

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, α^{20}_{D} =
+ 74.0°

(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} : -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_D^{20} : +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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