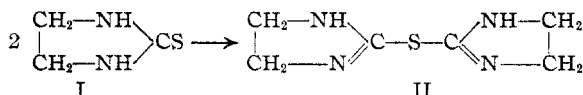


[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

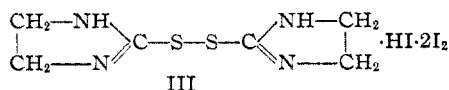
Complex Formations between Iodine and μ -Mercapto-dihydroglyoxalines¹BY TREAT B. JOHNSON AND C. O. EDENS²

In a recent paper from this Laboratory the authors³ reported on the characteristic behavior of ethylene-thiourea I when oxidized by 5,5-dibromoxyhydrouracil. They found that this cyclic ureide is transformed into a representative of a new class of glyoxaline sulfides, namely, dihydroglyoxaline sulfide II, which proved to be identical with a sulfur compound of unknown constitution,



obtained by Jaffe, in 1894, by interaction of ethylenediamine with thiophosgene. Since this change is brought about through the agency of hypobromous acid (HOBr) resulting from the dissociation of the pyrimidine, 5,5-dibromoxyhydrouracil, it was of interest to the authors to examine the behavior of ethylenethiourea I toward iodine solution. Practically no attention has hitherto been paid to the action of iodine on cyclic ureides of the thiodihydroglyoxaline type I. The experimentation has led to results of immediate interest, and opened a gate to a new field of heterocyclic sulfur compounds of biochemical significance.

Ethylene-thiourea I does not react with iodine in aqueous solution to form Jaffe's dihydroglyoxaline sulfide II. On the other hand, it undergoes the normal change of oxidation of a true thiol compound and is converted into a disulfide which combines at once with iodine to form the characteristic periodide III. Propylene-thiourea (2-thio-5-methyl-dihydroglyoxaline) interacts with iodine solution to yield a corresponding periodide derivative, while the unsaturated 2-thio-5-methylglyoxaline⁶ reacts under similar conditions to form periodide containing one molecule only of iodine IV. The simplest glyoxaline disulfate V or its periodide have not been described in the literature.



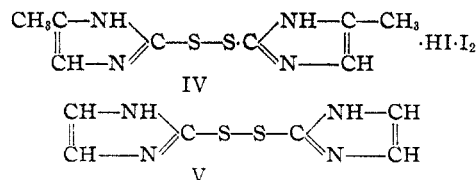
(1) A grant for partial support of this work made by the Rockefeller Foundation of New York City, is gratefully acknowledged by the authors.

(2) Sterling Professorship of Chemistry Research Assistant, 1940-1941.

(3) Johnson and Edens, *THIS JOURNAL*, **63**, 1058 (1941).

(4) Jaffe and Kuhn, *Ber.*, **27**, 1664 (1894).

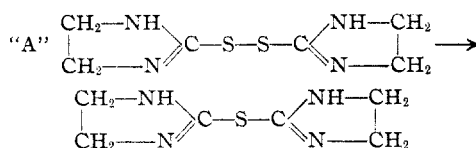
(5) Gabriel and Pinkus, *ibid.*, **26**, 2203 (1893).



Especially interesting is the behavior of the periodide III on hydrolysis. Boiling with water leads to decomposition of the molecule with evolution of iodine vapors and formation of the hydriodide of Jaffe's sulfur base—dihydroglyoxaline sulfide II. Free sulfur and sulfuric acid are also products of this change. The periodide III is also destroyed by treatment with aqueous ammonia. This leads to reduction of the disulfide grouping with regeneration of ethylene-thiourea I and formation of ammonium iodide.

Dihydroglyoxaline sulfide II likewise combines with iodine in aqueous solution to give a periodide conforming in constitution to the formula $\text{C}_6\text{H}_{10}\text{N}_4\text{C} \cdot \text{HI} \cdot \text{I}_3$. This dissociates quantitatively at 125° into iodine and the hydriodide of dihydroglyoxaline sulfide II.

Previously, the irreversible change expressed by equation "A" has not been emphasized.



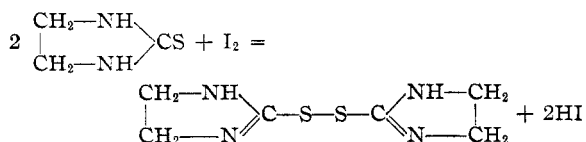
It is very possible that this interesting change of the sulfur linkage may be the cause of some of the irregularities in analytical results from the titration of certain 2-thioglyoxalines with iodine solutions. Further attention will be given to this problem as our work progresses, and when we have an opportunity to apply our technique to other representatives of the thiodihydroglyoxaline series.

Experimental Part

Periodide of 4,5-Dihydroglyoxaline-2-disulfide, $\text{C}_6\text{H}_{10}\text{N}_4\text{S}_2 \cdot \text{HI} \cdot 2\text{I}_2$, III.—A solution of five grams of ethylene-thiourea I dissolved in 200 ml. of water was cooled to room temperature and a solution of 0.4 N iodine, in aqueous potassium iodide, was added from a buret during vigorous stirring. The first few drops produced a yellowish-brown precipitate which redissolved immediately; further addition of iodine produced a permanent turbidity, which

gradually turned to a reddish-brown appearance. At this point, a dark red powder began to take form and settled to the bottom of the beaker. Iodine solution was added until there was no further precipitation, the volume consumed being 185 ml. or practically the equivalent of about 3 moles of iodine per mole of ethylene-thiourea I. A further addition of 25 ml. was added to assure an excess. This product was separated by filtration and washed with cold water and finally with carbon tetrachloride. The yield was 20.5 g. or 87.3% of the theoretical.

The equation leading to the formation of the unknown disulfide may be expressed as



This disulfide then adds iodine immediately, giving the above periodide derivative.

The periodide is a dark red substance of crystalline character. It melts at 119° and is extremely soluble in acetone, diethyl ether, ethanol, methanol, ethyl acetate and warm glycerol. It is moderately soluble in benzene and insoluble in carbon tetrachloride, petroleum ether and water. It can be recrystallized from dilute alcohol.

Anal. Calcd. for $\text{C}_6\text{H}_{11}\text{N}_4\text{S}_2\text{I}_5$: C, 8.60; H, 1.31; I, 75.85; S, 7.63. Found: C, 8.55; H, 1.28; I, 76.00; S, 7.55.

Behavior of the Periodide III on Heating with Water.—

Two grams of the above periodide of dihydroglyoxaline disulfide was digested with 75 ml. of boiling water for about forty-five minutes. Iodine vapors were evolved copiously, and the compound gradually changed to a dark oil, which finally dissolved yielding a pale-yellow aqueous solution. This was then concentrated to about 10 ml. *in vacuo* and cooled, when glistening needles crystallized from the solution. These melted at 284° and a mixed melt with the hydriodide of dihydroglyoxaline sulfide II ($\text{C}_6\text{H}_{10}\text{N}_4\text{S}\cdot\text{HI}$) gave no depression in melting point. The free base and picrate were likewise prepared and checked with mixed melts. Sulfuric acid was identified in the aqueous filtrate, and free sulfur also was present.

Anal. Calcd. for $\text{C}_6\text{H}_{10}\text{N}_4\text{S}\cdot\text{HI}$: N, 18.79; I, 42.6. Found: N, 18.63; I, 42.75.

Action of Ammonia on the Periodide $\text{C}_6\text{H}_{11}\text{N}_4\text{S}_2\text{I}_5$ (Ammonolysis).—The periodide interacts with aqueous ammonia with evolution of heat, and is decolorized almost immediately. The disulfide linkage is destroyed by this treatment with formation of ethylene-thiourea I and ammonium iodide. Other products are undoubtedly formed here, but after two applications to ammonolysis the only pure sulfur compound isolated was the cyclic ureide I. This reaction is under investigation in this Laboratory and the results of our experimentation will be reported in a subsequent paper.

Synthesis of Ethylene-thiourea (2-Thiol-dihydroglyoxaline I) and Propylene-thiourea (2-Thiol-4-methyl-dihydroglyoxaline).—These cyclic ureides are easily prepared from ethylenediamine and propylenediamine, respectively, according to the following procedure:

One hundred grams of carbon disulfide is placed in a 500-ml. flask attached to a reflux condenser. Then 75 g. of the respective commercial diamine (80%) is added dropwise with frequent shaking. The reaction is vigorous. After final addition of the amine, the mixture is then carefully refluxed for one-half hour and cooled. The excess of carbon disulfide is now poured off and the viscous reaction product dissolved by warming in 200 ml. of water. Ring closure of the respective dithiocarbamate intermediate is easily accomplished by adding 15 ml. of concentrated hydrochloric acid and finally refluxing the solution at 100° for one hour. On cooling, the dihydroglyoxaline separates in crystalline condition. Further material is obtained by concentration of the aqueous mother liquors. The ethylene-thiourea is obtained in a yield of 64.5 g. and melting at 198°, or 63%.⁶

Propylene-thiourea is easily purified by crystallization from benzene, and the yield was 64.5 g., melting at 100°. This ureide is much more soluble than ethylene-thiourea I.

Anal. Calcd. for $\text{C}_4\text{H}_9\text{N}_2\text{S}$: C, 41.33; H, 6.94; N, 24.11. Found: C, 41.41, 41.42; H, 6.62, 6.76; N, 24.38, 24.28.

Periodide of 5-Methyl-4,5-dihydroglyoxaline-2-disulfide, $\text{C}_8\text{H}_{14}\text{N}_4\text{S}_2\cdot\text{HI}\cdot 2\text{I}_2$.—To a solution of 5 g. of propylene-thiourea in 100 ml. of water was added dropwise with stirring the calculated volume of 163 ml. of 0.4 *N* iodine solution. The first addition produced an immediate turbidity and finally a compound separated in the form of a glistening viscous oil adhering to the sides and bottom of the beaker. After the addition of five atoms of iodine per mole of the propylene-thiourea, a further addition of 25 ml. of the standard iodine solution was made, the total volume added being 187 ml. On standing, the viscous oil finally solidified to a brittle solid which was washed with water and dried. After grinding it formed a heavy dark red powder melting at 67°. This periodide is very soluble in acetone, ether and ethanol; insoluble in water and carbon tetrachloride.

Anal. Calcd. for $\text{C}_8\text{H}_{14}\text{N}_4\text{S}_2\text{I}_5$: C, 11.09; H, 1.73; I, 73.31; S, 7.39. Found: C, 11.23; H, 1.79; I, 73.52; S, 7.28.

When this periodide was heated with boiling water iodine vapors were evolved and the compound completely dissolved. After concentrating the solution to 10 ml. and cooling no crystals separated as did in the case of the ethylene-thiourea experiment. Instead, a dark red oil separated that failed to crystallize on long standing. The solution gave a strong test for sulfuric acid.

4,5-Dihydroglyoxaline-2-thioglycolic Acid, $\text{C}_5\text{H}_8\text{O}_2\text{N}_2\text{S}$.—An aqueous solution (50 ml.) of 5 g. of ethylenethiourea I and 9.4 g. of chloroacetic acid was heated at its boiling point for three hours. It was then concentrated to a thick sirup and 50 ml. of ethanol added when the hydrochloride of this acid separated in crystalline form. The yield was 8 g. or 81%. The hydrochloride was purified by crystallization from hot ethanol, and melted at 223° with decomposition. Qualitative tests showed the presence of sulfur, nitrogen and chlorine. The cyclic ureide derivative is very resistant to hydrolysis.

(6) Hoffmann, *Ber.*, **5**, 242 (1872); Schacht, *Arch. Pharm.*, **235**, 442 (1897); Ruiz and Libenson, *Anales asoc. quim. Argentina*, **18**, 37 (1930); *C. A.*, **24**, 5726 (1930).

Anal. Calcd. for $C_6H_9O_2N_2SCl$: C, 30.53; H, 4.58; N, 18.05. Found: C, 30.59, 30.85; H, 4.54, 4.36; N, 18.00, 17.81.

5-Methyl-4,5-dihydroglyoxaline-2-thioglycolic Acid, $C_6H_{11}O_2N_2S$.—This was obtained in the form of its hydrochloride by digesting a solution of 5 g. of propylene-thiourea and 8.2 g. of chloroacetic acid in 50 ml. of water for three hours. The yield was 8 g. and the salt melted at 215° after crystallization from ethanol. This compound was recovered unaltered after digestion for two hours with 20% hydrochloric acid.

Anal. Calcd. for $C_6H_{11}O_2N_2SCl$: Cl, 16.86. Found: Cl, 16.85, 16.83.

Periodide of 4,5-Dihydroglyoxaline Sulfide, $C_6H_{10}N_4S \cdot HI \cdot I_3$.—This is easily prepared by dissolving the hydriodide of dihydroglyoxaline sulfide $C_6H_{10}N_4S \cdot HI$ (0.4 g.) II in 100 ml. of water at room temperature, and then adding dropwise 5 ml. of standard iodine solution (0.4 *N*). At this point no further precipitation was observed. The precipitate was filtered off and after washing it with cold water and carbon tetrachloride it was dried in a vacuum desiccator over sulfuric acid. This periodide crystallizes as a dark red powder melting at 170 – 175° . It is quite soluble in ether and acetone.

Anal. Calcd. for $C_6H_{11}N_4SI_4$: C, 10.83; H, 1.62; I, 74.81. Found: C, 10.61; H, 1.62; I, 74.55.

Dissociation of the above Periodide $C_6H_{11}N_4SI_4$ by Heating.—A small amount of the periodide was spread on a porous plate and exposed to the temperature of a drying oven at 125° . In fifteen minutes the three atoms of iodine had volatilized completely and a colorless powder remained behind. This was identified as the hydriodide of 4,5-dihydroglyoxaline sulfide and melted at 284° . No change in the linkage of sulfur had taken place.

Action of Chloroacetic Acid on Jaffe's Base—Dihydroglyoxaline Sulfide, II.—One gram of the glyoxaline derivative, $C_6H_{10}N_4S$, and 1.19 g. of chloroacetic acid were dissolved in 50 ml. of water and the solution boiled for three hours. The solution was then concentrated to 5 ml. and diluted with ethanol. The hydrochloride of Jaffe's sulfur base separated immediately. No other product was identified, and there was no evidence of desulfurization by this treatment or formation of a thioglycolic acid derivative.

Anal. Calcd. for $C_6H_{10}N_4S \cdot HCl$: Cl, 17.20. Found: Cl, 17.45.

Periodide of 5-Methylglyoxaline Disulfide, $C_8H_{16}N_4S_2 \cdot HI \cdot I_3$.—2-Thio-5-methylimidazole⁷ (0.5 g.) was dissolved in 100 ml. of cold water and a 0.4 *N* solution of iodine in aqueous potassium iodide added slowly with vigorous stirring. Addition of 5 ml. produced a deep yellow solution; 13.4 ml. led to the formation of a precipitate which was complete after adding 28.5 ml. The periodide separated as dark red crystals. After washing with cold water and chloroform it was dried in a vacuum over sulfuric acid. The compound decomposed on heating.

Anal. Calcd. for $C_8H_{16}N_4S_2I_3$: C, 15.75; H, 1.80; I, 62.44; S, 10.52. Found: C, 15.93, 15.77; H, 1.66, 1.64; I, 62.47; S, 10.41.

Summary

1. Ethylene-thiourea and propylene-thiourea interact with iodine in aqueous potassium iodide solution to form the periodides $C_6H_{10}N_4S_2 \cdot HI \cdot 2I_2$ and $C_8H_{14}N_4S_2 \cdot HI \cdot 2I_2$, respectively.

2. The periodide resulting from ethylene-thiourea is converted by hydrolysis into dihydroglyoxaline sulfide $C_6H_{10}N_4S$. Interaction with ammonia (ammonolysis) leads to the regeneration of ethylene-thiourea.

3. Dihydroglyoxaline sulfide reacts with iodine to give the periodide $C_6H_{10}N_4S \cdot HI \cdot I_3$ which dissociates at 125° yielding the hydriodic salt of dihydroglyoxaline sulfide.

4. Dihydroglyoxaline sulfide $C_6H_{10}N_4S$ is not desulfurized by digestion with chloroacetic acid.

5. Ethylene-thiourea and propylene-thiourea interact with chloroacetic acid to form the representative 2-thioglycolic acid derivatives without desulfurization.

6. 2-Thio-5-methylimidazole interacts with iodine in aqueous solution to give a periodide of formula $C_8H_{16}N_4S_2 \cdot HI \cdot I_2$.

NEW HAVEN, CONNECTICUT

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(7) Gabriel and Pinkus, *Ber.*, **26**, 2197 (1893).