thalene series should be regarded as provitamins.

2. A mechanism for the conversion of such compounds to phthalic acid has been proposed which was established by experimental data. Potassium 2-methyl-1,4-naphthoquinone-3-sulfonate and 2-methyl-1,4-naphthoquinone are readily converted into phthalic acid on heating with water or alkali. With the former, intermediate compounds have been isolated establishing the path of the conversion to phthalic acid.

3. The biochemical degradation hypothesis is consistent with all the known data and is in variance with the view of L. F. Fieser which holds that the biological activity of the simple synthetic analogs of vitamin K is not due to their action *per se* but to their transformation within the organism, by way of biosynthesis, into quinones of the type of vitamins K_1 and K_2.

4. Less soluble derivatives of phthalic acid such as the diamide and the diethyl ester show a much higher and more protracted antihemorrhagic activity than phthalic acid.

THE ALL-UNION INSTITUTE OF EXPERIMENTAL MEDICINE

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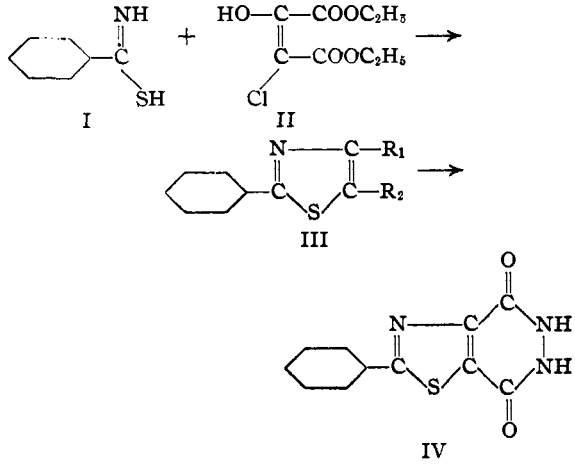
2-Phenylthiazole-4,5-dicarboxylic Acid Derivatives

BY ERNEST H. HUNTRESS AND KARL PFISTER, 3RD[1]

In connection with a study of the chemiluminescence shown under certain circumstances by some cyclohydrazides, occasion arose to prepare 2-phenylthiazole-4,5-dicarboxylic acid cyclohydrazide (IV). This was successfully accomplished by the following reactions



Application of the Hantzsch thiazole synthesis to an equimolal mixture of thiobenzamide (I) and diethyl oxalo-α-chloroacetate (II) gave excellent yields of 2-phenyl-4,5-dicarbethoxythiazole (III) (III, $R_1=R_2=COOC_2H_5$). Upon heating this ester in alcohol with an excess of strong hydrazine hydrate there resulted a mixture of the desired cyclohydrazide (IV) with the open chain 2-phenylthiazole-4,5-dicarboxylic acid dihydrazide. The relative amounts of these two products depended upon the duration of the reaction, the proportion of cyclohydrazide increasing with time. Since the open chain dihydrazide was insoluble in the excess hydrazine hydrate solution, it was readily filtered out and the soluble cyclohydrazide precipitated from the filtrate by acidification.

Hydrolysis of diethyl 2-phenylthiazole-4,5-dicarboxylate with methanolic potassium hydroxide gave according to the prevailing conditions either 2-phenylthiazole-4,5-dicarboxylic acid V (III, $R_1=R_2=COOH$) or its corresponding potassium acid salt VI (III, $R_1=COOK$, $R_2=COOH$). Pyrolysis of 2-phenylthiazole-4,5-dicarboxylic acid caused evolution of carbon dioxide and the formation of 2-phenylthiazole-4-carboxylic acid VII (III, $R_1=COOH$, $R_2=H$). The salt of this same monobasic acid also resulted from the pyrolysis of the potassium acid salt (VI) of the dibasic acid.

The structure of acid VII was demonstrated both positively and negatively. When 2-phenyl-4-chloromethylthiazole[2] is hydrolyzed with dilute alkali the corresponding 2-phenyl-4-hydroxymethylthiazole is readily obtained[3] and upon oxidation with aqueous chromic-sulfuric acid yields 2-phenylthiazole-4-carboxylic acid.[3] The product so obtained was in all respects identical with that from decarboxylation of the 2-phenylthiazole-4,5-dicarboxylic acid (either directly or through the potassium acid salt).

For comparison with 2-phenylthiazole-4-carboxylic acid (VII) the isomeric 2-phenylthiazole-5-carboxylic acid (VIII) (III, $R_1=R_2=COOH$) was also prepared by an independent synthesis. The condensation of thiobenzamide (I) with the sodium salt of ethyl α-formyl-α-chloroacetate gave 2-phenyl-5-carbethoxythiazole. Although the yield was not high (37%), use of the sodium salt gave better yields and purer product than did use of the conventional method with free aldehyde ester. Saponification of ethyl 2-phenylthiazole-5-carboxylate with methanolic potassium hydroxide gave a solution from which mineral acid

(1) This paper is constructed from part of a dissertation submitted in September, 1942, by Karl Pfister, 3rd, to the Faculty of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Hooper and Johnson, THIS JOURNAL, **56**, 484 (1934).

(3) Huntress and Pfister, *ibid.*, **65**, 1669 (1943).

precipitated the desired 2-phenylthiazole-5-carboxylic acid (VIII). This acid was converted to its acid chloride and its amide by conventional methods. All these compounds of the 5 series are entirely distinct from those of the 4 series as shown below

	2-Phenylthiazole-4-carboxylic acid series[3]	2-Phenylthiazole-5-carboxylic acid series
Acid	m. p. 175.7–176.7° cor.	192–193° cor.
Acid chloride	m. p. 97.7– 98.5° cor.	125.3–126.5° cor.
Acid amide	m. p. 143.3–143.8° cor.	213.7–214.5° cor.

Experimental

All melting points in this work were taken with a 360° rod form melting point thermometer by the Berl-Kullmann copper block method. As reported in this paper they are all corrected.

2-Phenylthiazole-4,5-dicarbethoxythiazole (III, R_1 = R_2 = $COOC_2H_5$).—A solution of thiobenzamide (3.43 g. = 0.025 mole) and diethyl oxalo-α-chloroacetate (5.57 g. = 0.025 mole) in absolute alcohol (15 ml.) was refluxed for thirty minutes. After being cooled, the resultant slurry was filtered and the long rods washed with a little cold alcohol to remove the yellow color. The yield of air-dried product was 6.3 g. (83% theoretical) of product of m. p. 94.9–96° cor. and giving no Beilstein test for halogen. Two recrystallizations from 60% alcohol gave colorless centimeter-long rods of m. p. 95.5–96.5° cor.

Anal. Calcd. for $C_{15}H_{15}O_4NS$: N, 4.59. Found: N, 4.84, 4.85.

Potassium Acid 2-Phenylthiazole-4,5-dicarboxylate (VI).—A sample of the above ester (4.58 g., 0.015 mole) was saponified by warming for three minutes with a solution of potassium hydroxide (2.25 g., 0.04 mole) in methanol (25 ml.). After dilution with 25 ml. of water, acidification to litmus with 3 *N* hydrochloric acid (6.5 ml.) gave 4.03 g. (94% yield) of potassium acid salt, m. p. 252–253° cor. with decomposition. On recrystallization from water this product separated in fine needles, m. p. 253–254° cor. dec. Since no loss of weight occurred after heating two hours at 110°, the absence of any hydrate was assured. The same product was also obtained in 89% yield by half neutralization of the free acid, but melted at 258–259.2° cor. with decomposition.

Anal. Calcd. for $C_{11}H_6O_4NSK$: neut. eq., 287.3. Found: neut. eq., 290.8.

2-Phenylthiazole-4,5-dicarboxylic Acid (V).—A sample of the above acid salt (VI) upon acidification with hydrochloric acid gave an 89% yield of the corresponding dibasic acid, nearly square prisms from water, m. p. 190.3–190.8° cor. with gas evolution (capillary tube inserted at 180°).

Anal. Calcd. for $C_{11}H_7O_4NS$: N, 5.62; neut. eq., 124.6. Found: N, 5.59, 5.47; neut. eq., 125.8.

The acid was slightly soluble in cold water, soluble in hot water, alcohol, acetone, glacial acetic acid, ethylene glycol and methyl ethyl ketone, but quite insoluble in chloroform.

2-Phenylthiazole-4,5-dicarboxylic Anhydride.—Finely powdered potassium acid salt (1.44 g., 0.005 mole) added to thionyl chloride (5 ml.) gave spontaneous reaction with considerable evolution of heat. After refluxing for thirty minutes the excess thionyl chloride was removed by heating in a dry air stream. The residue was recrystallized from hot benzene (30 ml.) using Norit decolorizing carbon, and the product washed with petroleum ether (b. p. 35–60°). The yield was 0.61 g. (53% theoretical) of material which melted at 187.2–191.2° cor. Another recrystallization from benzene raised the melting point to 200.3–202.3° cor. (capillary inserted at 197° cor.).

Anal. Calcd. for $C_{11}H_5O_3NS$: N, 6.06; sap. equiv., 115.6; mol. wt., 231. Found: N, 6.26, 6.26; sap. eq., 117.4; mol. wt. (Rast method in camphor), 213.

Attempts to prepare this anhydride from the acid by use of acetyl chloride were unsuccessful, as only unchanged acid was obtained. Similar attempts to use the conventional acetic anhydride method resulted in decarboxylation.

2-Phenylthiazole-4-carboxylic Acid (VII). From 2-Phenylthiazole-4,5-dicarboxylic Acid.—The diacid (1.0 g., 0.004 mole), placed in a large test-tube equipped with a cold-finger condenser, was heated at 165–170° (bath temperature) for thirty minutes. The product which sublimed was dissolved in cold ether, shaken with Norit and filtered. Evaporation of the solvent gave a slightly yellow solid which was further purified by solution in excess 0.1 *N* sodium hydroxide, further Norit treatment and reprecipitation with 0.1 *N* hydrochloric acid. After drying the yield was 0.75 g. (91.5% theoretical) of product melting at 168.9–170.9° cor. Still further purification by recrystallization from benzene or from a mixture of ether and light petroleum ether raised the melting point to 175.7–176.7° cor.

Anal. Calcd. for $C_{10}H_7O_2NS$: N, 6.83; neut. equiv., 205.2. Found: N, 6.82, 6.83; neut. equiv., 205.6.

This monobasic acid was sparingly soluble in hot water and in benzene, insoluble in petroleum ether (b. p. 35–60°) but easily soluble in ether or chloroform. It readily dissolved in cold dilute aqueous sodium carbonate solution.

From Potassium Acid 2-Phenylthiazole-4,5-dicarboxylate (VI).—A sample of this salt (3.03 g., 0.0105 mole) was heated in the same way as above except that the bath temperature was initially 200°, and was raised to 265° during fifteen minutes. After holding this temperature for ten minutes, the tube contents were taken up in water, decolorized with Norit, filtered and acidified with concentrated hydrochloric acid. The resultant precipitate of white needles after drying weighed 1.72 g. (80%) and melted at 174.7–176.2° cor. The melting point of a mixture of this product with that from the pyrolysis of the corresponding di-acid or with that obtained[3] by oxidation of 2-phenyl-4-hydroxymethylthiazole was not depressed.

2-Phenylthiazole-4,5-dicarboxylic Acid Dihydrazide.—2-Phenyl-4,5-dicarbethoxythiazole (3.05 g., 0.01 mole), hydrazine hydrate (1.6 g., 0.03 mole of 93.8%) and 95% alcohol (20 ml.) were placed in a pressure bottle and heated for four hours on a steam-bath. After cooling the contents of the bottle were treated with boiling water (200 ml.) and the suspension filtered hot. After washing with hot water and drying the residue weighed 1.18 g. (43%). This dihydrazide started to melt at about 200° cor., gave a transitory orange color and finally fused at 349.5–351.5° cor. When a small sample was heated at 200–220° until the orange color disappeared and no more base was evolved (thirty minutes), the resulting product failed to depress the melting point of the corresponding *cyclo*-hydrazide (see below). For analysis the open chain dihydrazide was twice recrystallized from alcohol and the long hair-fine pale yellow needles analyzed.

Anal. Calcd. for $C_{11}H_7O_2N_5S$: N, 25.2. Found: N, 25.0, 25.0.

The dihydrazide was insoluble in water, slightly soluble in hot ethanol, hot ethyl acetate, soluble in glacial acetic acid or dioxane. It gave no color with ferric chloride, but reduced ammoniacal silver nitrate on warming. Upon refluxing with acetone this dihydrazide gave a 91% yield of N,N'-diisopropylidene 2-phenylthiazole-4,5-dicarboxylic acid dihydrazide. This product formed silvery rods of melting point 252.9–253.2° cor.

Anal. Calcd. for $C_{17}H_{19}O_2N_5S$: N, 19.6. Found: N, 19.5, 19.6.

2-Phenylthiazole-4,5-dicarboxylic Acid Cyclohydrazide (IV).—2-Phenyl-4,5-dicarbethoxythiazole (4.58 g., 0.015 mole), hydrazine hydrate (2.40 g., 0.045 mole of 93.8%) and 95% alcohol (25 ml.) contained in a pressure bottle were heated for forty-eight hours on the steam-bath. After cooling the contents of the bottle were treated with hot

water (300 ml.) and the suspension filtered hot. After washing and drying, the residue (open chain dihydrazide) weighed 0.64 g. (15%). The filtrate was shaken with Norit, filtered, acidified with glacial acetic acid (10 ml.), and chilled. The resultant microcrystalline precipitate weighed 2.92 g. (79%) and melted at 347.3–350.3° cor. with decomposition. Further reprecipitation from alkali by acidification, followed by recrystallization from ethylene glycol, raised the melting point only to 348.5–350.5° cor. dec.

Anal. Calcd. for $C_{11}H_7O_2N_3S$: N, 17.1; neut. equiv., 245.2. Found: N, 17.3, 17.2; neut. equiv., 263.1.

This cyclohydrazide was very insoluble in water, slightly soluble in hot acetic acid (about 0.5 g. in 125 ml.), more soluble in hot ethylene glycol (0.5 g. in 50 ml.). With ferric chloride, its saturated aqueous solution gave a faint pink color but did not reduce ammoniacal silver nitrate even on heating. It was soluble in dilute sodium hydroxide, sodium carbonate, ammonium hydroxide or in warm pyridine.

Another otherwise similar preparative run which was heated only seventeen hours gave 69% of cyclohydrazide and 27% of open chain dihydrazide.

The cyclohydrazide failed to show any significant chemiluminescence on oxidation with potassium ferricyanide in dilute alkali containing hydrogen peroxide.

2-Phenyl-5-carbethoxythiazole.—The sodium salt of the (enolic) ethyl α-formyl-α-chloroacetate (3.45 g., 0.02 mole) and thiobenzamide (2.74 g., 0.02 mole) were refluxed in absolute alcohol (15 ml.) for one hour. The precipitated sodium chloride was filtered from the hot deep red solution which on dilution with water (15 ml.) and refrigeration deposited a crystalline precipitate. After drying the product weighed 1.71 g. (37%) and melted 62.8–64.3° cor. Recrystallization from 70% acetone and then from petroleum ether gave colorless rods, m. p. 64.8–65.8° cor.

The same compound was also obtained in somewhat lower yield by using ethyl α-formyl-α-chloroacetate in place of its sodium salt, or in 89% yield from 2-phenylthiazole-5-carboxylic acid chloride (see below) by boiling with absolute alcohol for five minutes. The products from all three methods were identical as shown by the method of mixed melting points.

Anal. Calcd. for $C_{12}H_{11}O_2NS$: N, 6.00. Found: N, 5.93, 5.96.

2-Phenylthiazole-5-carboxylic Acid (VIII).—A sample of 2-phenyl-5-carbethoxythiazole (2.33 g., 0.01 mole) was saponified by refluxing for one and one-half hours with a solution of potassium hydroxide (0.7 g.) in methanol (25 ml.). Cooling in a refrigerator for two hours gave 2.25 g. (93%) of the corresponding potassium salt. This was largely dissolved in water (25 ml.) at room temperature, shaken with Norit, filtered and acidified with concentrated hydrochloric acid (1 ml.). After filtering, washing and drying the fine white crystals of free acid weighed 1.79 g. (87% from ester) and melted 190.5–192.5° cor. with gas evolution. Recrystallization from acetone and then benzene raised the melting point to 192–193° cor. with gas evolution.

Anal. Calcd. for $C_{10}H_7O_2NS$: N, 6.83; neut. equiv., 205.2. Found: N, 6.74, 6.86; neut. equiv., 207.6.

2-Phenylthiazole-5-carboxylic Acid Chloride.—This was obtained in 82.4% yield by boiling the acid (0.31 g.) with thionyl chloride (4 ml.) until a clear solution resulted (two minutes), and evaporating excess reagent in a stream of dry air. Recrystallization from hot ligroin gave 0.28 g. of acid chloride of m. p. 125.3–126.5° cor.

2-Phenylthiazole-5-carboxylic Acid Amide.—The above acid chloride was finely powdered, warmed with concentrated ammonium hydroxide (5 ml.) and stood overnight. The product weighed 0.24 g. (92% yield), melted 212.5–213.5° cor. and this melting point was unchanged by recrystallization from benzene. From 50% alcohol, however, the amide separated in lustrous white rods melting at 213.7–214.5° cor.

Anal. Calcd. for $C_{10}H_8ON_2S$: N, 13.7. Found: N, 13.6, 13.4.

Summary

1. The cyclic hydrazide of 2-phenylthiazole-4,5-dicarboxylic acid was prepared and its capacity to show chemiluminescence on oxidation with potassium ferricyanide in dilute alkali containing hydrogen peroxide found negligible.

2. Pyrolysis of 2-phenylthiazole-4,5-dicarboxylic acid and of its potassium acid salt has been found to give 2-phenylthiazole-4-carboxylic acid and potassium 2-phenylthiazole-4-carboxylate, respectively.

3. A number of compounds related to 2-phenylthiazole-4,5-dicarboxylic acid and 2-phenylthiazole-5-carboxylic acid have been described.

CAMBRIDGE, MASSACHUSETTS RECEIVED JUNE 22, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

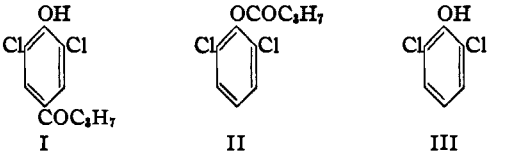
The Effect of Changes in the Acyl Group on the Fries Reaction with Esters of 2,6-Dichlorophenol and 2,6-Dimethylphenol

BY D. S. TARBELL AND PAUL E. FANTA

The Fries reaction of phenyl esters has been employed extensively in the synthesis of acylphenols. Most of the studies[1] of the effect of changes in structure on the reaction have been concerned with substituents in the phenoxyl group, rather than changes in the acyl radical. The present paper deals with the behavior of a series of esters of 2,6-dichloro- and 2,6-dimethylphenol when treated with aluminum chloride, and the results reported may be of some interest in connection with the general question of the Fries reaction.

(1) For a summary of this topic, see Blatt, *Chem. Rev.*, **27**, 429 (1940), and Vol. I of Adams' "Organic Reactions," John Wiley and Sons, New York, N. Y., 1942, pp. 342–369.

This study was suggested by some previous observations[2] in the synthesis of 3,5-dichloro-4-hydroxybutyrophenone (I) from 2,6-dichlorophenyl butyrate (II).



I II III

The ester II, when treated with aluminum chloride in nitrobenzene solution at room temperature

(2) Tarbell and Wilson, THIS JOURNAL, **64**, 1066 (1942).