to be the glycolamidine salt of glycolic acid (IV).

Anal. Calc'd for $C_4H_{10}N_2O_4$: C, 32.00; H, 6.66; N, 18.66.
Found: C, 32.61; H, 6.24; N, 18.06.

A separate 0.3 g. portion of I was dissolved in 2 cc. of water, and to this were added 2 cc. of ethanol, 1.20 g. of dimedone (5,5-dimethyl-1,3-cyclohexanedione), and one drop of piperidine. The mixture was refluxed for five minutes, then water was added to the cloud point and the solution was cooled in an ice-bath. The product was collected and was recrystallized from methanol and water; there was obtained 0.8 g. of a white solid, m.p. 192–193° (yield, 79%). The mixture melting point with an authentic dimedone derivative of glyoxal showed no depression.

Anal. Calc'd for $C_{34}H_{46}O_8$: C, 70.10; H, 7.90; O, 21.99.
Found: C, 69.58; H, 8.11; O, 22.31.

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SUMMARY

Glycolonitrile trimerizes in mildly basic solution to a white solid which has been identified as 4-amino-5-hydroxy-2,6-di(hydroxymethyl)pyrimidine.

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