

methyl acetate, ethyl acetate or isopropyl acetate; nitrites such as acetonitrile; alcohols such as methanol, ethanol, isopropanol or benzyl alcohol; water. Among others, aromatic hydrocarbons, ethers, aliphatic acid esters or water are preferably used. Toluene is a particularly preferable aromatic hydrocarbon, 1,4-dioxane is a particularly preferable ether, and ethyl acetate is a particularly preferable aliphatic acid ester. These solvents may be used alone or in a mixture of two or more solvents. Besides, if the above reaction accelerator is liquid at the above reaction temperature, the above reaction accelerator may be used so as to also serve as a reaction solvent.

[0076] The substituted-3-amino-2-hydroxypropionic acid derivatives (4) synthesized as described above may be isolated and/or purified by a conventional method such as extraction, crystallization, distillation, chromatography or the like. Alternatively, the reaction mixture may be used next in the third step as it is.

[0077] In the meantime, if the above reaction mixture, in particular, the reaction mixture obtained by carrying out the above second step under non-aqueous conditions is next supplied to the third step as it is without isolation and/or purification, an impurity is apt to be produced secondarily and the yield tends to decrease. The present inventors have intensively investigated the causes of the secondary production of the impurity as well as the decrease of the yield. As a result, they found that a by-product [hereinafter, also referred to as by-product (8)] represented by the following general formula (8):



[0078] wherein L and R⁴ are as defined above,

is produced secondarily in the second step, and it serves as a certain alkylating agent, whereby a N-substituted-3-amino-2-hydroxypropionic acid derivative [hereinafter, also referred to as impurity (9)], in which R⁴ is introduced onto the nitrogen atom in the above 3-amino-2-hydroxypropionic acid derivatives (1), and which is represented by the following general formula (9):



[0079] wherein R¹, R², R³ and R⁴ are as defined above, is produced secondarily as an impurity and the derivative causes the decrease of the yield and quality of the 3-amino-2-hydroxypropionic acid derivatives (1).

[0080] Accordingly, in order to minimize the secondary production of the impurity (9) and to maximize the yield in the third step, it is preferable to remove the above by-product (8) responsible for the above impurity (9), for example, by carrying out isolation and/or purification of the above substituted-3-amino-2-hydroxypropionic acid derivatives (4) to a pure form, for example, by obtaining the derivatives as crystals by crystallization.

[0081] If the above substituted-3-amino-2-hydroxypropionic acid derivatives (4) obtained according to the present

invention, in particular, 2-oxazolidinone-5-carboxylic acid ester derivatives (4') [compounds of the general formula (4) wherein S⁴ is an ester residue and S⁵ and S⁶, taken together, are a carbonyl group] are isolated and/or purified by crystallization into an almost pure form (as crystals), the derivatives may be purified and crystallized well using aromatic hydrocarbons as a solvent for crystallization. The aromatic hydrocarbons are not limited to particular ones, and include benzene, toluene, o-, m- or p-xylene, mesitylene, chlorobenzene or the like. Among others, toluene is used preferably.

[0082] In the crystallization of the above substituted-3-amino-2-hydroxypropionic acid derivatives (4), usual crystallization procedures such as cooling and/or concentration may be used without any limitation.

[0083] In the above crystallization, a solvent in a solution of the above substituted-3-amino-2-hydroxypropionic acid derivatives (4) other than the above aromatic hydrocarbons may be replaced to a solvent selected from the above aromatic hydrocarbons. Of course, with the progress of the solvent-replacement procedures, the above substituted-3-amino-2-hydroxypropionic acid derivatives (4) may be crystallized (so-called solvent-replacement crystallization). The above solvents other than aromatic hydrocarbons are not limited to particular ones, and include, for example, acetic acid esters such as ethyl acetate or isopropyl acetate; ethers such as tert-butyl methyl ether, tetrahydrofuran or 1,4-dioxane; alcohols such as methanol, ethanol or isopropanol; water.

[0084] The concentration of crystallization solution may be in a range capable of maintaining the fluidity of a crystallization solution. In general, the concentration is preferably below about 60% (w/v), more preferably below about 40% (w/v), and most preferably below about 20% (w/v).

[0085] The temperature at which the above crystallization is carried out is not limited to a particular range. In order to obtain a crystallization solution (slurry) having a good property, a slow progress of crystallization, for example, by a slow cooling is suitable. Also, addition of seed crystals is suitable for smooth crystallization.

[0086] The above substituted-3-amino-2-hydroxypropionic acid derivatives (4) crystallized may be separated using usual solid-liquid separation procedures such as filtration, centrifugation or the like. If necessary, separated wet solids of the substituted-3-amino-2-hydroxypropionic acid derivatives (4) may be further washed using, for example, the above aromatic hydrocarbons, and then dried at atmospheric pressure or under reduced pressure.

[0087] On the other hand, if a reaction mixture containing the above substituted-3-amino-2-hydroxypropionic acid derivatives (4) is used as it is without isolation and/or purification, the above reaction mixture is contacted with water and subjected to heat treatment to hydrolyze the above by-products (8) responsible for the above impurity (9), whereby the above by-products (8) may be made harmless to obtain effects similar to those obtained when carrying out isolation and/or purification. The above heat treatment in contact with water may be carried out in the second step, after carrying out the conversion into the above substituted-3-amino-2-hydroxypropionic acid derivatives (4) in a non-aqueous system, or simultaneously with the inversion of a