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PROCESS FOR THE PREPARATION OF VITAMIN B_1

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This invention relates to a new and useful process for the preparation of Vitamin B_1.

We have found that Vitamin B_1 can be manufactured in excellent yield by subjecting a member selected from the group: aceto-halogeno-butyrolacetone, aceto-halogeno-propyl alcohol, 2-methyl-2-oxy-3-halogeno-tetrahydrofurane, γ-aceto-γ-halogeno-propyl ether of the 2-methyl-2-oxy-3-halogeno-tetrahydrofurane to the action of formic acid or by subjecting 2-methyl-2,3-di-halogeno-tetrahydrofurane to the action of salts of formic acid and of formic acid and by condensing the obtained 2-methyl-2-formyloxy-3-halogeno-tetrahydrofurane with 2-methyl-4-amino-5-(thioformamido-methyl)-pyrimidine.

The 2-methyl-2-formyloxy-3-halogeno-tetrahydrofurane, unknown until now, is able to furnish Vitamin B_1 in an excellent yield and in an excellent degree of purity. The preparation of Vitamin B_1 is preferably carried out in formic acid as reaction medium. For this purpose preferably formic acid of about 90–100% is used. The condensation of the two reaction components is preferably carried out at a temperature of about 50–70°, thus, e. g. it is advantageous to carry out the reaction by heating for 40 hours at 50°.

The working up of the reaction mixture can be carried out by adding abs. alcohol and abs. alcohol containing hydrogene chloride gas and by separating after standing the Vitamin-B_1-hydrochloride by filtration. The obtained Vitamin B_1 is already in this state white and the yield is excellent. A purification through the picrate or picrolonate is unnecessary.

The preparation of the furane derivative used here for the preparation of Vitamin B_1 can be carried out in different ways. Thus, e. g. by treating 2-methyl-2,3-dichloro-tetrahydrofurane, which has been described in our U. S. co-pending application No. 390,124, with the calculated amount of anhydrous potassium formiate. This product can also be obtained by heating the compound, which has been supposed to be, until now, acetochloropropyl alcohol and the constitution formula of which has been discovered by Stevens and Stein (see Journal of the American Chemical Society, volume 62, page 1045), with formic acid of about 100%. This product can also be obtained by boiling for few hours acetochloro-butyrolacetone with 1 molecule of water and with an excess of formic acid of 100% and by obtaining the product by fractionation.

The following examples illustrate the methods of carrying out the present invention.

Examples

1. To 15.5 grams of 2-methyl-2,3-dichloro-tetrahydrofurane (see preparation of this compound in the U. S. co-pending application No. 390,124) 20 ccs of formic acid of about 100% and 9 grams of anhydrous pulverized potassium formiate are added. Reaction takes place and the heat of reaction is eliminated by cooling. In the meantime the reaction mixture gets hot up to about 60°. The reaction mixture is kept for half an hour on the boiling water bath during which time it gets slightly brown. The reaction mixture is cooled. 50 ccs of dry ether are added, the precipitated mineral salt is filtered off and the ether solution is evaporated to dryness, then the formic acid is distilled off at 20 mm of Hg. The residual oil is distilled in vacuo at about 1.5 mm of Hg. About 12 grams of 2-methyl-2-formyloxy-3-chloro-tetrahydrofurane distil, which boils in this vacuo at 86°. The product forms a colourless liquid, the specific weight of which is at 15° about 1.208 and which contains 21.8% of chlor.

5 ccs of the above product, 5 ccs of formic acid of about 99% and 5 grams of 2-methyl-4-amino-5-(thioformamido-methyl)-pyrimidine are kept for 24 hours at 50° in an incubator. To the slightly brown solution about 45 ccs of abs. alcohol and 5 ccs of abs. alcohol containing of about 20% of hydrochloric acid gas are added, the solution is boiled, then cooled. After standing for few hours the Vitamin B_1 crystals are filtered off and washed with abs. alcohol. One obtains 6 grams of Vitamin B_1, which is already in this state white and melts under decomposition at about 246° and contains 19.8% of chlor.

2. 13.6 grams of acetochloro-propyl alcohol, or its ether described by Stevens and Stein respectively (see Journal of the American Chemical Society, volume 62, page 1046, right column, first paragraph of the experimental part) are boiled with 16 ccs of anhydrous formic acid for 3 hours under reflux, then the formic acid is distilled off. The 2-methyl-2-formyloxy-3-chloro-tetrahydrofurane can be obtained from the residue by fractionation. It is more preferable to heat the residue once more with anhydrous formic acid, then to eliminate the formic acid and to fractionate the residue in vacuo. One obtains 10–12 grams of 2-methyl-2-formyloxy-3-chlorotetrahydrofurane.

12 ccs of the above product are kept with 10 ccs of formic acid of about 90% and 10 grams of 2-methyl-4-amino-5-(thioformamido-methyl)-pyrimidine for 40 hours at 50° in an incubator. To the reaction mixture 60 ccs abs. alcohol and

10 ccs of abs. alcohol containing about 20% of hydrochloric acid gas are added. One obtains a biscous crystal cake consisting of very fine crystals. It is heated, then cooled with ice-water and filtered, after standing, by suction. One obtains 9 grams of white Vitamin B_1 melting at 236° with decomposition.

3. To 16.2 grams of acetochloro-butyrolactone 1.8 ccs of water and 16–17 ccs of formic acid of about 100% are added and boiled for about 5 hours under reflux. Afterwards the formic acid is distilled off at reduced pressure and the dark coloured residue is distilled in vacuo at about 1.5 mm of Hg. One obtains 11–12 grams of 2-methyl-2-formyloxy-3-chloro - tetrahydrofurane which contains 22% of chlor.

10–12 ccs of the above product are kept with 10 ccs of formic acid of about 90% and with 10 grams of 2-methyl-4-amino-5-(thioformamidomethyl)-pyrimidine for 40 hours at 50° in an incubator. The working-up of the reaction mixture can be carried out by methods given in the examples 1 or 2. One obtains 10.7 grams of Vitamin B_1 which is already in this state white and which melts at 236°.

The experimental conditions given in the foregoing examples can be varied in numerous ways. E. g. one may carry out the preparation of Vitamin B_1 at higher temperature, e. g. at 70°, but in this case the time of heating is to be reduced.

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