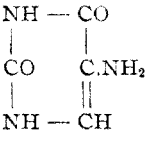
[CONTRIBUTIONS FROM THE SHEFFIELD CHEMICAL LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES. LXXXVII. ALKYLATION OF 5-AMINO-URACIL.

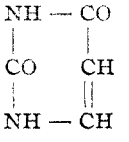
BY TREAT B. JOHNSON AND IWAO MATSUO.

Received February 24, 1919.

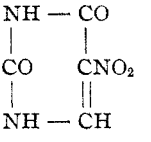
In the development of our work on the alkylation of pyrimidine combinations, it became necessary for us to determine the behavior of 5-amino-uracil (I) when subjected to the action of methyl iodide in the presence of alkali. Uracil (II) and 5-nitro-uracil (III), when exposed to conditions favorable for exhaustive alkylation with methyl iodide, give as final products of reaction the corresponding 1,3-dimethyl pyrimidines. 5-Amino-uracil, on the other hand, offers greater possibilities of substitution than



(I).



(II).



(III).

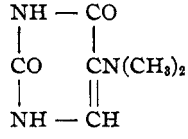
either of these two pyrimidines due to the presence of the basic amino group in the 5-position of the ring. Alkylation of this compound theoretically might proceed in several ways with production of a great variety of intermediate alkyl derivatives, leading finally to the formation of a tetramethyl derivative (VIII) as the end-product of the reaction.

If tautomeric formulas of 5-amino-uracil are disregarded, there are 3 positions only in this compound which need to be considered as open to attack for the substitution of methyl groups, namely, the two nitrogen atoms occupying positions 1 and 3 within the pyrimidine cycle and the basic amino group occupying position 5. Which constructions are the most susceptible to attack, namely, the cyclic acid amide group or the amino radical, has never been established.

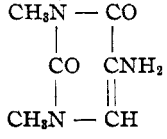
We now find that the potassium salt of amino-uracil interacts with methyl iodide at the temperature of boiling methyl alcohol with formation of a dimethyl derivative of amino-uracil. Furthermore, the substitution takes place entirely in the nucleus of the pyrimidine ring giving 1,3-dimethyl-5-amino-uracil (V). That substitution does not take place in the amino group with formation of dimethylamino- or monomethylamino-derivatives (IV, VI and VII) was established in the following manner: Of the 4 nitrogen substituted dimethyl derivatives theoretically possible of formation by alkylation with methyl iodide only one has hitherto been prepared, namely, 5-dimethyl-amino-uracil (IV). This was synthesized by heating 5-bromo-uracil with dimethylamine.[1] The two remaining isomers, which were hitherto unknown, have been prepared by us and we

[1] Wheeler and Jamieson, *Am. Chem. J.*, **32**, 355 (1904).

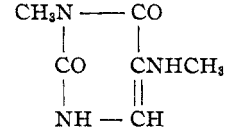
find that no one of these three isomers is identical with our pyrimidine obtained by alkylation of amino-uracil. The only structure left therefore to assign to our alkylation product is that represented by Formula V. In other words, 5-amino-uracil exhibits the same behavior towards methyl iodide as does uracil and 5-nitro-uracil and the presence of the amino radical in position 5 does not prevent substitution in the nucleus as might be expected from the nature of this radical.



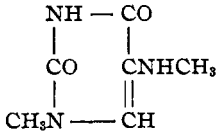
(IV).



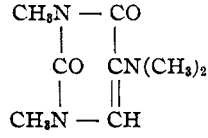
(V).



(VI).



(VII).



(VIII).

The two isomeric pyrimidines represented by Formulas VI and VII were prepared by heating the corresponding 5-bromopyrimidines with methylamine. A description of their properties and method of preparation is given in the experimental part of this paper. These various pyrimidine compounds are of particular interest to us in connection with our researches on the relationship between constitution and physiological action of organic bases.

Experimental Part.

The Conversion of Uracil into 5-Nitro-uracil.—It is known that uracil interacts smoothly with nitric acid of sp. gr. 1.5 giving 5-nitro-uracil. An acid of sp. gr. 1.4 is not capable of bringing about this change except by long digestion at 100° or when the nitration reaction is applied with a mixture of this acid and sulfuric acid.[1]

In applying the above reaction with nitric acid of sp. gr. 1.5 it has been our practice, in the past, to use for one part of uracil about 10 to 15 parts of nitric acid in order to produce the above change. We now find that this great excess of acid is unnecessary and, after completion of a series of nitration experiments in which varying proportions of acid were used (Table I) we find that treatment of uracil with as low as 4.5 parts of nitric acid (sp. gr. 1.5) is productive of almost a theoretical yield of nitro-uracil. Our method of operating is to dissolve one part of uracil in 4.5 parts of nitric acid of sp. gr. 1.5 and then to allow the solution to evaporate in an open porcelain dish at a temperature of 50–60°. This is accomplished by heating on the steam bath, and as the acid evaporates at this tempera-

[1] Wheeler and Bristol, *Am. Chem. J.*, **33**, 441 (1905).

ture the nitro-uracil is left behind in a very pure condition. This proportion of acid is productive of nitro-uracil which will not respond to Wheeler and Johnson's test for uracil.[1] We have prepared several hundred g. of this reagent in this manner. After nitration, the product is washed with cold water and dried in a desiccator over conc. sulfuric acid.

TABLE I.

Using 10 g. Uracil.

Nitric acid (1.525). Cc.	Yield of nitro-uracil. Grams.	% of theory.	Uracil test.
100	13.78	98.4	—
100	13.72	98.0	—
80	14.00	100.0	—
50	14.00	100.0	—
50	14.00	100.0	—
40	14.00	100.0	—
30	13.98	99.8	—
20	13.17	94.0	+

The 13.17 g. of crude nitro-uracil obtained by nitration of 10 g. of uracil with 20 cc. of nitric acid was given a second treatment with 10 cc. of nitric acid of sp. gr. 1.52. We obtained, after evaporation of the nitric acid, 13.87 g. of nitro-uracil or 99.4% of a theoretical yield. It did not respond to a uracil test.

Preparation of 5-Amino-uracil from 5-Nitro-uracil.—5-Nitro-uracil was reduced according to the different methods which have been described in the literature. Tin and hydrochloric acid were used,[2] ferrous sulfate in alkaline solution,[3] zinc and hydrochloric acid,[4] zinc and ammonia, and aluminum amalgam and ammonia.[5] After running through a series of comparative experiments we finally adopted for our work the following procedure:

Ten g. of nitro-uracil was dissolved in 600 cc. of hot water, and 150 cc. of strong ammonia solution added. A solution of 150 g. of ferrous sulfate in hot water was then poured at once into this alkaline mixture and the resulting mixture then boiled for 30 minutes. The precipitated ferric hydroxide was separated by filtration and the solution cooled. Part of the amino-uracil separated in the form of flakes and more was obtained after concentration of the solution.

The crude amino-uracil was purified by dissolving in the smallest possible volume of dil. hydrochloric acid and then neutralizing the acid solution with dil. ammonium hydroxide. Under these conditions the amino-uracil is precipitated. From 10 g. of nitro-uracil we obtained

[1] Wheeler and Johnson, *J. Biol. Chem.*, **3**, 183 (1907).

[2] Behrend, *Ann.*, **236**, 33 (1886).

[3] Widmann, *Ber.*, **29**, 1955 (1896).

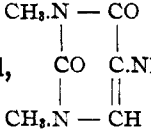
[4] Behrend, *Ann.*, **240**, 6 (1887).

[5] Behrend and Grünwald, *Ibid.*, **309**, 254 (1899).

generally about 5.5 g. of 5-amino-uracil or a yield corresponding to 67.6% of theory. This interacted with picric acid in aqueous solution giving Behrend and Grünwald's[1] characteristic picrate melting at 147°. This amino-pyrimidine responded to Wheeler and Johnson's test for uracil. This characteristic reaction takes place at room temperature with removal of the amino group from the 5-position of the ring by the action of bromine.

Alkylation of 5-Amino-uracil. Introduction of Methyl Groups.—The potassium salt of amino-uracil: Behrend and Grünwald[2] prepared the sodium salt of amino-uracil by dissolving the pyrimidine in dil. sodium hydroxide solution. The salt proved to be difficultly soluble and separated from a solution in a crystalline condition containing a half molecule of water. They did not describe the corresponding potassium salt but stated that it can be obtained and is very much more soluble than the sodium salt. In order to obtain this combination for our work we dissolved 10 g. of amino-uracil and one molecular proportion of potassium hydroxide in 150 cc. of boiling water and then concentrated the solution by evaporation and allowed it to cool. The potassium salt separated from saturated solution in a crystalline condition and was easily separated by filtration. It was purified by crystallization from dil. alcohol, and then dried in a vacuum over sulfuric acid. From 10 g. of the pyridine we obtained about 12 g. of the dry salt.

1,3-Dimethyl-5-amino-uracil,



—Thirteen g. of the potassium salt of the amino-uracil was suspended in 150 cc. of methyl alcohol, and 5 molecular proportions of methyl iodide were then added to the solution. This mixture was then digested on a steam bath until solution was complete. This required about 40 hours' digestion. On cooling, potassium iodide deposited and after separation by filtration, the filtrate was evaporated to dryness under diminished pressure. The residue, which remained behind, was washed with about 30 cc. of cold water and then dissolved in hot water and the solution decolorized by treatment with bone charcoal. On cooling, the alkylation product separated in a crystalline condition. The product was purified by recrystallization from 95% alcohol and separated in the form of colorless prisms. The yield of this material was small, only 1.3 g. of the pure substance being obtained. It melted at 275° to a clear oil without effervescence. It was very soluble in water and did not contain potassium, but gave a strong test for iodine. Nitrogen determinations by the Kjeldahl method agreed with the calculated

[1] Wheeler and Bristol, *Loc. cit.*

[2] *Ann.*, **309**, 257 (1900).

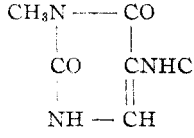
value for the hydriodic acid salt of a dimethyl derivative of amino-uracil. The salt was dried at 100°.

Calc. for $C_6H_9O_2N_3.HI$: N, 14.89. Found: 14.9, 14.65.

Preparation of the Free Base.—The hydriodic acid salt was dissolved in water, an excess of silver oxide suspended in the solution, and the mixture digested until all the iodine was precipitated as silver iodide. After filtering the filtrate was allowed to evaporate spontaneously when the free base was obtained in a crystalline condition. It was purified by crystallization from 95% alcohol and separated in the form of hexagonal plates or tables, which melted at 233–235° to a clear oil without effervescence. This pyrimidine was very soluble in cold water, moderately soluble in alcohol and insoluble in chloroform and ether. It did not give a test for iodine.

Calc. for $C_6H_9O_2N_3$: N, 27.09. Found: 27.08.

Picrate of the Dimethyl-amino-uracil.—This separated from aqueous solution in the form of fine, yellow needles which melted at 246° to a dark oil with strong effervescence.

1-Methyl-5-methylamino-uracil,  .—For the preparation of this pyrimidine, 1-methyl-5-bromo-uracil was first synthesized according to the method described by Johnson and Heyl.[1] This bromopyrimidine was then heated with an excess of methylamine in 33% aqueous solution at 150° for 3 hours and finally at 175° for 2 more hours. On cooling, the reaction product separated in the form of yellow, prismatic crystals. These were separated, dried and finally purified by crystallization from 95% alcohol. The pyrimidine separated in the form of needles and melted at 209° to a yellow oil without effervescence. This compound responded to Wheeler and Johnson's test for uracil. Nitrogen determination (Kjeldahl):

Calc. for $C_6H_9O_2N_3$: N, 27.09. Found: 27.2, 27.02.

Picrate of 1-Methyl-5-methylamino-uracil. — This salt crystallizes from water in the form of long, yellow needles, which melt at 175° to an oil without effervescence.

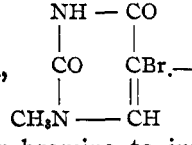
Preparation of 3-Methyluracil.—This pyrimidine was prepared by alkylation of 2-ethylmercapto-6-oxypyrimidine with methyl iodide[2] and then hydrolyzing the resulting 3-methyl derivative by digestion with hydrochloric acid.

[1] *Am. Chem. J.*, **37**, 633 (1907).

[2] Wheeler and Johnson, *Ibid.*, **42**, 33 (1903).

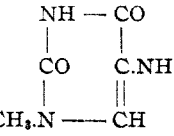
15.2 g. of the ethylmercapto-pyrimidine were alkylated under the conditions employed by Johnson and Heyl[1] for the preparation of 2-ethylmercapto-1-methyl-6-oxypyrimidine. After separation of this pyrimidine, the filtrate, containing the very soluble isomeric 3-methyl-pyrimidine, was diluted with about 40 cc. of 20% hydrochloric acid and the solution boiled for 8 hours when the evolution of ethylmercaptan had ceased indicating complete hydrolysis. The solution was then evaporated to dryness leaving behind a mixture of uracil, 1-methyl-uracil, 3-methyl-uracil and potassium iodide. Trituration with boiling 98% alcohol enabled us to separate the 3-methyl-uracil from the insoluble potassium iodide and uracil. On cooling the concentrated alcohol extract the 3-methyl-uracil separated in the form of needles and melted without further purification at 200°. This was purified by recrystallization from 95% alcohol and separated from this solvent in the form of needles melting at 229°. The pyrimidine was identical with that described by Wheeler and Johnson.[2] We were unable, however, to raise the melting point to 232°. This was undoubtedly due to the fact that the product was contaminated with a trace of the isomeric 1-methyl-uracil, which is not easily separated by crystallization from alcohol. 1-Methyl-uracil melts at 175°.[3] We succeeded in obtaining by this method of operating 1.4 g. of 3-methyl-uracil. The identification of this pyrimidine among the products of hydrolysis after alkylation is of especial interest to us, because it establishes the fact that 2-ethylmercapto-6-oxypyrimidine undergoes alkylation in both positions—1 and 3—when it interacts with methyl iodide in alkaline solution. Johnson and Heyl made no attempt to isolate the 2-ethylmercapto-3-methyl-6-oxypyrimidine or to establish its presence by hydrolysis.

3-Methyl-5-bromo-uracil,

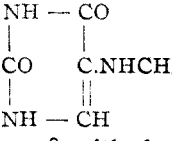


—Johnson and Clapp[4] prepared this compound by allowing bromine to interact with 3-methylcytosine in aqueous solution. We obtained the same combination by treatment of 3-methyl-uracil with bromine in glacial acetic acid solution. The reaction takes place at ordinary temperature and the yield is almost quantitative. The pyrimidine was purified by recrystallization from 95% alcohol and separated from this solvent in the form of needles which melted at 260° to an oil without effervescence.

[1] *Loc. cit.*
[2] *Am. Chem. J.*, **42**, 35 (1909).
[3] Johnson and Heyl, *Loc. cit.*
[4] *J. Biol. Chem.*, **5**, 64 (1908).

3-Methyl-5-methylamino-uracil,  —This pyrimidine was obtained by heating 3-methyl-5-bromo-uracil with an excess of methylamine in 33% aqueous solution. In order to bring about a complete reaction we heated the mixture for 2 hours at 150° and finally for 2 hours at 185–195°. When the bomb tube was opened the alkylated pyrimidine had partially separated in a crystalline condition. These crystals melted at 206°. The methylamine solution was evaporated to dryness and the residue obtained triturated with absolute alcohol to remove ammonium bromide, and finally recrystallized from 95% alcohol. On cooling, the methylated pyrimidine separated in the form of plates which melted at 206° to an oil without effervescence. A mixture of this pyrimidine and the isomeric 1-methyl-5-methylamino-uracil (melting at 209°) melted at 170–175°.

Calc. for $C_6H_9O_2N_3$: N, 27.09. Found: 27.05.

5-Methylamino-uracil,  —4-Methyl-5-bromo-uracil and methylamine interact at 150° with formation of the corresponding 5-methylamino derivative.[1] 5-Bromo-uracil reacts with dimethylamine in a similar manner with formation of dimethylamino-uracil.[2] The corresponding monomethyl derivative of uracil has not hitherto been described. We obtained this base by heating 5-bromo-uracil[3] with 4 molecular proportions of methylamine (33% aqueous solution) at 175–185° for 3 hours, and finally for the same period of time at 180–190°. This pyrimidine separated from the amine solution in a crystalline condition and was purified by recrystallization from 80% alcohol. No definite melting point can be assigned to this compound. When heated slowly in a capillary tube it gradually undergoes decomposition without melting, but when the bath is heated rapidly the pyrimidine darkens in color at 285° and finally melts at 297° with violent effervescence. This pyrimidine responds to Wheeler and Johnson's[4] test for uracil.

Calc. for $C_5H_6O_2N_2$: N, 29.78. Found: 29.55.

Picrate.—This salt crystallizes from water in the form of stout prisms which melt at 185° to an oil with effervescence.

Preparation of 1,3-Dimethyl-5-amino-uracil by Reduction of 1,3-Di-

[1] Wheeler and Jamieson, *Am. Chem. J.*, **32**, 355 (1904).

[2] Wheeler and Jamieson, *Loc. cit.*

[3] Wheeler and Merriam, *Ibid.*, **29**, 486 (1903).

[4] *Loc. cit.*

methyl-5-nitro-uracil.[1]—An attempt was made to bring about this reduction smoothly by subjecting the nitropyrimidine to the action of aluminum amalgam in dil. aqueous ammonia solution. The reaction was applied at a temperature of 40°. After complete reduction the aluminum hydroxide was filtered off and the filtrate then concentrated under diminished pressure. We obtained a syrupy residue which was extremely soluble in cold water and which only partially solidified after standing for a long time. The small amount of crystalline material was separated from the oil; washed with a small volume of cold alcohol in which solvent it was difficultly soluble and then recrystallized from water, when it separated on cooling in a crystalline condition and melted at 231–233°. The reduction of this nitropyrimidine is apparently not on easy operation and it was extremely difficult to obtain a sufficient amount of material by this method for an investigation. Due to the fact that Mr. Matsuo was obliged to discontinue his research, it was impossible to perfect the reaction by applying other methods of reduction and therefore the work was discontinued.

Summary.

5-Amino-uracil undergoes alkylation when its potassium salt is allowed to interact with methyl iodide and is converted into a dimethyl derivative. In this change the hydrogen atoms of the amino group are not replaced by methyl, but substitution takes place in the 1- and 3-positions of the pyrimidine ring with formation of 1,3-dimethyl-5-amino-uracil.

NEW HAVEN, CONN.

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

ORGANIC CHEMICAL REAGENTS. IV. THE PREPARATION OF ALKYL IODIDES.[2]

BY ROGER ADAMS AND V. VOORHEES.

Received February 27, 1919.

Of the alkyl iodides, methyl and ethyl iodides are by far the most important and at least one of them is made by almost every student in elementary organic chemistry. The propyl, butyl and amyl iodides are in less demand but nevertheless are often needed in large amounts. For the production of 50 to 100 g. of these products, the usual procedure described in laboratory manuals of adding powdered iodine in small portions to a mixture of red phosphorus and the alcohol is quite suitable. As soon as the size of the preparation becomes larger, however, the method is quite tedious and considerable amounts of material are lost by volatilization, particularly if the lowest two alcohols are used.

[1] Lehmann, *Ann.*, **253**, 77 (1889).

[2] For previous articles in this series see THIS JOURNAL, **40**, 1281, 1950 (1918); **41**, 276 (1919).