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PROCESS FOR THE SYNTHESIS OF BIOPTERIN
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5 Claims

ABSTRACT OF THE DISCLOSURE

Biopterin is synthesized by reacting 2,4,5-triamino-6-hydroxypyrimidine with 5-deoxy-L-arabinosone in aqueous solution at pH of about 7.5 to 10, acidifying and then recrystallizing by dissolving in basic solution and precipitating with acid. 5-deoxy-L-arabinosone is prepared by oxidizing 5-deoxy-L-arabinose, which is prepared from L-rhamnose, using cupric acetate.

This invention relates to a new process for the synthesis of biopterin.

Biopterin, which is 2-amino-4-hydroxy-6-[1,2-dihydroxypropyl-(L-erythro)]pteridine, is a growth factor for *Criethidia fasciculata* [Patterson et al., J. Am. Chem. Soc., 78:5871-5873 (1956)]. Biopterin also promotes weight gain of poultry, for example, feeding poultry a ration to which biopterin is added in an amount of about 10 to 100 mg. per 100 pounds of feed produces an increase in weight gain of the poultry.

In addition, biopterin is an article of commerce, for example a practical grade of biopterin is offered for sale in one gram quantities by General Biochemicals, Chagrin Falls, Ohio.

According to the known methods for synthesizing biopterin, 2,4,5-triamino-6-hydroxypyrimidine is reacted with 5-deoxy-L-arabinose in acid medium in the presence of hydrazine; Rembold et al., Chem. Ber., 96:1395-1405 (1963). However, this reaction produces a mixture of many compounds from which biopterin is extracted in low yield after laborious and complex purification procedures. The yield of biopterin by this method, reported by Rembold et al., Chem. Ber., 96:1395-1405 (1963) at p. 1402, varied according to the particular reaction conditions from 3.5 to 7% based on the triamino-hydroxypyrimidine sulfate starting material.

By the process of the present invention, biopterin is synthesized in improved yield and contaminated only with the corresponding 7-isomer, that is 2-amino-4-hydroxy-7-[1,2-dihydroxypropyl-(L-erythro)]pteridine, which will be designated herein as 7-biopterin, in a mixture containing about 80% biopterin and 20% 7-biopterin. For most purposes, this material is suitable and further purification is not necessary. However, pure biopterin may be obtained from this 80% biopterin-20% 7-biopterin mixture by chromatography, for example by the procedure described by Rembold et al., Chem. Ber. 96:1395-1405 (1963).

According to one aspect of this invention, biopterin is synthesized by reacting 2,4,5-triamino-6-hydroxypyrimidine with 5-deoxy-L-arabinosone in aqueous solution at pH of about 7.5 to 10, acidifying and then recrystallizing by dissolving in basic solution and precipitating with acid. Conveniently, the pyrimidine starting material is used in the form of a salt, such as 2,4,5-triamino-6-hydroxypyrimidine sulfate or hydrochloride. The reaction is carried out in aqueous solution at pH of about 7.5 to 10, preferably at pH of about 8 to 9, which is obtained by adding a suitable base such as sodium carbonate, sodium bicarbonate, sodium hydroxide or, preferably, aqueous ammonia. Conveniently, the reaction is carried out by

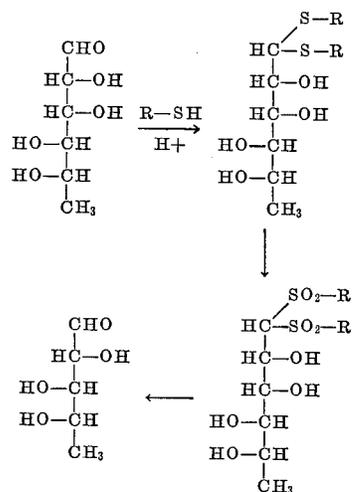
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stirring at about room temperature for about 1-3 hours. The reaction mixture is then acidified to pH of about 4 to 5 using, for example, hydrochloric acid and/or glacial acetic acid. The solid material is then filtered off and dried and recrystallized by dissolving in basic solution, such as aqueous ammonium hydroxide, and then adding acid, such as glacial acetic acid, to precipitate the product.

Purification by recrystallization as described above gives a product which is 80% biopterin and 20% 7-biopterin.

According to another aspect of this invention, biopterin is prepared by oxidizing 5-deoxy-L-arabinose using cupric acetate to give 5-deoxy-L-arabinosone and reacting the thus prepared 5-deoxy-L-arabinosone with 2,4,5-triamino-6-hydroxypyrimidine as described hereabove. The oxidation of 5-deoxy-L-arabinose is carried out preferably in a lower alkanol solvent, advantageously methanol, at elevated temperature, conveniently, at the reflux temperature of the solvent. Removing the precipitated copper by filtration, then adding anhydrous hydrogen sulfide and filtering gives a solution containing 5-deoxy-L-arabinosone. The solution is concentrated to a small volume and is used in the above described reaction with 2,4,5-triamino-6-hydroxypyrimidine to prepare biopterin.

5-deoxy-L-arabinose is prepared from L-rhamnose by the following procedure:



By the above procedure, L-rhamnose in acid solution is treated with at least two molar equivalents of a lower alkyl mercaptan, preferably ethyl mercaptan. The resulting 1,1-di-(lower alkylthio)-L-rhamnose is oxidized using, for example, peracetic acid. The reaction is conveniently carried out in a lower alkanol solvent, such as methanol, at room temperature to give 1,1-di-(lower alkylsulfonyl)-L-rhamnose. Treating this intermediate with aqueous ammonia and filtering off the resulting di-(lower alkylsulfonyl)methane gives a basic aqueous solution of 5-deoxy-L-arabinosone. This solution is concentrated and the 5-deoxy-L-arabinose is used as described hereabove to prepare biopterin.

The following example illustrates the process of this invention.

EXAMPLE

A mixture of 199 g. of L-rhamnose and 210 ml. of concentrated hydrochloric acid is stirred and chilled to 5-10° C. Ethyl mercaptan (200 g.) is added dropwise over a period of 1.5-2 hours. The reaction mixture is then stirred for an additional 15 minutes and then is allowed to stand at room temperature for 1.5 hours. The reaction mixture is stirred and cooled to 10° C. and filtered in vacuo. The solid material thus obtained is