[Contribution from the Chemical Laboratory of Indiana University]

THE SYNTHESIS OF TRIMETHYLENE-1,2,4-THIADIAZINE-3,5-DIONE-1,1-DIOXIDE. A NEW MOLECULAR REARRANGEMENT

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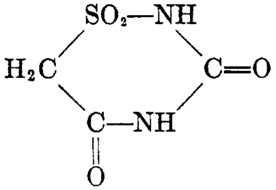
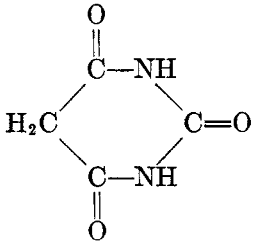
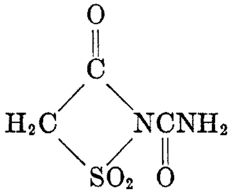
The close similarity of trimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide (I) to barbituric acid (II) is apparent by inspection of the following structures:



I



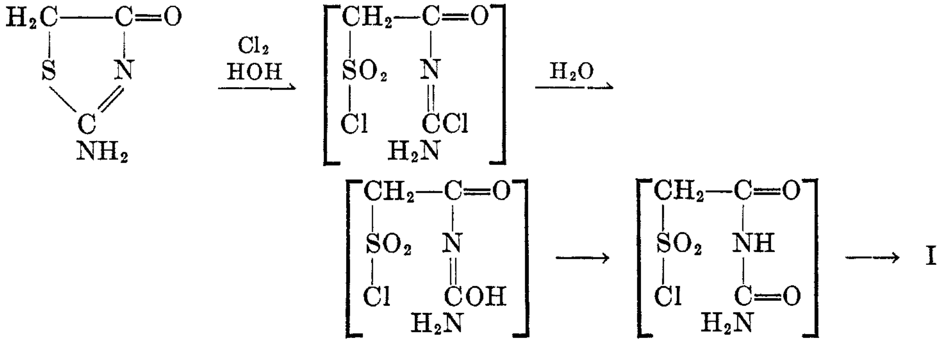
II



III

A comparison of the physiological activity of I and its 6-substituted derivatives with the corresponding barbituric acids seemed of interest. The ring system contained in I is unknown and previous attempts to prepare it or its 6-substituted derivatives met with failure (1).

Examination of the literature revealed that Kramp (2) in 1880 had investigated the reaction between chlorine gas and a dilute hydrochloric acid solution of 2-imino-4-thiazolidone. He reported only decomposition products when the reaction was carried out at room temperature. However, if the reaction was carried out at 0° a white, chlorine-free, precipitate formed to which he assigned the empirical formula, $C_3H_6N_2O_3S$. I required $C_3H_4N_2O_4S$ which however fits Kramp's analytical values very well. It is well known that certain S-alkylthiuronium salts will undergo cleavage with chlorine to give good yields of the alkylsulfonyl chloride (3). 2-Imino-4-thiazolidone hydrochloride may be considered a nitrogen-substituted S-alkylthiuronium salt which on chlorination might undergo a rearrangement similar to the following to give I.



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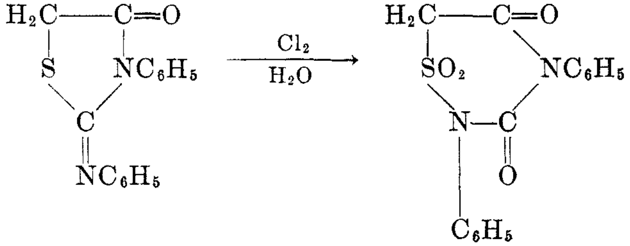
[1] From a thesis submitted by Paul N. Rylander to the Graduate School of Indiana University in partial fulfillment of the requirements for the degree, Doctor of Philosophy.

Kramp's work was, accordingly, repeated and a compound shown to be I was obtained in a maximum yield of 40%.

I was decomposed by boiling sodium bicarbonate solution into sulfoacetic acid. It dissolved easily in 10% potassium hydroxide but it was not reprecipitated by acidification of the solution with hydrochloric acid. Raney nickel desulfurized I to give a 79% yield of acetylurea, whereas degradation of 2-imino-4-thiazolidone with Raney nickel gave as the only isolated product N-formylacetamide. All of these facts taken together strongly indicate that I is the correct structure for the product obtained by the reaction of chlorine gas with a solution of 2-imino-4-thiazolidone.

Only one other structure (III) was given serious consideration. III, which is isomeric with I, could not be eliminated by any of the chemical evidence presented and no chemical test could be devised which would unequivocally distinguish between these possibilities. However, III was considered unlikely for it should be thermodynamically less stable than the strainless six-membered ring.

Direct proof that the six-membered ring can and does exist was made in the following reaction. N,N′-diphenyl-2-imino-4-thiazolidone (IV) was reacted with chlorine in dilute hydrochloric acid solution to give N,N′-diphenyltrimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide (V).



IV V

Formation of the four-membered ring was in this case impossible. V, like I, spontaneously lost sulfur dioxide. It was desulfurized with Raney nickel to give a solid which was a mixture of diphenylurea and N-acetyldiphenylurea. On repeated recrystallization of this mixture from dilute alcohol, the melting point rose until a mixed melting point with authentic diphenylurea showed no depression. Acetyldiphenylurea, the product expected in this degradation, is reported to be readily hydrolyzed to diphenylurea (4). Desulfurization of IV with Raney nickel gave aniline and acetanilide, probably due to the ease of hydrolysis of the expected N-acetyl-N,N′-diphenylformamidine.

The reaction of chlorine with 5-methyl-2-imino-4-thiazolidone (VI) produced as expected 6-methyltrimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide (VII), which was subsequently desulfurized with Raney nickel to give propionylurea in good yield.[2]

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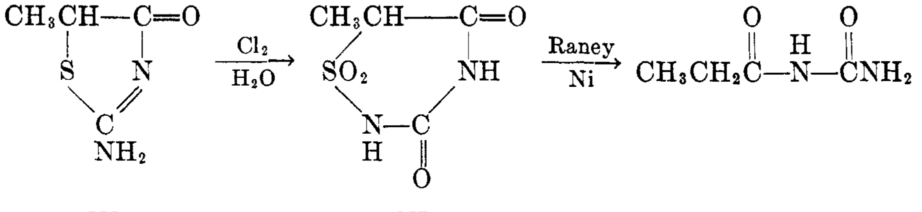
[2] There was an annoying side reaction connected with this chlorination. Explosive by-products were formed which decomposed even when in water. This disturbing phenomenon was largely circumvented by using small quantities of pure starting materials, keeping the



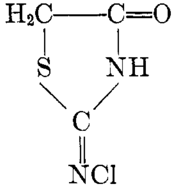
VI VII

To determine the influence of other substituents on the reaction, 5-carbethoxy-, 5-benzal-, 5-benzyl-, and the heretofore unknown 5-phenyl-, 5-carboxamido-, and 5,5-diphenyl-2-imino-4-thiazolidone were prepared and chlorinated. The main reaction in each case was oxidation of the sulfur to sulfate ion; there was no evidence of any rearrangement. It seems that those factors which might be expected to stabilize the rearranged product are the very ones which promote cleavage of the methylene carbon-sulfur bond in aqueous solution.

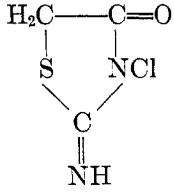
Chlorination of 5-ethyl-2-imino-4-thiazolidone proceeded in a manner entirely different from that of its two lower homologs. The precipitate formed was so unstable, disappearing at intervals in a puff of smoke, that it could not be purified for analysis. It contained chlorine, but this chlorine was not ionic, for a precipitate formed with silver nitrate only after shaking for several seconds. The precipitate oxidized iodide ion to iodine, indicating that a "positive" halogen was present. A compound of such marked instability probably has a nitrogen-chlorine linkage.

Chlorination of 5,5-dimethyl-2-imino-4-thiazolidone in ice-cold dilute hydrochloric acid gave a "positive" halogen compound of much greater stability than that derived from the 5-ethyl derivative. A sample was kept in the dry state for several months without apparent decomposition, but it too decomposed suddenly and unexpectedly. Analysis of the compound for chlorine showed slightly less than one chlorine per molecule.

An attempt was made to obtain a possible intermediate, 3-chlorotrimethylene-1,2,4-thiadiazine-5-one, by chlorination of 2-imino-4-thiazolidone in the non-polar solvent, chloroform. However, the product isolated contained a "positive" chlorine, indicating a nitrogen-chlorine linkage. Analysis for chlorine agreed well with the formula corresponding to the structure for VIII or IX.



VIII



IX

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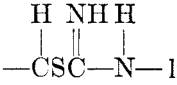
solution below 5° at all times, and bubbling the chlorine gas in at a very slow rate. See reference (1), page 98.

This product is not an intermediate in the formation of I from 2-imino-4-thiazolidone for I was not formed when VIII or IX was dissolved in ice-cold, dilute hydrochloric acid, or when chlorine gas was bubbled through this solution.

Since the molecular rearrangement of 2-imino-4-thiazolidone is a new reaction, it was thought desirable to determine if the reaction was applicable to other compounds containing the  $-\overset{\overset{H}{|}}{C}S\overset{\overset{NH}{\|}}{C}-\overset{\overset{H}{|}}{N}-$ linkage. Accordingly, 2-iminothiazolidine, 2-aminothiazole, 2-amino-4-methylthiazole, and 2-amino-4-phenylthiazole were chlorinated under these conditions. No rearranged product was detected with any of these compounds.

From the reaction studied certain generalizations relating the structure of the 2-imino-4-thiazolidone to the course of the reaction can be made. Electron-releasing groups on the methylene carbon tend to promote substitution of the nitrogen atom by chlorine; electron-attracting groups cause cleavage of the carbon-sulfur bond. These statements apply to all cases studied in the 4-thiazolidone series. Substitution of the electron-attracting carbonyl group in 2-imino-4-thiazolidone by a methylene group to give 2-iminothiazolidine would be expected to increase the amount of nitrogen substitution. Experiment bore out this observation for a "positive" halogen compound seemed to be the only product produced by the chlorination of this thiazolidone. In the 2-amino-thiazole series the electron-releasing methyl group in the 4-position favored nitrogen substitution to such an extent that the product vigorously decomposed as fast as it was formed, a phenyl substituent in the 4-position caused cleavage of the sulfur to give sulfate ion, and as might be expected both of these effects occurred with the unsubstituted 2-aminothiazole. Therefore it seems that structural requirements are too exacting for the rearrangement reaction to have wide application.

EXPERIMENTAL

2-Imino-4-thiazolidones. All the compounds in this series were prepared in yields of 50 to 80% according to the procedure of *Organic Syntheses* (5) by the reaction of the appropriate alpha-haloacid or alpha-haloester with thiourea.

5,5-Diphenyl-2-imino-4-thiazolidone (IV). Ten grams of crude diphenylchloroacetic acid (6) was refluxed for two hours with 4 g. of thiourea, 1 g. of sodium acetate, and 75 ml. of ethanol. The solution was cooled and a 15% solution of sodium carbonate was added until basic. The precipitate was recrystallized twice from dilute alcohol; m.p. 270° with decomposition.

Anal. Calc'd for $C_{15}H_{12}N_2OS$: S, 11.92. Found: S, 12.10.

5-Phenyl-2-imino-4-thiazolidone was prepared from ethyl α-chlorophenyl acetate and thiourea in the manner just described; m.p. 234° with decomposition.

Anal. Calc'd for $C_9H_8N_2OS$: S, 16.67. Found: S, 16.89.

2-Imino-4-thiazolidone-5-carboxamide. Ten grams of 5-carbethoxy-2-imino-4-thiazolidone was suspended in 75 ml. of conc'd ammonia solution at room temperature for twelve days. By the third day small red crystals appeared in the flask and by the eighth day all the material had been converted to red crystals. These crystals were soluble in dilute hydrochloric acid but were not reprecipitated by the addition of base. The product was purified by dissolving in warm water, adding Norit, filtering, and cooling the filtrate in an ice-box. The compound had a slight reddish tinge; m.p. 219–221°.

Anal. Calc'd for $C_4H_5N_3O_2$ S: S, 20.14. Found: S, 20.55.

Trimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide (I). All chlorinations carried out in aqueous solvents were run in the manner described below. Ten grams of 2-imino-4-thiazolidone hydrochloride was dissolved in 50 ml. of water, four drops of hydrochloric acid were added, the solution was cooled to 0–5°, and maintained at this temperature while chlorine gas was bubbled slowly through the mixture. In a short time a flocculent precipitate formed. The flow of gas was continued until no further precipitate formed. The precipitate was washed with water, alcohol, and ether. The yield of dry, snow-white product was 3.7 g., or 38%. The melting range of 110–120° varied greatly with the rate of heating. The compound was very slightly soluble in water, ethanol, ether, or dilute hydrochloric acid. It could be recrystallized from water with considerable loss, and reacted with nitrous acid at 0°, producing sulfur dioxide and nitrogen. The compound did not react with Fuchsin aldehyde reagent, Fehling's solution, nor 2,4-dinitrophenylhydrazine test reagent. It slowly lost sulfur dioxide, even in a vacuum desiccator over phosphorus pentoxide. No similar product was obtained when 2-imino-4-thiazolidone was treated with other oxidizing agents, such as hydrogen peroxide or potassium permanganate.

When samples were made for analyses, they were prepared from analytically pure starting material, washed with distilled water, alcohol, and ether, dried quickly under vacuum, and analyzed immediately.

Anal. Calc'd for $C_3H_4N_2O_4S$: S, 19.49. Found: S, 19.32.

6-Methyltrimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide (VII). This compound was prepared by chlorination of 5-methyl-2-imino-4-thiazolidone hydrochloride in the manner just described. The yields varied from 0 to 30% depending on whether or not the reaction exploded. The melting point, about 140°, varied widely with the rate of heating.

Anal. Calc'd for $C_4H_6N_2O_4S$: S, 18.00. Found: S, 18.05.

N,N'Diphenyltrimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide (V). This substance was prepared by chlorinating N,N′-diphenyl-2-imino-4-thiazolidone in the manner described above. The compound lost sulfur dioxide so readily that analyses for sulfur were low and not reproducible.

Oxidation of other 5-substituted-2-imino-4-thiazolidones. Due to the explosive nature of the products obtained when hydrochloric acid suspensions of 5-carbethoxy-, 5-benzal-, 5-benzyl-, 5-phenyl-, 5,5-diphenyl-, and 5-carboxamido-2-imino-4-thiazolidones were treated with chlorine, these compounds were not studied after preliminary tests which showed in each case that a great deal of free sulfate ion was produced. In one quantitative estimation, using 5-phenyl-2-imino-4-thiazolidone, 66.4% of the sulfur was found as free sulfate. The main reactions were evidently cleavage of the carbon-sulfur bond to give sulfate, and formation of an unstable nitrogen-chlorine bond.

Chlorination of 2-imino-4-thiazolidone in chloroform. Two grams of finely ground 2-imino-4-thiazolidone was suspended in 40 ml. of chloroform at 25°. The mixture was stirred mechanically while chlorine gas was slowly bubbled in. The suspension soon became very flocculent and after twenty minutes it was filtered. The precipitate was dried by suction, m.p. 170–175° dec. A water suspension of the precipitate oxidized iodide ion to iodine, showing the presence of "positive" chlorine.

Anal. Calc'd for $C_3H_3ClN_2OS$: Cl, 23.53. Found: Cl, 23.27.

Desulfurization of trimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide. Two grams of this compound, 25 ml. of Raney nickel (7), and 130 ml. of 75% ethanol were refluxed for four hours. The hot solution was filtered and the Raney nickel was washed with 200 ml. of hot 95% ethanol. The alcohol was evaporated under vacuum and the residue was recrystallized from alcohol; yield 1.1 g. (79%), m.p. 215–216°. A mixture melting point with an authentic sample of *acetylurea* showed no depression.

Desulfurization of 6-methyltrimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide. This compound was degraded in the same manner as its lower homolog. The solid obtained by evaporation of the solvent alcohol was recrystallized from diluted alcohol, and melted at 209°. A mixture melting point with an authentic sample of *propionylurea* showed no depression.

Desulfurization of N,N'-diphenyltrimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide. Two grams of this compound was desulfurized as above, and the residue, after evaporation of the solvent, was recrystallized from dilute alcohol. The product melted over the range 206–216°. Five recrystallizations were required to raise the melting range to 233–235°, and a mixture melting point determination with an authentic sample of *sym*-diphenylurea (8) m.p. 235°, showed no depression (233–235°).

Attempts to prepare N-acetyldiphenylurea from *sym*-diphenylurea and acetylchloride led to low-melting crude mixtures which on recrystallization from dilute alcohol, were gradually converted to diphenylurea again.

Desulfurization of N,N'-diphenyl-2-imino-4-thiazolidone. Two grams of this compound was refluxed with 25 ml. of Raney nickel suspension in 100 ml. of 70% ethanol for six hours. After filtering, the hot solution was evaporated to a small volume. The characteristic aniline odor was evident, so an aliquot portion was extracted with ether, dried, and precipitated with dry hydrogen chloride. The crystalline hydrochloride so obtained melted at 197°, and did not depress the melting point of an authentic sample of *aniline hydrochloride*. The remaining filtrate was evaporated to dryness and recrystallized from dilute acid and then water, giving white needles, m.p. 113–114°, which did not depress the melting point of an authentic sample of *acetanilide*.

Chlorination of 5-ethyl-2-imino-4-thiazolidone. When this compound was chlorinated in the manner described for its lower homologs, a sticky, light-brown precipitate formed which disappeared in a puff of smoke from time to time. It was soluble in alcohol and ether. Chlorination of the thiazolidone in concentrated hydrochloric acid gave the same results.

SUMMARY

Oxidative cleavage of 2-imino-4-thiazolidone with chlorine in dilute hydrochloric acid caused rearrangement to a six-membered ring, trimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide. 5-Methyl-2-imino-4-thiazolidone gave a similar rearrangement, but other substituents in the 5-position gave unstable products.

The properties of several new 1,2,4-thiadiazine-1,1-dioxides and thiazolidones are described.

BLOOMINGTON, INDIANA

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(5) *Org. Syntheses*, **27**, 71 (1947).
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(7) MOZINGO, FOLKERS, WOLF, AND HARRIS, *J. Am. Chem. Soc.*, **65**, 1013 (1943).
(8) *Org. Syntheses*, Coll. Vol. *I*, 2nd. ed., p. 453 (1941).