(11) 1429926

PATENT SPECIFICATION

1429926

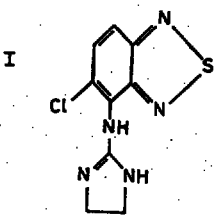
(21) Application No. 45632/75 (22) Filed 7 May 1973
(62) Divided out of No. 1429683
(31) Convention Application No. 6865/72 (32) Filed 9 May 1972 in
(33) Switzerland (CH)
(44) Complete Specification published 31 March 1976
(51) INT CL² C07D 417/12 A61K 31/425//(C07D 417/12 233/04 285/14)
(52) Index at acceptance
C2C 1412 1442 213 215 247 250 252 256 25Y 28X 29X 29Y 305 313 31Y 320 322 326 32Y 337 373 37Y 380 45X 45Y 48X 616 620 62Y 656 670 69Y 723 746 74Y 752 755 758 75X 76X 775 78Y 790 79Y NB NF RH SM

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(71) We, WANDER LTD., of 115 Monbijoustrasse, 3001 Berne, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

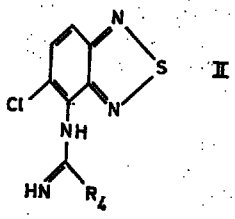
The present invention relates to the compound of formula I,



which is 5 - chloro - 4 - (2 - imidazolin - 2 - ylamino) - 2,1,3 - benzothiadiazole.

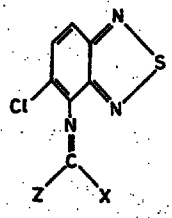
Further, in accordance with the invention, a compound of formula I may be obtained by a process comprising

a) reacting a compound of formula II,



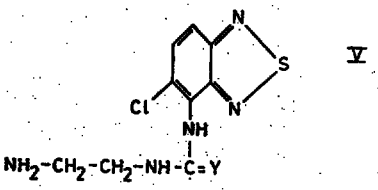
wherein R_4 is a reactive group other than halogen, capable of being split off with a hydrogen atom of an amine, with ethylene diamine, or

b) reacting a compound of formula IV,



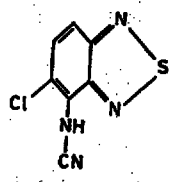
wherein each of X and Z is, independently, a reactive group capable of being split off with the hydrogen atom of an amine, with the proviso that when X is halogen Z is halogen, with ethylene diamine, or

c) subjecting a compound of formula V,



wherein Y is oxygen or sulphur, to a ring closure, or

d) reacting a compound of formula VI,



with ethylene diamine.

Process variants a), c) and d) are the preferred processes.

Process variant a) may be effected as follows:—

In the compound of formula II the reactive group R_4 conveniently is —NH—NO_2, or —S—R_5, —O—R_5 or especially —NH—R_6, wherein R_6 is hydrogen or alkyl of 1 to 3 carbon atoms. The reaction is conveniently effected at a temperature from 50 to 200°C, preferably from 110 to 170°C. The reaction is conveniently effected in an inert solvent such as an alcohol of 1 to 8 carbon atoms, e.g. methanol, ethanol or amyl alcohol, conveniently in the presence of water, or a mixture of two or more of the foregoing alcohols, e.g. a mixture of methanol and ethanol, or dioxane, nitromethane or nitrobenzene. Alternatively, the reaction is conveniently effected in excess ethylene diamine. The ethylene diamine may be in free base form or in monoacid addition salt form. Conveniently the compounds of formula II are in free base form when the ethylene diamine used is in monoacid addition salt form.

Monoacid addition salts of ethylene diamine are preferably the hydriodides and tosylates.

Acid addition salts of compounds of formula II are preferably the hydriodides, hydrobromides or hydrochlorides.

Process variant b) may be effected as follows:—

In the compound of formula IV the reactive groups X and Z may be the same or different. Conveniently both X and Z signify halogen, preferably chlorine. Alternative convenient significances for X and Z are —NH—NO_2, or —S—R_5, —O—R_6 or —NH—R_6, wherein R_6 is as defined above. The reaction may be conveniently effected in the presence of an excess of ethylene diamine. Alternatively, an inert solvent may be used such as an alcohol of 1 to 8 carbon atoms, for example methanol or ethoxyethanol, dioxane, acetone, nitrobenzene, xylene or toluene. The reaction temperature is conveniently from 0°C to the temperature of the reaction mixture boiling under reflux.

When X or Z in the compound of formula IV is a halogen atom, then the reaction with ethylene diamine liberates hydrogen halide. A corresponding equivalent additional amount of ethylene diamine or a corresponding equivalent amount of an acid acceptor such as an alkali metal carbonate, an alkali or a tertiary amine is then preferably present.

Process variant c) may be effected as follows:—

The ring closure of a compound of formula V is conveniently effected in an inert solvent, preferably an alcohol of 1 to 5 carbon atoms such as methanol or ethanol, water or dimethyl formamide. The reaction is conveniently effected at a temperature from 20 to 150°C, preferably from 60 to 110°C. The reaction is conveniently effected in the presence of a base, e.g. an alkaline earth metal hydroxide, an alkali metal hydroxide such as potassium or sodium hydroxide, or a heavy metal compound such as mercury oxide or lead acetate.

Process variant d) may be effected as follows:—

The reaction is conveniently effected in an inert organic solvent, e.g. an alcohol of 3 to 8 carbon atoms, such as n - pentanol, or an excess of ethylene diamine may be used. The reaction temperature is conveniently from 50 to 200°C, preferably from 110 to 160°C.

The reaction is preferably effected in the presence of an excess of a monoacid addition salt of ethylene diamine.

Insofar as the production of starting materials is not particularly described, these are known or may be produced and purified in accordance with known processes, or in a manner analogous to the processes described herein or to known processes, or processes described in our pending application No. 21631/73 (Patent Specification No. 1429683). Similar considerations apply to the processes mentioned above.

For example the compound of formula I may be obtained in a manner analogous to that described in Example 5 of the above mentioned pending application.

Free base forms of the compound of formula I may be converted into acid addition salt forms in conventional manner, and vice versa. Suitable acids for acid addition salt formation include hydrochloric acid.

The compound of formula I exhibits antitremor activity, as indicated by, for example, the following test with mice:

The evening before the test day the mice used for the test (50% males and 50% females) are deprived of feed. Groups of ten animals each are used for the test, one group forming the control group.

The compound is administered to the animals in each group, the doses increasing from group to group. A physiological common salt solution is given to the animals of the control group. 30 minutes after administration of the compound to be tested, 100 mg/kg animal body weight of the compound producing the tremor (2,6 - dichlorophenyl - acetimidoyl ureide) is administered p.o. to all the animals.

5, 10, 15 and 20 minutes after administration of the compound producing the tremor, the animals are judged in accordance with the following scale:

2=strong tremor
1=weak tremor
0=no tremor

Evaluation

For the three first measurements (5, 10 and 15 minutes after administration), the behaviour of each mouse is determined and the group average values are estimated as follows:—

group with strong tremor=averages 1.5—2.0
group with weak tremor=averages 0.5—1.5
group without tremor =averages 0.0—0.5

The compound of formula I is therefore indicated for use as an anti-tremor agent.

The compound of formula I also exhibits anti-rigor activity as indicated by, for example, the following test with rats:

Rats are injected i.p. with 7.5 mg/kg animal body weight of Thalamonal (Registered Trade Mark), whereupon these animals develop a rigor which can be measured with an electromyograph. The dose of active compound which must be injected i.v. in order to inhibit the rigor of the rats is ascertained.

The compound of formula I is therefore further indicated for use as an anti-rigor agent.

For the above-mentioned uses, i.e. as anti-rigor and anti-tremor agents an indicated daily dose is from 10 to 400 mg of the compound of formula I, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from 2.5 to 200 mg of the compound, or in sustained release form.

The compound of formula I additionally exhibits muscle relaxing activity, as indicated in standard animal tests, e.g. in rabbits in accordance with the method of Teschendorf et al [Arch. exp. Pharmacol. *266*, 467—468 1970)].

The compound is therefore further indicated for use as a myotonolytic for the treatment of spastic conditions and also as a muscle relaxant. This indicated use of the compound of formula I is the preferred use.

The compound of formula I may be administered in free base form or in acid addition salt form. Such acid addition salt forms have the same order of activity as the free base form. A representative pharmaceutically acceptable acid addition salt is the hydrochloride.

A pharmaceutical composition may comprise a compound of formula I, in free base or in acid addition salt form, in association with a pharmaceutical carrier or diluent.

Such compositions may be made in conventional manner to be in the form of, for example, a tablet.

In the following non-limitative Examples all temperatures are indicated in degrees Centigrade, room temperatures is between 20 and 30°C, unless otherwise indicated. The chloroform solutions are dried either with sodium sulphate (anhydrous) or Sikkon (Trade Mark).

EXAMPLE 1

5 - chloro - 4 - (2 - imidazolin - 2 - yl - amino) - 2,1,3 - benzothiadiazole

9.8 g of S - methyl - N - (5 - chloro - 2,1,3 - benzothiadiazol - 4 - yl)isothiuronium iodide are heated to the boil at reflux for one hour together with 50 cc of methanol and 1.8 cc of ethylene diamine. The solvent is then removed by evaporation and the moist residue is boiled at reflux for one hour together with 20 cc of n - amyl alcohol. The mixture is subsequently shaken with 500 cc of chloroform and 150 cc of water until all the material is dissolved. 40 cc of a 2N aqueous sodium hydroxide solution are added to the aqueous phase and extraction is effected with 200 cc of chloroform. The organic phase is dried and concentrated by evaporation. After recrystallizing the residue from methanol with the addition of some active charcoal, 4 - (2 - imidazolin - 2 - yl - amino) - 5 - chloro - 2,1,3 - benzothiadiazole, having a M.P. of 221—223°C, is obtained.

The starting material used in this Example is obtained as follows:

14 cc of benzoyl chloride are added to a solution of 11.5 g of ammonium thiocyanate in 150 cc of acetone in an ice bath and the mixture is then stirred for 10 minutes. This solution is heated to the boil at reflux together with 19 g of 4 - amino - 5 - chloro - 2,1,3 - benzothiadiazole. The solution is cooled to room temperature and diluted with a 4-fold quantity of water. The precipitate is filtered off and rapidly brought to a boil together with 150 cc of 2N aqueous sodium hydroxide solution and kept at the boil for 5 minutes. The solution is cooled to room temperature, is acidified weakly with glacial acetic acid, the precipitate is filtered off, washed with ether and recrystallized from methanol.

The N - (5 - chloro - 2,1,3 - benzothiadiazol - 4 - yl) thiourea, obtained in this manner, is boiled for one hour together with 9 g of methyl iodide in 150 cc of methanol, and the mixture is then evaporated to dryness. Crude S - methyl - N - (5 - chloro - 2,1,3 - benzothiadiazol - 4 - yl)isothiuronium iodide is obtained and is used for the above reaction without purification.

EXAMPLE 2

5 - chloro - 4 - (2 - imidazolin - 2 - yl - amino) - 2,1,3 - benzothiadiazole

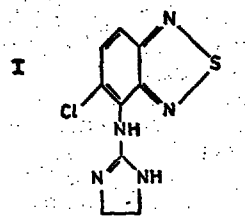
12 g of 5 - chloro - 4 - cyanamino - 2,1,3 - benzothiadiazole are heated to the boil at reflux for 2 hours together with 28 g of ethylene - diamine - mono - *p* - toluenesulphonate in 300 cc of n - pentanol. The solvent is then removed by evaporation. The residue is taken up in 300 cc of methanol whilst hot, the solution is rendered alkaline with a 2N caustic soda solution, is diluted with a two-fold volume of water and subsequently concentrated to half its volume. The precipitate obtained after cooling is separated, washed with water and stirred twice with 300 cc amounts of ether and filtered. After recrystallization from methanol, 5 - chloro - 4 - (2 - imidazolin - 2 - yl - amino) - 2,1,3 - benzothiadiazole, having a M.P. of 221—223°C, is obtained.

The starting material used in this Example is obtained as follows:

15 g of N - (5 - chloro - 2,1,3 - benzothiadiazol - 4 - yl) thiourea (M.P. 193—194°) are suspended in 120 cc of water and heated to the boil. The boiling solutions of 35 g of potassium hydroxide in 90 cc of water and of 28 g of lead acetate in 65 cc of water are then added thereto. The mixture is stirred vigorously for 5 minutes and is rapidly filtered. The filtrate is cooled and acidified weakly with glacial acetic acid. The precipitate is 5 - chloro - 4 - cyanamino - 2,1,3 - benzothiadiazole (M.P. 215—220°), which is used for the above reaction without further purification.

WHAT WE CLAIM IS:—

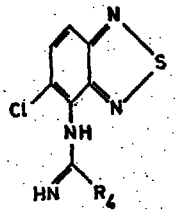
1. A process for the production of a compound of formula I,



I

which is 5 - chloro - 4 - (2 - imidazolin - 2 - yl - amino) - 2,1,3 - benzothiadiazole, which comprises

a) reacting a compound of formula II,

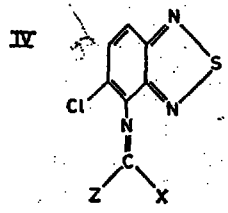


II

wherein R_4 is a reactive group other than halogen, capable of being split off with a hydrogen atom of an amine, with ethylene diamine.

2. A process for the production of a compound of formula I, defined in claim 1, which comprises

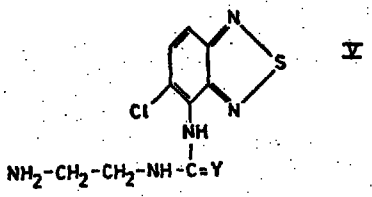
b) reacting a compound of formula IV,



IV

wherein each of X and Z is, independently, a reactive group capable of being split off with the hydrogen atom of an amine, with the proviso that when X is halogen Z is halogen, with ethylene diamine, or

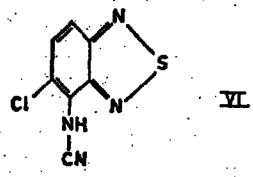
c) subjecting a compound of formula V,



V

wherein Y is oxygen or sulphur, to a ring closure, or

d) reacting a compound of formula VI,



VI

3. A process for the production of a compound of formula I, defined in claim 1, substantially as herein before described with reference to Example 1.

4. A process for the production of a compound of formula I, defined in claim 1, substantially as herein before described with reference to Example 2.

5. A compound of formula I whenever produced by a process as claimed in any one of the preceding claims.

6. A compound of formula I as defined in claim 1.

7. A compound according to claim 5 or 6 in free base form.

8. A compound according to claim 5 or 6 in acid addition salt form.

9. A pharmaceutical composition comprising a compound according to claim 5 or 6 in free base form or in pharmaceutical acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

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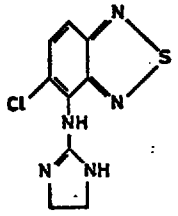
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15 g of N - (5 - chloro - 2,1,3 - benzothiadiazol - 4 - yl) thiourea (M.P. 193—194°) are suspended in 120 cc of water and heated to the boil. The boiling solutions of 35 g of potassium hydroxide in 90 cc of water and of 28 g of lead acetate in 65 cc of water are then added thereto. The mixture is stirred vigorously for 5 minutes and is rapidly filtered. The filtrate is cooled and acidified weakly with glacial acetic acid. The precipitate is 5 - chloro - 4 - cyanamino - 2,1,3 - benzothiadiazole (M.P. 215—220°), which is used for the above reaction without further purification.

WHAT WE CLAIM IS:—

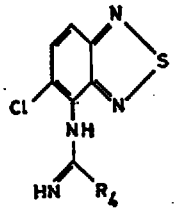
1. A process for the production of a compound of formula I,



I

which is 5 - chloro - 4 - (2 - imidazolin - 2 - yl - amino) - 2,1,3 - benzothiadiazole, which comprises

a) reacting a compound of formula II,

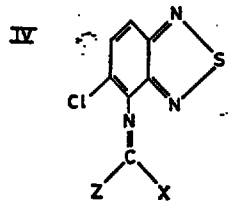


II

wherein R_4 is a reactive group other than halogen, capable of being split off with a hydrogen atom of an amine, with ethylene diamine.

2. A process for the production of a compound of formula I, defined in claim 1, which comprises

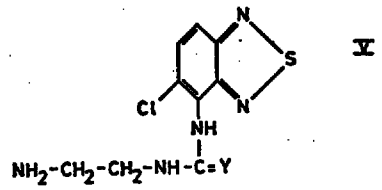
b) reacting a compound of formula IV,



IV

wherein each of X and Z is, independently, a reactive group capable of being split off with the hydrogen atom of an amine, with the proviso that when X is halogen Z is halogen, with ethylene diamine, or

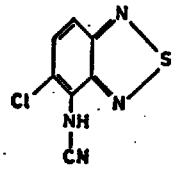
c) subjecting a compound of formula V,



V

wherein Y is oxygen or sulphur, to a ring closure, or

d) reacting a compound of formula VI,



VI

3. A process for the production of a compound of formula I, defined in claim 1, substantially as herein before described with reference to Example 1.

4. A process for the production of a compound of formula I, defined in claim 1, substantially as herein before described with reference to Example 2.

5. A compound of formula I whenever produced by a process as claimed in any one of the preceding claims.

6. A compound of formula I as defined in claim 1.

7. A compound according to claim 5 or 6 in free base form.

8. A compound according to claim 5 or 6 in acid addition salt form.

9. A pharmaceutical composition comprising a compound according to claim 5 or 6 in free base form or in pharmaceutical acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

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