

Preparation and use of salts of the pure enantiomers of α -lipoic acid

Description

The invention relates to new optically active salts of α -lipoic acid and of optically active α -methylbenzylamine and a process for the preparation of the enantiomerically pure α -lipoic acids and of the enantiomerically pure dihydrolipoic acids.

α -lipoic acid is 1,2-dithiolane-3-pentanoic acid (thioctic acid).

As a coenzyme of α -ketonic acid dehydrogenases α -lipoic acid is widespread in plants and animals; the naturally occurring form has the R-configuration. When " α -lipoic acid" is referred to hereinbelow, this is always an α -lipoic acid with unknown stereochemical composition.

α -lipoic acid is pharmacologically active and has anti-inflammatory and antinociceptive (analgesic) as well as cytoprotective properties.

A series of salts are known of α -lipoic acid, for example salts of α -lipoic acid with optically active bases such as with the basic amino acids arginine and lysine. (Spanish patent No. 313,056). Neither the reaction of L-arginine with D,L- α -lipoic acid nor the reaction of DL-lysine with D,L- α -lipoic acid yields separable diastereomeric salt pairs.

Known syntheses of enantiomerically pure α -lipoic acid always pass through chiral primary steps which are split in the course of the synthesis. In Walton, Wagner, Peterson, Holly and Folkers (J. Amer. chem. Soc. 76 (1954), page 4748 et seq.) the intermediate step 7-carbethoxy-3-acetylthioheptanoic acid is split with L-ephedrine. Another process published by the same

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authors in J. Amer. Chem. Soc. 77 (1955) page 5144 involves the same intermediate step. Japanese patent 7970 describes the addition compound of α -lipoic acid with beta-cyclodextrin without mentioning the separation into enantiomeric compounds.

Object of the invention is the preparation of enantiomerically pure salts of α -lipoic acid using an optically active auxiliary base and the subsequent liberation of the pure optical isomers of α -lipoic acid. In the pure optical isomers of α -lipoic acid (R- and S-form, i.e. R- α -lipoic acid and S- α -lipoic acid) the R-enantiomer is predominantly anti-inflammatory and the S-enantiomer is predominantly antinociceptive in contrast to the racemate (EP 0427247, 08.11.90).

The invention also relates to the preparation of salts of the pure optical isomers of α -lipoic acid with the pure optical isomers of α -methylbenzylamine. This is carried out by dissolving the isomers in an appropriate solvent at elevated temperature, for example at 30°C - 60°C, in particular at 40°C, and isolating the pure diastereomeric salts by crystallization at low temperature, for example at 10°C to 30°C, in particular at 25°C. Solvents apart from water that may be considered are: aliphatic hydrocarbons with a carbon chain length between 3 and 10 carbon atoms, aromatic hydrocarbons that are liquid, esters of aliphatic or cycloaliphatic carboxylic acids with 2 to 6 carbon atoms and aliphatic or cycloaliphatic alcohols with 2 to 6 carbon atoms, aliphatic or cycloaliphatic alcohols with 1 to 6 carbon atoms, ethers and glycol ethers or homogenous mixtures of the solvents named. Particularly preferred solvents are toluene, acetic acid ethyl ester and cyclohexane. To prepare the diastereomeric salts the mixture of free R- α -lipoic acid and S- α -lipoic acid is then preferably either directly reacted with α -methylbenzylamine or also the mixture of R- α -lipoic acid and S- α -lipoic acid as a salt, e.g. alkali or ammonium salt is reacted with a salt of

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α -methylbenzylamine, e.g. hydrochloride or acetate. It is also possible to react an alkaline earth salt of α -lipoic acid with a sulfate of α -methylbenzylamine.

It has now surprisingly been found that the diastereomeric salt pairs display solubility differences with the result that when reacting the racemate of α -lipoic acid with an optically pure isomer of α -methylbenzylamine, one diastereomeric salt pair is selectively preferably isolated. It is particularly advantageous to add to the racemic α -lipoic acid solution only 0.3 - 0.8, but preferably 0.5 - 0.6 of the molar equivalent of a pure enantiomer of α -methylbenzylamine. Here it is possible to selectively prefer a diastereomeric salt pair. The enantiomer of α -lipoic acid, now greatly enriched in the mother liquor, can be obtained in particularly enriched form through addition of the other enantiomer of α -methylbenzylamine. This procedure is suitable for a continuous preparation process of both R- α -lipoic acid and also S- α -lipoic acid, it largely being possible to obtain the two pure enantiomers without loss. These diastereomeric salt pairs can be purified through recrystallization from the pure, already mentioned solvents or their homogenous mixtures, so that pure salt pairs are finally obtained.

The pure salt pairs of R- α -lipoic acid and R- α -methylbenzylamine or S- α -lipoic acid and S- α -methylbenzylamine can be split by addition of acids, e.g. mineral acids, and the pure R- α -lipoic acid or the pure S- α -lipoic acid isolated by extraction.

The purity of the optical isomers and the diastereomeric salt pairs was determined using the specific optical rotation values.

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Relative contents of the optical isomers of α -lipoic acid were then determined by gas chromatography in optically active columns with a detection limit $>0.5\%$. The values are given as enantiomer excesses (ee-values).

Enantiomerically pure R- α -lipoic acid or S- α -lipoic acid can be converted with diphenylmethylamine into a stable, easy to handle salt; the optical purity of the α -lipoic acid can then be determined via the specific optical rotation value.

The present invention will now be explained in greater detail with reference to the following examples.

Example 1

20.6 g (100 mmol) R- α -lipoic acid were dissolved at 40°C in 200 ml toluene. 12.1 g (100 mmol) R-(+)- α -methylbenzylamine were measured thereto within 5 minutes. The mixture was cooled to 25°C within 2 hours. The precipitate was filtered off and rewashed twice with in each case 30 ml toluene. The salt pair was dried in a vacuum at 45°C .

32.4 g (99% of theory) were obtained.

R- α -lipoic acid-R- α -methylbenzylamine salt, $\alpha^{20}_{\text{D}} = + 74.0^{\circ}$

(c=1; ethanol), ee.: $>99\%$ (GC) solubility in toluene 0.09% (25°C), in water 1.16% (25°C) melting point $109-115^{\circ}\text{C}$.

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Example 2

20.6 g (100 mmol) S- α -lipoic acid were dissolved at 40°C in 200 ml toluene. 12.1 g (100 mmol) R- α -methylbenzylamine were measured thereto within 5 minutes. The mixture was cooled to 25°C over 2 hours. The precipitate was filtered off and rewashed twice with in each case 30 ml toluene. The salt pair was dried in a vacuum at 45°C.

32.1 g (98% of theory) were obtained.

S- α -lipoic acid-R- α -methylbenzylamine salt,

$\alpha_D^{20} = -59.2^\circ$

(c=1; ethanol), ee.: >99% (GC).

Solubility in toluene 0.12% (25°C), in water 1.41% (25°C)

melting point: 113-117°C.

Example 3

20.6 g (100 mmol) S- α -lipoic acid were dissolved at 40°C in 200 ml toluene. 12.1 g (100 mmol) S- α -methylbenzylamine were measured thereto within 5 minutes and working carried out as described in Example 1.

32.3 g (99% of theory) were obtained.

S- α -lipoic acid-S- α -methylbenzylamine salt, $\alpha_D^{20} = -74.2^\circ$

(c=1; ethanol), ee.: >99% (GC).

Solubility in toluene 0.09% (25°C), in water 1.17% (25°C)

melting point 109-115°C.

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Example 4

20.6 g (100 mmol) R- α -lipoic acid were dissolved at 40°C in 200 ml toluene. 12.1 g (100 mmol) S- α -methylbenzylamine were measured thereto within 5 minutes and working carried out as described in Example 2.

32.0 g (98% of theory) were obtained.

R- α -lipoic acid-S- α -methylbenzylamine salt, $\alpha_D^{20} = +59.4^\circ$

(c=1; ethanol), ee.: >99% (GC).

Solubility in toluene 0.12% (25°C), in water 1.40% (25°C)
melting point: 113-117°C.

Example 5

4.0 g (19.4 mmol) R- α -lipoic acid were dissolved at 40°C in 30 ml diethyl ether and reacted with a solution of 3.55 g (19.4 mmol) diphenylmethylaniline in 100 ml ether. The precipitate was crystallized out from 30 ml methanol/150 ml diisopropyl ether. 17.5 g (18.4 mmol) (95% of theory) were obtained.

R- α -lipoic acid-diphenylmethylaniline salt with a melting point of 123-4°C. ee.: > 99%,

$\alpha_D^{25} = +58.8^\circ$ (c = 1.4; pyridine);

$\alpha_D^{25} = +60.2^\circ$ (c = 0.3; pyridine).

Example 6

With exclusion of light the hot solution of 1.03 g (5 mmol) racemic α -lipoic acid in 75 ml of ethyl acetate dried with K_2CO_3 was reacted with 0.303 g (2.5 mmol) R- α -phenylethylamine and then cooled, first to room temperature and then in a refrigerator. 730 mg (89%) crystallized out which consisted mainly of the R- α -lipoic acid-R- α -methylbenzylamine salt. This was recrystallized twice from in each case 30 ml ethyl acetate, 550 mg (67%) purified diastereomeric salt being obtained.

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To release the R- α -lipoic acid the salt was dissolved in water, the solution covered with a layer of ether and acidulated with shaking with 0.1 N hydrochloric acid. The R- α -lipoic acid was extracted three times with fresh ether, washed the unified ether phases neutral and after drying and evaporation R- α -lipoic acid was obtained in virtually quantitative yield.

135 mg (0.654 mmol) of the R- α -lipoic acid so obtained were dissolved in 1 ml ether and reacted with the solution of 152 mg (0.83 mmol) diphenylmethanamine in 3.5 ml ether. The precipitate was recrystallized from methanol (1 ml) diisopropyl ether (5 ml). R- α -lipoic acid-diphenylmethanamine salt was obtained with a melting point of 120°C, $\alpha_D^{20} = +51^\circ$ (c=0.3; pyridine).

Example 7

20.6 g (100 mmol) racemic α -lipoic acid were dissolved at 40°C in 200 ml ethyl acetate. Over 5 minutes 6.59 g (54 mmol) R-(+)- α -methylbenzylamine were measured thereto. The mixture was then cooled within 2 hours to 25°C. The precipitate was filtered off and rewashed twice with in each case 35 ml ethyl acetate. The moist salt pair was recrystallized four times from in each case 400 ml ethyl acetate and then dried in a vacuum at 45°C. 9.3 g diastereomeric salt were obtained from R- α -lipoic acid and R-(+)- α -methylbenzylamine, $\alpha_D^{20} = +66.0^\circ$ (c=1; ethanol).

The salt pair was suspended in 300 ml water at 25°C and reacted with 100 ml cyclohexane. The mixture was slowly adjusted to a pH value of 1 with 1 N hydrochloric acid with ice cooling and then heated to 40°C. The phases were separated and the water phase re-extracted once more with 30 ml cyclohexane. The combined cyclohexane extracts were cooled to 5-10°C and post-stirred at

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this temperature for 5 hours for crystallization. The precipitate was filtered off, rewashed once with 30 ml cyclohexane and dried at 25°C in a vacuum. 4.1 g (40% of theory) R- α -lipoic acid, $\alpha_D^{28} = +104.1^\circ$ (c=1; benzene) were obtained.

Example 8

20.6 g (100 mmol) racemic α -lipoic acid were dissolved at 40°C in 200 ml toluene. 6.59 g (54 mmol) R-(+)- α -methylbenzylamine were metered thereto over 5 min. The mixture was then cooled within 2 hours to 25°C, filtered and the sediment rewashed twice with in each case 35 ml toluene. The moist salt pair was recrystallized four times from in each case 400 ml toluene and then dried in a vacuum at 45°C. 10.6 g diastereomeric salt were obtained,
 $\alpha_D^{20} = +72.5^\circ$ (c=1; ethanol).

The salt pair was split as described in Example 7 and the α -lipoic acid obtained in crystalline form from cyclohexane. 4.6 g (45% of theory) R- α -lipoic acid were obtained, $\alpha_D^{28} = +115.0^\circ$ (c=1; benzene)

ee.: >99% (GC).

Example 9

A)

103 g (500 mmol) racemic α -lipoic acid were dissolved at 40°C in 1.0 l toluene. 33.0 g (270 mmol) R-(+)- α -methylbenzylamine were added thereto within 5 minutes. The mixture was then cooled within 2 hours to 25°C, filtered and the precipitate washed twice with in each case 150 ml toluene.

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The moist salt pair was recrystallized as described in Example 8. 53.0 g (162 mmol) R- α -lipoic acid-R-(+)- α -methylbenzylamine salt were obtained after drying.

The mother liquors of the recrystallization were substantially concentrated in a vacuum and the residue taken up with the crystallization mother liquor. This was extracted with 120 ml aqueous hydrochloric acid (solution R), sufficient hydrochloric acid being added thereto for the aqueous phase to have a pH value of 1. The toluene phase was then washed twice with 100 ml water.

B).

A further 66.0 g (320 mmol) racemic α -lipoic acid were dissolved in the toluenic α -lipoic acid solution from A) and reacted at 40°C with 52.1 g (430 mmol) S-(-)- α -methylbenzylamine and then cooled within 2 hours to 25°C. The precipitate was filtered off and rewashed twice with in each case 150 ml toluene. The moist salt pair was recrystallized as stated in Example 8. After drying, 91.7 g (280 mmol) S- α -lipoic acid-S-(-)- α -methylbenzylamine salt were obtained. The mother liquors of the recrystallization were largely concentrated in a vacuum and the residue taken up with the crystallization mother liquor. These were extracted with 170 ml aqueous hydrochloric acid (solution S), sufficient hydrochloric acid being added thereto so that the aqueous phase had a pH value of 1. The toluene phase was then washed with twice 100 ml.

C)

A further 51.6 g (250 mmol) racemic α -lipoic acid were dissolved in the toluenic α -lipoic acid solution from B) and reacted at 40°C with 47.3 g (390 mol) R-(+)- α -methylbenzylamine and worked up as set out in A). 83.2 g (254 mmol) R- α -lipoic acid-R-(+)- α -methylbenzylamine salt were obtained.

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D)

A further 51.6 g (250 mmol) racemic α -lipoic acid were dissolved in the toluenic α -lipoic acid solution from C) and reacted at 40°C with 47.3 g (390 mol) S-(+)- α -methylbenzylamine and worked up as set out in B). 81.2 g (248 mmol) S- α -lipoic acid-S-(-)- α -methylbenzylamine salt were obtained.

E)

136 g (416 mmol) R- α -lipoic acid-R-(+)- α -methylbenzylamine salt were split as described in Example 2, 60.9 g (295 mmol) R- α -lipoic acid being obtained in crystalline form from cyclohexane. $\alpha_D^{20} = +119.9^\circ$ (c = 1; ethanol);

$\alpha_D^{20} = +117.2^\circ$ (c = 1.8; benzene);

ee.: >99%, mp.: 49-50°C. The mother liquor can be used for further crystallization trials. The hydrochloride solution of the R-(+)- α -methylbenzylamine was combined with the solutions R from A) and C), adjusted to a pH value of 13 with sodium hydroxide solution and extracted with toluene. The toluene phase was concentrated and yielded the R-(+)- α -methylbenzylamine in almost quantitative amount.

F)

172 g (528 mmol) S-(-)- α -lipoic acid-S- α -methylbenzylamine salt were split as described in Example 2, 75.3 g (365 mmol) S- α -lipoic acid being obtained in crystalline form from cyclohexane.

$\alpha_D^{20} = -119.4^\circ$ (c = 1; ethanol); mp.: 49-50°C.

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The hydrochloride solution of S-(-)- α -methylbenzylamine was combined with solutions S from B) and D), adjusted to a pH value of 13 with sodium hydroxide solution and extracted with toluene. The toluene phase was concentrated and yielded S-(-)- α -methylbenzylamine in almost quantitative amount.

Example 10

14.0 g sodium hydroxide were prepared in 130 ml water. 20.6 g R- α -lipoic acid (100 mmol) were added at room temperature and post-stirred until a clear solution was obtained. 2.4 g (63 mmol) sodium borohydride dissolved in 35 ml water were then added dropwise at 20-25°C within 10 minutes. The mixture was then heated to 95°C within 1 hour and post-stirred at 95°C for 4 hours. After cooling, 100 ml toluene were added and adjusted to a pH value of 1-1.5 at 10-15°C with semi-concentrated hydrochloric acid. After phase separation the water phase was extracted once again with 50 ml toluene. The combined organic extracts were concentrated in a vacuum. 20.3 g (98% of theory) of R-6,8-dimercaptooctanoic acid were obtained. The distillation supplied 18.5 g. (bp 145-6°C, 0.3 mbar).

α^{20}_D : -10.7°

D

(C=1, ethanol).

Example 11

21.0 g sodium hydroxide were prepared in 195 ml water. 30.9 g S- α -lipoic acid were added at room temperature and post-stirred until a clear solution was obtained. At 20-25°C, 3.6 g (95 mmol) sodium borohydride dissolved in 50 ml water were then added dropwise within 10 minutes. The mixture was then heated to 95°C within 1 hour and post-stirred at 95°C for 4 hours. After cooling, 150 ml toluene were added and adjusted to a pH value of 1-1.5 at 10-15°C with semi-concentrated hydrochloric acid. After phase separation the water phase was extracted once again with

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75 ml toluene. The combined organic extracts were concentrated in a vacuum. 30.3 g (97% of theory) of S-6,8-dimercaptooctanoic acid were obtained. The distillation supplied 28.7 g. (bp 145-6°C, 0.3 mbar).

α^{20}_D : +10.7°

(C=1, ethanol).

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Claims

1. Salt pair composed of R- α -lipoic acid and R-(+)- α -methylbenzylamine, salt pair composed of R- α -lipoic acid and S-(-)- α -methylbenzylamine, salt pair composed of S- α -lipoic acid and R- α -methylbenzylamine and salt pair composed of S- α -lipoic acid and S-(-)- α -methylbenzylamine.
2. Preparation and isolation of salts of the pure optical isomers of α -lipoic acid and the optical antipodes of α -methylbenzylamine, characterized in that a racemic mixture of R- α -lipoic acid and S- α -lipoic acid or any mixture of R- α -lipoic acid and S- α -lipoic acid with the optical antipodes of α -methylbenzylamine are reacted in solution, the diastereomeric compounds being allowed to crystallize out.
3. Preparation and isolation of salts of the pure optical isomers of α -lipoic acid and the optical antipodes of α -methylbenzylamine, characterized in that the mixtures of the racemic mixture of α -lipoic acid and the solution of α -methylbenzylamine are reacted at temperatures between 20°C and 60°C and that a precipitate of diastereomeric compound is obtained by cooling to 10°C to 15°C.
4. Continuous process for the preparation of pure diastereomeric salts of a racemic mixture of α -lipoic acid or of a mixture of R- α -lipoic acid and S- α -lipoic acid and enantiomerically pure α -methylbenzylamine, characterized in that the precipitated salt is filtered off after reaction and the mother liquors further processed.

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5. Isolation of the optically pure isomers of α -lipoic acid by splitting of the pure diastereomeric salts of (R)- α -lipoic acid and α -methylbenzylamine and of S- α -lipoic acid and α -methylbenzylamine, characterized in that the pure diastereomeric salts are split by reaction with inorganic or organic acids.
6. Preparation of the optically pure enantiomers of 6,8-dimercaptooctanoic acid, characterized in that the pure isomers of α -lipoic acid, which were obtained using the process according to the present claims, or in another manner, are reduced by reduction agents such as sodium borohydride.

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Abstract

The preparation of the pure enantiomers of α -lipoic acid by formation of the diastereomeric salt pairs with the optical antipodes of α -methylbenzylamine in solution is described.

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authors in J. Amer. Chem. Soc. 77 (1955) page 5144 involves the same intermediate step. Japanese patent 7970 describes the addition compound of alpha-lipoic acid with beta-cyclodextrin without mentioning the separation into enantiomeric compounds.

In (J. Amer. Chem. Soc. 79(24), 6483-6487 (1957)), Acker and Wayne describe the preparation of (+)- α -lipoic acid and (-)- α -lipoic acid by reduction of the enantiomerically pure precursor (+)-6,8-dichlorooctanoic acid and (-)-6,8-dichlorooctanoic acid respectively. The enantiomerically pure dichlorooctanoic acids are obtained by racemate resolution from the racemic mixture ($\pm$)-6,8-dichlorooctanoic acid by reaction with (-)-ephedrine.

The object of the invention is the preparation of enantiomerically pure salts of alpha-lipoic acid using an optically active auxiliary base and the subsequent liberation of the pure optical isomers of alpha-lipoic acid. In the pure optical isomers of alpha-lipoic acid (R- and S-form, i.e. R-alpha-lipoic acid and S-alpha-lipoic acid) the R-enantiomer is predominantly anti-inflammatory and the S-enantiomer is predominantly antinociceptive in contrast to the racemate (EP 0,427,247, 08.11.90).

The invention also relates to the preparation of salts of the pure optical isomers of alpha-lipoic acid with the pure optical isomers of alpha-methylbenzylamine. This is carried out by dissolving the isomers in an appropriate solvent at elevated temperature, for example at 30°C - 60°C, in particular at 40°C, and isolating the pure diastereomeric salts by crystallization at low temperature, for example at 10°C to 30°C, in particular at 25°C. Solvents apart from water that may be considered are: aliphatic and cycloaliphatic hydrocarbons with a carbon chain length between 3 and 10 carbon atoms, aromatic hydrocarbons that are liquid, esters of aliphatic or cycloaliphatic carboxylic acids with 2 to 6 carbon atoms and aliphatic or cycloaliphatic alcohols with 2 to 6 carbon atoms, aliphatic or cycloaliphatic alcohols with 1 to 6 carbon atoms, ethers and glycol ethers or homogenous mixtures of the solvents named.

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Particularly preferred solvents are toluene, acetic acid ethyl ester and cyclohexane. To prepare the diastereomeric salts the mixture of free R- α -lipoic acid and S- α -lipoic acid is then preferably either directly reacted with α -methylbenzylamine or also the mixture of R- α -lipoic acid and S- α -lipoic acid as a salt, e.g. alkali or ammonium salt is reacted with a salt of α -methylbenzylamine, e.g. hydrochloride or acetate. It is also possible to react an alkaline earth salt of α -lipoic acid with a sulfate of α -methylbenzylamine.

It has now surprisingly been found that the diastereomeric salt pairs display solubility differences with the result that when reacting the racemate of α -lipoic acid with an optically pure isomer of α -methylbenzylamine, one diastereomeric salt pair is selectively preferably isolated. It is particularly advantageous to add to the racemic α -lipoic acid solution only 0.3 - 0.8, but preferably 0.5 - 0.6 of the molar equivalent of a pure enantiomer of α -methylbenzylamine. Here it is possible to selectively prefer a diastereomeric salt pair. The enantiomer of α -lipoic acid, now greatly enriched in the mother liquor, can be obtained in particularly enriched form through addition of the other enantiomer of α -methylbenzylamine. This procedure is suitable for a continuous preparation process of both R- α -lipoic acid and also S- α -lipoic acid, it largely being possible to obtain the two pure enantiomers without loss. These diastereomeric salt pairs can be purified through recrystallization from the pure, already mentioned solvents or their homogenous mixtures, so that pure salt pairs are finally obtained.

The pure salt pairs of R- α -lipoic acid and R- α -methylbenzylamine or S- α -lipoic acid and S- α -methylbenzylamine can be split by addition of acids, e.g. mineral acids, and the pure R- α -lipoic acid or the pure S- α -lipoic acid isolated by extraction.

The purity of the optical isomers and the diastereomeric salt pairs was determined using the specific optical rotation values.

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Example 4

20.6 g (100 mmol) R-alpha-lipoic acid were dissolved at 40°C in 200 ml toluene. 12.1 g (100 mmol) S-alpha-methylbenzylamine were added within 5 minutes and working carried out as described in Example 2.

32.0 g (98% of theory) were obtained.

R-alpha-lipoic acid-S-alpha-methylbenzylamine salt, $\alpha_D^{20} = + 59.4^\circ$

(c=1; ethanol), ee.: >99% (GC).

Solubility in toluene 0.12% (25°C), in water 1.40% (25°C)
melting point: 113-117°C.

Example 5

With exclusion of light the hot solution of 1.03 g (5 mmol) racemic alpha-lipoic acid in 75 ml of ethyl acetate dried with K_2CO_3 was reacted with 0.303 g (2.5 mmol) R-alpha-phenylethylamine and then cooled, first to room temperature and then in a refrigerator. 730 mg (89%) crystallized out which consisted mainly of the R-alpha-lipoic acid-R-alpha-methylbenzylamine salt. This was recrystallized twice from in each case 30 ml ethyl acetate, 550 mg (67%) purified diastereomeric salt being obtained.

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To release the R-alpha-lipoic acid the salt was dissolved in water, the solution covered with a layer of ether and acidulated with shaking with 0.1 N hydrochloric acid. The R-alpha-lipoic acid was extracted three times with fresh ether, the unified ether phases were washed neutral and after drying and evaporation R-alpha-lipoic acid was obtained in virtually quantitative yield.

135 mg (0.654 mmol) of the R-alpha-lipoic acid so obtained were dissolved in 1 ml ether and reacted with the solution of 152 mg (0.83 mmol) diphenylmethylaniline in 3.5 ml ether. The precipitate was recrystallized from methanol (1 ml) diisopropyl ether (5 ml). R-alpha-lipoic acid-diphenylmethylaniline salt was obtained with a melting point of 120°C, $\alpha_D^{20} = +51^\circ$ (c=0.3; pyridine).

Example 6

20.6 g (100 mmol) racemic alpha-lipoic acid were dissolved at 40°C in 200 ml ethyl acetate. Over 5 minutes 6.59 g (54 mmol) R-(+)-alpha-methylbenzylaniline were added thereto. The mixture was then cooled within 2 hours to 25°C. The precipitate was filtered off and rewashed twice with in each case 35 ml ethyl acetate. The moist salt pair was recrystallized four times from in each case 400 ml ethyl acetate and then dried in a vacuum at 45°C. 9.3 g diastereomeric salt were obtained from R-alpha-lipoic acid and R-(+)-alpha-methylbenzylaniline, $\alpha_D^{20} = +66.0^\circ$ (c=1; ethanol).

The salt pair was suspended in 300 ml water at 25°C and reacted with 100 ml cyclohexane. The mixture was slowly adjusted to a pH value of 1 with 1 N hydrochloric acid with ice cooling and then heated to 40°C. The phases were separated and the water phase re-extracted once more with 30 ml cyclohexane. The combined cyclohexane extracts were cooled to 5-10°C and post-stirred at

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this temperature for 5 hours for crystallization. The precipitate was filtered off, rewashed once with 30 ml cyclohexane and dried at 25°C in a vacuum. 4.1 g (40% of theory) R-alpha-lipoic acid, $\alpha_D^{28} = +104.1^\circ$ (c=1; benzene) were obtained.

Example 7

20.6 g (100 mmol) racemic alpha-lipoic acid were dissolved at 40°C in 200 ml toluene. 6.59 g (54 mmol) R-(+)-alpha-methylbenzylamine were added over 5 min. The mixture was then cooled within 2 hours to 25°C, filtered and the sediment rewashed twice with in each case 35 ml toluene. The moist salt pair was recrystallized four times from in each case 400 ml toluene and then dried in a vacuum at 45°C. 10.6 g diastereomeric salt were obtained, $\alpha_D^{20} = +72.5^\circ$ (c=1; ethanol).

The salt pair was split as described in Example 7 and the alpha-lipoic acid obtained in crystalline form from cyclohexane. 4.6 g (45% of theory) R-alpha-lipoic acid were obtained, $\alpha_D^{28} = +115.0^\circ$ (c=1; benzene)

ee.: >99% (GC).

Example 8

A)

103 g (500 mmol) racemic alpha-lipoic acid were dissolved at 40°C in 1.0 l toluene. 33.0 g (270 mmol) R-(+)-alpha-methylbenzylamine were added within 5 minutes. The mixture was then cooled within 2 hours to 25°C, filtered and the precipitate washed twice with in each case 150 ml toluene.

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The hydrochloride solution of S-(-)-alpha-methylbenzylamine was combined with solutions S from B) and D), adjusted to a pH value of 13 with sodium hydroxide solution and extracted with toluene. The toluene phase was concentrated and yielded S-(-)-alpha-methylbenzylamine in almost quantitative amount.

Example 9 (Not according to the invention)

14.0 g sodium hydroxide were prepared in 130 ml water. 20.6 g R-alpha-lipoic acid (100 mmol) were added at room temperature and post-stirred until a clear solution was obtained. 2.4 g (63 mmol) sodium borohydride dissolved in 35 ml water were then added dropwise at 20-25°C within 10 minutes. The mixture was then heated to 95°C within 1 hour and post-stirred at 95°C for 4 hours. After cooling, 100 ml toluene were added and adjusted to a pH value of 1-1.5 at 10-15°C with semi-concentrated hydrochloric acid. After phase separation the water phase was extracted once again with 50 ml toluene. The combined organic extracts were concentrated in a vacuum. 20.3 g (98% of theory) of R-6,8-dimercaptooctanoic acid were obtained. The distillation supplied 18.5 g. (bp 145-6°C, 0.3 mbar).
 α^{20} : -10.7° (C=1, ethanol).

Example 10 (Not according to the invention)

21.0 g sodium hydroxide were prepared in 195 ml water. 30.9 g S-alpha-lipoic acid were added at room temperature and post-stirred until a clear solution was obtained. At 20-25°C, 3.6 g (95 mmol) sodium borohydride dissolved in 50 ml water were then added dropwise within 10 minutes. The mixture was then heated to 95°C within 1 hour and post-stirred at 95°C for 4 hours. After cooling, 150 ml toluene were added and adjusted to a pH value of 1-1.5 at 10-15°C with semi-concentrated hydrochloric acid. After phase separation the water phase was extracted once again with 75 ml toluene. The combined organic extracts were concentrated in a vacuum. 30.3 g (97% of theory) of S-6,8-dimercaptooctanoic acid were obtained. The distillation supplied 28.7 g. (bp 145-6°C, 0.3 mbar).
 α^{20} : +10.7° (C=1, ethanol).

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Claims

1. Process for the separation of a mixture of R- α -lipoic acid and S- α -lipoic acid, which mixture is racemic or is of any composition with regard to the enantiomers, into the optically pure isomers thereof, characterised in that the mixtures are reacted with an optically pure antipode of α -methylbenzylamine at temperatures of between 20°C and 60°C in toluene, ethyl acetate or cyclohexane and the mixture is cooled to 10°C to 30°C and the precipitate is isolated and the mother liquors are further processed and the pure diastereomeric salt pairs are resolved by reaction with inorganic or organic acids.
2. Process according to claim 1, characterised in that the process is performed continuously.
3. Salt pair consisting of R- α -lipoic acid and R-(+)- α -methylbenzylamine, salt pair consisting of R- α -lipoic acid and S-(-)- α -methylbenzylamine, salt pair consisting of S- α -lipoic acid and R- α -methylbenzylamine and salt pair consisting of S- α -lipoic acid and S-(-)- α -methylbenzylamine.

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PREPARATION AND USE OF SALTS OF THE PURE ENANTIOMERS
OF α -LIPOIC ACID

ABSTRACT

The preparation of the pure enantiomers of alpha-lipoic acid by formation of the diastereomeric salt pairs with the optical antipodes of alpha-methylbenzylamine in solution is described.

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Preparation and use of salts of the pure enantiomers of α -lipoic acid

Description

The invention relates to new optically active salts of α -lipoic acid and of optically active α -methylbenzylamine and a process for the preparation of the enantiomerically pure α -lipoic acids and of the enantiomerically pure dihydrolipoic acids.

α -lipoic acid is 1,2-dithiolane-3-pentanoic acid (thioctic acid).

As a coenzyme of α -ketonic acid dehydrogenases α -lipoic acid is widespread in plants and animals; the naturally occurring form has the R-configuration. When " α -lipoic acid" is referred to hereinbelow, this is always an α -lipoic acid with unknown stereochemical composition.

α -lipoic acid is pharmacologically active and has anti-inflammatory and antinociceptive (analgesic) as well as cytoprotective properties.

A series of salts are known of α -lipoic acid, for example salts of α -lipoic acid with optically active bases such as with the basic amino acids arginine and lysine. (Spanish patent No. 313,056). Neither the reaction of L-arginine with D,L- α -lipoic acid nor the reaction of DL-lysine with D,L- α -lipoic acid yields separable diastereomeric salt pairs.

Known syntheses of enantiomerically pure α -lipoic acid always pass through chiral primary steps which are split in the course of the synthesis. In Walton, Wagner, Peterson, Holly and Folkers (J. Amer. chem. Soc. 76 (1954), page 4748 et seq.) the intermediate step 7-carbethoxy-3-acetylthioheptanoic acid is split with L-ephedrine. Another process published by the same

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Preparation and use of salts of the pure enantiomers of α -lipoic acid

Abstract

The preparation of the pure enantiomers of α -lipoic acid by formation of the diastereomeric salt pairs with the optical antipodes of α -methylbenzylamine in solution is described.

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~~PREPARATION AND USE OF SALTS OF THE PURE ENANTIOMERS OF ALPHA-LIPOIC ACID~~Description

This invention relates to novel optically active salts prepared from α -lipoic acid and optically active α -methylbenzylamine and to a process for the production of enantiomerically pure α -lipoic acid and of enantiomerically pure dihydrolipoic acids. α -Lipoic acid is 1,2-dithiolane-3-pentanoic acid (thioctic acid).

α -Lipoic acid is widely distributed in plants and animals as a coenzyme of α -keto acid dehydrogenases; the naturally occurring form has the R configuration. Whenever α -lipoic acid is mentioned below, the term is taken to refer to α -lipoic acid of an unknown stereochemical composition. α -Lipoic acid is pharmacologically active and has anti-inflammatory and anti-nociceptive (analgesic) as well as cytoprotective properties.

A series of α -lipoic acid salts are known, including for example salts of α -lipoic acid with optically active bases, such as for example with the basic amino acids arginine and lysine (Spanish patent no. 313 056). Neither the reaction of L-arginine with D,L- α -lipoic acid nor the reaction of D,L-lysine with D,L- α -lipoic acid yield separable diastereomeric salt pairs.

Known methods for synthesising enantiomerically pure α -lipoic acid always proceed via chiral precursors, which are resolved over the course of the synthesis. Thus, in Wagner, Peterson, Holly and Folkers (*J. Amer. Chem. Soc.* 76 (1954), page 4748 et seq.), the intermediate 7-carbethoxy-3-acetylthioheptanoic acid is resolved with L-ephedrine. Another process proceeding via the same intermediate is published by the same authors in *J. Amer. Chem. Soc.* 77 (1955), page 5144. Japanese patent 7970 describes the addition compound of α -lipoic acid with β -cyclodextrin, without mentioning separation into enantiomeric compounds.

In (*J. Amer. Chem. Soc.* 79 (24), 6483-6487 (1957)), Acker and Wayne describe the preparation of (+)- α -lipoic acid and (-)- α -lipoic acid by reduction of the enantiomerically pure precursor (+)-6,8-dichlorooctanoic acid and (-)-6,8-

dichlorooctanoic acid respectively. The enantiomerically pure dichlorooctanoic acids are obtained by racemate resolution from the racemic mixture ($\pm$)-6,8-dichlorooctanoic acid by reaction with (-)-ephedrine.

The object of the invention is to produce enantiomerically pure salts of α -lipoic acid using an optically active auxiliary base and subsequent liberation of the pure optical isomers of α -lipoic acid. With regard to the pure optical isomers of α -lipoic acid (R and S form, i.e. R- α -lipoic acid and S- α -lipoic acid), in contrast with the racemate, the R enantiomer has a predominantly anti-inflammatory action and the S enantiomer has a predominantly anti-nociceptive action (EP 0 427 247, 08.11.90).

This invention also relates to the production of salts of the pure optical isomers of α -lipoic acid with the pure optical isomers of α -methylbenzylamine. The method used here is that the isomers are dissolved in a suitable solvent at elevated temperature, for example at 30°C-60°C, in particular at 40°C, and the pure diastereomeric salts are isolated by crystallisation at a lower temperature, for example at 10°C to 30°C, in particular at 25°C. Solvents other than water which may be considered are: aliphatic and cycloaliphatic hydrocarbons with a carbon chain length of between 3 and 10 carbon atoms, aromatic hydrocarbons, which are liquid, esters prepared from aliphatic or cycloaliphatic carboxylic acids with 2 to 6 carbon atoms and aliphatic or cycloaliphatic alcohols with 2 to 6 carbon atoms, aliphatic or cycloaliphatic alcohols with 1 to 6 carbon atoms, ethers and glycol ethers or homogeneous mixtures of the stated solvents. Toluene, ethyl acetate and cyclohexane are particularly preferred solvents. During production of the diastereomeric salts, it is preferable either to react the mixture of the free R- α -lipoic acid and S- α -lipoic acid directly with α -methylbenzylamine or also

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to react the mixture of R- α -lipoic and S- α -lipoic acid in salt form, for example as an alkali metal or ammonium salt, with an α -methylbenzylamine salt, for example the hydrochloride or acetate. It is also possible to react an alkaline earth metal salt of α -lipoic acid with a sulfate of α -methylbenzylamine.

Surprisingly, the diastereomeric salt pairs now exhibit differences in solubility, such that when the α -lipoic acid racemate is reacted with an optically pure isomer of α -methylbenzylamine, a diastereomeric salt pair is preferentially selectively isolated. It is particularly advantageous to add only 0.3-0.8, but preferably 0.5-0.6 of a molar equivalent of a pure enantiomer of α -methylbenzylamine to the racemic α -lipoic acid solution. In this manner, a diastereomeric salt pair may preferentially be selectively isolated. The α -lipoic acid enantiomer which is now highly concentrated in the mother liquor may be obtained in a particularly concentrated form by adding the other α -methylbenzylamine enantiomer. This method is suitable for a continuous production process both for R- α -lipoic acid and for S- α -lipoic acid, wherein the two pure enantiomers may be obtained substantially without loss. These diastereomeric salt pairs may be purified by recrystallisation from the above-stated pure solvents or the homogeneous mixtures thereof, such that pure salt pairs are finally obtained.

The pure salt pairs of R- α -lipoic acid and R- α -methylbenzylamine and of S- α -lipoic acid and S- α -methylbenzylamine may be resolved by the addition of acids, for example mineral acids, and the pure R- α -lipoic acid or the pure S- α -lipoic acid isolated by extraction.

The purity of the optical isomers and of the diastereomeric salt pairs was determined by means of their specific optical angles of rotation.

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The relative contents of the optical isomers of α -lipoic acid were also determined by gas chromatography on optically active columns with a detection limit of $> 0.5\%$. The values are stated as enantiomer excesses (ee values).

Enantiomerically pure R- α -lipoic acid or S- α -lipoic acid may be converted into a stable, easily handled salt with diphenylmethanamine; optical purity of the α -lipoic acid may here be determined by means of the specific optical angle of rotation.

The following examples illustrate the present invention in greater detail.

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Example 1

20.6 g (100 mmol) of R- α -lipoic acid were dissolved at 40°C in 200 ml of toluene. 12.1 g (100 mmol) of R-(+)- α -methylbenzylamine were apportioned within 5 minutes. The temperature was reduced to 25°C within 2 hours. The precipitate was filtered out and rewashed twice with 30 ml portions of toluene. The salt pair was vacuum dried at 45°C.

32.4 g (99% of theoretical) of R- α -lipoic acid/R- α -methylbenzylamine salt, $\alpha_D^{20} = + 74.0^\circ$, were obtained.

(c = 1; ethanol), ee: > 99% (GC) solubility in toluene 0.09% (25°C), in water 1.16% (25°C), melting point 109-115°C.

Example 2

20.6 g (100 mmol) of S- α -lipoic acid were dissolved at 40°C in 200 ml of toluene. 12.1 g (100 mmol) of R- α -methylbenzylamine were apportioned within 5 minutes. The temperature was reduced to 25°C within 2 hours. The precipitate was filtered out and rewashed twice with 30 ml portions of toluene. The salt pair was vacuum dried at 45°C.

32.1 g (98% of theoretical) of S- α -lipoic acid/R- α -methylbenzylamine salt, $\alpha_D^{20} = - 59.2^\circ$, were obtained.

(c = 1; ethanol), ee: > 99% GC.
Solubility in toluene 0.12% (25°C), in water 1.41% (25°C).
Melting point: 113-117°C.

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Example 3

20.6 g (100 mmol) of S- α -lipoic acid were dissolved at 40°C in 200 ml of toluene. 12.1 g (100 mmol) of S- α -methylbenzylamine were apportioned within 5 minutes and working up was performed as described in example 1.

32.3 g (99% of theoretical) of S- α -lipoic acid/S- α -methylbenzylamine salt, $\alpha^{20}_D = -74.2^\circ$, were obtained.

(c = 1; ethanol), ee: > 99% GC.

Solubility in toluene 0.09% (25°C), in water 1.17% (25°C).

Melting point: 109-115°C.

Example 4

20.6 g (100 mmol) of R- α -lipoic acid were dissolved at 40°C in 200 ml of toluene. 12.1 g (100 mmol) of S- α -methylbenzylamine were apportioned within 5 minutes and working up was performed as described in example 2. 32.0 g (98% of theoretical) of R- α -lipoic acid/S- α -methylbenzylamine salt, $\alpha^{20}_D = +59.4^\circ$, were obtained.

(c = 1; ethanol), ee: > 99% GC.

Solubility in toluene 0.12% (25°C), in water 1.40% (25°C).

Melting point: 113-117°C.

Example 5

A warm solution of 1.03 g (5 mmol) of racemic α -lipoic acid in 75 ml of ethyl acetate dried with K_2CO_3 was combined with exclusion of light with 0.303 g (2.5 mmol) of R- α -methylbenzylamine and cooled to room temperature and then in a refrigerator. 730 mg (89%) of product crystallised out, primarily consisting of R- α -lipoic acid/R- α -methylbenzylamine salt. This was recrystallised twice from 30 ml

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portions of ethyl acetate, wherein 550 mg (67%) of purified diastereomeric salts were obtained.

The salt was dissolved in water to release the R- α -lipoic acid, a layer of ether was poured onto the solution and acidified with 0.1 N hydrochloric acid with shaking. The R- α -lipoic acid was extracted three times with fresh ether, the combined ether phases were washed to neutrality and a virtually quantitative yield of R- α -lipoic acid was obtained after drying and evaporation.

135 mg (0.654 mmol) of the R- α -lipoic acid obtained in this manner were dissolved in 1 ml of ether and combined with a solution of 152 mg (0.83 mmol) of diphenylmethylaniline in 3.5 ml of ether. The precipitate was recrystallised from methanol (1 ml), diisopropyl ether (5 ml). R-(α)-lipoic acid/diphenylmethylaniline salt with a melting point of 120°C, $\alpha^{20}_D = + 51^\circ$, was obtained ($c = 0.3$: pyridine).

Example 6

20.6 g (100 mmol) of racemic α -lipoic acid were dissolved at 40°C in 200 ml of ethyl acetate. 6.59 g (54 mmol) of R-(+)- α -methylbenzylamine were apportioned within 5 minutes. The temperature was then reduced to 25°C within 2 hours. The precipitate was filtered out and rewashed twice with 35 ml portions of ethyl acetate. The moist salt pair was recrystallised four times from 400 ml portions of ethyl acetate and then vacuum dried at 45°C. 9.3 g of diastereomeric salt of R- α -lipoic acid and R-(+)- α -methylbenzylamine, $\alpha^{20}_D = + 66.0^\circ$ ($c = 1$; ethanol) were obtained.

The salt pair was suspended in 300 ml of water at 25°C and combined with 100 ml of cyclohexane. The mixture was slowly adjusted, while being cooled with ice, to a pH of 1 using 1 N hydrochloric acid and the temperature was then raised to 40°C. The phases were separated and the aqueous phase

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extracted once more with 30 ml of cyclohexane. The combined cyclohexane extracts were cooled to 5-10°C and stirred for 5 hours at this temperature for crystallisation. The precipitate was filtered out, washed once more with 30 ml of cyclohexane and vacuum dried at 25°C. 4.1 g (40% of theoretical) of R-(α)-lipoic acid, $\alpha^{28}_D = + 104.1^\circ$ (c = 1; benzene) were obtained.

Example 7

20.6 g (100 mmol) of racemic α -lipoic acid were dissolved at 40°C in 200 ml of ethyl acetate. 6.59 g (54 mmol) of R-(+)- α -methylbenzylamine were apportioned within 5 minutes. The temperature was then reduced to 25°C within 2 hours, the mixture filtered and the precipitate rewashed twice with 35 ml portions of toluene. The moist salt pair was recrystallised four times from 400 ml portions of toluene and then vacuum dried at 45°C. 10.6 g of diastereomeric salt, $\alpha^{20}_D = + 72.5^\circ$ (c = 1; ethanol) were obtained.

The salt pair was resolved as described in example 7 and the α -lipoic acid obtained in crystalline form from cyclohexane. 4.6 g (45% of theoretical) of R-(α)-lipoic acid, $\alpha^{28}_D = + 115.0^\circ$ (c = 1; benzene) were obtained.

ee: > 99% (GC).

Example 8

A)

103 g (500 mmol) of racemic α -lipoic acid were dissolved at 40°C in 1.0 l of toluene. 33.0 g (270 mmol) of R-(+)- α -methylbenzylamine were then added within 5 minutes. The temperature was then reduced to 25°C within 2 hours, the mixture filtered and the precipitate rewashed twice with 150 ml portions of toluene.

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The moist salt pair was recrystallised as stated in example 8. After drying, 53.0 g (162 mmol) of R- α -lipoic acid/R-(+)- α -methylbenzylamine salt were obtained.

The mother liquors from recrystallisation were largely evaporated under a vacuum and the residue redissolved in the crystallisation mother liquor. This was extracted with 120 ml of aqueous hydrochloric acid (solution R), wherein the hydrochloric acid was added in a quantity such that the aqueous phase had a pH of 1.

The toluene phase was then washed twice with 100 ml portions of water.

B)

A further 66.0 g (320 mmol) of racemic α -lipoic acid were dissolved in the α -lipoic acid solution in toluene from A) and the mixture was combined at 40°C with 52.1 g (430 mmol) of S-(-)- α -methyl-benzylamine and cooled to 25°C within 2 hours. The precipitate was filtered out and rewashed twice with 150 ml portions of toluene. The moist salt pair was recrystallised as stated in example 8. After drying, 91.7 g (280 mmol) of S- α -lipoic acid/S-(-)- α -methylbenzylamine salt were obtained. The mother liquors from recrystallisation were largely evaporated under a vacuum and the residue redissolved in the crystallisation mother liquor. This was extracted with 170 ml of aqueous hydrochloric acid (solution S), wherein the hydrochloric acid was added in a quantity such that the aqueous phase had a pH of 1. The toluene phase was then washed twice with 100 ml portions of water.

C)

A further 51.6 g (250 mmol) of racemic α -lipoic acid were dissolved in the α -lipoic acid solution in toluene and the mixture was combined at 40°C with 47.3 g (390 mol) of

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R-(+)- α -methylbenzylamine and worked up as in A). 83.2 g (254 mmol) of R- α -lipoic acid/R-(+)- α -methylbenzylamine salt were obtained.

D)

A further 51.6 g (250 mmol) of racemic α -lipoic acid were dissolved in the α -lipoic acid solution in toluene and the mixture was combined at 40°C with 47.3 g (390 mmol) of S-(+)- α -methylbenzylamine and worked up as in B). 81.2 g (248 mmol) of S- α -lipoic acid/(-)- α -methylbenzylamine salt were obtained.

E)

136 g (416 mmol) of R- α -lipoic acid/R-(+)- α -methylbenzylamine salt were resolved as described in example 2 and 60.9 g (295 mmol) of R- α -lipoic acid were obtained in crystalline form from cyclohexane, $\alpha^{20}_D = + 119.0^\circ$ (c = 1; ethanol); $\alpha^{20}_D = + 117.2^\circ$ (c = 1.8; benzene); ee: > 99%; m.p. 49-50°C. The mother liquor may be used for further crystallisation tests. The hydrochloride solution of the R-(+)- α -methylbenzylamine was combined with the solutions R from A) and C), the mixture adjusted to a pH value of 13 with sodium hydroxide solution and extracted with toluene. The toluene phase was evaporated and returned a virtually quantitative yield of R-(+)- α -methylbenzylamine.

F)

172 g (528 mmol) of S-(-)- α -lipoic acid/S- α -methylbenzylamine salt were resolved as described in example 2 and 75.3 g (365 mmol) of S- α -lipoic acid were obtained in crystalline form from cyclohexane, $\alpha^{20}_D = - 119.4^\circ$ (c = 1; ethanol); m.p. 49-50°C.

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The hydrochloride solution of the S-(+)- α -methylbenzylamine was combined with the solutions S from B) and D), the mixture adjusted to a pH value of 13 with sodium hydroxide solution and extracted with toluene. The toluene phase was evaporated and returned a virtually quantitative yield of S-(+)- α -methylbenzylamine.

Example 9 (not according to the invention)

14.0 g of sodium hydroxide were initially introduced into 130 ml of water. 20.6 g of R- α -lipoic acid (100 mmol) were introduced at room temperature and stirred until a clear solution was formed. 2.4 g (63 mmol) of sodium hydridoborate dissolved in 35 ml of water were then added dropwise within 10 minutes at 20-25°C. The temperature was then raised to 95°C within 1 hour and stirring continued for 4 hours at 95°C. Once the mixture had cooled, 100 ml of toluene were added and, at 10-15°C, the pH adjusted to 1-1.5 with semi-concentrated hydrochloric acid. Once the phases had been separated, the aqueous phase was extracted once more with 50 ml of toluene. The combined organic extracts were evaporated under a vacuum. 20.3 g (98% of theoretical) of R-6,8-dimercaptooctanoic acid were obtained. Distillation produced 18.5 g (bp 145-6°C, 0.3 mbar), α^{20}_D : - 10.7°

(c = 1, ethanol).

Example 10 (not according to the invention)

21.0 g of sodium hydroxide were initially introduced into 195 ml of water. 30.9 g of S- α -lipoic acid were introduced at room temperature and stirred until a clear solution was formed. 3.6 g (95 mmol) of sodium hydridoborate dissolved in 50 ml of water were then added dropwise within 10 minutes at 20-25°C. The temperature was then raised to 95°C within 1 hour and stirring continued for 4 hours at 95°C.

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Once the mixture had cooled, 150 ml of toluene were added and, at 10-15°C, the pH adjusted to 1-1.5 with semi-concentrated hydrochloric acid. Once the phases had been separated, the aqueous phase was extracted once more with 75 ml of toluene. The combined organic extracts were evaporated under a vacuum. 30.3 g (97% of theoretical) of S-6,8-dimercaptooctanoic acid were obtained. Distillation produced 28.7 g (bp 145-6°C, 0.3 mbar), α_D^{20} : + 10.7°

(c = 1, ethanol).

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Claims

1. Process for the separation of a mixture of R- α -lipoic acid and S- α -lipoic acid, which mixture is racemic or is of any composition with regard to the enantiomers, into the optically pure isomers thereof, characterised in that the mixtures are reacted with an optically pure antipode of α -methylbenzylamine at temperatures of between 20°C and 60°C in toluene, ethyl acetate or cyclohexane and the mixture is cooled to 10°C to 30°C and the precipitate is isolated and the mother liquors are further processed and the pure diastereomeric salt pairs are resolved by reaction with inorganic or organic acids.
2. Process according to claim 1, characterised in that the process is performed continuously.
3. Salt pair consisting of R- α -lipoic acid and R-(+)- α -methylbenzylamine, salt pair consisting of R- α -lipoic acid and S-(-)- α -methylbenzylamine, salt pair consisting of S- α -lipoic acid and R- α -methylbenzylamine and salt pair consisting of S- α -lipoic acid and S-(-)- α -methylbenzylamine.



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PREPARATION AND USE OF SALTS OF THE PURE ENANTIOMERS
OF α -LIPOIC ACID

ABSTRACT

The preparation of the pure enantiomers of alpha-lipoic acid by formation of the diastereomeric salt pairs with the optical antipodes of alpha-methylbenzylamine in solution is described.

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