CHEMISTRY OF THIO-CHOLINE HALIDE (TRIMETHYL THIO-ETHYL AMMONIUM HALIDE). NEW THIO-CHOLINE BROMIDE AND ITS DERIVATIVES. I.

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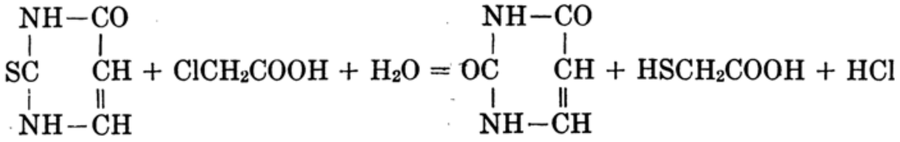
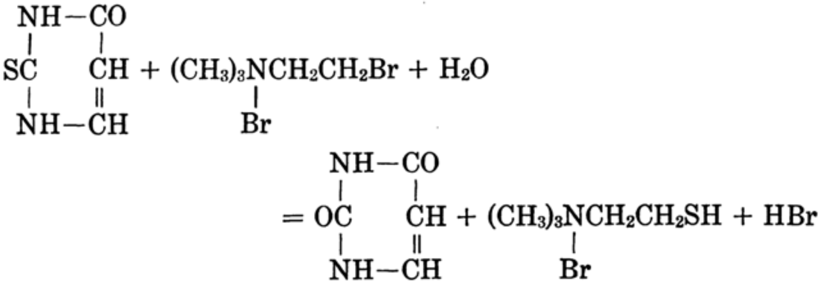
In 1882 Nencki and Sieber(1) obtained 4-methyl-2-thio-uracil by the condensation of thio-urea and acetic ester. List(2) has shown that 4-methyl-2-thio-uracil gives 4-methyl uracil, when heated with concentrated hydrochloric acid for a few hours at 150°—160° C.

Recently Wheeler and Bristol(3) have found that when 2-thio-uracil, like other compounds of this class, is boiled with an aqueous solution of chloracetic acid, in slight excess, sulphur is easily removed with the formation of uracil and thio-acetic acid, the reaction being in accordance with the following equations:



$$\begin{array}{l}\mathrm{NH-CO}\\ |\qquad\; |\\ \mathrm{SC}\quad\;\mathrm{CH}\\ |\qquad\; \|\\ \mathrm{NH-CH}\end{array} + \mathrm{ClCH_2COOH} + \mathrm{H_2O} = \begin{array}{l}\mathrm{NH-CO}\\ |\qquad\; |\\ \mathrm{OC}\quad\;\mathrm{CH}\\ |\qquad\; \|\\ \mathrm{NH-CH}\end{array} + \mathrm{HSCH_2COOH} + \mathrm{HCl}$$

This reaction gives an important means for the replacement of the halogen atom by the —SH group. This exchange takes place with more difficulty between 4-methyl-2-thio-uracil and bromo-choline bromide than between 2-thio-uracil and the bromide. Almost the theoretical yields of the corresponding uracils were obtained. The reaction may be formulated as follows, for example, in the case of 2-thio-uracil:



$$\begin{array}{l}\mathrm{NH-CO}\\ |\qquad\; |\\ \mathrm{SC}\quad\;\mathrm{CH}\\ |\qquad\; \|\\ \mathrm{NH-CH}\end{array} + \mathrm{(CH_3)_3}\underset{\underset{\mathrm{Br}}{|}}{\mathrm{N}}\mathrm{CH_2CH_2Br} + \mathrm{H_2O}$$

$$= \begin{array}{l}\mathrm{NH-CO}\\ |\qquad\; |\\ \mathrm{OC}\quad\;\mathrm{CH}\\ |\qquad\; \|\\ \mathrm{NH-CH}\end{array} + \mathrm{(CH_3)_3}\underset{\underset{\mathrm{Br}}{|}}{\mathrm{N}}\mathrm{CH_2CH_2SH} + \mathrm{HBr}$$

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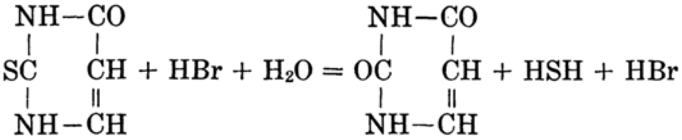
(1) *J. Prakt. Chem. N. F.*, **25** (1882), 72; Behrend, *Ann.*, **229** (1885), 13.

(2) List, *Ann.*, **236** (1886), 18.

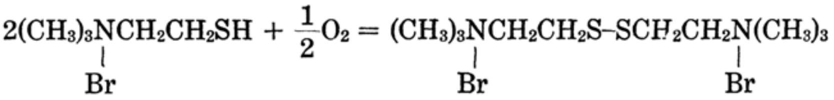
(3) *Am. Chem. J.*, **33** (1905), 458.

However, quantitative thio-choline bromide was not obtained, owing to partial formation of the following reaction and also formation of its oxidation product; the disulphide, ammonium bromide and a silver derivative of the compound in the following purification method.



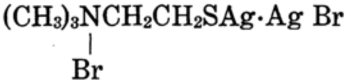
$$\begin{array}{ll} NH-CO & \\ | \quad\;\; | & \\ SC \quad CH & \\ | \quad\;\; \| & \\ NH-CH & \end{array} + HBr + H_2O = \begin{array}{l} NH-CO \\ | \quad\;\; | \\ OC \quad CH \\ | \quad\;\; \| \\ NH-CH \end{array} + HSH + HBr$$

The compound is very hygroscopic in nature, and is very soluble in both alcohol and water. The compound is easily oxidized on heating with hydrobromic acid yielding the disulphide.



$$2\underset{\displaystyle Br}{(CH_3)_3\overset{}{N}}CH_2CH_2SH + \frac{1}{2}O_2 = \underset{\displaystyle Br}{(CH_3)_3N}CH_2CH_2S-SCH_2CH_2\underset{\displaystyle Br}{N(CH_3)_3}$$

Its decomposition begins slowly at above 220°C., On continuous heating it boils at 243°C. (uncorr.) with a dark brown coloration. The isoelectric point of this compound was found to be P_H 7.00 by the colorimetric method.(1) It is interesting to note that the compound with an excess of silver oxide resulted in a solution containing a strong base, which on neutralizing with hydrobromic acid, gave an insoluble, white asbestos-like crystalline salt. This salt decomposes into silver bromide and the original type of compound on boiling with a strong acid. The mechanism of the formation was not clear. However, it appears to be the following formula:



$$\underset{\displaystyle Br}{(CH_3)_3N}CH_2CH_2SAg\cdot Ag\,Br$$

It decomposes slowly at above 211°C., and melts and boils at 214°C. (uncorr.) with a dark brown coloration, similar to thio-choline bromide. The base, in a brown syrup, on drying was supposed to be a hydroxyl compound containing silver bromide in the same molecule. With acid the aqueous solution precipitates silver bromide. This subject was not studied further.

Experimental Part.

2-Thio-uracil. The sodium salt of ethyl formylacetate was prepared according to Wislicenus' directions(2) as follows: 42 gr. metallic sodium dis-

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(1) Clarke, "The determination of hydrogen ions," (1925).

(2) *Ber.*, **20** (1887), 2931.

solved in 500–600 c.c. of dry ether containing 150 gr. of ethyl formate and 150 gr. of ethyl acetate. The solution was kept cool with running water. The reaction took place slowly at the beginning and later it became more or less violent, the solution becoming turbid and light brown in color. This was permitted to stand over night and the condensation product was filtered through filter paper. The yellow powder-like substance, $NaOCH=CHCOOC_2H_5$, was obtained, washed with ether and dried in a dessicater. It yielded about 100 gr. 75 gr. of this salt was treated with 25 gr. of thiourea according to Wheeler and Bristol(1) in saturated aqueous solution form. After standing in the cold one hour, it was heated on the steam bath for a short time, and then cooled. A yellowish white precipitate weighing about 25 gr. was separated by acidifying with acetic acid. It was crystallized from ammonium hydroxide by boiling with a small quantity of "norit" to decolorize it. A portion of this material was crystallized from water until it was obtained in colorless monoclinic plates. When heated, it effervesces at above 300°C. It is difficultly soluble in water and alcohol but its solubility increases by heating the solvents. A second run, for the preparation of this material was carried out according to Wheeler and Liddle(2) as follows: 70 gr. of saturated aqueous thio-urea solution was added directly to the condensation product, $NaOCH=CHCOO-C_2H_5$, in the ethereal solution, instead of powdered form, as in the preceding case. About 70 gr. of 2-thiouracil was obtained by this method.

Bromo-choline bromide. This compound(3) was prepared according to the directions of Hutckiss(4) by the condensation of trimethylamine with ethylene bromide. Trimethylamine (b.p. 3.5°C.) was generated by dropping a saturated solution containing 30 gr. of trimethylamine hydrochloride slowly into granulated sodium hydroxide. The evolved gas dried over KOH, was liquefied at a low temperature by means of ice and salt and collected in a cooled pressure bottle containing 50 gr. of redistilled ethylene bromide at 130°C. and 15 c.c. of toluene. The toluene was added merely to prevent the condensation product forming in a hard cake. The pressure bottle was corked tightly, placed in an iron frame and allowed to come slowly to room temperature. The bottle was placed in a water bath and the temperature raised gradually to about 50°C. and held at this temperature for three hours or more. Upon cooling, the product was removed, and recrystallized from hot 95% alcohol, then washed with ether. It yielded about 55 gr. Its decomposition begins at 235°C., and melts and boils at 238°C.

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(1) *Am. Chem. J.*, **33** (1905), 458.

(2) Wheeler and Liddle, ibid., **40** (1908), 547.

(3) Krüger and Bergell, *Ber.* **36** (1903), 2901.

(4) Thesis, Now York University, 1926.

Thio-choline bromide. One molecular proportion, or slightly an excess, 9.6 gr. of bromo-choline bromide, was mixed with one molecular proportion 5 gr. of 2-thio-uracil or 5.5 gr. of 4-methyl-2-thio-uracil⁽¹⁾ in powdered state. This was sealed with 25 c.c. of water in a closed tube or pressure bottle whose capacity was about 150 c.c. The pressure bottle was framed with an iron cage and heated in an oil bath. In order to get a complete reaction it was found necessary to heat it for more than two hours at around 150°C. or in the case of 4-methyl-2-thio-uracil for several hours at around 170°C. At these temperatures the mixtures became a transparent yellowish colored solution. On cooling, uracil deposits almost quantitatively. About 4.2 gr. of uracil and 4.3 gr. of 4-methyl-uracil were obtained respectively. In these reactions, a considerable amount of hydrogen sulphide was evolved. In order to purify this compound, the mixture of reaction products was washed down into a beaker with 95% alcohol, then filtered with suction to remove the uracil and the other unreacted insoluble substances. The filtrate was evaporated down to about 30 c.c. on the steam bath, then cooled with ice for a while, and then filtered again to remove further impurities. The filtrate was made up to about 300 c.c. with water. The solution thus obtained was slightly yellow in color and strongly acidic owing to the formation of hydrobromic acid in the reaction.

It was neutrallized with a base, such as ammonium hydroxide, or carefully with silver oxide, until the solution became slightly acidic. However, an excess of silver oxide leads to the formation of a double salt of silver derivative of thio-choline bromide and silver bromide, as an insoluble white asbestos-like crystalline substance. Therefore, the solution was treated with the amount of silver oxide obtained from about 6.6 gr., (one molecular proportion) or slightly less, to the HBr acid formed in the above reaction of silver nitrate with sodium hydroxide, and then filtered. The filtrate was light yellow in color. In order to remove further colored impurities it was on some occasions heated with 0.5 gr. of "norit" for a short time and filtered. With evaporation on the steam bath, and cooling, it gave colorless crystals. It may be re-crystallized out from hot butyl alcohol by repeating with or without a small amount of 95% alcohol. In this way an average of about 1.5 gr., or 19% of thio-choline bromide was obtained as beautiful colorless transparent monoclinic plates. It decomposes slowly at above 220°C. On continuous heating it boils at 243°C. with a dark brown coloration. If the temperature is maintained at 234°C. it also gives the same results using paraffin as the liquid for heating the bath.

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(1) The author wishes to express his thanks to Dr. R.R. Renshaw for his kindness in supplying this material.

10 c.c. of 0.005 N. (0.2%) solution of this compound, with water of P_H 6.80, or with water having P_H 7.20, containing a trace of NaOH, gave the same P_H value, 7.00. Likewise with water of P_H 7.00, there was no change in its value, using bromo-thymol blue as the indicator.

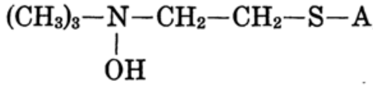
The compound is very hygroscopic in nature, 0.2314 gr. of the dried substance over P_2O_5 increased to 0.2326, 0.2339 and 0.2352 gr. respectively after one, two and three hours standing in the air.

Anal. Subst. = 0.2314, 0.2010; AgBr = 0.2173, 0.1891 gr. Subst. = 0.2163 (Carius' method); $BaSO_4$ = 0.2541 gr. Found: Br = 39.92, 40.07; S = 16.14%. Calc. for $C_5H_{14}NSBr$: Br = 39.94; S = 16.02%.

Disulphide. When thio-choline bromide was heated for a prolonged period with hydrobromic acid, the disulphide was formed, which is a slightly yellowish colored syrup and is hygroscopic in nature. It does not form any silver derivative and is a less ionizable substance than thio-choline bromide in aqueous solution. It may be purified with butyl alcohol.

Anal. Subst. = 0.2286; AgBr = 0.2148 gr. Found: Br = 40.27%. Calc. for $C_{10}H_{26}N_2S_2Br_2$: Br = 40.20%.

Silver derivatives. The formation of a silver derivative of thio-choline bromide usually occurred, when the strongly acidic bromide solution was treated with an excess of silver oxide and was brought back to a neutral or slightly acidic point with HBr acid in alcoholic solution, as stated before. The compound is an insoluble white asbestos-like crystalline substance. It becomes brown in color at above 211°C., and on continuous heating, melts and boils at 214°C. with a dark brown coloration. The compound, like silver bromide, is slightly soluble in ammonium hydroxide but is insoluble in acid and alcohol. The compound was also obtained when pure thio-choline bromide solution was treated with silver oxide and hydrobromic acid, as before. However the compound of the basic type,



$$(CH_3)_3-\underset{\displaystyle OH}{\underset{|}{N}}-CH_2-CH_2-S-Ag,$$

was not isolated.

The compound precipitated silver bromide completely on boiling with strong acid such as hydrobromic, nitric acid, etc.

The following analytical results were obtained by the following methods.

1. The substance was decomposed by strong hydrobromic acid on boiling, into silver bromide. It was found that the filtrate did not precipitate silver bromide on heating with concentrated nitric acid.

Anal. Subst. = 0.2095; AgBr. = 0.1601 gr. Found: AgBr = 76.42%. Calc. for $C_5H_{13}NSAg_2Br_2$: AgBr = 75.91; S = 6.48%.

2. The compound was decomposed by nitric acid on boiling. The filtrate did not give silver bromide with silver nitrate solution.

Anal. Subst. = 0.2252, 0.2088; AgBr = 0.1703, 0.1582 gr. Found: AgBr = 75.62, 75.77%.

3. Carius' method.

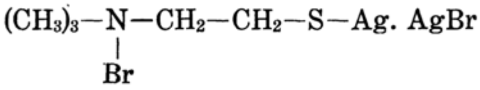
Anal. Subst. = 0.2874; AgBr = 0.2178; $BaSO_4$ = 0.1377 gr. Found: AgBr = 75.78; S = 6.57%.

Summary.

1. Thio-choline bromide was prepared by heating bromocholine bromide with 2-thio-uracil or 4-methyl-2-thio-uracil with water in a closed tube or pressure bottle at 150° and 170°C. for two and five hours respectively. The compound is hygroscopic in nature, and is very soluble in both alcohol and water. It decomposes at 243°C. on heating. Its isoelectric point was found to be 7.00.

2. By heating with hydrobromic acid the compound is easily oxidized to its disulphide, which is a syrupy and less pronounced ionizable substance, in aqueous solution.

3. On treating an aqueous solution of this compound, with an excess of silver oxide, and neutrallizing with hydrobromic acid and heating on the steam bath, an insoluble white asbestos-like crystalline substance was formed. It appears to be the following formula:



$$(CH_3)_3-\underset{\overset{|}{Br}}{N}-CH_2-CH_2-S-Ag.\ AgBr$$

The compound is slightly soluble in alkaline solution. It decomposes at 214°C.

In conclusion the author wishes to express his appreciation to Prof. Renshaw of New York University, who suggested this researth, for his advice rendered during this investigation.

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