the ethereal layer with 10% sodium carbonate solution, precipitated by adding hydrochloric acid, and recrystallized from benzene forming needles of m.p. 159° (uncorr.). *Anal.* Calcd. for $C_{10}H_9O_3Cl$: C, 56.48; H, 4.27. Found: C, 56.43; H, 4.61.

The same condensation was carried out with *p*-dichlorobenzene, evolving some quantities of chlorine, which could be recognized with a filter paper moistend with aqueous solution of fluorescein and potassium bromide. The solution was treated as above, and yielded propionic acid of m.p. 159°, showing no depression by fusion with the above acid.

Oxidation of β-(*o*-Chlorobenzoyl)-propionic Acid—A solution of 0.5 g. of β-(*o*-chlorobenzoyl)-propionic acid, 20 cc. of 2% sodium hydroxide, and 2 g. of potassium permanganate was heated at 80° for 3 hours and filtered. The filtrate was evaporated *in vacuo*, acidified with hydrochloric acid, and extracted with ether. The extract was freed from the solvent and the residue was recrystallized from benzene to m.p. 138~139°, undepressed by admixture with *o*-chlorobenzoic acid.

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Yujiro Hara and Sin-ichiro Fujise: The Synthesis of some Thiazole Derivatives from Levulinic Acid.

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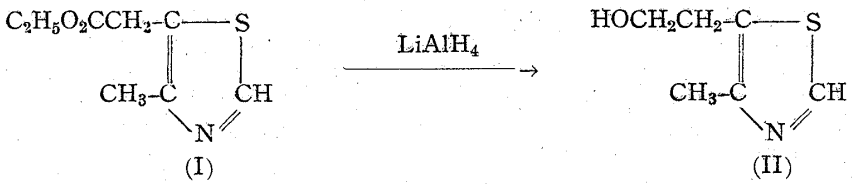
The present series of experiments were performed as the preliminary synthesis of the thiazole fragment of vitamin B_1. After completing this work, we read a similar report[1], but have decided to publish our deta. Ethyl 2-mercapto-4-methylthiazole-5-acetate (V) and some of its derivatives were obtained by the condensation of ethyl β-bromolevulinate and ammonium dithiocarbamate. The thiazole moiety of vitamin B_1 was obtained from ethyl 4-methylthiazole-5-acetate (I) by its reduction with lithium aluminum hydride. The synthesis of some thiazole derivatives from ethyl β-bromolevulinate which was derived from levulinic acid has been reported previously by Cerecedo and Tolpin[2] and Gregory and Wiggins[3]. Cerecedo and Tolpin failed in the attempted reduction of ethyl 4-methylthiazole-5-acetate (I) to obtain the thiazole fragment of vitamin B_1, 4-methyl-5-β-hydroxyethylthiazole (II). However, they suggested the possibility of obtaining the alcohol (II) from the ester (I) by some reductive agent.



In the present series of experiments, reduction of the ester (I) was attempted first by the use of lithium aluminum hydride as the mildest agent. and this proved to be successful. The results obtained thereby are described. The studies are being continued in search of a more economical method for reduction of the ester (I).

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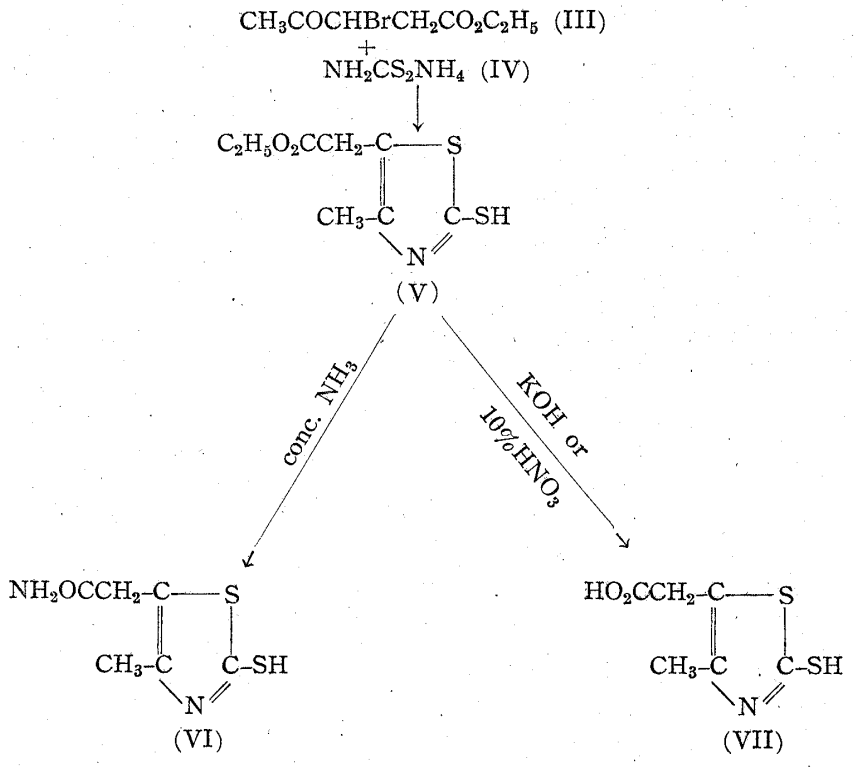
1) Dornow, Petsch: Ber., 86, 1404 (1953).
2) Cerecedo, Tolpin: J. Am. Chem. Soc., 59, 1660 (1937).
3) Gregory, Wiggins: J. Chem. Soc., 1947, 590.



As the next step, ethyl 2-mercapto-4-methylthiazole-5-acetate (V) was obtained by the condensation of ethyl β-bromolevulinate (III) with ammonium dithiocarbamate (IV). On treating the ester (V) with conc. ammonia the amide (VI) was obtained, and on hydrolysis with potassium hydroxide or 10% nitric acid the free acid (VII) was produced.

The authors wish to express their thanks to Prof. Eiji Ochiai of Tokyo University, Dr. Taizo Matsukawa of the Takeda Laboratories in Osaka, Assist. Prof. Taro Yamazaki, and Mr. Sinzaburo Hisida for their assistance in this work. They are also grateful to Sanko Chemical Industries, Ltd. for supplying the levulinic acid used in this work, and to Analysis Division of the Takeda Laboratories and to Miss. T. Kishinami for the elemental analyses of the samples given in this report.

Experimental[4]

Levulinic Acid—Levulinic acid, $b.p_{11\sim12}$ 142° by redistillation, a by-product, produced by the Azinomoto Co., Ltd., which was obtained through Sanko Chemical Industries, Ltd., was used as the starting material.

Reduction of Ethyl 4-Methylthiazole-5-acetate (I) with $LiAlH_4$—The ester (I) was prepared by the method previously reported by Cerecedo and Tolpin[2].

Procedure A: In a 100-cc. three-necked flask equipped with a sealed stirrer, a reflux condenser, and a dropping funnel, a solution of 3.0 g. of the ester (I) in 10 cc. of dry ether was placed and 15 cc. of a $LiAlH_4$ stock solution[5] was added in small portions during 15 min. under ice cooling and vigorous stirring. During the addition, a white precipitate appeared. After the addition, the flask was heated for 1 hr. After being cooled, a small amount of water was slowly added to decompose excess $LiAlH_4$ and then 10% NaOH solution to dissolve the precipitated alumina. The solution was extracted with 200 cc. of ether. The ethereal extract was dried over sodium sulfate and after the removal of ether, the residue was distilled under a reduced pressure and very viscous liquid, $b.p_5$ 123°, was obtained. The yield was about 70% of the theoretical.

On treatment with picric acid in ethanol, a picrate of m.p. 164° was obtained by two recrystallisations from ethanol. The picrate did not depress the melting point by mixed fusion with an authentic sample[6]. *Anal.* Calcd. for $C_{12}H_{12}O_8N_4S$: N, 15.05. Found: N, 15.16.

4) All boiling points and melting points are uncorrected.
5) Org. Reactions, 6, 484.
6) The authentic sample was offered by the Takeda Pharmaceutical Industries, Ltd.

Procedure B: 15 cc. of a $LiAlH_4$ stock solution[5] was placed in the above-mentioned flask. A solution of 3.7 g. (0.02 mole) of the ester (I) in 10 cc. of dry ether was added during 15 min. under ice-cooling and stirring. After the addition, ice cooling was continued for 1 hr., then the mixture was heated for 1 hr. on a steam bath, and cooled again. To the reaction mixture was added a small amount of water and 10% NaOH solution, and the solution extracted with 200 cc. of ether. The water layer was continuously extracted for 10 hrs. with ether by means of the Soxhlet extractor. Both ether extractions were combined and dried over sodium sulfate. After the removal of ether, the residue was distilled under a reduced pressure and a very viscous liquid, $b.p_4$ 120°, 2.65 g., was obtained. The yield was almost quantitative, being 93% of the theoretical. The picrate did not depress the melting point by mixed fusion with an authentic sample.[6] *Anal.* Calcd. for $C_{12}H_{12}O_8N_4S$: N, 15.05. Found: N, 15.11.

Ethyl 2-Mercapto-4-methylthiazole-5-acetate (V)—45 g. (0.2 mole) of ethyl β-bromolevulinate (III) was slowly added to 22 g. (0.2 mole) of ammonium dithiocarbamate (IV) in 45 cc. of absolute ethanol in a flask placed in an ice bath, under vigorous stirring. The flask was removed from the ice bath, allowed to stand at room temperature overnight, and heated for 1 hr. on a steam bath. After cooling, the ammonium bromide was filtered off, and ethanol was distilled off under a reduced pressure. After leaving the syrupy residue in the ice box overnight, the crystals that separated were filtered and washed with ether. The crystals were recrystallized from ethanol, m.p. 111~112°, soluble in ethanol, water, and benzene, and insoluble in ether. Yield, 55% of the theoretical. *Anal.* Calcd. for $C_8H_{11}O_2NS_2$: C, 44.21; H, 5.11; N, 6.45. Found: C, 44.41; H, 4.91; N, 6.46.

2-Mercapto-4-methylthiazole-5-acetamide (VI)—A mixture of 1.1 g. (0.005 mole) of ethyl 2-mercapto-4-methylthiazole-5-acetate (V) with 10 cc. of conc. ammonia was left to stand one day at a room temperature. The amide was recrystallized twice from dil. 80% ethanol to cream colored needles, m.p. 244.5~245° (decomp.), soluble in dioxane, ethanol, and water, insoluble in benzene and ether. The yield was 75% as a crude meterial. *Anal.* Calcd. for $C_6H_8ON_2S_2$: C, 38,26; H, 4.28; N, 14.88. Found: C, 38.38; H, 3.96; N, 14.60.

2-Mercapto-4-methylthiazole-5-acetic Acid (VII)—The ester (V) (2.2 g., 0.01 mole) was refluxed on a water bath for 3 hrs. with 180 cc. of ethanol containing 1 g. of KOH. The alcohol was distilled off under reduced pressure, the residue was dissolved in 5 cc. of water, and acidified with about 4 cc. of 6*N* hydrochloric acid. The crude acid was separated and washed with ether.

After two recrystallisations from ethanol, needle crystals, m.p. 208.5~209° (decomp.), were obtained, soluble in hot water and hot ethanol, insoluble in cold water and cold ethanol. The yield was 68% of the theoretical. *Anal.* Calcd. for $C_6H_7O_2NS_2$: C, 38.06; H, 3.73; N, 7.40. Found: C, 38.21; H, 3.63; N, 7.24.

A solution of 4.4 g. (0.02 mole) of the ester (V) in 65 cc. of 10% nitric acid was heated for 20 min. at 95~100° on a water bath. After cooling, 3.4 g. of needle crystals were separated and recrystallised twice from ethanol, m.p. 208.5~209° (decomp.), yield, 83%, soluble in hot water and hot ethanol, insoluble in cold water and cold ethanol. The crystals did not depress the melting point by admixture with the one obtained by the treatment with KOH. *Anal.* Calcd. for $C_6H_7O_2NS_2$: C, 38.06; H, 3.73; N, 7.40. Found: C, 37.81; H, 3.47; N, 7.24.

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