(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
19 April 2007 (19.04.2007)

(10) International Publication Number
WO 2007/042848 A2

(51) **International Patent Classification:**
C07D 241/02 (2006.01)

(21) **International Application Number:**
PCT/HU2006/000092

(22) **International Filing Date:** 12 October 2006 (12.10.2006)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
P 05 00940 12 October 2005 (12.10.2005) HU

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available):* 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, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ,

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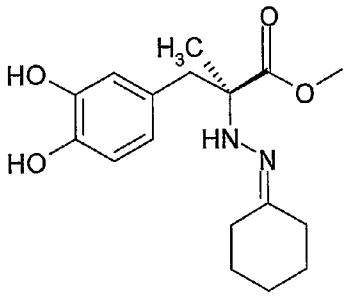
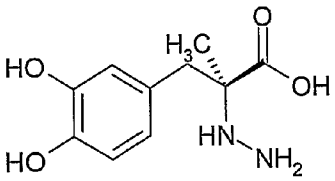
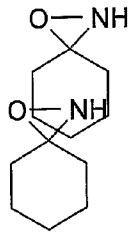
(54) **Title:** PROCESS FOR THE PREPARATION OF CARBIDOPA



(I)



(II)



(IV)

(57) Abstract: The invention relates to a process for the preparation of (-) - (L) -3- (3,4-dihydroxyphenyl) -2-hydrazino-2 -methyl propionic acid (carbidopa) of the formula (II) by using 3, 3 -pentamethylene oxaziridine of the formula (IV), which comprises reacting L-α-methyldopa methyl ester of the formula (III) with 3,3-penta- methylene oxaziridine of the formula (IV), isolating the thus-obtained (+) - (L) -2- (N' - cyclohexylidene-hydrazino) -3- (3 , 4-dihydroxy phenyl) -2 -methyl propionic acid methyl ester of the formula (I) (I) and subjecting it to hydrolysis with an acid. (+) - (L) -2- (N' -cyclohexylidene-hydrazino) -3-(3,4-dihydroxyphenyl) -2-methyl propionic acid methyl ester of the formula (I) is a new intermediate . (-) - (L)-3-(3,4-dihydroxyphenyl) -2-hydrazino-2- methyl propionic acid (carbidopa) of the formula (XI) thus obtained is a valuable therapeutic active ingredient having the international non-proprietary name carbidopa.

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NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PROCESS FOR THE PREPARATION OF CARBIDOPA

Technical field of the invention

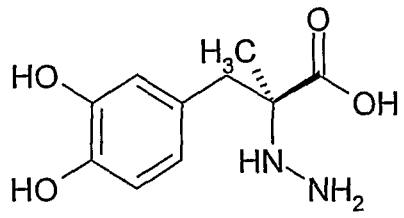
The invention relates to a new process for the preparation of carbidopa. More specifically, the invention relates to the preparation of carbidopa by using 3,3-pentamethylene oxaziridine, a new intermediate useful for the said process, and to the preparation of this intermediate.

Background of the invention

It is known that (-)-(L)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropionic acid (referred to as carbidopa; international nonpropritary name) combined with another pharmaceutical ingredient known under the international nonproprietary name levodopa, is one of the most important medicine for the treatment of symptoms of Parkinson's disease.

Several methods have been provided in the literature for the preparation of carbidopa.

According to one of the known processes the racemic form of carbidopa of the formula (II)



(II)

is prepared, which is then subjected to resolution to obtain optically active (-)-(L)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methyl-propionic acid (German patent specification No. 1,173,487).

When separating optically active isomers the undesired optical isomer is either subjected to racemization or made innocuous as an unnecessary side-product. Practically 55-70% of the racemate used for the separation of the optical isomers become an unnecessary side-product. In order to avoid such a considerable loss in the methods of the organic chemistry directed to the preparation of optically active compounds, a separation in an early phase of the synthesis is tried to be achieved. Thus, the loss can be reduced, as the undesirable optically active intermediate being formed and becoming unnecessary in the course of the

resolution process is less valuable than the undesirable optical isomer formed in the last phases of the synthesis. According to the process described in German patent specification No. 1,173,487, the resolution of the racemic compound is carried out in the final step of the synthesis, which is a rather unfavourable solution in respect of economical and environmental protection considerations.

The aim of the improved processes is to avoid resolution as the final step of the synthesis. As intermediates the optically active amino acids obtained by resolution during the preceding steps of the synthesis or disposable in industrial quantities or the derivatives thereof are applied in the course of these processes .

One of the possible starting compounds is L-α-methyldopa or the intermediates thereof. The chemical structure of carbidopa of the formula (II) is highly similar to that of L-α-methyldopa. This latter substance is a generally applied hypertensive drug, which has been on the market for a long time and which is manufactured on an industrial scale. The structural difference between the two compounds

is that while carbidopa contains a hydrazino group at the carbon atom adjacent to the carboxylic acid, L-α-methyldopa contains an amino group of the same steric position. In the course of the synthesis of L-α-methyldopa the separation of the optical isomers is carried out in a phase of the process wherein the undesired enantiomer being formed as a side-product can readily be changed into a racemic form and returned to the synthesis . Thus , side-products do not form in the synthesis, consequently the manufacturing process of L-α-methyldopa is highly economical . That is why the application of L-α-methyldopa for the synthesis of carbidopa is particularly preferable from economical considerations .

According to a process provided in US patent specification No. 3,734,937 using L-α-methy¬ldopa as starting substance, the compound is first diazotated to obtain L-α-bromocarboxylic acid. The bromine atom can be exchanged directly for a hydrazino group by reacting said compound with hydrazine, but because of the inversion occurring in the course of the reaction the isomer having the undesired steric position is formed. In order to avoid this situation the bromine atom is exchanged for an

iodine atom by a reaction with sodium iodide, which reaction also involves an inversion. The thus-obtained D-iodocarboxylic acid is then reacted with hydrazine resulting in an inversion to obtain L-carbidopa of the appropriate steric position. The reaction is illustrated in reaction scheme 1. During the reaction carried out with sodium iodide a partial racemization occurs because of the iodine-iodine exchange under the circumstances of the bromine-iodine exchange. The low yield of the process and the insufficient optical purity of the thus-obtained product can in part be explained by this fact.

According to another synthesis the hydrazino group is formed from the amino group by N-amination. This reaction namely does not affect the optical centre, consequently no racemization takes place. Several methods have been provided for the conversion of the amino group into hydrazino group. S. Karady at al. (J.Org.Chem. 36, 1949-1951 (1971)) have published three processes applying as starting substance the optically active intermediate of L-α-methyldopa. In this starting substance the two aromatic hydroxyl groups are protected by dimethoxy groups.

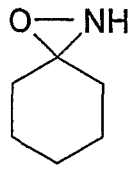
According to one of these processes dimethoxy-α-methyldopa is reacted with hydroxylamine O-sulphonic acid. Thus the dimethoxy derivative of carbidopa of the formula (II) is obtained, which, however, can only be purified by chromatography. In the final reaction step carbidopa is obtained by removing the two methoxy groups. The process is illustrated by reaction scheme 2. This process, however, is not suitable for an industrial scale production because of the very expensive hydroxylamine O-sulphonic acid and the chromatographic purification of the dimethoxy derivative obtained as an intermediate.

According to the second process the amino group of the dimethoxy derivative of L-ot-methyldopa is acylated, a salt is formed with sodium hydride from the thus-obtained optically active L-acetamide, the salt is reacted with chloro-amine, and carbidopa of the formula (II) is obtained by the acidic hydrolysis of the acetyl group. The process is illustrated by reaction scheme 3. A serious drawback of this process is that it requires the application of very expensive reagents (sodium hydride, chloro-amine), special reaction circumstances and

equipment, furthermore the thus-obtained product is to be purified by chromatography. This process is also unsuitable for an industrial scale production.

According to the third process the dimethoxy derivative of L-α-methyldopa is reacted with potassium cyanate, the thus-obtained carbamide derivative is converted into the dimethoxy derivative of carbidopa of the formula (II) by treatment with sodium hypochlorite, which is then demethylated in the final reaction step with concentrated aqueous hydrogen bromide solution. The process is illustrated by reaction scheme 3. This process requires a chromatographic purification, and the total yield following the purification of the product by chromatography is only 27%. Due to the low yield and the purification by chromatography the process is unsuitable for an industrial scale production.

According to German patent specification DD 240,818, the methyl ester of dimethoxy-L-oc-methyldopa is reacted with 3,3-pentamethylene oxaziridine of the formula (IV),



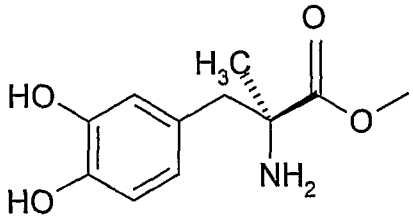
(IV)

the ester group and two dimethoxy groups of the compound of the formula (2) containing the desired hydrazino group are then subjected to hydrolysis together, in one reaction step, to obtain the desired compound of the formula (II) in a yield of 60%. The process is illustrated by reaction scheme 5. A drawback of the process is that the N-amination with the oxaziridine derivative of the formula (IV) is carried out by using a starting substance containing protected phenolic hydroxy1 groups. This protected compound can be the appropriate dialkoxy derivative (generally dimethoxy derivative), diacetoxy derivative or iso-propylenedioxy derivative. The protecting groups of the phenolic hydroxy groups are usually removed in a later phase of the synthesis, often under drastic reaction conditions (concentrated aqueous hydrogen bromide, high temperature). Consequently, side-products may be formed, which reduce the quality of the compound of the formula (II), and the removal thereof is expensive and causes losses. Thus, side-products (4-hydroxy-3-

methoxyphenyl , 3-hydroxy-4-mehtoxyphenyl derivatives, furthermore L-α-methyldopa) are formed with structures and properties similar to those of the end-product of the formula (II) , consequently the removal thereof is cumbersome and expensive. In this process the amount of the decomposition product to be kept mostly in view, that is L-oc-methyldopa being formed in the course of the vigorous hydrolysis , can be kept below the limit of 0.5 w/w% specified in the pharmacopoeiae only after several purification procedures .

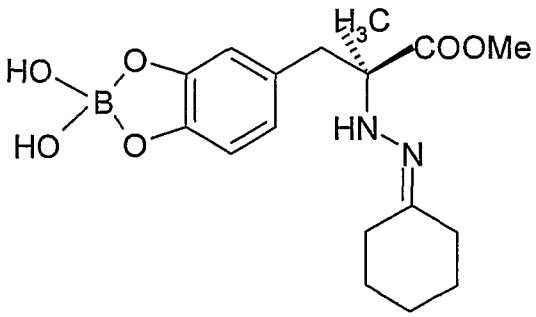
According to a further known process the phenolic hydroxyl groups of L-α-methyldopa ester are protected with a boron compound suitable for the formation of a transitional complex. For this purpose ortho-boronic acid or ortho-boronic acid derivatives (such as sodium tetraborate) are applied. During the process the desired carbidopa of the formula (II) is produced according to reaction scheme 6 by starting from the methyl ester of L-α-methyldopa (the compound of the formula III) in a biphasic reaction mixture (toluene and aqueous phase) .

In the course of the process the boronic acid complex of the formula (3) is prepared first from the starting substance of the formula (III),



(III)

which is then reacted in a biphasic reaction mixture with 3,3-pentamethylene oxaziridine of the formula (IV). The thus-obtained hydrazine compound of the formula (4) is transferred into the aqueous phase in the form of the hydrochloride salt, the ester group is then subjected to hydrolysis with hydrogen chloride to obtain the compound of the formula (II). The mechanism of the N-amination reaction has not been clarified yet, but it is supposed that as intermediate the cyclohexylidene derivative of the formula (5)



(5)

is obtained .

The amination reaction is carried out in a biphasic reaction mixture. The boronic acid complex of the formula (3) being in the aqueous phase is reacted with a solution of 3,3-pentamethylene oxaziridine of the formula (IV) in toluene. The drawback of this process resides in the fact that the reaction between the boronic acid complex of the formula (3) soluble in the aqueous phase and 3,3-pentamethylene oxaziridine of the formula (IV) being in the toluene phase takes place in a heterogeneous phase. The contact between the two phases is promoted by strong stirring and the application of a phase transfer catalyst. Due to the two phases the process is complicated. Besides, an aqueous solution containing a high amount of boronic acid and unreacted boron complex of the formula (3) is obtained, and the recovery of the boronic acid

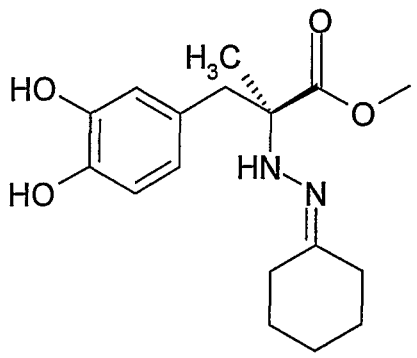
from this solution has not been solved yet. A further considerable disadvantage resides in the fact that in the course of the reaction between the starting substance of the formula (III) and 3,3-pentamethylene oxaziridine of the formula (IV) the 3-membered ring of the oxaziridine component can be opened in several different ways, which leads to the formation of several undesired side-products. During the transfer of the hydrochloride salt into the aqueous phase the side-products of the oxaziridine reaction get also into the aqueous phase, and the removal thereof is cumbersome due to their similar chemical characters.

The aim of the invention was to elaborate a method suitable for an industrial scale preparation of carbidopa of the formula (II), which eliminates the drawbacks of the afore¬mentioned processes and provides said compound in a high yield and in high purity.

Now it has been found that this aim can be achieved by the process of the present invention.

Summary of the invention

According to the present invention there is provided a process for the preparation of (-)-(L)-3-(3,4-dihγdroxyphenyl)-2-hydrazino-2-methylpropionic acid (carbidopa) of the formula (II) by using 3,3-pentamethylene oxaziridine of the formula (IV), which comprises reacting L-oc-methyldopa methyl ester of the formula (III) with 3,3-pentamethylene oxaziridine of the formula (IV), isolating the thus-obtained (+)-(L)-2-(N'-cyclohexylidene-hydrazino)-3-(3,4-dihydroxyphenyl)-2-methylpropionic acid methyl ester of the formula (I)



(I)

and subjecting it to acidic hydrolysis.

Detailed description of the invention

The invention is based on the recognition that (+)-(£)-2-(N'-cyclohexylidene-hydrazino)-3-(3,4-dihydroxyphenyl)-2-methylpropionic acid

methyl ester of the formula (I) obtained in the course of the reaction of L-α-methyldopa methyl ester of the formula (III) with 3,3-penta-methylidene oxazolidine of the formula (IV) is a compound that can be prepared in a homogeneous reaction mixture and isolated in a pure crystalline form. This recognition is surprising because in the course of the hitherto known processes a derivative of L-α-methyldopa ester containing the hydroxyl group in a protected form was used for the reaction with the oxazolidine derivative of the formula (IV). For the reaction - as it was mentioned above - either the appropriate dialkoxy, diacetoxy, isopropylidenedioxy derivative was used or the derivative protected in borate form was applied. Surprisingly it has been found that even when L-α-methyldopa containing free hydroxyl groups is applied, the reaction provides the new (+)-(L)-2-(N'-cyclohexylidene-hydrazino)-3-(3,4-dihydroxyphenyl)-2-methyl-propionic acid methyl ester of the formula (I) in an excellent yield and in a readily isolable, pure crystalline form.

A particular advantage of the process according to this invention resides in the fact that - contrary to the biphase reaction mixture

consisting of toluene and an aqueous phase - it can be carried out in a homogeneous reaction medium. Namely, in the applied organic solvent boiling at a temperature of higher than 80 ^{0}C - preferably in toluene - both L-α-methyldopa methyl ester of the formula (III) and 3,3-pentamethylene oxaziridine of the formula (IV) can be dissolved. The thus-obtained (+)-(L)-2-(N'-cyclohexylidene-hydrazino)-3-(3,4-dihydroxyphenyl)-2-methylpropionic acid methyl ester of the formula (I) separates from the reaction mixture, a number of side-products obtained as a consequence of the opening of the 3-membered ring of the compound of the formula (IV) in different ways and the unreacted starting substances remain in the toluene mother liquor and can be readily isolated from the separated compound of the formula (I). The process can be readily accomplished also on an industrial scale. It is not necessary to apply a phase transfer catalyst, and the organic solvent used as reaction medium can be completely recovered by distillation after the isolation of the compound of the formula (I) and returned to the process.

The reaction between (+)-(L)-2-(N'-cyclohexylidene-hydrazino)-3-(3,4-dihydroxy-

phenyl) -2-methylpropionic acid methyl ester of the formula (III) and 3,3-pentamethylene oxazolidine of the formula (IV) is carried out in a solvent boiling at a temperature of higher than 80 ^{0}C. As reaction medium aromatic hydrocarbons (e.g. toluene or xylene) or halogenated aliphatic hydrocarbons (e.g. dichloroethane) can be applied. As organic solvent it particularly preferable to use toluene.

The reaction can be carried out at a temperature between 80 ^{0}C and 130 ^{0}C depending on the boliling point of the solvent. It is preferable to carry out the reaction at a temperature between 100 ^{0}C and 105 ^{0}C. The reaction is accomplished within a short period of time, usually within 1 - 2 hour(s).

The thus-obtained compound of the formula (I) can be isolated from the reaction mixture by filtration or centrifugation. The compound of the formula (I) separates from the reaction mixture in a highly pure crystalline form. The side-products and the unreacted starting substances are contained in the organic mother liquor.

The thus-obtained compound of the formula (I) is then converted into (-)-(L)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropionic acid of the formula (II) by acidic hydrolysis. The hydrolysis is preferably carried out with hydrogen chloride, particularly with 20 % hydrogen chloride solution. The hydrolysis is carried out at a temperature between 90 ^{0}C and 100 ^{0}C, preferably at 93-95 ^{0}C. The reaction takes place in a few hours (generally between 3 and 6 hours, preferably in 5 hours).

Following the acidic hydrolysis the reaction mixture is evaporated, some water is added to the evaporation residue and it is made alkaline. For this purpose alkali hydroxides (e.g. potassium hydroxide or sodium hydroxide) or ammonium hydroxide can be applied. The thus-obtained (-)-(L)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropionic acid of the formula (II) separating in a highly pure crystalline form can be isolated by filtration or centrifugation.

According to another aspect of the present invention there is provided the new (+)-(L)-2-(N'-cyclohexylidene-hydrazino)-3-(3,4-di-

hydroxyphenyl) -2-methylpropionic acid methyl ester of the formula (I) .

According to a preferable aspect of the present invention there is provided the new (+) - (Z) -2- (N' -cyclohexylidene-hydrazino) -3- (3 ,4-di-hydroxyphenyl) -2-methylpropionic acid methyl ester of the formula (I) in a crystalline form.

According to a further aspect of the present invention there is provided a process for the preparation of (+) - (L) -2- (N' -cyclohexylidene-hydrazino) -3- (3,4-dihydroxyphenyl) -2-methyl¬ propionic acid methyl ester of the formula (I) , which comprises reacting L-oc-methyldopa methyl ester of the formula (III) with 3,3-penta-methylene oxaziridine of the formula (IV) and isolating the thus-obtained compound of the formula (I) .

The process according to the invention involves the following advantages :

- it provides the desired compound in a high yield;

- it provides pure (-) - (L) -3- (3 ,4-dihydroxyphenyl) -2-hydrazino-2-methyl-propionic acid of the formula (I) ;

- it can be carried out in a homogeneous reaction mixture consisting of one single phase ;

- the new intermediate, that is (+)-(JD)-2-(N'-cyclohexylidene-hydrazino)-3-(3,4-dihydroxy-phenyl)-2-methylpropionic acid methyl ester of the formula (I), can be readily isolated in a pure crystalline form, while the side-products and the unreacted starting substances remain in the organic mother liquor ;

- the process can be readily and economically accomplished on an industrial scale.

Further details of the present invention are to be found in the Examples without limiting our invention to the said Examples .

Examples

Example 1

Preparation of (+) - (L) -2- (N' -cyclohexylidene-hydrazino) -3- (3,4-dihydroxyphenyl) -2-methyl-propionic acid methyl ester (I)

To a suspension of L-cc-methyldopa methyl ester ((III), 337.5 g, 1.5 moles) in toluene (3400 ml) 3,3-pentamethylene oxaziridine (oxaziridine content: 4 m/m %, 5000 ml, l.δ moles) are added in about 50 minutes, at a temperature of 100 to 105 ^{0}C. The reaction mixture is allowed to react at the same temperature for 30 minutes, cooled to 5 ^{0}C, the separated crystals are filtered off and washed on the filter subsequently with toluene (400 ml) and water (400 ml).

Product: 403.7 g (84 %) of fawn-colored crystals.

M.p.: 105-107 ^{0}C (toluene).

Rotation: $[\alpha]^{20}_{D}$= + 33,73 ° (c=l, methanol).

IR (KBr): 1607 (C=N), 1737 (C=O) cm^{-1}.

^{1}HNMR (DMSO, 200): 8.68 (2H, bs); 6.59 (IH, d, J=8.1 Hz); 6.45 (IH, d, J=2.2 Hz); 6.31 (IH, dd, J=8,l, 1,5 Hz); 5.52 (IH, s); 3.56 (3H, s); 2.76 (2H, dd, J=17.4, 13.4); 2.22-2.02 (4H, m); 1.50 (6H, s); 1.25 (3H, s) ppm.

^{13}CNMR (DMSO), 200) : 175.4; 151.5; 144.9; 144.0; 127.2; 121.0; 117.6; 115.3; 64.5; 51.6; 42.6; 35.2; 27.2; 25.6; 25.4; 21.5 ppm.

Elementary analysis for the formula $Ci_7H_{24}N_2O_4$ (320.39)

	C %	H %	N %
calculated:	63,73	7,55	8,74
found:	63,35	7,65	8,60

Example 2

Preparation of (-)-(L)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropionic acid (II)

A solution of (+)-(£)-2-(N'-cyclohexylidene-hydrazino)-3-(3,4-dihydroxyphenyl)-2-methyl-propionic acid methyl ester ((I), 403.7 g, 1.26 moles) in 20 % hydrochloric acid (2500 ml) is stirred at an elevated temperature, then evaporated to dryness in vacuo at a temperature of 60 ^{0}C. To the evaporation residue some water (900 ml) is added, and the pH of the solution is adjusted to 3.5 with 25% ammonium hydroxide solution. The separated crystals are filtered off.

Product: 267.7 g (87 %) of white crystals.

M.p.: 207-209 ^{0}C (water).

Rotation : $[\alpha]^{20}_D$= -24,3 ° (c=l, water, $AlCl_3$).

IR (KBr): 3529 (COOH), 3112 (NH) 1630 (C=O) can^{-1}.

^{1}HNMR (DMSO, 200): 6.55 (IH, d, J=2.2 Hz); 6.59 (IH, d, J=8.1 Hz); 6.44 (IH, dd, J=8.1, 2.2 Hz); 2.80 (IH, d, J=13.6); 2.68 (IH, d, J=13.6); 1.15 (3H, s) ppm.

^{13}CNMR (DMSO), 200): 174.7; 145.0; 144.2; 127.0; 121.3; 118.1; 115.3; 65.6; 41.2; 20.2 ppm.

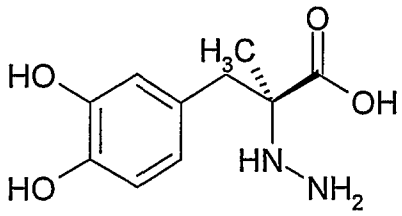
Elementary analysis : $Ci_0Hi_4N_2O_4H_2O$ (244,25)

	C%	H %	N%
calculated :	49,18	6,60	11,,47
found:	49,58	6,46	11,,84

HPLC (USP) methyldopa	<	0,2 w/w %
single impurities	<	0,lw/w each%
total impurities	<	0,5 w/w %.

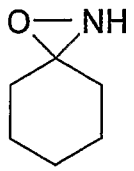
What we claim is:

1. A process for the preparation of (-)-(L)-3-(3,4-dihydroxyphenyl) -2-hydrazino-2-methyl propionic acid (carbidopa) of the formula (II)



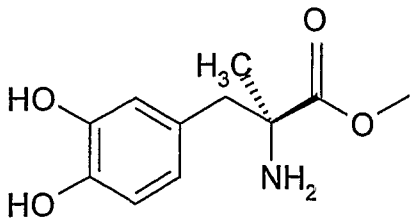
(II)

by using 3,3-pentamethylene oxaziridine of the formula (IV),



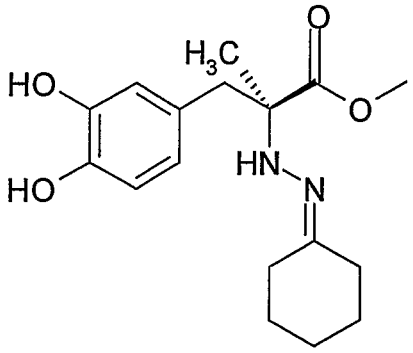
(IV)

which comprises reacting L-α-methyldopa methyl ester of the formula (III)



(III)

with 3,3-pentamethylene oxaziridine of the formula (IV), isolating the thus-obtained (+)-(L)-2-(N'-cyclohexylidene-hydrazino)-3-(3,4-dihydroxyphenyl)-2-methyl propionic acid methyl ester of the formula (I)



(I)

and subjecting it to hydrolysis with an acid.

2. A process as claimed in claim 1, which comprises carrying out the reaction of L-oc-methyldopa methyl ester of the formula (III) with 3,3-pentamethylene oxaziridine of the formula (IV) in an organic solvent having a boiling point of higher than 80 ^{0}C.

3. A process as claimed in claim 2, which comprises using as organic solvent having a boiling point of higher than 80 ^{0}C an aromatic hydrocarbon or a halogenated aliphatic solvent.

4. A process as claimed in claim 3, which comprises using as organic solvent toluene, xilene or dichloroethane.

5. A process as claimed in claim 4, which comprises using toluene as organic solvent.

6. A process as claimed in any of claims 1 to 5, which comprises carrying out the reaction at a temperature between 80 ^{0}C and 130 ^{0}C, preferably between 100 ^{0}C and 105 ^{0}C.

7. A process as claimed in any of claims 1 to 6, which comprises carrying out the hydrolysis of the compound of the formula (I) with hydrogen chloride.

8. A process as claimed in claim 7, which comprises using 20 % hydrogen chloride.

9. A process as claimed in any of claims 6 to 8, which comprises carrying out the hydrolysis at a temperature between 90 ^{0}C and 100 ^{0}C.

10. A process as claimed in claim 1 or any of claims 6 to 9, which comprises evaporating the reaction mixture following the acidic hydrolysis, and then making it alkaline.

11. A process as claimed in claim 10, which comprises carrying out the alkalination with ammonium hydroxide, sodium hydroxide or potassium hydroxide.

12. (+)-(L)-2-(N'-cyclohexylidene-hydrazino)-3-(3,4-dihydroxyphenyl)-2-methylpropionic acid methyl ester of the formula (I).

13. Crystalline (+)-(L)-2-(N'-cyclohexylidene-hydrazino)-3-(3,4-dihydroxyphenyl)-2-methyl¬propionic acid methyl ester of the formula (I).

14. A process for the preparation of (+)-(L)-2-(N'-cyclohexylidene-hydrazino)-3-(3,4-di¬hydroxyphenyl)-2-methylpropionic acid methyl ester of the formula (I) as claimed in claim 12 or 13, which comprises reacting L-α-methyldopa methyl ester of the formula (III) with 3,3-pentamethylene oxaziridine of the formula (IV), and isolating the thus-obtained compound of the formula (I).

15. A process as claimed in claim 14, which comprises carrying out the reaction in an organic solvent having a boiling point of higher than 80 ^{0}C.

16. A process as claimed in claim 15, which comprises using toluene as organic solvent.

Reaction Scheme 1

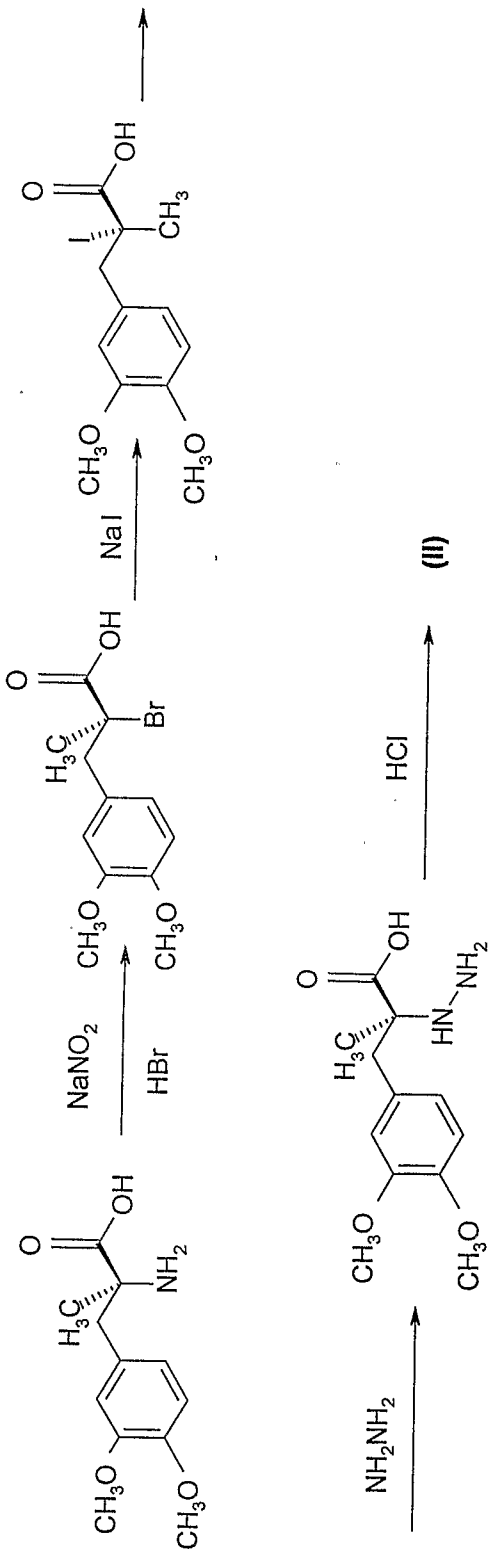


Fig. 1

Reaction Scheme 2

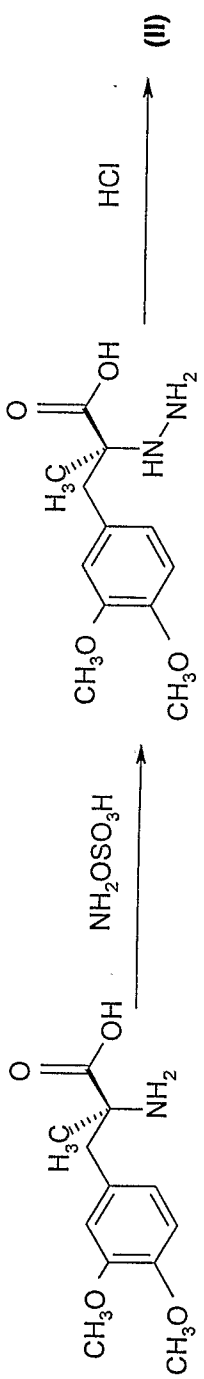


Fig. 2

Fig. 3

Reaction Scheme 3

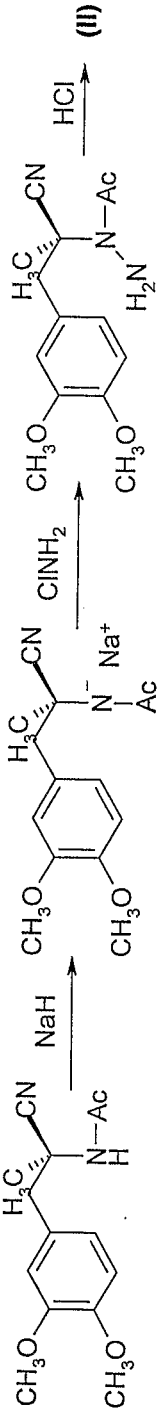
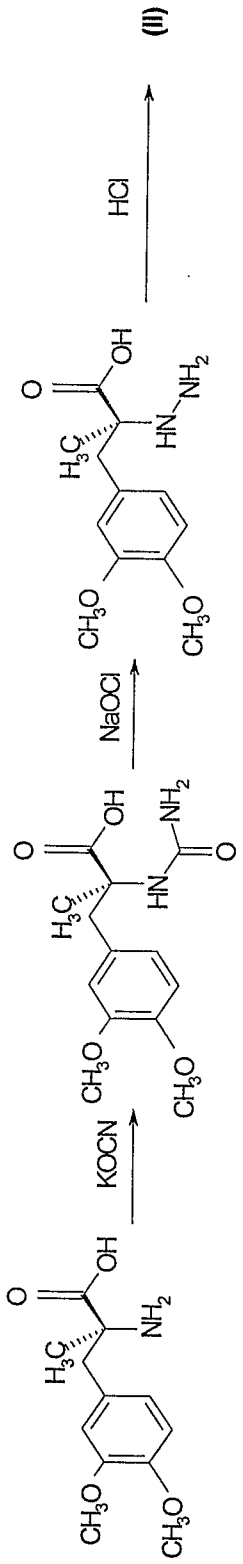


Fig. 4

Reaction Scheme 4



Reaction Scheme 5

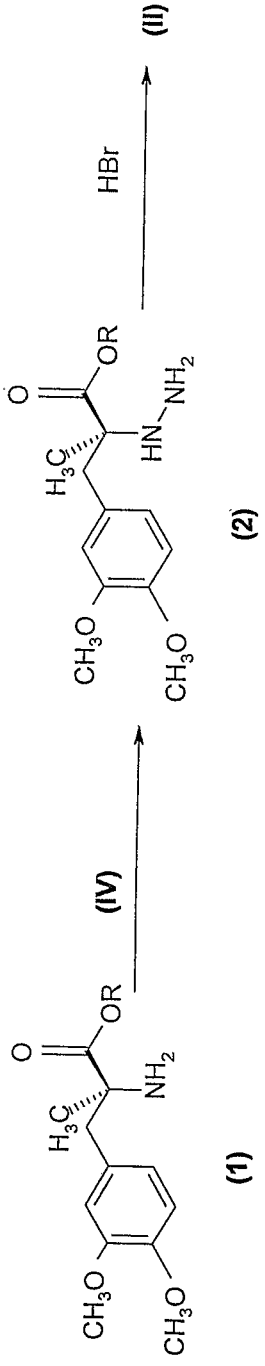


Fig. 5

Reaction Scheme 6

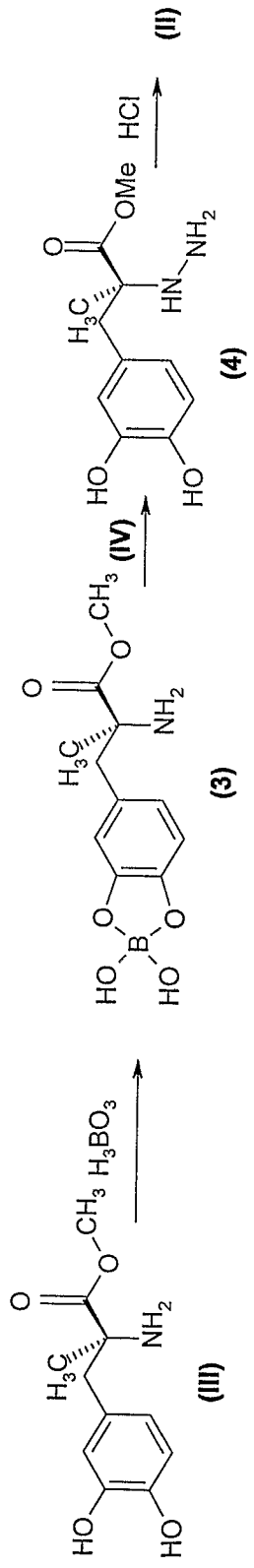


Fig. 6