

5 The compounds of the invention can be administered by intracerebral injection. While this would be a means of administration of last resort in therapy, it has particular significance in research into diseases of the central nervous system. There is much interest currently in
10 developing an understanding of the action of certain compounds produced by the body on the central nervous system (CNS) of vertebrate mammals. Certain receptors in the CNS are excited by amino acids or derivatives thereof. These exciters cause neuronal degeneration and are believed
15 to be responsible for example for Huntington's Chorea disease. Current research is directed at identifying antagonists which block the receptors against exciters. A problem, however, is in determining which receptors are blocked by which antagonists. We have now surprisingly
20 found that (-)-D-amino phosphonoheptanoic acid is a blocker of ibotenic acid-excited receptors but not a blocker of Kainic acid-excited receptors. This compound is therefore of great value in CNS research as a means of blocking ibotenic acid-excited receptors while leaving Kainic acid-
25 excited receptors free to be acted on by candidate antagonists.

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$$\begin{array}{c} \text{X-R-CH-COOB} \\ | \\ \text{NHA} \end{array} \quad (I)$$

R stands for an aliphatic radical of 5C atoms.

which may be optionally substituted,
X stands for an acidic radical, especially a
radical of phosphonic acid, sulphonic acid,
boronic acid or tetrazole, and

5 A and B independently of each other stand for a
lipophilic radical, especially an ester radical,
or one of A and B can stand for a hydrogen atom,
or salts thereof, or pharmaceutically acceptable biopre-
cursors thereof.

10 Examples of lipophilic radicals A are an imine or
substituted imine, e.g. $-N = C - \text{C}_6\text{H}_4 - R$, $-N(CH_3)_2$,
 $-NHCH_3$ or $-N(CH_3)_3$. Examples of lipophilic radicals
B are pivaloyloxy, pivaloyloxymethyl, amide, benzyloxy-
carbonyl or ester (e.g. methyl or ethyl ester) radicals.

15 For the purpose of this specification the term
'pharmaceutically acceptable bioprecursor' of an active
compound of the invention means a compound having a
structural formula different from the active compound
but which nonetheless, upon administration to an animal
20 or human being is converted in the patient's body to
the active compound.

In preferred compounds R represents C_5H_{10} .

The present invention further relates to processes
for the production of compounds of the present invention
25 in which:

(a) if a compound of formula (I) in which X stands for
a phosphonic acid radical is required,

a dibromo compound of the general formula



in which

30 R has the abovementioned meaning,

- 3 -

is reacted with a compound of the general formula



in which

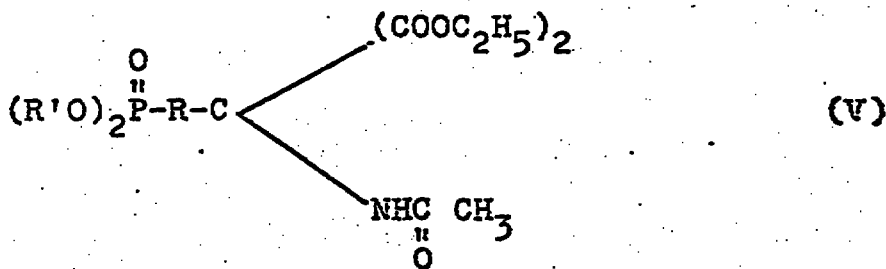
R' stands for an alkyl group, preferably an ethyl group,

M[⊕] stands for an alkali metal cation, preferably a sodium cation,

and the resulting compound of the general formula

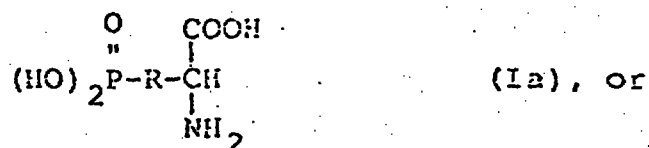


is heated, preferably in ethanol, with diethyl acetamidomalonate, and the resulting condensation product of the general formula

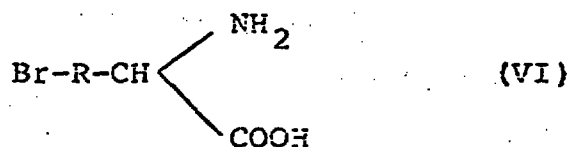


is subjected to decarboxylation, preferably in boiling hydrochloric acid, or, especially, using iodotrimethyl silane,

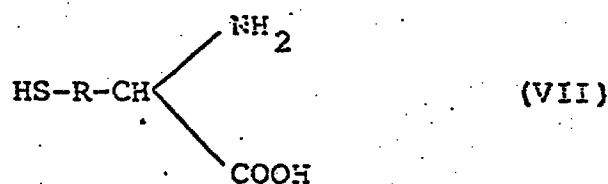
to give a compound according to the present invention of the general formula



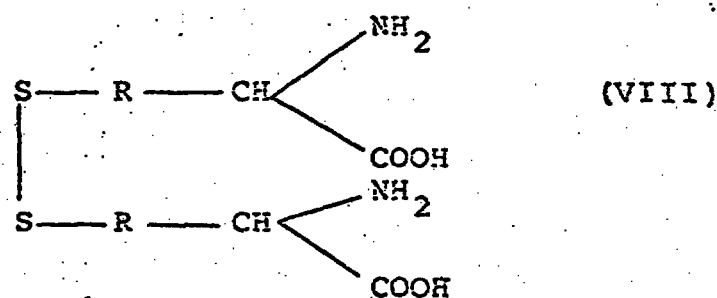
(b) if a compound of formula (I) in which X stands for a sulphonic acid radical is required, a compound of the general formula



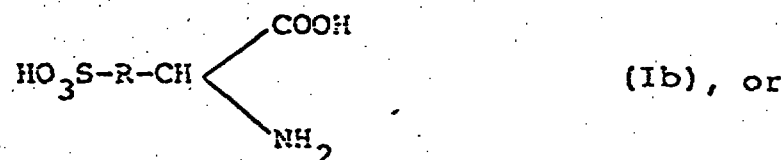
in which R has the abovementioned meaning, is reacted with sodium sulphide, to give a compound of the general formula



which is then heated to give a compound of the general formula



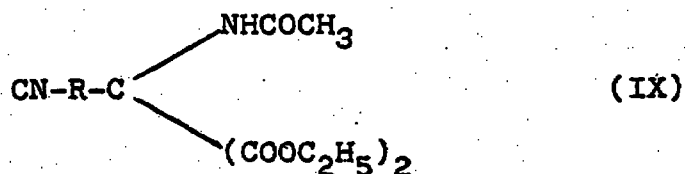
which then is reacted with bromine to give a compound according to the present invention of the general formula



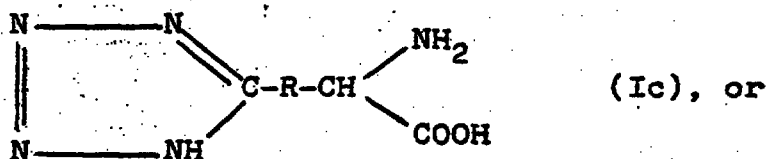
(c) if a compound of formula (I) in which X stands for a

tetrazolyl radical is required,

a compound of the general formula

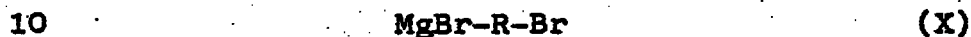


is reacted with sodium azide to give a compound according to the present invention of the general formula



(d) if a compound of formula (I) in which X stands for a boronic acid radical is required,

a compound of the general formula



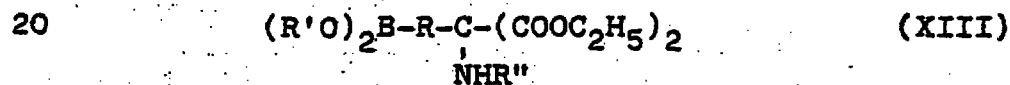
in which R has the abovementioned meaning, is reacted with a trialkyl borate, especially triethyl borate, of the general formula



15 in which R' represents an alkyl group, to give a compound of the general formula

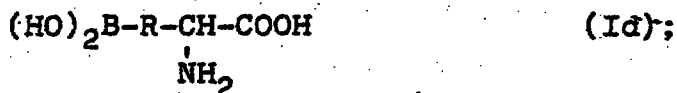


which is then reacted with a diethylacetamidomalonate and the product of the general formula



in which R'' represents $-\text{CO}-\text{CH}_3$,

is then hydrolysed to give a compound according to the present invention of the general formula

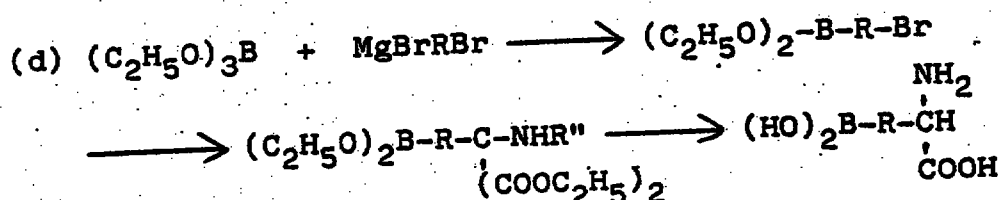
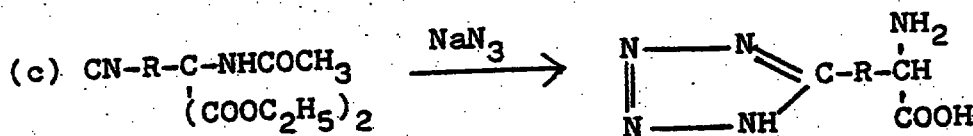
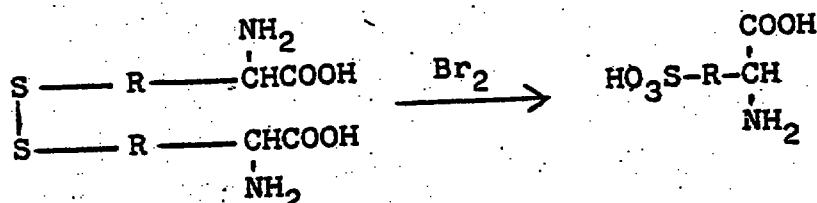
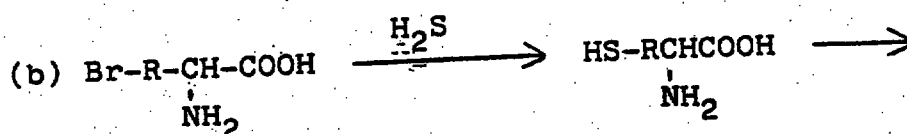


Among the new salts of the isomers of the present invention, those salts that are pharmaceutically acceptable are particularly important and are preferred.

The separation of the (-)-D-isomer may be carried out by generally known methods, such as reacting the racemic mixture with an optically active base and separating out the salts formed. An appropriate method of separation has been found to be reacting the racemic mixture produced by a process of the invention with L-lysine, thereby forming diastereomers, separating the salt containing the (-)-D-isomer by crystallisation, followed by decomposition of the salt to obtain the (-)-D-isomer.

All the process variants are preferably carried out in the presence of an inert organic solvent as the diluent. It is preferred that the reactions are carried out at the boiling point of the solvent used, that is to say, at reflux temperature.

$$\begin{aligned} & \text{(a) } \text{Br} - \text{R} - \text{Br} \longrightarrow (\text{C}_2\text{H}_5\text{O})_2\overset{\text{O}}{\underset{\cdot}{\text{P}}} - \text{RBr} \longrightarrow \\ & (\text{C}_2\text{H}_5\text{O})_2\overset{\text{O}}{\underset{\cdot}{\text{P}}} - \text{R} - \underset{\underset{(\text{COOC}_2\text{H}_5)_2}{|}}{\text{C}} - \text{NHCOCH}_3 \longrightarrow (\text{HO})_2\overset{\text{O}}{\underset{\cdot}{\text{P}}} - \text{R} - \underset{\underset{\text{NH}_2}{|}}{\text{CH}}\text{COOH} \end{aligned}$$



R'' = -CO-CH₃

lipophilic radicals are then added in each case to the NH₂ and COOH groups.

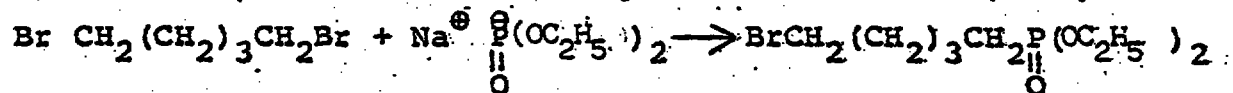
5 The isomers of the present invention have use in the treatment of diseases of the central nervous system, particularly Alzheimer's disease and also Huntingtons disease and certain forms of epilepsy. Those isomers may be applied by conventional pharmaceutical administration routes such as parenteral administration, 10 e.g. intravenous administration.

Accordingly the invention further provides pharmaceutical compositions comprising the isomers of the present invention in admixture with a pharmaceutical 15 carrier or excipient.

The following Example illustrates a process for the production of an isomer of the present invention.

Example

(a) Synthesis of (-)-2-amino-7-phosphonoheptanoic acid
1,5-dibromopentane $\longrightarrow$ diethyl-5-bromopentane phosphonate



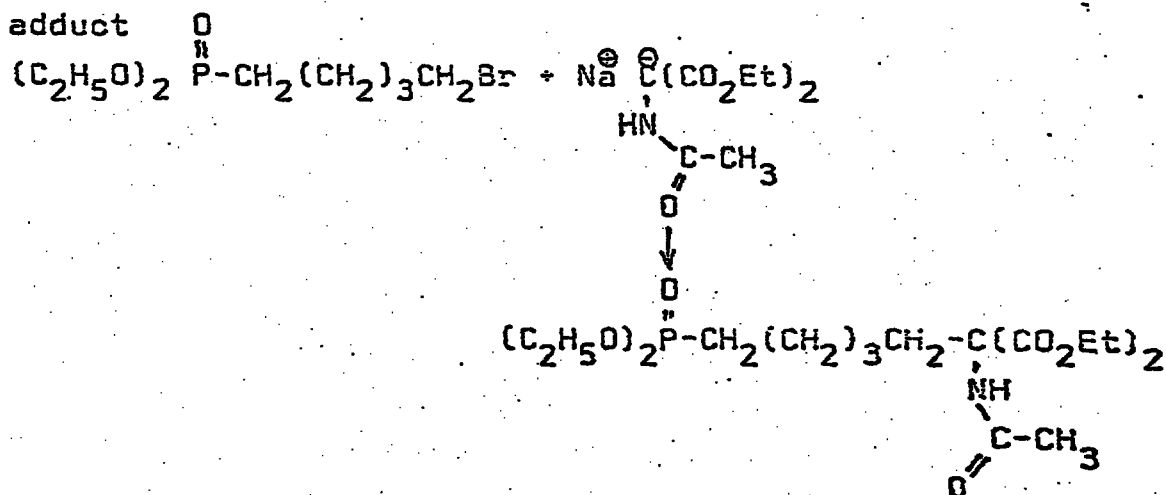
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Diethyl phosphite was dissolved in anhydrous diethyl ether, and an equimolar quantity of sodium added in small pieces over a period of $\frac{1}{2}$ hr, hydrogen being given off during this reaction. Four mole equivalents of 1,5-dibromopentane were dissolved in anhydrous diethyl ether, and the sodium salt of diethyl phosphite added, as a suspension, with stirring. The mixture was stirred for 36 hours, then refluxed for 2 hours, during this process, the fine precipitate of NaBr flocculated, and was filtered off. The ether was evaporated off to leave a colourless liquid. Excess dibromopentane was distilled off at 1 mm Hg, to leave a colourless oil which was taken up in 50/50 petroleum ether/ether and columned on Kieselgel 60 in 50/50 petroleum ether/ether. The first fraction contained unreacted diethyl phosphite; the product came off in pure diethyl ether.

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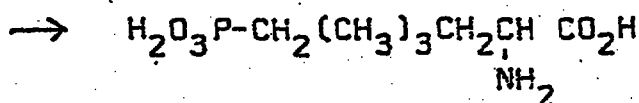
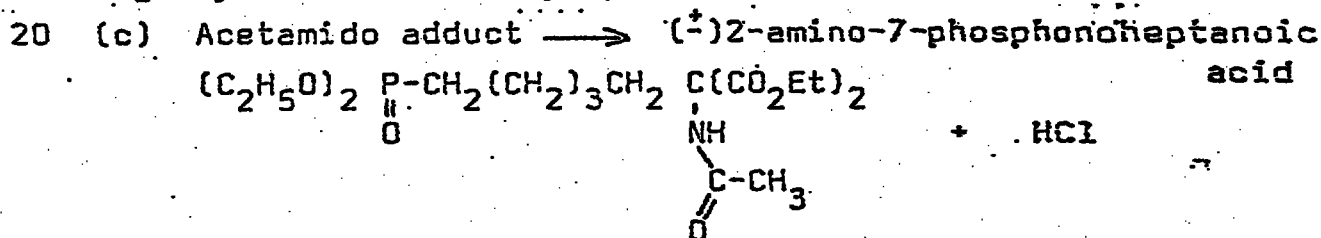
(b) Diethyl-5-bromopentane phosphonate $\longrightarrow$ acetamido adduct



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The sodium salt of diethyl acetamidomalonate, was

prepared by dissolving sodium in a slight excess of ethyl alcohol, and adding an equimolar quantity of diethyl acetamido malonate. The mixture was refluxed until a brown colouration indicated the formation of the sodium salt. The ethyl alcohol was evaporated off at 80°C, in vacuo, to leave a tan syrup; the remaining alcohol was removed by successive distillations with dry toluene, to leave a tan solid. The sodium salt was suspended in dry toluene, and diethyl carbonate added; the diethyl-5-bromopentane phosphonate was added, and the mixture refluxed for 3 days. The resulting NaBr was filtered off, and the solvents evaporated to leave a sticky, dark brown syrup. This was taken up in diethyl ether and columned on Kieselgel 60. Unreacted diethyl acetamido malonate, and diethyl-5-bromopentane phosphonate, came off with diethyl ether, and were separated by crystallisation of diethyl acetamido malonate from ether solution. The product was eluted off the column with chloroform, as a light yellow viscous syrup.



The acetamido adduct was refluxed together with 6M HCl overnight; the solution was evaporated to dryness, and the solid taken up in 5% aqueous ethanol. The free acid was precipitated by careful addition of propylene oxide and filtered off. The acid was dissolved in water and passed down on "Dowex" (Trade Mark) 50 x 8 (H+) column. The acid was washed with 5 bed volumes of water followed by elution with 2M aqueous pyridine. The amino acid containing

fractions were evaporated to dryness, and the product recrystallised from water/ethanol.

(d) Resolution of 2-amino-7-phosphonoheptanoic acid

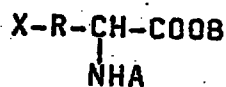
- Equimolar quantities of the phosphonic acid, and
- 5 L-lysine, were dissolved in water and warmed for $\frac{1}{2}$ hr at 60°C. Two volumes of hot methanol were then added and the mixture brought to room temperature. Diethyl ether was added carefully, until a slight cloudiness appeared in the solution, which was left to stand. The phosphonic acid/
- 10 lysine salt was filtered off and dissolved in water. A "Dowex" 50 x 8 column was prepared by passed 2M pyridine down it, and washing with water, the lysine salt solution was passed down the column and washed through with water, the phosphonic acid passing straight through. The amine
- 15 acid containing fractions were collected and evaporated to dryness; a solution of known concentration was then made up, and the rotation of plane polarised light recorded on a "TBL" Automatic Polarimeter 143D using a mercury lamp. The first isomer to be precipitated was found to be (-),
- 20 and circular dichroism studies indicated it to have the D configuration.
- (e) Lipophilic radicals can then be added on to the product by conventional methods such as esterification.

It is surprising that the (-)-D-isomers of the present invention should exhibit activity as anti-convulsants. The required dosage levels compare favourably to those of known drugs used for epilepsy. The spectrum of activity of the present compounds and the routes by which they can be administered are especially remarkable. In particular it is surprising that the active compounds can pass the blood-brain barrier to permit intraperitoneal and intravenous administration in addition to intracerebroventricular administration. (Thus, even the possibility of oral administration seems worth investigating.) Thus the compounds of this invention are an unexpected advance in the art.



Claims

1. (-)-D-isomers of compounds of the general formula



(I)

in which

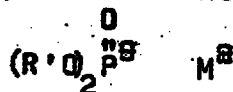
- 5 R stands for an aliphatic radical of 5 C atoms, which may optionally be substituted,
X stands for an acidic radical, and
A and B independently of each other stand for a lipophilic radical, or one of A and B can stand for a hydrogen atom,
10 or salts thereof, or pharmaceutically acceptable bioprecursors thereof.
2. Compounds according to claim 1, in which X stands for a radical of phosphonic acid, sulphonic acid, boronic acid or tetrazole, and/or R stands for C_5H_{10} -
- 15 3. Compounds according to claim 1 or 2, in which A and B independently of each other stand for an ester radical.
4. A process for the production of a compound according to any of claims 1 to 3, in which (with R having the same meaning as in claim 1 or 2 in all cases)
- 20 (a) if a compound of formula (I) in which X stands for a phosphonic acid radical is required,
a dibromo compound of the general formula



(II)

25. in which

is reacted with a compound of the general formula

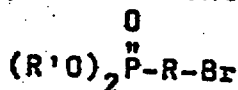


(III)

in which

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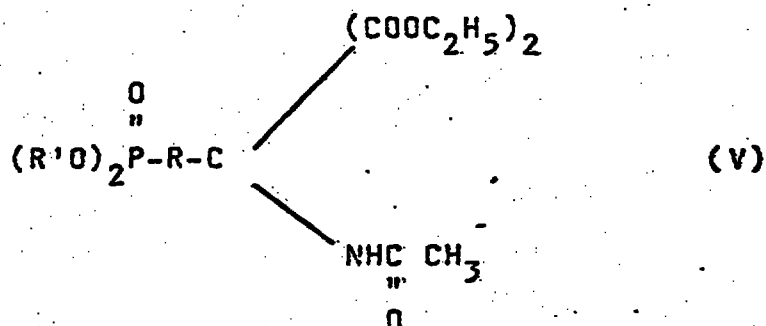
- R' stands for an alkyl group,
 M^{B} stands for an alkali metal cation,
and the resulting compound of the general formula



(IV)



is heated with diethyl acetamidomalonate, and the resulting condensation product of the general formula

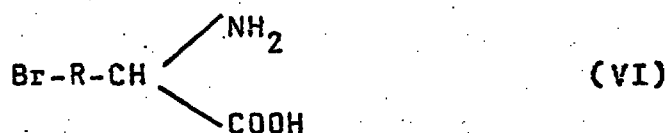


5 is subjected to decarboxylation, to give a compound according to the present invention the general formula

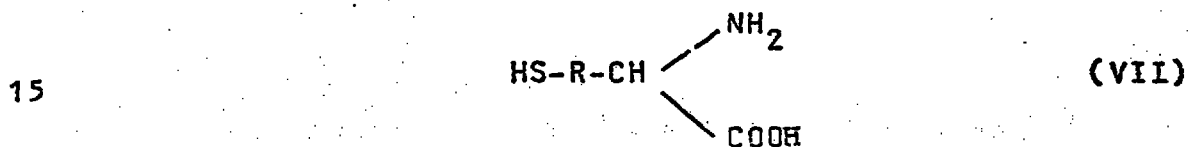


(b) if a compound of formula (I) in which X stands for a sulphonic acid radical is required,

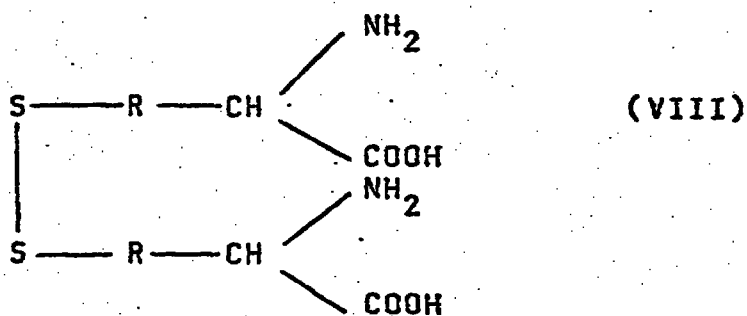
10 a compound of the general formula



in which R has the abovementioned meaning, is reacted with hydrogen sulphide, to give a compound of the general formula



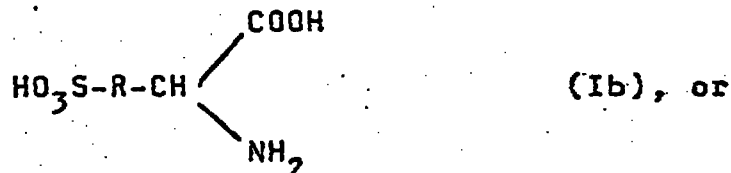
15 which is then heated to give a compound of the general formula





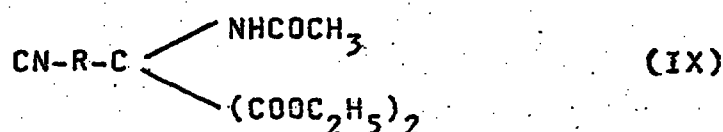
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which then is reacted with bromine to give a compound according to the present invention of the general formula

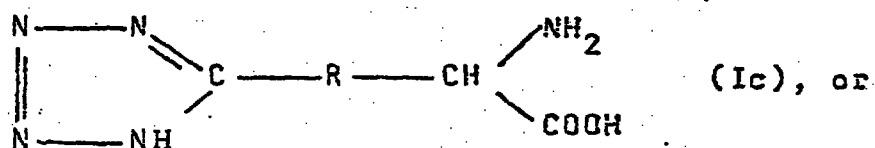


- 5 (c) if a compound of formula (I) in which X stands for a tetrazolyl radical is required.

a compound of the general formula

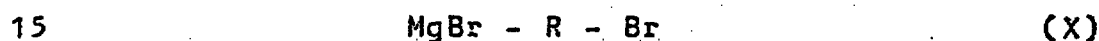


- 10 is reacted with sodium azide to give a compound according to the present invention of the general formula



- (d) if a compound for formula (I) in which X stands for a boronic acid radical is required,

a compound of the general formula



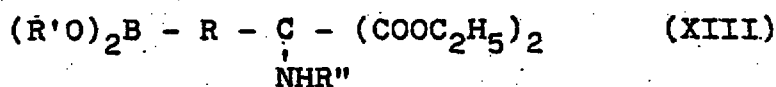
in which R has the abovementioned meaning, is reacted with a trialkyl borate of the general formula



- 20 in which R' represents an alkyl group, to give a compound of the general formula

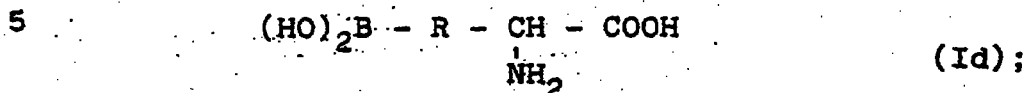


which is then reacted with a diethylacetamidomalonate and the product of the general formula



in which R'' represents CO-CH₃,

is then hydrolysed to give a compound according to the present invention of the general formula



and the product of reaction variant a), b), c) or d) of formula (Ia), (Ib), (Ic) or (Id), respectively, is, before or after separation of the (-)-D-isomer, converted into a corresponding compound in which the amino group and/or carboxylic acid group carry a lipophilic group and also, if desired, is converted into a salt thereof.

10 5. A process according to claim 4a), in which R' stands for an ethyl group.

6. A process according to claim 4a) or 5, in which 15 M⁺ stands for a sodium cation.

7. A process according to any of claims 4a), 5 and 6 in which the compound of formula (IV) is heated with diethyl acetamidomalonate in ethanol.

8. A process according to any of claims 4a) and 5 to 20 7 in which the decarboxylation is carried out using boiling hydrochloric acid or iodotrimethylsilane.

9. A process according to claim 4d), in which the trialkyl borate is triethyl borate.

10. A compound according to claim 1, whenever produced 25 by the process of any of claims 4 to 9.

11. A compound according to any of claims 1 to 3 and 10, for use in the treatment of diseases of the central nervous system.

12. A pharmaceutical composition comprising a compound 30 according to any of claims 1 to 3 and 10 in admixture with a pharmaceutical carrier or excipient.