

PATENT SPECIFICATION

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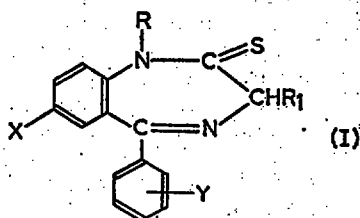


(54) NOVEL BENZODIAZEPINES AND PROCESS FOR THEIR MANUFACTURE

(71) We, SCHERICO LTD., of Topferstrasse 5, Lucerne, Switzerland, a body corporate constituted under the laws of Switzerland, 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:—

This invention relates to novel substituted benzodiazepines, to their preparation and to compositions containing such compounds.

The present invention provides in one of its aspects novel 1 - (polyfluoroalkyl) - 5 - aryl - 2H - 1, 4 - benzodiazepin - 2 - thione compounds. More specifically the compounds of the present invention are novel 1,4-benzodiazepine compounds of the general formula



and the 4 - N - oxides and the pharmaceutically acceptable salts thereof, wherein, in the formula I, X is halogen, a trifluoromethyl group or a nitro group, Y is hydrogen, halogen, trifluoromethyl, nitro, hydroxy, lower alkyl or lower alkoxy, R is polyfluoro-lower alkyl, and R₁ is hydrogen or lower alkyl.

The term "lower alkyl" as used herein means a straight, branched-chain or cyclic saturated hydrocarbon radical having up to six carbon atoms. Examples include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl and cyclopropylmethyl. The term "lower alkoxy" as used herein means a - O - lower alkyl radical, wherein the lower alkyl moiety is as defined above. Examples include methoxy, ethoxy and propoxy. The term "halogen" as used herein comprehends fluorine, chlorine, bromine and iodine. Chloro is the preferred X substituent and ortho-fluoro is the preferred Y substituent.

[Price 25p]

The term "polyfluoro-lower alkyl" means a lower alkyl radical (wherein the term "lower alkyl" is as defined above) substituted with more than one fluoro radical. Examples of such radicals include 2,2,2-trifluoroethyl, trifluoromethyl, 2,2,3,3,3-pentafluoropropyl, 3,3,3-trifluoropropyl and tetrafluorocyclopropylmethyl. In a preferred embodiment of this invention the polyfluoro-lower alkyl moiety has two alpha hydrogen atoms, i.e. R₁CH₂— wherein R₁ is polyfluoroalkyl. Most preferably, R₁ is trifluoromethyl and accordingly R in formula I is a 2,2,2-trifluoroethyl group.

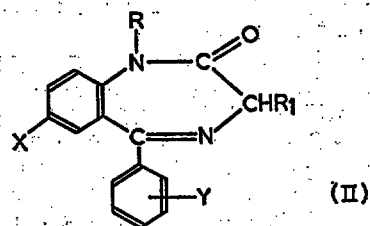
A preferred compound of this invention is 7 - chloro - 1 - (2,2,2 - trifluoroethyl) - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepin - 2 - thione.

The pharmaceutically acceptable salts of the compounds of the general formula I include acid addition salts formed in conventional manner from both organic and inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, acetic acid, formic acid, succinic acid, maleic acid and p-toluenesulfonic acid.

The compounds of the present invention exert an effect on mammalian central nervous systems and as such are useful as sedatives, anti-anxiety agents and anti-convulsants.

The compounds of the present invention may be prepared by the use of methods known for the preparation of previously described compounds having similar structure.

Thus a benzodiazepin - 2 - one of the general formula II



may be treated with a suitable thiating agent,

preferably with phosphorus pentasulphide, to give the required compound of the general formula I. The reaction is conveniently carried out in an inert medium at elevated temperature. Typically, the inert medium is an inert organic solvent such as dioxane, pyridine, dimethylaniline, tetralin, quinoline, xylenes and the like solvents, and reaction is effected under reflux conditions.

- 5 Isolation and purification of the required product of the formula I may be effected using known techniques. Where desired, the product may be converted prior or subsequent to isolation into a corresponding 4 - N - oxide and/or a pharmaceutically acceptable salt using conventional techniques.

- 10 The benzodiazepin - 2 - one starting materials of the general formula II may be obtained by, for example, the methods disclosed in Belgian Patent No. 692,621. The benzodiazepin - 2 - one starting materials may also be obtained by oxidation of the corresponding 2,3-dihydrobenzodiazepines disclosed in our co-pending Patent Application No. 21325/71 (Serial No. 1,297,206) with a suitable oxidising agent such as ruthenium tetroxide or chromium trioxide.

- 15 The following examples illustrate the preparation of representative compounds of this invention.

Example 1

- 20 Preparation of 7 - chloro - 1 - (2,2,2 - trifluoroethyl) - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - thione
- 25 To a solution of 25.0 grams of 7 - chloro - 1 - (2,2,2 - trifluoroethyl) - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one (0.071 mole) in 250 ml. of p-dioxane is added 17.31 grams of phosphorus pentasulphide (0.078 mole). The mixture is refluxed for 5 hours and then the solvent is removed under reduced pressure. The residue is diluted with methylene chloride and filtered through 375 grams of alumina; the same solvent is used for elution. The impure product thus obtained is then chromatographed on 1 kilogram of silica gel, using benzene as the eluant. The pure product is recrystallised from methylene chloride-cyclohexane and yields 8.73 grams of the title compound, m.p. 169—170°C.

Example 2

- 30 Preparation of 7 - chloro - 1 - (2,2,2 - trifluoroethyl) - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepin - 2 - thione
- 35 To a solution of 1.8 grams 7 - chloro - 1,3 - dihydro - 5 - o - fluorophenyl - 1 - (2,2,2 - trifluoroethyl) - 2H - 1,4 - benzodiazepin - 2 - one (0.005 mole) in 20 ml. of anhydrous p-dioxane is added 1.1 gram phosphorus pentasulphide (0.005 mole). The mixture is boiled under reflux for 4 hours with a calcium chloride drying tube to protect from atmospheric moisture. The solu-

tion is evaporated in vacuo. The residue is dissolved in methylene chloride and filtered through 200 grams of silica gel in a column. After concentration of the filtrate the residue is crystallised from methylene chloride-hexane and yields 1.2 grams of the title compound, m.p. 137.5—139°C.

In a similar manner by substituting the corresponding 1 - polyfluoroalkyl - 1,4 - benzodiazepin - 2 - one in the process of Example 1, one can prepare:

7 - Nitro - 1 - (2,2,2 - trifluoroethyl) - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepin - 2 - thione;

7 - Chloro - 1 - (2,2,2 - trifluoroethyl) - 1,3 - dihydro - 5 - (2 - chlorophenyl) - 2H - 1,4 - benzodiazepin - 2 - thione;

7 - Bromo - 1 - (2,2,3,3 - tetrafluorocyclopropyl) - methyl - 1,3 - dihydro - 5 - (3 - trifluoromethylphenyl) - 2H - 1,4 - benzodiazepin - 2 - thione;

7 - Trifluoromethyl - 1 - (2,2 - difluoroethyl) - 1,3 - dihydro - 5 - (3 - nitrophenyl) - 2H - 1,4 - benzodiazepin - 2 - thione;

7 - Fluoro - 1 - (3,3,3 - trifluoropropyl) - 1,3 - dihydro - 5 - (p - tolyl) - 2H - 1,4 - benzodiazepin - 2 - thione;

7 - Iodo - 1 - (2,2,3,3,3 - pentafluoropropyl) - 1,3 - dihydro - 3 - methyl - 5 - (p - anisyl) - 2H - 1,4 - benzodiazepin - 2 - thione.

The compounds of this invention exert an effect on the mammalian central nervous system as determined by standard pharmacological evaluation and as such are useful as sedative-hypnotic, tranquiliser and anti-anxiety agents. Additionally, they exhibit valuable anti-convulsant properties. In pharmacological testing there has been observed significant differentials between sedative doses and doses which cause neuro-logical impairment, e.g. ataxia.

Based upon standard laboratory investigative procedures such as the Antagonism of Pentylene Tetrazole, Everett and Richard, J. Pharm. and Exp. Ther., Vol. 81, pg. 402 (1944) and Antagonism of Maximal Electro-Shock-Induced Seizures in Mice, Synward, E. A. et al., J. Pharm. and Exp. Ther., Vol. 106, pg. 319 (1952) for anti-convulsant activity; the Central Nervous System Activity and Acute Toxicity, Irwin, Science 136, pg. 123 (1962) for sedative-hypnotic activities; and Antagonism of Foot-Shock Induced Fighting in Mice, Tedeschi, et al., J. Pharm. and Exp. Ther., Vol. 125, pg. 28 (1959) and Taming Activity in Monkeys, Randall, Diseases of the Nervous System, Vol. 21, pg. 7 (1960) for anti-anxiety activity; it is found that when used as an anti-anxiety agent the dosage range is about 0.03 to 3 mg/kg. of body weight per day, preferably administered orally in divided dosages. When used as an anti-convulsant the dosage range is about

0.005 to 0.5 mg/kg. of body weight per day, preferably orally administered in divided doses. When used as a sedative-hypnotic the dosage range is about 0.06 to 2.5 mg/kg. of body weight preferably orally administered in a single dose.

The compounds of this invention may be administered alone or combined with other medicaments. In any event, a suitable pharmaceutically acceptable carrier is generally employed. A carrier is selected according to the route of administration to be used as well as according to the physical properties of the compounds and standard pharmaceutical practice. It should not react chemically with the compound to be administered. In a preferred embodiment the compositions of this invention are administered orally, although parenteral and topical administration are also contemplated. The preparations containing the active ingredients of this invention may be in the form of tablets, capsules, syrups, elixirs, suspensions and the like.

In the formulations of pharmaceutical preparations there can be employed such pharmaceutically acceptable diluents as for example, water, gelatin, lactose, starches, magnesium stearate, talc, vegetable oils and gums. The following examples illustrate typical tablet and capsule formulations incorporating the compounds of this invention. The formulations are merely illustrative and no limitation is intended.

Tablet Formulations

I. Formula and method of manufacture for 7 - chloro - 1 - (2,2,2 - trifluoroethyl) - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepin - 2 - thione.

Coated Tablets	mg/core
7 - Chloro - 1 - (2,2,2 - trifluoroethyl) - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepin - 2 - thione	4
Lactose, USP	62
Dicalcium Phosphate	40
Sodium Lauryl Sulfate	10
Polyvinylpyrrolidone	10
Water 50 ml/1000 cores	
Corn Starch	20
Dry	
Sodium Lauryl Sulfate	2
Magnesium Stearate	2

Tablet Weight 150

Procedure

The 7 - chloro - 1 - (2,2,2 - trifluoroethyl) - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepin - 2 - thione is mixed with the lactose, dicalcium phosphate, and sodium lauryl sulfate. The above mixture is screened through a No. 60 screen and granulated with an aqueous solution con-

taining polyvinylpyrrolidone. Add additional water, if necessary, to bring powders to a pasty mass. Add corn starch and continue mixing until uniform granules are formed. Pass through a No. 10 screen, tray and dry in oven at 100°C for 12—14 hours. Reduce the dried granulation through a No. 16 screen, add sodium lauryl sulfate and magnesium sulfate, mix and compress into desired shape on a tablet machine.

Coating

The above cores are treated with a lacquer and dusted with talc to prevent moisture absorption. Sub-coat layers are added to round out the core. A sufficient number of lacquer coats are applied to make the core enteric. Additional sub-coats and smoothing coats are applied to completely round out and smooth the tablet. Colour coats are applied until the desired shade is obtained. After drying, the coated tablets are polished to give the tablets an even gloss.

II. Capsule Formulations

Formula	mg/capsule
7 - Chloro - 1 - (2,2,2 - trifluoroethyl) - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepine - 2 - thione	4
Sodium Lauryl Sulfate	20
Lactose	150
Magnesium Stearate	76
	250

Procedure

Mix together 7 - chloro - 1 - (2,2,2 - trifluoroethyl) - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepin - 2 - thione, sodium lauryl sulfate and lactose. Pass through a No. 80 screen. Add magnesium stearate, mix and encapsulate into the proper size two-piece gelatin capsule.

III. Suppository

Formula	mg/2gs.
7 - Chloro - 1 - (2,2,2 - trifluoroethyl) - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepin - 2 - thione, micronized	8
Theobroma Oil, Pharm. Grade to make	2 gms.

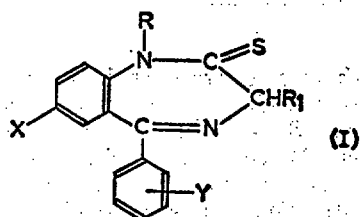
Method of Preparation

Prepare a slurry of the 7 - chloro - 1 - (2,2,2 - trifluoroethyl) - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepin - 2 - thione with a portion of the melted theobroma oil to bring the batch to final weight. Pour the melted mix, while maintaining uniformity, into appropriately prepared molds and allow to cool.

Numerous variations of the above compositions of matter and processes for the manufacture will be apparent to one skilled in the art within the present invention.

5 WHAT WE CLAIM IS:—

1. A 1,4-benzodiazepine compound of the general formula I



wherein, in the formula I, X is a halogen, trifluoromethyl or nitro, Y is hydrogen, halogen, trifluoromethyl, nitro, hydroxy, lower alkyl (as defined herein) or lower alkoxy (as defined herein), R is polyfluoro-lower alkyl (as defined herein) and R₁ is hydrogen or lower alkyl (as defined herein).

2. A compound according to claim 1, wherein R is a 2,2,2-trifluoroethyl group.

3. A compound according to claim 1 or claim 2, wherein X is chloro.

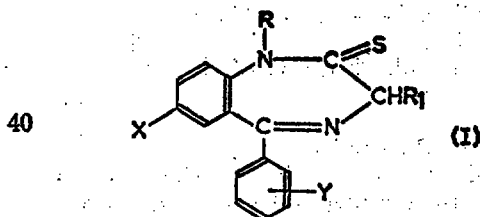
4. A compound according to any one of claims 1 to 3, wherein Y is an ortho-fluoro-substituent.

5. A 4 - N - oxide of a compound according to any preceding claim.

6. A pharmaceutically acceptable salt of a compound according to any one of claims 1 to 4 or of a 4 - N - oxide as claimed in claim 5.

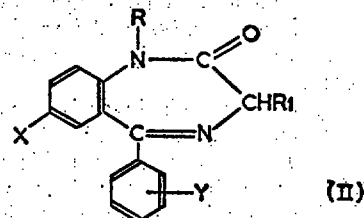
7. 7 - Chloro - 1 - (2,2,2 - trifluoroethyl) - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepin - 2 - thione, its 4 - N - oxide or a pharmaceutically acceptable salt of 7 - chloro - 1 - (2,2,2 - trifluoroethyl) - 1,3 - dihydro - 5 - (2 - fluorophenyl) - 2H - 1,4 - benzodiazepin - 2 - thione or of its 4 - N - oxide.

8. Process for the preparation of a 1,4-benzodiazepine compound of the general formula I



or of a 4 - N - oxide thereof or of a pharmaceutically acceptable salt of said 1,4-benzodiazepine compound or of said 4 - N - oxide, wherein in the formula I X, Y, R and R₁ are

as defined in Claim 1, which comprises treating a compound of the general formula II



wherein X, Y, R and R₁ are as defined in claim 1, with a thiating agent and, if desired, transforming the so-obtained compound of the general formula I into a corresponding 4 - N - oxide and/or a pharmaceutically acceptable salt.

9. Process according to claim 8 wherein the thiating agent is phosphorus pentasulphide.

10. Process for the preparation of a 1,4-benzodiazepine compound of the formula I, or a 4 - N - oxide of said compound or a pharmaceutically acceptable salt of said compound or 4 - N - oxide substantially as hereinbefore described and exemplified.

11. A 1,4-benzodiazepine compound of the general formula I, or a 4 - N - oxide of said compound or a pharmaceutically acceptable salt of said compound or 4 - N - oxide whenever obtained by a process according to any one of claims 8 to 10.

12. A pharmaceutical composition comprising as an active ingredient a compound as claimed in any one of claims 1 to 7 and 11 in admixture with a suitable pharmaceutically acceptable carrier.

13. Process for the preparation of a pharmaceutical composition which comprises bringing a compound as claimed in any one of claims 1 to 7 and 11 into a form suitable for therapeutic administration.

14. Process according to claim 13, which comprises admixing the compound as claimed in any one of claims 1 to 7 and 11 with a suitable pharmaceutically acceptable carrier.

15. Process for the preparation of a pharmaceutically acceptable composition according to claim 13 and substantially as hereinbefore described and exemplified.

16. A pharmaceutical composition whenever prepared by a process according to any one of claims 13 to 15.

17. A pharmaceutical composition according to claim 12 or claim 16 in the form of a solid shaped dosage unit.

18. A pharmaceutical composition as claimed in claim 17, wherein the dosage unit is a tablet.

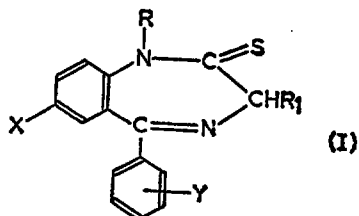
19. A pharmaceutical composition as claimed in claim 17, wherein the dosage unit is a capsule.

20. A pharmaceutical composition accord-

Numerous variations of the above compositions of matter and processes for the manufacture will be apparent to one skilled in the art within the present invention.

5 WHAT WE CLAIM IS:—

1. A 1,4-benzodiazepine compound of the general formula I



10 wherein, in the formula I, X is a halogen, trifluoromethyl or nitro, Y is hydrogen, halogen, trifluoromethyl, nitro, hydroxy, lower alkyl (as defined herein) or lower alkoxy (as defined herein), R is polyfluoro-lower alkyl (as defined herein) and R₁ is hydrogen or lower alkyl (as defined herein).

15 2. A compound according to claim 1, wherein R is a 2,2,2-trifluoroethyl group.

3. A compound according to claim 1 or claim 2, wherein X is chloro.

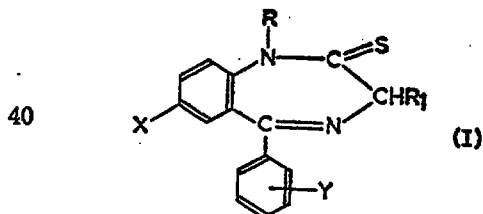
20 4. A compound according to any one of claims 1 to 3, wherein Y is an ortho-fluoro-substituent.

5. A 4-N-oxide of a compound according to any preceding claim.

25 6. A pharmaceutically acceptable salt of a compound according to any one of claims 1 to 4 or of a 4-N-oxide as claimed in claim 5.

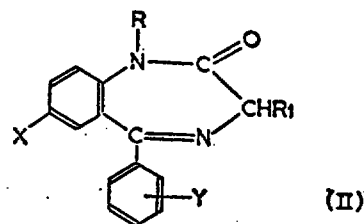
30 7. 7-Chloro-1-(2,2,2-trifluoroethyl)-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-thione, its 4-N-oxide or a pharmaceutically acceptable salt of 7-chloro-1-(2,2,2-trifluoroethyl)-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-thione or of its 4-N-oxide.

35 8. Process for the preparation of a 1,4-benzodiazepine compound of the general formula I



40 or of a 4-N-oxide thereof or of a pharmaceutically acceptable salt of said 1,4-benzodiazepine compound or of said 4-N-oxide, wherein in the formula I X, Y, R and R₁ are

as defined in Claim 1, which comprises treating a compound of the general formula II



wherein X, Y, R and R₁ are as defined in claim 1, with a thiating agent and, if desired, transforming the so-obtained compound of the general formula I into a corresponding 4-N-oxide and/or a pharmaceutically acceptable salt.

9. Process according to claim 8 wherein the thiating agent is phosphorus pentasulphide.

10. Process for the preparation of a 1,4-benzodiazepine compound of the formula I, or a 4-N-oxide of said compound or a pharmaceutically acceptable salt of said compound or 4-N-oxide substantially as hereinbefore described and exemplified.

11. A 1,4-benzodiazepine compound of the general formula I, or a 4-N-oxide of said compound or a pharmaceutically acceptable salt of said compound or 4-N-oxide whenever obtained by a process according to any one of claims 8 to 10.

12. A pharmaceutical composition comprising as an active ingredient a compound as claimed in any one of claims 1 to 7 and 11 in admixture with a suitable pharmaceutically acceptable carrier.

13. Process for the preparation of a pharmaceutical composition which comprises bringing a compound as claimed in any one of claims 1 to 7 and 11 into a form suitable for therapeutic administration.

14. Process according to claim 13, which comprises admixing the compound as claimed in any one of claims 1 to 7 and 11 with a suitable pharmaceutically acceptable carrier.

15. Process for the preparation of a pharmaceutically acceptable composition according to claim 13 and substantially as hereinbefore described and exemplified.

16. A pharmaceutical composition whenever prepared by a process according to any one of claims 13 to 15.

17. A pharmaceutical composition according to claim 12 or claim 16 in the form of a solid shaped dosage unit.

18. A pharmaceutical composition as claimed in claim 17, wherein the dosage unit is a tablet.

19. A pharmaceutical composition as claimed in claim 17, wherein the dosage unit is a capsule.

20. A pharmaceutical composition accord-



ing to claim 12 or claim 16 in the form of a liquid solution or suspension.

21. A pharmaceutical composition as claimed in claim 20, wherein the liquid is sterile, for use as an injectable.
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