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RESOLUTION OF AMINO ACIDS

Joseph L. Purvis, Northbrook, Ill., assignor to International Minerals & Chemical Corporation, a corporation of New York

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This invention relates to a process for resolving racemic modifications of optically active compounds, and more particularly, to the resolution of racemic modifications of alpha-amino carboxylic acids.

Glutamic acid and aspartic acid are well known optically active compounds. However, only L-glutamic acid and L-aspartic acid are useful at the present time, there being no known utility for D-glutamic acid and D-aspartic acid or their racemic modification; namely, DL-glutamic acid or DL-aspartic acid. Chemical processes for the synthesis of glutamic acid and aspartic acid, however, result in the formation of racemic modifications of these compounds, that is, optically neutral DL-glutamic acid and DL-aspartic acid, respectively. These racemic modifications, although having no value in commerce as such, would be very valuable if a simple inexpensive method were available for resolving them to produce the optically active L-glutamic acid and L-aspartic acid. One of the factors which has heretofore prevented the commercial production of synthetic L-glutamic acid and L-aspartic acid has been the lack of a commercially feasible procedure for resolving racemic modifications of glutamic acid and aspartic acid into their respective enantiomorphs.

One object of the instant invention is to provide a process for the resolution of DL-alpha-amino carboxylic acids.

Another object of the instant invention is to provide a process for the resolution of DL-glutamic acid.

Another object of this invention is to provide a process for the resolution of DL-aspartic acid.

Another object of this invention is to provide a process for the resolution of DL-leucine.

A further object of this invention is to provide a commercially feasible process for the resolution of DL-alpha-amino carboxylic acids which do not require the use of expensive reagents or equipment.

In accordance with this invention, a racemic modification of an alpha-amino carboxylic acid, such as, for example, aspartic acid, glutamic acid, or leucine, is resolved by preparing a solution containing the racemic modification and an optically active form of another alpha-amino carboxylic acid, and separating solids from the solution by crystallization. The crystals thus separated comprise a quantity of an optically active form of the racemic modification originally in the solution and a quantity of the racemic modification in the unresolved state with perhaps some of the optically active form of the resolving compound. The optically active form of the racemic modification being subjected to the resolution process may be separated from the other compounds by standard procedures.

It is preferred to apply the process of this invention to the resolution of DL-alpha-amino carboxylic acids containing between about four and about nine carbon atoms and containing less than three carboxy groups, using as the resolving compound an optically active form of an alpha-amino carboxylic acid containing between about four and about nine carbon atoms and containing less than three carboxy groups. Alpha-amino carboxylic acids which are particularly useful in this invention are those having a solubility in water at room temperature of less than about 8 grams per 100 grams of water. Specific alpha-amino carboxylic acids, in addition to leucine, aspartic acid and glutamic acid, which may be utilized include tyrosine, isoleucine, norleucine, valine, and the like. All of these compounds may be utilized as resolving compounds or may be resolved when in their racemic modifications according to the process of this invention. All of these compounds are characterized as non-basic alpha-amino carboxylic acids for the reason that all contain not more than one amino group per carboxy group in the molecule. Alpha-amino carboxylic acids containing more than one amino group per carboxy group in the molecule, such as lysine, are not operable in this invention.

A preferred practice of the instant invention comprises preparing an aqueous solution of a racemic modification of either aspartic acid or glutamic acid, the solution also containing an optically active form of that one of these two compounds which is not being resolved. For example, if it is desired to resolve DL-aspartic acid in accordance with this invention, a solution is prepared containing DL-aspartic acid and an optically active form of, for example, glutamic acid, that is, either L-glutamic acid or D-glutamic acid. Alternatively, if it is desired to resolve DL-glutamic acid in accordance with this invention, a solution is prepared containing DL-glutamic acid and an optically active form of aspartic acid, that is, D-aspartic acid or L-aspartic acid.

A convenient method for preparing the solution comprises preparing an aqueous slurry of the racemic modification and an optically active form of the resolving compound, for example, an aqueous slurry of DL-aspartic acid and L-glutamic acid, and adding alkali to the slurry in sufficient amount to dissolve the solids and form a true solution. The solution is then adjusted to about the isoelectric point of the racemic modification by the addition of an inorganic acid, such as aqueous hydrochloric acid, and the volume of the solution is adjusted by adding or removing water so that the solution will be supersaturated with respect to the racemic modification at the isoelectric point. It is desirable that the solution being subjected to crystallization contain between about 3% and about 5% of the racemic modification and between about 1% and about 2% of the resolving compound. The solution is then allowed to stand with gentle agitation until crystallization is complete. Crystallization is usually carried out at room temperature, but higher or lower temperatures may be utilized if desired. The crystals will contain a substantial quantity of an optically active form of the racemic modification being resolved and having a rotation opposite to that of the resolving compound. The crystals will also contain some of the racemic modification in the unresolved state and possibly a small quantity of the resolving compound in the optically active form utilized. Correspondingly, there will remain in solution a preponderance or possibly all of the resolving compound, a substantial quantity of the optically active form of the racemic modification corresponding in rotation to that of the resolving compound, and also a substantial quantity of the racemic modification.

In accordance with a specific embodiment of this invention, DL-aspartic acid and L-glutamic acid are slurried in water, and aqueous sodium hydroxide is added to the slurry with agitation until the pH of the liquid phase is adjusted, preferably to about 7.0. Under these conditions the DL-aspartic acid and L-glutamic acid dissolve to form a true solution. The solution is then adjusted to about pH 3.1 by the addition of concentrated aqueous hydrochloric acid, and the volume of the solution is adjusted

by adding or removing (by evaporation) water so that the solution at pH 3.1 will be supersaturated with respect to DL-aspartic acid. The solution is then allowed to stand with gentle agitation for about 72 hours at room temperature and filtered. The crystals obtained comprise about 45% DL-aspartic acid, about 40% of D-aspartic acid, and about 15% of L-glutamic acid. The filtrate contains about 63% of the DL-aspartic acid originally in solution, about 8% L-aspartic acid (based upon total solids in solution) and about 90% of the L-glutamic acid originally added.

In carrying out the process of this invention, it is desirable that the crystallization be carried out at a temperature of about room temperature or below, but higher temperatures may be utilized for particular purposes. The solution of the racemic modification and the resolving compound may be prepared in any convenient manner so long as the solution upon adjustment to about the isoelectric point of the racemic modification is supersaturated with respect to the racemic modification. It is not necessary that the resolving compound be at its saturation concentration at the time of crystallization if less than optimum resolution is permissible. The best yields, however, are obtained if the resolving compound is at its saturation concentration at the time that crystallization begins. Crystallization is carried out until the formation of crystals discontinues, that is, until equilibrium conditions obtain or are substantially achieved.

The term "resolving compound" as used herein refers to an optically active form of either glutamic acid or aspartic acid, or similar non-basic alpha-amino carboxylic acid, for example, L-aspartic acid, D-aspartic acid, L-glutamic acid, or D-glutamic acid, etc. When DL-aspartic acid is subjected to resolution in accordance with this invention, the resolving compound is preferably either L-glutamic acid or D-glutamic acid. Conversely, when DL-glutamic acid is resolved in accordance with this invention, the resolving compound is preferably L-aspartic acid or D-aspartic acid.

The following examples represent specific embodiments of this invention. All parts and percentages are by weight unless otherwise indicated.

Example I

About 10 parts of DL-asparatic acid and about 5 parts of L-glutamic acid were slurried with about 200 parts water. To the slurry was added a 50% aqueous of sodium hydroxide until the pH of the aqueous phase amounted to about 7.0. Addition of the sodium hydroxide solution resulted in the dissolution of the DL-aspartic acid and L-glutamic acid to form a true solution. The solution was adjusted to pH 3.1 by the addition of 37% aqueous hydrochloric acid and then sufficient water was added to the solution to adjust the weight of the solution to 250 parts. The solution was allowed to stand with gentle agitation for about 72 hours at room temperature and then filtered to remove the crystals which had formed. The crystals amounted to 5.8 parts and had the following composition by weight:

	Percent
D-aspartic acid	37.0
DL-aspartic acid	54.5
L-glutamic acid	8.5

The filtrate amounted to 240 parts and contained the following solids:

	Parts
L-aspartic acid	2.1
DL-aspartic acid	2.6
L-glutamic acid	4.4

Thus, the treatment of the DL-aspartic acid with L-glutamic acid had resulted in about a 42% resolution of the DL-aspartic acid. The crystalline D-aspartic acid was separated from the crystals of DL-aspartic and L-glutamic acid by re-crystallizing the D-aspartic acid at its isoelectric point (pH 3.1).

The L-aspartic acid was isolated from the filtrate by first separating L-glutamic acid by crystallization of L-glutamic acid hydrochloride, adjusting the pH to 3.1 and crystallizing L-aspartic acid.

Example II

Twelve parts DL-aspartic acid and 8 parts L-glutamic acid were slurried in water and dissolved by adjusting the pH of the aqueous phase to about 7.0 by the addition of a 50% aqueous solution of sodium hydroxide. The solution was then adjusted to pH 3.2 by the addition of 30% aqueous hydrochloric acid, and the weight of the solution was then adjusted to 400 parts by adding water. The solution was allowed to stand with gentle agitation for about 72 hours and then filtered to remove the crystals which had formed. The crystals amounted to 3.5 parts and had the following compositions:

	Percent
D-aspartic acid	40
DL-aspartic acid	45
L-glutamic acid	15

The filtrate amounted to 393 parts and contained the following solids:

	Parts
L-aspartic acid	1.4
DL-aspartic acid	7.6
L-glutamic acid	7.2

The optically active forms of aspartic acid and glutamic acid were recovered by the procedures outlined in Example I.

Example III

About 10 parts of DL-glutamic acid and about 5 parts of L-aspartic acid were slurried in about 200 parts water. To the slurry was added a 50% aqueous solution of sodium hydroxide until the pH of the aqueous phase amounted to about 7.0. Addition of the sodium hydroxide solution resulted in dissolution of the DL-glutamic acid and L-aspartic acid to form a true solution. The solution was adjusted to pH 3.2 by the addition of 37% aqueous hydrochloric acid and then sufficient water was added to the solution to adjust the weight of the solution to 250 parts. The solution was allowed to stand with gentle agitation for about 72 hours at room temperature and then filtered to remove the crystals which had formed. The crystals amounted to about 5 parts and had the following composition by weight:

	Percent
D-glutamic acid	10
DL-glutamic acid	78
L-aspartic acid	12

Example IV

About 16.8 parts of DL-glutamic acid monohydrate and about 9 parts of L-leucine were dissolved in dilute hydrochloric acid at pH 1.0. The solution was then adjusted to pH 3.2 by the addition of a 50% aqueous sodium hydroxide solution. The final solution amounted to about 300 parts. The solution was agitated gently over a period of about 24 hours at about 25° C. to permit crystallization to proceed, and the crystals were removed by filtration. The crystals amounted to 9.4 parts and comprised 1.8 parts D-glutamic acid and 7.6 parts DL-glutamic acid. The D-glutamic acid was separated from the DL-glutamic acid by recrystallization from 300 parts of water at about 25° C.

Having thus fully described and illustrated the character of the instant invention, what is desired to be secured and claimed by Letters Patent is:

1. A process for resolving a racemic modification of a non-basic alpha-amino carboxylic acid comprising preparing a solution containing said racemic modification and an optically active form of another non-basic alpha-

amino carboxylic acid, and separating solids comprising an optically active form of the racemic modification from the solution by crystallization.

2. A process for resolving a racemic modification selected from the group consisting of DL-aspartic acid and DL-glutamic acid, comprising preparing a solution containing one of said racemic modifications and an optically active form of the other, and separating solids comprising an optically active form of the racemic modification from the solution by crystallization.

3. A process for resolving a racemic modification selected from the group consisting of DL-aspartic acid and DL-glutamic acid, comprising preparing an aqueous solution supersaturated with one of said racemic modifications, and containing an optically active form of the other, and separating solids comprising an optically active form of the racemic modification from the solution by crystallization.

4. A process for resolving DL-aspartic acid which comprises preparing an aqueous solution supersaturated with respect to DL-aspartic acid and also containing L-glutamic acid, and separating solids comprising an optically active form of aspartic acid from the solution by crystallization at pH 3.1.

5. A process for resolving DL-aspartic acid which comprises preparing an aqueous solution supersaturated with respect to DL-aspartic acid and saturated with L-glutamic acid, and separating solids comprising an optically active form of aspartic acid from the solution by crystallization at pH 3.1.

6. A process for resolving DL-aspartic acid which comprises preparing an aqueous solution supersaturated with respect to DL-aspartic acid and also containing D-glutamic acid, and separating solids comprising an optically active form of aspartic acid from the solution by crystallization.

7. A process for resolving DL-aspartic acid which comprises preparing an aqueous solution supersaturated with respect to DL-aspartic acid and saturated with D-glutamic acid, and separating solids comprising an optically active form of aspartic acid from the solution by crystallization.

8. A process for resolving DL-glutamic acid which comprises preparing an aqueous solution supersaturated with respect to DL-glutamic acid and also containing L-aspartic acid, and separating solids comprising an optically active form of glutamic acid from the solution by crystallization at pH 3.2.

9. A process for resolving DL-glutamic acid which comprises preparing an aqueous solution supersaturated with respect to DL-glutamic acid and saturated with L-aspartic acid, and separating solids comprising an optically active form of glutamic acid from the solution by crystallization at pH 3.2.

10. A process for resolving DL-glutamic acid which comprises preparing an aqueous solution supersaturated with respect to DL-glutamic acid and also containing D-aspartic acid, and separating solids comprising an optically active form of glutamic acid from the solution by crystallization.

11. A process for resolving DL-glutamic acid which comprises preparing an aqueous solution supersaturated with respect to DL-glutamic acid and saturated with D-aspartic acid, and separating solids comprising an optically active form of glutamic acid from the solution by crystallization.

12. A process for resolving DL-glutamic acid which comprises preparing an aqueous solution supersaturated with respect to DL-glutamic acid and containing an optically active form of leucine, and separating solids comprising an optically active form of glutamic acid from the solution by crystallization.

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