hydroxyethyl group substituted in one of the amino groups have been synthesized. Several similar derivatives of 4-amino-4′-nitrodiphenyl sulfone were prepared. The preparation and the properties of the compounds are described.

The antipneumococcal and antitubercular activities of certain of the compounds are recorded.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KENTUCKY]

The Preparation of 1,4-Thiazine

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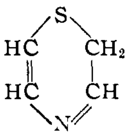
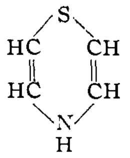
Compounds containing the uncondensed heterocyclic 1,4-thiazine ring have never been thoroughly investigated although, condensed with the benzene ring, this heterocyclic structure occurs in the important thiazine dyes. 1,4-Thiazine, which can theoretically exist in two forms (I) and (II), has never been described in the literature.



I



II

It has been found possible to synthesize 1,4-thiazine by making the imide of thiodiglycolic acid and reducing this imide with aluminum powder at an elevated temperature.

Thioglycolic acid, the starting point in the synthesis of 1,4-thiazine can be made easily by the usual method of the reaction of monochloroacetic acid with sodium sulfide. By extracting the acid from the reaction mixture with ether yields of 90% can be obtained.

The imide of thiodiglycolic acid was mentioned by Schulze in 1865 but no further reference to this interesting imide could be found. It was found that thiodiglycolimide could be made in excellent yields by heating the dry ammonium salt of thiodiglycolic acid in a partial vacuum.

The reduction of thiodiglycolimide to 1,4-thiazine is comparable to the preparation of pyrrole from succinimide. A literature search easily reveals that the reduction of succinimide, in spite of the large amount of space devoted to it by standard texts, is of very little preparative value and no one recommends this reduction as a means of making pyrrole or pyrrolidine. The most encouraging reduction method appeared to be that of Ray and Dutt,[2] who heated succinimide at an elevated temperature with aluminum powder instead of the customary zinc dust and obtained a 15% yield of pyrrole. The high temperature recommended, namely, dull red heat, placed some doubt as to whether the sulfur of the ring would survive such treatment. After many modifications of the original method, however, yields of 13% of 1,4-thiazine were finally obtained.

1,4-Thiazine, the mother substance of this interesting type of ring structure, is a colorless liquid boiling at 76.5–77°, miscible with water in all proportions, and is a weak base, $K = 4.0 \times 10^{-9}$. It has an ammoniacal odor combined with a faint but detectable odor of sauerkraut. It does not form a sulfonamide by the Hinsberg method and appears to be a tertiary amine having the structure corresponding to formula (I).

In investigating the many methods of reduction that have been tried on imides the reduction of chloro substituted imides appeared to offer some possibilities. Succinimide when treated with phosphorus pentachloride can be chlorinated to dichlorosuccinimide[3] which on further treatment gives tetrachloropyrrole. Prolonged treatment of thiodiglycolimide with phosphorus pentachloride completely destroyed the imide but careful heating of the imide with small amounts of phosphorus pentachloride gave a white crystalline compound having only one chlorine in the molecule. At first it was thought that this compound, because of the ease of hydrolysis of the chlorine, was an iminochloride. Mild treatment with alkali, however, did not regenerate the imide but produced instead thioglycolic acid, glyoxalic acid and ammonia. This would indicate that the chlorine had entered the α-position and that on hydrolysis a cyclic hemithioacetal was produced which on further hydrolysis gave the above products.

Experimental

Thiodiglycolic Acid.—Nine hundred and forty-five grams (10 moles) of monochloroacetic acid was placed in a 5 liter round-bottomed flask and dissolved in 1500 ml. of water. To this solution was added slowly with stirring 840 g. (10 moles) of solid sodium bicarbonate until the solution was neutral to litmus. The flask was placed in an ice-bath and 1320 g. (5.1 moles) of hydrated sodium sulfide dissolved in 1850 ml. of water was added slowly with stirring keeping the temperature between 25–30°. The solution was allowed to stand in the ice-bath for one hour and then 750 ml. of concentrated sulfuric acid was added with stirring, keeping the temperature between 25–30°.

The resulting solution was placed in a continuous extractor and ether passed through the solution at the rate of about 6 ml. per minute for twelve hours. At the end of each twelve-hour period fresh ether was placed in the extractor and the extraction continued for a total of thirty-

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(1) Taken in part from a thesis presented in partial fulfillment of the requirements for the degree of Master of Science, University of Kentucky, August, 1947.

(2) A. C. Ray and S. B. Dutt, *J. Ind. Chem. Soc.*, **5**, 103 (1928).

(3) R. Anschutz, *Ann.*, **295**, 27 (1897).

six hours. Since thiodiglycolic acid is as soluble in water as it is in ether, an efficient extractor had to be designed which would also be capable of accommodating the large volume of solution to be extracted. The extractor was made by connecting two 2-liter round-bottom flasks and one 1-liter round-bottom flask to a 40-mm. diameter glass tube so that the over-all height was 2200 mm. The ether was conducted to the bottom of the apparatus by a 5 mm. tube to which was sealed a sintered glass filter stick. The combined ether extracts were evaporated to dryness and the crude acid dissolved in 2 liters of hot water, decolorized with charcoal and, after filtering, concentrated to a volume of 750 ml. After cooling with ice the crystals were filtered off and washed with three small portions of ice water. In order to remove such a small amount of liquid from the large mass of crystals a high vacuum was necessary. The acid on air-drying weighed 580 g., had a m. p. 129° and neut. equiv., 75.5. The filtrate was concentrated to 250 ml. and the acid obtained was recrystallized from 150 ml. of water. Seventy-two grams of acid of the same purity was obtained. The combined filtrates were concentrated to 100 ml. and this crop of acid recrystallized from 20 ml. of water. Eleven grams more of the same purity was obtained; total yield, 663 g. (88% yield).

Thiodiglycolimide.—One hundred and fifty grams of pure thiodiglycolic acid was placed in a 500-ml. three-necked round-bottom flask fitted with ground glass joints. A capillary tube was fitted into one of the openings and a short wide adapter connected the flask by a ground joint to a liter three-necked round-bottom flask. This was cooled with water and connected to a water pump. To the acid was added 150 ml. of concentrated ammonium hydroxide and the contents heated first to 100° in an oil-bath using a slight vacuum and then to 190° for one hour. Toward the end a vacuum was used to remove last traces of water. After substituting a clean flask for the receiver, the oil-bath was raised to 215–220° and a vacuum of about 10 mm. applied. The imide was slowly formed and distilled into the flask. It was necessary to heat the connecting tube to prevent the imide from blocking the opening. A total of two hours was necessary to complete the distillation.

The crude imide was dissolved in 400 ml. of 95% alcohol and, after decolorizing with charcoal, the solution was concentrated to 150 ml. On cooling and filtering 100 g. of the imide was obtained melting at 128°. On concentrating the filtrate 5.7 g. of imide of like purity was obtained; total yield 105.5 g. (82%).

The yields in this preparation are dependent on the purity of the acid. A quantity of acid from one run gave an excellent yield of the imide while that from another identical preparation gave practically no yield. This was rather remarkable since both samples of the acid had the same melting point and neutralization equivalent. One crystallization of this impure acid gave a product that produced an excellent yield of the imide. The nature of this interfering impurity was not determined but apparently only traces are necessary to interfere with the synthesis.

1,4-Thiazine.—Ten grams of thiodiglycolimide was placed in a six-inch test-tube fitted with a sealed inlet tube which extended to the bottom of the test-tube and an outlet tube fitted with a ground joint. The test-tube was connected to a glass tube 100 cm. long and 2 cm. in diameter packed to three-fourths of its length with pumice which had been coated with aluminum powder. A 500-ml. flask surrounded with ice was attached to this tube and the latter attached to a glass spiral cooled with ice and salt. The end of the spiral was allowed to dip into 300 ml. of 10% potassium hydroxide solution. The long glass tube was heated for three-fourths of its length to 450° in an electric furnace and a rapid stream of carbon dioxide was passed through the test-tube containing the imide which had been melted and heated to 180–190° by an oil-bath. In this manner the imide was slowly volatilized through the long tube. After the imide had been volatilized the receiving apparatus was washed well with water and the washings combined with the potassium hydroxide solution.

The water solution from five such runs was combined and saturated with potassium carbonate. One-half of this solution was distilled and the distillate treated in the same manner. This was continued until a volume of 20–25 ml. was obtained. On saturating this solution with potassium carbonate the upper layer was separated, allowed to stand over powdered potassium hydroxide and then distilled. On redistillation the 1,4-thiazine boiled at 76–76.5°; yield 5.5 g. (13.4%), $n^{25}\text{D}$ 1.5975, d^{25}_4 0.8465. *Anal.* Calcd for C_4H_5NS: S, 32.30. Found: S, 32.40.

This base gave no derivative when boiled with benzenesulfonyl chloride in pyridine for one hour. A water solution on warming reduced potassium permanganate and only oily products were obtained when the base was allowed to react with methyl iodide or methyl *p*-toluenesulfonate. A picrate formed readily which had m. p. 158–159°. It also formed a very insoluble chloroplatinate which, after washing well with alcohol and drying, melted at 236–238°. *Anal.* Calcd. for $(C_4H_5NS)_2 \cdot H_2PtCl_6$: Pt, 32.1. Found: Pt, 31.9. On passing dry hydrochloric acid gas through an anhydrous ether solution of the base a white precipitate of 1,4-thiazine hydrochloride was formed. This salt is very hygroscopic but after drying in a vacuum desiccator over phosphorus pentoxide melted at 74–75°.

α-Monochlorothiodiglycolimide.—In a 200-ml. round-bottom flask was placed 5 g. of thiodiglycolimide, 8 g. of phosphorus pentachloride and 10 ml. of toluene. On heating in a water-bath the solids dissolved and after one-half hour a yellowish white solid separated from the black solution. The reaction mixture was cooled and the black liquid decanted from the solid. The solid was dissolved in 200 ml. of boiling toluene, decolorized with charcoal and concentrated to 100 ml. On cooling, light yellow crystals separated which were filtered off and dried in a vacuum desiccator. The crystals had a m. p. of 135°. Repeated crystallization raised the m. p. to 135.5°. *Anal.* Calcd. for $C_4H_4O_2NSCl$: Cl, 21.4; S, 19.4. Found: Cl, 21.5; S, 19.8.

The α-monochlorothiodiglycolimide when treated in the cold with dilute sodium hydroxide solution readily lost the chlorine but on acidification the original imide was not obtained and the odor of thioglycolic acid was detected. On warming the alkaline solution, ammonia was evolved showing that a profound decomposition of the compound had taken place.

Summary

1,4-Thiazine, the mother substance of the 1,4-thiazine series, has been prepared for the first time by the reduction of thiodiglycolimide and some of its properties have been described.

Methods of preparation of thiodiglycolic acid and thiodiglycolimide have been investigated and a satisfactory method giving excellent yields has been worked out for each. Thiodiglycolimide has been chlorinated to α-monochlorothiodiglycolimide by means of phosphorus pentachloride.

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