



PATENT SPECIFICATION

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COMPLETE SPECIFICATION

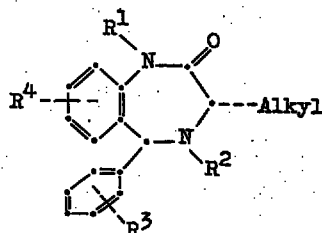
Benzodiazepine Derivatives and their manufacture

We, F. HOFFMANN-LA ROCHE & Co. Aktiengesellschaft, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we

5 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:

10 The present invention relates to novel benzodiazepine derivatives and the manufacture thereof; more particularly, it is concerned with novel 1,4-disubstituted 1,4-benzodiazepine derivatives and with a process for the manufacture thereof.

15 The novel 1,4-disubstituted 1,4-benzodiazepine derivatives provided by the invention are compounds of the general formula



20 wherein one of the symbols R¹ and R² stands for an N,N-disubstituted-aminoalkyl group of the formula (X)(Y)N-alkylene- in which the alkylene group contains from two to seven carbon atoms and in which X and Y are alkyl groups and the other symbol stands for an

25 alkyl group, the symbol R³ stands for a halogen atom, the symbol R⁴ stands for a halogen atom or a trifluoromethyl or nitro group. and the broken lines denote that the atoms or groups attached thereby are optional, and acid

30 addition salts thereof. The alkyl groups referred to herein are straight chain and branched chain alkyl groups containing up to seven carbon atoms; for example, the methyl, ethyl, propyl and

35 isopropyl groups.

The foregoing compounds and their pharmaceutically acceptable acid addition salts are useful as anticonvulsants, analgesics, sedatives and muscle relaxants; they can be used as

40 medicaments in the form of pharmaceutical preparations which contain one or more of the compounds or salts in association with a compatible pharmaceutical organic or inorganic, solid or liquid, carrier, suitable for enteral

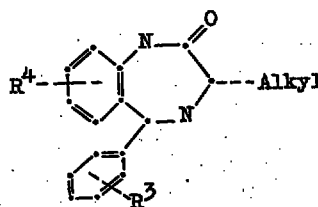
45 (e.g. oral) or parenteral administration. For making up the preparations there may be employed inert substances such as water, gelatin, lactose, starches, magnesium stearate, talc, vegetable oils, gums, polyalkylene-

50 glycols, petroleum jelly or any other compatible carrier useful for the preparation of medicaments. The pharmaceutical preparations may be in solid form (for example as tablets, dragées, suppositories or capsules) or

55 in liquid form (for example as solutions, emulsions or suspensions). If desired, they may be sterilized and/or contain auxiliary substances such as preserving agents, stabilizing agents, wetting or emulsifying agents,

60 salts for varying the osmotic pressure or buffers. They may also contain other therapeutically useful substances.

65 According to the process provided by the invention, the novel 1,4-disubstituted 1,4-benzodiazepine derivatives aforesaid are manufactured by treating a compound of the



which carries as a 1- or 4-substituent an alkyl

group, in the form of an N¹-(alkali-metal) derivative thereof in the case where the compound is N⁴-substituted, with a halide of the formula



in order to introduced the substituent (X)(Y)N-alkylene- at the 4- or 1-position and, if required, converting the product into an acid addition salt—in the foregoing formulae R³, R⁴, (X)(Y)N-alkylene- and the broken lines having the significance given earlier and 'halogen' standing for a chlorine, bromine or iodine atom.

Those 1-alkyl compounds used as starting materials for the process are claimed *per se* in the specification of our Letters Patent No. 972,968. Those 4-alkyl compounds used as starting materials for the process in which the 3-alkyl group is absent and R⁴ (when present) represents a halogen atom are claimed *per se* in the specification of our Letters Patent No. 988,634.

The introduction of an (X)(Y)N-alkylene-substituent at the 1-position is carried out using a 1-(alkali metal) derivative of an N⁴-alkyl substituted starting compound. The 1-sodio derivative is preferably used and this can be obtained by treating an N⁴-alkyl substituted starting compound with, for example, sodium methoxide or sodium hydride.

The treatment with the halide can be carried out in an inert organic solvent medium consisting of one or more inert organic solvents such as methanol, ethanol, N,N-dimethyl-formamide, benzene or toluene. The temperature and pressure are not critical and the treatment can be carried out either at room temperature and atmospheric pressure or at elevated temperatures and/or elevated pressures.

The novel 1,4-disubstituted 1,4-benzodiazepine derivatives provided by the invention form acid addition salts with acids. Suitable acids are inorganic acids (such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid and nitric acid) and organic acids (such as tartaric acid, salicylic acid, toluene-sulphonic acid, ascorbic acid, maleic acid, succinic acid, formic acid and acetic acid).

The invention also provides a modification of those acid addition salts of compounds of the first formula hereinbefore in which R² is an alkyl group, which modification comprises quaternary salts in which the acid addition moieties of the said salts are replaced by alkyl halide moieties. These quaternary salts can be obtained by treating a compound of the second formula hereinbefore in which an (X)(Y)N-alkylene substituent is present at the 1-position [many of which are claimed *per se* in the specification of our copending Application for Letters Patent No. 1040548 47911/

64 (now serial no:)] with an alkyl halide.

The following examples illustrate the process of the invention.

EXAMPLE 1

A) The preparation of the starting material:

The 7-chloro-4-methyl-5-(2-fluoro-phenyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone (2) starting material was prepared as described in the specification of our Letters Patent No. 988,634.

The sodio derivative of 7-chloro-4-methyl-5-(2-fluoro-phenyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2) was prepared by the slow addition of sodium methoxide in methanol (10 ml of a solution containing 4.35 mmol per ml) at 0°C to a stirred solution of 10 g of the parent compound in 60 ml of N,N-dimethyl-formamide. The mixture was stirred at ca 20°C for 0.25 hour and was then ready for use.

B) The process:

5.6 g (18.3 mmol) of the sodio derivative of 7-chloro-4-methyl-5-(2-fluoro-phenyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2) in 20 ml of N,N-dimethyl-formamide were added to a toluene solution of 36.6 mmol of 2-diethylamino-ethyl chloride. The resulting mixture was allowed to stand for 70 hours and was then concentrated to a small volume under reduced pressure. The residue was dissolved in 100 ml of methylene chloride, washed with 75 ml of water and with three 50 ml portions of saturated sodium chloride solution and then filtered through neutral alumina (grade 1). The filtrate was evaporated to dryness yielding a residue which, upon recrystallization from petroleum ether (boiling point 30°–60°C), was found to be 7-chloro-1-(2-diethylamino-ethyl)-5-(2-fluoro-phenyl)-4-methyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2) of melting point 83°–85°C.

The toluene solution of 2-diethylamino-ethyl chloride aforesaid was prepared as follows: Diethylamino-ethyl chloride hydrochloride was dissolved in cold dilute sodium hydroxide solution and diethylamino-ethyl chloride was extracted from the resulting solution using four portions of toluene. The toluene extracts were combined, dried with anhydrous sodium sulphate and filtered.

EXAMPLE 2

A) The preparation of the starting material:

A suspension of 0.3 g of platinum oxide in 30 ml of glacial acetic acid was hydrogenated. To the reduced catalyst, a solution of 4.6 g (15.1 mmol) of 7-chloro-1-methyl-5-(2-fluoro-phenyl)-2,3-dihydro-1H-1,4-benzodiazepinone-(2) in 45 ml of glacial acetic acid was added and the mixture hydrogenated to completion (338 ml, 15.1 mmol of hydrogen). The catalyst was removed by filtration and the acetic acid evaporated under reduced

pressure. The residue was taken up in 50 ml of methylene chloride and washed with two 20 ml portions of a 30% solution of sodium carbonate. The resulting solution was washed free from alkali, dried and concentrated. Recrystallization from an acetone/(petroleum ether) (boiling point 30°-60°C) mixture gave 7-chloro-5-(2-fluoro-phenyl)-1-methyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2) of melting point 125°-136°C.

B) *The process:*

A solution of 2.0 g (6.5 mmol) of 7-chloro-5-(2-fluoro-phenyl)-1-methyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2) in 10 ml of N,N-dimethyl-formamide was treated with a toluene solution of 5.3 g (34.8 mmol) of diethylamino-ethyl chloride. 1 g (66 mmol) of sodium iodide was added and the mixture was stirred at 50°C for 16 hours. Solvents were removed under reduced pressure and the residue dissolved in 75 ml of methylene chloride. The solution was washed, dried, filtered over 10 g of alumina and concentrated to dryness. The residue was dissolved in ether and hydrogen chloride. The product was filtered. Recrystallization from acetone gave 7-chloro-4-(2-diethylamino-ethyl)-5-(2-fluoro-phenyl)-1-methyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2) hydrochloride of melting point 186°-193°C.

EXAMPLE 3

A) *The preparation of the starting material:*

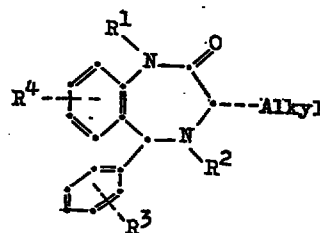
The 7-chloro-1-(2-diethylamino-ethyl)-5-(2-fluoro-phenyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2) starting material was prepared as described in the specification of our copending Application for Letters Patent No. 1040548 47911/64 (now Serial No.).

B) *The process:*

A mixture of 6 g (15.5 mmol) of 7-chloro-1-(2-diethylamino-ethyl)-5-(2-fluoro-phenyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2) and 8.8 g (62 mmol) of methyl iodide in 20 ml of N,N-dimethyl-formamide was stirred for 17 hours at ca 20°C. The mixture was poured into 1 litre of water and the product extracted into two 35 ml portions of methylene chloride. The methylene chloride extracts were combined, washed, dried and evaporated. The product was recrystallized from an acetone/ether mixture to give 7-chloro-1-(2-diethylamino-ethyl)-4-methyl-5-(2-fluoro-phenyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2) methiodide of melting point 185°-190°C.

WHAT WE CLAIM IS:—

1) Compounds of the general formula

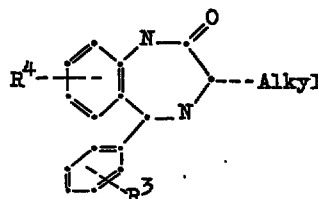


wherein one of the symbols R¹ and R² stands for an N,N-disubstituted-aminoalkyl group of the formula (X)(Y)N-alkylene- in which the alkylene group contains from two to seven carbon atoms and in which X and Y are alkyl groups and the other symbol stands for an alkyl group, the symbol R³ stands for a halogen atom, the symbol R⁴ stands for a halogen atom or a trifluoromethyl or nitro group and the broken lines denote that the atoms or groups attached thereby are optional, and acid addition salts thereof.

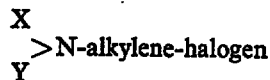
2) 7-Chloro-1-(2-diethylamino-ethyl)-4-methyl-5-(2-fluoro-phenyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2).

3) A pharmaceutical composition comprising one or more of the substances claimed in claim 1 hereof in association with a compatible pharmaceutical carrier.

4) A process for the manufacture of the substances claimed in claim 1 hereof, which process comprises treating a compound of the formula



which carries as a 1- or 4-substituent an alkyl group, in the form of an N¹-(alkali metal) derivative thereof in the case where the compound is N⁴-substituted, with a halide of the formula



in order to introduce the substituent (X)(Y)N-alkylene- at the 4- or 1-position and, if required, converting the product into an acid addition salt—in the foregoing formulae R³, R⁴, (X)(Y)N-alkylene- and the broken lines having the significance given in claim 1 and 'halogen' standing for a chlorine, bromine or iodine atom.

5) A process in accordance with claim 4,

pressure. The residue was taken up in 50 ml of methylene chloride and washed with two 20 ml portions of a 30% solution of sodium carbonate. The resulting solution was washed free from alkali, dried and concentrated. Recrystallization from an acetone/(petroleum ether) (boiling point 30°—60°C) mixture gave 7-chloro-5-(2-fluoro-phenyl)-1-methyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2) of melting point 125°—136°C.

B) The process:

A solution of 2.0 g (6.5 mmol) of 7-chloro-5-(2-fluoro-phenyl)-1-methyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2) in 10 ml of N,N-dimethyl-formamide was treated with a toluene solution of 5.3 g (34.8 mmol) of diethylamino-ethyl chloride. 1 g (66 mmol) of sodium iodide was added and the mixture was stirred at 50°C for 16 hours. Solvents were removed under reduced pressure and the residue dissolved in 75 ml of methylene chloride. The solution was washed, dried, filtered over 10 g of alumina and concentrated to dryness. The residue was dissolved in ether and hydrogen chloride. The product was filtered. Recrystallization from acetone gave 7-chloro-4-(2-diethylamino-ethyl)-5-(2-fluoro-phenyl)-1-methyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2) hydrochloride of melting point 186°—193°C.

EXAMPLE 3

A) The preparation of the starting material:

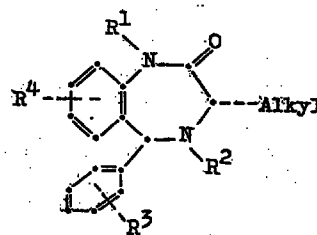
The 7-chloro-1-(2-diethylamino-ethyl)-5-(2-fluoro-phenyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2) starting material was prepared as described in the specification of our copending Application for Letters Patent No. 1040548 47911/64 (now Serial No.).

B) The process:

A mixture of 6 g (15.5 mmol) of 7-chloro-1-(2-diethylamino-ethyl)-5-(2-fluoro-phenyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2) and 8.8 g (62 mmol) of methyl iodide in 20 ml of N,N-dimethyl-formamide was stirred for 17 hours at ca 20°C. The mixture was poured into 1 litre of water and the product extracted into two 35 ml portions of methylene chloride. The methylene chloride extracts were combined, washed, dried and evaporated. The product was recrystallized from an acetone/ether mixture to give 7-chloro-1-(2-diethylamino-ethyl)-4-methyl-5-(2-fluoro-phenyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2) methiodide of melting point 185°—190°C.

WHAT WE CLAIM IS:—

1) Compounds of the general formula

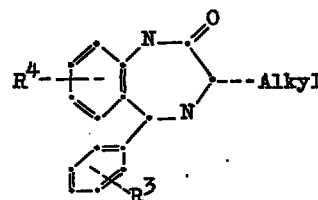


wherein one of the symbols R^1 and R^2 stands for an N,N-disubstituted-aminoalkyl group of the formula (X)(Y)N-alkylene- in which the alkylene group contains from two to seven carbon atoms and in which X and Y are alkyl groups and the other symbol stands for an alkyl group, the symbol R^3 stands for a halogen atom, the symbol R^4 stands for a halogen atom or a trifluoromethyl or nitro group and the broken lines denote that the atoms or groups attached thereby are optional, and acid addition salts thereof.

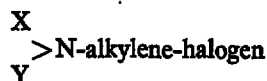
2) 7-Chloro-1-(2-diethylamino-ethyl)-4-methyl-5-(2-fluoro-phenyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepinone-(2).

3) A pharmaceutical composition comprising one or more of the substances claimed in claim 1 hereof in association with a compatible pharmaceutical carrier.

4) A process for the manufacture of the substances claimed in claim 1 hereof, which process comprises treating a compound of the formula



which carries as a 1- or 4-substituent an alkyl group, in the form of an N^1 -(alkali metal) derivative thereof in the case where the compound is N^4 -substituted, with a halide of the formula



in order to introduce the substituent (X)(Y)N-alkylene- at the 4- or 1-position and, if required, converting the product into an acid addition salt—in the foregoing formulae R^3 , R^4 , (X)(Y)N-alkylene- and the broken lines having the significance given in claim 1 and 'halogen' standing for a chlorine, bromine or iodine atom.

5) A process in accordance with claim 4,

wherein said N^1 -(alkali metal) derivative is the N^1 -sodio derivative.

5 6) A process for the manufacture of the substances claimed in claim 1, substantially as described with reference to part B of Examples 1 and 2.

10 7) Compounds as formulated in claim 1, and acid addition salts thereof, when manufactured by the process claimed in claim 4, claim 5 or claim 6.

8) A modification of the invention as

claimed in claim 1 insofar as it relates to acid addition salts of compounds in which R^2 stands for an alkyl group, which modification comprises quaternary salts in which the acid addition moieties of the salts of said claim are replaced by alkyl halide moieties. 15

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