

ALIEN PROPERTY CUSTODIAN

PROCESS FOR THE PREPARATION OF VITAMINS OF THE TYPE B₁

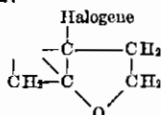
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The present invention relates to a new useful process for the preparation of Vitamin B₁ and of similarly built compounds. This process consists in subjecting 2-methyl-2,3-dihalogene-tetrahydrofuranes to the action of reagents generally used for splitting off haloic acids and in subjecting the product, thus obtained, i. e. the unsaturated—with the elements of 1 mol. water poorer—derivative of 2-methyl-2-oxy-3-halogene-tetrahydrofurane to the action of 2-alkyl-4-amino-5-(thioformamido-alkyl)-pyrimidine.

An advantageous form of this process consists in subjecting 2-methyl-2,3-dichloro-tetrahydrofurane to the action of reagents generally used for splitting off hydrochloric acid and in subjecting the product, thus obtained, i. e. the unsaturated—with the elements of 1 mol. water poorer—derivative of 2-methyl-2-oxy-3-chloro-tetrahydrofurane to the action of 2-methyl-4-amino-5-(thioformamido-methyl)-pyrimidine.

The unsaturated—with the elements of 1 mol. water poorer—derivatives of the 2-methyl-2-oxy-3-halogene-tetrahydrofurane, which are intermediary products in the present process, have the following formula:



in which two vicinals of the three free valences form a double bound while the third free valence is saturated with hydrogen, to the action of 2-methyl-4-amino-5-(thioformamido-methyl) pyrimidine.

These products can be obtained, as already mentioned, by splitting off haloic acid from the 2-methyl-2,3-dihalogene-tetrahydrofurane, such as 2-methyl-2,3-dichloro-tetrahydrofurane, or directly from aceto-chloro-propyl alcohol as well by the action of phosphorous halogenides, such as phosphorous oxychloride, or phosphorous trichloride and by treating the reaction mixture with agents, such as pyridine, capable of splitting off haloic acid.

The preparation of 2-methyl-2,3-dihalogene-compounds is described in details in our co-pending patent application Ser. No. 390,124, filed April 24, 1941. Therefore, we describe in the following the preparation of the starting materials only in brief outlines. So e. g. 50 g of aceto-chloro-propyl alcohol or its ether described by Stevens and Stein (Journ. Amer. Chem. Soc., 1940, page 1046), which boils in vacuo of 1 mm Hg pressure at 111-112°C, are saturated undercooling in a

frigorific mixture with hydrogen chloride gas, then anhydrous sodium sulphate is added to the reaction mixture, the oil is decanted and distilled in a vacuo of 2 mm Hg. At about 45° about 50 g of 2-methyl-2,3-dichloro-tetrahydrofurane distille. Out of this product the unsaturated—with the elements of 1 mol. water poorer—derivative of 2-methyl-2-oxy-3-chloro-tetrahydrofurane can be obtained in the following manner:

To 15 g of 2-methyl-2,3-dichloro-tetrahydrofurane the calculated amount of dry pyridine is added, whereupon a white crystalline mass of salt is formed, which is heated for about ½ hour (at an inside temperature of about 110-130° C). Two layers separate. After cooling the upper layer is decanted, or separated in another way. The oil is distilled at a pressure of 50 mm Hg. At about 50° 7-8 g of the unsaturated—with the elements of 1 mol. water poorer—derivative of 2-methyl-2-oxy-3-chloro-tetrahydrofurane are obtained.

The splitting off the haloic acid can also be preferably effected by salts of organic acids:

15.5 g of 2-methyl-2,3-dichloro-tetrahydrofurane and 14.4 g of dry sodium benzoate are mixed. A development of heat can be observed. The mixture is stirred while cooling. When the sodium benzoate has gone into solution the mixture is kept for an hour in a water bath of about 60° C. Then the reaction mixture is distilled at a pressure of about 50 mm Hg in an oil bath. The recipient is kept in a frigorific mixture. During the distillation the temperature of the oil bath is slowly elevated until 120° C is reached. The distillation weighs about 10.2 g and distilles at about 40 mm Hg pressure at about 49-50° C. The chlor content of the product is 29.8%.

The unsaturated furane derivative can also be prepared from dihalogene furane derivatives, obtained in another way. For instance one may transform acetochloro-propyl alcohol with thionylchloride into 2,3-dichloro-furane derivative and split off from this hydrogen chloride. But one may also proceed by mixing, under cooling, 3 mol. of aceto-chloro-propyl alcohol with cca 1-1.5 mol. of phosphorous oxychloride or phosphorous trichloride (preferably in chloroforme as medium), then by adding a quantity of pyridine equivalent to the chlor content of the phosphorous halogenide and by heating the reaction mixture. The chloroforme is distilled off and the unsaturated—with the elements of 1 mol. water poorer—derivative of 2-methyl-2-oxy-3-chloro-tetrahydrofurane is separated from the residue either directly by distillation or by extracting with a solvent.

Details of the preparation of Vitamin B₁ or of similarly built compounds can be found in the following:

10 g of 2-methyl-4-amino-5-(thioformamido-methyl)-pyrimidine, 14 g of the unsaturated—
with the elements of 1 mol. water poorer—deriva- 5
tive of 2-methyl-2-oxy-3-chloro-tetrahydrofu-
rane and 10 ccm formic acid of about 91% are
heated for 40 hours at 50° in an incubator. Then
100 ccm of abs. alcohol and 10 ccm of abs. alco- 10
hol containing 30% of hydrogen chloride gas
are added to the light brown reaction mixture.
After standing for some hours 9–10 g of Vitamin
B₁ crystallize in form of white crystalline powder.

It melts at about 243–245°. Its content of chlor
is 20%.

One proceeds in the same manner when start-
ing from the corresponding bromo-tetrahydro-
furane derivative condensing this with 2-methyl-
4-amino-5-(thioformamido - methyl) -pyrimidine
or by starting from the chloro-tetrahydrofurane
derivative condensing this with 2-methyl-4-
amino-5-(thioformamido-ethyl)-pyrimidine.

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