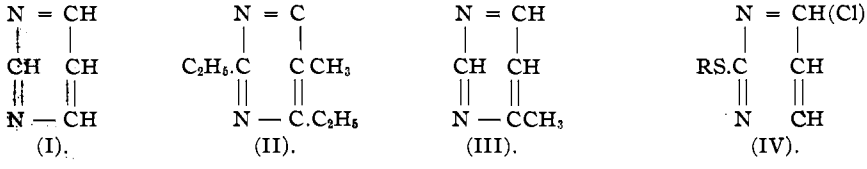
[CONTRIBUTIONS FROM THE SHEFFIELD CHEMICAL LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES. LXXXII. THE SYNTHESIS OF 1,3-DIAMINES BY REDUCTION OF 2-MERCAPTO-6-OXYPYRIMIDINES.[1]

BY TREAT B. JOHNSON AND A. WILLARD JOYCE.

Received July 7, 1916.

The first investigator to observe the formation of acyclic derivatives by the reduction of pyrimidines was apparently E. von Meyer.[2] In his early work on the determination of the constitution of "Kyanäthins," he investigated the action of sodium amalgam on 2,4-diethyl-5-methyl-6-aminopyrimidine (II), in acid solution, and showed that this pyrimidine underwent reduction with cleavage of the ring giving ammonia, propionic aldehyde and a basic oil of unknown constitution. The same products were also formed, according to him, by reduction of this pyrimidine with sodium and alcohol. So far as the writers are aware this work of von Meyer's has never been repeated and consequently the structure of this basic reduction product has never been established. The next investigator to observe a cleavage of the pyrimidine ring by reduction in alkaline solution was Byk[3] who reduced 4-methylpyrimidine with sodium and alcohol and showed that it was transformed into 1,3-diaminobutane. Recently, Johnson and Joyce[4] have contributed further data on this subject. They investigated the action of sodium and alcohol on 2-mercapto-6-chloropyrimidines and found that such combinations easily break down by reduction with the above reagents, forming 1,3-diamines.



(I). (II). (III). (IV).

In the light of these interesting results it was important to extend further our investigations and examine the behavior of mercaptooxypyrimidines towards alkaline reducing agents. Combinations of this type are more available than representatives of the above series and can be synthesized easily in quantity. The electrolytic reduction of oxypyrimidines has been applied with success by Tafel and his co-workers. According to these investigators 4-methyluracil[5] is reduced by electrolysis

[1] This paper and also that entitled "The Reduction of 2-Mercapto-6-chloropyrimidines" (THIS JOURNAL, **38**, 1385 (1916)) were constructed from a dissertation presented by Asa Willard Joyce to the Faculty of the Graduate School of Yale University, 1916, in candidacy for the Degree of Doctor of Philosophy.

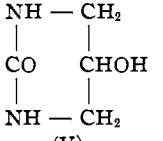
[2] *J. prakt. Chem.*, [2] **39**, 262 (1889).

[3] *Ber.*, **36**, 1917 (1903).

[4] THIS JOURNAL, **38**, 1385 (1916).

[5] Tafel and Weinschenk, *Ber.*, **33**, 3378 (1900).

in acid solution to methyltrimethylene urea, and with partial cleavage of the ring forming diaminobutane, $NH_2.CH(CH_3)CH_2.CH_2NH_2$. Barbituric acid[1] gave by reduction under similar conditions hydrouracil and trimethyleneurea. These same products were formed by reduction of dialuric acid[2] and also oxytrimethylene urea (V), while alloxan and uramil were transformed into hydrouracil. 5-Ethylbarbituric acid[3] reacted in a similar manner as barbituric acid, giving 5-ethylhydrouracil while *veronal* (5,5-diethylbarbituric acid) underwent an abnormal change and was converted into 5,5-diethyl-4,6-dioxyhexahydropyrimidine, (VI). Einhorn and Diesbach[4] have shown that 2-thio-5,5-diethylbarbituric acid is reduced by the action of sodium amalgam with cleavage of the pyrimidine ring forming diethylmalonamide (VII), formic acid and hydrogen sulfide. Veronal, on the other hand, was not reduced when subjected to similar conditions.



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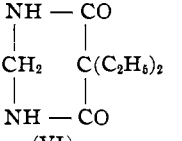
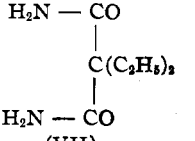


(VI).



(VII).

We have now investigated the action of sodium and alcohol on six 2-mercapto-6-oxypyrimidines and one 2-thio combination, namely:

(1) 2-Methylmercapto-6-oxypyrimidine.[5]
(2) 2-Ethylmercapto-5-ethoxy-6-oxypyrimidine.[6]
(3) 2-Ethylmercapto-4-methyl-6-oxypyrimidine.[7]
(4) 2-Ethylmercapto-5-methyl-6-oxypyrimidine.[8]
(5) 2-Ethylmercapto-1-methyl-6-oxypyrimidine.[9]
(6) 2-Ethylmercapto-1,4-dimethyl-6-oxypyrimidine and
(7) 2-Thio-4-methyl-6-oxypyrimidine.[10]

All of these combinations have been described in the literature, with the single exception of 2-ethylmercapto-1,4-dimethyl-6-oxypyrimidine (6). This was prepared by alkylation of 2-ethylmercapto-4-methyl-6-oxypyrimidine with methyliodide. Its structure was established by the fact that it underwent hydrolysis with concentrated hydrochloric acid giving 1,4-dimethyluracil[11] and ethyl mercaptan.

[1] Tafel and Weinschenk, *Loc. cit.*
[2] Tafel and Reindl, *Ber.*, 34, 3286 (1901).
[3] Tafel and Thompson, *Ibid.*, 40, 4489 (1907).
[4] *Ber.*, 40, 4902 (1907).
[5] Wheeler and Merriam, *Am. Chem. J.*, 29, 483 (1903).
[6] Johnson and McCollum, *J. Biol. Chem.*, 1, 44 (1906).
[7] Johns, *Am. Chem. J.*, 40, 351 (1908).
[8] Wheeler and Johnson, *Ibid.*, 31, 595 (1904).
[9] Johnson and Heyl, *Ibid.*, 37, 633 (1907).
[10] List, *Ann.*, 236, 12 (1886).
[11] Johnson and Heyl, *Loc. cit.*

We now find that all of these seven pyrimidines are reduced smoothly by means of sodium and alcohol with formation of acyclic compounds. In other words, they undergo reduction with cleavage of the pyrimidine ring, giving their corresponding 1,3-diamines. These are as follows:

(1) and (2) Trimethylenediamine, $NH_2CH_2CH_2CH_2NH_2$.[1]

(3) and (7) Diaminobutane, $NH_2.CH(CH_3)CH_2CH_2NH_2$.[2]

(4) 1,3-Diaminoisobutane, $NH_2CH_2CH(CH_3)CH_2NH_2$.

(5) 1-Amino-3-methylaminopropane, $CH_3NH.CH_2CH_2CH_2NH_2$.

(6) 1-Methylamino-3-aminobutane, $CH_3NH.CH_2CH_2CH(CH_3).NH_2$.

In no case were we able to isolate an intermediate mercapto derivative of a reduced pyrimidine. The constant evolution of mercaptan during the reaction indicated the instability of such combinations when formed. The reduction of this type of pyrimidine combinations with sodium and alcohol, therefore, affords a practical method for the synthesis of 1,3-diamines. Bases of this type should be of physiological and pharmacological interest, and our method of synthesis should make available new combinations which it would be very difficult to prepare by other known methods.

Attempts to synthesize the amino ether, $NH_2CH_2CH(OC_2H_5)CH_2NH_2$, by reduction of 2-ethylmercapto-5-ethoxy-6-oxypyrimidine were unsuccessful. In every experiment tried the ethoxy group ($.OC_2H_5$) was reduced and trimethylenediamine was the final product of the reaction. That the ethoxy group is destroyed by reduction with sodium has been observed in other cases. *o*-Ethoxybenzoic acid[3] reacts in a manner similar to that of our pyrimidine, when reduced with sodium and alcohol, giving hexahydrobenzoic acid. 1,4-Ethoxynaphthoic acid is also transformed by reduction with sodium amalgam into tetrahydro-α-naphthoic acid.[4]

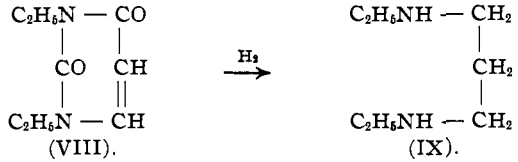
The difficulty of obtaining mono-alkylated diamines is well known and, as far as the writers are aware, no alkyl derivatives of 1,3-diamines, containing alkyl groups linked to one or both nitrogen atoms are described in the literature. Our method of synthesis enables us to obtain such combinations without difficulty. The 2-mercapto-pyrimidines easily undergo alkylation, and by reduction of the resulting alkyl derivatives with sodium and alcohol the corresponding mono-alkylated diamines are formed. Dialkylated pyrimidines like 1,3-diethyluracil (VIII) theoretically should undergo reduction with formation of symmetrically substituted amines (IX).

[1] Fischer and Koch, *Ber.*, 17, 1799 (1884); Gabriel and Wiener, *Ibid.*, 21, 2670 (1888).

[2] Byk, *Loc. cit.*; Tafel, *Ber.*, 33, 3382 (1900).

[3] Einhorn and Sumsden, *Ann.*, 286, 265 (1895).

[4] Kamm and McCluggage, THIS JOURNAL, 38, 424 (1916).



(VIII). (IX).

This investigation will be continued in this laboratory.

Experimental Part.

The Reduction of 2-Methylmercapto-6-oxypyrimidine with Sodium and Alcohol. The Formation of Trimethylene Diamine, $NH_2.CH_2.CH_2.CH_2.NH_2$.—The 2-methylmercapto-6-oxypyrimidine used in this experiment was prepared according to the method described by Wheeler and Merriam[1] by the condensation of pseudomethylthiourea hydriodide with the sodium salt of ethyl formylacetate. Twenty grams of sodium (2 molecular proportions) were placed in a liter flask, connected with dropping funnel and return condenser, and a solution of 10 g. of the pyrimidine in 200 cc. of absolute alcohol allowed to drop upon the sodium. If all the sodium failed to dissolve, after the addition of this solution, the mixture was heated on the steam bath and enough alcohol added to effect complete solution. During the operation methylmercaptan and ammonia were evolved and the solution assumed a dark, reddish brown color. After complete reduction air was blown through the mixture to expel as much ammonia as possible and the solution subjected to a steam distillation. Methylmercaptan distilled over with the trimethylene diamine. The distillate was conducted into hydrochloric acid solution, and after the operation was over, the acid solution was then concentrated by evaporation under diminished pressure. The diamine hydrochloride separated from the saturated solution as colorless, prismatic crystals. It was purified by crystallization from 25% alcohol and melted with decomposition at 243–245°. The yield was 5 g. or 47% of theory.

Calc. for $C_3H_{10}N_2.2HCl$: N, 19.04. Found: N, 19.04, 19.02.

The Behavior of 2-Methylmercapto-6-oxypyrimidine towards Sodium Amalgam.—Five grams of the oxypyrimidine and 2.0 g. of sodium hydroxide were dissolved in 50–100 cc. of water. One hundred and twelve grams of 3% sodium amalgam were then added in small amounts at a time, and the solution heated until there was no evolution of hydrogen gas. During this operation there was no evolution of mercaptan or ammonia indicating that the pyrimidine ring was not reduced. The aqueous solution did not give an alkaline distillate after steam distillation. After the steam distillation the alkaline solution was acidified with hydrochloric acid and cooled, when a colorless precipitate separated. This was filtered off and crystallized from hot water, from which it separated, on cooling, in glisten-

[1] *Loc. cit.*

ing plates. These melted at 197–199° and were identified as the unaltered mercaptopyrimidine. Three grams of the pyrimidine were recovered here. The filtrates were evaporated to dryness and the residue digested with 75 cc. of absolute alcohol. This solution was filtered from inorganic salts and cooled when we recovered one gram more of the pyrimidine. In other words, the mercaptopyrimidine was not reduced by the amalgam.

Reduction of 2-Ethylmercapto-5-ethoxy-6-oxypyrimidine.—The pyrimidine used for reduction was prepared according to the method originally described by Johnson and McCollum.[1] Ten grams of the pyrimidine were taken for reduction and the operation conducted under similar conditions as described in the previous experiment. The base was removed as usual by steam distillation and obtained in the form of its hydrochloride. This crystallized from hot water in the form of needle-like prisms and melted at 243–244° with decomposition. The melting point of a mixture of this salt and the hydrochloride of trimethylenediamine melted at 243–244° proving that the two were identical. The yield of this salt in this case was 3.0 g. or 40% of theory.

Calc. for $C_8H_{10}N_2.2HCl$: N, 19.04. Found: N, 19.2.

Reduction of 2-Ethylmercapto-4-methyl-6-oxypyrimidine. The Formation of 1,3-Diaminobutane, $CH_3.\underset{\displaystyle NH_2}{\underset{|}{CH}}.CH_2.CH_2.NH_2$.—The 2-ethylmercapto-4-methyl-6-oxypyrimidine used was prepared according to the directions of Johns[1] by condensing pseudoethylthiourea with the sodium salt of ethyl acetoacetate. Fifteen grams were taken for reduction and the operation carried out as described in the previous experiments. Since difficulty was encountered in accomplishing a separation of the hydrochloride of the base from ammonium chloride, the mixture of the two salts was treated with a 30% solution of sodium hydroxide when the amine separated as an oil. Air was blown through the mixture to expel ammonia, and the diamine extracted with ether and dried over potassium hydroxide. The ether solution was then saturated with carbon dioxide when the carbonate of the diamine separated. This was filtered out and decomposed by treatment with an alcoholic solution of hydrochloric acid. The hydrochloride separated in the form of hexagonal prisms melting at 169–170°. According to Byk[1] the hydrochloride of this base melts at 167°. Tafel[1] assigned to it a melting point of 170–172°. The yield was 6.2 g. or 65% of the theoretical.

Calc. for $C_4H_{12}N_2.2HCl$: N, 17.37. Found: N, 17.37, 17.34.

Reduction of 2-Ethylmercapto-5-methyl-6-oxypyrimidine. The Formation of 1,3-Diaminoisobutane, $NH_2CH_2CH(CH_3)CH_2NH_2$.—The 2-ethylmercapto-5-methyl-6-oxypyrimidine was prepared according to the

[1] *Loc. cit.*

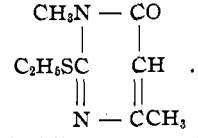
method described by Wheeler and Johnson.[1] Ten grams of the pyrimidine were used for reduction. The hydrochloride of the 1,3-diaminoisobutane was purified by crystallization from absolute alcohol and separated in the form of needles. They melted at 196° to a colorless oil. About 3 g. of this salt dissolves in 200–225 cc. of boiling absolute alcohol. The yield was 5 g. or 52% of theory.

Calc. for $C_4H_{12}N_2.2HCl$: N, 17.37. Found: N, 17.43, 17.50.

Reduction of 1-Methyl-2-ethylmercapto-6-oxypyrimidine. The Formation of 1-Amino-3-methylaminopropane, $CH_3NH.CH_2.CH_2.CH_2.NH_2$.—The 1-methyl-2-ethylmercapto-6-oxypyrimidine was prepared by the alkylation of 2-ethylmercapto-6-oxypyrimidine[2] with methyliodide. The reduction was carried on as described above but in this case we obtained a poorer yield of the base. We also encountered difficulty in separating the hydrochloride from ammonium chloride. This was accomplished by repeated crystallizations from absolute alcohol and was obtained in the form of colorless plates which melted at 185–190° to an oil. The yield of crude salt was 37% of theory.

Calc. for $C_4H_{12}N_2.HCl$: N, 22.47. Found: N, 22.3, 22.21.

1,4-Dimethyl-2-ethylmercapto-6-oxypyrimidine,



Thirty grams of 2-ethylmercapto-4-methyl-6-oxypyrimidine were dissolved in 100 cc. of an alcoholic solution containing 10 g. of potassium hydroxide. The pyrimidine dissolved readily. After cooling, 30 g. of methyl iodide were added and the mixture warmed gently until it gave no alkaline reaction. After filtering off potassium iodide the excess of alcohol was evaporated when an oil was obtained. This was extracted with ether and dried over anhydrous sodium sulfate. Calcium chloride could not be used as a drying agent as it combined with the pyrimidine. The yield was 17.2 g. This pyrimidine was purified by crystallization from ether and deposited in the form of prisms which melted at 63–64° to a clear oil. The compound is soluble in ether, benzene and alcohol and insoluble in water, alkalies and acid solutions.

Calc. for $C_8H_{12}ON_2S$: N, 15.21. Found: N, 15.15, 15.24.

The structure of this pyrimidine was established by its behavior on hydrolysis. When digested with concentrated hydrochloric acid ethylmercaptan was evolved and 2-oxy-1,4-dimethylpyrimidine was formed, melting at 260°.[1]

Reduction of 1,4-Dimethyl-2-ethylmercapto-6-oxypyrimidine. The Formation of 1-Methylamino-3-aminobutane, $CH_3NH.CH_2.CH_2.CH$-

[1] *Loc. cit.*

[2] Johnson and Heyl, *Ibid.*

$(CH_3).NH_2$.—This transformation was accomplished by reduction with sodium and alcohol. The hydrochloride of the diamine was obtained in the form of plates melting at 223°. It was purified by crystallization from absolute alcohol. The salt is very soluble in water, moderately soluble in absolute alcohol and insoluble in ether and benzene.

Calc. for $C_5H_{14}N_2.HCl$: N, 20.2. Found: N, 20.5, 20.2.

Reduction of 2-Thio-4-methyl-6-oxypyrimidine. The Formation of 1,3-Diaminobutane, $NH_2.CH_2.CH_2.CH(CH_3).NH_2$.—The thiopyrimidine was prepared according to the directions of List.[1] Five grams of the pyrimidine were suspended in 100 cc. of absolute alcohol and 20 g. of sodium gradually added. Ammonia was evolved and 150 cc. of alcohol were finally added to complete the solution of the sodium. The amine was removed by distillation with steam and converted into its hydrochloride. We obtained 1.9 g. of the salt melting at 165–167°. A mixture of this with some pure hydrochloride of 1,3-diaminobutane melted at the same temperature. The hot alkaline solution remaining after the steam distillation was filtered and neutralized with hydrochloric acid. On cooling, 2 g. of unaltered 2-thio-4-methyluracil were recovered.

Diurea of 1,3-Diaminobutane, $NH_2CONH.CH_2.CH(CH_3).CH_2.NH.CO.NH_2$.—One-half gram of the hydrochloride of 1,3-diaminoisobutane was dissolved in 10 cc. of water and one gram of silver cyanate added. The mixture was then digested on the steam bath for 15–20 minutes and the silver chloride separated by filtration. The urea was obtained by evaporation to dryness and purified by crystallization from alcohol. It separated in the form of clusters of distorted needles melting at 172°.

Calc. for $C_6H_{14}O_2N_4$: N, 32.16. Found: N, 32.09.

Picrate of 1,3-Diaminobutane.—This salt crystallizes from hot water in the form of yellow needles which melt at 240–245° with decomposition.

Calc. for $C_4H_{12}N_2(C_6H_3O_7N_3)_2$: N, 20.51. Found: N, 20.24.

NEW HAVEN, CONN.

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

RESEARCHES ON THIOCYANATES AND ISOTHIOCYANATES. X. THE UTILIZATION OF TETRACHLOROMETHYLMERCAPTAN FOR THE PREPARATION OF ALKYL ISOTHIOCYANATES.[2]

BY TREAT B. JOHNSON AND E. HEATON HEMINGWAY.

Received July 7, 1916.

Tetrachloromethylmercaptan VI, and amines combine to give representatives of an interesting class of compounds which have not been

[1] *Loc. cit.*

[2] This paper and also that entitled "Ethyl Isothiocyanacetate" (THIS JOURNAL, 38, 1550) were constructed from a dissertation presented by Earl Heaton Hemingway to the Faculty of the Graduate School of Yale University, 1916, in candidacy for the Degree of Doctor of Philosophy.