

NEW AMINOACID ISOMERS, THEIR PRODUCTION
AND THEIR MEDICINAL USE

The present invention relates to certain new isomers which have use in the treatment of diseases of the central nervous system and to processes for their production.

According to the present invention we provide, a
5 pharmaceutical composition containing as an active ingredient a compound which is the (-)-D-isomer of a compound of the general formula



10 in which R stands for an aliphatic radical of 5 C atoms, which may be optionally substituted, and X stands for a radical of phosphonic acid, sulphonic acid, boronic acid or tetrazole, or a salt thereof, or a bioprecursor thereof, in admixture with a pharmaceutical diluent (as ^{hereinafter} ~~hereinbefore~~ defined), or in the form of an aqueous solution which is both sterile and isotonic with blood plasma.

15 The active compounds show a very marked action in combating diseases of the central nervous system. When so used, the compounds can be administered, e.g. parenterally.

The active compounds can be administered by intracerebral injection, which has particular significance in research into
20 diseases of the central nervous system. There is much interest currently in 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
25 degeneration and are believed 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 found that
30 (-)-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 also of great value in CNS research as a means of blocking ibotenic acid-excited receptors while leaving Kainic acid-excited receptors free to be acted on by candidate antagonists.

The ~~new~~^{active} (-)-D compounds of the present invention show considerably greater activity than a corresponding racemic mixture. Although a certain difference in activity might be expected between isomers, it is surprising that compounds of the present invention should show such a markedly improved action in combating diseases of the central nervous system. The ~~new~~^{active} compounds of the invention thus represent a significant contribution to the range of active compounds available to the pharmacist.

Preferably R is C_5H_{10} or C_5H_8 .

The present invention further relates to processes for the production of ^{active} compounds of the present invention, in which

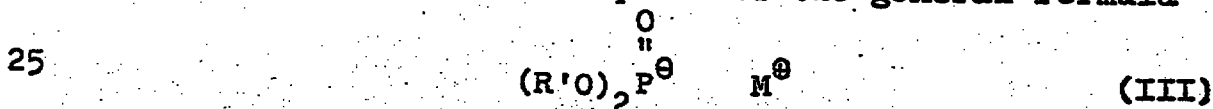
(a) if a compound of formula (I) in which X stands for a phosphonic acid radical is required,

a dibromo compound of the general formula



in which, R has the abovementioned meaning,

is reacted with a compound of the general formula



in which

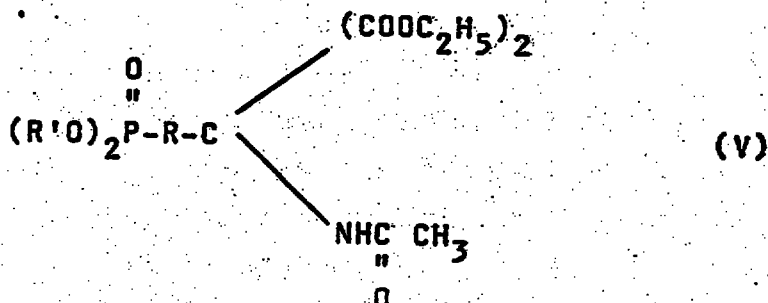
R' stands for an alkyl group, preferably an ethyl group, and

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

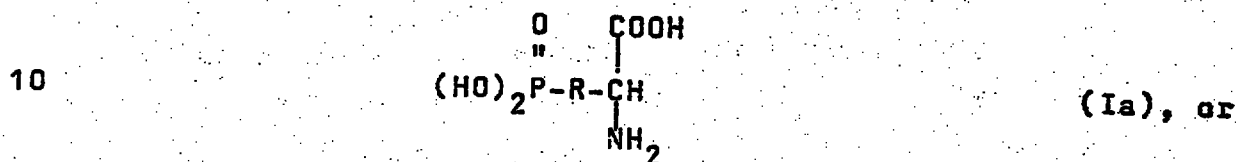
and the resulting compound of the general formula



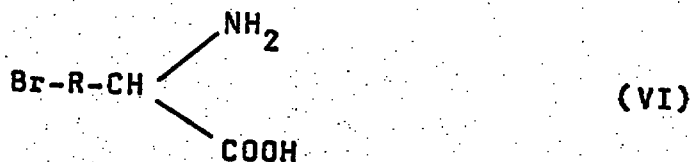
is heated, preferably in ethanol, with diethyl acetamidomalonate, and the resulting condensation product of the general formula



5 is subjected to decarboxylation, preferably in boiling hydrochloric acid, or, especially, using iodotrimethylsilane, to give a compound according to the present invention of the general formula



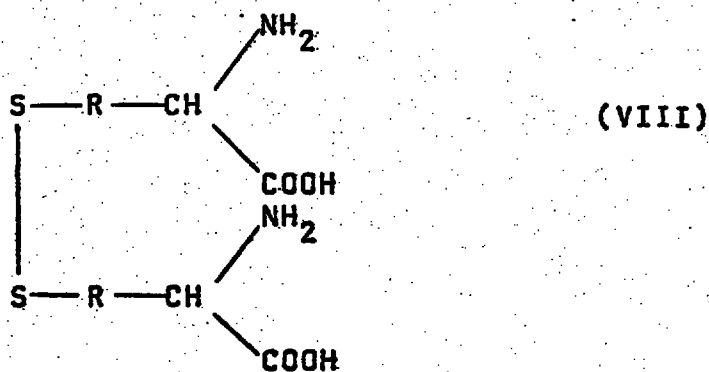
(b) if a compound of formula (I) in which X stands for a sulphonic acid radical is required, a compound of the general formula



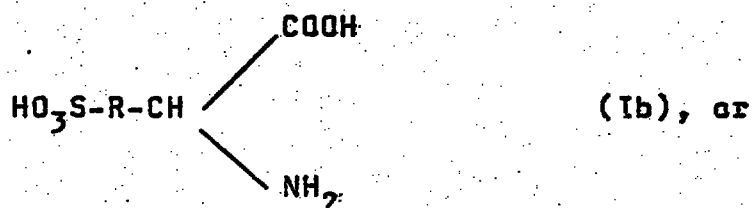
15 in which R has the abovementioned meaning, is reacted with sodium hydrosulphide, to give a compound of the general formula



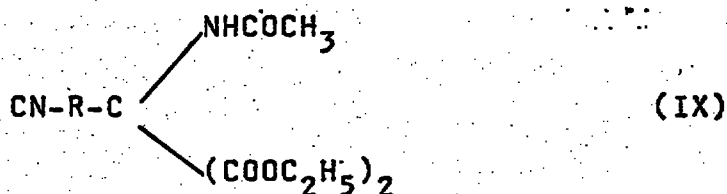
20 which is then heated to give a compound of the general formula



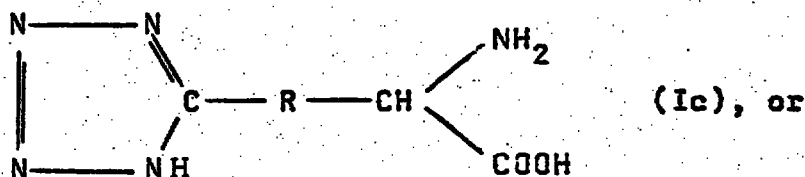
which then is reacted with bromine to give a compound according to the present invention of the general formula



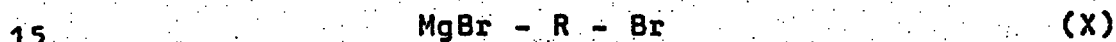
- 5 (c) if a compound of formula (I) in which X stands for a tetrazolyl radical is required, a compound of the general formula



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



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



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

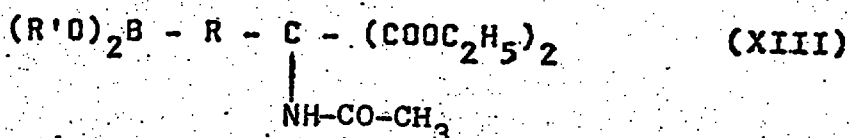
general formula



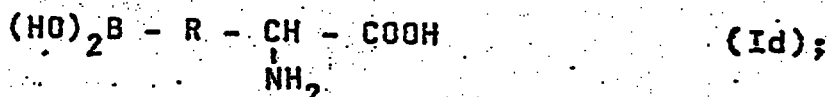
in which R' represents an alkyl group, to give a compound of the general formula



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



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



in which R has the abovementioned meaning, and the product of reaction variant a), b), c) or d) of formula (Ia), (Ib), (Ic) or (Id), respectively is, before or after the separation of the (-)-D-isomer, converted into a salt thereof, if required.

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

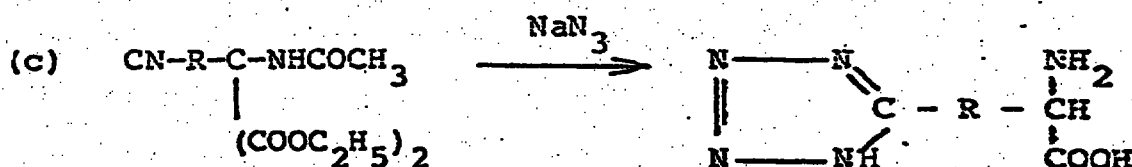
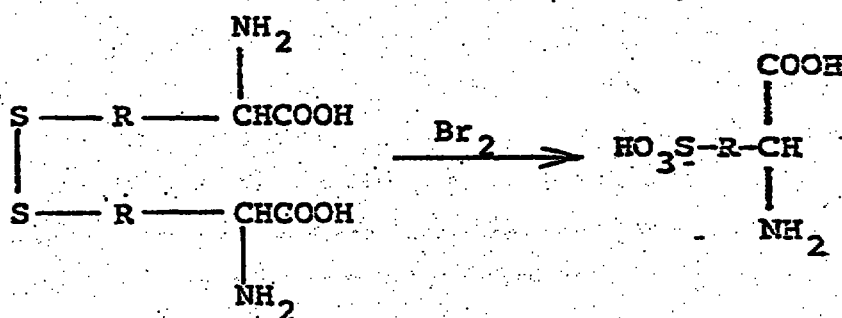
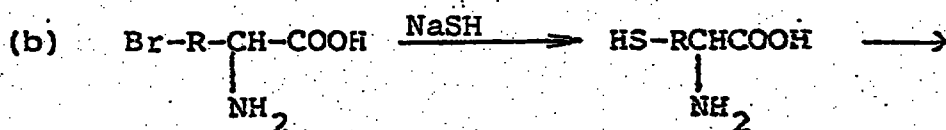
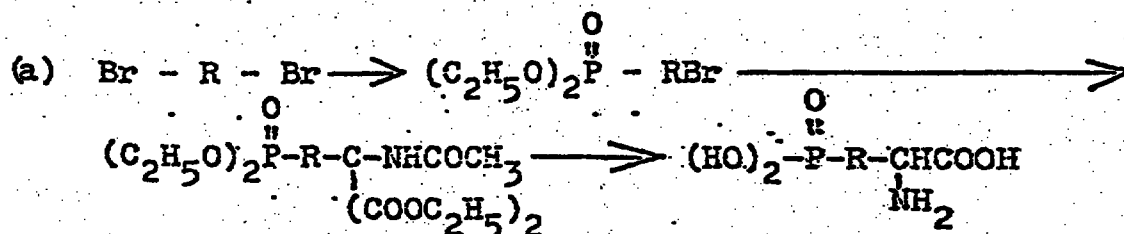
The new free isomers of the general formula (I) and their salts can be interconverted in any suitable manner; methods for such interconversion are known in the art.

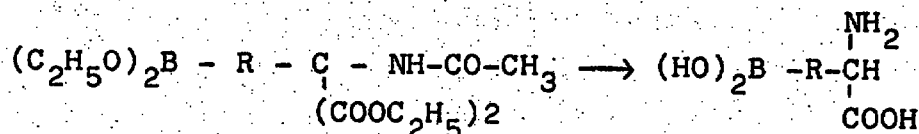
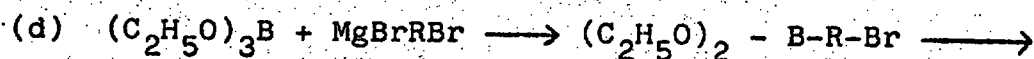
The separation of the (-)-D-isomer may be carried out by generally known methods, such as reacting the racemic mixture with an optically active base and separating out the salts formed. An appropriate method of separation has been found to be reacting the racemic mixture produced by a process of the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

The starting compounds used in the process variants according to the present invention are known compounds or can be produced by processes similar to those used for the production of such known compounds.

5 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.

10 The following reaction schemes illustrate the processes according to the present invention:





R in reaction variants (a), (b), (c) and (d) having the meaning given previously.

The isomers^{which are active compounds} 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.

As indicated above the invention also relates to the compounds of the invention for use in human and veterinary medicine in treating diseases of the central nervous system.

~~There is further provided according to the present invention, a pharmaceutical composition containing as active ingredient a compound of the invention in admixture a pharmaceutical diluent.~~

As used herein "pharmaceutical diluent" means a solid, liquefied gas or liquid and, where the liquid is a solvent it must either be surfactant-containing or have a high molecular weight ("high molecular weight" in this context meaning a weight above 150).

~~The invention further provides a pharmaceutical composition containing as active ingredient a compound of the invention in the form of an aqueous solution which is isotonic with blood plasma, or sterile, or both.~~

The invention also provides a medicament in the form of capsules or ampules, or otherwise in dosage unit form.

The term "medicament" used in this specification means that the active compound is in portions which are physically discrete and coherent and are suitable for medical administration. When that medicament is in
5 "dosage unit form" it is made up in association with a carrier and/or enclosed within an envelope, as separate units suitable for medical administration, which units individually provide

the daily dose or a multiple or fraction thereof. Naturally the size of the dosage unit corresponds directly to the frequency of its administration.

The pharmaceutical composition according to the invention may, for example, take the form of suspensions, solutions and emulsions of the active ingredient in aqueous or non-aqueous diluents.

The pharmaceutical compositions which are solutions and emulsions can contain liquid diluents (with, of course, the above-mentioned exclusion of surfactant-free solvents, not being high molecular weight solvents) such as solvents, dissolving agents and emulsifiers; specific examples of such diluents are water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butyleneglycol, dimethylformamide, oils (for example ground nut oil), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitol or mixtures thereof.

For parenteral administration, solutions and emulsions should be sterile, and, if appropriate, isotonic with blood plasma.

The pharmaceutical compositions which are suspensions can contain liquid diluents such as water, ethyl alcohol, propylene glycol, surface-active agents (e.g. ethoxylated isostearyl alcohols, polyoxyethylene sorbite and sorbitane esters), microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth or mixtures thereof.

The pharmaceutical compositions according to the invention generally contain from 0.1 to 99% of the active ingredient by weight of the total composition.

Pharmaceutical compositions and medicaments according to the invention, in addition to a compound of the invention, can also contain other pharmaceutically active compounds. They may also contain a plurality of compounds of the invention.

Diluents in the medicaments of the present invention

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may be any of those mentioned above in relation to the pharmaceutical compositions of the present invention. But such medicaments may also include as the sole diluent solvents which are not high molecular weight solvents.

5 The shape or packaging for medical administration normally produces the discrete coherent portions constituting the medicament according to the invention and may be, for example: capsules and ampoules.

10 The production of the above-mentioned pharmaceutical compositions and medicaments is carried out conventionally, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition and, if appropriate, then forming the composition into the separate portions of the medicament.

15 This invention further provides the compounds of the invention for use in combating (including prevention, relief and cure of) diseases of the central nervous system in human and non-human animals.

20 It is envisaged that these active compounds will preferably be administered parenterally (for example intramuscularly, intraperitoneally, subcutaneously and intravenously).

25 Preferred pharmaceutical compositions and medicaments are therefore those adapted for administration such as parenteral administration. Administration in the method of the invention is preferably parenteral administration.

30 However, where alternative methods of administration are found to be appropriate, it is a simple matter for the skilled worker to prepare pharmaceutical compositions or medicaments appropriate to that alternative administration route.

The present invention also comprises pharmaceutically acceptable bioprecursors of the active compounds of the present invention.

35 For the purposes of this specification the term

'pharmaceutically acceptable bioprecursors' 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 or human being is converted in the patient's body to the active compound.

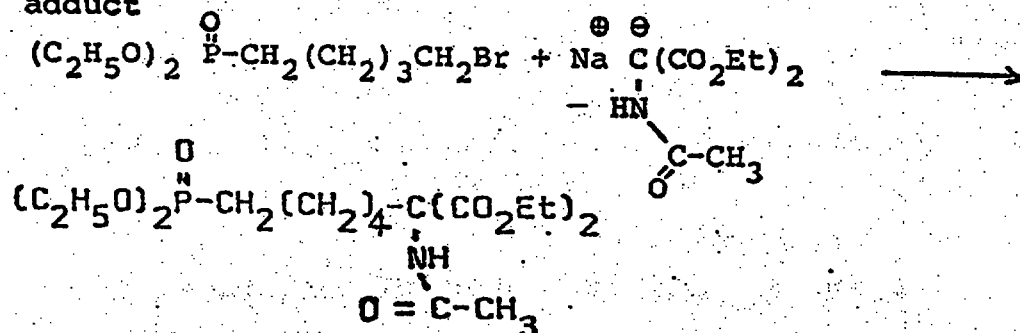
The following Examples illustrate a process for the production of an isomer of the present invention.

Example 1

10 (a) Synthesis of (-)-2-amino-7-phosphonoheptanoic acid
1,5-dibromopentane $\longrightarrow$ diethyl-5-bromopentane phosphite
$$\text{BrCH}_2(\text{CH}_2)_3\text{CH}_2\text{Br} + \text{Na}^+ \text{P}^-(\text{OC}_2\text{H}_5)_2 \longrightarrow \text{BrCH}_2(\text{CH}_2)_3\text{CH}_2\text{P}^-(\text{OC}_2\text{H}_5)_2$$

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.

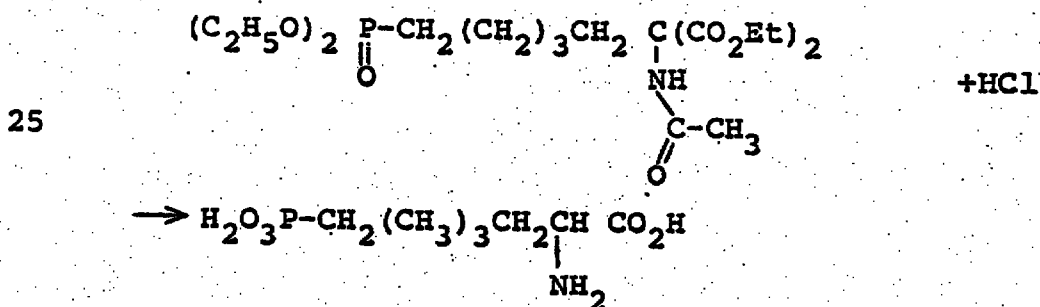
30 (b) Diethyl-5-bromopentane phosphonate $\longrightarrow$ acetamido adduct



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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 acetamidomalonate. 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 sodium diethyl acetamidomalonate, and diethyl-5-bromopentane phosphonate, came off with diethyl ether, and were separated by crystallisation of sodium diethyl acetamido malonate from ether solution. The product was eluted off the column with chloroform, as a light yellow viscous syrup.

(c) Acetamido adduct $\rightarrow$ (+) 2-amino-7-phosphonoheptanoic acid



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.

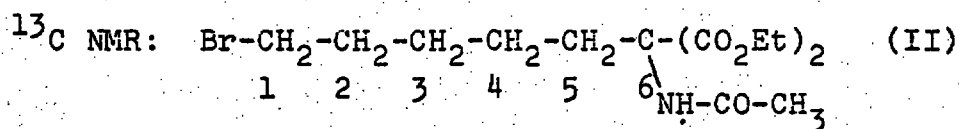
Example 2

Synthesis of (-)-2-amino-7-sulphonoheptanoic acid

(a) Preparation of diethyl acetamido adduct of 1,5-dibromo pentane:

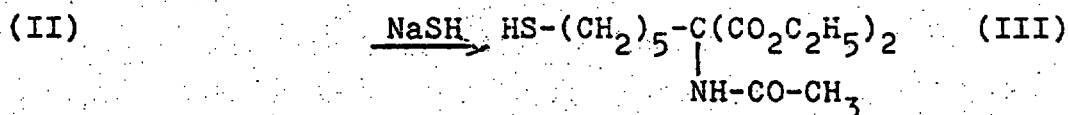
- 5 0.04 mol of the sodium diethyl acetamido malonate were reacted with 0.2 mol of dibromopentane, $\text{Br}-(\text{CH}_2)_5-\text{Br}$ (I). The product was isolated after filtering off the NaBr by evaporation of the solvent, and vacuum distillation of the resulting liquid to drive
10 off the excess dibromopentane. The remaining oil was columned on silica, residual dibromopentane being brought off in 1:1 diethyl ether: petroleum ether, the product following this using the same eluant; unreacted diethyl acetamido malonate was removed from
15 the column by changing the eluent to pure diethyl ether. The product, a white crystalline solid from ether/petroleum ether; m.pt. 50°C ; yield 0.0186 mol (47%).

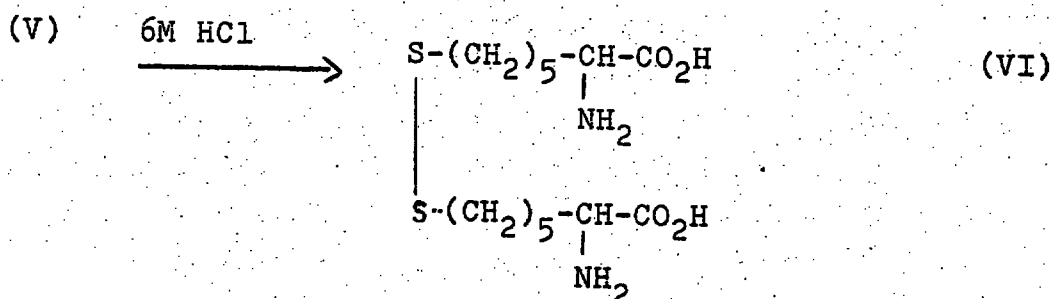
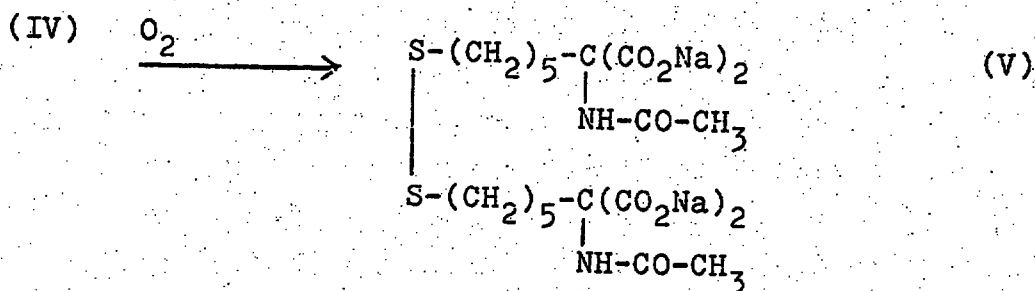
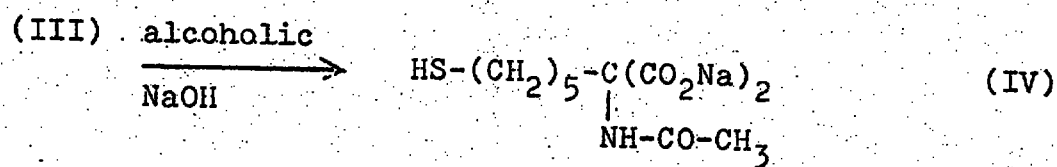
A sample was submitted for ^{13}C NMR analysis:



20	carbons 1 to 5	23.4; 28.4; 32.7; 33.0; 34.15ppm
	carbon 6	57.12 ppm
	acetamido CH_3	67.1 ppm
	ester CH_3	14.6 ppm
	ester $\text{O}-\text{CH}_2$	62.9 ppm
25	ester carboxyl $\text{C}=\text{O}$	168.8 ppm
	acetamido carbonyl $\text{C}=\text{O}$	170.9 ppm rel TMS

(b) Preparation of 2-amino-7,7'-dithiobisheptane carboxylic acid:





The diethyl acetamidobromo alkane dicarboxylate (II) from preparation (a) was converted into the diethyl acetamido thioalkane dicarboxylate (III) which in turn was converted into the acetamido thioalkane dicarboxylic acid sodium salt (IV). The latter was converted into the acetamido dithiobis-alkane dicarboxylic acid (V) which in turn was converted into the 2-amino-dithiobis-alkane carboxylic acid (VI). This series of reactions was carried out precisely as described by du Vigneaud et al with no deviations. (When preparing the compound (III), the reagent NaSH was prepared by bubbling H₂S through a solution of sodium sulphide (dissolved in its own water of crystallisation). It was found necessary to exclude additional moisture in order to avoid hydrolysis of the reactive sodium hydrosulphide). See Journal of Biological Chemistry, Vol 106, pp 401-407 (1934).

10



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5.

found

$$1 \quad 2 \quad 3 \quad 4 \quad 5 \quad 6 \text{NH}_2$$

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(VII)

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- 17 -

passed through an Amberlite IRA 45 [OH⁻] ion-exchange resin column. The column was washed with 3 bed volumes of water until no further ninhydrin-staining material was present in the washings. This material was
 5 analysed by TLC and found to be identical to a sample of L-lysine run at the same time. The column was then washed through with 5 M aqueous acetic acid and all the ninhydrin-staining fractions collected. The combined solution was evaporated to dryness and the residual acetic
 10 acid was driven off by repeated solution and evaporation. A TLC of the product proved to be identical to a sample of ± aminosulphono heptanoate.

The compound was made up in a solution of concentration 10 g/100 ml; the rotation was measured in a
 15 Thorn automatic polarimeter at 546 nm.

Rotation of 2-amino-7-sulphoncheptanoate, first out of solution

Blank = 0.00°
 Sample = -0.112°
 20 α_{546}^{25} = -5.6°

The mother liquor was passed through a column of Amberlite [OH⁻] and washed with water. The product was eluted with 5 M aqueous acetic acid and the product isolated as above. A TLC of the product proved to be identical to
 25 a sample of ± aminosulphonheptanoate. The sample was made up to 10g/100 mls of water and the rotation determined as above.

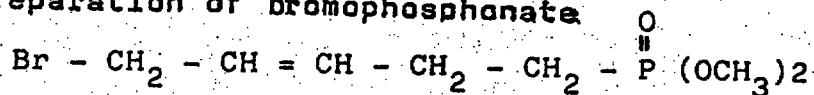
Rotation of 2-amino-7-sulphoncheptanoate, second out of solution

Blank = 0.00°
 Sample = +0.101°
 30 α_{546}^{25} = + 5.05°

Examples 1 and 2 illustrate the production of a compound wherein R is saturated. The following example relates to the production of a compound wherein R is unsaturated.

5 Example 3.

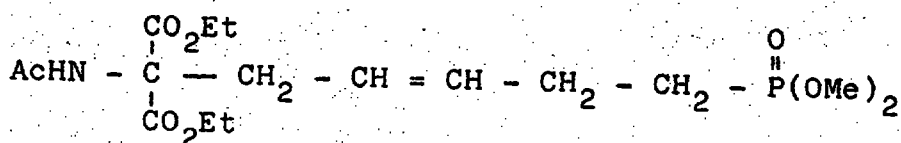
(a) Preparation of bromophosphonate



Butyl lithium (50 mmols) was slowly added to a solution of dimethoxy methylphosphonate (6.2 gms, 50 mmols) in dry tetrahydrofuran (120 mls), under nitrogen, at -78°C. The temperature was kept below -70°C during the addition. The mixture was stirred for a further 10 mins. at -78°C, after addition and then dibromobutene (12.84 gms, 60 mmols) in dry tetrahydrofuran (100 mls) was gradually added. The temperature was again kept below -70°C. After the addition the mixture was allowed to warm to room temperature and left to stir overnight.

The solvent was removed, in vacuo, and the residue dissolved in water (120 mls) and extracted with ether (4 x 100 mls). Drying over MgSO_4 , filtration and evaporation of the solvent, in vacuo, afforded a yellow oil which was chromatographed on silica gel (450 gms) using, initially, ethyl acetate as eluant and then ethyl acetate/ethanol (5:1 and 4:1). The initial fraction was unreacted bromobutene, the second pure bromophosphonate (7.35 gms, 42%).

(b) Preparation of diethyl acetamidomalonate adduct

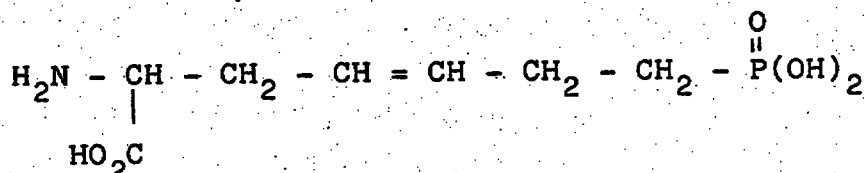


To a solution of sodium diethyl acetamidomalonate (230 mg sodium, 2.17 gms malonate, 10 mmols) in methanol (30 mls), under nitrogen, the bromophosphonate (2.57 gms,

10 mmols), prepared previously, in methanol (10 mls) was slowly added at room temperature. The mixture was then heated under reflux for 24 hrs.

5 After evaporation of the solvent, in vacuo, the residue was dissolved in water (30 mls) and extracted with ethyl acetate (4 x 50 mls). Drying over $MgSO_4$, filtration, and evaporation of the solvent, in vacuo, gave a dark yellow oil. Chromatography on silica gel (50 gms) using initially ethyl acetate (to remove any
10 unreacted malonate) and then ethyl acetate/ethanol (5:1 3:1) gave pure acetamido adduct (3.15 gms, 81%).

(c) Preparation of amino acid



15 The acetamido adduct (1.98 gms, 5 mmols) was dissolved in 6M HCl (25 mls) and the solution heated under reflux for 18 hrs. The solvent was then evaporated in vacuo, and the amino acid isolated by ion-exchange methods (Dowex 50W - X8 resin). Recrystallization from water/methanol afforded the pure acid (770 mgs, 70%).

The action of the compounds of the present invention on the central nervous system is illustrated by the following biotest Examples.

Example A

5 Anticonvulsant activity of excitatory amino acid antagonists in DBA/2 mice

DBA/2 mice were chosen as being an inbred strain in which, within a critical age range, a fixed sequence of seizure response can be induced by a loud sound. Groups of DBA/2 mice (N = 6 to 10), 21 to 28 days old, were injected intracerebroventricularly under light ether anesthesia with 10 μ l of drug solution or phosphate buffer alone (pH 7.3). Auditory stimulation (electric bell generating 109 dB at mouse level) was applied 45 minutes later for 60 seconds or until tonic extension was observed and the incidence and timing of the phases of the seizure response were recorded. These included an initial wild running phase (WR) followed by myoclonus, tonic flexion, and extension and, frequently, respiratory arrest. Seizure response was scored as described in Eur. J. Pharmacol 59, 75 (1979), and comparisons between groups of control and drug-treated animals were made by using Fisher's exact probability test. Successive doses, with a geometric factor of 3, were tested until an adequate log dose-response curve (three to six points) could be constructed for each antagonist for each phase of the seizure response, and ED₅₀ values were graphically determined. A rank order of anticonvulsant potency was allocated to each antagonist for comparison with iontophoretic data; 0 denoting no activity and X to XXXX denoting increasingly marked activity.

Antagonist	Minimum dose to suppress WR* (μ mole)	ED ₅₀ (μ mole)	Relative anti- convulsant potency	Relative NMDA antagonist potency*
<u>Comparative compounds</u>				
D-α-Aminoadipic acid	(0.25)†		0	
Glutamic acid diethylester	(3.3)†		0	
γ-D-Glutamylglycine	0.1	0.058 0.046 0.054	X	
(+)-2-Amino-4-phosphonobuty- ric acid	(0.5)†		0	(X)
(+)-2-Amino-5-phosphonopen- tanoic acid	0.1	0.046 0.022 0.025	X	XX
(+)-2-Amino-6-phosphonohex- anoic acid	0.25	0.17 0.14 0.15	(X)	(X)
(+)-2-Amino-7-phosphonohep- tanoic acid	0.01	0.004 0.018 0.0008	XXX	XXX
(+)-2-Amino-7-phosphonohep- tanoic acid	0.033	0.0135 0.0018 0.0018	XX	XX
<u>Compound according to the invention</u>				
(-)-2-Amino-7-phosphonohep- tanoic acid	0.0033	0.0022 0.0008 0.0008	XXXX	XXXX
*P < .01. † Inactive				

As will be seen the compound according to the invention both has a superior anticonvulsant potency, and suppresses WR at a considerably lower dosage than the minimum dosage for the comparative compounds.

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Example B

Effect of (+)-2-amino-7-phosphonoheptanoic acid on audiogenically induced and pentylenetetrazol-induced seizures in mice

- 5 Studies of audiogenic seizures were performed as described in Example A. For intraperitoneal administration the antagonist was injected with 0.1 ml of saline 45 minutes before testing. Antagonism of pentylenetetrazol (PTZ: threshold) seizures was studied in random-bred Swiss
- 10 mice (Tuck T/O strain: 28 days old; 20 to 23 g). Mice in groups (N=10) received pentylenetetrazol (85 mg/kg: 0.85 percent solution in 0.9 percent sodium chloride) subcutaneously in a loose fold of skin on the back of the neck 45 minutes after intracerebroventricular or intra-
- 15 peritoneal administration of drug or vehicle. During the 30-minute observation period sustained rhythmic clonic jerking with tonic spasms occurred in 90 to 100 percent of control mice. The incidence and timing of clonic episodes was recorded with absence of sustained clonic jerking (no
- 20 episode of 5 seconds duration or longer) being defined as protection. The ED₅₀ values and 95 percent fiducial limits were estimated by using the method of moving averages (by the method described in Biometrics 8, 249 (1952) with data from four successive dose levels.

Antagonist	Route of administration	Minimum dose to suppress WR*	ED ₅₀		ED ₅₀ v PTZ (95% fiducial limites)
			WR*	Clonus Tonus	
(+)-2-Amino-7-phosphonoheptanoic acid	Intracerebro-ventricular	0.01 μ mole	0.004	0.0018	0.64 (0.19-2.13) μ mole
	Intraperitoneal	0.33 mmole/kg	0.18	0.04	1.18 (0.97-1.43) mmole/kg

*P < .01.

This Example shows that intraperitoneal administration may also be carried out with the racemic mixture indicated and therefore that the (-)D-isomer can also be administered in this manner. A similar reduction of dose for the compound of the invention as compared with racemic mixtures to that shown in Example A would be expected for this administration route also.

Intravenous administration of the compound of the invention to baboons, Papio papio, at a dosage rate of 1.0 mmoles/kg was also found to suppress photosensitive epileptic responses.

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.



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CLAIMS:-

1. A pharmaceutical composition containing as an active ingredient a compound which is the (-)-D-isomer of a compound of the general formula



5 in which

R stands for an aliphatic radical of 5 C atoms, which may be optionally substituted, and X stands for a radical^{of} phosphonic acid, sulphonic acid, boronic acid or tetrazole;

10 or a salt thereof, or a bioprecursor thereof, in admixture with a pharmaceutical diluent (as hereinbefore defined), or in the form of an aqueous solution which is both sterile and isotonic with blood plasma.

15 2. A pharmaceutical composition according to claim 1, in which R stands for C₅H₁₀,

3. A pharmaceutical composition according to claim 1, in which the active compound is (-)-D-2-amino-7-phosphonoheptanoic acid or a salt thereof.

20 4. A composition according to any one of claims 1 to 3 containing from 0.1 to 99% by weight of the said active compound.

5. A medicament in dosage unit form comprising an active compound as defined in any one of claims 1, 2
25 and 3.

6. A medicament in the form of capsules or ampoules comprising an active compound as defined in any one of claims 1, 2 and 3.

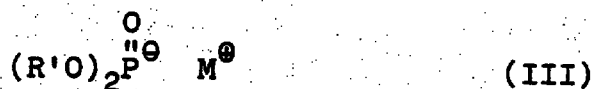


7. A process for the production of an active compound as defined in any of claims 1, 2 and 3, in which

5 (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



10 in which, R has the meaning given in claim 1, is reacted with a compound of the general formula

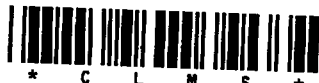


in which

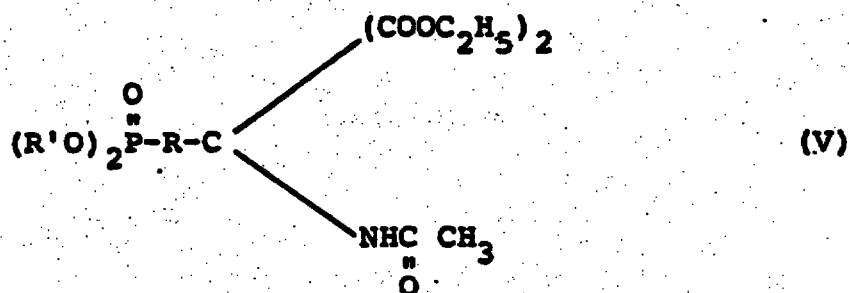
15 R' stands for an alkyl group,
M[⊕] stands for an alkali metal cation,
and the resulting compound of the general formula



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



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



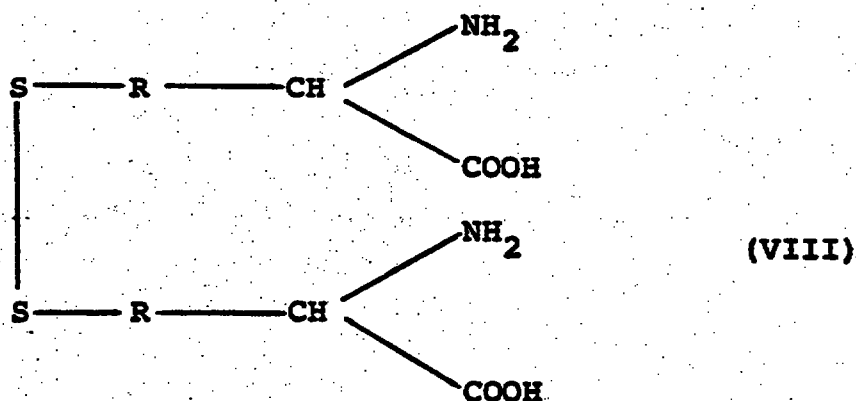
- 5 (b), if a compound of formula (I) in which X stands for a sulphonic acid radical is required, a compound of the general formula



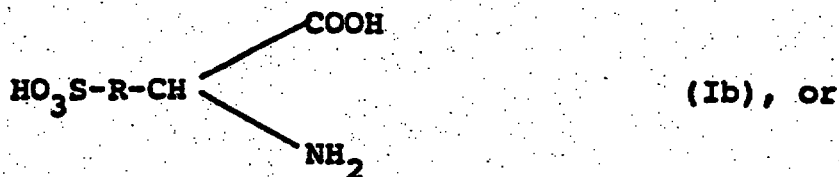
- 10 is reacted with sodium hydrosulphide, to give a compound of the general formula



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

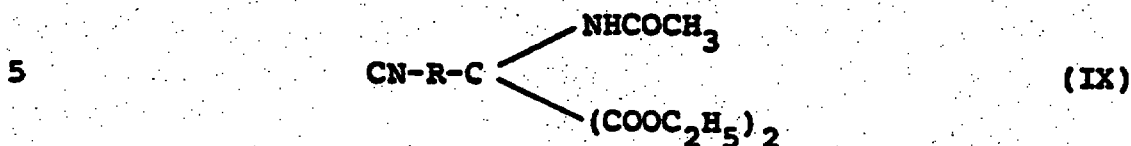


- 15 which is then reacted with bromine to give a compound according to the present invention of the general formula

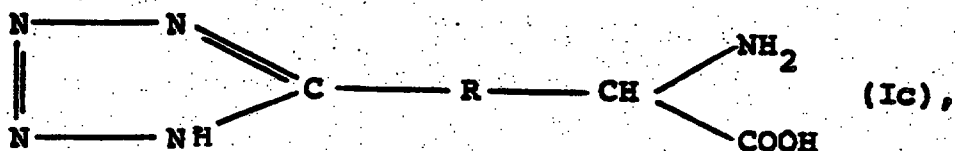


(c), if a compound of formula (I) in which X stands for a tetrazolyl radical is required.

a compound of the general formula

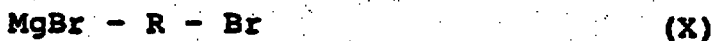


is reacted with sodium azide to give a compound according to the present invention of the general formula



or

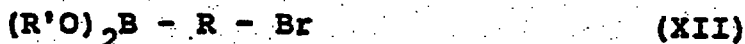
- 10 (d) if a compound of formula (I) in which X stands for a boronic acid radical is required,
a compound of the general formula



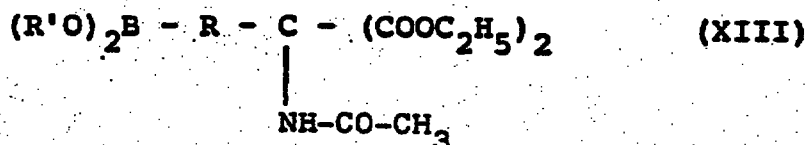
is reacted with a trialkyl borate of the general formula



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



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

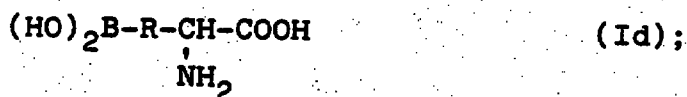


is then hydrolysed to give a compound according to the present invention of the general formula



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- and the product of reaction variant a), b), c) or d) of formula (Ia), (Ib), (Ic) or (Id), is optionally, before or after the separation of the (-)-D-isomer, converted into a salt thereof; R in reaction variants a), b), c) and d) having the meaning given in claim 1.
- 5 8. A process according to claim 7 a), in which R' denotes an ethyl group.
9. A process according to claim 7 a) or 8, in which the compound of formula (IV) is heated with diethyl acetamido malonate in the presence of ethanol.
- 10 10. A process according to any of claims 7 a) or 8, in which the decarboxylation of the compound of formula (V) is carried out in boiling hydrochloric acid or iodotrimethyl silane.
- 15 11. A process according to claim ^{7(d)} 12, in which the trialkyl borate is triethyl borate.
12. A process according to any of claims 7 to 11 in which the compound of formula (Ia), (Ib), (Ic) or (Id) is reacted with L-lysine, thereby forming diastereomers thereof, the salt containing the (-)-D-isomer is separated by crystallisation and is thereafter converted, if desired, into the free acid or into another salt thereof.
- 20 13. A process for the production of an active compound as defined in claim 1, substantially as described in Example 1 or 3.
14. Compounds as defined in claim 1 whenever prepared by a process according to any of claims 7 to 13.
- 30 15. The active compound as defined in any of claims 1, 2 to 3 for use in combating diseases of the central nervous system.
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