THE SYNTHESIS OF THE SODIUM SALT OF β-OXYBUTYRIC ACID FROM THE ACETOACETIC ESTER

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Existing methods of preparing β-oxybutyric acid and its salts [2,3,5-7] do not satisfy the requirements for biochemical investigations. A disadvantage is that they require for their preparation substances which are in short supply, or else that they give very low yields. In some cases [7] the preparation of β-oxybutyric acid obtained contained toxic impurities which made it impossible to use it in biochemical experiments. By the method described below, which is simple, quite a good yield of sodium oxybutyrate is obtained, and the material from which it is produced (acetoacetic ester is readily obtainable. From 25 g of acetoacetic ester, more than 7 g of a 100% pure preparation of sodium oxybutyrate may be obtained. The purity of the preparation was tested by the method of Klingmüller and his collaborators [4]. The preparation was tested by oxidative phosphorylation of homogenates of rabbit heart muscle, and on the mitochondria of the rat liver. The principle of the method is to reduce acetoacetic ester by means of an amalgam of aluminum in moist ethyl sulfate [1] and then to saponify the ethyl ester of β-oxybutyric acid so obtained to form sodium β-oxybutyrate.

The following reagents were used: 1) commercial acetoacetic ester, redistilled in vacuum; 2) metallic aluminium turnings; 3) a 2% solution of mercuric chloride; 4) moist ethyl sulfate (commercial ethyl sulfate is washed twice with water in a separating funnel, then an equal volume of water is added, and after 15 minutes the ethyl sulfate is separated from the water, and it is then ready for use); 5) a 12% caustic soda solution; 6) absolute ethyl alcohol.

I. Preparing the aluminium amalgam. Thirty-five grams aluminium turnings are added to 200 ml of 12% sodium hydroxide, and hydrogen is liberated. After a few minutes, when the hydrogen is being evolved vigorously, the sodium hydroxide is poured off, and the aluminium turnings are washed three times in 200 ml of distilled water. Two hundred ml of a 2% solution of mercuric chloride is now added to the aluminium turnings which have been cleaned in this way. Hydrogen is then liberated, and the turnings become shiny. One or two minutes after the amalgam has formed, the turnings are quickly washed in 400-600 ml of water, when the mixture becomes hot and the hydrogen is rapidly evolved. The amalgam is prepared immediately before it is required.

II. Preparation of the ethyl ester of β-oxybutyric acid. The following substances are now added to a round-bottomed flask fitted with a reflux condenser: 25 g of acetoacetic ester, the whole of the freshly prepared amount of aluminium amalgam, and 250 ml of moist ethyl sulfate; the mixture is left to stand in a water bath at room temperature for 4-6 hours (if the flask becomes hot, it must be cooled in ice water). As the reaction proceeds, the contents of the flask increase considerably in volume, so that for some time after the onset of the reaction there may be some interference with the liberation of hydrogen. If so, up to 400 ml of moist ethyl sulfate is added. The mixture is then left overnight (if hydrogen is evolved rapidly, it is stood in a bath with ice).

On the next day, the contents of the flask are filtered and repeatedly washed on a Buchner funnel with dry ethyl sulfate. If the filtrate is turbid it must be passed through a No. 2 glass filter.

The transparent filtered ester is dried for 1-2 days over fused sodium sulfate, after which the ethyl sulfate is evaporated away on a water bath at 35°, the ethyl ester of β-oxybutyric acid is distilled and the fraction coming off between 76 and 77° at 15 mm is collected. Here it must be remembered that the boiling point of acetoacetic acid is 73° at 15 mm, and is close to that of the ester of β-oxybutyric acid.

III. Saponification of the ester of β-oxybutyric acid. To 10 ml (about 10 g) of the ester of β-oxybutyric acid which has been prepared, an equivalent amount of a 7% solution of sodium hydroxide is added.

When the ester of β-oxybutyric acid is mixed with the alkali, an oil is formed which passes into solution after 10-30 minutes. Immediately afterwards, the solution is evaporated in a vacuum at 35-40° and 15 mm pressure until a syrup remains, which crystallizes out on cooling. The crystals of sodium β-oxybutyrate rapidly volatilize in air, and they must therefore immediately be transferred to a vacuum dessicator, where they are dried over phosphorus pentoxide for 1-2 days.

IV. Purifying the sodium β-oxybutyrate. It is cleaned by boiling in absolute alcohol. Before doing so, it should be well dried, because traces of water greatly increase the solubility of the salt in alcohol. For this reason, all the reagents used in the purification process are protected from the access of atmospheric moisture.

The sodium β-oxybutyrate is placed in a flask fitted with a reflux condenser and a calcium chloride tube, and is heated with 50-70 ml of absolute alcohol on a closed stove. Then, after a short period when the mixture of salt and alcohol has become fluid, the contents of the flask appear white from the crystals which separate out. If a thick yellowish fluid is formed in the flask, more alcohol must be added until crystallization starts.

The crystals are immediately separated from the hot alcohol on a glass filter No. 1, and are rapidly washed several times with cold absolute alcohol. The snow-white flaky crystals of the sodium salt of β-oxybutyric acid are dried in a vacuum dessicator over phosphorus pentoxide.

After about half the alcohol has been driven off from the mother liquor, and it has been left for the night to cool, a further considerable quantity of crystals can be obtained, which are then cleaned as described above. The total yield of sodium β-oxybutyrate is 7.7 g, which represents 33% of the theoretical yield from the acetoacetic ester.

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SUMMARY

A method is described for preparing the sodium salt of β-oxybutyric acid from acetoacetic ester. The acetoacetic ester is reduced by aluminium amalgam in moist sulphuric acid, and the β-oxybutyric acid thus obtained is then saponified to form the sodium salt of β-oxybutyric acid. The yield is approximately 30%.

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