CHEMISTRY OF THIO-CHOLINE HALIDE (TRIMETHYL THIO-ETHYL AMMONIUM HALIDE). II.

NEW THIO-CHOLINE CHLORIDE AND ITS DERIVATIVES.

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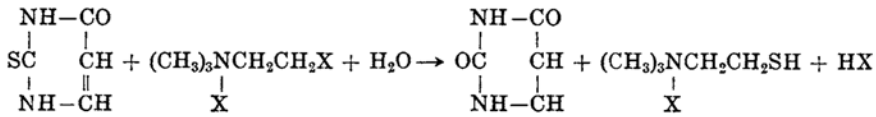
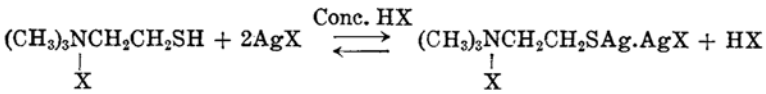
In a previous paper[1] in this Bulletin the author described the preparation of thio-choline bromide and its silver derivatives. The present paper is the continuation of the research on thio-choline compounds. According to the author's previous paper the reaction between 2-thio-uracil and halogeno-choline chloride is represented by the following reaction equation:



The yield was rather small in the pure state owing to side reactions.

Thio-choline chloride forms colorless, transparent monoclinic plates. Above 200°C. thio-choline chloride decomposes slowly. It is interesting to note that the substance forms an addition compound with silver halides giving a complex salt and releasing hydrochloric acid; the reaction becomes decidedly acid. The change may be represented by the following equation:



The new complex compound is a lustrous asbestos-like crystalline salt. The reaction proceeds to the right when the solution is neutral at the start. The compound decomposes slowly into the original constituents under the action of a strong acid or with temperatures above 70°C. It ionizes in aqueous solution probably to form $((CH_3)_3NCH_2CH_2SAg.AgX)^+ + X^-$ ions.

Shortly after the author's first publication, Vickery and Leavenworth[2] reported that cysteine combines with silver sulphate to form a silver compound, $(C_3H_5O_2NS\ Ag)_2Ag_2SO_4$, similar to that of the choline.

Thio-choline halides are very soluble substances both in water and in ethyl alcohol while the silver derivatives are not. The solubility of the

(1) This Bulletin, **4** (1929), 171.

(2) *J. Biol. Chem.*, **83** (1929), 523; **86** (1930), 129.

chlorine compound of the silver derivative, however, is slightly greater in water than that of the corresponding bromide. As a material for the preparation of thio-choline chloride, chloro-choline chloride was prepared by condensation of trimethylamine with ethylene chloride according to the author's previous method for the bromide.[1]

The reaction equation may be represented as follows:

$$(CH_3)_3N + ClCH_2CH_2Cl \rightarrow (CH_3)_3NCH_2CH_2Cl \quad (Cl)$$

Chloro-choline chloride decomposes slowly above 163°C. and at 242°C. melts and boils, the color becoming reddish brown. None of these compounds have definite decomposition or melting points.

Experimental Part.

Chloro-Choline Chloride. Forty grams of ethylene chloride were condensed with trimethylamine which was generated from a saturated aqueous solution containing thirty grams of trimethylamine hydrogen chloride in a well-stoppered pressure bottle with a rubber stopper which was framed with an iron cage. It was slowly heated in a water bath, then maintained for several hours at the boiling point of water. With such treatment chloro-choline chloride condensed in the form of a white snow-like salt. The substance obtained was washed with ether and dried over calcium chloride in a desiccator. The yield was forty grams. It can be recrystallized from 95 % ethyl alcohol in a large colorless monoclinic form. It decomposed above 163°C. (approximately), assuming a yellowish tint. At 242°C. (not sharp) it melts and boils changing its color into a reddish brown.

Anal. Subst.=0.2368, 0.1834; AgCl=0.4297, 0.3332 gr. (Carius' method). Found: Cl=44.85, 44.94%. Calc. for $C_5H_{13}NCl_2$: Cl=44.87%.

Thio-Choline Chloride. One molecular proportion (6 gr.) of Chloro-choline chloride was heated with one molecular proportion (5 gr.) of 2-thio uracil together with 25 c.c. of water in a sealed bomb tube at about 150°C. for one to three hours depending upon the size of the tube. After cooling, the sealed tube was opened and transferred to a beaker for the separation of the insoluble uracil formed. The solution was pale yellowish in color. The filtrate was neutralized with a solution of ammonia. The volume of the solution was reduced to a suitable amount on a steam bath. Cooling

(1) This Bulletin, **4** (1929), 171.

permitted further separation of the uracil. The total uracil obtained was 3.91 gr. in the impure state.

Fractional crystallization was then carried out as in the case of thio-choline bromide[1] on the filtrate from the impure uracil. This solution contains ammonium chloride, chloro-choline chloride, and thio-choline chloride. It was treated with butyl alcohol with or without ethyl alcohol and cooled with a mixture of salt and ice. By this repetition a small amount of the transparent colorless monoclinic crystalline form of the substance sought was obtained. The yield in the pure state was about 0.5 gr. It was noticed that some amount of the salt remained in the mother solution.

The compound is a very soluble substance both in water and in ethyl alcohol. Its isoelectric point was found to be at P_H 7.0. Above 200° C. (approximately), it decomposes slowly darkening in color and at 238°C. (not sharp) it melts and boils with a deep brown discoloration.

Anal. Subst.=0.2992; AgCl=0.2744 gr. Found: Cl=22.62%. Calc. for $C_5H_{14}NSCl$: Cl=22.78; S=20.59%.

Subst.=0.2020; AgCl=0.1862; $BaSO_4$=0.3040 gr. (Carius' method). Found: Cl=22.80; S=20.67%.

Silver Derivative of Thio-Choline Chloride. It was found that thio-choline chloride dissolves freshly prepared silver chloride in a slightly acidic or neutral solution giving a pale yellowish solution without any evolution of hydrogen, but with the formation of hydrochloric acid. An excess of freshly prepared silver chloride was dissolved in a solution of thio-choline chloride by constant stirring; the solution becomes a transparent pale yellow. The excess of silver chloride was separated simply by filtration. The filtrate was diluted with 95% alcohol, filtered again, then allowed to stand over-night. From this solution a white lustrous asbestos-like compound was crystallized out. It was separated by filtration, washed with water, alcohol, and ether. Finally it was dried over calcium chloride in a desiccator in the dark,

Second and third crops from the mother solution could be obtained. This was continued until no further separation was evident. The yield is approximately quantitative. It slowly decomposes above 70°C. (approximately); the color changes to gray and then to deep brown; it melts and boils turning dark brown above 228°C. (not sharp). In all probability, this is due mainly to its thermal decomposition products, thio-choline chloride and silver chloride. It ionizes in an aqueous solution, the chlorine-ion precipitating silver chloride from a solution of silver nitrate. The solubility

(1) Ibid, **4** (1929), 174.

of the compound in 100 c.c. of water at 37°C. was found to be 0.1215 gr. while the bromide compound appears to be almost insoluble, that is, 0.0326 gr. under the same conditions.

Hydrogen-ion concentration of the saturated solution of the compound at 37°C. gives P_H 6.9. The structural formula for the compound is still under investigation.

Anal. Subst.=0.1986; AgCl=0.1406 gr. Found: AgCl=70.79%. Calc. for $C_5H_{13}NSAg_2Cl_2$: AgCl=70.63; S=7.90%.

Subst.=0.2400; AgCl=0.1681; $BaSO_4$=0.1398 gr. (Carius' method). Found: AgCl=70.42; S=8.00%.

In concluding, the author withes to express his thanks to Prof. Kraus of Brown University, Prof. Stieglitz of Chicago University, and Dean Whitmore, School of Chemistry and Physics, Pennsylvania State College for valuable private advices regarding the constitution of the silver compound.

Summary.

1. Chloro-choline chloride was obtained by the condensation of trimethylamine with ethylene chloride. It decomposes slowly above 163°C. melting and boiling at 242°C. with a reddish brown discoloration.

2. Thio-choline chloride was prepared from chloro-choline chloride by the action of 2-thio uracil at 150°C. Its isoelectric point was found to be at P_H 7.0. It decomposes slowly above 200°C. (approximately), melting and boiling at 238°C.

3. Thio-choline chloride reacts with silver chloride to form $(CH_3)_3\underset{\displaystyle Cl}{\underset{|}{N}}CH_2CH_2SAg.AgCl$ whose solubility in water at 37° was found to be 0.1215 gr. It decomposes slowly above 70°C. (approximately), melting and boiling around 228°C.

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