Nitrogen determinations (Kjeldahl):

Calculated for $C_{16}H_{14}O_6N_2$: N, 8.5; found: N, 8.59.

NEW HAVEN, CONN.

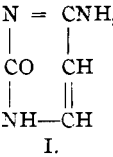
[CONTRIBUTIONS FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES. LXIV. SYNTHESIS OF 4-METHYL-5-ETHYLCYTOSINE.

BY TREAT B. JOHNSON AND GEORGE C. BAILEY.

Received July 1, 1913.

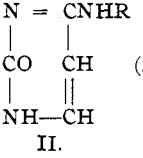
Fourteen alkyl derivatives of cytosine, I, have been described in the



I.

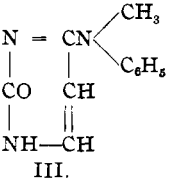
pyrimidine papers published from this laboratory. They may be classed in two groups as follows:

Group One.—This includes all those derivatives of the base I, where a substitution has been made in the amino group of the pyrimidine, namely, 7-phenylcytosine and the corresponding *o*- and *p*-tolyl-, anisyl- and *m*-nitrophenyl compounds,[1] which may be represented by the general formula II, 7,7-methylphenyl- and 3-methyl-7,7-methylphenylcytosines[2]



II. ($R = C_6H_5$, $CH_3C_6H_4$–, $CH_3OC_6H_4$– and $NO_2C_6H_4$–)

(III and IV), and 7-methyl- and 4,7-dimethylcytosines[3] represented by formulas V and VI, respectively.



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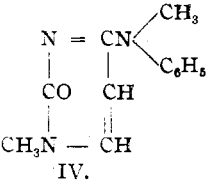

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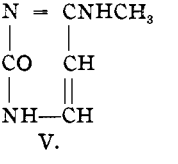

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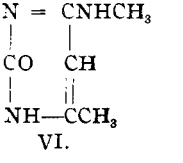


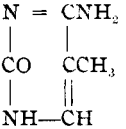
VI.

[1] Wheeler and Bristol, *Am. Chem. J.*, **33**, 448; Johnson, Johns and Heyl, *Ibid.*, **36**, 160.

[2] Johnson and Clapp, *J. Biol. Chem.*, **5**, 49.

[3] Johns, *Ibid.*, **9**, 161; **11**, 393.

Group Two.—This includes all those alkyl derivatives where no substitution has been made in the amino group of the pyrimidine base, I, namely, 5-methylcytosine,[1] VII, 5-ethylcytosine,[2] VIII, 3,5-dimethylcytosine, IX, 3-methylcytosine,[3] X, and 4-methylcytosine,[4] XI. No 4,5-dialkyl derivatives of cytosine have been described. In this paper we shall give a description of the synthesis and properties of 4-methyl-5-ethylcytosine, XII.



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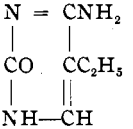

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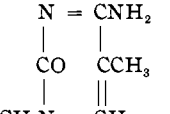
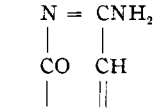
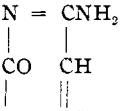


IX.



X.



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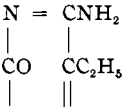


XII.

The β-ketone ester ethyl ethylacetoacetate,[5] XIII, and thiourea interact normally, when warmed together in sodium alcoholate solution, forming 2-thio-4-methyl-5-ethyl-6-oxypyrimidine, XIV. This pyrimidine is converted quantitatively into 4-methyl-5-ethyluracil,[6] XVI, by desulfurization with chloracetic acid and undergoes alkylation smoothly, when its sodium salt is digested in alcohol with ethyl bromide and benzyl chloride, giving the corresponding mercaptopyrimidines, namely, 2-ethylmercapto-4-methyl-5-ethyl-6-oxypyrimidine, XVIII, and 2-benzylmercapto-4-methyl-5-ethyl-6-oxypyrimidine, XV. Both of these mercapto compounds are converted into 4-methyl-5-ethyluracil, XVI, by hydrolysis with acids. It is also an interesting fact that this transformation can be effected by digesting the mercaptopyrimidine, XVIII, with an aqueous solution of chloroacetic acid.[7]

When 2-ethylmercapto-4-methyl-5-ethyl-6-oxypyrimidine, XVIII, was heated with aniline at 100° and with alcoholic ammonia at 150°–160°, mercaptan was evolved and the corresponding anilino- and aminopyrimidines, XIX and XVII, were formed.

2-Ethylmercapto-4-methyl-5-ethyl-6-oxypyrimidine, XVIII, reacts

[1] Wheeler and Johnson, *Am. Chem. J.*, **31**, 591.

[2] Johnson and Menge, *J. Biol. Chem.*, **2**, 105.

[3] Johnson and Clapp, *Loc. cit.*

[4] Johns, *Am. Chem. J.*, **40**, 348.

[5] Bischoff, *Ber.*, **28**, 2616.

[6] Wheeler and Merriam, *Am. Chem. J.*, **29**, 478.

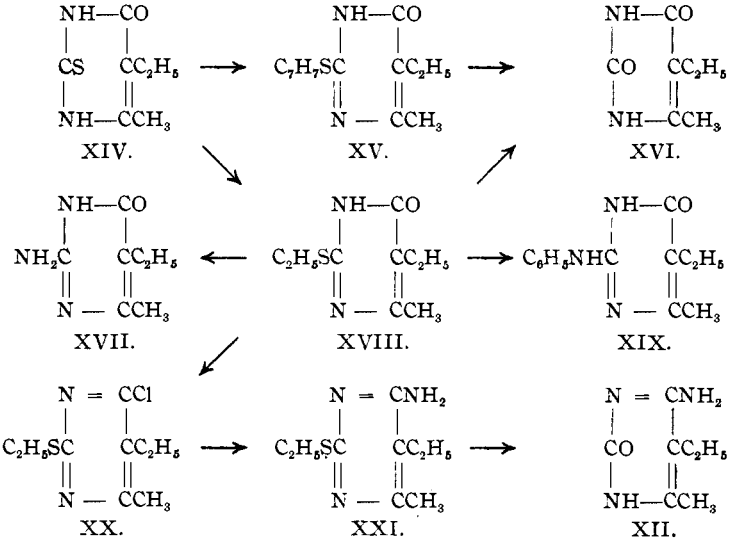
[7] NOTE.—Dr. Arthur J. Hill is investigating this interesting reaction and the results of his investigation will be published in a later paper.—T. B. JOHNSON.

smoothly with phosphorus pentachloride, when warmed at 100°, with evolution of hydrochloric acid gas and formation of 2-ethylmercapto-4-methyl-5-ethyl-6-chloropyrimidine, XX. This compound was obtained as an oil, which could be distilled under diminished pressure without decomposition. The pyrimidine is quite stable in the presence of water, but is decomposed when warmed with alcohol. When the chloride was heated, at 140°–150°, with alcohol, saturated at 0° with dry ammonia gas, the chlorine atom was removed and 2-ethylmercapto-4-methyl-5-ethyl-6-aminopyrimidine, XXI, was formed. We obtained no evidence of the formation of 2,6-diamino-4-methyl-5-ethylpyrimidine.

The mercaptopyrimidine, XXI, is converted quantitatively into 4-methyl-5-ethylcytosine, XII, by hydrolysis with concentrated hydrochloric acid. These various transformations are represented by the following structural formulas:

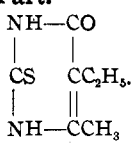
$CH_3COCH(C_2H_5)COOC_2H_5 + CS(NH_2)_2 \longrightarrow$

XIII.



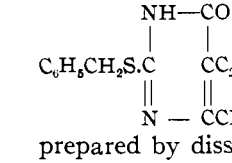
4-Methyl-5-ethylcytosine, XII, is more soluble than cytosine and does not contain water of crystallization. It forms normal salts with hydrochloric and hydrobromic acids, which crystallize from water in an anhydrous condition. The pyrimidine is precipitated from an aqueous solution by addition of phosphotungstic acid. It also gives an insoluble, brown precipitate with potassio-bismuth iodide. Mercuric chloride produces a white precipitate in aqueous solution, which dissolves when the solution is warmed. Picric acid gives a crystallin salt which separates from water in distorted needles or hairs.

Experimental Part.

2-Thio-4-methyl-5-ethyl-6-oxypyrimidine,  .—This new pyrimidine was prepared by condensation of thiourea with ethyl ethylacetoacetate.[1] Eighteen and one-tenth grams of sodium were dissolved in 360 grams of absolute alcohol and 30 grams of thiourea and 61 grams of the β-ketone ester dissolved in the solution. The mixture was then heated on the steam bath for 3–4 hours and the excess of alcohol then evaporated at 100°. We obtained the colorless sodium salt of the pyrimidine. This was dissolved in cold water and the solution acidified with acetic acid. The pyrimidine separated at once in a crystallin condition. Care must be taken in precipitating with the acid to have the salt solution well concentrated, otherwise the pyrimidine will not separate. It is quite soluble in water and acetic acid. It was purified for analysis by crystallization from hot water and separated in colorless prisms, which melted at 212°. From 30 grams of the β-ketone ester we obtained 30 grams of the pure pyrimidine and in another experiment 39 grams. In a third experiment we obtained 25 grams of the pyrimidine from 20 grams of the acetoacetic ester or a yield of 60% of the theoretical. Nitrogen determination (Kjeldahl):

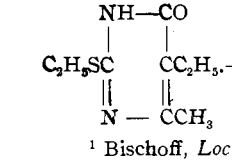
Calculated for $C_7H_{10}ON_2S$: N, 16.4; found: N, 16.1.

2-Benzylmercapto-4-methyl-5-ethyl-6-oxypyrimidine,

 .—The sodium salt of the above pyrimidine was prepared by dissolving 1.1 grams of sodium in 25 cc. of absolute alcohol and then dissolving in this solution 8 grams of the 2-thiopyrimidine. Six grams of pure benzyl chloride were then added when there was an immediate reaction and sodium chloride began to deposit. After heating until the reaction was complete, the solution was cooled. The pyrimidine separated and was purified by crystallization from hot water. It separated in the form of blocks and melted at 160° to an oil. Nitrogen determination (Kjeldahl):

Calculated for $C_{14}H_{16}ON_2S$: N, 10.4; found: N, 10.53.

2-Ethylmercapto-4-methyl-5-ethyl-6-oxypyrimidine,

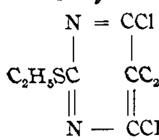
 .—This was prepared by digesting the sodium salt of

[1] Bischoff, *Loc. cit.*

the above 2-thiopyrimidine, in alcohol, with an excess of ethyl bromide. After the reaction was complete the sodium bromide and mercaptopyrimidine were filtered off and the pyrimidine separated from the salt by trituration with cold water. More of the pyrimidine was obtained by concentrating the alcoholic filtrate. The compound was purified by crystallization from hot water and separated in colorless crystals melting at 138° to a clear oil. The yield was 25 grams, or 70% of the theoretical. In two other experiments we used the same quantities of sodium salt and obtained 31 and 29 grams of the pyrimidine. Nitrogen determinations (Kjeldahl):

Calculated for $C_9H_{14}ON_2S$: N, 14.1; found: N, 13.9, 14.1.

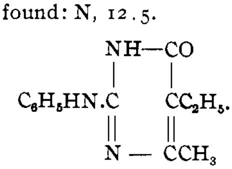
2-Ethylmercapto-4-methyl-5-ethyl-6-chloropyrimidine,



— Thirty grams of the 2-ethylmercapto-4-methyl-5-ethyl-6-oxypyrimidine and a molecular proportion of phosphorus pentachloride were placed in a flask and moistened with phosphorus oxychloride. The mixture was then heated at 100°, when an immediate reaction resulted and hydrochloric acid was evolved. The heating was continued until the evolution of hydrochloric acid gas ceased (10–12 hours), and the excess of phosphorus oxychloride was then removed by heating at 100° under diminished pressure. We obtained a thick oil, which was poured upon crushed ice and the mixture finally warmed gently to destroy any complex phosphorus compounds present. The chloride was finally extracted with a large volume of ether and washed with a dilute sodium hydroxide solution and finally with water. After drying over anhydrous calcium chloride the ether was removed and the pyrimidine purified by distillation under diminished pressure. It practically all distilled between 177°–180° at 23–21 mm. We collected, however, from 175°–185°, and the weight was 15 grams. The experiment was repeated, using 52 grams of the pyrimidine, when we obtained 37 grams of the chlorine compound. This yield corresponds to 66% of the theoretical. Nitrogen determination (Kjeldahl):

Calculated for $C_9H_{13}N_2SCl$: N, 12.9; found: N, 12.5.

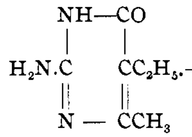
2-Anilino-4-methyl-5-ethyl-6-oxypyrimidine,



— This pyrimidine is easily obtained by heating the preceding 2-ethylmercapto-6-oxypyrimidine, in alcoholic solution, with the required proportion of pure aniline. The reaction, however, is sluggish and it was necessary to

heat for several hours before the evolution of ethyl mercaptan ceased. The pyrimidine is practically insoluble in water and difficultly soluble in alcohol. It melts at 195°. Nitrogen determination (Kjeldahl):

Calculated for $C_{13}H_{15}ON_3$: N, 18.2; found: N, 17.9.

2-Amino-4-methyl-5-ethyl-6-oxypyrimidine,  —This compound was prepared by heating 2-ethylmercapto-4-methyl-5-ethyl-6-oxypyrimidine with alcoholic ammonia at 150°–160° for 3 hours. The pyrimidine was purified by crystallization from boiling water and separated, on cooling, in minute prisms, which melted at 281°–282° with decomposition. It gave no test for sulfur and did not contain water of crystallization. This pyrimidine is much less soluble in alcohol, chloroform or ether than the isomeric 6-aminopyrimidine described below. Nitrogen determination (Kjeldahl):

Calculated for $C_7H_{11}ON_3$: N, 27.4; found: N, 27.2.

Hydrobromide.—This salt crystallizes from water in an anhydrous condition and separates as needles, which melt at 160°–175°, according to the rate of heating. Nitrogen determination (Kjeldahl):

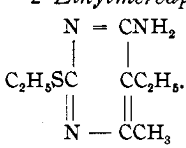
Calculated for $C_7H_{11}ON_3.HBr$: N, 17.9; found: N, 17.8.

Hydrochloride.—This salt is extremely soluble in water and apparently crystallizes with one molecule of water. It began to shrivel at 80° and melted at 115° to an oil. It was dried, for analysis, in a desiccator over concentrated sulfuric acid. Nitrogen determinations (Kjeldahl):

Calculated for $C_7H_{11}ON_3.HCl$: N, 22.1

Calculated for $C_7H_{11}ON_3.HCl.H_2O$: N, 20.2; found: N, 19.8, 19.0.

2-Ethylmercapto-4-methyl-5-ethyl-6-aminopyrimidine,

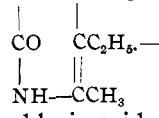


—This pyrimidine is formed smoothly by heating the above chloride with strong alcoholic ammonia at 140°–150° for 3–4 hours. An attempt to replace the chlorine by heating at 120°–130° was unsuccessful. When the reaction was complete, the solution was allowed to cool and the ammonium chloride formed was filtered off and the liquid evaporated. The pyrimidine was left behind mixed with some ammonium chloride. It was separated from the salt by trituration with cold water, dissolved in benzene and thoroughly dried over calcium chloride. The benzene was then evaporated and the pyrimidine purified by crystallization from ethyl acetate. It separated in stout blocks, which melted at 89°–91° to a clear oil without decomposition. The pyrimidine is insoluble

in water, but very soluble in benzene, alcohol, chloroform and petroleum ether. It gave a strong test for sulfur. Nitrogen determinations (Kjeldahl):

Calculated for $C_9H_{13}N_3S$: N, 21.3; found: N, 21.32, 21.4.

2-Oxy-4-methyl-5-ethyl-6-aminopyrimidine (or Methylethylcytosine),



—This pyrimidine was obtained in the form of its hydrochloric acid salt by hydrolysis of the above mercaptopyrimidine with hydrochloric acid. Two and five-tenths grams of the mercaptopyrimidine were boiled with 100 cc. of concentrated hydrochloric acid until the evolution of ethylmercaptan practically ceased (12–14 hours). The solution was then evaporated to complete dryness and the hydrochloride of the pyrimidine purified by crystallization from 95% alcohol. The salt separated, on cooling, as a colorless powder, which decomposed at 125° with effervescence. The salt is very soluble in water and insoluble in benzene. The salt was dried at 100° for one hour without loss of weight. The yield was 3.3 grams.

Chlorine determination:

Calculated for $C_7H_{11}ON_3.HCl$: Cl, 18.6; found: Cl, 18.25.

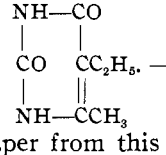
In order to obtain the cytosine derivative, this hydrochloride was dissolved in water and the chlorine precipitated as silver chloride by digestion with the required amount of pure, dry silver carbonate. After filtering from silver chloride, the clear solution was then diluted with a little hydrogen sulfide water, to remove any silver as the sulfide, and then concentrated on the steam bath. The pyrimidine was obtained in a crystallin condition and was purified by crystallization from alcohol. It separated in characteristic blocks or rectangular prisms, which melted at 295° with decomposition. Nitrogen determination (Kjeldahl):

Calculated for $C_7H_{11}ON_3$: N, 27.4; found: N, 27.4.

Hydrobromide.—This salt crystallizes from water in large blocks which decompose at about 260°. Nitrogen determination (Kjeldahl):

Calculated for $C_7H_{11}ON_3.HBr$: N, 17.9; found: N, 17.7.

4-Methyl-5-ethyluracil,

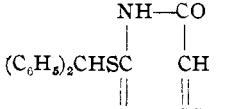


— This pyrimidine has been described in a previous paper from this laboratory.[1] A quantitative yield of the compound is obtained by hydrolysis of 2-ethylmercapto-4-methyl-5-ethyl-6-oxypyrimidine with chloroacetic acid. Four grams of the mer-

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

captopyrimidine and 8 grams of chloroacetic acid were dissolved in water and the solution boiled for 5 hours. Mercaptan was evolved immediately on heating. After the reaction was complete the solution was evaporated to dryness and the residue purified by crystallization from alcohol. This pyrimidine separated at once, on cooling, and melted at 236°–237°. The yield was quantitative. It gave no test for sulfur.

2-Diphenylmethylmercapto-4-methyl-6-oxypyrimidine,



.—The bromodiphenylmethane, $(C_6H_5)_2CHBr$, which was used in this experiment, was prepared according to the direc tions of Friedel and Balsohn.[1] This pyrimidine was obtained by the action of this bromide on the sodium salt of 2-thio-4-methyluracil in alcoholic solution. The yield, however, was small, since most of the bromide was decomposed by the alcohol, on heating, forming the corresponding ether, $(C_6H_5)_2CHOC_2H_5$. The pyrimidine was separated from the recovered 2-thio-4-methyluracil by dissolving in alcohol. It was purified by crystallization from this solvent and it melted at 214°. A nitrogen determination gave:

Calculated for $C_{18}H_{16}ON_2S$: N, 9.0; found: N, 8.7.

NEW HAVEN, CONN.,
June 28, 1913.

[CONTRIBUTIONS FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

A NEW METHOD OF SYNTHESIZING THE HIGHER PHENOLS.

BY TREAT B. JOHNSON AND WILLARD W. HODGE.

Received June 11, 1913.

In connection with some work, now in progress, on the antiseptic action of phenols it was necessary to obtain in quantity certain phenols containing long, aliphatic side chains, *viz.*, the higher homologues of the cresols and corresponding derivatives of the dihydroxybenzenes. The lower members of these types of aromatic compounds have been described. On the other hand, we have little knowledge of the higher homologues and no practical method is known by which they can be prepared easily. Regarding their antiseptic properties we have no knowledge. The primary object of the work described in this paper was to develop a new method of introducing alkyl groups into the benzene nucleus of mono- and dihydric phenols.

Ketones in general undergo reduction, under ordinary pressure, with formation of alcohols or pinacones. It has been shown, however, that they can be reduced directly to their corresponding hydrocarbons. The

[1] *Bull. soc. chim.*, **33**, 337.