[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Researches on Pyrimidines. CXXXV. Uracil-glycol

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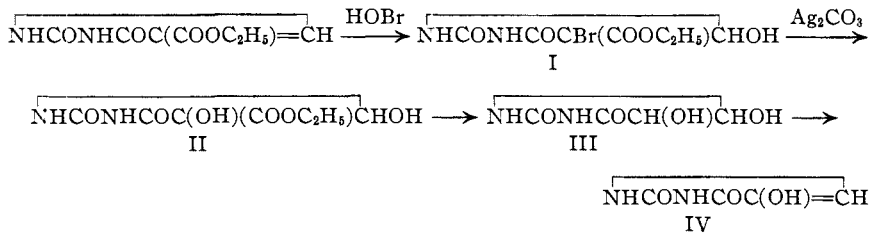
An investigation of methods for synthesizing uracil-glycol (5,6-dihydroxyhydrouracil) was undertaken in order to compare the properties of this pyrimidine with those of the corresponding thymine-glycol previously prepared in this Laboratory.[2]

The method used successfully by Baudisch and Davidson to prepare thymine-glycol is not directly applicable to uracil-glycol because of the non-existence of the necessary bromoxyuracil.[3] The 5-carbethoxy derivative of uracil glycol (II), however, was obtained in good yield by this method by starting with uracil-5-ethylcarboxylate and operating through the hydroxybromo ester represented by Formula I. The glycol II was obtained by the action of silver carbonate on this hydrogenated pyrimidine I.



The glycol ester (II) was expected to give uracil-glycol (III) upon saponification and decarboxylation. The product obtained, however, was not the desired glycol, but isobarbituric acid (IV). This pyrimidine was produced in all attempts at hydrolysis of the glycol ester (II), even under the mildest of experimental conditions. The intermediate 5-carboxylic acid could not be isolated, since it decomposed as soon as formed with the simultaneous elimination of carbon dioxide and water and the formation of isobarbituric acid. An acetyl derivative of the glycol ester (II) could be prepared, but it too gave only isobarbituric acid on hydrolysis.

The formation of isobarbituric acid instead of uracil-glycol was found to be a general reaction in other procedures designed to give the uracil-glycol. When isodialuric acid was reduced catalytically, isobarbituric acid was obtained. Even when the hydroxyl groups of isodialuric acid were protected through the use of the corresponding diacetate, the product formed was isobarbituric acid or its monoacetyl derivative.

The uracil-glycol configuration is thus seen to be too unstable for isolation. This is in marked contrast to the behavior of thymine-glycol, which

(1) The Chemical Foundation, Incorporated, Research Fellow in Organic Chemistry.

(2) Baudisch and Davidson, *J. Biol. Chem.*, **64**, 233 (1925); Johnson, Baudisch and Hoffmann, THIS JOURNAL, **54**, 1106 (1932).

(3) Wheeler and Johnson, *J. Biol. Chem.*, **3**, 187 (1907).

may easily be prepared and purified,[2] and which forms an anhydride only on long standing in acid solution. It may, therefore, be concluded that loss of water takes place in uracil-glycol by withdrawal of the hydroxyl group in the 6-position with the free hydrogen atom in the 5-position of the pyrimidine ring. An analogous mobility of groups in the 6-position of 2,4-dioxypyrimidines has been demonstrated by Biltz.[4]

The tendency of derivatives of uracil-glycol to pass into isobarbituric acid is of interest in connection with the fact that the latter substance is known to be an oxidation product of uracil.[5] Evidence that isobarbituric acid may be an intermediate product in the metabolism of uracil *in vivo* as well as *in vitro* has been presented recently by Cerecedo.[6] It is conceivable that the unstable uracil-glycol may be the precursor of the isobarbituric acid in any metabolic processes involving oxidation.

Experimental Part

5-Carbethoxy-5-bromo-6-hydroxyhydrouracil (I).—Eight grams of powdered 5-carbethoxyuracil[7] was suspended in 70 cc. of water, 2.5 cc. of bromine (1.1 equivalent) was added, and the mixture was allowed to stand for twelve hours at ordinary temperature with occasional shaking. As the original ester dissolved, colorless crystals of the bromoxy ester were formed. The precipitate was filtered, washed with water, dissolved in 150 cc. of boiling water and the solution filtered hot. The pyrimidine crystallized from the cooled solution in the form of long, colorless needles, melting at 178° (corr.) with effervescence; yield 7.3 g. (59%).

Anal. Calcd. for $C_7H_9O_5N_2Br$: N, 9.96; Br, 28.47. Found: N, 9.90, 9.87; Br, 28.29, 28.12.

The ester was decomposed by heat or by acids with the loss of hypobromous acid. By action of silver carbonate it was transformed into the glycol ester (II).

5-Carbethoxy-5,6-dihydroxyhydrouracil (II).—Four grams of (I) and 2.2 g. of powdered silver carbonate (1.1 equivalent) were suspended in 150 cc. of water, and the mixture was stirred for ten hours at room temperature. After adding alcohol to prevent foaming, the precipitated silver bromide was filtered through a norit mat and the excess of silver then removed from the solution with hydrogen sulfide, and the clear colorless filtrate evaporated to dryness *in vacuo* at 40–50°. The crystalline residue was dissolved in a small quantity of dry acetone, filtered from traces of inorganic matter and the filtrate evaporated nearly to dryness. The pure glycol ester was then precipitated by adding ether to the concentrated acetone solution; yield 3.0 g. (97%).

The immediate product of the reaction was a hydrated form of the glycol ester which readily lost one mole of water of crystallization when heated *in vacuo* at 61°. The pure hydrated form, when heated in a melting point tube, softened at 72°, melted partially around 110°, with violent effervescence at 125°. The anhydrous modification melted sharply with effervescence at 135–136° (corr.). The glycol ester is insoluble in ether, but very soluble in alcohol, water and acetone, from which it crystallizes upon evaporation as colorless plates. It gives no blue color with ferric chloride, unlike isobarbituric acid.[8]

(4) Biltz and Paetzold, *Ann.*, **452**, 71 (1927).
(5) Baudisch, *J. Biol. Chem.*, **60**, 155 (1924).
(6) Cerecedo, *ibid.*, **88**, 695 (1930).
(7) Wheeler, Johnson and Johns, *Am. Chem. J.*, **37**, 398 (1907).
(8) Biltz and Paetzold, *Ann.*, **452**, 87 (1927).

Anal. Hydrate: Calcd. for $C_7H_{10}O_6N_2.H_2O$: H_2O, 7.63. Found: H_2O, 7.94. Anhydrous form: Calcd. for $C_7H_{10}O_6N_2$: C, 38.53; H, 4.59; N, 12.84. Found: C, 38.53, 38.10; H, 4.85, 4.61; N, 12.87, 12.79.

Hydrolysis of II.—When a dilute hydrochloric acid solution of the glycol ester II was warmed, carbon dioxide was evolved immediately, and a granular precipitate separated, which was identical in properties and analysis with an authentic specimen of isobarbituric acid.[8] When the glycol ester was saponified with one equivalent of potassium hydroxide in cold absolute alcohol solution, a white amorphous potassium salt was obtained. By careful acidification of this salt in cold aqueous solution, isobarbituric acid was the only product obtained.

Monoacetate of 5-Carbethoxy-5,6-dihydroxyhydrouracil.—A mixture of 1 g. of the glycol ester and 8 cc. of acetic anhydride was boiled for three minutes. The resulting solution was concentrated in a vacuum desiccator until the monoacetate crystallized; yield 0.4 g. (33%). This substance was moderately soluble in cold acetone, from which it crystallized as clusters of colorless needles, melting at 178° (corr.) with effervescence.

Anal. Calcd. for $C_9H_{12}O_7N_2$: C, 41.52; H, 4.65; N, 10.77. Found: C, 41.86; H, 4.84; N, 10.95.

Study of Other Methods Applied for Synthesizing Uracil-glycol

(1) **Bromination of 5-Carboxyluracil.**—Attempts to add one equivalent of hypobromous acid to 5-carboxyluracil[9] suspended in water resulted in the partial decarboxylation of the acid, even in the cold, with the formation of 5,5'-dibromo-6-hydroxyhydrouracil. The product was identical in properties and analysis with a synthetic specimen.[3] The remainder consisted solely of unchanged 5-carboxyluracil. By using two equivalents of bromine water, a 90% yield of the dibromohydroxyhydrouracil was obtained.

(2) **Reduction of Isodialuric Acid and Diacetyl-isodialuric Acid.**—Upon reduction of 4 g. of pure isodialuric acid[10] in ethanol solution with the Adams platinum catalyst,[11] 0.3 g. of isobarbituric acid was isolated together with 3.4 g. of unchanged isodialuric acid. When 2.4 g. of diacetylisodialuric acid[12] was hydrogenated in glacial acetic acid solution, 0.7 g. of isobarbituric acid was obtained. Similarly, when the solvent was a mixture of acetic acid and acetic anhydride, acetyl isobarbituric acid[12] was formed in 66% yield.

(3) **Oxidation of Uracil with Peracetic Acid.**—Uracil was not attacked by treatment with 90% peracetic acid[13] for long periods at 25°, 40° or at 80° under pressure. Experiments were carried out both with and without solvents (water and acetic acid).

(4) **Reduction of Isouramil.**—Attempts to obtain dihydroisouramil by catalytic reduction of isouramil[14] in aqueous ammonia solutions were unsuccessful.

Summary

Free uracil-glycol could not be isolated because of its great tendency to pass into isobarbituric acid with loss of water. The lability of this pyrimidine glycol is in marked contrast to the comparative stability of the corresponding 5-methyl derivative (thymine-glycol) and the 5-carbethoxy derivative described in this paper.

NEW HAVEN, CONNECTICUT RECEIVED MAY 18, 1933
PUBLISHED SEPTEMBER 5, 1933

(9) Wheeler, Johnson and Johns, *Am. Chem. J.*, **37**, 399 (1907).
(10) Behrend and Roosen, *Ann.*, **251**, 242 (1889).
(11) "Organic Syntheses," 1928, Vol. VIII, p. 92.
(12) Biltz and Paetzold, *Ann.*, **452**, 88, 89 (1927).
(13) Arbusow, *J. prakt. Chem.*, **131**, 365 (1931).
(14) Bogert and Davidson, *Proc. Nat. Acad. Sci.*, **18**, 495 (1932).