

A METHOD OF SYNTHESISING AN AMINO ACID DERIVATIVE OF AZELAIC ACID

Field of Invention

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This present invention relates to a method of producing derivative of azelaic acid. In more particular, the present invention relates to a method of producing amide ester derivative of azelaic acid under anhydrous condition.

10 Background of The Invention

It has been well-known that azelaic acid or nonanedioic acid is used as topical drug for treating acne vulgaris. However, this saturated dicarboxylic acid has a crystalline structure with high melting point ranging from 98°C-103°C, therefore it will be
15 difficult to incorporate into cream formulation under standard condition.

A dosage of azelaic acid at 20% concentration is required in the cream formulation to exhibit significant dermatological performance with efficacy equivalent to 4% hydroquinone. But this dosage is high enough to cause a slightly great level of
20 peeling, burning and stinging to the skin.

The discovery of potassium azeloyl diglycinate as a new derivative of azelaic acid can effectively perform as an anti-acne agent by using only 5% in formulation. There are some prior arts relating to several compounds or compositions for cosmetic,
25 pharmaceutical and dermatological applications.

United States Patent No. 6528068(B1) discloses a cosmetic composition comprising n-acyl neutral amino acid esters of lower alcohols. Based on the prior art, it is an oily material containing structure of long straight-chain or branched-chain with saturated
30 or unsaturated acyl group, where the hydrocarbon group of the alcohol constituting the ester is a branched-chain or straight-chain alkyl or alkenyl group. The composition

the ester is a branched-chain or straight-chain alkyl or alkenyl group. The composition can be further added with an ultraviolet ray adsorbent and an inorganic pigment.

A PCT application Patent No. 2006010590(A1) describes about n-acylated derivatives of dicarboxylic acids with amino acids and/or peptides of vegetable protein hydrolysates for the preparation of cosmetic and pharmaceutical formulations. The compounds are produced by acylation of dicarboxylic acids according to conventional Schotten-Bauman condition.

10 In the conventional Schotten-Bauman condition, acylation reaction forming an amide linkage between carboxylic group and N-terminal of amino acid is achieved through an exothermic reaction of an acyl halide and amino source in an alkaline aqueous medium. In the prior art, azeloyl dichloride is reacted with glycine under a controlled pH of 9-11 by using 40% potassium hydroxide solution in aqueous medium. The
15 aqueous medium is then adjusted to pH of 7-7.5 with lactic acid and shall give a clear colorless to pale yellow solution as final product.

But often, the conventional method has several limitations. Due to high sensitivity towards moisture, precaution has to be taken for preventing the acyl halide from
20 hydrolyzes to its corresponding carboxylic acid. Besides, it is important to monitor the alkalinity of the aqueous medium closely because excess base would cause hydrolysis of acyl halide as well.

Contamination of products can be caused by traces amount of halide ions dissociated
25 from acyl halide and this is not acceptable in cosmetic and pharmaceutical applications. Furthermore, the conventional Schotten-Bauman condition often provide good yield for the neutral amino acids only.

In another hand, amino acids such as L-aspartic acid, L-glutamic acid, L-methionine,
30 L-cysteine or L-serine will require precaution steps of protecting the side chain

functional groups to minimize side products formation. The acyl transfer reaction through the conventional Schotten-Bauman condition will result in product which is soluble in water and hence it is often complex to isolate the pure product by involving the removal of aqueous medium.

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It is important to invent a method of producing derivative of azelaic acid by a modified Schotten-Bauman condition which utilizes aprotic solvents and anhydrous salt for establishing a dry state favourable to the reactants and desired product which is obtained by acylation reaction. Besides, it is also desirable to introduce a method
10 which provides a high yield of desired product but minimizes the yield of side products.

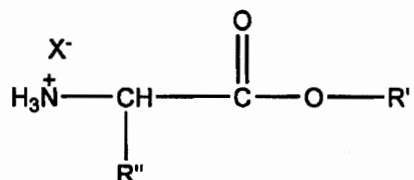
Summary of The Invention

15 The primary object of the present invention is to invent a method of producing derivative of azelaic acid in a favourable dry state for acylation reaction by utilizing aprotic solvents and anhydrous salt. Therefore, reactant such as acyl halide which is sensitive to moisture will be less convertible to its corresponding carboxylic acid by hydrolysis and it can be less complex to isolate the desired product since an aqueous
20 medium is not required in the reaction.

Another object of the present invention is to invent a method of producing derivative of azelaic acid in high yield but low amount of unnecessary side products. Through this modified Schotten-Bauman condition, high yield of the desired product can be
25 produced from not only the neutral amino acids, but also amino acids possessing different functional groups as side chains.

At least one of the preceding objects is met, in whole or in part, by the present invention, in which the embodiment of the present invention describes a method of
30 producing amide ester derivative of azelaic acid comprising treating glycine ethyl

ester hydrochloride or an amino acid hydrohalide of the general formula:



wherein R' is substituted or unsubstituted alkyl group moiety, cyclic alkyl or aromatic moiety and R'' is side chain group of the amino acid selected from substituted or unsubstituted alkyl moiety, cyclic alkyl or aromatic moiety and X⁻ is halide ion to be dissolved in an aprotic solvent with an organic base to effect deprotonation, reacting the deprotonated product with an azelaic acid halide also dissolved in an aprotic solvent, subjecting the reactant mixture in contact with an aqueous medium, contacting the reactant mixture with an anhydrous salt to remove any moisture therefrom and removing the aprotic solvent from the reactant mixture.

The present invention describes a method of producing amide ester derivative of azelaic acid by a modified Schotten-Bauman condition. An anhydrous state is established throughout the acylation reaction by utilizing aprotic solvents and anhydrous salt.

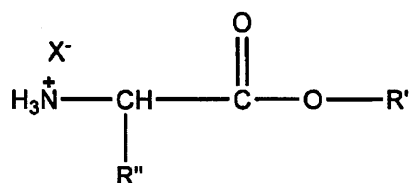
Moreover, an organic base such as pyridine is used for removing hydrohalide molecules. Hence, it is advantageous that this method shall allow the desired products to be easily isolated from the anhydrous medium.

Detailed Description of The Invention

One skilled in the art will readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The embodiment described herein is not intended as limitations

on the scope of the invention.

The present invention discloses a method of producing amide ester derivative of azelaic acid comprising treating glycine ethyl ester hydrochloride or an amino acid
5 hydrohalide of the general formula:



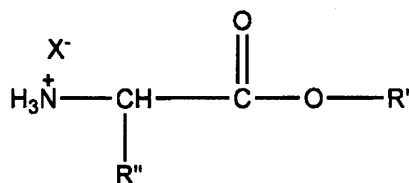
wherein R' is substituted or unsubstituted alkyl group moiety, cyclic alkyl or aromatic
10 moiety and R'' is side chain group of the amino acid selected from substituted or unsubstituted alkyl moiety, cyclic alkyl or aromatic moiety and X⁻ is halide ion to be dissolved in an aprotic solvent with an organic base to effect deprotonation, reacting the deprotonated product with an azelaic acid halide also dissolved in an aprotic solvent, subjecting the reactant mixture in contact with an aqueous medium,
15 contacting the reactant mixture with an anhydrous salt to remove any moisture therefrom and removing the aprotic solvent from the reactant mixture.

In the present invention, the method of producing amide ester derivative of azelaic acid is by acylation reaction between the deprotonated amino acid ester hydrohalide
20 and azelaic acid halide. An aprotic solvent for dissolving both amino acid ester hydrohalide and azelaic acid halide is preferably tetrahydrofuran, dioxane, chloroform, dichloroform or any combination thereof.

As further described in the present invention, the amino acid ester hydrohalide is
25 treated with an organic base to effect deprotonation. Protonation on the amino acid ester is necessary to prevent direct nucleophilic attack among other amino acid ester molecules to form diketopiperazine as undesirable product.

The general formula structure shown as below is a protonated form of the amino acid ester by hydrohalide:

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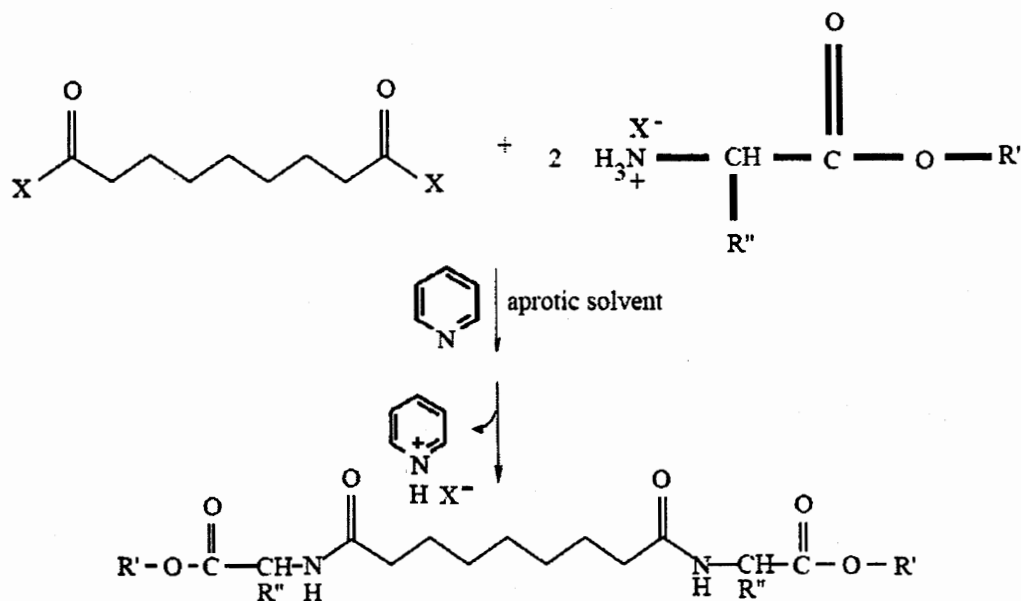


- wherein R is substituted or unsubstituted alkyl group moiety, cyclic alkyl or aromatic moiety and R'' is side chain group of the amino acid selected from substituted or unsubstituted alkyl moiety, cyclic alkyl or aromatic moiety and X⁻ is halide ion.

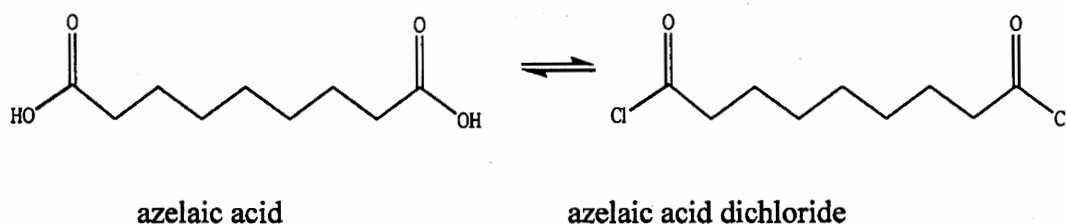
- However, deprotonating the amino acid ester hydrohalide on its ammonium group by an organic base is important to cause a free amino group with an electron pair to be available for nucleophilic attack on the carbonyl group of the azelaic acid dihalide.
- Thus, acylation reaction can take place and produce the amide ester derivative of azelaic acid.

- The most preferred amino acid ester hydrohalide used is amino acid ethyl ester hydrochloride which includes neutral α-amino acids such as glycine ethyl ester hydrochloride, L-valine ethyl ester hydrochloride, L-alanine ethyl ester hydrochloride, L-leucine ethyl ester hydrochloride; amino acids containing sulphur side chain such as L-methionine ethyl ester hydrochloride, L-cysteine ethyl ester hydrochloride; amino acid containing hydroxyl side chain such as L-serine ethyl ester hydrochloride; amino acid containing carbonyl side chain such as L-glutamic acid diethyl ester hydrochloride or any combination of the amino acids.

For the acylation reaction, the molar ratio of amino acid ester hydrohalide to azelaic



By using the aprotic solvent, an anhydrous reaction condition can be established and thus causing the azelaic acid halide, shown below as azelaic acid dichloride which is sensitive to moisture will be less convertible to its corresponding carboxylic acid by hydrolysis:



As disclosed in the present invention, an organic base which is pyridine can be used as a deprotonizing agent to remove out hydrohalide molecules. Taking for as an
15 example, pyridine can function as a hydrochloric acid extractor for removing

hydrochloride molecules.

In a preferred embodiment of the present invention, pyridine is added into the amino acid ester hydrochloride dissolved in aprotic solvent to remove the hydrochloride molecules as pyridinium hydrochloride salts thus resulting in deprotonation of the ester compound.

In the present invention, the azelaic acid halide solution is added drop wise into the deprotonated amino acid ester hydrohalide solution to initiate the acylation reaction. A preferred embodiment has described an acylation reaction between azelaic acid dichloride with deprotonated amino acid ester hydrochloride. Further hydrochloride molecules produced from the acyl transfer reaction can also be removed by pyridine.

Hereinafter, the present invention claims a method of producing amide ester derivative of azelaic acid comprising the step of contacting the reactant mixture with an anhydrous salt to remove any moisture therefrom and removing the aprotic solvent from the reactant mixture.

One of the preferred embodiments in the present invention has disclosed that the aprotic solvent phase of the solution mixture shall be retained and dried with the anhydrous salt preferably anhydrous sodium sulfate. Subsequently, the aprotic solvent is removed by vacuum evaporation.

In the present invention, the percent crude yield of amide ester derivative of azelaic acid with amino acid ester shall be in a range from 9.6% to 87%. A sample of the crude product shall be analyzed for its purity via High Performance Liquid Chromatography (HPLC) method.

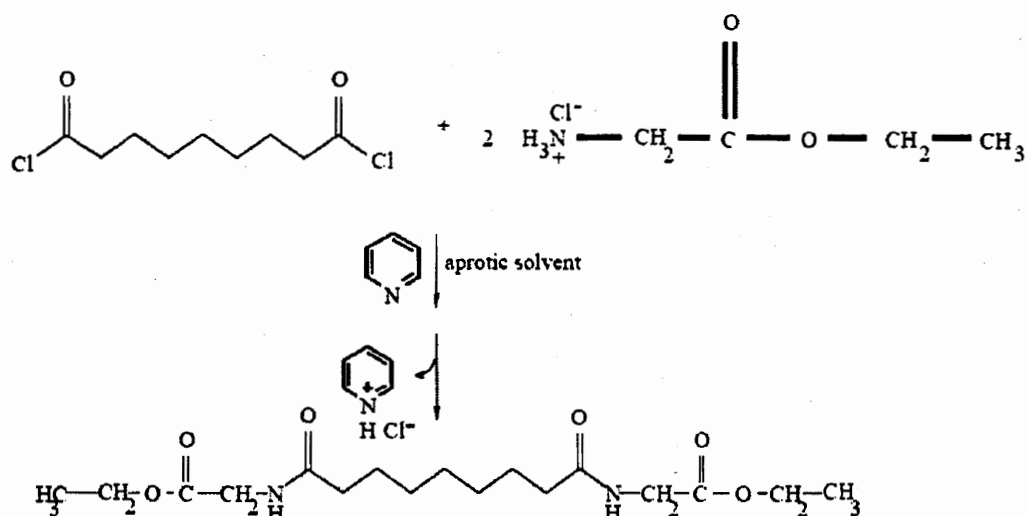
Examples

Example 1

Preparation of 0.25 mol glycine ethyl ester hydrochloride by weighing 35g into a 500ml 3-neck round bottom flask is added with 200ml chloroform. Approximately 5 40ml pyridine is subsequently added into the solution and stirred at room temperature until homogeneous. 0.13 mol azelaic acid dichloride is prepared by dissolving an amount of 28g into 200ml chloroform. The azelaic acid dichloride solution is added drop wise into the glycine ethyl ester hydrochloride solution to initiate the reaction by stirring for 2 hours and the solution mixture is chilled overnight at temperature 5°C.

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The chemical reaction that has taken place is shown as below:



The solution mixture is washed with several portions of 200ml deionized water to remove pyridinium hydrochloride salts formed during acylation reaction. subsequently, several portions of diluted hydrochloric acid solution is used to 15 neutralize the unreacted pyridine and further pyridinium hydrochloride salts will be removed by washing with another several portions of 200ml deionized water. But alternatively, the hydrochloric acid solution can be also added straight after the solution is chilled. The chloroform phase is retained and dried with anhydrous sodium

sulphate.

Moreover, chloroform is then removed by vacuum evaporation and finally the residue shall be washed with petroleum ether to remove azelaic acid ester if presence. The
5 amide ester derivative of azelaic acid with glycine ethyl ester obtained will give a percent crude yield of 78.50%. A crude sample will be recrystallized from chilled isopropanol and its purity tested via HPLC has set in a range of 74.90% to 99.89%.

From the HPLC analysis, the recrystallized sample has shown a peak at retention time
10 of 10.16min under conditions using column 5 μ -ODS-3 with dimensions of 250mm x 4.6mm, mobile phase containing 30% acetonitrile and 70% distilled water and flow rate of 1.0ml/min.

Example 2

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Preparation of 0.25 mol L-valine ethyl ester hydrochloride by weighing 46g into a 500ml 3-neck round bottom flask is added with 100ml dichloromethane. Approximately 40ml pyridine is subsequently added into the solution and stirred at room temperature until homogeneous. 0.13 mol azelaic acid dichloride is prepared by
20 dissolving an amount of 28g into 100ml dichloromethane. The azelaic acid dichloride solution is added drop wise into the L-valine ethyl ester hydrochloride solution to initiate the reaction by stirring for 2 hours and the solution mixture is chilled overnight at temperature 5°C.

25 The solution mixture is washed with several portions of 200ml deionized water to remove pyridinium hydrochloride salts formed during acylation reaction. subsequently, several portions of diluted hydrochloric acid solution is used to neutralize the unreacted pyridine and further pyridinium hydrochloride salts will be removed by washing with another several portions of 200ml deionized water. The
30 dichloromethane phase is retained and dried with anhydrous sodium sulphate.

Moreover, dichloromethane is then removed by vacuum evaporation and finally the residue shall be washed with petroleum ether to remove azelaic acid ester if presence. The amide ester derivative of azelaic acid with L-valine ethyl ester obtained will give
5 a percent crude yield of 76.38%.

In the HPLC analysis, the recrystallized sample shall give optimized peak resolution tested under conditions of using column 5 μ -ODS-3 with dimensions of 250mm x 4.6mm, mobile phase containing 60% acetonitrile and 40% distilled water, flow rate
10 of 1.5ml/min, 0.1793g sample in 10ml acetonitrile and 50 μ L injection volume.

The component in the crude sample is resolved to several peaks with the major peak occurring at 4.80min giving 81.76% peak area. Two other small peaks are occurred at 3.90min and 6.39min whereby each occupying peak area of 15.06% and 3.00%
15 respectively. The specific rotation $[\alpha]_{20}$ is recorded as -23.05° for 1.30g sample in 100cm³ absolute ethanol whereas the specific rotation $[\alpha]_{20}$ of the starting L-amino acid ethyl ester hydrochloride is indicated as $+22.34^\circ$ for 1.14g sample in 100cm³ absolute ethanol.

20 Example 3

Preparation of 0.25 mol L-alanine ethyl ester hydrochloride by weighing 39g into a 500ml 3-neck round bottom flask is added with 100ml dichloromethane. Approximately 40ml pyridine is subsequently added into the solution and stirred at
25 room temperature until homogeneous. 0.13 mol azelaic acid dichloride is prepared by dissolving an amount of 28g into 100ml dichloromethane. The azelaic acid dichloride solution is added drop wise into the L-alanine ethyl ester hydrochloride solution to initiate the reaction by stirring for 2 hours and the solution mixture is chilled overnight at temperature 5°C.

The solution mixture is washed with several portions of 200ml deionized water to remove pyridinium hydrochloride salts formed during acylation reaction. subsequently, several portions of diluted hydrochloric acid solution is used to neutralize the unreacted pyridine and further pyridinium hydrochloride salts will be removed by washing with another several portions of 200ml deionized water. The dichloromethane phase is retained and dried with anhydrous sodium sulphate.

Moreover, dichloromethane is then removed by vacuum evaporation and finally the residue shall be washed with petroleum ether to remove azelaic acid ester if presence.

10 The amide ester derivative of azelaic acid with L-alanine ethyl ester obtained will give a percent crude yield of 87.01%.

In the HPLC analysis, the recrystallized sample shall give optimized peak resolution tested under conditions of using column 5 μ -ODS-3 with dimensions of 250mm x 4.6mm, mobile phase containing 40% acetonitrile and 60% distilled water, flow rate of 1.5ml/min, 0.2510g sample in 10ml acetonitrile and 50 μ L injection volume.

The component in the crude sample is resolved to several peaks with the major peak occurring at 7.11min giving 86.74% peak area. Two other small peaks are occurred at 2.32min and 5.65min whereby each occupying peak area of 1.48% and 5.14% respectively. The specific rotation $[\alpha]_{20}$ is recorded as -44.10° for 1.11g sample in 100cm³ absolute ethanol whereas the specific rotation $[\alpha]_{20}$ of the starting L-amino acid ethyl ester hydrochloride is indicated as $+6.99^\circ$ for 1.70g sample in 100cm³ absolute ethanol.

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Example 4

Preparation of 0.25 mol L-leucine ethyl ester hydrochloride by weighing 49g into a 500ml 3-neck round bottom flask is added with 100ml dichloromethane.

30 Approximately 40ml pyridine is subsequently added into the solution and stirred at

room temperature until homogeneous. 0.13 mol azelaic acid dichloride is prepared by dissolving an amount of 28g into 100ml dichloromethane. The azelaic acid dichloride solution is added drop wise into the L-leucine ethyl ester hydrochloride solution to initiate the reaction by stirring for 2 hours and the solution mixture is chilled
5 overnight at temperature 5°C.

The solution mixture is washed with several portions of 200ml deionized water to remove pyridinium hydrochloride salts formed during acylation reaction. subsequently, several portions of diluted hydrochloric acid solution is used to
10 neutralize the unreacted pyridine and further pyridinium hydrochloride salts will be removed by washing with another several portions of 200ml deionized water. The dichloromethane phase is retained and dried with anhydrous sodium sulphate.

Moreover, dichloromethane is then removed by vacuum evaporation and finally the
15 residue shall be washed with petroleum ether to remove azelaic acid ester if presence. The amide ester derivative of azelaic acid with L-leucine ethyl ester obtained will give a percent crude yield of 83.64%.

In the HPLC analysis, the recrystallized sample shall give optimized peak resolution
20 tested under conditions of using column 5 μ -ODS-3 with dimensions of 250mm x 4.6mm, mobile phase containing 60% acetonitrile and 40% distilled water, flow rate of 1.0ml/min, 0.5790g sample in 10ml acetonitrile and 50 μ L injection volume.

The component in the crude sample is resolved to several peaks with the major peak
25 occurring at 7.39min giving 82.20% peak area. Two other small peaks are occurred at 2.31min and 5.92min whereby each occupying peak area of 5.10% and 4.64% respectively. The specific rotation $[\alpha]_{20}$ is recorded as -30.99° for 1.37g sample in 100cm³ absolute ethanol whereas the specific rotation $[\alpha]_{20}$ of the starting L-amino acid ethyl ester hydrochloride is indicated as +24.73° for 1.05g sample in 100cm³
30 absolute ethanol.

Example 5

Preparation of 0.16 mol L-serine ethyl ester hydrochloride by weighing 27g into a
5 250ml 3-neck round bottom flask is added with 50ml dichloromethane.
Approximately 26ml pyridine is subsequently added into the solution and stirred at
room temperature until homogeneous. 0.08 mol azelaic acid dichloride is prepared by
dissolving an amount of 18g into 70ml dichloromethane. The azelaic acid dichloride
solution is added drop wise into the L-serine ethyl ester hydrochloride solution to
10 initiate the reaction by stirring for 2 hours and the solution mixture is chilled
overnight at temperature 5°C.

The solution mixture is washed with several portions of 150ml deionized water to
remove pyridinium hydrochloride salts formed during acylation reaction.
15 subsequently, several portions of diluted hydrochloric acid solution is used to
neutralize the unreacted pyridine and further pyridinium hydrochloride salts will be
removed by washing with another several portions of 150ml deionized water. The
dichloromethane phase is retained and dried with anhydrous sodium sulphate.

20 Moreover, dichloromethane is then removed by vacuum evaporation and finally the
residue shall be washed with petroleum ether to remove azelaic acid ester if presence.
The amide ester derivative of azelaic acid with L-serine ethyl ester obtained will give
a percent crude yield of 9.58%.

25 In the HPLC analysis, the recrystallized sample shall give optimized peak resolution
tested under conditions of using column 5 μ -ODS-3 with dimensions of 250mm x
4.6mm, mobile phase containing 50% acetonitrile and 50% distilled water, flow rate
of 1.2ml/min, 0.1992g sample in 10ml of acetonitrile:water in 1:1 ratio and 50 μ L
injection volume.

The component in the hard yellowish solid crude sample based on 2:1 mol reactant ratio is resolved to several peaks with the major single peak occurring at 4.61min giving 50.78% peak area. Two groups of other peaks are occurred at 2.62min and 3.75min whereby each occupying peak area of 16.57% and 32.71% respectively. The specific rotation $[\alpha]_{20}$ is recorded as -3.805° for 1.05g sample in 100cm³ absolute ethanol.

Example 6

- 10 Preparation of 0.16 mol L-serine ethyl ester hydrochloride by weighing 27g into a 250ml 3-neck round bottom flask is added with 100ml dichloromethane. Approximately 39ml pyridine is subsequently added into the solution and stirred at room temperature until homogeneous. 0.16 mol azelaic acid dichloride is prepared by dissolving an amount of 35g into 70ml dichloromethane. The azelaic acid dichloride solution is added drop wise into the L-serine ethyl ester hydrochloride solution to initiate the reaction by stirring for 2 hours and chilled overnight at temperature 5°C.

- The solution mixture is washed with several portions of 150ml deionized water to remove pyridinium hydrochloride salts formed during acylation reaction. subsequently, several portions of diluted hydrochloric acid solution is used to neutralize the unreacted pyridine and further pyridinium hydrochloride salts will be removed by washing with another several portions of 150ml deionized water. The dichloromethane phase is retained and dried with anhydrous sodium sulphate.
- 25 Moreover, dichloromethane is then removed by vacuum evaporation and finally the residue shall be washed with petroleum ether to remove azelaic acid ester if presence. A translucent yellowish paste based on 1:1 mol reactant ratio shall have a much higher % crude yield which is recorded as 44.64g as compared to 2:1 mol reactant ratio.

- 30 The crude sample is resolved under conditions of using column 5 μ -ODS-3 with

dimensions of 250mm x 4.6mm, mobile phase containing 50% acetonitrile and 50% distilled water and flow rate of 1.2ml/min. In the HPLC analysis, it has revealed that the % area peak at 4.53min reduced drastically from 50% to only 6.20%.

- 5 However, other peaks represented by the groups of small peaks appearing before and after peak at 4.5min increased in total % peak area from 16.57% to 23.96% and 32.71% to 69.80% respectively. The specific rotation $[\alpha]_{20}$ is recorded as $+6.92^\circ$ for 1.59g sample in 100cm³ absolute ethanol.

10 Example 7

- Preparation of 0.15 mol L-cysteine ethyl ester hydrochloride by weighing 27.9g into a 500ml 3-neck round bottom flask is added with 100ml dichloromethane. Approximately 24ml pyridine is subsequently added into the solution and stirred at
15 room temperature until homogeneous. 0.08 mol azelaic acid dichloride is prepared by dissolving an amount of 17g into 100ml dichloromethane. The azelaic acid dichloride solution is added drop wise into the L-cysteine ethyl ester hydrochloride solution to initiate the reaction by stirring for 2 hours and the solution mixture is chilled overnight at temperature 5°C.

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- The solution mixture is washed with several portions of 200ml deionized water to remove pyridinium hydrochloride salts formed during acylation reaction. subsequently, several portions of diluted hydrochloric acid solution is used to neutralize the unreacted pyridine and further pyridinium hydrochloride salts will be
25 removed by washing with another several portions of 200ml deionized water. The dichloromethane phase is retained and dried with anhydrous sodium sulphate.

- Moreover, dichloromethane is then removed by vacuum evaporation and finally the residue shall be washed with petroleum ether to remove azelaic acid ester if presence.
30 The amide ester derivative of azelaic acid with L-cysteine ethyl ester obtained will

give a percent crude yield of 76.92%.

In the HPLC analysis, the crude sample shall give optimized peak resolution tested under conditions of using column 5 μ -ODS-3 with dimensions of 250mm x 4.6mm, mobile phase containing 50% acetonitrile and 50% distilled water, flow rate of 1.2ml/min, 0.2262g sample in 10ml of acetonitrile:water in 1:1 ratio and 50 μ L injection volume.

The component contained in a hard white translucent wax like solid of crude sample is resolved to several peaks with the major peak occurring at 8.698min giving 49.097% peak area. Four other small peaks are occurred at 5.62min, 12.09min, 14.58min and 26.47min whereby each occupying peak area of 10.27%, 9.30%, 9.91% and 12.80% respectively. The specific rotation $[\alpha]_{20}$ is recorded as -24.49° for 1.29g sample in 100cm³ absolute ethanol.

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Example 8

Preparation of 0.07 mol L-methionine ethyl ester hydrochloride by weighing 15g into a 250ml 3-neck round bottom flask is added with 50ml dichloromethane. Approximately 12ml pyridine is subsequently added into the solution and stirred at room temperature until homogeneous. 0.04 mol azelaic acid dichloride is prepared by dissolving an amount of 7.6g into 50ml dichloromethane. The azelaic acid dichloride solution is added drop wise into the L-methionine ethyl ester hydrochloride solution to initiate the reaction by stirring for 2 hours and the solution mixture is chilled overnight at temperature 5°C.

The solution mixture is washed with several portions of 150ml deionized water to remove pyridinium hydrochloride salts formed during acylation reaction. subsequently, several portions of diluted hydrochloric acid solution is used to neutralize the unreacted pyridine and further pyridinium hydrochloride salts will be

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removed by washing with another several portions of 150ml deionized water. The dichloromethane phase is retained and dried with anhydrous sodium sulphate.

Moreover, dichloromethane is then removed by vacuum evaporation and finally the residue shall be washed with petroleum ether to remove azelaic acid ester if presence. The amide ester derivative of azelaic acid with L-methionine ethyl ester obtained will give a percent crude yield of 75.53%.

In the HPLC analysis, the crude sample shall give optimized peak resolution tested under conditions of using column 5 μ -ODS-3 with dimensions of 250mm x 4.6mm, mobile phase containing 50% acetonitrile and 50% distilled water, flow rate of 1.2ml/min, 0.1052g sample in 10ml acetonitrile and 50 μ L injection volume.

The final crude product is isolated as a beige powder with pungent thio odor. By resolving the component in the crude sample via HPLC analysis, several peaks with the major peak occurring at 12.29min giving 70.56% peak area.

Five other small peaks are occurred at 6.50min, 14.55min, 16.36min, 17.47min and 19.06min whereby each occupying peak area of 9.22%, 7.15%, 2.19%, 1.75% and 2.00% respectively. The specific rotation $[\alpha]_{20}$ is recorded as -22.96° for 1.33g sample in 100cm³ absolute ethanol.

Example 9

Preparation of 0.08 mol L-glutamic acid diethyl ester hydrochloride by weighing 20g into a 250ml 3-neck round bottom flask is added with 25ml dichloromethane. Approximately 13ml pyridine is subsequently added into the solution and stirred at room temperature until homogeneous. 0.04 mol azelaic acid dichloride is prepared by dissolving an amount of 9g into 40ml dichloromethane. The azelaic acid dichloride solution is added drop wise into the L-glutamic acid diethyl ester hydrochloride

solution to initiate the reaction by stirring for 2 hours and the solution mixture is chilled overnight at temperature 5°C.

5 The solution mixture is washed with several portions of 150ml deionized water to remove pyridinium hydrochloride salts formed during acylation reaction. subsequently, several portions of diluted hydrochloric acid solution is used to neutralize the unreacted pyridine and further pyridinium hydrochloride salts will be removed by washing with another several portions of 150ml deionized water. The dichloromethane phase is retained and dried with anhydrous sodium sulphate.

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Moreover, dichloromethane is then removed by vacuum evaporation and finally the residue shall be washed with petroleum ether to remove azelaic acid ester if presence. The amide ester derivative of azelaic acid with L-glutamic acid diethyl ester obtained will give a percent crude yield of 79.27%.

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In the HPLC analysis, the crude sample shall give optimized peak resolution tested under conditions of using column 5 μ -ODS-3 with dimensions of 250mm x 4.6mm, mobile phase containing 60% acetonitrile and 40% distilled water, flow rate of 1.0ml/min, 0.2706g sample in 10ml acetonitrile and 50 μ L injection volume.

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By resolving the component in the crude sample via HPLC analysis, three peaks with the major peak occurring at 7.28min has resulted in giving 89.89% peak area. Two other small peaks are occurred at 5.56min and 10.25min whereby each occupying peak area of 6.08% and 1.36% respectively. The specific rotation $[\alpha]_{20}$ is recorded as

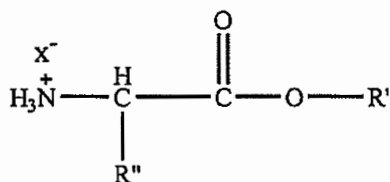
25 -17.48° for 1.20g sample in 100cm³ absolute ethanol.

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Claims

1. A method of producing amide ester derivative of azelaic acid comprising:
treating an amino acid hydrohalide of the general formula,

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- wherein R' and R'' are each alkyl group moiety and side chain group of the amino acid both selected from substituted or unsubstituted alkyl moiety, cyclic alkyl or aromatic moiety to be dissolved in an aprotic solvent with pyridine to effect deprotonation, in
- 10 which the amino acid ester hydrohalide is glycine ethyl ester hydrochloride, L-valine ethyl ester hydrochloride, L-alanine ethyl ester hydrochloride, L-leucine ethyl ester hydrochloride, L-methionine ethyl ester hydrochloride, L-cysteine ethyl ester hydrochloride, L-serine ethyl ester hydrochloride, L-glutamic acid diethyl ester
- 15 hydrochloride or any combination thereof;
- adding azelaic acid halide which is also dissolved in pyridine in a drop wise manner into the deprotonated product;
- washing the reactant mixture with an aqueous medium while retaining the aprotic solvent phase;
- 20 adding an anhydrous salt to the retained phase so as to remove any moisture therefrom; and
- removing the aprotic solvent from the reactant mixture.

2. A method as claimed in claim 1, wherein the aprotic solvent is tetrahydrofuran, dioxane, chloroform, dichloroform or any combination thereof.

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3. A method as claimed in claim 1, wherein the anhydrous salt is anhydrous sodium

sulfate.

4. An amide ester derivative of azelaic acid as claimed in claim 1 is azelaic acid diglycinate ethyl ester, azelaic acid divalinate ethyl ester, azelaic acid dialaninate ethyl ester, azelaic acid dileucinate ethyl ester, azelaic acid diserinate ethyl ester, azelaic acid dicysteinate ethyl ester, azelaic acid dimethionate ethyl ester or azelaic acid di glutamic acid diethyl ester.

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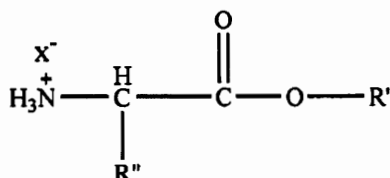
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Abstract

**A METHOD OF PRODUCING
DERIVATIVE OF AZELAIC ACID**

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A method of producing amide ester derivative of azelaic acid comprising treating an amino acid hydrohalide of the general formula,



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wherein R' and R'' are each alkyl group moiety and side chain group of the amino acid both selected from substituted or unsubstituted alkyl moiety, cyclic alkyl or aromatic moiety to be dissolved in an aprotic solvent with an organic base to effect deprotonation, reacting the deprotonated product with an azelaic acid halide also dissolved in an aprotic solvent, contacting the reactant mixture with an anhydrous salt to remove any moisture therefrom and removing the aprotic solvent from the reactant mixture.

(No drawing disclosed.)

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