and 3.2 grams of potassium hydroxide in 20 cc. of water were warmed on the steam bath. In a half hour the solution was acid to litmus. It was made alkaline and boiled for a short time. On acidifying the solution with hydrochloric acid and cooling, crystals separated; this material weighed 2.7 grams. It crystallized from water in needle-like prisms or in prismatic plates, and melted constantly at 239°–240° to a clear oil without effervescence. It forms beautiful, transparent prisms from alcohol.

Analysis I.

From Uracil-3-acetic Acid: Uracil acetic acid (1.2 grams) and four molecular proportions of potassium hydroxide were dissolved in a little water. An excess of methyl iodide (5 grams) was added and sufficient methyl alcohol to effect solution. The mixture was allowed to stand in a warm place for two days when the solution was acid to litmus. It was evaporated to dryness and the residue was crystallized from water containing a little sulphur dioxide. This gave 0.6 gram of material crystallizing in thin prismatic plates and having properties identical with the acid from 1-methyl uracil. When these substances were mixed, the melting point was not lowered. Analysis II.

Calculated for $C_7H_8O_4N_2$: N, 15.21; found: I, 15.18; II, 15.41.

NEW HAVEN, CONN., May, 1908.

[CONTRIBUTIONS FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES: SYNTHESIS OF URACIL-4-ACETIC ACID.

[THIRTY-SECOND PAPER.]

BY HENRY L. WHEELER AND LEONARD M. LIDDLE.

Received May 8, 1908.

Pinner has shown that acetone dicarboxylic ester condenses with benzamidine giving phenyloxypyrimidine acetic ester.[1] He also found that the ester condenses with other aromatic amidines of the general formula, $R—C(NH_2)NH$. Acetamidine and phenylacetamidine, he states did not give crystalline products.

The pseudothioureas may be viewed as amidines derived from the iminothiocarbonic esters. 2-Ethylpseudothiourea is ethylthiocarbamidine or mercaptoformamidine:

$$C_2H_5S—C(OR)NH \rightarrow C_2H_5S—C(NH_2)NH.$$

In accordance with this we have found that 2-ethylpseudothiourea condenses very smoothly, in alkaline solution, with acetonediethylcarboxylate, yielding 2-ethylmercapto-6-oxypyrimidine-4-ethyl acetate (I). The condensation may be represented as follows:

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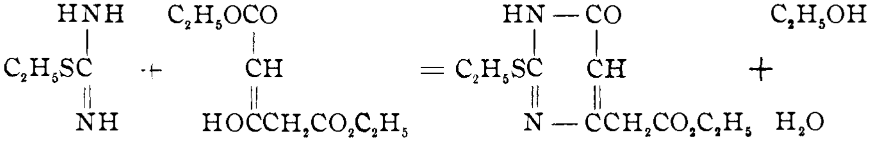
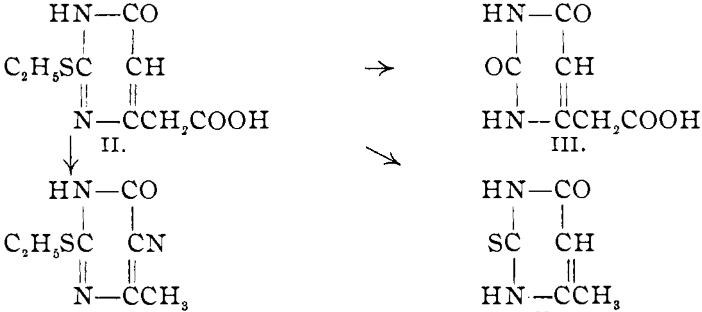
[1] *Ber.*, 28, 480 (1895).



$$\begin{array}{c}HNH\\ |\\ C_2H_5SC\\ \|\\ NH\end{array} + \begin{array}{c}C_2H_5OCO\\ |\\ CH\\ \|\\ HOCCH_2CO_2C_2H_5\end{array} = \begin{array}{rcl}HN & - & CO\\ | & & |\\ C_2H_5SC & & CH\\ \| & & \|\\ N & - & CCH_2CO_2C_2H_5\end{array} + \begin{array}{c}C_2H_5OH\\ \\ \\ \\ H_2O\end{array}$$

I.

When this pyrimidine ester, I, is warmed with aqueous alkali it is readily saponified, and on acidifying the solution with hydrochloric acid, 2-ethylmercapto-6-oxypyrimidine-4-acetic acid, II, is obtained. When this mercapto acid is digested on the steam bath with concentrated hydrochloric acid, mercaptan is given off and uracil-4-acetic acid, III, results.

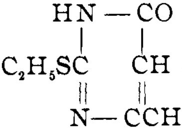


$$\begin{array}{ccc}\begin{array}{rcl}HN & - & CO\\ | & & |\\ C_2H_5SC & & CH\\ \| & & \|\\ N & - & CCH_2COOH\end{array} & \rightarrow & \begin{array}{rcl}HN & - & CO\\ | & & |\\ OC & & CH\\ | & & \|\\ HN & - & CCH_2COOH\end{array}\\ \text{II.} & & \text{III.}\\ \downarrow & \searrow & \\ \begin{array}{rcl}HN & - & CO\\ | & & |\\ C_2H_5SC & & CN\\ \| & & \|\\ N & - & CCH_3\end{array} & & \begin{array}{rcl}HN & - & CO\\ | & & |\\ SC & & CH\\ | & & \|\\ HN & - & CCH_3\end{array}\\ \text{IV.} & & \text{V.}\end{array}$$

On melting 2-ethylmercapto-6-oxypyrimidine-4-acetic acid, carbon dioxide escapes and the material is converted into 2-ethylmercapto-4-methyl-6-oxypyrimidine, IV. If melted in a stream of dry hydrogen chloride ethyl chloride is given off, in addition to carbon dioxide, and 2-thio-4-methyluracil, V, is formed. These last two pyrimidines have been described by List[1] who obtained them in a different manner.

The action of dry hydrogen chloride on the mercaptopyrimidines, leading to the formation of 2-thiopyrimidines with loss of alkyl halide, is a new reaction in the pyrimidine series. We have found that it can be applied in other cases. Taken in connection with the action of dilute nitric acid (Marckwald[2]) or hydrogen peroxide (Traube[3]) we are now able to replace a 2-alkylmercapto group by hydrogen. This is of importance for synthetic work since formamidine has not yet been shown to lend itself to pyrimidine condensations.

Experimental Part.

2-Ethylmercapto-6-oxypyrimidine-4-ethylacetate,  $\begin{array}{rcl}HN & - & CO\\ | & & |\\ C_2H_5SC & & CH\\ \| & & \|\\ N & - & CCH_2CO_2C_2H_5\end{array}$ —Twelve

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[1] *Ann. chem.* (Liebig), **236**, 3 (1886).

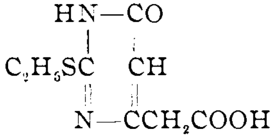
[2] *Ber.*, **25**, 3112 (1892).

[3] *Ann. chem.* (Liebig), **331**, 71 (1904).

grams of potassium hydroxide were dissolved in 20 cc. of water and to this cold solution 18.3 grams of the ethyl bromide addition product of thiourea were added. As soon as solution took place, 20 grams of acetone diethylcarboxylate were slowly added and the mixture was allowed to stand for about an hour, then warmed for a short time on the steam bath. On cooling, and acidifying with acetic acid, 17 grams of the condensation product separated. This was found to be very soluble in hot alcohol, hot water and acetic acid, less soluble in cold alcohol and nearly insoluble in cold water. On crystallizing from hot alcohol long, colorless, silky needles were obtained which melted sharply to an oil at 131°.

Calculated for $C_{10}H_{14}O_3N_2S$: N, 11.57; found, 11.60, 11.67.

2-Ethylmercapto-6-oxypyrimidine-4-acetic acid,



$$\begin{array}{ll} & HN-CO \\ & \;| \qquad \vdots \\ C_2H_5SC & \quad CH \\ & \;\| \qquad \| \\ & N-CCH_2COOH \end{array}$$

Two grams of the above ester were dissolved in 25 cc. of water containing 1.5 grams of potassium hydroxide. The solution was heated on the steam bath for a half hour, then cooled and the acid precipitated with hydrochloric acid. The crystalline precipitate weighed 1.5 grams or 86 per cent. of the calculated. It was readily soluble in hot alcohol and it gave burrs of colorless needles. It was less soluble in water and it melted at 155° with vigorous effervescence.

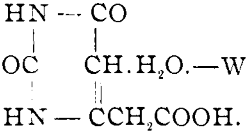
Calculated for $C_8H_{10}O_3N_2S$: N, 13.08; found, 13.10, 13.24.

This acid is not precipitated from alkaline solution by acetic acid.

One gram of 2-ethylmercapto-6-oxypyrimidine-4-acetic acid was heated in an oil bath at 170° until effervescence ceased. The residue was decolorized with charcoal and recrystallized from water. It melted at 145–147°, and when mixed with 2-ethylmercapto-4-methyl-6-oxypyrimidine the melting point was not altered. One gram of the acid was melted in an oil bath at 170° and a stream of dry hydrogen chloride was then allowed to pass over the substance. It immediately solidified. On crystallizing from water, it formed colorless prisms which gave a strong test for sulphur. This material had all the properties of 2-thio-4-methyluracil. Analysis:

Calculated for $C_5H_6ON_2S$: N, 19.71; found, 19.78.

Uracil-4-acetic acid,



$$\begin{array}{ll} & HN-CO \\ & \;| \qquad | \\ OC & \quad CH.H_2O \\ & \;| \qquad \| \\ & HN-CCH_2COOH. \end{array}$$

—When the above mercapto acid was warmed on the steam bath with concentrated hydrochloric acid, it readily evolved mercaptan and gave a quantitative yield of uracil-

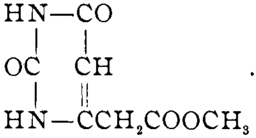
4-acetic acid. The acid was crystallized from water. It formed flat prisms which sintered above 300° and melted with effervescence at 340°. In concentrated aqueous solution, it separates at first in an anhydrous condition then in crystals containing one molecule of water.

Calculated for $C_6H_6O_4N_2.H_2O$: H_2O = 9.57; found, 9.97.
Calculated for $C_6H_6O_4N_2$: N, 16.47; found, 16.95.

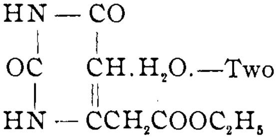
Uracil-4-acetic acid is soluble in about 8 parts of boiling water and in 30 parts of cold. It is much less soluble in alcohol. It is a strong acid and the aqueous solution reddens litmus. It does not give a precipitate with barium chloride or mercuric chloride. It forms an amorphous silver salt soluble in ammonia.

The Potassium Salt, $C_6H_5O_4N_2K$.—Two grams of the acid were dissolved in a little water containing 0.7 gram of potassium hydroxide. On adding alcohol, balls of a minute, colorless crystal separated. The salt was very soluble in water and insoluble in alcohol. It was dried in a desiccator for analysis.

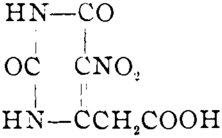
Calculated for $C_6H_5O_4N_2K$: N, 13.46; found, 13.40.

Uracil-4-methylacetate,  $\begin{array}{l} HN-CO \\ |\qquad\ | \\ OC\quad CH \\ |\qquad\ \| \\ HN-CCH_2COOCH_3 \end{array}$.—Eight-tenths gram of anhydrous acid was esterified by dissolving in 15 cc. of methyl alcohol containing two drops of concentrated sulphuric acid and warming the solution for one hour. On concentrating the solution to about 7 cc., 0.5 gram of ester separated. The material was washed with water and recrystallized from water. It then formed large, elongated, six-sided prisms which melted to an oil at 216–218° with slight effervescence. It was very soluble in hot water and hot alcohol. It was dried over sulphuric acid for analysis.

Calculated for $C_7H_8O_4N_2$: N, 15.21; found, 15.39.

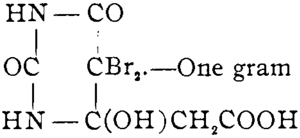
Uracil-4-ethylacetate,  $\begin{array}{l} HN-CO \\ |\qquad\ | \\ OC\quad CH.H_2O \\ |\qquad\ \| \\ HN-CCH_2COOC_2H_5 \end{array}$.—Two grams of uracil-4-acetic acid were dissolved in 25 cc. of absolute alcohol containing several drops of concentrated hydrochloric acid and the solution was boiled for three hours. It was then evaporated to dryness and the residue crystallized three times from about 90 per cent. alcohol. There was then obtained about 0.8 gram of ester. It was very soluble in hot alcohol and it separated, on cooling, in colorless prisms, which curiously contained a molecule of water of crystallization. This is the first pyrimidine ester that has been found to have water of crystallization. It melted to an oil at 187–189°. It was dried over sulphuric acid for analysis.

Calculated for $C_8H_{10}O_4N_2.H_2O$: H_2O = 8.33; found, 8.25; N = 12.96; found, 12.97.

5-Nitrouracil-4-acetic acid, 

.—Uracil-4-acetic acid was nitrated by dissolving 1 gram of the acid in 4 cc. of a mixture of two parts concentrated nitric acid and one of sulphuric acid. The solution was then heated on the steam bath. The product was insoluble in alcohol and difficultly soluble in hot water. It formed minute cubes which melted with effervescence at 153°.

Calculated for $C_6H_5O_6N_3$: N, 19.53; found, 19.39.

Dibromoxyhydrouracil-4-acetic acid, 

.—One gram of uracil-4-acetic acid was dissolved in water and a large excess of bromine was added. On spontaneous evaporation colorless, elongated plates separated. They became dark colored above 180° and melted with effervescence at 240°. The substance appears to crystallize with a half molecule of water of crystallization.

Calculated for $C_6H_6O_5N_2Br_2.{}^1/_2H_2O$: H_2O = 2.54; found, 2.89. N = 7.87, found, 7.55.

A nitrogen determination in the case of the substance dried at 106° gave 8.43 per cent. nitrogen while the calculated is 8.10 per cent.

New Haven, Conn., May, 1908.

[Contribution from the Bureau of Chemistry, U. S. Dept. of Agriculture, Laboratory of Animal Physiological Chemistry.]

THE INVERSION OF CANE SUGAR BY INVERTASE.[1]

By C. S. Hudson.

Received May 8, 1908.

It is the purpose of this preliminary communication to draw attention to a source of large error in the polariscopic measurement of the rate of inversion of cane sugar by invertase. This rate of inversion has been studied very often and the conclusion of all the observers except O'Sullivan and Tompson[2] is that the inversion does not follow the unimolecular reaction formula. This conclusion has received much notice and in most text books the inversion by invertase is said to follow a totally different

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[1] Published by permission of the Secretary of Agriculture.

[2] *J. Chem. Soc.*, **57**, 834–931 (1890).