I wish also to express my indebtedness to the C. M. Warren Fund, by the aid of which much material was procured for this research.

CAMBRIDGE, MASSACHUSETTS.

[CONTRIBUTIONS FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

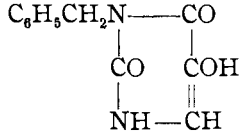
RESEARCHES ON PYRIMIDINES: SYNTHESIS OF 1-METHYL-5-HYDROXYURACIL.

[FORTY-SECOND PAPER.]

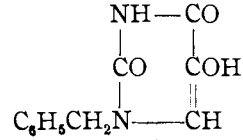
BY TREAT B. JOHNSON AND D. BREESE JONES.

Received March 19, 1909.

In a previous paper from this laboratory, Johnson and McCollum[1] described a new synthesis of 5-hydroxyuracil (isobarbituric acid). They showed that this pyrimidine is formed quantitatively by hydrolysis of 2-ethylmercapto-5-ethoxy-6-oxypyrimidine with hydrochloric acid. In a recent paper, Johnson and Jones[2] have shown that nitrogen-alkyl derivatives of this mercaptopyrimidine can be obtained easily and also undergo hydrolysis, giving nitrogen-alkyl derivatives of 5-hydroxyuracil. They prepared by this method 1- and 3-benzyl-5-hydroxyuracils, I., and II.



I.

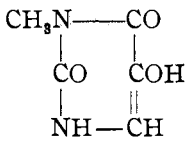


II.

The object of the work described in this paper was to prepare the nitrogen-methyl derivatives of 2-ethylmercapto-5-ethoxy-6-oxypyrimidine[3] and study their behavior on hydrolysis.

5-Hydroxyuracil and nitrogen-alkyl derivatives of this pyrimidine are prepared, according to Behrend's[4] synthesis, by the reduction of 5-nitrouracil and its alkyl derivatives with tin and hydrochloric acid. The only nitrogen-alkyl derivatives of 5-hydroxyuracil that have been synthesized by this method, are methyl-5-hydroxyuracil (methylisobarbituric acid) and ethyl-5-hydroxyuracil (ethylisobarbituric acid). These pyrimidines are incorrectly represented in Beilstein's Handbuch[5] as 1-alkyl pyrimidines III, and IV, and were prepared by Lehmann[6] by reducing methyl- and ethylnitrouracils, to which he assigned, without proof, formulas V, and VI.

[1] *J. Biol. Chem.*, 1, 437.
[2] *Am. Chem. J.*, 40, 538.
[3] *Loc. cit.*
[4] *Ann.*, 249, 39; *Ibid.*, 251, 239.
[5] Vol. I, 1347, 1348.
[6] *Ann.*, 253, 77.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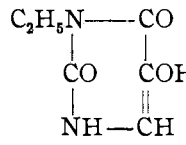
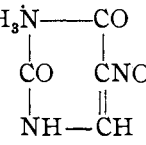

IV.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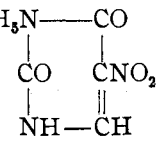
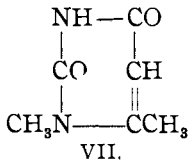
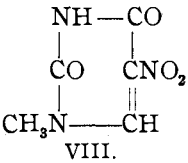
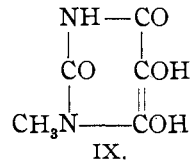
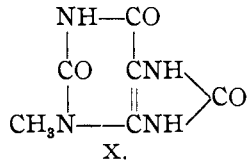

VI.

The structures of these alkyl nitrouracils, and consequently the corresponding 5-hydroxyuracils of Lehmann's were correctly established by Behrend and Thurm[1] who showed that they are to be represented as 3-alkyl-pyrimidines; for example, 3,4-dimethyluracil (α-dimethyluracil), VII, and nitric acid reacted giving the same nitromethyluracil, VIII, as originally was obtained by Lehmann[2] by methylation of nitrouracil. Furthermore, the oxidation of Lehmann's methyl-5-hydroxyuracil with bromine water gave a methylisodialuric acid, IX, which condensed with urea, giving 3-methyluric acid (*d*-acid) X.[3] Lehmann's


VII.


VIII.


IX.


X.

ethylnitrouracil reacted with methyl iodide, giving the same ethylmethylpyrimidine as was obtained from 1-methylnitrouracil and ethyl iodide.[4]

Johnson and Jones[5] observed that 1-benzyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidine is the chief product of the reaction when benzyl chloride acts on 2-ethylmercapto-5-ethoxy-6-oxypyrimidine, XI, in presence of alkali. We now find that methyl iodide reacts with this mercaptopyrimidine, giving a mixture of the corresponding 1 and 3-methylpyrimidines which contains about 70 per cent. of the theoretical yield of 1-methyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidine, XII.

2-Ethylmercapto-3-methyl-5-ethoxy-6-oxypyrimidine, XVI, possessed the unique property of combining with potassium iodide, giving a definite, double compound. We suspected this substance, at first, of being an addition product of methyl iodide and the potassium salt of 1- or 3-methyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidines. This assumption, however, proved to be incorrect, since the same compound was formed quantitatively by crystallizing 2-ethylmercapto-3-methyl-5-ethoxy-6-oxypyrimidine from an alcoholic solution of potassium iodide. The analytical determinations agreed with the calculated values for a double compound

[1] *Ann.*, **323**, 160.

[2] *Loc. cit.*

[3] E. Fischer and Ach, *Ber.*, **32**, 2721. Loeben, *Ann.*, **298**, 181. Behrend and Dietrich, *Ann.*, **309**, 260.

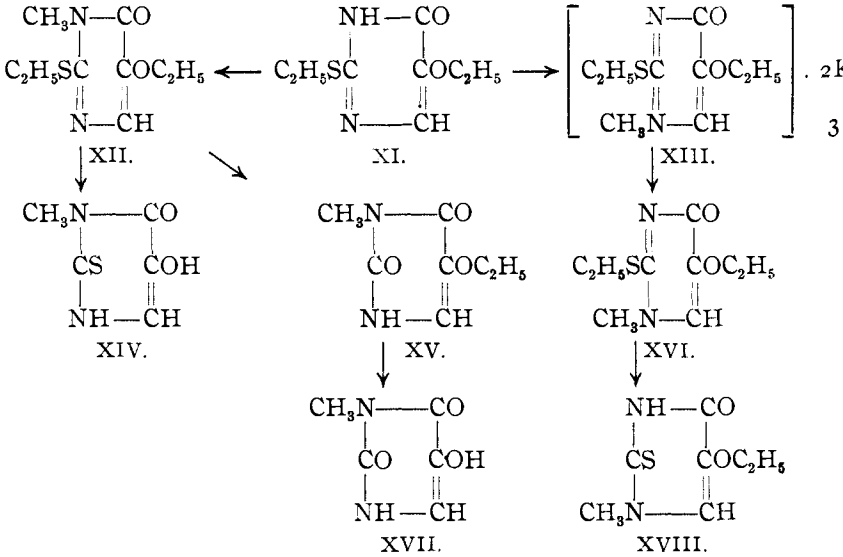
[4] Behrend and Thurm, *Loc. cit.*

[5] *Loc. cit.*

containing 3 molecules of the 3·methylpyrimidine and 2 molecules of potassium iodide, XIII.

2·Ethylmercapto·1·methyl-5-ethoxy·6·oxypyrimidine, XII, is converted smoothly into 1·methyl·5-ethoxyuracil, XV, by digestion with hydrochloric acid. When this pyrimidine or the mercaptopyrimidine are heated with strong hydrochloric acid at 120–130°, they are changed practically quantitatively into 1·methyl-5·hydroxyuracil, XVII. Hydrolysis of 2-ethylmercapto-1·methyl·5-ethoxy·6-oxypyrimidine with boiling hydrobromic acid gave a mixture of 1-methyl-2·thio-5·hydroxyuracil, XIV, and 1-methyl·5·ethoxyuracil, XV. The formation of 2-thiopyrimidines from the corresponding mercapto derivatives by hydrolysis with acids has previously been observed by Johnson and Clapp;[1] for example, 2·ethylmercapto·3,5-dimethyl-6·oxypyrimidine gave 2·thio-3,5·dimethyl-6-oxypyrimidine when digested with hydrobromic acid.

The sulphur in 2·thio·1-methyl-5-hydroxy·6·oxypyrimidine, XIV, is very firmly bound. It cannot be removed by digestion with chloracetic acid.[2] The pyrimidine combines with this acid, giving 1-methyl·2-thioglycollic·acid·5-hydroxy-6-oxypyrimidine which can be digested with concentrated hydrochloric acid without decomposition. When the double compound of 2·ethylmercapto-3-methyl-5-ethoxy·6-oxypyrimidine and potassium iodide, XIII, was digested with hydrochloric acid, it was converted into 2·thio-3-methyl-5-ethoxy-6-oxypyrimidine, XVIII.

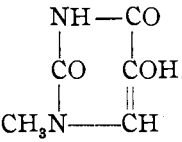


[1] *Jour. Biolog. Chem.*, **5**, 57.

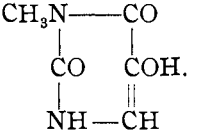
[2] Wheeler and Liddle, *Am. Chem. J.*, 40, 547.

Summary.

1. Alkylation of 5-nitrouracil with methyl iodide gives chiefly 3-methyl-5-nitrouracil. Reduction of this nitropyrimidine gives 3-methyl-5-aminouracil and *3-methyl-5-hydroxyuracil*,

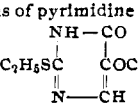


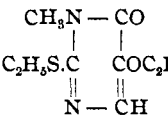
2. Alkylation of 2-ethylmercapto-5-ethoxy-6-oxypyrimidine with methyl iodide gives chiefly 1-methyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidine. Hydrolysis of this mercaptopyrimidine with hydrochloric acid at 120–130° gives quantitatively *1-methyl-5-hydroxyuracil*,



Experimental Part.

The 2-ethylmercapto-5-ethoxy-6-oxypyrimidine that was used in this work was prepared from ethyl formate and ethyl ethylglycollate according to the directions of Johnson and McCollum.[1] This pyrimidine can be obtained easily in good yield by this method. The yields of pyrimidine obtained in five different condensations are given in the following table:

	Grams $C_2H_5OCH_2COOC_2H_5$.	Grams $HCOOC_2H_5$.	Grams $NH_2C(SC_2H_5):NHHBr$.	Grams of pyrimidine obtained, 	Per cent. of calculated.
1	113	75	79·5	42·0	48.8
2	102	65	71.8	35·0	45·1
3	109	70	76.7	44·5	53·6
4	76	50	53·5	27·5	47·5
5	76	50	53·5	32·0	55·3

1-Methyl-2-ethylmercapto-5-ethoxy·6·oxypyrimidine,  — Fifteen grams of 2-ethylmercapto-5-ethoxy-6-oxypyrimidine[1] and 4.5 grams (1 mol.) of pulverized potassium hydroxide were dissolved in 150 cc. of boiling, absolute alcohol. Fourteen grams of methyl iodide were then added and the mixture warmed, in a water-bath, until it gave no alkaline reaction, when tested with moistened turmeric paper (45 minutes). After cooling, the insoluble potassium iodide (11 grams) was filtered

[1] *Loc. cit.*

off and the excess of alcohol expelled by evaporation under diminished pressure. This method of procedure was adopted after we had observed, in a preliminary experiment, that the methyl pyrimidine volatilized with alcohol vapors by distillation at ordinary pressure. We obtained a crystalline substance which was extracted several times with an excess of ether and the insoluble part saved (see below). After evaporation of the ether we obtained 11.0 grams of the 1-methylpyrimidine melting at 45–50°. This yield corresponds to about 69 per cent. of the theoretical.

In a second experiment 10.0 grams of 2-ethylmercapto-5-ethoxy-6-oxypyrimidine and 2.85 grams of potassium hydroxide were dissolved in 100 cc. of boiling, absolute alcohol and the solution cooled to 10°. Ten and six-tenths grams of methyl iodide (1.5 mols.) were then added and the solution allowed to stand at 20–5°. Potassium iodide began to separate in one-half an hour and after 3 hours the reaction was complete. The weight of undissolved potassium iodide was 6.25 grams. After evaporation of the alcohol at 40–50° at 47 mm. pressure the residue was then extracted, as usual, with an excess of ether. The yield of 1-methylpyrimidine corresponded to about 71 per cent. of the theoretical. The product insoluble in ether was saved (see below).

The 2-ethylmercapto-1-methylpyrimidine is extremely soluble in ethyl alcohol, benzene and acetone. It crystallized from ether and water in plates melting at 50° to a clear oil. Analysis (Kjeldahl):

Calculated for $C_9H_{14}O_2N_2S$: N 13.08; found, 13.4, 13.20.

The Material Insoluble in Ether.—This substance was extremely soluble in water and difficultly soluble in cold alcohol. It crystallized from a saturated, aqueous solution in characteristic needles arranged in the form of rosettes and from 95 per cent. alcohol in well-developed prisms. It decomposed, when heated slowly, at 177–8° into an oil and a crystalline substance, which did not melt below 250°. The compound contained sulphur and iodine and left an inorganic residue when fused on platinum foil. When some of the compound was dissolved in cold water, and silver nitrate solution added, a gelatinous, white silver salt separated which decomposed, when the solution was warmed, giving yellow silver iodide. The crystalline habit and characteristic properties indicated that we were dealing with a definite compound and not a mixture of a pyrimidine and potassium iodide. Our analytical determinations agreed with the calculated values in a double compound containing 3 molecules of *2-ethylmercapto-3-methyl-5-ethoxy-6-oxypyrimidine* and 2 molecules of potassium iodide, $(C_9H_{14}O_2N_2S)_3.2KI$.

Calculated: N, 8.60 ; I, 25.00
Found: N. 8.26, 8.35, 8.40; I, 24.55

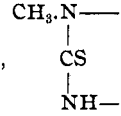
2-Ethylmercapto-3-methyl-5-ethoxy-6-oxypyrimidine, $C_2H_5SC(=N-CO-)COC_2H_5$ / CH_3N-CH.—Some of the double compound (above) was heated, in an oil bath, at 175–90° for about 30 minutes. We obtained a crystalline substance, on cooling, which was thoroughly pulverized and digested for a long time with an excess of anhydrous ethyl acetate. After expelling the excess of ethyl acetate at 100°, we obtained a crystalline substance which was extremely soluble in cold water and alcohol. It crystallized from ethyl acetate in clusters of small prisms melting at 149–51°. They were free from iodine but gave a strong test for sulphur. The compound slowly sublimed when heated at 100°. A mixture of the pyrimidine and 2-ethylmercapto-5-ethoxy-6-oxypyrimidine[1] (melting

[1] *Loc. cit.*

at 169°) melted at 118–25°. Analysis (Kjeldahl): Calculated for $C_9H_{14}O_2N_2S$, N 13.0; found, 13.4.

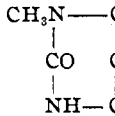
Crystallization of 2-Ethylmercapto-3-methyl-5-ethoxy-6-oxypyrimidine from an Alcoholic Solution of Potassium Iodide.—About 0.5 gram of the pyrimidine was dissolved in 25 cc. of hot, absolute alcohol, which had previously been saturated with potassium iodide. On cooling, the double compound, described above, separated in colorless prisms which decomposed at 178°. Analysis (Kjeldahl): Calculated for $(C_6H_{14}O_2N_2S)_3 \cdot 2KI$, N 8.60; found, 8.5.

1-Methyl-2-thio-5-hydroxyuracil,



—Three and five-tenths grams of 1-methyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidine were digested with 20 cc. of hydrobromic acid for about 14 hours. The solution was then evaporated to dryness, when we obtained a crystalline substance which dissolved in boiling water. Upon cooling, about 2.0 grams of slender prisms separated which were extremely insoluble in cold water and boiling alcohol. The material had no definite melting point and gave a strong test for sulphur. It crystallized from hot water without water of crystallization. Analysis (Kjeldahl): Calculated for $C_5H_6O_2N_2S$, N 17.7; found, 17.39, 17.5.

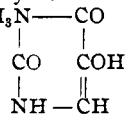
1-Methyl-2,6-dioxy-5-ethoxypyrimidine,



—After separation of the 2-thiopyrimidine, in the preceding experiment, the aqueous filtrate was evaporated to dryness. We obtained a crystalline substance which crystallized from hot water in aggregates of short prisms. They turned brown, when heated above 220°, and then melted to an oil at about 240° according to the rate of heating. The compound did not contain sulphur, and reacted with diazobenzene sulphonic acid giving a strong, red color. Analysis (Kjeldahl): Calculated for $C_7H_{10}O_3N_2$, N 16.47; found, 16.7.

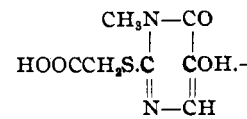
This same pyrimidine is obtained smoothly and practically free from 1-methyl-2-thio-5-hydroxyuracil by digestion of 1-methyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidine with concentrated hydrochloric acid for several hours.

1-Methyl-5-hydroxyuracil,



—This pyrimidine was formed practically quantitatively when 1-methyl-2,6-dioxy-5-ethoxypyrimidine or 1-methyl-2-ethylmercapto-5-ethoxy-6-oxypyrimidine was heated with concentrated hydrochloric acid at 120–30° for 2–3 hours. The pyrimidine is more soluble in water than the isomeric 3-methyl-5-hydroxyuracil.[1] It dissolves readily in boiling water and alcohol and separates from hot aqueous solutions in clusters of radiating prisms which melt at 247° to an oil with slight effervescence. The isomeric pyrimidine decomposes above 260° without melting, with violent effervescence. A mixture of the 1- and 3-methyl-5-hydroxyuracils melted at 217–30° to an oil. Analysis: Calculated for $C_5H_6O_3N_2$, N 19.71; found, 19.9.

1-Methyl-2-thioglycollic-acid-5-hydroxy-6-oxypyrimidine,



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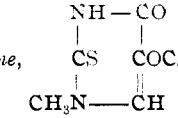
[1] *Loc. cit.*

Two grams of chloracetic acid and 1 gram of 1-methyl-2-thio-5-hydroxyuracil were dissolved in boiling water and the solution evaporated to dryness. We obtained a crystalline compound, which separated from hot water in stout prisms, and decomposed at 217° with effervescence. It gave a strong test for sulphur and crystallized from water without water of crystallization. Analysis (Kjeldahl): Calculated for $C_7H_8O_4N_2S$, N 12.96; found, 12.8.

This pyrimidine was extremely stable in presence of hydrochloric acid. Some of the compound was dissolved in a large excess of concentrated acid and the solution evaporated to dryness. The pyrimidine was recovered unaltered and decomposed sharply at 217°. Analysis (Kjeldahl): Calculated for $C_7H_8O_4N_2S$, N 12.96; found, 12.94.

2-Thio-3-methyl-5-ethoxy-6-oxypyrimidine,  .—This pyrimidine was obtained, in small amount, when the double compound of potassium iodide and 2-ethylmercapto-3-methyl-5-ethoxy-6-oxypyrimidine was digested with hydrochloric acid. After expelling the hydrochloric acid, we obtained a crystalline substance which was washed with alcohol and then crystallized from hot water. It separated in long needles which melted at 210–1° to an oil, without effervescence. It contained sulphur and gave a violet colored solution by treatment with bromine water and barium hydroxide. Analysis (Kjeldahl): Calculated for $C_7H_{10}O_2N_2S$, N 15.05; found, 15.05.

NEW HAVEN, CONN.

THE SLOW OXIDATION OF 2,2-DICHLORVINYL ETHYL ETHER.[1]

BY WILLIAM FOSTER.

Received March 19, 1909.

I. Introduction.—It is well known that halogen substitution products of ethylene, such as dibromethylene, $CH_2:CBr_2$, undergo oxidation even on exposure to the air—$2CH_2:CBr_2 + O_2 \longrightarrow 2CH_2Br.COBr$.[2]

By the oxidation of compounds of this type, there appears to be a direct absorption of oxygen with the formation of an acid chloride, bromide or fluoride.

Halogenated vinyl ethyl ethers, at least some of them, are also susceptible of oxidation by treatment with oxygen, but they have not been thoroughly investigated.

At the suggestion of Professor Fred Neher, the author has made a careful study of the action of oxygen gas on 2,2-dichlorvinyl ethyl ether, $CCl_2:CH.OC_2H_5$, and the main facts observed in connection with the oxidation may be expressed by the following equations:

[1] Read before the New York Section of the American Chemical Society, March 5, 1909.

[2] Denıole, *Ber.*, 11, 316, 1307.