TABLE IV

VALUES OF THE CONSTANT OF EQUATION (8)

t	ω	t	ω	t	ω
0	−40	25	290	50	700
5	0	30	370	55	780
10	50	35	460	60	860
15	130	40	550		
20	210	45	640		

In Fig. 2, we have plotted ΔH against $\mu^{1/2}$ at 0, 20, 40 and 60°. We have also indicated the limiting slope of the Debye and Hückel theory for the relative partial molal heat content of the ions of water. Our results should approach these slopes in very dilute solution (m = 0.001 or less). Since they cannot be extended to low dilutions with a high accuracy, no attempt has been made to employ the limiting laws for the purpose of extrapolation. As a confirmation of the correct character of the results at higher concentrations, we may compare our data with values of the same quantity determined from calorimetric measurements of the heat of neutralization of hydrochloric acid and sodium hydroxide by Richards and Rowe[9] at 20°. Their results are represented by the dots in Fig. 2. The agreement is within the limit of 40 cal.

(9) Richards and Rowe, THIS JOURNAL, **44**, 684 (1922).

Summary

1. Measurements of the cells

H_2 | NaOH (0.01), NaCl (m) | AgCl | Ag

H_2 | HCl (0.01), NaCl (m) | AgCl | Ag

in aqueous solution from 0 to 60° have been made.

2. From these the value of the ionic activity coefficient product of water in sodium chloride solutions has been computed.

3. It is shown that the logarithm of the ionization in alkaline halide solutions, $\log m_H m_{OH}$, at a given concentration varies nearly linearly with the sum of the reciprocal of the ionic radii. This is only a rough approximation but serves to show that ions of smaller radii cause the greater dissociation of the solvent.

4. The total heat content of the ionization of water and the relative partial molal heat content of the hydrogen and hydroxyl ions in sodium chloride solutions has been determined from 0 to 60°. Good agreement with the calorimetric heat of neutralization is found at 20°.

NEW HAVEN, CONNECTICUT RECEIVED JUNE 18, 1935

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, COLUMBIA UNIVERSITY]

Studies of Crystalline Vitamin B_1. XII. The Sulfur-Containing Moiety

BY H. T. CLARKE AND S. GURIN

The chemical investigation of vitamin B_1 was undertaken in this Laboratory on the invitation of Mr. R. R. Williams, who acquainted us with the sulfite cleavage reaction[1] and kindly furnished a supply of the crystalline vitamin and its basic cleavage product. Early in the course of our work we were able to suggest the presence of a thiazole nucleus in vitamin B_1, and this suggestion was incorporated by Williams in his tentative formula.[2]

In view of the presence of sulfur in the vitamin molecule,[3] our attention was primarily directed toward elucidation of the manner in which this element is combined, by the use of methods recently developed[4] for the study of sulfur in proteins. In the preliminary stages of this investigation, the recognition of the vitamin and its basic cleavage product as derivatives of thiazole was greatly aided by a study of their behavior toward alkaline plumbite and toward bromine water. Striking contrasts were observed between the two compounds with both reagents. When heated with the lead reagent, the vitamin yields lead sulfide relatively rapidly, while the thiazole base gives a visible precipitate only after several hours. Conversely, on treatment with bromine the base is largely oxidized to sulfuric acid under conditions in which the vitamin remains almost entirely unchanged and suffers little or no loss of physiological activity. On the basis of considerations discussed elsewhere,[4] the conclusion was almost inescapable that the sulfur atom in the base is linked to two carbon atoms in a structure of which the carbon groupings are more susceptible to oxidative attack than is the sulfur.

While this study was in progress, it was re-

(1) Williams, Waterman, Keresztesy and Buchman, THIS JOURNAL, **57**, 536 (1935).

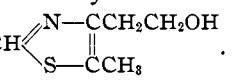
(2) Williams, *ibid.*, **57**, 229 (1935).

(3) Windaus, Tschesche, Ruhkopf, Laquer and Schultz, *Z. physiol. Chem.*, **204**, 123 (1932).

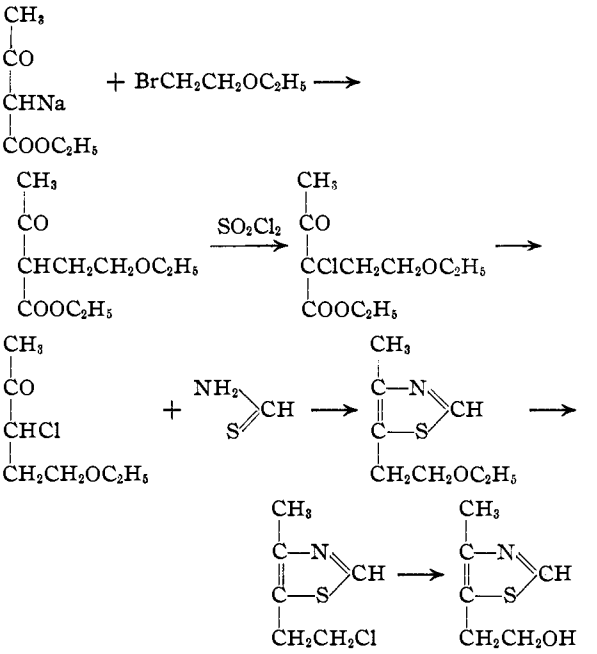
(4) Blumenthal and Clarke, *J. Biol. Chem.*, **110**, 343 (1935).

ported by Windaus, Tschesche and Grewe[5] that the vitamin could be split by the action of nitric acid into two fragments of which one contained the atom of sulfur originally present in the vitamin. Buchman, Williams and Keresztesy[6] then established the close relationship of the basic cleavage product to the acid $C_5H_5O_2NS$ of Windaus by demonstrating the formation of the acid from the base by oxidation with nitric acid.

A striking feature of this acid is its property of yielding lead sulfide on treatment with alkaline plumbite,[5] a clear indication of the bivalent condition of the sulfur. This resistance of sulfur to oxidation by nitric acid is characteristic of the thiazole nucleus; Roubleff[7] found dimethylthiazole-carboxylic acid to be stable toward boiling nitric acid, though other oxidizing agents broke down the ring with formation of sulfuric acid. Among the descriptions of the known methylthiazole-carboxylic acids, that of the 4,5 isomer[8] seemed to agree most closely with the observed properties of the acid prepared from the vitamin. Synthesis of this compound by an application of the simplified procedure of Willstätter and Wirth,[9] followed by a comparison of the methyl esters, established the identity of the two. The absorption spectra of the acids, determined in this Laboratory by Mr. A. E. Ruehle, showed almost exact coincidence.[10]

On oxidation with nitric acid, the basic cleavage product of the vitamin loses one carbon atom,[6] the resulting carboxyl group being derived from a hydroxyethyl group. The base may therefore be assigned the constitution  .

The position of the hydroxyl group was inferred by Buchman, Williams and Keresztesy[6] from the optical inactivity and failure of the iodoform test; it can be rigorously established only by synthesis.[11] This has been accomplished by the accompanying scheme.



The last two products were found to be identical with the corresponding compounds derived from vitamin B. Attempts to employ ethylene chlorohydrin or β-chloroethyl acetate in the first step were unsuccessful. In the second step, reliance was placed on the specific action of sulfuryl chloride, which causes the introduction of chlorine exclusively at the α position in acetoacetic esters.

Reference has been made above to the contrasting behavior of the vitamin and the thiazole cleavage product toward plumbite and bromine. Precisely similar differences obtain with synthetic thiazoles and their quaternary salts; the former yield lead sulfide with difficulty and sulfate readily, the latter yield lead sulfide relatively rapidly[12] and sulfate slowly or not at all. This parallelism supports the idea[1] that in vitamin B_1 the thiazole moiety exists in the form of a quaternary salt.

This view is strengthened by the results obtained by Birch and Harris,[13] Moggridge and Ogston[14] and Williams and Ruehle[15] in electrometric titrations of the vitamin hydrochloride. These indicate reversible reaction with three instead of the anticipated two equivalents of alkali, the extra equivalent reacting at around *p*H 9, as if a pseudo acid were formed. 4-Methyl-

(5) Windaus, Tschesche and Grewe, *Z. physiol. Chem.*, **228**, 27 (1934).

(6) Buchman, Williams and Keresztesy, THIS JOURNAL, **57**, 1849 (1935).

(7) Roubleff, *Ann.*, **259**, 253 (1890).

(8) Wohmann, *ibid.*, **259**, 299 (1890).

(9) Willstätter and Wirth, *Ber.*, **42**, 1908 (1909).

(10) Ruehle, THIS JOURNAL **57**, 1887 (1935).

(11) At the New York Meeting of the Society (April, 1935) Dr. E. R. Buchman announced the synthesis of the base by condensation of brominated acetopropyl alcohol with thioformamide.

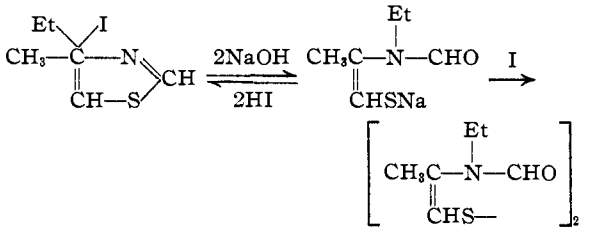
(12) The methylthiazole-carboxylic acid forms an exception to this generalization, in that its response to plumbite is nearly as rapid as that of the quaternary thiazolium salts. This effect is undoubtedly a reflection of the influence of the carboxylic group, which largely determines the instability to alkali in the case of cysteine and its derivatives.

(13) Birch and Harris, *Nature*, **135**, 654 (1935).

(14) Moggridge and Ogston, *Biochem. J.*, **29**, 866 (1935).

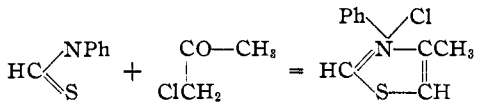
(15) Williams and Ruehle, THIS JOURNAL, **57**, 1856 (1935).

thiazole ethiodide behaves in a strictly analogous fashion.[15] We find that when this substance is treated with two equivalents of alkali in dilute solution, it acquires the ability to reduce one equivalent of iodine. The resulting product, which contains no iodine and is devoid of basic properties, is also formed by the action of air upon an alkaline solution of 4-methylthiazole ethiodide. Mills, Clark and Aeschlimann[16] have shown that alkali reversibly opens the thiazole ring in benzothiazole methiodide, with the formation of a sulfhydryl compound. It seems possible that a similar reaction occurs with the simple quaternary thiazolium base



Alkaline solutions of the vitamin also reduce iodine, but (possibly owing to side reactions attributable to the pyrimidine moiety) in considerably larger proportions. These questions are under investigation.

The reaction between vitamin B_1 and sulfite appears to be a function of the pyrimidine portion of the molecule, for attempts to regenerate thiazole bases from their ethiodides by the action of sulfite were uniformly unsuccessful; nor was cleavage under the same conditions observed with N-phenylthiazolium salts. The readiness with which this type of salt is synthesized



by the action of chloroacetone upon thioacylanilides is worthy of attention. These compounds, like vitamin B_1 and the thiazole ethiodides, respond readily to the alkaline plumbite test but not to that with bromine.

It seems probable that the opening of the ring by the action of alkali upon thiazolium salts is responsible for the readiness with which vitamin B_1 and other quaternary thiazole derivatives yield lead sulfide upon treatment with plumbite. The free thiazole bases presumably exist in the ammonium form to only a minute extent in the presence of alkali, and it is therefore not surprising that they break down extremely slowly under the experimental conditions.

(16) Mills, Clark and Aeschlimann, *J. Chem. Soc.*, **123**, 2353 (1923).

Experimental

Action of Bromine on Vitamin B_1.—The extent to which sulfate is formed from the vitamin hydrochloride by bromine depends largely upon the concentration, as well as upon the temperature.

No sulfate is formed from relatively concentrated solutions. To a solution of 5.685 mg. of vitamin hydrochloride in 0.2 cc. of water bromine vapor was added by aspiration. A yellow, oily precipitate formed; the mixture was heated in boiling water, when the oil dissolved and the bromine escaped. This process was repeated twice. The resulting solution gave no precipitate with barium chloride. On heating with alkaline plumbite a black precipitate formed.

A solution of 3.07 mg. of vitamin hydrochloride in 1 cc. of water containing a visible excess of bromine was allowed to stand at room temperature for two hours, then warmed on the water-bath. On addition of barium chloride, 0.29 mg. of barium sulfate precipitated. This corresponds to 13.4% of the sulfur. In a similar experiment in which the warming was omitted, only 4.9% of the sulfur was converted into sulfate. When, on the other hand, a solution of 6.66 mg. of vitamin hydrochloride in 2.5 cc. of water was heated with excess of bromine for six hours at about 95°, the yield of sulfate was 71%.

Action of Iodine upon Vitamin B_1.—Addition of iodine in potassium iodide to solutions of the vitamin hydrochloride caused, even in very high dilutions, the precipitation of a resinous addition product which is almost insoluble in water or dilute mineral acid, readily soluble in alcohol, but not in chloroform. It dissociates on shaking with water and ether, the iodine passing into the ether; the vitamin was found, with unimpaired physiological activity, in the aqueous phase. No sulfate was produced.

Action of Alkaline Plumbite upon Vitamin B_1.—To 5.62 mg. of the vitamin hydrochloride were added 0.1 cc. of 10% lead acetate solution and 1 cc. of 10% sodium hydroxide. The clear, yellow solution was heated in a sealed tube under nitrogen at 90–95°. Precipitation of lead sulfide became apparent almost immediately, and appeared complete at the end of forty hours. After seventy-two hours the precipitate was collected and oxidized; it yielded 3.28 mg. of barium sulfate (80% of the theoretical amount). In a similar experiment, a 61% yield of sulfate was obtained after three hours' heating.

Action of Bromine upon $C_6H_9ONS \cdot HCl$.—A solution of 5.87 mg. of the hydrochloride of the basic cleavage product of the vitamin in 1 cc. of water was treated with bromine vapor as above. After being allowed to stand for twenty hours at room temperature, barium chloride was added: the resulting barium sulfate weighed 5.60 mg., corresponding to 73.3% of the sulfur. The supernatant solution was again treated with bromine; after twenty-four hours a further 0.23 mg. of barium sulfate had formed, bringing the total yield of sulfate to 76.4% of the theoretical amount. More sulfate was readily obtained from the supernatant by warming with bromine after neutralization with barium hydroxide.

Action of Alkaline Plumbite on C_6H_9ONS.—To 6.00 mg. of the hydrochloride was added 1 cc. of a solution prepared by adding to 10% lead acetate solution twice the volume of 2 *N* sodium hydroxide necessary to form a clear solution. The mixture was heated in a sealed tube at 95°. After sixteen hours a small amount of lead sulfide had precipitated. After one hundred and twelve hours, the contents were acidified with hydrochloric acid and the liberated hydrogen sulfide distilled into a solution of bromine in dilute alkali. The resulting sulfate yielded 2.01 mg. of barium sulfate, corresponding to 25.7% of the sulfur. The volatile base in the residual solution required 1.15 cc. of 0.01 *N* acid, corresponding to 34.5% of the nitrogen; on treatment with mercuric oxide according to the process of Weber and Wilson,[17] the base removed corresponded to 0.65 cc. of 0.01 *N* acid, whence the yield of ammonia was 19.5% of the theoretical. This figure is undoubtedly too low owing to incomplete reaction with the mercuric oxide.

In the ensuing account, the temperatures indicated are uncorrected.

4-Methylthiazole.—This substance, previously prepared by reduction of 4-methyl-2-oxythiazole[18] and by diazotization of 4-methyl-2-aminothiazole,[19] was more conveniently obtained by an adaptation of the method of Willstätter and Wirth.[9] A solution of 5 g. of crude thioformamide[20] in 20 cc. of absolute alcohol was boiled with 8 g. of chloroacetone for one hour under reflux. Some ammonium chloride was filtered off; the filtrate was made distinctly acid with hydrochloric acid and evaporated to dryness. The residue was made alkaline and distilled; the distillate was freed from moisture and ammonia by warming with solid potassium hydroxide. The product, amounting to 3–4 g., distilled at 130°.

On treatment with bromine, a dilute solution of the hydrochloride yielded a yellow oily precipitate, soluble in acetic acid or alcohol; sulfate is rapidly formed in the cold. When heated with alkaline plumbite in a sealed tube at 95°, lead sulfide is formed, but so slowly as to be perceptible only after about four hours.

The ethiodide, prepared by heating the base with twice its volume of ethyl iodide in a sealed tube for forty hours at 95°, crystallizes from absolute alcohol in colorless bars, m. p. 144.5°.

Anal. Calcd. for $C_6H_{10}NSI$: I, 49.77. Found: I, 49.94.

On treatment in aqueous solution with bromine it yields an oily precipitate, but no sulfate is formed in the cold. With plumbite at 95°, lead sulfide forms rapidly, and precipitation appears to be complete after three hours.

On adding platinic chloride to a solution of the base in 0.2 *N* hydrochloric acid, a precipitate separated slowly. This was recrystallized from 0.1 *N* hydrochloric acid in 50% alcohol. The composition of the product, which melted without decomposition at 198°, indicated that the platinichloride had lost the elements of hydrochloric acid.[21]

Anal. Calcd. for $C_5H_{12}N_2S_2Cl_4Pt$: Pt, 36.35; S, 11.95. Found: Pt, 35.90; S, 11.41; after a second recrystallization, Pt, 37.08; S, 12.16.

2,4-Dimethylthiazole.—The base, b. p. 140°, was prepared from thioacetamide and chloroacetone in the same manner as the 4-methylthiazole; the yield was twice as large. The ethiodide[22] melted with decomposition at 212°.

Anal. Calcd. for $C_7H_{12}NSI$: I, 47.18. Found: I, 47.76.

4-Methylthiazole-5-carboxylic Acid.—To a solution of 5 g. of thioformamide in 100 cc. of ether was added 14 g. of ethyl α-chloroacetoacetate.[23] The mixture was allowed to stand for ninety-six hours at 0–5°, during which time 8.5 g. of thiazole carboxylic ester hydrochloride separated in colorless needles. After washing with ether, this was dissolved in water; the solution was made alkaline to thymolphthalein and shaken with five 20-cc. portions of ether. The ethereal solution was dried with sodium sulfate and evaporated. The residue, which crystallized on chilling, was distilled under reduced pressure; b. p. 140° (12 mm.); yield, 5.0 g. of ethyl 4-methylthiazole-5-carboxylate,[24] m. p. 28°.

The ethyl ester was hydrolyzed by boiling a solution of 1.2 g. of it in 25 cc. of alcohol containing 1.4 g. of sodium hydroxide for fifteen minutes under reflux. The alcohol was evaporated under reduced pressure, and the residue, dissolved in 10 cc. of water, was acidified to *p*H 3–4 with concentrated hydrochloric acid. The resulting precipitate was twice recrystallized from 150-cc. portions of boiling water; yield, 0.8 g. of colorless bars which sublimed at 255°.

Anal. Calcd. for $C_6H_5O_2NS$: C, 41.93; H, 3.52; N, 9.78; S, 22.4. Found: C, 42.03; H, 3.59; N, 9.51; S, 22.55.

The methyl ester, prepared by adding ethereal diazomethane to a suspension of the acid in dry ether, and evaporating to dryness, formed needles which melted sharply at 75° without recrystallization.

Anal. Calcd. for $C_6H_7O_2NS$: C, 45.82; H, 4.49; N, 8.92; S, 20.4. Found: C, 45.90; H, 4.52; N, 8.61; S, 20.34.

The melting point was unchanged by admixture of the methyl ester of the acid[6] prepared from vitamin B_1.

As observed by Windaus, Tschesche and Grewe,[5] the acid readily yields lead sulfide and ammonia on heating with alkaline plumbite. At 95°, the precipitation of sulfide was noticeable after less than an hour; after forty-four hours the yield of ammonia was 95% of the theoretical amount. On treating a solution in 0.05 *N* hydrochloric acid with bromine, sulfate is formed very slowly in the cold but rapidly on warming.

Ethyl α-2-Ethoxyethylacetoacetate.—To a solution of 11.5 g. of sodium in 350 cc. of absolute alcohol 65 g. of ethyl acetoacetate was added; to the gently boiling solution there was added 84 g. of ethyl β-bromoethyl ether during one and one-half hours. Heating was continued for ten hours under reflux with stirring. A small amount

(17) Weber and Wilson, *J. Biol. Chem.*, **35**, 385 (1918).
(18) Arapides, *Ann.*, **249**, 23 (1888).
(19) Popp, *ibid.*, **250**, 277 (1888).
(20) Gabriel, *Ber.*, **49**, 1115 (1916).
(21) An analogous change was observed in the case of thiazole by Willstätter and Wirth.[4]
(22) Fisher and Hamer, *J. Chem. Soc.*, 2509 (1930).
(23) Allihn, *Ber.*, **11**, 567 (1878).
(24) Wohmann, *Ann.*, **259**, 298 (1890).

of unreacted alkali was neutralized with alcoholic hydrogen chloride, the salts were precipitated with ether, and the filtrate evaporated under reduced pressure at room temperature. The residue, weighing 80 g., was fractionally distilled and the principal fraction collected at 85–90° (10 mm.). The yield was 56 g. (55% of the theoretical amount) of a colorless liquid.

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.40; H, 8.91. Found: C, 59.20; H, 8.82.

Ethyl α-Chloro-α-2-ethoxyethylacetoacetate.—To 20.2 g. of ethyl α-2-ethoxyethylacetoacetate 15.2 g. of sulfuryl chloride was added, with stirring and ice-cooling, during thirty to forty minutes. Stirring was continued for an hour, while the temperature rose to 20–25°; 50 cc. of the ether was then added, and the mixture gently boiled for an hour to complete the evolution of sulfur dioxide and hydrogen chloride. The ether was distilled off and the residue fractionally distilled *in vacuo*. The first fraction (85–90° (12 mm.)), amounting to 6.7 g., consisted mainly of unchanged starting material; the principal fraction (115–118° (12 mm.)), weighing 15 g., was found by analysis to be not quite pure, but was not improved on further fractionation. It formed a colorless liquid with a pungent odor.

Anal. Calcd. for $C_{10}H_{17}O_4Cl$: Cl, 15.0. Found: Cl, 16.8.

Methyl α-Chloro-γ-ethoxypropyl Ketone.—A solution of 10 g. of the above chlorinated ester in a mixture of 20 cc. of acetic acid and 20 cc. of 15% aqueous sulfuric acid was boiled for four hours under reflux. Ethyl acetate and alcohol were then distilled off under slightly reduced pressure at 30–40°. A mixture of 20 cc. each of acetic acid and 15% sulfuric acid was added, and the whole again boiled for four hours. It was then diluted with an equal volume of water and shaken repeatedly with ether. After removal of moisture with sodium sulfate and evaporation of ether, the residue from the ethereal solution was distilled under reduced pressure; yield, 3.5 g. (50% of the theoretical amount), b. p. 72–73° (12 mm.).

Anal. Calcd. for $C_7H_{13}O_2Cl$: Cl, 21.6. Found: Cl, 22.7.

4-Methyl-5-β-ethoxyethylthiazole.—A mixture of 3.0 g. of the above chloroketone and 2.0 g. of thioformamide was allowed to stand for two days at 0–5° and was then warmed at 100° for one hour; 1.0 g. more of thioformamide was added and the mixture again heated for one hour. It was then dissolved in 10 cc. of water, acidified to Congo Red with concentrated hydrochloric acid, shaken repeatedly with ether, boiled to expel hydrogen sulfide, and made alkaline to thymolphthalein. After expelling the bulk of the ammonia by boiling under reflux, the volatile organic base was distilled out with steam. There was thus obtained 1.5 g. of a pale yellow oil, slightly soluble in water, miscible with alcohol and ether; b. p. 235° (with decomp.) by the capillary tube method of Emich.

No attempt was made to purify the base. It formed with platinic chloride a crystalline, sparingly soluble precipitate, consisting of orange needles, melting with decomposition at 154–155°.

Anal. Calcd. for $C_{16}H_{28}O_2N_2S_2Cl_6Pt$: S, 8.51; Pt, 25.95. Found: S, 8.69; Pt, 25.98.

On recrystallization from hot 50% acetone this changed, by loss of the elements of hydrogen chloride, into a nearly colorless, crystalline substance which melted without decomposition at 144–145°.

Anal. Calcd. for $C_{16}H_{26}O_2N_2S_2Cl_4Pt$: S, 9.42; Pt, 28.74. Found: S, 9.22; Pt, 27.8.

The base, on treatment with ethereal picric acid, yielded a sparingly soluble picrate, which after recrystallization from alcohol melted at 112°.

Anal. Calcd. for $C_{14}H_{16}O_8N_4S$: S, 8.00. Found: S, 8.02.

4-Methyl-5-β-chloroethylthiazole.—A solution of 0.627 g. of the ethoxy base in 5 cc. of concentrated hydrochloric acid was heated in a sealed tube for three hours at 150°. Ethyl chloride and excess hydrochloric acid were evaporated, and the residue was twice recrystallized from a mixture of absolute alcohol and ether; yield, 0.206 g.

Anal. Calcd. for $C_6H_8NSCl\cdot HCl$: N, 7.07; S, 16.16; Cl, 35.85; Cl^-, 17.93. Found: N, 7.32; S, 16.13; Cl, 35.55; Cl^-, 18.07.

The melting point, 127–128°, was unchanged on admixture of a sample (m. p. 130°) of the product originating[6] from vitamin B_1.

On treatment with picric acid in 50% alcohol, the hydrochloride yielded a sparingly soluble picrate, crystallizing in needles from absolute alcohol.

Anal. Calcd. for $C_{12}H_{11}O_7N_4SCl$: S, 8.19; Cl, 9.09. Found: S, 8.33; Cl, 9.04.

Its melting point, 138°, was unchanged on addition of the picrate (m. p. 139°) of the compound secured from the vitamin.

4-Methyl-5-β-hydroxyethylthiazole.—The mother liquor from the above hydrochloride was evaporated to dryness, dissolved in 5 cc. of water, heated in a sealed tube for four hours at 150°, and again evaporated to dryness. The hygroscopic, crystalline residue was recrystallized from a mixture of absolute alcohol with ether or dioxane; yield, 0.223 g.

Anal. Calcd. for $C_6H_9ONS\cdot HCl$: N, 7.80; S, 17.85; Cl, 19.74. Found: N, 7.89; S, 17.70; Cl, 19.90.

In crystalline form it was indistinguishable from the hydrochloride of the basic product from the vitamin.

A picrate separated on the addition of ethereal picric acid to the hydrochloride in alcohol. On recrystallization from absolute alcohol it melted at 162°.

Anal. Calcd. for $C_{12}H_{12}O_8N_4S$: N, 15.00; S, 8.60. Found: N, 15.05; S, 8.74.

The corresponding picrate originating from the vitamin melted at 162–163°; mixed m. p. 162–163°.

Action of Alkali and Iodine upon 4-Methylthiazole Ethiodide.—To a solution of 0.1244 g. of 4-methylthiazole ethiodide (4.88 millimole) in 10 cc. of water was added 13.1 cc. of 0.076 *N* sodium hydroxide. The colorless solution was titrated with 0.10 *N* iodine. On the addition of each drop, a red-brown precipitate formed which rapidly dissolved; 5.00 cc. was required (102% of the theoretical amount).

The solution, on being allowed to stand, deposited needles which after washing with water and recrystallizing from aqueous alcohol melted at 101–102°. Further crops

were obtained by concentrating the mother liquors and recrystallizing; yield, 0.0578 g. The product is sparingly soluble in cold water and dilute hydrochloric acid, readily soluble in alcohol and in ether.

Anal. Calcd. for $C_{12}H_{20}O_2N_2S_2$: N, 9.72; S, 22.22. Found: N, 9.53; S, 22.36.

The same product was obtained by aeration: to a solution of 0.2 g. of the ethiodide in 10 cc. of water, 2 *N* sodium hydroxide was added until the *p*H was 10. A trace of ferrous sulfate was added and air was bubbled through the solution for forty hours. A yield of 0.072 g. of colorless needles, m. p. 101–102°, separated during the aeration; further quantities were obtained by extraction with ether.

2,4-Dimethyl-3-phenylthiazolium Salts.—A mixture of 7.0 g. of thioacetanilide, 5.7 g. of chloroacetone, and 5 cc. of absolute alcohol was boiled gently under reflux for one and one-half hours and then evaporated at 100°. The sirupy residue was repeatedly stirred with ether; the insoluble portion was dissolved in water and decolorized with charcoal. The chloride could not be crystallized; addition of picric acid caused the precipitation of an oil. Platinic chloride yielded a crystalline platinichloride, insoluble in water and in alcohol, which melted with decomposition at 245° after darkening at 240°.

Anal. Calcd. for $C_{22}H_{24}N_2S_2Cl_6Pt$: C, 33.49; H, 3.05; S, 8.13; Pt, 24.77. Found: C, 33.50; H, 2.80; S, 8.35; Pt, 24.86.

On adding potassium iodide in excess to an aqueous solution of the chloride, the iodide crystallized in the form of colorless needles, soluble in water, ethyl alcohol, chloroform, and ethylene chloride, sparingly soluble in butyl alcohol, insoluble in acetone, m. p. 210°.

Anal. Calcd. for $C_{11}H_{12}NSI$: C, 41.77; H, 3.79; N, 4.42; S, 10.09; I, 40.1. Found: C, 41.73; H, 3.49; N, 4.47; S, 10.19; I, 39.76.

No sulfate is formed by the action of bromine upon this substance, either in the cold or on warming for a short time. With alkaline plumbite, lead sulfide is rapidly produced at 95°.

4-Methyl-3-phenylthiazolium Iodide.—A mixture of 2.0 g. of thioformanilide and 5 cc. of chloroacetone was warmed to 50° for a few minutes; the resulting solution was allowed to cool to room temperature during two hours. On addition of ether, the product precipitated as a liquid. This was dissolved in 50 cc. of water, decolorized with charcoal, and treated with 3 g. of potassium iodide. The crystals which formed were recrystallized from water: colorless, rectangular plates, m. p. 241°.

Anal. Calcd. for $C_{10}H_{10}NSI$: S, 10.56; I, 41.9. Found: S, 10.67; I, 41.9.

The properties of this iodide closely resemble those of the 2,4-dimethyl compound.

Summary

1. The acid $C_5H_5O_2NS$ obtained by Windaus and collaborators by the action of nitric acid upon vitamin B_1 is shown to be 4-methylthiazole-5-carboxylic acid.

2. The basic product, obtained by Williams and his colleagues by treating vitamin B_1 with sulfite, is shown to be 4-methyl-5-β-hydroxyethylthiazole. This substance has been synthesized.

3. Experimental evidence is given in support of the view that the thiazole exists in the vitamin in the form of a quaternary salt.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Action of Hydrogen Bromide on the Nitrogen Afterglow

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Rodebush and Ewart[1] reported that the addition of hydrogen bromide to the nitrogen afterglow, produced in moist nitrogen by means of the electrodeless discharge, caused quenching of the nitrogen afterglow with the simultaneous production of a brilliant orange glow at the point where the gases mixed. When this orange light was viewed with a small spectroscope, it appeared to consist of the prominent red and yellow first positive bands of nitrogen, and an orange band which they also attributed to nitrogen. With hydrogen iodide they observed that the nitrogen afterglow was quenched, and that a blue afterglow was produced which extended from the point where the gases mixed to the liquid-air cooled trap of the mercury vapor diffusion pump. This blue afterglow was attributed to iodine. With both hydrogen bromide and hydrogen iodide, considerable quantities of the corresponding ammonium halide were produced in the reaction tube.

It has been suggested, however, that the orange bands might be bromine bands. If this were true, the reactions of hydrogen bromide and hydrogen iodide with active nitrogen would be entirely similar since there was no doubt that the spectrum obtained when hydrogen iodide is added to active nitrogen is due to the iodine molecule. The behavior in the two cases, however, is so different as to cast doubt upon this point of view. The

(1) Ewart and Rodebush, THIS JOURNAL, **56**, 97 (1934).