dissolved in water. After washing with ether to remove a trace of oil, the uramil was precipitated by addition of hydrochloric acid. It separated as an oil, which finally solidified on standing. The yield was 2.1 g. or 35% of theory. It was purified by crystallization from alcohol and separated in stout, prismatic blocks. They melted at 219–220° to a clear oil, which soon began to decompose with effervescence. This pyrimidine is very soluble in glacial acetic acid, moderately soluble in hot benzene and cold ether, and very difficultly soluble in hot water. The condensation was repeated with four molecular proportions of sodium, but the yield of pyrimidine was not increased. A portion of the malonic ester undergoes decomposition during the reaction and α-anilino-β-phenylpropionic acid is fomed.

Calc. for $C_{17}H_{18}O_2N_2S$: N, 12.92; found: N, 12.75, 12.69, 13.03.

NEW HAVEN, CONN.

May 20, 1914.

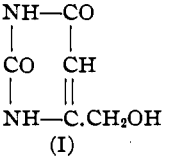
[CONTRIBUTIONS FROM THE SHEFFIELD CHEMICAL LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES: LXXI. SYNTHESIS OF THE PYRIMIDINE NUCLEOSIDE, 4-HYDROXYMETHYLURACIL.

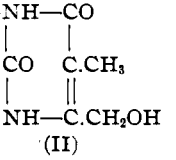
BY TREAT B. JOHNSON AND LEWIS H. CHERNOFF.

Received June 6, 1914.

This paper is our third contribution to the chemistry of pyrimidine nucleosides.[1] It includes a description of the synthesis and properties of the simple nucleoside of uracil, namely, *2,6-dioxy-4-hydroxymethylpyrimidine* represented by Formula (I).



(I)



(II)

The method of synthesis, which has been applied successfully for the preparation of this interesting pyrimidine, is perfectly analogous to that employed for the preparation of the corresponding simple nucleoside of thymine, namely, 2,6-dioxy-4-hydroxymethyl-5-methylpyrimidine[2] represented by Formula (II). The starting point, in this case, was the ethyl ester of ethoxyacetic acid (III), which was prepared in quantity by interaction of sodium ethylate with ethyl chloroacetate, and also from the nitrile $C_2H_5O.CH_2CN$[3] by direct esterification with ethyl alcohol in the presence of hydrochloric acid (imidoester method). The ester undergoes condensation with ethyl bromoacetate, in the presence of amalgamated

[1] Johnson and Chernoff, *J. Biol. Chem.*, 14, 307; THIS JOURNAL, 35, 585 (1913).

[2] Johnson and Chernoff, *Loc cit.*

[3] Sommelet, *Compt. rend.*, 143, 827.

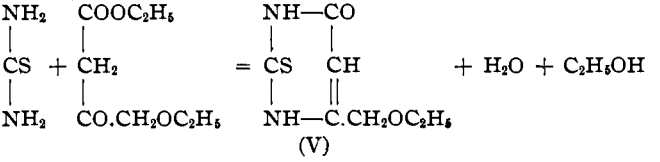
zinc,[1] giving the β-ketone ester—*ethyl γ-ethoxyacetoacetate* (IV). The reaction may be expressed by the following equation:[2]

$$C_2H_5OCH_2COOC_2H_5 + Zn.Hg + Br.CH_2.COOC_2H_5 =$$
(III)

$$C_2H_5OCH_2C(OC_2H_5)(OZnBr)—CH_2COOC_2H_5 \xrightarrow{H_2O}$$

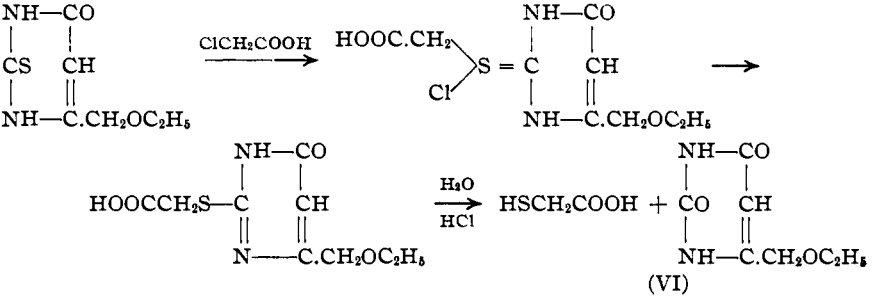
$$C_2H_5OH + Zn(OH)Br + C_2H_5O.CH_2.COCH_2COOC_2H_5$$
(IV)

This ester (IV) exhibits the normal properties of a β-ketone ester and condenses normally with thiourea in alcoholic solution and in the presence of sodium ethylate, forming the sodium salt of the thiopyrimidine represented by Formula (V). The yield of this pyrimidine was excellent. The condensation may be represented as follows:



(V)

Little difficulty was encountered in converting quantitatively this thiopyrimidine (V), into its corresponding oxygen derivative (VI). This was accomplished by digesting the thiopyrimidine, in aqueous solution, with chloroacetic acid. The mechanism of this change may be represented by the following formulas:



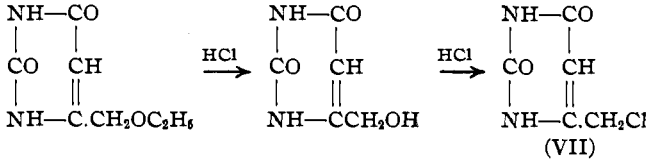
(VI)

4-Ethoxymethyluracil (VI) is very stable in the presence of acids. It undergoes no change when heated with 10% sulfuric acid at 140°. When heated with concentrated hydrochloric acid at 100°, ethyl chloride

[1] Johnson, THIS JOURNAL, **35**, 582 (1913).

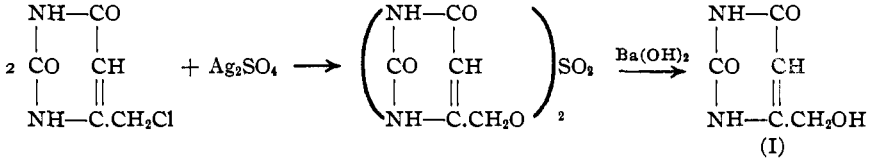
[2] This reaction has been applied successfully with a number of other esters and the interesting results, which have been obtained, will be discussed in future papers. These types of β-ketone have hitherto received practically no attention, and should be of value for the synthesis of other important combinations of immediate biochemical and therapeutic interest. (T. B. Johnson.)

was evolved and the pyrimidine ether was converted smoothly into the primary halide, 2,6-dioxy-4-chloromethylpyrimidine (VII).



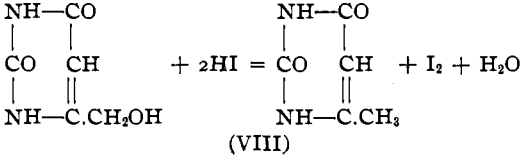
(VII)

In order to convert this chloropyrimidine (VII), into the simple nucleoside of uracil (I), it was first digested in aqueous solution, with silver sulfate to remove the halogen and the resulting sulfate was then decomposed by digesting with an aqueous solution of barium hydroxide. In this manner, the nucleoside (I) was easily obtained in a colorless, crystalline condition. A description of this compound is given in the experimental part of this paper.



(I)

The structures of the ethers (V) and (VI), the halide (VII), and the nucleoside (I), were all established by the behavior of the uracil-nucleoside on reduction. When digested in hydriodic acid solution, in the presence of a small amount of phosphorus, it underwent reduction smoothly and was converted into Behrend's 4-methyluracil (VIII).



(VIII)

Experimental Part.

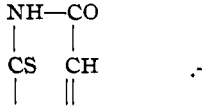
Ethyl γ-Ethoxyacetoacetate, $C_2H_5OCH_2CO.CH_2COOC_2H_5$.—The boiling point of this ester has previously been recorded in a paper from this laboratory.[1] The ester is easily obtained by interaction of molecular proportions of ethyl ethoxyacetate and ethyl bromoacetate in the presence of amalgamated zinc. The esters were mixed with one or two molecular proportions of amalgamated zinc, in a dry flask connected to a reflux condenser, and the mixture then warmed on a steam bath. At first, there was no apparent evidence of a reaction, but, on continued warming, there was finally a great evolution of heat and the reaction became so violent that it was necessary to cool with ice water. Within a few minutes, however, the violent reaction was over and the mixture was then heated

[1] Johnson, *loc. cit.*

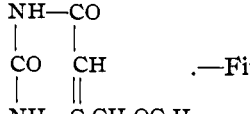
at 100° for 10 hours. We obtained a dark colored syrupy product, which was poured into cold water to decompose the double zinc compound. After acidifying with hydrochloric acid, to complete the decomposition and to dissolve the zinc hydroxide, the oil was thoroughly extracted with ether and the acid filtrate discarded. The ether solution of the crude oil was then washed several times with cold, dilute sodium hydroxide solution in order to remove the β-ketone ester. On acidifying this alkaline solution with hydrochloric acid (cold) the ketone ester separated at once and was dissolved in ether. After washing with water and finally drying over anhydrous calcium chloride, it was then purified by distillation under diminished pressure. Some of the observed boiling points of different preparations are recorded below:

Pressure in mm.....	22	26	30	30	32	52
Boiling point.....	113°	116–120°	120–125°	117°	121°	132°

The average yield obtained was about 15% of the theoretical. The ketone ester can also be obtained by applying the condensation with ethyl chloroacetate, but the yield is smaller.

2-Thio-4-ethoxymethyl-6-oxypyrimidine,  .—For the preparation of this new pyrimidine, molecular proportions of thiourea were condensed with ethyl γ-ethoxyacetoacetate in the presence of sodium ethylate. The quantities of reagents used in one experiment were as follows: 13.5 g. of the ketone ester, 5.9 g. of thiourea and 3.6 g. of metallic sodium. The sodium was dissolved in 50 cc. of absolute alcohol and, after cooling, the thiourea and ketone ester added. The mixture was then digested on the steam bath for 7 hrs. to complete the reaction and the alcohol finally removed by evaporation on a water bath. We obtained the sodium salt of the pyrimidine as a colorless solid, which was very soluble in water. On acidifying this solution with acetic acid the pyrimidine separated as a heavy crystalline precipitate. This was separated by filtration, washed with water and finally purified by crystallization from hot water. It deposited in large radiating prisms, which melted at 180–1° to a clear oil. The yield was 7.1 g.

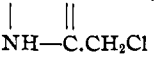
Calc. for $C_7H_{10}O_2N_2S$: N, 15.05. Found: N, 15.07.

2,6-Dioxy-4-ethoxymethylpyrimidine,  .—Five grams of the preceding 2-thiopyrimidine and 5 g. of chloroacetic acid were dissolved in hot water (50–75 cc.) and the solution boiled for 3 hrs. when the de-

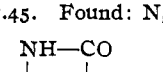
sulfurization of the thiopyrimidine was apparently complete. The mixture was then evaporated on the steam bath and the residue obtained finally triturated with cold water. The above pyrimidine was obtained in crystalline condition by this treatment. It was washed with cold water and finally purified by crystallization from hot alcohol. It separated in rhombic prisms which melted at 175° to an oil. The yield of purified pyrimidine was 2.5 g.

Calc. for $C_7H_{10}O_3N_2$: N, 16.47. Found: N, 16.44.

Behavior of 2,6-Dioxy-4-ethoxymethylpyrimidine when heated with Sulfuric Acid.—One gram of the pyrimidine and 25 cc. of 10% sulfuric acid were heated in a bomb tube for 3 hrs. at 125°. On cooling, the pyrimidine crystallized out apparently unaltered. The heating was continued for 3 hrs. at 140°, and the sulfuric acid then removed from the solution by precipitation as barium sulfate. After filtering off the sulfate, the neutral solution was concentrated and cooled, when the unaltered pyrimidine separated in the form of prismatic crystals. It melted at 174°. The pyrimidine, therefore, did not undergo conversion to uracil.

2,6-Dioxy-4-chloromethylpyrimidine,  .—This halogen derivative was formed by interaction of the above ethoxypyrimidine with hydrochloric acid. Two grams of the pyrimidine were heated with 50 cc. of concentrated hydrochloric acid for about 24 hrs. at 100°. The contents of the tube were then transferred to a beaker and evaporated to dryness at 100°, when a dark colored residue was obtained. This was dissolved in hot water, the solution decolorized by digesting with bone-coal and finally concentrated again to a small volume. On cooling, the chloropyrimidine finally separated in the form of small radiating prisms, which decomposed at 204–215°, depending on the rate of heating. The dust from this compound irritates the membranes of the nose producing sneezing.

Calc. for $C_5H_5O_2N_2Cl$: N, 17.45. Found: N, 17.7.

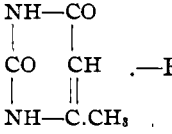
2,6-Dioxy-4-hydroxymethylpyrimidine,  .—In order to obtain this simple nucleoside of uracil we proceeded as follows: to an aqueous solution of the above chloropyrimidine (1.4 g. in 200 cc. of water) was added an excess of silver sulfate (2.5 g.) and the mixture boiled in an open dish for about one hour, keeping the volume constant by addition of water. The insoluble silver chloride was then filtered off and the excess

of silver in solution precipitated as sulfide by hydrogen sulfide. The solution was then boiled to remove all free hydrogen sulfide and the silver sulfide separated by filtration. The sulfuric acid was then separated by precipitation as sulfate with barium hydroxide and the excess of barium precipitated as carbonate by saturating the solution with carbon dioxide. The neutral solution was then concentrated and cooled, when the nucleoside separated in prismatic crystals. This pyrimidine was purified for analysis by crystallization from hot water and separated on cooling, in small plates. They did not possess a sharp melting point. On heating in a capillary tube the pyrimidine began to show signs of melting at about 240° and then decomposed quite sharply a 254°. This decomposition point varies according to the rate of heating. The yield of purified nucleoside was 0.6 g.

Calc. for $C_5H_6O_2N_2$: N, 19.72. Found: N, 19.42.

The structure of this nucleoside was established by its behavior on reduction with hydriodic acid.

The Formation of 4-Methyluracil,



.—Five-tenths of a gram of the nucleoside was dissolved in 15 cc. of hydriodic acid (sp. gr. 1.7) and about 0.1 g. red phosphorus added to the solution. The solution was then boiled for 4 hrs., diluted with water and finally filtered to remove the phosphorus. The halogen and phosphate radicals were then removed by digesting with an excess of silver carbonate. After filtering, the excess of silver was then precipitated as sulfide with hydrogen sulfide and the aqueous solution then decolorized by boiling with bone-coal. The solution was then concentrated and cooled, when 4-methyluracil deposited in colorless crystals. It was purified by recrystallization from hot water. It did not melt or undergo decomposition below 300° and when mixed with pure 4-methyluracil this behavior, on heating, was not altered.

Calc. for $C_5H_6O_2N_2$: N, 22.22. Found: N, 21.9.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF TEXAS.]

THE ACTION OF MONOCHLOROACETIC ACID ON SEMICARBAZIDE AND HYDRAZINE.

BY J. R. BAILEY AND W. T. READ.

Received June 8, 1914.

Introduction.

Hydrazine derivatives have been prepared by the action of monochloroacetic acid on phenylhydrazine,[1] and on hydrazine,[2] but no inves-

[1] *Ber.*, **28**, 1231 (1895); **36**, 3887 (1903).

[2] *J. prakt. Chem.*, [2] **83**, 249 (1861).