drous benzene was refluxed with stirring for 6 hr. and allowed to cool. Water (100 ml.) and sufficient potassium carbonate to give a slightly alkaline reaction were added to the crystalline suspension. The solid was removed by filtration, washed successively with benzene and water and air-dried. The crude product was purified by recrystallization.

Procedure B—Reactions with Acyl Isocyanates.—(a) Anhydrous ammonia or methylamine was passed into a stirred solution of 0.1 mole of the acyl isocyanate in 200 ml. of pentane for 2 hr. The solution, from which the product gradually separated, was allowed to stand overnight at room temperature. The crude material was removed by filtration and purified by recrystallization.

(b) A solution of 0.25 mole of the acyl isocyanate and 0.275 mole of acetamide or urea in 400 ml. of toluene was refluxed for 6 hr. The suspension was cooled in the refrigerator, filtered and the precipitate purified by recrystallization.

Procedure C—Hydrogenation.—A solution of 0.1 mole of the unsaturated acylurea in 300 ml. of dimethylformamide was hydrogenated in the presence of palladium oxide catalyst at 3.5 kg./cm.^{2} pressure. The absorption of hydrogen was complete in 45 min. The catalyst was filtered off, the solvent removed by distillation under reduced pressure and the residue was purified by recrystallization.

Procedure D—Diels–Alder Condensation.—Freshly distilled cyclopentadiene (0.35 mole) was added to a solution of 1.0 g. of hydroquinone and 0.25 mole of the dienophile in an appropriate solvent (maleuric acid[9] in 2 l. of acetic acid, methyl maleurate[9] in 500 ml. of acetone and N-carbamylmaleimide[9] in 1500 ml. of dioxane). The mixture was heated at 50–60° for 2 hr., an additional 0.15 mole of cyclopentadiene added and heating was continued for an additional 2 hr. The product, which was separated by filtration or by distillation of the solvent, was purified by recrystallization.

Some Aspects of the Chemistry of 5-Ethyl-6-phenyl-*meta*-thiazane-2,4-dione, an Anesthetic Agent

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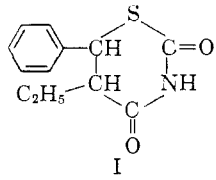
Received January 13, 1962

The loss of potency of aqueous solutions of the sodium salt of 5-ethyl-6-phenyl-*meta*-thiazane-2,4-dione was found to be due to hydrolysis to a linear product. Reactions carried out upon the dione established that it was stable enough so that derivatives could be prepared directly from it. Further, the sites where substitutions could be made without damage to the ring were established. Several derivatives and decomposition products were isolated and some preliminary pharmacological observations were made.

5-Ethyl-6-phenyl-*meta*-thiazane-2,4-dione (I) has been demonstrated to be an anesthetic agent of considerable interest.[1,2] How-



I

ever, the material has also exhibited undesirable side effects, including thrombophlebitis upon intravenous injection.[3,4] In previous studies of the compound in our laboratory, a simple procedure for its preparation was developed.[5] Therefore, because of the new availability of the dione, some aspects of its chemistry were studied to see whether new analogs could be made directly from it. Further, it was of interest to study the hydrolysis of its sodium salt in order to establish the mechanism by which preparations of the material decreased in potency on standing.

The dione itself is water insoluble, but by virtue of the acidic imide hydrogen present in the molecule, it dissolves in an equivalent of base. Solutions of 2.5% concentration were found to be convenient for pharmacological purposes and therefore were used for our decomposition studies.

The pH of freshly prepared 2.5% solutions containing equivalents of the dione and sodium hydroxide was 11.8. After short standing of the solution at room temperature, decomposition was apparent by the appearance of precipitate, the generation of mercaptan odor and by a decrease of pH. Hydrolysis to a linear thiol was indicated because the solutions could be titrated iodometrically after standing. The dione in solution was found to be 12.5% hydrolyzed, after 26 hr. of standing at room temperature, by titration.

A large quantity of the dione was dissolved in sodium hydroxide solution and allowed to stand for 7 days at room temperature. During this time, a considerable amount of crystalline product formed, which on filtration, was shown to be the starting dione. An additional small amount of starting material was obtained from the clear filtrate

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by saturation with carbon dioxide. The decomposition product was then extracted by ether from the filtrate and identified as N-carboxy-2-ethyl-3-phenyl-3-mercaptopropionamide (II). The precipitation of I during the decomposition can be explained by a simple competition for the solubilizing sodium ion between I and II. Since II is a stronger acid because of its carboxyl group, upon forming, it removes sodium from I and precipitates the latter because of its insolubility in water.

A further study of the dione consisted of performing both an acylation and alkylation of the imidic nitrogen. In the first case, the sodium salt was prepared by reacting the dione with an equivalent of sodium hydride in benzene. This suspension, on reaction with ethyl chlorocarbonate at room temperature produced 3-carboxyethyl-5-ethyl-6-phenyl-*meta*-thiazane-2,4-dione. Attempts to remove the ester group by acid hydrolysis were not successful and basic hydrolysis could not be used because of the sensitivity of the *meta*-thiazane ring to aqueous alkali.

N Methylation was performed in a similar manner; however, the incorporation of dimethylformamide as a co-solvent made it easier to obtain the final product. In this solvent system, an interesting phenomenon occurred on adding sodium hydride to the dione. Within several minutes, an intense blue color developed which persisted for 10 min. and was discharged immediately upon the addition of the alkylating agent, methyl iodide. Reaction at room temperature then yielded the desired 3-methyl-5-ethyl-6-phenyl-*meta*-thiazane-2,4-dione.

The dione was also nitrated successfully under classical conditions indicating its stability to strong oxidizing acids. The nitrophenyl derivative then was reduced to the acetamido compound by means of zinc and glacial acetic acid. From theoretical considerations, it can be unequivocally stated that the phenyl ring was the only site where the nitro group could attach itself. However, its position on the ring was not established.

Treatment of the dione with 30% hydrogen peroxide in glacial acetic acid caused cleavage at the thiol ester bond and the first imide bond in the *meta*-thiazane ring. In addition, the formed thiol group underwent oxidation to a sulfonic acid group resulting in the isolation of 2-carboxamido-1-phenylbutane-1-sulfonic acid monohydrate in good yields as the final product of the reaction.

Although the dione is very sensitive to aqueous base, it is quite stable to strong acids and neutral and non-ionic reaction media as illustrated by the reactions described here. Therefore, this investi-

gation has demonstrated that the phenyl ring and the imide nitrogen could be exploited as functional sites for preparing further and more potentially desirable analogues of I without extensive decomposition taking place during the reaction. Due to the availability of the dione, derivatives made directly from it should be more easily synthesized than those from variously substituted linear precursors. Furthermore, the dione has been demonstrated to serve as a convenient intermediate for *beta*-mercapto or *beta*-sulfopropionic acid derivatives.

Pharmacology.—Solutions of the sodium salt of the purified hydrolysis product, *dl*-N-carboxy-2-ethyl-3-phenyl-3-mercaptopropionamide, did not exhibit anesthetic properties in rabbits by intravenous administration at doses equivalent to that of the dione, though some depression was observed for several hours in mice following the intraperitoneal administration of 200–300 mg./kg. The dione itself, produced complete anesthesia in rabbits for 5 min. at 10 mg./kg. A similar type of depression occurs in rabbits recovering from anesthesia by the dione where the animals could easily be roused by gentle cutaneous stimuli, but would relapse into an inactive state within minutes.

3-Carboxyethyl-5-ethyl-6-phenyl-*meta*-thiazane-2,4-dione exhibited anesthesia in rabbits by intravenous administration although of lesser duration than the parent compound at equivalent dosage. The nitro derivative and the N-methyl derivative produced no anesthesia but did exhibit a depressant effect on the animals.

Experimental

Thiol Determination of Solutions of 5-Ethyl-6-phenyl-*meta*-thiazane-2,4-dione (I).—Aliquots of the solutions (3 ml.) were removed at intervals and 0.2 ml. of glacial acetic acid, 1 ml. of saturated potassium iodide solution and 0.5 ml. of starch solution were added. The aliquots were then titrated to a blue end point with 0.01 *N* potassium iodate solution.

Isolation of the Hydrolysis Product of I.—Fifty grams (0.21 mole) of I[5] was dissolved into 250 ml. of water containing 10.0 g. of sodium hydroxide and the solution filtered to remove a small amount of insoluble matter. Very soon after the preparation of the solution, large amounts of solid began to precipitate. The mixture was allowed to stand for 7 days at room temperature and then saturated with carbon dioxide to precipitate any remaining unhydrolyzed starting dione. The solution was filtered and the clear filtrate acidified with hydrochloric acid to pH 2 and extracted with three 50 ml. portions of ether. The ether portions were combined and evaporated to dryness in the atmosphere at room temperature to yield 21.6 g. of a white, shiny, amorphous solid. A portion was crystallized from chloroform to give N-carboxy-2-ethyl-3-phenyl-3-mercaptopropionamide, m.p. 174.5–176°.

Anal. Calcd. for $C_{12}H_{15}NO_3S$: C, 56.89; H, 5.96; N, 5.53; SH (iodometric), 13.05. Found: C, 56.86; H, 5.94; N, 5.35; SH (iodometric), 12.80.

Nitration of 5-Ethyl-6-phenyl-*meta*-thiazane-2,4-dione.—Twenty-four grams (0.1 mole) of I was dissolved into 100 ml. of concd. sulfuric acid, the solution was cooled with ice and nitrated over 45 min. with a pre-cooled mixture of 15 ml. concd. nitric acid and 20 ml. of concd. sulfuric acid. The temperature was maintained at 8–13° during the addition and then allowed to warm to room temperature and stand for 1 hr. The reaction mixture was poured onto 1 kg. of ice and filtered, after the ice had melted, to give 20 g. of product. Upon crystallization from 500 ml. of ethanol, 10.1 g. (36% yield) of cream-colored crystalline 5-ethyl-6-nitrophenyl-*meta*-thiazine-2,4-dione was obtained, m.p. 190–193°. A sample was recrystallized for assay.

Anal. Calcd. for $C_{12}H_{12}N_2O_4S$: C, 51.42; H, 4.39; N, 9.99. Found: C, 51.41; H, 4.17; N, 9.86.

When this time of nitration was increased, no improvement in the yield of product could be brought about.

Reduction of 5-Ethyl-6-nitrophenyl-*meta*-thiazane-2,4-dione.—Five grams (0.018 mole) of the nitrated dione was dissolved into 50 ml. of glacial acetic acid in a 250 ml. flask fitted with a reflux condenser and the solution was heated to approximately 80°. Zinc dust (20 g.) was then added over 20 min. in a vigorous exothermic action. The mixture was refluxed overnight, filtered while hot and the residue washed with two 20-ml. portions of hot glacial acetic acid. The filtrate was poured into 150 ml. of water to give a gummy product which was separated by decantation after 24 hr. of standing. Recrystallization of the solid from 150 ml. of ethanol and 250 ml. of water yielded 2.8 g. (61%) of 5-ethyl-6-acetamidophenyl-*meta*-thiazane-2,4-dione, m.p. 176–180°. A portion was recrystallized to give an analytically pure sample, m.p. 181° (with effervescence).

Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.51; H, 5.52; N, 9.58. Found: C, 57.45; H, 5.36; H, 9.92.

N-Carboxyethylation of 5-Ethyl-6-phenyl-*meta*-thiazane-2,4-dione.—To 10 g. (0.043 mole) of **I**, dissolved into 200 ml. of dry benzene, was added 2.0 g. (0.047 mole) of 50% sodium hydride mull to give a suspension of a white solid. While stirring rapidly, 4.6 g. (0.042 mole) of redistilled ethyl chlorocarbonate in 50 ml. of benzene was added. The mixture was then stirred at room temperature for 18 hr. and filtered to remove the suspended sodium chloride. The filtrate was reduced to dryness under vacuum at 60° to give 11.5 g. (87%) of 3-carboxyethyl-5-ethyl-6-phenyl-*meta*-thiazane-2,4-dione, m.p. 111–113°, which possessed a sweet ester-like odor. A portion was recrystallized from ethanol to give an analytical sample, m.p. 113.5–115°.

Anal. Calcd. for $C_{15}H_{17}NO_4S$: C, 58.61; H, 5.57; N, 4.56; S, 10.43. Found: C, 58.91; H, 5.64; N, 4.59; S, 10.51.

N-Methylation of 5-Ethyl-6-phenyl-*meta*-thiazane-2,4-dione.—Ten grams (0.043 mole) of I was dissolved in a mixture of 100 ml. of benzene and 100 ml. of redistilled dimethylformamide followed by the addition of 2.0 g. (0.042 mole) of 50% sodium hydride mull. Shortly after the addition of the sodium hydride an intense blue color formed which slowly faded after about 10 min. to be replaced by a white suspension. The identity of this suspension as the sodium salt of I was confirmed by removing a small portion by filtration. This residue was soluble in water and the solution yielded I upon acidification. While the reaction mixture was being stirred, 4.0 ml. (9.2 g., 0.065 mole) of methyl iodide in 20 ml. of benzene was added and the mixture stirred for 18 hr. at room temperature. Potassium iodide (9 g., 0.054 mole) was filtered from the mixture and the filtrate

taken to dryness under vacuum on a steam bath. The residue was crystallized from ethanol to give 6.7 g. (62.5%) of 3-methyl-5-ethyl-6-phenyl-*meta*-thiazane-2,4-dione, m.p. 99–100°.

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.07; N, 5.62. Found: C, 63.33; H, 6.33; N, 5.28.

Action of Hydrogen Peroxide on the Dione.—A mixture of 10.0 g. (0.043 mole) of the dione, 100 ml. of glacial acetic acid and 15 ml. of 30% hydrogen peroxide was stirred for 19 hr. at room temperature. All of the solvents were then removed under vacuum while heating on a steam bath. A glassy residue was obtained which when refluxed with chloroform gave a white solid. The chloroform solution was cooled and filtered to give 9.6 g. (88% yield) of 2-ethyl-3-phenyl-3-sulfopropionamide monohydrate. The product was very soluble in water forming strongly acidic solutions. A portion was crystallized from ethanol and chloroform to give an analytically pure sample, m.p. 201–203°.

Anal. Calcd. for $C_{11}H_{17}NO_5S$: C, 47.98; H, 6.22; N, 5.09; S, 11.64. Found: C, 48.08; H, 5.79; N, 5.06; S, 11.44.

Acetylenic Amines. III. The Haloethynyl Derivatives

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Received January 27, 1962

The preparation of some haloethynyl analogs of acetylenic amines and their pharmacological evaluation in hypertensive rats is reported. The bromo analogs are more potent than the corresponding chloro compounds. The most potent compound in this series is 3-*t*-butylamino-3-methyl-1-bromo-1-butyne hydrochloride, and this material is about as potent as the nonhalogenated analog (XVI).

The availability of a large number of acetylenic amines by the Hennion synthesis[1,2,3] and the antihypertensive activity[4] of some of these amines prompted us to prepare the haloethynyl derivatives of selected members of these series.

Since the reaction of the aminoacetylenes with N-bromosuccinimide (used to prepare 1-bromo-3-*t*-butylamino-3-methyl-1-butyne) proved

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