lization from 4 parts of methyl alcohol, melted at 65–66° (cor.) and rotated $[\alpha]^{20}D$ −8.2° in chloroform (*c*, 1.0).

Anal. Calcd. for $C_{30}H_{28}O_{10}$: C, 65.69; H, 5.15; saponification, 0.1047 g. requires 9.54 cc. 0.1 *N* sodium hydroxide. Found: C, 65.58; H, 5.16; saponification, 0.1047 g. consumed 9.47 cc. 0.1 *N* sodium hydroxide.

2,3-Diacetyl-1,4,5-tribenzoyl-D-arabitol.—This substance was prepared from 2,3-benzylidene-1,4,5-tribenzoyl-D-arabitol and the acid acetylating mixture. It was obtained as a sirup which gave correct carbon, hydrogen and saponification analyses for a diacetyl-tribenzoyl-D-arabitol. The fact that the specific rotation $[\alpha]^{20}D$ of the sirup in chloroform, namely, +19.1°, was different in sign and magnitude from that (−8.2°) of the isomeric 1,3-diacetyl-2,4,5-tribenzoyl-D-arabitol described in the preceding paragraph would seem to exclude the possibility that the tribenzoyl-benzylidene-D-arabitols from which the diacetates are derived are stereoisomers and we accordingly designate them as structural isomers.

Anal. Calcd. for $C_{30}H_{28}O_{10}$: C, 65.69; H, 5.15; saponification, 0.1164 g. requires 10.61 cc. 0.1 *N* sodium hydroxide. Found: C, 65.63; H, 5.24; saponification, 0.1164 g. consumed 10.41 cc. 0.1 *N* sodium hydroxide.

Summary

A new benzylidene-D-arabitol has been obtained by the debenzoylation of the 1,5-dibenzoyl-benzylidene-D-arabitol that is obtained by condensing 1,5-dibenzoyl-D-arabitol with benzaldehyde under the catalytic action of fused zinc chloride. The new acetal has been shown to be 2,3-benzylidene-D-arabitol since it is oxidized by sodium periodate to a sirupy product, presumably 2,3-benzylidene-D-threose, which gives a quantitative yield of D-threose upon acid hydrolysis. It has been shown that the acetal can be converted into a crystalline 1,4,5-tribenzoyl-2,3-benzylidene-D-arabitol which is different from the isomeric crystalline tribenzoyl-benzylidene-D-arabitol obtained by the benzoylation of the known benzylidene-D-arabitol of Steiger and Reichstein; these tribenzoates, upon treatment with an acid acetylating mixture, are transformed into two different isomeric tribenzoyl-diacetyl-D-arabitols. These facts indicate that the two benzylidene-D-arabitols are position rather than stereo isomers and lead to the conclusion that the known benzylidene-D-arabitol of Steiger and Reichstein, which also yields D-threose upon oxidation with lead tetraacetate, is 1,3-benzylidene-D-arabitol. The substance which Emil Fischer prepared is the enantiomorphic 1,3-benzylidene-L-arabitol.

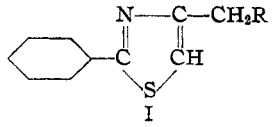
BETHESDA, MARYLAND RECEIVED MAY 27, 1943

[CONTRIBUTION NO. 285 FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

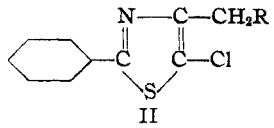
The Conversion of 2-Phenyl-4-chloromethylthiazole to 2-Phenyl-4-hydroxymethyl-5-chlorothiazole

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

In the course of an investigation of certain 2-phenylthiazole-4,5-dicarboxylic acid derivatives, samples of the hitherto unreported 2-phenylthiazole-4-carboxylic acid became necessary. In view of the ready accessibility of 2-phenyl-4-chloromethylthiazole (I, R = Cl) by condensation of equivalent amounts of thiobenzamide and *sym*-dichloroacetone,[2] conversion of this compound to the desired acid by oxidation of the 4-chloromethyl side chain seemed an unequivocal synthesis for the desired acid. By the use of aqueous chromic–sulfuric acid mixture on the corresponding alcohol, the desired 2-phenylthiazole-4-carboxylic acid was finally obtained although in low yield.



I



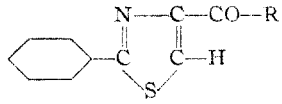
II

During our study of alternative oxidants for this purpose, however, the observation was made that when 2-phenyl-4-chloromethylthiazole was boiled with dilute aqueous nitric acid there could be isolated in 57.5% yield a neutral compound still containing halogen. The work described in this paper proves that this unexpected product is the hitherto unknown 2-phenyl-4-hydroxymethyl-5-chlorothiazole (I, R = OH). This paper also reports that similar treatment of 2-phenylthiazole-4-carboxylic acid chloride yields 2-phenyl-5-chlorothiazole-4-carboxylic acid. Such surprising changes in the location of the halogen substituent do not appear previously to have been observed in the thiazole series.

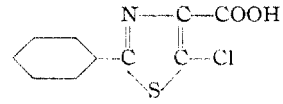
(1) This paper is constructed from part of a dissertation submitted in September, 1942, by Karl Pfister, 3rd, to the Faculty of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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

In view of these observations further authentication of the parent 2-phenyl-4-chloromethylthiazole seemed desirable. Upon alkaline hydrolysis it yielded the corresponding alcohol which was converted to its acetate. Oxidation of the alcohol gave a corresponding monobasic acid, which yielded by the usual methods an acid chloride and amide. By conventional reactions the chlorine atom of the initial chlorothiazole was converted to an iodothiazole and a cyanothiazole, the latter being hydrolyzable to 2-phenylthiazole-



III



IV

4-acetic acid identical with that already on record.[3] All of the new compounds were analyzed with satisfying results.

That the product of the action of hot dilute nitric acid upon 2-phenyl-4-chloromethylthiazole ($C_{10}H_8NClS$) is in fact 2-phenyl-5-chloro-4-hydroxymethylthiazole (II, R = OH) is demonstrated by the following behavior. Its combustion analysis for nitrogen and its molecular weight are in accord with the composition $C_{10}H_8ONClS$, showing that the reaction resulted in the introduction of one additional oxygen atom. This new oxygen atom forms part of a hydroxyl group since the new product (unlike its precursor) readily yielded an acetate and a 3,5-dinitrobenzoate both of which still contained the chlorine atom and gave correct analyses for nitrogen. The molecular weight of the acetate also checked appropriately. Furthermore, upon dichromate oxidation the compound yielded a monobasic acid (IV) still containing a single atom of (unreactive) chlorine.

The single chlorine atom in the new 2-phenyl-5-chloro-4-hydroxymethylthiazole was completely unaffected by hot dilute sodium hydroxide under conditions which readily converted the initial 2-phenyl-4-chloromethylthiazole in excellent yield to the corresponding halogen-free alcohol.

This unreactivity is in sharp contrast to its behavior in the precursor and becomes evidence for nuclear substitution. Such substitution did not occur in the benzene residue, however, for oxidation of the new product with alkaline potassium permanganate gave benzoic acid, and not chlorobenzoic acid. The only remaining location for the chlorine atom consistent with all these circumstances is position 5 of the thiazole nucleus.

The most plausible hypothesis to account for the conversion of 2-phenyl-4-chloromethylthiazole to 2-phenyl-5-chloro-4-hydroxymethylthiazole would appear to be a series of reactions involving first hydrolysis to the carbinol, and subsequent chlorination of the thiazole nucleus of the latter by the hot though extremely dilute hydrochloric/nitric acid mixture. Such a mechanism would appear to account similarly for the observed conversion of 2-phenylthiazole-4-carboxylic acid chloride to 2-phenyl-5-chlorothiazole-4-carboxylic acid. If such is really the mechanism of these changes then in the former case it is necessary to conclude that under the given circumstances chlorination of the thiazole nucleus occurs more readily than oxidation of either the chlorinated or unchlorinated carbinol.

The matter will under present conditions have to await opportunity for further study.

Experimental Section

The melting points in this work were taken with a 360° rod-form melting point thermometer by the Berl–Kullmann copper block method. They are here reported corrected for stem exposure.

2-Phenyl-4-chloromethylthiazole (I, R = Cl).—This compound was prepared by condensation of equivalent quantities of *sym*-dichloroacetone with thiobenzamide in acetone solution essentially according to Hooper and Johnson.[3] The yield of the intermediate "sulfide hydrochloride" was 95%; upon refluxing with concd. hydrochloric acid in acetone this gave by ring closure 80% yield of 2-phenyl-4-chloromethylthiazole hydrochloride; conversion of this salt to the free base was effected in 93.5% yield. The over-all yield was, therefore, 71%, m. p. 48.2–51.2° cor. (recorded,[3] m. p. 51°).

2-Phenyl-4-hydroxymethylthiazole (I, R = OH).—A suspension of 2-phenyl-4-chloromethylthiazole (3.1 g. = 0.015 mole) in 0.1 *N* aqueous sodium hydroxide (300 ml. = 0.030 mole) was refluxed for two and a half hours. From the ice-cold solution there separated after seeding and standing for one hour a crystalline precipitate. After recrystallization from ligroin (150 ml., b. p. 90–100°) there was obtained 2-phenyl-4-hydroxymethylthiazole (2.15 g. = 74.9% yield) of m. p. 66–69° cor.

Anal. Calcd. for $C_{10}H_9ONS$: N, 7.33. Found: N, 6.98, 7.21.

This alcohol was very soluble in methanol, ethanol or ether; slightly soluble in hot water and in hot ligroin (b. p. 90–100°), but insoluble in petroleum ether (b. p. 35–60°). Recrystallization of one gram of material from benzene (5 ml.) and ligroin (20 ml.) gave long, fine colorless needles which had a characteristic springy nature. After filtering, washing with petroleum ether and drying further recrystallization yielded material which gave negative Beilstein

(3) Suter and Johnson, *Rec. trav. chim.*, **49**, 1066 (1930).

and fuchsin aldehyde tests and showed constant melting point of 67.4–68.4° cor.

2-Phenyl-4-acetoxymethylthiazole (I, R = $OCOCH_3$).—2-Phenyl-4-chloromethylthiazole (0.63 g.), after twenty-four-hour refluxing with anhydrous potassium acetate in glacial acetic acid, gave the acetoxy derivative. From petroleum ether the product (0.39 g. = 55.7% yield) formed white needles, m. p. 42–43° cor. The same acetate was also obtained from the alcohol via the acetic anhydride method.

Anal. Calcd. for $C_{12}H_{11}O_2NS$: N, 6.00. Found: N, 5.88, 5.71.

2-Phenylthiazole-4-carboxylic Acid (III, R = OH).—A mixture of 2-phenyl-4-hydroxymethylthiazole (0.38 g. = 0.002 mole) with 2 ml. of chromium trioxide–sulfuric acid solution was triturated at room temperature, finally warmed on a steam-bath, then cooled and diluted with an equal volume of water. Extraction with ether gave upon evaporation of the solvent a solid residue which was largely dissolved by 0.1 *N* sodium hydroxide. After filtering out the trace of residue and acidifying to congo red with concd. hydrochloric acid, needles of crude 2-phenylthiazole-4-carboxylic acid (0.09 g. = 22% yield) with m. p. 162.3–164.3° were deposited. The products from a number of similar runs after recrystallization from a mixture of benzene and ligroin, gave a product with melting point 175–176.5° cor. A mixed melting point of this material with that obtained by pyrolysis of either 2-phenylthiazole-4,5-dicarboxylic acid or its potassium acid salt[4] was undepressed.

Anal. Calcd. for $C_{10}H_7O_2NS$: neut. eq., 205.2. Found: neut. eq., 206.0.

2-Phenylthiazole-4-carboxylic Acid Chloride (III, R = Cl).—This was obtained from the acid (0.62 g.) with warm thionyl chloride (5 ml.). From hot ligroin it separates in small prisms; wt. 0.57 g. (85% yield); m. p. 97.7–98.5° cor.

2-Phenylthiazole-4-carboxylic Acid Amide (III, R = NH_2).—The above acid chloride (0.57 g.) after standing six hours in warm concd. ammonium hydroxide gave 0.50 g. (96% yield) of the corresponding amide, lustrous needles from hot benzene or hot dilute alcohol, m. p. 143.3–143.8° cor.

Anal. Calcd. for $C_{10}H_8ON_2S$: N, 13.7. Found: N, 13.7, 13.9.

2-Phenyl-4-iodomethylthiazole (I, R = I).—Conversion of the 2-phenyl-4-chloromethylthiazole (2.1 g.) to the corresponding iodo compound (2.6 g., 85% yield) was effected with sodium iodide in acetone. Two recrystallizations from ligroin (25 ml.) yielded flat rectangular prisms of m. p. 103.5–104.6° cor.

Anal. Calcd. for $C_{10}H_8NIS$: N, 4.65. Found: N, 4.73, 4.87.

2-Phenyl-4-cyanomethylthiazole (I, R = CN).—2-Phenyl-4-chloromethylthiazole (10.5 g.) on boiling with alcoholic sodium cyanide gave 8.1 g. (81%) of the corresponding nitrile, most of which boiled at 147–148° at 2 mm. Upon standing, this pale yellow distillate crystallized in the receiver to a solid, m. p. 39.1–44.1°. Recrystallization from a mixture of benzene, ligroin and petroleum ether or from a mixture of ether and petroleum ether (1:2) gave either long colorless rods or flat rectangular prisms, m. p. 43.1–44.2° cor.[5]

Anal. Calcd. for $C_{11}H_8N_2S$: N, 14.0. Found: N, 13.83, 13.95.

Hydrolysis of this nitrile with boiling 6 *N* hydrochloric acid for one hour yielded on appropriate cooling, scratching and standing in an ice box crystals of crude 2-phenylthiazole-4-acetic acid hydrochloride (0.49 g. = 96% yield). Recrystallization from 6 *N* hydrochloric acid gave small white prisms, m. p. 203.1–205.1° cor. with evolution of gas, recorded[3] 206–207°.

Part of this hydrochloride (0.38 g.) was dissolved in 10% sodium hydroxide (5 ml.). Because lustrous plates of the sodium salt precipitated an additional 5 ml. of water was added. The resultant solution was shaken with Norit, filtered and acidified with concentrated hydrochloric acid. After cooling in an ice box, the precipitate of fine needles of 2-phenylthiazole-4-acetic acid (0.18 g. = 54.5%) showed m. p. 87.8–89.3° cor. Recrystallization from ether–petroleum ether (1:1) gave long hair-fine needles, m. p. 88.8–89.8° cor.; recorded[3] 90°.

2-Phenyl-4-hydroxymethyl-5-chlorothiazole (II, R = OH).—A solution of 2-phenyl-4-chloromethylthiazole (1.05 g. = 0.005 mole) in concentrated nitric acid (10 ml., sp. gr. 1.42) and water (24 ml.) was refluxed for three hours. After the first twenty minutes nitrous fumes appeared in the condenser. On pouring into cold water (50 ml.) fine white needles (0.65 g. = 57.5% yield) precipitated. These melted at 111.3–113.8° cor. but after recrystallization from hot ligroin and then 50% alcohol the melting point became constant at 116.5–118° cor.

Studies on the influence of various factors showed that less nitric acid or lower concentrations gave the same product but in lower yield. The time of refluxing could be varied over the range two and one-half to three and one-half hours with little effect, but one-half hour of refluxing was entirely inadequate.

The product was slightly soluble in hot water, soluble in alcohol, ether, glacial acetic acid and ligroin (b. p. 90–100°), sparingly soluble in hot petroleum ether (b. p. 35–60°). It was soluble in 6 *N* hydrochloric acid (although precipitated by dilution with water), but insoluble in 0.1 *N* sodium hydroxide.

The usual sodium fusion test for elements gave positive results for nitrogen, sulfur and halogen, the latter being confirmed by a strong Beilstein test. Negative results were obtained with tests for nitro group (neutral zinc dust reduction), carbonyl group (fuchsin aldehyde and phenylhydrazine), or unsaturated linkages (bromine). No reaction could be obtained on attempted reduction with zinc dust and boiling acetic acid or on attempted methylation with ethereal diazomethane. Attempts to effect hydrolysis of the chlorine by two-hour refluxing in 100 parts of 0.1 *N* aqueous sodium hydroxide restored unchanged the original material.

(4) Paper in press.

(5) This boiling point is considerably lower than that (180–185° at 4–5 mm.) reported by Suter and Johnson.[3] However, since our compound solidified to crystals of sharp melting point, gave satisfactory analysis for nitrogen, and upon hydrolysis yielded an acid and acid hydrochloride in complete accord with the corresponding products of Suter and Johnson, there seems to be no doubt as to the structure of the nitrile.

Anal. Calcd. for $C_{10}H_8ONClS$: N, 6.21; mol. wt., 225.5. Found: N, 6.06, 6.18; mol. wt. 231.5 (Rast method).

When 2-phenyl-4-hydroxymethyl-5-chlorothiazole was boiled with dilute alkaline potassium permanganate, however, there was isolated by conventional methods a 29.2% yield of benzoic acid which was identified by the mixed melting point method.

2-Phenyl-4-acetoxymethyl-5-chlorothiazole (II, R = $OCOCH_3$).—This was obtained in 98% yield from the alcohol by refluxing with acetic anhydride. From petroleum ether (b. p. 35–60°) it formed long pale yellow rods, m. p. 63.3–64.1° cor.

Anal. Calcd. for $C_{12}H_{10}O_2NClS$: N, 5.23; mol. wt., 267.7. Found: N, 5.40, 5.50; mol. wt. (Rast method), 259.

Although this material gave a strong Beilstein test for halogen, the latter could not be removed by boiling alcoholic silver nitrate.

2-Phenyl-4-(3,5-dinitrobenzoxy)-methyl-5-chlorothiazole (II, R = $OCOC_6H_3(NO_2)_2$).—This ester was obtained in 93% yield from the alcohol with 3,5-dinitrobenzoyl chloride and pyridine. Recrystallization from acetone or from benzene/ligroin (2:1) gave rosets of very fine pale yellow needles, m. p. 155.1–155.3° cor.

Anal. Calcd. for $C_{17}H_{10}O_6N_3ClS$: N, 10.0. Found: N, 10.2, 10.2.

2-Phenyl-5-chloromethylthiazole-4-carboxylic Acid (IV).—A mixture of 2-phenyl-4-hydroxymethyl-5-chlorothiazole (0.45 g. = 0.002 mole) and chromic acid/sulfuric acid reagent (8 ml. of a solution of 10 g. of chromium trioxide dissolved in a mixture of 8 ml. of concd. sulfuric acid in 60 ml. of water) was worked with a stirring rod for ten minutes. The mixture was then heated on a steam-bath for twenty minutes, cooled, filtered with suction and the residue washed with water. Extraction of this residue with dilute sodium carbonate followed by filtration and acidification of the filtrate with dilute hydrochloric acid gave a yield of 0.20 g. (41.6% theoretical) of 2-phenyl-5-chlorothiazole-4-carboxylic acid, m. p. 194.4–195.5° cor. Further purification from benzene and subsequently from acetone yielded fern-like clusters of very fine lustrous needles, m. p. 198.8–199.3° cor. with evolution of gas.

Anal. Calcd. for $C_{10}H_6O_2NClS$: N, 5.84; neut. eq., 239.7. Found: N, 5.97, 6.05; neut. eq., 239.3.

This same 2-phenyl-5-chlorothiazole-4-carboxylic acid was also obtained in 21% yield from 2-phenylthiazole-4-carboxylic acid chloride (0.22 g. = 0.001 mole) upon refluxing for one hour with a solution of concd. nitric acid (1.0 ml.) in water (2.4 ml.). The product which separated on cooling was recrystallized from a mixture of ligroin (b. p. 90–100°) and benzene, giving 0.05 g. of material which melted at 184.2–189.2° cor. However, it gave a positive Beilstein test and failed to depress the melting point of an authentic sample of 2-phenyl-5-chlorothiazole-4-carboxylic acid prepared with chromic acid from 2-phenyl-4-hydroxymethyl-5-chlorothiazole. From the nitric acid filtrate there was obtained a 54% yield of 2-phenylthiazole-4-carboxylic acid, resulting from simultaneous hydrolysis of the original acid chloride.

Summary

1. Treatment of 2-phenyl-4-chloromethylthiazole and of 2-phenylthiazole-4-carboxylic acid chloride with hot dilute nitric acid has been found to yield 2-phenyl-4-hydroxymethyl-5-chlorothiazole and 2-phenyl-5-chlorothiazole-4-carboxylic acid, respectively. This surprising change in the position of the halogen does not appear previously to have been observed in the thiazole series.

2. A number of 4-substituted derivatives of 2-phenylthiazole have been characterized.

CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 10, 1943

[CONTRIBUTION FROM THE LABORATORY OF HIGH MOLECULAR CHEMISTRY, THE HEBREW UNIVERSITY]

Derivatives of N-Carboxy-α-amino Acid Esters

BY MAX FRANKEL AND EPHRAIM KATCHALSKI

In a preliminary note[1] it was reported that new compounds were obtained from α-amino acid esters and carbon dioxide for which the constitution of N-carboxy-α-amino acid esters was proposed. Subsequently it was found that the new compounds isolated were salts of one molecule of the free N-carboxy-α-amino acid ester with one molecule of the corresponding α-amino acid ester formed according to the following scheme

$$2R{-}CH(NH_2)COOR_1 + CO_2 = R{-}CHNHCOOH_2NCH{-}R \quad (COOR_1 \quad COOR_1)$$

The present paper gives details of the preparation of these new compounds and offers proof of their constitution.

It is further known that carbon dioxide is able to react with ammonia, primary and secondary amines. With ammonia the ammonium salt of carbamic acid H_2NCOOH_4N[2] is formed. With primary or secondary amines the following reaction takes place[3]

$$2RNH_2 + CO_2 = RNHCOOH_2NR$$
$$2R_2NH + CO_2 = R_2NCOOH_2NR_2$$

(1) Frankel, Neufeld and Katchalski, *Nature*, **144**, 832 (1939).

(2) *Cf.* Meyer and Jacobson, "Lehrbuch der organischen Chemie," Vol. I, part 2, 1370 (1913).

(3) Fichter and Becker, *Ber.*, **44**, 3481 (1911).