[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FORDHAM UNIVERSITY]

Studies on Thiazoles. I. 4-Methylthiazole-5-acetic Acid and Some of its Derivatives

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The structure of the sulfur-containing moiety of vitamin B_1 was elucidated by Clarke and Gurin.[1] The correctness of their proof has been established by the syntheses of the vitamin, reported by Cline, Williams and Finkelstein[2] and by Todd and Bergel.[3] In connection with experiments along similar lines that are being carried out in this Laboratory, a study of 4-methylthiazole-5-acetic acid and some of its derivatives suggested itself. We chose this acid because its ethyl ester can be obtained easily in the form of the hydrobromide or hydrochloride by the condensation of ethyl β-bromolevulinate or ethyl β-chlorolevulinate, respectively, with thioformamide. The hydrobromide of the ester gave on treatment with ammonia the free ester. On hydrolysis, the ester yielded the free acid. From the ester we also prepared the amide and the hydrazide.

Our attempts to find a convenient method for the direct reduction of ethyl 4-methylthiazole-5-acetate to the corresponding alcohol, which would have given us the sulfur-containing moiety of vitamin B_1, were unsuccessful. The evidence available at this time indicates that some methods of reduction[4] decompose the compound, while others[5] leave it unchanged. The reduction apparently took place in one experiment in which the hydrobromide of the ester was treated with sodium in the presence of absolute alcohol. The yield, however, was extremely small and was sufficient only for the preparation of a few milligrams of the picrate.

Picrates of all the compounds mentioned, except that of 4-methylthiazole-5-acetic acid, were prepared. They were found to be quite useful for identification purposes.

(1) Clarke and Gurin, THIS JOURNAL, **57**, 1876 (1935).

(2) Cline, Williams and Finkelstein, *ibid.*, **59**, 1052 (1937).

(3) Todd and Bergel, *J. Chem. Soc.*, 364 (1937).

(4) The methods used were: reduction (a) with sodium in the presence of absolute ethyl alcohol (or methyl alcohol) (Bouveault and Blanc); (b) with sodium in the presence of moist ether [Wislicenus and Hentschel, *Ann.*, **275**, 322 (1893)]; (c) with sodium in the presence of absolute alcohol (methyl and ethyl) saturated with hydrogen chloride; (d) with 3% sodium amalgam in the presence of (1) glacial acetic acid, (2) absolute ethyl alcohol, (3) ethyl alcohol and water, (4) hydrobromic acid.

(5) Reduction with sodium in the presence of (a) acetic acid and sodium acetate [Prins, *Rec. trav. chim.*, **42**, 1050 (1923)]; (b) glacial acetic acid and absolute alcohol (ethyl and methyl); (c) glacial acetic acid.

After completion of our work, we read a British Patent[6] in which the preparation of several compounds that had been synthesized independently in this Laboratory is described. We have decided to publish our data at the present time, because one of us (J. G. T.) will not be able to continue this phase of the investigation.

Experimental Part

Ethyl 4-Methylthiazole-5-acetate (I).—Thioformamide[7] (66.8 g.) was dissolved in 30 cc. of absolute ethyl alcohol. To this solution 155 g. of ethyl β-bromolevulinate, prepared according to Conrad and Guthzeit,[8] was added slowly, the temperature of the reaction mixture being maintained between −5 and 15°. After standing in the ice box overnight, the mixture was kept for one day at room temperature. The crystalline precipitate was then filtered and washed with ether. From the mother liquor an additional amount of the substance was recovered. The crystals were recrystallized from ethyl alcohol, m. p. 168°; yield 71%.

Anal. Calcd. for $C_8H_{12}O_2NSBr$: C, 36.09; H, 4.55; N, 5.27; S, 12.05. Found: C, 35.95; H, 4.66; N, 5.29; S, 12.02.

When ethyl β-chlorolevulinate[8] was used instead of the brominated compound, the reaction was slower. The hydrochloride resembled in appearance the hydrobromide and melted at 153°.

The hydrobromide was dissolved in a small amount of water and made slightly alkaline with ammonia, care being taken not to use an excess of the base. The liberated ester was extracted with ether, dried with sodium sulfate, and distilled. The fraction boiling between 107 and 112° at 3 mm. was collected. The ester is soluble in alcohol, ether, acetic acid and benzene.

Anal. Calcd. for $C_8H_{11}O_2NS$: C, 51.89; H, 5.99; N, 7.57; S, 17.30. Found: C, 51.65; H, 6.16; N, 7.54; S, 17.46.

The ester was treated with picric acid in alcohol solution, and on standing the crystalline picrate was obtained which, after recrystallization from alcohol, melted at 130°.

Anal. Calcd. for $C_{14}H_{14}O_9N_4S$: C, 40.58; H, 3.38;

(6) British Patent 456,751, Nov. 13, 1936. An abstract of this patent appeared in *C. A.*, **31**, 2232 (1937). A photoprint was received from the U. S. Patent Office June 9, 1937.

(7) The crude product was used. For the preparation of large quantities of thioformamide it is advantageous and economical to use technical phosphorus pentasulfide and to combine the methods of Willstätter and Wirth, *Ber.*, **42**, 1908 (1909), and of Gabriel, *Ber.*, **49**, 1150 (1916) as follows. The formamide is covered with dry ether and freshly powdered phosphorus pentasulfide is added in several portions under cooling. The reaction flask is left overnight in cold water and is then shaken for fifteen hours.

(8) Conrad and Guthzeit, *Ber.*, **17**, 2285 (1884).

N, 13.53; S, 7.74. Found: C, 40.67; H, 3.70; N, 13.28; S, 7.90.

4-Methylthiazole-5-acetic Acid (II).—The ester (I) (2.6 g.) was heated on the steam-bath for twenty minutes with 95 cc. of ethyl alcohol containing twice the calculated amount of potassium hydroxide. The alcohol was then evaporated under reduced pressure, the residue dissolved in a small amount of water and acidified with hydrochloric acid to a *p*H ranging from 5.3 to 4.8. The acid separated in small crystals which on recrystallization from hot water acquired the form of long cream-colored needles melting at 189°; yield 59%.

Anal. Calcd. for $C_6H_7O_2NS$: C, 45.82; H, 4.49; N, 8.92; S, 20.40. Found: C, 45.74; H, 4.76; N, 8.90; S, 20.32.

Methyl 4-Methylthiazole-5-acetate (III).—The acid (II) (0.8 g.) was dissolved in 10 cc. of absolute methyl alcohol and treated with about 0.5 cc. of absolute methyl alcohol saturated with hydrogen chloride. After warming the solution on the steam-bath for twenty-four hours, the solvent was distilled off. The residue was dissolved in 15 cc. of ether, and the solution, after neutralization with sodium bicarbonate, refluxed for two hours. The solution was then filtered, and the ether evaporated off. The residue boiled at 111° at 18 mm.; yield 67%. The properties of this ester resemble those of the ethyl ester.

Anal. Calcd. for $C_7H_9O_2NS$: C, 49.07; H, 5.30; N, 8.19; S, 18.73. Found: C, 48.82; H, 5.32; N, 8.23; S, 18.72.

An alcoholic solution of the ester gave with picric acid the picrate; after recrystallization from alcohol, m. p. 145°.

Anal. Calcd. for $C_{13}H_{12}O_9N_4S$: N, 14.00. Found: N, 14.16, 14.10.

4-Methylthiazole-5-acetamide (IV).—The ester (I) (23.5 g.) was shaken with an excess of concentrated ammonia for one hour and fifteen minutes, whereupon the ester dissolved. On standing, crystals of the amide separated out. The solution was evaporated on the steam-bath under reduced pressure, the resultant residue redissolved in concentrated ammonia and evaporated once more to dryness. After recrystallizing the residue twice from dioxane, the amide was obtained as silky white needles melting at 136°, in a yield of 73%.

Anal. Calcd. for $C_6H_8ON_2S$: C, 46.11; H, 5.16; N, 17.94; S, 20.53. Found: C, 46.17; H, 5.17; N, 17.95; S, 20.68.

Treatment of the amide with alcoholic picric acid gave a picrate crystallizing from alcohol in rhombic plates, m. p. 203°.

Anal. Calcd. for $C_{12}H_{11}O_8N_5S$: N, 18.18. Found: N, 18.10.

4-Methylthiazole-5-acethydrazide (V).—A solution of 5.33 g. of the ester (I) in 10 cc. of absolute ethyl alcohol was treated with 2.92 g. of 50% hydrazine hydrate. After refluxing for four hours, the solution was evaporated slowly on the steam-bath. After washing the residue with benzene, crude crystals separated in the cold. The yield of this crude material was 81%. The hydrazide is soluble in water and alcohol, sparingly soluble in benzene and petroleum ether. It separated from benzene in long colorless prisms, m. p. 111°.

Anal. Calcd. for $C_6H_9ON_3S$: C, 42.07; H, 5.30; N, 24.56; S, 18.73. Found: C, 42.01; H, 5.38; N, 24.62; S, 18.64.

An alcoholic solution of the hydrazide yielded with picric acid a picrate which separated in very fine prisms and melted with decomposition at 258°.

Anal. Calcd. for $C_{12}H_{12}O_8N_6S$: N, 21.00. Found: N, 20.94.

Reduction of Ethyl 4-Methylthiazole-5-acetate.—A solution of 3.195 g. of the ester (I) hydrobromide in 60 cc. of absolute ethyl alcohol was added dropwise to 2.563 g. of sodium under anhydrous conditions. When all the sodium had gone into solution, water was added, the alcohol distilled off, and the remaining solution extracted with ether. After evaporation of the ether, a very small amount of residue was obtained. It was taken up in ether once more and treated with alcoholic picric acid. On standing in the ice-box for two days, a picrate separated, m. p. 164°.

Anal. Calcd. for $C_{12}H_{12}O_8N_4S$: N, 15.05. Found: N, 14.60.

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Summary

The preparation of 4-methylthiazole-5-acetic acid and some of its derivatives has been described.

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