

PATENT SPECIFICATION

NO DRAWINGS

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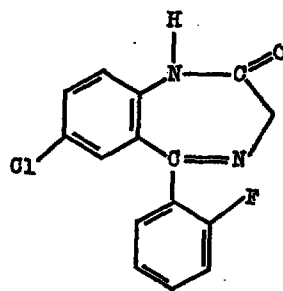
COMPLETE SPECIFICATION

Benzodiazepine Derivatives and a Process for the Manufacture Thereof

We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, 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:—

The present invention is concerned with benzodiazepine derivatives and a process for the manufacture thereof.

The benzodiazepine derivatives provided by the invention are compounds of the general formula



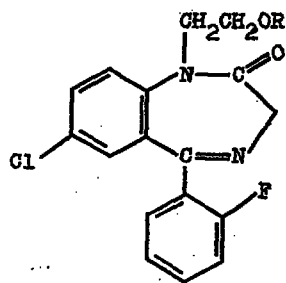
II

with a 2-haloethanol or with ethylene oxide, if desired, esterifying the compound obtained with an acid agent containing a lower alkanoyl moiety and, also if desired, transforming a product obtained in to an acid addition salt.

Preferred haloethanols are 2 - bromoethanol and 2 - chloroethanol. The reaction of the 1 - sodio derivative of the compound of formula II with a 2 - haloethanol is preferably effected in the presence of any suitable inert organic solvent. Preferred among the many inert organic solvents suitable for this purpose are lower alkanols such as methanol, ethers such as diethyl ether and tetrahydrofuran, N, N - dimethylformamide and dimethylsulfoxide.

As esterification agents, there can efficaciously be utilized acetic anhydride, acetyl chloride and propionyl chloride.

The esterification with an acyl halide or an acid anhydride is conducted in accordance with procedures conventional in the art and well documented in the literature.



I

wherein R represents hydrogen or lower alkanoyl and acid addition salts thereof.

The term lower alkanoyl connotes a moiety containing up to 7 carbon atoms either in a branched or straight chain such as acetyl, propionyl and butyryl.

The process of the present invention comprises reacting the 1-sodio derivative of the compound of the formula

[Price 5s. 0d.]

For example, with an acid anhydride (e.g. acetic anhydride) or with an acyl halide, the esterification can proceed to the desired ester by permitting the esterification medium to stand at room temperature, particularly if pyridine is utilized as the solvent medium.

As is evident from the foregoing, the particular conditions for esterifying the compound of formula I in which R is hydrogen are not critical and can be selected by one of ordinary skill in the art depending upon the agent used to provide the lower alkanoyl group, particularly when viewing the esterification desired in the light of the prior art on the subject. By a cursory perusal of the literature, one can readily ascertain the suitable reagents capable of functioning efficaciously in the formation of an ester of the formula I.

The esterification, as is evident from the foregoing, can be conducted in a conventional organic solvent such as dimethylformamide, pyridine or a hydrocarbon such as toluene. However, it is preferred to effect the esterification in the presence of pyridine. Moreover, it has been found that in the case where an alkanoyl anhydride is used as the agent providing the lower alkanoyl group, such alkanoyl anhydride can itself serve as the esterification medium. The esterification is preferably conducted at room temperature but it can also proceed to the desired product efficaciously at above or below room temperature depending upon the esterification agent utilized.

Compounds of formula I are useful as sedatives in view of their capability of inducing sleep. Said compounds or their pharmaceutically acceptable acid addition salts can be administered with dosage adjusted to individual requirements and fitted to the pharmaceutical exigencies of a situation. For example, they can be administered internally, i.e. enterally or parenterally, in the form of tablets, suspensions, solutions, capsules and dragees according to conventional pharmaceutical procedures. The invention also includes pharmaceutical preparations comprising a compound of formula I or a pharmaceutically acceptable acid addition salt thereof in association with a compatible pharmaceutical carrier.

The compounds of formula I form pharmaceutically acceptable acid addition salts with both inorganic and organic pharmaceutically acceptable acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, succinic acid, methanesulfonic acid and para-toluenesulfonic acid.

[2 - Hydroxy - (lower alkyl)] - benzodiazepines have been known in the art. However, no one has recognized the particular efficacious capability of the 1 - 2 - hydroxyethyl - 7 - chloro - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one of formula I above to function to induce sleep.

The discovery of this heretofore undisclosed compound within a known genus and its unusual ability to function as a particularly efficacious sedative constitutes the major part of the present invention.

The following examples are illustrative of the present invention. All temperatures are stated in degrees centigrade.

EXAMPLE 1

A solution of 10 g (0.0346 m) of 7 - chloro - 5 - (2 - fluoro - phenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one hydrochloride in 25 ml of N,N - dimethyl - formamide was treated with 10.6 ml of a solution containing 0.0415 m of sodium methoxide in methanol. The solution was stirred at room temperature for 30 minutes and 8.7 g (0.0692 m) of 2 - bromoethanol were added. The reaction mixture was heated at 80° for 2 hours and then poured into 200 ml of water. The reaction products were removed by filtration, dissolved in 100 ml of dichloromethane which was then washed with water (2×100 ml), saturated brine, dried over sodium sulfate and evaporated. The residual oil (10.5 g) was crystallized from ether and the ether medium was filtered. The mother liquors were evaporated, dissolved in benzene and filtered over 200 g of silica. The silica was eluted with ether until all impurities had been removed and 7 - chloro - 5 - (2 - fluorophenyl) - 1 - (2 - hydroxyethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one was then obtained by using methanol as the eluant.

Removal of the solvent gave the product as an oil. An excess of ethanolic hydrogen chloride was added, followed by ether to precipitate the salt. Three recrystallizations of the salt from a mixture of methanol and ether gave 7 - chloro - 1 - (2 - hydroxyethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one hydrochloride as pale yellow prisms, m.p. 194—196° dec.

EXAMPLE 2

A solution of 1 g (0.00346m) of 7 - chloro - 5 - (2 - fluorophenyl) - 3H - 1,4 - benzodiazepin - 2(1H) - one in 15 ml of dry N,N - dimethylformamide was treated with 0.9 ml (0.00415 m) of a 4.69 N solution of sodium methoxide in methanol. The mixture was stirred for 0.5 hour and then a solution of 0.45 g (0.0105 m) of ethylene oxide in 5 ml of dry N,N - dimethylformamide was added. The reaction mixture was stirred at room temperature for 2 hours and at 60° for 1 hour. Solvent was removed under reduced pressure and the residue was treated with 1.5 g (0.015 m) of succinic anhydride and 50 ml of toluene. The solution was heated under reflux for 3 hours, then cooled in an ice bath, made basic (pH 9) with ammonium hydroxide and the layers were separated. The aqueous layer was treated with 5 ml of 3N sodium

hydroxide solution and, after 30 minutes, the mixture was first acidified with concentrated hydrochloric acid and then made basic with ammonium hydroxide. The product was extracted into 100 ml of dichloromethane, which was then washed with 50 ml of saturated brine, dried over anhydrous sodium sulfate and evaporated to dryness.

The residual oil was dissolved in 15 ml of benzene and filtered through 50 g of silica gel. The silica gel was eluted with 200 ml of benzene and then with 250 ml of ethyl acetate. The ethyl acetate fraction was evaporated to dryness, dissolved in 5 ml of ethanol and treated with an excess of ethanolic hydrogen chloride. Ether was added and 7-chloro - 1 - (2 - hydroxyethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one hydrochloride was separated by filtration as pale yellow prisms melting at 195—197° (sealed tube).

EXAMPLE 3

A mixture of 2 g (0.00604 m) of 7-chloro - 5 - (2 - fluorophenyl) - 1 - (2 - hydroxyethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one, 20 ml of acetic anhydride and 3 g of potassium acetate was allowed to stand at room temperature for 16 hours and was then poured onto ice. The solution was made basic with saturated potassium carbonate solution and extracted with 2×100 ml of dichloromethane. The organic layers were combined, washed with saturated brine, dried over anhydrous sodium sulfate and evaporated to dryness. The product was crystallized from ether and then recrystallized from a mixture of dichloromethane and hexane to give 1 - (2 - acetoxyethyl) - 7 - chloro - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one as white prisms melting at 103—105°.

EXAMPLE 4

A capsule dosage form containing the following ingredients:

	Per Capsule
7 - Chloro - 5 - (2 - fluoro-phenyl) - 1 - (2 - hydroxy - ethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one	10 mg
Lactose	165 mg
Corn Starch	30 mg
Talc	5 mg

Total Weight 210 mg

was prepared as follows: 7 - Chloro - 5 - (2 - fluorophenyl) - 1 - (2 - hydroxyethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one, the lactose and the corn starch were mixed in a suitable mixer. The mixture was further blended by passing through a comminuting machine with a screen with knives

forward. The blended powder was returned to the mixer, the talc added and blended thoroughly. The mixture was filled into hard shell gelatin capsules on a capsulating machine.

EXAMPLE 5

A parenteral dosage formulation containing the following ingredients:

	Per ml	
7 - Chloro - 5 - (2 - fluoro - phenyl) - 1 - (2 - hydroxy - ethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one	5.0 mg	70
Propylene Glycol	0.4 ml	
Benzyl Alcohol (Benzaldehyde free)	0.015 ml	75
Ethanol 95 per cent	0.10 ml	
Sodium Benzoate	48.8 mg	
Benzoic Acid	1.2 mg	
Water for Injection q.s.	1.0 ml	

was prepared (for 10,000 ml) as follows: 50 g of 7 - chloro - 5 - (2 - fluorophenyl) - 1 - (2 - hydroxyethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one were dissolved in 150 ml of benzyl alcohol; 4,000 ml of propylene glycol and 1,000 ml of ethanol were added. 12 g of benzoic acid were dissolved in the resulting mixture. 48.9 g of sodium benzoate dissolved in 3,000 ml of Water for Injection were added. The solution was brought up to final volume of 10,000 ml with Water for Injection. The solution was filtered through a SELAS candle, filled into suitable size ampoules, gassed with nitrogen and sealed. It was then autoclaved at 0.7 atm. for 30 minutes. The word 'SELAS' hereinbefore is a Registered Trade Mark.

EXAMPLE 6

A tablet dosage formulation containing the following ingredients:

	Per Tablet	
7 - Chloro - 5 - (2 - fluoro - phenyl) - 1 - (2 - hydroxy - ethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one	25.00 mg	100
Dicalcium Phosphate Dihydrate, Unmilled	175.00 mg	105
Corn Starch	24.00 mg	
Magnesium Stearate	1.00 mg	

Total Weight 225.00 mg

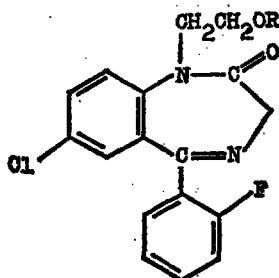
was prepared as follows: 7 - Chloro - 5 - (2 - fluorophenyl) - 1 - (2 - hydroxyethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one and corn starch were mixed together and passed through a screen with hammers forward. This premix was then mixed with dicalcium phosphate and one-half of the magnesium stearate, passed through a screen with

knives forward and slugged. The slugs were passed through a plate at slow speed with knives forward and the remaining magnesium stearate was added. The mixture was mixed and compressed.

Having regard to the provisions of Section 9 of the Patents Act, 1949, attention is directed to the claims of Patents Nos. 972,964 and 972,968.

10 WHAT WE CLAIM IS:—

1. Compounds of the general formula



wherein R represents hydrogen or lower alkanoyl, and acid addition salts thereof.

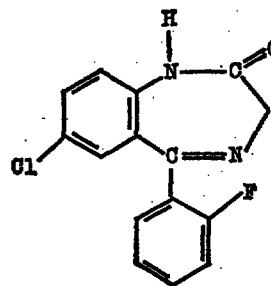
15 2. 7 - Chloro - 5 - (2 - fluorophenyl) - 1 - (2 - hydroxyethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

20 3. 1 - (2 - Acetoxyethyl) - 7 - chloro - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

4. A pharmaceutical preparation comprising a compound as claimed in claim 1 or a pharmaceutically acceptable acid addition salt thereof in association with a compatible pharmaceutical carrier.

25 5. A process for the manufacture of the benzodiazepine derivatives claimed in claim 1,

which process comprises reacting the 1 - sodio derivative of the compound of the formula



with a 2-haloethanol or with ethylene oxide, if desired, esterifying the compound obtained with an acid agent containing a lower alkanoyl moiety and, also if desired, transforming a product obtained into an acid addition salt.

35 6. A process according to claim 5, wherein 2 - chloroethanol or 2 - bromoethanol is used as the 2 - haloethanol.

40 7. A process according to claim 5 or claim 6, wherein R represents acetyl.

8. A process according to claim 5 or claim 6, wherein R represents hydrogen.

45 9. A process for the manufacture of the benzodiazepine derivatives claimed in claim 1, substantially as hereinbefore described with reference to Examples 1 to 3.

50 10. Benzodiazepine derivatives as claimed in claim 1, when manufactured by the process claimed in any one of claims 5 to 9 inclusive.

W. D. WHITTAKER,
Patent Agent.

For:

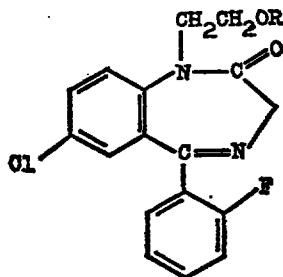
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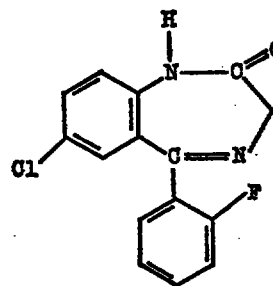
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20 3. 1 - (2 - Acetoxyethyl) - 7 - chloro - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

4. A pharmaceutical preparation comprising a compound as claimed in claim 1 or a pharmaceutically acceptable acid addition salt thereof in association with a compatible pharmaceutical carrier.

5. A process for the manufacture of the benzodiazepine derivatives claimed in claim 1,

which process comprises reacting the 1 - sodio derivative of the compound of the formula



with a 2-haloethanol or with ethylene oxide, if desired, esterifying the compound obtained with an acid agent containing a lower alkanoyl moiety and, also if desired, transforming a product obtained into an acid addition salt.

6. A process according to claim 5, wherein 2 - chloroethanol or 2 - bromoethanol is used as the 2 - haloethanol.

7. A process according to claim 5 or claim 6, wherein R represents acetyl.

8. A process according to claim 5 or claim 6, wherein R represents hydrogen.

9. A process for the manufacture of the benzodiazepine derivatives claimed in claim 1, substantially as hereinbefore described with reference to Examples 1 to 3.

10. Benzodiazepine derivatives as claimed in claim 1, when manufactured by the process claimed in any one of claims 5 to 9 inclusive.

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