

[54] **ALKYL ESTERS OF ASPARTYL ALIPHATIC AMINO ACID DIPEPTIDES**

[75] Inventors: **Robert H. Mazur**, Deerfield,
James M. Schlatter, Glenview,
both of Ill.

[73] Assignee: **G. D. Searle & Co.**,
Chicago, Ill.

[22] Filed: **Oct. 30, 1972**

[21] Appl. No.: **302,040**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 89,115, Nov. 12, 1970, abandoned.

[30] **Foreign Application Priority Data**

Nov. 11, 1971 Australia..... 35358/71

[52] U.S. Cl..... **260/112.5, 99/141 A**

[51] Int. Cl..... **C07c 103/52, A23l 1/26**

[58] Field of Search..... **260/112.5**

[56] **References Cited**

UNITED STATES PATENTS

3,695,898 10/1972 Hill et al..... 260/112.5
3,714,139 1/1973 Schlatter et al..... 260/112.5

OTHER PUBLICATIONS

Mazur et al., J. Am. Chem. Soc., 91, 2684-2691 (1969).

Mazur et al., J. Med. Chem., 13, 1217-1221 (1970).

Ernest L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Co., New York (1962), pp. 88-95.

Primary Examiner—Lewis Gotts

Assistant Examiner—Reginald J. Suyat

Attorney, Agent, or Firm—Elliot N. Schubert

[57]

ABSTRACT

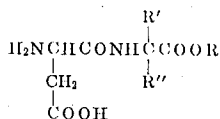
Coupling of the appropriate (S)-aspartic acid derivative with an aliphatic amino acid alkyl ester followed by hydrogenolysis of the protecting groups affords the corresponding (S)-aspartyl-(R)-(aliphatic-) amino acid alkyl esters, which exhibit potent sweetening properties.

12 Claims, No Drawings

ALKYL ESTERS OF ASPARTYL ALIPHATIC AMINO ACID DIPEPTIDES

This application is a continuation-in-part of our co-pending application Ser. No. 89,115, filed Nov. 12, 1970 now abandoned.

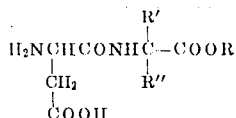
The present invention relates to alkyl esters of (S)-aspartyl (R) aliphatic amino acid dipeptides represented by the following structural formula



wherein R and R' are alkyl radicals containing less than four carbon atoms and R'' is hydrogen or an alkyl radical containing less than four carbon atoms, with the provision that, when R' and R'' are dissimilar, the carbon atom to which R' and R'' are attached possesses the (R) stereochemical configuration.

The alkyl radicals containing less than four carbon atoms symbolized in the foregoing formulas include methyl, ethyl, propyl, and isopropyl.

The instant compounds are useful in consequence of their potent sweetening properties. The fact that the compounds of the formula



having the (S)-(R) configuration are sweet is most surprising and completely unexpected, especially in view of the knowledge of the art. U.S. Pat. Nos. 3,475,403, issued Oct. 28, 1969, and 3,492,131, issued Jan. 27, 1970, thus describe sweet aspartyl dipeptides characterized by the (S)-(S) configuration. The (S)-(S) dipeptides corresponding to the compounds of the present invention are, however, either bitter or tasteless.

The sweetening property of the compounds of the present invention is dependent upon the stereochemical configuration of the individual amino acids from which the dipeptides are derived. The aspartyl portion of the molecule must be derived from (S)-aspartic acid. It is, of course, apparent that the corresponding (RS)-aspartyl derivatives, which contain the (S)-aspartyl isomer, are also sweet and that such isomeric mixtures are within the scope of this invention. In the situation where asymmetry is possible in the amino acid ester portion of the molecule, i.e., where R' and R'' are dissimilar, that moiety must have the (R) stereochemical configuration. It is likewise apparent here that isomeric mixtures containing the (R)-isomer, i.e., the corresponding (RS) aliphatic amino acid ester derivatives, are also sweet and are within the scope of this invention.

A convenient method for manufacture of the instant compounds involves a two-step process whereby a suitable protected (S)-aspartic acid derivative is coupled with the appropriate aliphatic amino acid ester and the resulting protected dipeptide ester is submitted to hydrogenolysis, thus removing the protecting groups. An

especially useful starting material is N-benzyloxycarbonyl-(S)-aspartic acid α -p-nitrophenyl β -benzyl diester. Reaction of that substance with the amino acid ester results in replacement of the reactive p-nitrophenoxy group, thus forming the peptide bond. A specific example of that process is the reaction of that protected (S)-aspartic acid derivative with (R)-alanine isopropyl ester to afford β -benzyl-N-benzyloxycarbonyl-(S)-aspartyl-(R)-alanine isopropyl ester. Hydrogenolysis of the latter substance in the presence of a palladium catalyst results in removal of the protecting groups, thus affording the desired (S)-aspartyl-(R)-alanine isopropyl ester.

The instant compounds are utilized as substitutes for sugar in edible materials, which thus may be advantageously used by diabetics or others who desire to reduce their caloric intake. Examples of edible materials which are sweetened by the instant compounds are fruits, vegetables, juices, meat products such as ham, bacon, and sausage, egg products, fruit concentrates, gelatins and gelatin-like products such as jams, jellies and preserves, milk products such as ice cream, sherbet and sour cream, icings, syrups, corn, wheat, rye, soybean, oat and rice products such as breads, cereals, pasta and cake mixes, fish, cheese and cheese products, nut meats, and nut products, beverages such as coffee, tea, non-carbonated and carbonated soft drinks, beers, wines and other liquors, confections such as candy and fruit-flavored drops, condiments such as herbs, spices and seasonings, and flavor enhancers such as monosodium glutamate. In addition, consumable products such as chewing gum, toiletries such as mouthwashes and toothpastes, and proprietary and non-proprietary pharmaceutical preparations can be thus sweetened.

The instant sweetening agents can be utilized in a variety of physical forms, for example solid forms such as powders, tablets, granules and dragees, as well as liquid forms typified by solutions, suspensions, syrups and emulsions, and also other commonly employed forms particularly suited for combination with edible materials. These forms may consist of the sweetening agent alone or in combination with suitable non-toxic carriers, for example liquids such as water, ethanol, sorbitol, glycerol, corn oil, peanut oil, soybean oil, sesame oil, propylene glycol, corn syrup and maple syrup as well as solids such as citric acid, lactose, cellulose, starch, dextran and other modified starches, calcium sulfate and di- and tri-calcium phosphate.

An example of the preparation of a typical sweetened edible material is given by the following description for a sweetened orange soda.

A stock supply of bottler's syrup is prepared by mixing 5.5 ml. of a 50 percent aqueous citric acid solution with 150 ml. of water, dissolving 1 g. of (S)-aspartyl-(R) alanine isopropyl ester in that solution, adding successively 7.02 ml. of the orange flavor base manufactured by the A. E. Illes Company, Dallas, Tex., labelled FO-78, and 2.7 g. of sodium benzoate and diluting that mixture to 200 ml. with water. One-ounce samples of that bottler's syrup are transferred to 6-ounce bottles and 110 ml. of cold tap water is added to each bottle. To each bottle 42 ml. of cold charged bottling water (5 volumes carbon dioxide) is then added to achieve carbonation. Each bottle is capped and the contents mixed.

The invention will appear more fully from the examples which follow. These examples are given by way of

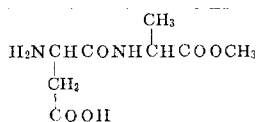
illustration only and are not to be construed as limiting the invention either in spirit or in scope as many modifications both in materials and methods will be apparent to those skilled in the art. In these examples temperatures are given in degrees centigrade (°C) and quantities of materials in parts by weight unless otherwise noted.

EXAMPLE 1

To 400 parts of methanol is added 17.5 parts by volume of thionyl chloride while maintaining the temperature at about -20°. To the resulting solution is then added 17.8 parts of (R)-alanine and that reaction mixture is heated the reflux temperature for about 24 hours. Concentration of that mixture under reduced pressure results in a syrupy residue, which is stirred rapidly with about 350 parts of anhydrous ether. The crystalline product separates upon cooling at about 5° for about 16 hours and is collected by filtration, then washed with ether and dried to afford (R)-alanine methyl ester hydrochloride, melting at about 105°-110°.

2.2 Parts of (R)-alanine methyl ester prepared from (R)-alanine methyl ester hydrochloride by neutralization with saturated aqueous potassium carbonate followed by extraction with methylene dichloride, drying over anhydrous magnesium sulfate and removal of the solvent under reduced pressure, is added to a solution of 9.56 parts of N-benzyloxycarbonyl-(S)-aspartic acid α -p-nitrophenyl, β -benzyl diester dissolved in 70 parts of ether. The resulting mixture is allowed to stand at room temperature and crystals begin to form after about 2 hours. After standing at room temperature for a total of about 24 hours, the mixture is cooled to about 5° and kept at that temperature for about 3 hours, then is filtered and the filter cake is washed with ether and dried to afford β -benzyl N-benzyloxycarbonyl-(S)-aspartyl-(R)-alanine methyl ester, melting at about 113°-114° and exhibiting an optical rotation of -4.5° in dimethylformamide.

A mixture consisting of 4.42 parts of β -benzyl N-benzyloxycarbonyl-(S)-aspartyl-(R)-alanine methyl ester, 0.4 part of palladium black and 100 parts of 75 percent acetic acid is stirred with hydrogen at atmospheric pressure and room temperature until the uptake of gas ceases. The catalyst is then removed by filtration and the filtrate is concentrated to dryness under reduced pressure. The resulting residue is dissolved in water, the solution concentrated to dryness, and this residue dissolved in ethanol and the solution concentrated to dryness. The residual crude product is triturated with ether, then collected by filtration and dried to afford (S)-aspartyl-(R)-alanine methyl ester, exhibiting a double melting point with decomposition at about 150°-151° and at about 200°. This compound is represented by the following structural formula



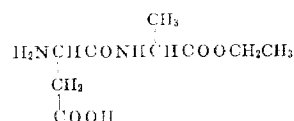
EXAMPLE 2

The procedure described in Example 1 is repeated,

however substituting 960 parts of ethanol, 43.6 parts by volume of thionyl chloride and 44.5 parts of (R)-alanine, thus producing (R)-alanine ethyl ester hydrochloride, melting at about 75°-78.5°.

A mixture containing 23.9 parts of N-benzyloxycarbonyl-(S)-aspartic acid α -p-nitrophenyl, β -benzyl diester, 4.5 parts of tetrahydrofuran and 35 parts of ether is heated on the steam bath until solution is complete. That solution is then diluted with ether to afford a volume of 500 parts and (R)-alanine ethyl ester, prepared by the procedure described in Example 1 from 8.39 parts of (R)-alanine ethyl ester hydrochloride is added. The reaction mixture is allowed to stand for about 24 hours, then is cooled to 5° and kept at that temperature for about 16 hours. The resulting crystals are collected by filtration, washed with ether and dried to afford β -benzyl N-benzyloxycarbonyl-(S)-aspartyl-(R)-alanine ethyl ester, melting at about 107°-108.5°.

When an equivalent quantity of β -benzyl N-benzyloxycarbonyl-(S)-aspartyl-(R)-alanine ethyl ester is hydrogenolyzed by the procedure described in Example 1, there is produced (S)-aspartyl-(R)-alanine ethyl ester, represented by the following structural formula



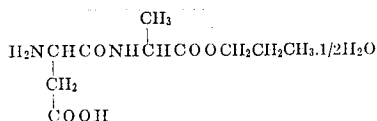
EXAMPLE 3

The esterification procedure described in Example 2 is repeated, however substituting 960 parts of n-propyl alcohol, and the reaction mixture is partially concentrated, then diluted with a large volume of ether. The resulting crystalline product is collected by filtration, washed on the filter with ether and dried, thus affording (R)-alanine n-propyl ester hydrochloride, melting at about 91°-97.5°.

To a solution of 23.9 parts of N-benzyloxycarbonyl-(S)-aspartic acid α -p-nitrophenyl, β -benzyl diester in 140 parts of ether is added (R)-alanine n-propyl ester, prepared from 9.2 parts of (R)-alanine n-propyl ester hydrochloride, and the resulting mixture is allowed to react for about 24 hours, then is stored at about 5° for about 16 hours. The resulting product is collected by filtration, washed with ether and dried to afford β -benzyl N-benzyloxycarbonyl-(S)-aspartyl-(R)-alanine n-propyl ester, melting at about 94°-95°.

A mixture containing 14.1 parts of β -benzyl N-benzyloxycarbonyl-(S)-aspartyl-(R)-alanine n-propyl ester, 300 parts by volume of 90 percent aqueous n-propyl alcohol and 1.4 parts of palladium black is shaken in a hydrogen atmosphere until the uptake of gas ceases. The catalyst is removed by filtration, and the filtrate is concentrated to dryness under reduced pressure. The resulting residue is dissolved in water, then decolorized with activated carbon, and that solution is stripped of solvent by distillation under reduced pressure to afford, as a solid foam, (S)-aspartyl-(R)-alanine n-propyl ester hemihydrate, characterized by the following structural formula

5

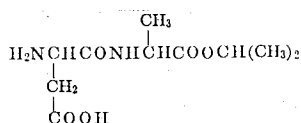


EXAMPLE 4

The esterification described in Example 3 is repeated, except that isopropyl alcohol is substituted, and the resulting oily crude product is purified by recrystallization from ether to afford (S)-alanine isopropyl ester hydrochloride, melting at about 85°-89.5°.

The coupling procedure described in Example 2 is repeated, except that 9.2 parts of (S)-alanine isopropyl ester hydrochloride is substituted. The reaction mixture is cooled to about 5° for about 3 hours, and the resulting crystalline product is isolated by filtration, then dried to afford β-benzyl N-benzyloxycarbonyl-(S)-aspartyl-(R)-alanine isopropyl ester, melting at about 104.5°-105°.

To a solution of 7.05 parts of β-benzyl N-benzyloxycarbonyl-(S)-aspartyl-(R)-alanine isopropyl ester in 168 parts of isopropyl alcohol is added 70 parts of water and 0.7 part of palladium black and that reaction mixture is stirred with hydrogen at atmospheric pressure and room temperature until the uptake of gas ceases. The catalyst is removed by filtration and the filtrate is concentrated to dryness to afford, as a white solid, (S)-aspartyl-(R)-alanine isopropyl ester, melting with decomposition at about 146°-148° and represented by the following structural formula



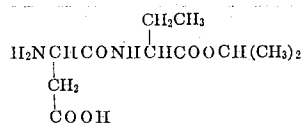
EXAMPLE 5

To a solution of 5.8 parts by volume of thionyl chloride in 160 parts of isopropyl alcohol is added 4.13 parts of (R)-α-aminobutyric acid and the resulting mixture is heated at the reflux temperature for about 65 hours. Concentration of that mixture under reduced pressure affords a solid residue, which is purified by dissolution in a small quantity of isopropyl alcohol followed by dilution with a large quantity of ether. The resulting crystalline product is isolated by filtration and dried to afford (R)-α-aminobutyric acid isopropyl ester hydrochloride.

To a solution of 14.35 parts of N-benzyloxycarbonyl-(S)-aspartic acid α-p-nitrophenyl, β-benzyl diester in 105 parts of ether is added (R)-α-aminobutyric acid isopropyl ester, prepared from 5.45 parts of the corresponding hydrochloride, and the resulting reaction mixture is allowed to stand at room temperature for about 24 hours. The mixture is then cooled at 0° for about 4 hours and the resulting crystals are collected by filtration, washed with ether and dried, thus affording β-benzyl N-benzyloxycarbonyl-(S)-aspartyl-(R)-α-aminobutyric acid isopropyl ester, melting at about 90°-91°.

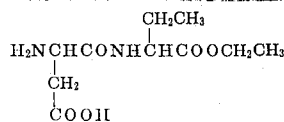
6

A mixture containing 8.73 parts of β-benzyl N-benzyloxycarbonyl-(S)-aspartyl-(R)-α-aminobutyric acid isopropyl ester, 300 parts of 90 percent aqueous isopropyl alcohol and 0.9 part of palladium black is stirred with hydrogen at atmospheric pressure and room temperature until the absorption of gas ceases, then is filtered to remove the catalyst. The filtrate is concentrated to dryness by distillation under reduced pressure. The resulting residue is purified by dissolution in water and clarification with activated charcoal followed by evaporation to dryness, thus affording (S)-aspartyl-(R)-α-aminobutyric acid isopropyl ester, melting with decomposition at about 167° and characterized by the following structural formula



EXAMPLE 6

By substituting an equivalent quantity of ethanol, D-α-aminobutyric acid ethyl ester hydrochloride and β-benzyl N-benzyloxycarbonyl-(S)-aspartyl-(R)-α-aminobutyric acid ethyl ester in the successive processes described in Example 5, there is produced (S)-aspartyl-(R)-α-aminobutyric acid ethyl ester, represented by the following structural formula



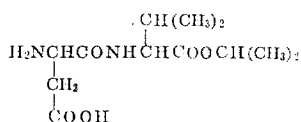
EXAMPLE 7

560 Parts of isopropyl alcohol is cooled to about -5° and 71.4 parts of thionyl chloride is added dropwise over a period of about 45 minutes, keeping the temperature below 0°. To that solution is then added 23.4 parts of (R)-valine and the reaction mixture is heated at the reflux temperature for about 16 hours, then is concentrated to dryness, thus affording a yellow oily residue. That material is dissolved in ether and the solution cooled to about -5° in order to promote crystallization. The resulting (R)-valine isopropyl ester hydrochloride is isolated by filtration as a white fluffy solid, melting at about 108°-109°.

To a solution containing 23.5 parts of (R)-valine isopropyl ester hydrochloride, 64.5 parts of N-benzyloxycarbonyl-(S)-aspartic acid α-p-nitrophenyl, β-benzyl diester and 375 parts of dimethylformamide is added 12.1 parts of N-methylmorpholine and that reaction mixture is allowed to stand at room temperature for about 5 days, then is diluted with a large volume of ethyl acetate. The resulting solution is washed successively with dilute hydrochloric acid, dilute aqueous potassium carbonate and aqueous sodium sulfate, then dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure. Successive crystallization of the resulting yellow oily residue from hexane and aqueous isopropyl alcohol results in β-benzyl N-

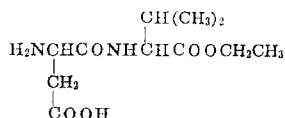
benzyloxycarbonyl-(S)-aspartyl-(R)-valine isopropyl ester, melting at about 70°–71° and exhibiting an optical rotation, in methanol, of –7.3°.

The hydrogenolysis of an equivalent quantity of β -benzyl N-benzyloxycarbonyl-(S)-aspartyl-(R)-valine isopropyl ester by the procedure described in Example 1 results in (S)-aspartyl-(R)-valine isopropyl ester, melting at about 144°–145° and represented by the following structural formula



EXAMPLE 8

When equivalent quantities of ethanol, (R)-valine ethyl ester hydrochloride and β -benzyl N-benzyloxycarbonyl-(S)-aspartyl-(R)-valine ethyl ester are substituted in the successive processes described in Example 7, there is obtained (S)-aspartyl-(R)-valine ethyl ester, represented by the following structural formula



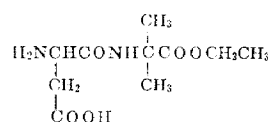
EXAMPLE 9

To a solution of 8.8 parts by volume of thionyl chloride in 240 parts of ethanol is added 10.3 parts of α -methylalanine and the resulting reaction mixture is heated at the reflux temperature for about 30 hours. That mixture is partially concentrated until crystallization begins, then is heated to the point of solution and diluted with ether. The resulting mixture is cooled at about 5° for about 16 hours and the crystals which form are isolated by filtration and dried, thus producing α -methylalanine ethyl ester hydrochloride.

To a cooled solution of 19.82 parts of N-benzyloxycarbonyl-(S)-aspartic acid, β -benzyl ester in 180 parts of tetrahydrofuran is added first 6.4 parts by volume of N-methylmorpholine, then, at –30°, 7.3 parts by volume of isobutyl chloroformate. The resulting mixture is stirred at about –20° for a few minutes, at the end of which time α -methylalanine ethyl ester, prepared from 8.8 parts of α -methylalanine ethyl ester hydrochloride by the neutralization procedure described in Example 1, is added. That reaction mixture is kept at about 5° for about 16 hours, and 1 part of dimethylaminoethylamine is added. Filtration of the mixture affords a filtrate, which is stripped of solvent under reduced pressure and the resulting oil is dissolved in ethyl acetate. That organic solution is washed successively with dilute hydrochloric acid, water, dilute aqueous potassium carbonate and water, then dried over anhydrous magnesium sulfate and stripped of solvent by distillation under reduced pressure. The resulting crude product is recrystallized from a mixture of ether and pentane to afford β -benzyl N-

benzyloxycarbonyl-(S)-aspartyl- α -methylalanine ethyl ester, melting at about 68°–70°.

To a solution of 16.48 parts of β -benzyl N-benzyloxycarbonyl-(S)-aspartyl- α -methylalanine ethyl ester in 500 parts by volume of 90 percent aqueous ethanol is added 1.6 parts of palladium black and the resulting reaction mixture is stirred with hydrogen at atmospheric pressure and room temperature until the uptake of gas ceases. The mixture is then filtered to remove the catalyst and the filtrate is concentrated to dryness under reduced pressure. The resulting residue is dissolved in water and the solution decolorized with activated charcoal, then concentrated to dryness to afford (S)-aspartyl- α -methylalanine ethyl ester, melting at about 90°–95° and characterized by the following structural formula



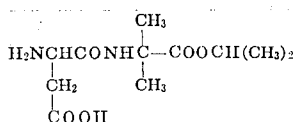
EXAMPLE 10

To a solution containing 17.5 parts by volume of thionyl chloride dissolved in 280 parts of isopropyl alcohol is added 20.62 parts of α -methylalanine and the resulting reaction mixture is heated at the reflux temperature for about 24 hours, then concentrated to dryness under reduced pressure. The resulting thick, oily residue is extracted with hot ether and the extract is filtered, then partially concentrated under reduced pressure. After cooling at about –18° for about 20 hours, the mixture is filtered, thus affording α -methylalanine isopropyl ester hydrochloride, melting at about 111°–113.5°.

To a solution of 17.2 parts of N-benzyloxycarbonyl-(S)-aspartic acid α -p-nitrophenyl, β -benzyl diester in 210 parts of ether is added 5.6 parts of α -methylalanine isopropyl ester, prepared from the corresponding hydrochloride by the neutralization method described in Example 1, and the resulting mixture is allowed to stand at room temperature for about 3 days. At the end of that time, 1 part of dimethylaminoethylamine is added and the solution is extracted with saturated aqueous potassium carbonate. The ether layer is separated, washed successively with water, dilute hydrochloric acid and water, then dried over anhydrous magnesium sulfate and concentrated to dryness under reduced pressure. The initially oily residue crystallizes upon standing, thus affording β -benzyl N-benzyloxycarbonyl-(S)-aspartyl- α -methylalanine isopropyl ester, melting at about 60°–62°.

A mixture containing 10.6 parts of β -benzyl N-benzyloxycarbonyl-(S)-aspartyl- α -methylalanine isopropyl ester, 1 part of palladium black and 200 parts of 90 percent aqueous isopropyl alcohol is shaken with hydrogen at atmospheric pressure and room temperature until the uptake of gas ceases, then is filtered in order to remove the catalyst. The resulting filtrate is concentrated to dryness to afford an oily residue, which is extracted with isopropyl alcohol. Concentration of that extract to dryness under reduced pressure affords (S)-aspartyl- α -methylalanine isopropyl ester, characterized by the following structural formula

9

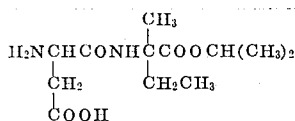


EXAMPLE 11

To 44 parts by volume of thionyl chloride in 470 parts of isopropyl alcohol is added 35.1 parts of (RS)-isovaline. 260 parts of benzene is then added and the resulting mixture is distilled at a slow rate for a period of 48 hours. At the end of that time, 200 parts by volume of a 1:3 by volume isopropyl alcohol-benzene mixture is added and the distillation is continued for another 48 hour period. The residue is stripped of remaining solvent and the resulting gum is dissolved in approximately 360 parts of ethyl ether. That solution is stored at 5° for 16 hours, then filtered. The filtrate is stored at 5° for 5 days, then stripped, shaken with pentane and stripped again to afford crystalline (RS)-isovaline isopropyl ester hydrochloride.

53.6 parts of N-benzoyloxycarbonyl-(S)-aspartic acid β -benzyl ester is dissolved in 89 parts of tetrahydrofuran and 16.5 parts by volume of N-methylmorpholine is added. The resulting mixture is cooled to -30° and 19.9 parts by volume of isobutyl chloroformate is added, keeping the temperature below -15°. After 10 minutes, (RS)-isovaline isopropyl ester, prepared from 29.5 parts of (RS)-isovaline isopropyl ester hydrochloride by the neutralization procedure described in Example 1, is added. The reaction mixture is kept at -10° for 16 hours and then 2 parts by volume of dimethylaminoethylamine is added. The mixture is diluted with 400 parts of water and 213 parts of ethyl ether. The layers are separated and the aqueous layer is extracted with ether. The ether layers are combined, washed three times with 1 N hydrochloric acid, then once with water, twice with aqueous potassium carbonate and twice more with water and then dried over anhydrous magnesium sulfate, stripped of solvent and concentrated to dryness under reduced pressure. There is thus obtained β -benzyl N-benzoyloxycarbonyl-(S)-aspartyl-(RS)-isovaline isopropyl ester.

39.9 parts of β -benzyl N-benzoyloxycarbonyl-(S)-aspartyl-(RS)-isovaline isopropyl ester is hydrogenolyzed in 300 parts by volume of 90 percent aqueous isopropyl alcohol, using 4 parts of palladium black catalyst. The resulting mixture is stripped, affording a foam which is then dissolved in 100 parts of water, decolorized with activated charcoal, filtered and stripped again. The resulting foam is concentrated to dryness under reduced pressure, affording (S)-aspartyl-(RS)-isovaline isopropyl ester, which is characterized by a specific rotation of +28.27° in 1 N hydrochloric acid. It is represented by the following structural formula



EXAMPLE 12

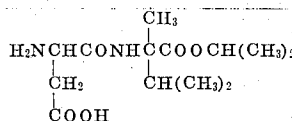
26.4 parts of (RS)- α -methylvaline, 31 parts of isopro-

10

pyl alcohol, 358 parts of toluene and 16.7 parts by volume of concentrated sulphuric acid are combined and refluxed. The toluene-water-isopropyl alcohol azeotrope is slowly distilled off over a 48-hour period. The reaction mixture is stripped to an oil at 40° and 100 parts by volume of 5 M aqueous potassium carbonate is added. 134 parts of methylene chloride is then added and the resulting mixture is shaken vigorously. The solids are allowed to settle and the supernatant liquid is decanted. The residue is extracted twice more with methylene chloride. The methylene chloride extracts are dried over anhydrous magnesium sulfate, stripped of solvent and then dried under reduced pressure to afford (RS)- α -methylvaline isopropyl ester.

19.7 parts of N-benzoyloxycarbonyl-(S)-aspartic acid β -benzyl ester is dissolved in 53 parts of tetrahydrofuran and 6.07 parts by volume of N-methylmorpholine is added. The resulting mixture is cooled to -30° and 7.3 parts by volume of isobutyl chloroformate is added, keeping the temperature below -15°. After 10 minutes, 9.53 parts of (RS)- α -methylvaline isopropyl ester is added and the resulting mixture is stored for 72 hours at 5°. The mixture is filtered and 1 part by volume of dimethylaminoethylamine is added. The mixture is then stripped of solvent, diluted with ethyl ester, washed in the manner described in Example 11, then dried over anhydrous magnesium sulfate and stripped of solvent. The resulting oil solidifies and the waxy solid thus obtained is chromatographed on a silica gel column, eluting with a 1:9 by volume ethyl acetatebenzene mixture. The eluate is decolorized with activated charcoal, stripped and seeded to afford crystalline β -N-benzoyloxycarbonyl-(S)-aspartyl-(RS)- α -methylvaline isopropyl ester, melting at 70°-86°.

12.8 parts of β -benzyl N-benzoyloxycarbonyl-(S)-aspartyl-(RS)- α -methylvaline isopropyl alcohol, using 1.2 parts of palladium black catalyst. The resulting mixture is stripped to dryness and then stirred with water, decolorized with activated charcoal and filtered. The filtrate is stripped to give, as a solid foam, (S)-aspartyl-(RS)- α -methylvaline isopropyl ester. That product exhibits a specific rotation of +28.29° in 1 N hydrochloric acid. It is represented by the following structural formula



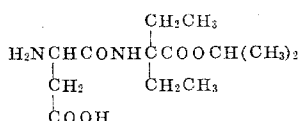
EXAMPLE 13

To 29 parts by volume of thionyl chloride, 230 parts of isopropyl alcohol and 176 parts of benzene is added to 26.23 parts of α -amino- α -ethylbutyric acid and the mixture is azeotropically distilled over a period of about 48 hours. An additional 176 parts of benzene is then added and azeotropic distillation is continued for 48 hours longer. The remaining solvents are removed by distillation to give a solid residue. That material is dissolved in water and the solution made basic by the addition of aqueous sodium carbonate. Extraction with methylene chloride affords an organic solution, which is washed with water, dried over anhydrous magnesium

sulfate and stripped of solvent to afford, as an oil α -amino- α -ethylbutyric acid isopropyl ester.

To a solution of 18.01 parts of N-benzyloxycarbonyl-(S)-aspartic acid β -benzyl ester in 27 parts of tetrahydrofuran is added 5.8 parts by volume of N-methylmorpholine and the resulting solution is cooled to -30° . To that solution is then added 6.95 parts by volume of isobutyl chloroformate, keeping the temperature between -30° and -15° . After an additional stirring period of about 10 minutes, 8.66 parts of α -amino- α -ethylbutyric acid isopropyl ester is added at -15° . That reaction mixture is stored at 5° for about 16 hours, then is filtered and 0.5 part by volume of dimethylaminoethylamine is added. After standing for a few minutes, the mixture is diluted with water and the product is extracted into methylene chloride. The extract is washed successively with dilute hydrochloric acid and water, dried over anhydrous magnesium sulfate and distilled to dryness to afford the product as an oil. Purification by chromatography on silica gel and elution with 5 percent ethyl acetate in benzene affords β -benzyl N-benzyloxycarbonyl-(S)-aspartyl- α -amino- α -ethylbutyric acid isopropyl ester.

A mixture containing 9 parts of β -benzyl-N-benzyloxycarbonyl-(S)-aspartyl- α -amino- α -ethylbutyric acid isopropyl ester, 200 parts by volume of 90 percent aqueous isopropyl alcohol and 0.9 part of palladium black is shaken with hydrogen at atmospheric pressure and room temperature until the uptake of gas ceases. The catalyst is removed by filtration, the solvent by distillation and the resulting residue is dissolved in water. The aqueous solution is decolorized with activated carbon and the water is distilled to afford (S)-aspartyl- α -amino- α -ethylbutyric acid isopropyl ester. It exhibits an optical rotation, in 1 Molar hydrochloric acid, of $+35^\circ$ and is represented by the following structural formula



EXAMPLE 14

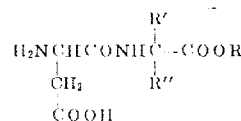
When the procedures of Example 11 are carried out, substituting an equivalent quantity of (R)-isovaline as the starting material, (S)- α -aspartyl-(R)-isovaline isopropyl ester is produced.

EXAMPLE 15

The substitution, as the starting material, of an equivalent quantity of (R)- α -methylvaline in the procedures of Example 12 results in (S)-aspartyl-(R)- α -methylvaline isopropyl ester.

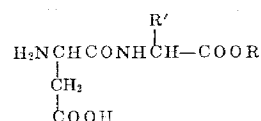
What is claimed is:

1. A compound of the formula



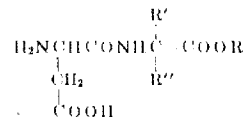
wherein R and R' are lower alkyl radicals containing less than four carbon atoms and R'' is hydrogen or a lower alkyl radical containing less than four carbon atoms, with the provision that, when R' and R'' are dissimilar, the carbon atom to which R' and R'' are attached possesses the (R) stereochemical configuration.

2. As in claim 1, a compound of the formula



wherein R, R' and R'' are lower alkyl radicals containing less than four carbon atoms with the provision that, when R' and R'' are dissimilar, the carbon atom to which R' and R'' are attached possesses the (R) stereochemical configuration.

3. As in claim 1, a compound of the formula



wherein R and R' are lower alkyl radicals containing less than four carbon atoms, with the provision that the carbon atom to which R' is attached possesses the (R) stereochemical configuration.

4. As in claim 1, the compound which is (S)-aspartyl-(R)-alanine n-propyl ester.

5. As in claim 1, the compound which is (S)-aspartyl-(R)-alanine isopropyl ester.

6. As in claim 1, the compound which is (S)-aspartyl-(R)-alanine methyl ester.

7. As in claim 1, the compound which is (S)-aspartyl-(R)- α -aminobutyric acid isopropyl ester.

8. As in claim 1, the compound which is (S)-aspartyl-(R)-valine isopropyl ester.

9. As in claim 1, the compound which is (S)-aspartyl- α -methylalanine isopropyl ester.

10. As in claim 1, the compound which is (S)-aspartyl- α -methylalanine ethyl ester.

11. As in claim 1, the compound which is (S)-aspartyl-(R)-isovaline isopropyl ester.

12. As in claim 1, the compound which is (S)-aspartyl-(R)- α -methylvaline isopropyl ester.

* * * * *