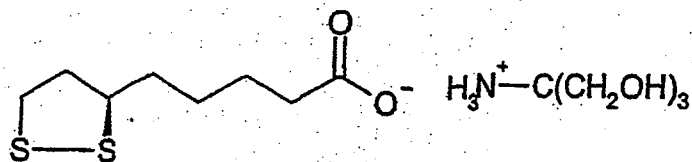


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Novel modifications of the trometamol salt of R-thioctic acid and method for producing the same

The invention relates to novel modifications of the trometamol salt of R-thioctic acid of the formula I



a method for the production thereof, pharmaceutical preparations containing these modifications, and the medical use thereof.

This compound has, for example, antiinflammatory and cytoprotective activity (EP 427247) and is used for the treatment of diabetes mellitus and of insulin resistance (DE 4,343,593), and for glucose metabolism disorders of the CNS (DE 4,343,592) and as appetite suppressant (DE 19,818,563) and can thus be employed in pharmaceutical preparations (EP 702953).

The requirements to be met by an active ingredient in relation to the physicochemical properties relevant to pharmaceutical processability and bioavailability are determined both by the nature and the technology of production of the particular pharmaceutical preparation.

The pharmaceutical processability and bioavailability are considerably influenced by the physicochemical properties, in particular in the case of high-dose active ingredients, which include the trometamol salt of R-thioctic acid.

It is therefore advantageous with an active ingredient of this type for various modifications, and mixtures thereof, which display different physicochemical properties, to be available for different

pharmaceutical preparations and technologies of production.

No modifications of compound I have been disclosed to date.

5 The invention is therefore based on the object of providing the compound I in various modifications, and mixtures thereof, in accordance with pharmaceutical requirements.

10 The two modifications, called A and B, have different physicochemical properties. These two modifications of the compound of the formula I are identified by means of the respective characteristic x-ray powder diffractograms. The modifications also differ in their
15 DSC plots (differential scanning calorimetry), by the typical crystal forms in each case, the different solubilities or rates of dissolution, and by the different flow properties.

20 The x-ray diffractograms as shown in Figures 1-6 were recorded with CuK_α radiation using a powder diffractometer.

Modification A is characterized by:

25 - the x-ray diffractogram (see Figs. 1-3 and Fig. 6), with reflections not coinciding with the reflections of the other modifications being observed inter alia at

30 14.87°2 θ (5.96Å), 19.99°2 θ (4.44Å), 20.88°2 θ (4.25Å),
22.78°2 θ (3.90Å), 24.53°2 θ (3.63Å), 25.66°2 θ (3.47Å),
30.05°2 θ (2.97Å) and at 37.29°2 θ (2.41Å).

- the melting point in the region of about 117.1 to 118.4°C.

35

It is mainly in the form of platelets.

Modification B is characterized by:

- 3 -

- the x-ray diffractogram (see Figs. 1, 2 and 4, and Fig. 6), with reflections not coinciding with the reflections of the other modifications being observed inter alia at
 5 13.80°2 θ (6.41Å), 15.22°2 θ (5.82Å), 17.50°2 θ (5.06Å) and at 23.48°2 θ (3.79Å).

- the melting point in the region of about 115.2 to 116.8°C.

10

It is mainly in the form of aggregates.

The x-ray diffractograms of mixtures of the A/B modifications are characterized by superimposition of
 15 the reflections of A and B (A/B mixture = about 1:1, see Figs. 1, 2 and 5, 6).

The solubility or rate of dissolution of modification A in water and organic solvents such as, for example,
 20 lower alcohols, octanol and acetone, and mixtures thereof with water, is higher than for modification B. The angle of repose α of the modifications as a measure of the flow properties or flowability likewise differs:

25

Angle of repose α^1

Modification A	46°
Modification B	32°
Mixture of modifications A/B = 1:1	34°

30

¹⁾ Determined in accordance with R. Voigt, Lehrbuch der pharmazeutischen Technologie, 3rd edition, 1979, page 165

35 It is generally known that R-thioctic acid readily polymerizes and is prone to such reactions especially in polar media.

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It is therefore surprising that polymer-free products can be obtained in the reaction of R-thioctic acid with trometamol when the trometamol is metered into a solution of R-thioctic acid in polar solvents such as, for example, lower alcohols, where appropriate with addition of water, and the resulting suspension is heated to give a solution.

"Lower alcohols" mean in this connection straight-chain or branched alcohols having 1 to 6 C atoms.

Crystallization subsequently takes place on cooling. Concentration of the solution under mild conditions and cooling affords further product from the mother liquor.

It is surprisingly possible for modifications A and B of compound I, and mixtures thereof of any composition, to be produced both by salt formation of R-thioctic acid with trometamol in suitable polar solvents such as, for example, lower alcohols and by modification conversion under specific reaction conditions.

It is thus possible to provide either pure modifications of compound I and mixtures thereof of varying composition for producing different pharmaceutical preparations.

The formation of modifications A and B and mixtures thereof through salt formation of R-thioctic acid with trometamol depends on the purity of the R-thioctic acid employed (content of trace impurities resulting from the synthesis).

Thus, with R-thioctic acid obtained by racemate resolution in accordance with DE 4,137,773 (referred to as synthetic route a hereinafter), modification A is obtained.

By contrast, with R-thioctic acid into which sulfur is introduced at the end of the synthesis for its preparation (referred to as synthetic route b hereinafter; for example DE 4,037,440, DE 19,533,881, DE 19,533,882, DE 19,709,069), the main product obtained is modification B in addition to a small

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amount of A. It is possible by one or more additional purification steps on the R-thioctic acid obtained by synthetic route b (e.g. recrystallization from inert solvents such as cyclohexane, cyclohexane/ethyl acetate (in particular 19:1), n-heptane/toluene, n-hexane/toluene, where appropriate with addition of water or dilute mineral acid, and reprecipitation from dilute alkali metal hydroxide solution/dilute mineral acid with simultaneous extraction, for example with cyclohexane/ethyl acetate, for trace impurities resulting from the synthesis to be cleaned gradually in such a way that the salt formation results either in a mixture of A/B modifications or in modification A as main products.

On the other hand, the main product obtained through addition of nucleophilic compounds such as, for example, sodium sulfite or 6,8-dimercaptooctanoic acid on salt formation with R-thioctic acid prepared by synthetic route a is modification B.

The modifications can also be produced by modification conversion, in which case complete or partial conversion both of A to B and of B to A may take place. It is moreover possible to employ both pure modifications A and B and mixtures thereof. Conversion in the direction of formation of a pure modification is preferred on use of mixtures.

The following methods can be employed:

- recrystallization from lower alcohols, where appropriate with addition of water
- prolonged heating in lower alcohols, where appropriate with addition of water, at temperatures up to a boiling point and subsequent crystallization with cooling
- concentration of solutions in lower alcohols, where appropriate with addition of water, by removal of the

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solvent by distillation under atmospheric pressure or in vacuo

- reprecipitation from solvent mixtures
- conversion of the salt I suspended in solvents
- 5 - thermal phase conversion below the melting point or by melting processes

Production of modification A

- 10 - Recrystallization of modification B or A/B mixtures from lower alcohols.
- Removal of the solvent by distillation in vacuo from solutions of modification B or A/B mixtures in lower alcohols.
- 15 - Suspension of modification B or of A/B mixtures in lower alcohols, where appropriate with addition of water, at temperatures of about 0 to 60°C, preferably at about 20 to 40°C, and with stirring times of, in general, 1 to 24 h, in particular about 2 to 15 h.
- 20 - Reprecipitation by addition of hydrocarbons to the solution of modification A in lower alcohols.

Production of modification B

- 25 - Recrystallization of modification A or A/B mixtures from lower alcohols, where appropriate with addition of water.
- Removal of the solvent by distillation from solutions of modification A in lower alcohols.
- 30 - Heating of a melt of modification A, preferably for about 10 to 40 min at about 115-130°C, in particular 15 to 25 min at about 115-120°C, and crystallization by cooling.
- Recrystallization of modification A from lower
- 35 alcohols, where appropriate with addition of water,

adding nucleophilic compounds such as, for example, sodium sulfite or 6,8-dimercaptooctanoic acid.

Production of A/B modification mixtures

5

- Heating of a solution of modification A in lower alcohols at the reflux temperature in general for about 2 to 12 h, preferably about 4 to 8 h, and subsequent crystallization with cooling.

10

- Removal of the solvent by distillation from solutions of modification A in lower alcohols, where appropriate with addition of water.

- Brief melting of modification A and crystallization with cooling.

15

- Reprecipitation through addition of acetone to a solution of modification A in water or dimethylformamide.

20

- Recrystallization of modification A from lower alcohols, where appropriate with addition of water, and by addition of nucleophilic compounds such as, for example, sodium sulfite or 6,8-dimercaptooctanoic acid.

25

- Recrystallization of modification A from dipolar aprotic solvents such as, for example, N,N-dimethylacetamide, ethylene glycol dimethyl ether, 1,2-dichloroethane, methyl ethyl ketone and dimethyl carbonate.

- Recrystallization of modification A or B from lower alcohols, where appropriate with addition of water.

30

Modifications A and B and mixtures thereof can be processed in a conventional way with suitable carriers and/or excipients to give pharmaceutical preparations. Preferred use forms are tablets and capsules.

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They are, for example, valuable compositions for the treatment of insulin resistance, of diabetes mellitus and of glucose metabolism disorders of the CNS.

- 5 The methods for producing modifications A and B and mixtures thereof are to be explained in more detail by means of examples.

Examples

- 10 After filtration with suction, the modifications of compound I were, unless otherwise indicated, washed with the particular cooled solvent and dried at 50°C for 2 h.

- 15 Formation of modifications in the production of the trometamol salt of R-thioctic acid

Example 1

- 20 12.1 g (0.1 mol) of trometamol were introduced into a solution of 41.2 g (0.2 mol) of R-thioctic acid (produced by method a) in 220 ml of ethanol (96%) and heated with stirring to 55°C.

- 1 g of Diacel (filter aid) was added to the solution,
25 heated at 55-57°C for 20 min, clarified by suction, slowly cooled and then stirred at -5 to -10°C for 2 h.

Yield: 58.0 g (88.6% of theory) of I, modification A.

- 30 Concentration of the mother liquor to about 1/5 of the original volume resulted in a further 1.7 g (2.6% of theory) of I, modification A.

Example 2

35

41.2 g (0.2 mol) of R-thioctic acid (produced by method a) were dissolved in 600 ml of ethanol (anhydrous). While stirring, 24.2 g (0.2 mol) of trometamol were introduced, heated at 50-55°C to give a solution and,

after addition of 2 g of Diacel, stirred at 50-55°C for about 10 min and clarified by suction. The mixture underwent slow (3-4 h) approximately linear cooling to -5°C and was then stirred at -5 to -10°C for 4-5 h.

5

Yield: 55.5 g (84.9% of theory) of I, modification A.

Concentration of the mother liquor to about 20% resulted in a further 4.1 g (6.3% of theory) of I, modification A.

10

Example 3

41.2 g (0.2 mol) of R-thioctic acid (produced by method a) were dissolved in 230 ml of ethanol (anhydrous). 24.2 g (0.2 mol) of trometamol were introduced and stirred at 55 to 60°C until dissolution was complete. Clarification by suction was followed by slow cooling to 0 to 5°C, stirring in this temperature range for 2 to 4 h, filtration with suction, washing with cold ethanol and drying.

15

20

Yield: 61.0 g (93.1% of theory) of I, modification A.

Concentration of the mother liquor in vacuo to about 20% resulted in a further 2.4 g (3.7% of theory) of I, modification A.

25

Example 4

30

41.2 g (0.2 mol) of R-thioctic acid (produced by method b with subsequent recrystallization from cyclohexane/ethyl acetate/water in accordance with Example 31) were dissolved in 600 ml of ethanol (anhydrous). Then 24.2 g (0.2 mol) of trometamol were introduced and heated to 50-55°C with stirring. 2 g of Diacel were added to the solution, stirred for 20 min, clarified by suction and slowly cooled.

35

- 10 -

Seeding was carried out at 30°C. Stirring was continued in the range from -5 to -10°C for 4 h.

Yield: 56.1 g (85.7% of theory) of I, modification A.

5

Concentration of the mother liquor to about 1/5 resulted in a further 6.7 g (10.2% of theory) of I, modification A.

10 Example 5

In analogy to Example 4, R-thioctic acid (produced by method b with subsequent single recrystallization from cyclohexane) resulted in 54.9 g (83.9% of theory) of first crystals of I, A/B (approx. 1:1) modification mixture, and concentration of the mother liquor resulted in 6.8 g (10.4% of theory) of I, modification A.

20 Example 6

25.8 g (0.125 mol) of R-thioctic acid (produced by method b) were dissolved in 375 ml of ethanol (anhydrous). Then 15.13 g (0.125 mol) of trometamol were introduced and heated with stirring at 50-55°C to give a solution.

After addition of 1.25 g of Diacel and clarification by suction, the solution was slowly cooled, seeded at 30°C and cooled at -5 to -12°C for 4 h.

30

Yield: 28.1 g (68.6% of theory) of I, modification B.

Concentration of the mother liquor gives 70 ml and cooling resulted in 9.3 g (22.6% of theory) of I, modification A.

35

Example 7

41.2 g (0.2 mol) of R-thioctic acid (produced by method b) were dissolved in 250 ml of ethanol (anhydrous). Then 24.2 g (0.2 mol) of trometamol were introduced and heated with stirring at 55-57°C to give a solution.

- 5 After addition of 1.25 g of Diacel and clarification by suction, the solution was slowly (about 1-2 h) cooled and stirred at -5 to -10°C for 2 h.

Yield: 55.0 g (84.1% of theory) of I, modification B.

10

Concentration of the mother liquor to 70 ml and cooling resulted in 5.7 g (8.7% of theory) of I, modification A.

15 Example 8

- 41.2 g (0.2 mol) of R-thioctic acid (produced by method b) were dissolved in 220 ml of ethanol (anhydrous). Then 24.2 g (0.2 mol) of trometamol were added and
20 heated to 57°C.

- The solution became clear after 10 min and 2 g of Diacel were introduced, stirred at 55-57°C for 20 min, clarified by suction and slowly cooled. Stirring was
25 continued at -5 to -10°C for 2 h.

Yield: 57.8 g (88.4% of theory) of I, modification B.

- Concentration of the mother liquor to about 20% and
30 cooling resulted in 3.7 g (5.7% of theory) of I, modification A.

Example 9

- 35 20.6 g (0.1 mol) of R-thioctic acid (produced by method a) were dissolved in 300 ml of ethanol (anhydrous). Subsequent addition of 12.1 g (0.1 mol) of trometamol and 0.5 g of 6,8-dimercaptooctanoic acid was followed by heating at 55°C to give a solution. Addition of 1 g

of Diacel was followed by stirring at 53-55°C for 20 min and clarification by suction, and the solution was slowly cooled. Stirring was continued at -8 to -12°C (2 h).

- 5 1.9 g (5.8% of theory) were isolated from the flask wall (modification mixture B > A).

After the mother liquor had been concentrated to one half and cooled at -5 to -10°C overnight, it afforded 20.2 g (61.8% of theory) of I, modification B.

- 10 Further concentration to about one half and cooling resulted in 1.9 g (5.8% of theory) of I, modification A.

Example 10

15

20.6 g (0.1 mol) of R-thioctic acid (produced by method a) were dissolved in 110 ml of ethanol (96%). Then 12.1 g (0.1 mol) of trometamol and 2 g of sodium sulfite were introduced and heated to 55°C.

- 20 Addition of 1 g of Diacel was followed by stirring at 53-55°C for 20 min, clarification by suction and slow cooling. Stirring was continued at -5 to -10°C for 2 h.

- 25 8.1 g (yield 24.8% of theory) of I, modification A, were obtained.

The mother liquor was concentrated to about one half and cooled at -5 to -10°C overnight.

- 30 19.1 g (yield 58.4% of theory) of I, modification B were obtained.

Production of modifications by conversion

Example 11

35

10 g of I, modification B, were dissolved in 85 ml of ethanol (anhydrous) at 50-55°C. The solution was slowly cooled to -5 to -10°C while stirring, seeding at 30°C with I, modification A.

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After the stirring at -5 to -10°C (2 h) and standing in a deep freeze overnight, 5.4 g (54% of theory) of I, modification B, were recovered.

5

Concentration of the mother liquor to 1/5 and cooling in a deep freeze overnight resulted in 4.0 g (40% of theory) of I, modification A.

10 Example 12

1 g of I, modification B, were dissolved in 10 ml of ethanol (anhydrous) at 55°C, the solvent was stripped off at room temperature, and the residue was investigated after drying (2 h, 50°C): I, modification A.

Example 13

20 30 ml of n-heptane are added to a solution of 3 g of I, modification B, in 25 ml of anhydrous ethanol at 57°C, and the mixture is then cooled to -5 to -10°C. The crystals are dried (2 h, 50°C).

25 Yield: 2.5 g (75% of theory) of I, modification A.

Example 14

30 2 g of a mixture consisting of 80% of modification A and 20% of modification B were suspended in 3 ml of ethanol (96%) and stirred at 35°C for 11 h, resulting in pure modification A.

Example 15

35

20 g of I consisting of about 50% each of modifications A and B were dissolved in 170 ml of ethanol (anhydrous) at 50-55°C and, after addition of 0.5 g of Diacel, clarified by suction. The filtrate was rapidly cooled

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to -5 to -10°C with stirring and then stirred at this temperature for 2 h.

Yield 16.8 g (84% of theory) of I, modification A.

5

Example 16

20 g of I, modification A, were dissolved in 170 ml of ethanol (anhydrous) at 50-55°C. The filtrate was slowly
10 cooled to -5 to -10°C, seeding at 31°C. Stirring was continued at -5 to -10°C for 2 h.

16.9 g (84.5% of theory) of I, modification A, were recovered.

15

Concentration of the mother liquor to 1/5 and cooling resulted in 2.0 g (10% of theory) of I, modification B with traces A.

The same result was obtained even without seeding.

20

Example 17

40 g of I, A > B mixture, were dissolved in 120 ml of ethanol (96%) at 50-55°C, rapidly cooled to -5 to -10°C
25 and then stirred in the same temperature range for 2 h.

Yield: 34 g (85% of theory) of I, modification B.

Example 18

30

10 g of I, modification A, were heated to reflux in 85 ml of ethanol (anhydrous) for 6 h, subsequently cooled and then stirred at -5 to -10°C for 1 h.

35 Yield: 8.3 g (83% of theory) of I, mixture of modifications A and B (approx. 1:1).

The mother liquor was concentrated to 20%: 0.91 g (9.1% of theory) of I, modification B.

Example 19

5 Heating 10 g of I, modification A, in 30 ml of ethanol (96%) at reflux (6 h), cooling and stirring (1 h at -5 to -10°C) resulted in 8.6 g of first crystals of I (yield 86% of theory) as modification mixture (B > A).

Example 20

10

15 15 g of I, modification B, were dissolved in 70 ml of ethanol (96%) at 55°C. The solution was cooled and stirred at -5 to -8°C for 2 h.

20 Yield: 12.8 g (84.8% of theory) of I, A/B modification mixture (approx. 1:1)

25 Concentration of the mother liquor to about 20% and cooling resulted in 0.6 g (3.9% of theory) of I, modification A.

Example 21

30 5 g of I, modification A, were dissolved in 200 ml of isopropanol at 50-55°C. It was rapidly cooled and then stirred at -5 to -10°C for 1 h.

35 4.2 g (84% of theory) of I, A/B modification mixture, were obtained.

40 Concentration of the mother liquor to 20% and cooling resulted in a further 0.4 g (8% of theory) of I, A/B modification mixture.

35 Example 22

3 g of I, modification A, were dissolved in 3 ml of N,N-dimethylacetamide at 50-55°C. It was cooled and stirred at -5 to -10°C for 1 h.

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Yield: 1.6 g (53.3% of theory) of I, modification mixture (A > B)

5 Example 23

10 g of I, modification A, were dissolved in 90 ml of ethanol (anhydrous) at 55°C. Most of the solvent was removed by distillation under atmospheric pressure, and
10 the remainder in vacuo. The resulting oil crystallized on cooling: I, modification B, quantitative yield.

Example 24

15 10 g of I, modification A, were dissolved in 30 ml of ethanol (96%) at 55°C. The solution was then concentrated in a rotary evaporator up to a maximum bath temperature of 100°C, finally in vacuo. The oil crystallized on cooling: mixture (approx. 1:1) of
20 modifications A and B, quantitative yield.

Example 25

2 g of I, modification A, were melted at a bath
25 temperature of 115-120°C and kept at this temperature for 20 min. The crystals obtained on cooling consisted mainly of modification B with a trace of A plus polymer.

30 Example 26

2 g of I, modification A, were briefly melted at a bath temperature of about 140°C and then rapidly cooled. The crystals consisted of an A/B modification mixture plus
35 polymer.

Example 27

400 ml of acetone were added to a solution of 3 g of I, modification A in 8 ml of water, and cooled at -5 to
5 -8°C (2 h).

Yield: 1.8 g (60% of theory) of I, modification mixture (B > A).

10 Example 28

80 ml of acetone were added to a solution of 3 g of I, modification A in 12 ml of dimethylformamide. It was cooled to -5°C and stirred at this temperature for
15 90 min.

Yield: 2.75 g (91.3% of theory) of I, modification B with traces of A.

20 Example 29

20 g of I, modification A, and 2 g of sodium sulfite were respectively dissolved and suspended in 50 ml of ethanol (96%) at 50-55°C. Addition of 1 g of Diacel was
25 followed by clarification by suction, slowly cooling to -6 to -8°C and stirring at this temperature for 2 h.

Yield: 15.9 g (79.5% of theory) of I, modification mixture (B > A).

30

Example 30

10 g of I, modification A, and 0.25 g of 6,8-dimercaptooctanoic acid were dissolved in 85 ml of
35 ethanol (anhydrous) at 50-55°C. Addition of 1 g of Diacel was followed by clarification by suction, slow cooling to -8 to -12°C and stirring in this temperature range for 2 h.

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Yield: 1.9 g (19% of theory) of I, modification mixture
(B > A).

Concentration of the mother liquor to about 50% and
5 cooling resulted in 6.1 g (61% of theory) of
modification B.

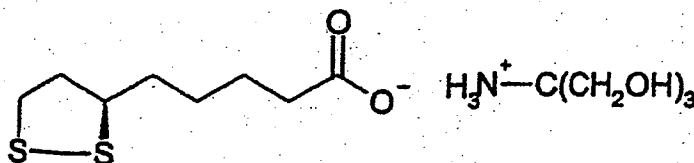
Example 31

10 100 g of R-thioctic acid (produced by method b) were
dissolved in a mixture consisting of 760 ml of
cyclohexane and 40 ml of water-saturated ethyl acetate
(water content: 3.2%) at 40-42°C. Addition of 5 g of
Diacel was followed by clarification by suction, slow
15 cooling to -5°C, stirring at this temperature for 1 h,
filtration with suction, washing with cyclohexane and
drying at 30°C.

Yield: 87.5 g (87.5% of theory) of R-thioctic acid,
20 pure.

Claims

1. Modification A of compound I



I

characterized by the x-ray diffractogram, with reflections not coinciding with the reflections of the other modification being observed inter alia at

14.87°2θ(5.96Å), 19.99°2θ(4.44Å), 20.88°2θ(4.25Å), 22.78°2θ(3.90Å), 24.53°2θ(3.63Å), 25.66°2θ(3.47Å), 30.05°2θ(2.97Å) and at 37.29°2θ(2.41Å).

2. Modification B of compound I characterized by the x-ray diffractogram, with reflections not coinciding with the reflections of the other modification being observed inter alia at 13.80°2θ(6.41Å), 15.22°2θ(5.82Å), 17.50°2θ(5.06Å) and at 23.48°2θ(3.79Å).
3. A mixture of modifications A and B of compound I of any composition.
4. The production of modifications A and B and of A/B mixtures of any composition by reacting R-thioctic acid with trometamol, characterized in that trometamol is metered into a solution of R-thioctic acid in a polar solvent, the suspension is heated to give a solution, and crystallization is brought about by cooling, where appropriate after concentration.

5. The method for producing modifications A and B, and A/B mixtures of any composition, as claimed in claim 4, characterized in that straight-chain or branched alcohols having 1 to 6 C atoms, and mixtures thereof with water, are employed as polar solvents.
6. The method for producing modification A as claimed in claims 4 and 5, characterized in that an R-thioctic acid produced by racemate resolution is employed in the reaction.
7. The method for producing modification A as claimed in claims 4 and 5, characterized in that an R-thioctic acid produced by introduction of sulfur in the final stage of the synthesis and highly purified by recrystallization or reprecipitation is employed in the reaction.
8. The method for producing modification B as claimed in claims 4 and 5, characterized in that an R-thioctic acid produced by introduction of sulfur in the final stage of the synthesis is employed in the reaction.
9. The method for producing an A/B modification mixture of any composition as claimed in claims 4 and 5, characterized in that an R-thioctic acid which has been produced by introduction of sulfur in the final stage of the synthesis and only partially purified by recrystallization or reprecipitation is employed in the reaction.
10. The method for producing modification B as claimed in claims 4 and 5, characterized in that an R-thioctic acid produced by racemate resolution is employed in the reaction with addition of nucleophilic compounds.

11. A method for producing modification A, characterized in that modification B or A/B mixtures are recrystallized from straight-chain or branched alcohols having 1 to 6 C atoms.
12. A method for producing modification A, characterized in that modification B or A/B mixtures are dissolved in straight-chain or branched alcohols having 1 to 6 C atoms, where appropriate with addition of water, and the solvent is removed by distillation in vacuo.
13. A method for producing modification A, characterized in that modifications B or A/B mixtures, suspended in straight-chain or branched alcohols having 1 to 6 C atoms, where appropriate with addition of water, are stirred as suspension at temperatures of about 0 to 60°C, preferably at about 20 to 40°C, and with reaction times of in general 1 to 24 h, in particular about 2 to 15 h.
14. A method for producing modification A, characterized in that nonpolar solvents are added to the modification B which is dissolved in straight-chain or branched alcohols having 1 to 6 C atoms, where appropriate with addition of water, followed by cooling.
15. A method for producing modification B, characterized in that modification A or A/B mixtures are recrystallized from straight-chain or branched alcohols having 1 to 6 C atoms, where appropriate with addition of water.
16. A method for producing modification B, characterized in that modification A is dissolved in straight-chain or branched alcohols having 1 to

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6 C atoms, and the solvent is removed by distillation.

17. A method for producing modification B, characterized in that a melt of modification A is kept preferably at about 115-130°C for about 10 to 40 min, in particular at about 115-120°C for 15 to 25 min, and is induced to crystallize by cooling.
18. A method for producing modification B, characterized in that modification A is recrystallized from straight-chain or branched alcohols having 1 to 6 C atoms with addition of nucleophilic compounds, where appropriate with addition of water.
19. A method for producing A/B modification mixtures, characterized in that modification A in straight-chain or branched alcohols having 1 to 6 C atoms is heated in general for about 2 to 12 h, preferably about 4 to 8 h, and then crystallized by cooling.
20. A method for producing A/B modification mixtures, characterized in that modification A is dissolved in straight-chain or branched alcohols having 1 to 6 C atoms with addition of water, and the solvent is removed by distillation.
21. A method for producing A/B modification mixtures, characterized in that modification A is briefly melted and the melt is rapidly cooled.
22. A method for producing A/B modification mixtures, characterized in that modification A is dissolved in water or dimethylformamide, and the A/B modification mixture is precipitated by adding acetone.

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23. A method for producing A/B modification mixtures, characterized in that modification A is recrystallized from straight-chain or branched alcohols having 1 to 6 C atoms with addition of nucleophilic compounds, where appropriate with addition of water.
24. A method for producing A/B modification mixtures, characterized in that modification A is recrystallized from dipolar aprotic solvents.
25. A method for producing A/B modification mixtures, characterized in that modification B is recrystallized from straight-chain or branched alcohols having 1 to 6 C atoms, where appropriate with addition of water.
26. The use of modifications A and B and of A/B modification mixtures of any composition of compound I for the production of pharmaceutical preparations.
27. A medicament comprising modifications A or B or A/B modification mixtures of any composition of compound I and, where appropriate carriers and/or excipients.