

(57) Abstract: A process for the preparation of 1,4-dihydropyridine-3,5-dicarboxylic acid derivative of formula (I) reacting compound of formula (III) with compound of formula (IV) to yield 1,4-dihydropyridine-3,5-dicarboxylic acid derivative of formula (I) and its pharmaceutically acceptable salts.

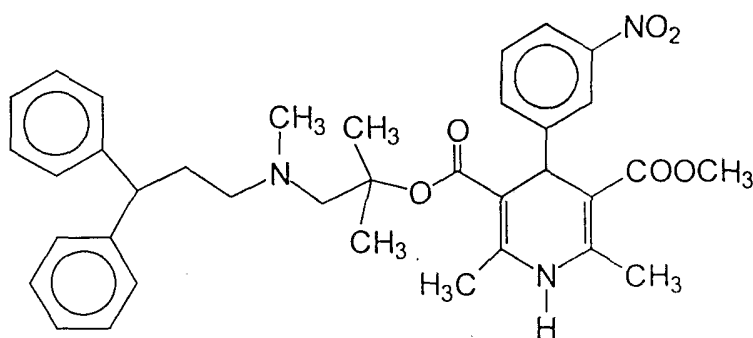


- CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
 - as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
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A PROCESS FOR THE PREPARATION OF 1,4-DIHYDROPYRIDINE-3,5-DICARBOXYLIC ACID DERIVATIVE

- 5 The present invention relates to a process for the preparation of 1,4-dihydropyridine-3,5-dicarboxylic acid derivative of formula I, commonly known as lercanidipine and its pharmaceutically acceptable salts. Lercanidipine (INN name) is used in the treatment of hypertension.

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Formula I

- United States Patent No. 4,705,797 (assigned to M/S Recordati) provides compound of
15 formula I and its pharmaceutically acceptable acid addition salt and the process of its preparation. This patent discloses preparation of compound of formula I using different routes wherein

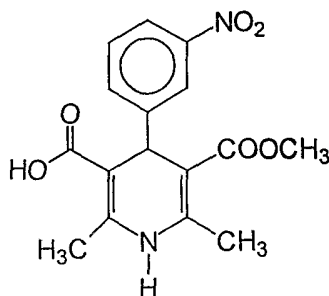
(a) 3-nitrobenzaldehyde may be reacted with 1,1,N-trimethyl-N-(3,3-diphenylpropyl)-2-aminoethylacetoacetate for 3 days in pharmaceutically

restricted / non acceptable solvent like chloroform to give 1,1,N-trimethyl-N-(3,3- diphenylpropyl)-2- aminoethyl- α -acetyl-3-nitro-cinnamate, followed by condensation with methyl-3- amino crotonate followed by purification with flash chromatography to give compound of formula I.

- 5 (b) Alternatively 3-nitrobenzaldehyde is reacted with 1-methyl-2-chloroethylacetoacetate to yield 1-methyl-2-chloroethyl- α -acetyl-3-nitro cinnamate which on treatment with methyl-3-amino crotonate gives the dihydropyridine intermediate. The dihydropyridine intermediate, methyl 1-methyl-2-chloroethyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-
10 dicarboxylate, on condensation with N-methyl-3,3- diphenylpropylamine yields compound analogous to compound of formula I. The reaction of nitro benzaldehyde is very sluggish and requires 2 days for analogous compounds and also involves purification steps such as column chromatography which is industrially not feasible.
- 15 (c) The compound of formula I may be prepared by coupling of 2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid with 2,N-dimethyl-N-(3,3-diphenylpropyl)-1-amino-2-propanol in presence of DCC/DMAP. The esterification step is very sluggish requiring 8 days for analogous compounds methyl 1, N -dimethyl-N(3,3-diphenylpropyl)-3-
20 aminopropyl-1,4- dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.

United States Patent No. 5912351 (assigned to M/s Recordati) reports a different process for the preparation of compound of formula I from

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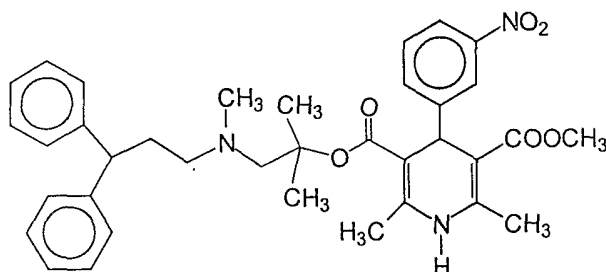
Formula II

2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid, compound of formula II, by converting to its acid chloride derivative and reacting with 2,N-dimethyl-N-(3,3-diphenylpropyl)-1-amino-2-propanol. The drawback of this process is the preparation of 2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid, compound of formula II, which requires selective hydrolysis of the ester group. The reaction conditions for the same are very tricky and one needs to be skilled to consistently achieve the desired mono carboxylic acid in good yield and purity. There is a possibility of formation of dicarboxylic acid intermediate instead of the desired monocarboxylic acid which would lead to the formation of undesired side products during esterification reaction to form compound of formula I. Moreover the compound of formula II is isolated from water and requires to be dried for very long periods to achieve low moisture content which is essential for the subsequent conversion to its acid chloride derivative.

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OBJECT OF THE INVENTION

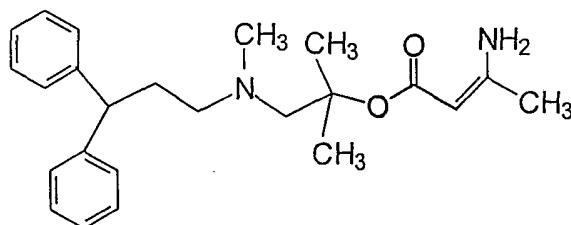
An object of the present invention is to provide a simple, commercially feasible process for the preparation of 1,4-dihydropyridine-3,5-dicarboxylic acid derivative of formula I
5 from a novel intermediate, 3-amino-but-2-enoic acid-2[(3,3-diphenylpropyl) methylamino] 1,1-dimethyl ethyl ester, compound of formula III, without tedious purification steps.



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formula I

It is yet another object to provide a novel intermediate, compound of formula III, and the
15 process for its preparation.



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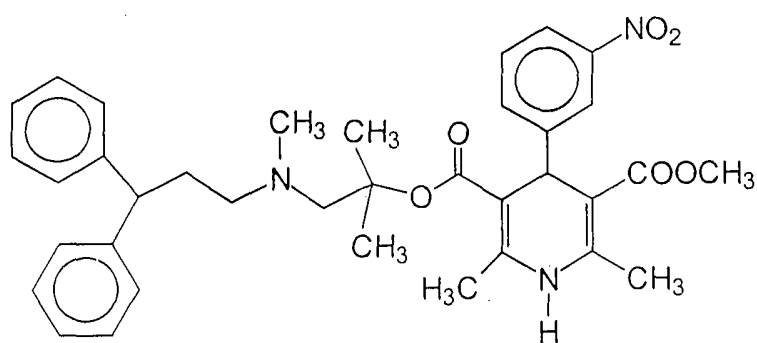
Formula III

We have found a novel process for the preparation of 1,4-dihydropyridine-3,5-dicarboxylic acid derivative of formula I via a new intermediate, compound of formula
5 III, hitherto not reported in the literature.

SUMMARY OF THE INVENTION

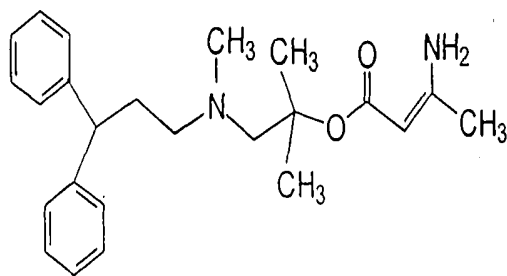
A process for the preparation of 1,4-dihydropyridine-3,5-dicarboxylic acid derivative of
formula I and its enantiomers comprising

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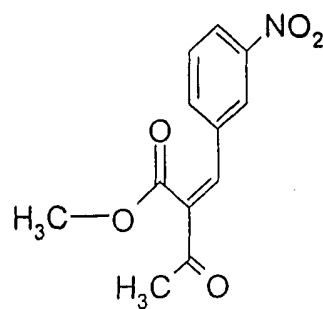


Formula I

15 reacting compound of formula III with compound of formula IV



Formula III



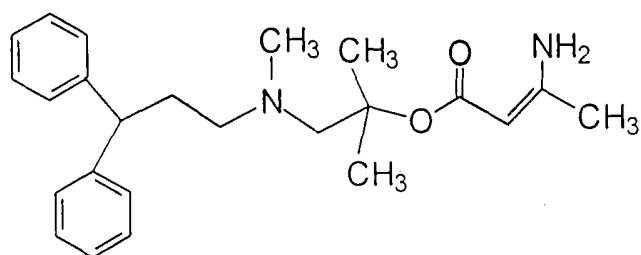
Formula IV.

to yield 1,4-dihydropyridine-3,5-dicarboxylic acid derivative of formula I.

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Novel intermediate compound of formula III

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Formula III

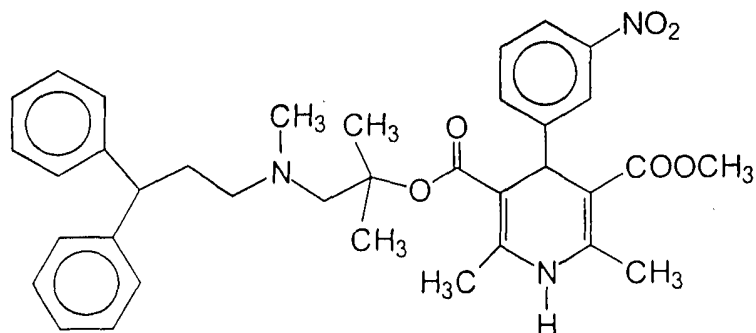
15 and the process of its preparation.

DETAILED DESCRIPTION OF THE INVENTION

We have now developed a novel process for the preparation of 1,4-dihydropyridine-3,5-dicarboxylic acid derivative of formula I. The present invention describes a method for preparing 1,4-dihydropyridine-3,5-dicarboxylic acid derivative of formula 1 via a novel

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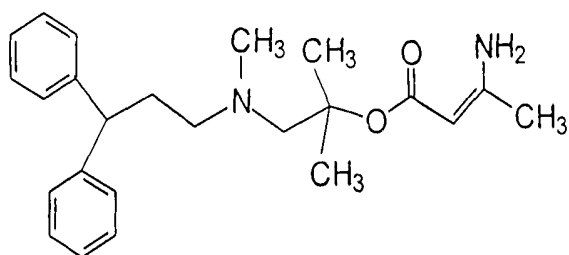
intermediate, 3-amino-but-2-enoic acid-2[(3,3-diphenylpropyl) methylamino] 1,1-dimethyl ethyl ester compound of formula III.



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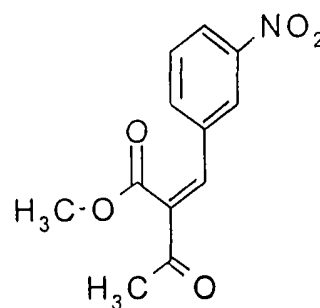
Formula I

According to one embodiment of the process of the present invention, 1, 4-dihydropyridine-3,5-dicarboxylic acid derivative of formula I is obtained by reacting
 10 novel intermediate, 3-amino-but-2-enoic acid-2[(3,3-diphenylpropyl) methylamino] 1,1-dimethyl ethyl ester, compound of formula III with 2-(3-Nitrobenzylidene)-3-oxo-butyric acid methyl ester, compound of formula IV.



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formula III



formula IV

The reaction of novel intermediate, compound of formula III with compound of formula IV may be carried out at temperature greater than about 50 °C.

- 5 The reaction of novel intermediate, compound of formula III with compound of formula IV may be carried out for more than about 0.5 to 3 hours.

The reaction of novel intermediate, compound of formula III with compound of formula IV may be carried out in solvent(s). The solvent(s) may be selected from ethers such as
10 diethylether, di-isopropylether, diphenylether, dioxane, tetrahydrofuran and the like; alcohols such as methanol, ethanol, isopropanol and the like; linear or cyclic aliphatic or aromatic hydrocarbons such as n-hexane, n-heptane, cyclohexane, methylcyclohexane, toluene, ethylbenzene, xylene and the like; aliphatic or aromatic halogenated hydrocarbons such as methylene dichloride, ethylene dichloride, tetrachloroethane,
15 trichloroethane, chlorobenzene, dichlorobenzene and the like; nitriles such as acetonitrile, benzonitrile and the like; amides such as acetamide, dimethylformamide, dimethylacetamide and the like; esters such as ethyl acetate and the like; ketones such as acetone, methyl ethyl ketone and the like; sulphoxides such as dimethylsulfoxide, sulfolane and the like; water and their mixtures.

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The reaction of novel intermediate, compound of formula III with compound of formula IV may be carried out in presence of ammonia source. The ammonia source may be selected from ammonium salts, ammonium hydroxide, liquor ammonia, hexamine,

hexamethyldisilazane and the like. The ammonium salts may be selected from ammonium formate, ammonium acetate and the like. The molar ratio of compound of formula III to the ammonia source may be selected from about 1: 0.05 to 1: 5.

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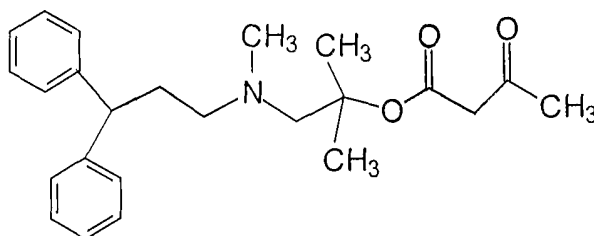
The resulting 1, 4-dihydropyridine-3,5-dicarboxylic acid derivative of formula I, may be isolated from the reaction mixture by conventional means.

1,4-dihydropyridine-3,5-dicarboxylic acid derivative of formula I, obtained by following
10 the process of the present invention may be converted to its pharmaceutically acceptable salts by using appropriate acid.

The pharmaceutically acceptable salts may be selected from mineral acid salts such as hydrochloride, hydrobromide, sulfate and the like; organic acid salts such as oxalate,
15 citrate, succinate, maleate, fumarate, malate, tartrate, and the like; and sulfonates such as methanesulfonate, benzenesulfonate, toluenesulfonate and the like; preferably hydrochloride.

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According to another embodiment of the present invention is the novel intermediate, compound of formula III and the process of its preparation. Compound of formula III may be prepared by the reaction of 1,1,N-trimethyl-N-(3,3-diphenylpropyl)-2-aminoethyl acetoacetate, compound of formula V with ammonia source followed by reaction with
5 compound of formula IV insitu to give 1, 4-dihydropyridine-3,5-dicarboxylic acid derivative of formula I, in single pot. This avoids the step of isolation of compound of formula III and then reacting compound of formula III with compound of formula IV.



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formula V

Alternatively, the novel intermediate, compound of formula III may be isolated and reacted with compound of formula IV to yield 1, 4-dihydropyridine-3,5-dicarboxylic
15 acid derivative of formula I.

Accordingly, in the process for the preparation of novel intermediate, compound of formula III the ammonia source may be selected from ammonium salts, ammonium hydroxide, liquor ammonia, hexamine, hexamethyldisilazane and the like. The ammonium salts maybe selected from ammonium formate, ammonium acetate, 5 ammonium carbonate and the like.

The process for the preparation of novel intermediate, compound of formula III may be carried out by reacting compound of formula V with ammonia source in solvent(s).

10 The solvent(s) may be selected from ethers such as diethylether, di-isopropylether, diphenylether, dioxane, tetrahydrofuran and the like; alcohols such as methanol, ethanol, isopropanol and the like; linear or cyclic aliphatic or aromatic hydrocarbons such as n-hexane, n-heptane, cyclohexane, methylcyclohexane, toluene, ethylbenzene, xylene and the like; aliphatic or aromatic halogenated hydrocarbons such as methylene dichloride, 15 ethylene dichloride, tetrachloroethane, trichloroethane, chlorobenzene, dichlorobenzene and the like; nitriles such as acetonitrile, benzonitrile and the like; sulphoxides such as dimethylsulfoxide, sulfolane and the like amides such as acetamide, dimethylformamide, dimethylacetamide and the like; esters such as ethyl acetate and the like; ketones such as acetone, methyl ethyl ketone and the like; water and their mixtures .

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The process for the preparation of novel intermediate, compound of formula III may be carried out by reacting compound of formula V with ammonia source at temperature greater than 20 °C.

The process for the preparation of novel intermediate, compound of formula III may be carried out by reacting compound of formula V with ammonia source for greater than about 15 hour.

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Compound of formula V may be prepared by any method known to those skilled in the art such as United States Patent No. 4,705,797.

Compound of formula IV may be prepared using any process known to a person skilled
10 in the art such as reacting m-nitrobenzaldehyde with methyl acetoacetate.

In case of preparation of enantiomers, appropriate technology may be employed to obtain the individual isomers.

15 The invention is illustrated but not restricted by the description in the following examples.

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Examples

Example 1

- 5 **A. Preparation of 3-amino-but-2-enoic acid-2[(3,3diphenylpropyl)methylamino]1,1-dimethyl ethyl ester, compound of formula III**

a) Preparation of 1,1,N-trimethyl-N-(3,3-diphenylpropyl)-2-aminoethyl acetoacetate, compound of formula V

- 10 To a three necked round bottom flask containing 500ml of toluene, 100g of 1,1,N-trimethyl-N-(3,3-diphenylpropyl)-1-amino-2-ethanol was added with stirring to get a solution. The solution was gradually heated to 80-85°C. 1 g of p-toluene sulphonic acid was added followed by addition of 63.7 ml of 2,2,6-trimethyl – 4H- 1,3-dioxin-4-one (diketene acetone adduct) slowly. The temperature of the reaction mixture was raised to
- 15 100-105°C and maintained for 3-4 hours. After completion of the reaction the contents of the flask were cooled to 30°C and the organic layer was first washed with 2% aqueous NaOH followed by water and brine. The toluene layer was separated and distilled off under vacuum to give 1,1,N-trimethyl-N-(3,3-diphenylpropyl)-2-aminoethyl acetoacetate, compound of formula V.

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(b) Conversion of 1,1,N-trimethyl-N-(3,3-diphenylpropyl)-2-aminoethyl acetoacetate, compound of formula V, to 3-amino-but-2-enoic acid-2[(3,3- diphenylpropyl) methylamino] 1,1-dimethyl ethyl ester, compound of formula III

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In 500ml autoclave 150 ml of isopropyl alcohol, 25 g of 1,1,N-trimethyl-N-(3,3-diphenylpropyl)-2-aminoethyl acetoacetate, compound of formula V, and 150 ml of aqueous ammonia were charged and kept for 24-48 hours at room temperature with intermittent stirring. The solvent was distilled off under vacuum to give 3-amino-but-2-enoic acid-2[(3,3-diphenylpropyl) methylamino] 1,1-dimethyl ethyl ester, compound of formula III.

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B. Preparation of 2-(3-Nitrobenzylidene)-3-oxo-butyric acid methyl ester, compound of formula IV.

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In a three-necked round bottom flask containing 200 ml of isopropyl alcohol, 50g of m-nitrobenzaldehyde and 46g of methyl acetoacetate were charged. 1.2 ml of piperidine and 0.7 ml of acetic acid were added and the contents of the flask were stirred. The contents of the flask were heated to 50-55°C and the temperature was maintained for 3-4 hours. After completion of the reaction, the reaction mixture was cooled to about 25°C and allowed to stir. The resultant solid was filtered and the cake was dried to give 2-(3-Nitrobenzylidene)-3-oxo-butyric acid methyl ester, compound of formula IV.

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C Preparation of hydrochloride salt of 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylic acid 2-[(3,3-diphenylpropyl)- methylamino]-1,1-dimethylethyl methyl ester, compound of formula I

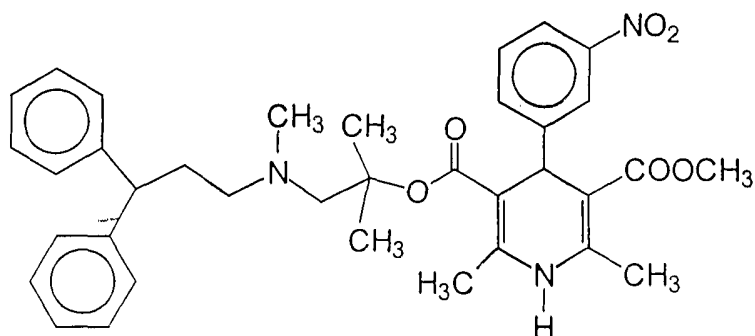
5 8.0 g of 3-amino-but-2-enoic acid-2[(3,3-diphenylpropyl)methylamino]1,1-dimethyl, ethyl ester, compound of formula III is added to a three necked round bottom flask containing 32 ml of isopropyl alcohol. 5.76 g of 2-(3-Nitrobenzylidene)-3-oxo-butyric acid methyl ester, compound of formula IV, and 0.16 g of ammonium acetate are also added and the resultant suspension is heated to reflux for 2 hours. After completion of
10 reaction the flask was cooled slowly to 10-15°C and treated with 2.6 ml of concentrated hydrochloric acid and the mixture stirred for 10-15 minutes. The solvent was distilled off to yield hydrochloride salt of 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylic acid 2-[(3,3-diphenylpropyl)- methylamino]-1,1-dimethylethyl methyl ester, compound of formula I.

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We claim

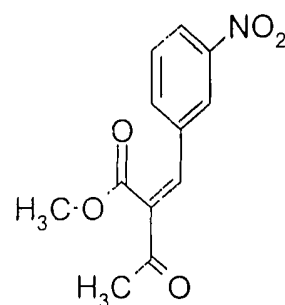
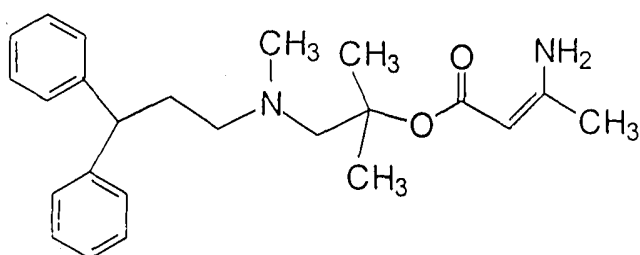
1. A process for the preparation of 1,4-dihydropyridine-3,5-dicarboxylic acid derivative of formula I and its enantiomers comprising



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Formula I

reacting compound of formula III with compound of formula IV



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Formula III

Formula IV

to yield 1,4-dihydropyridine-3,5-dicarboxylic acid derivative of formula I and its pharmaceutically acceptable salts.

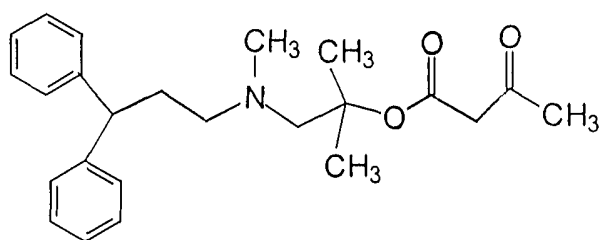
2. A process as claimed in claim 1 wherein the reaction is carried out in the presence of ammonia source.

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3. A process as claimed in claim 1 wherein the ammonia source is selected from ammonium salts, ammonium hydroxide, liquor ammonia, hexamine and hexamethyldisilazane.

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4. A process as claimed in claim 1 wherein the compound of formula III is prepared by reacting compound of formula V with ammonia source.



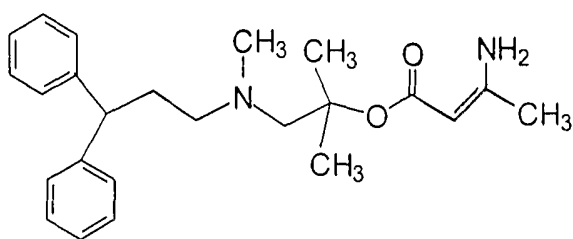
Formula V

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5. A process as claimed in claim 4 wherein the ammonia source is selected from ammonium salts, ammonia gas, liquor ammonia, hexamethyldisilazane, hexamine.

6. Compound of formula III

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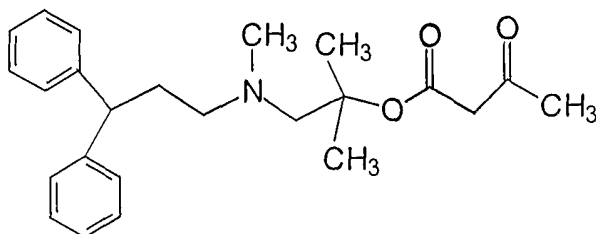


Formula III

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7. A process for the preparation of compound of formula III comprising reacting compound of formula V with ammonia source.

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Formula V

8. A process as claimed in claim 7 wherein the ammonia source is selected from ammonium salts, ammonia gas, liquor ammonia, hexamethyldisilazane, hexamine .

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9. A process for the preparation of compound of formula I as claimed in claims 1 to 8 substantially as herein described and illustrated by example 1.

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