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Preparation of Thiamine from Dihydrothiamine

Three methods have already been reported on the synthesis of dihydrothiamine by Karrer, *et al.*,[1] Iwatsu,[2] and Hennessy, *et al.*[3] Among these the method of Iwatsu is the most noteworthy because it not only comprises an interesting reaction, namely condensation of 4-amino-5-aminomethyl-2-methylpyrimidine, 3-acetyl-3-mercaptopropanol, and formaldehyde, but also requires neither thiamine nor its derivative as the other methods do and the reaction proceeds very smoothly, giving a good result. In the course of his study, Iwatsu also found that there are three isomers of dihydrothiamine, i.e. normal, iso, and pseudo, and each of their structures was later established.[4] Since dihydrothiamine is readily synthesized, a new practical method for obtaining thiamine will be offered if it is produced by the oxidation of dihydrothiamine. In fact, Karrer, *et al.*, produced thiamine by oxidizing dihydrothiamine with iodine and Iwatsu by oxidizing with ferric chloride, sodium nitroprusside, or potassium ferricyanide. These reactions, however, present a difficulty because it is difficult to separate the resulting thiamine from the coexisting inorganic substances. In the present work, the oxidation was attempted with oxygen (or air) as shown below to eliminate the above shortcomings.

An amount of 1.3 g. of activated carbon was added to a solution of 3.3 g. *n*-dihydrothiamine in 70 cc. of 2% hydrochloric acid and oxygen was introduced into the mixture at room temperature with shaking. When the theoretical amount of oxygen was absorbed in several hours, the active carbon was filtered off and 99% ethanol was added to the concentrated filtrate, whereupon the resulting thiamine separated out in crystalline form; yield, 3 g. The product was recrystallized from ethanol in colorless needles, m.p. 250°(decomp.)(*Anal.* Calcd. for $C_{12}H_{18}ONCl_2S$: C, 42.73; H, 5.34; N, 16.62. Found : C, 42.59; H, 5.64; N, 16.39). This reaction could be applied also to iso- and pseudo-dihydrothiamine. In the absence of activated carbon, the reaction proceeded very slowly and was incomplete, and activated carbon could not be substituted by alumina or activated clay.

As mentioned above, the reaction was found to be adaptable as a new method for the preparation of thiamine and the fact that thiamine can be produced under such mild conditions is very interesting when considered together with the problems of thiamine biosynthesis.

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