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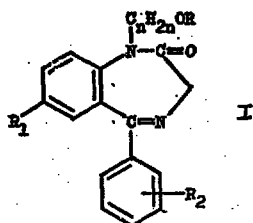
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(54) BENZODIAZEPINE DERIVATIVES AND A PROCESS FOR THE MANUFACTURE THEREOF

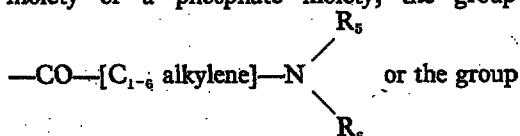
(71) We, HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following 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



wherein R₁ represents hydrogen, halogen, nitro or trifluoromethyl, R₂ represents hydrogen, halogen or nitro and R₃ represents halo-(lower alkanoyl), (lower alkoxy)-lower alkanoyl, aroyl, aryl-(lower alkanoyl), the monoacyl moiety of a dibasic acid, the acyl moiety of a lower alkenoic acid, a carbamate moiety, a sulfate moiety or a phosphate moiety, the group



—C_mH_{2m}OH, R₅ and R₆ represent hydrogen or lower alkyl or taken together with the

nitrogen atom a heterocyclic moiety containing at the most one additional nitrogen or oxygen atom and n and m are integers from 2—7, and salts thereof.

By the term “lower alkyl” as utilized herein, both straight and branched chain C₁—C₇, preferably C₁—C₄, alkyl group are intended such as methyl, ethyl, isobutyl and isopropyl. By the term “lower alkoxy”, there is similarly intended both straight and branched chain C₁—C₇, preferably C₁—C₄, alkoxy groups such as methoxy and ethoxy. The term “halogen” or “halide” as used herein is intended to connote all four forms thereof, i.e. chlorine, bromine, fluorine and iodine. The term “lower alkanoyl” connotes a moiety containing 1—7 carbon atoms, either in a branched or straight chain, such as methylcarbonyl, ethylcarbonyl and isopropylcarbonyl. The term “lower alkenoic acid” connotes an alkenoic acid containing 4—7 carbon atoms.

The radical —C_nH_{2n}— may be a straight or branched chain grouping such as ethylene, propylene, ethylethylene and pentamethylene.

Examples of halo-(lower alkanoyl) groups are haloacetyl, halopropionyl (e.g. 3-chloropropionyl) and halo-butyryl (e.g. 4'-chlorobutyryl) groups and examples of (lower alkoxy)-(lower alkanoyl) groups are methoxyacetyl and ethoxyacetyl.

An aroyl group may be represented preferably by benzoyl or substituted benzoyl such as (lower alkyl)-benzoyl, p-(lower alkyl)-benzoyl, di(lower alkoxy)-benzoyl such as dimethoxy-benzoyl and tri(lower alkoxy)-benzoyl such as trimethoxy-benzoyl. Aroyl may be further illustrated by the acyl group of heterocyclic acids such as picolinic acid, isonicotinic acid and nicotinic acid which may be unsubstituted or substituted with such groupings as lower alkoxy, halo and lower alkyl. Represent-



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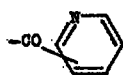
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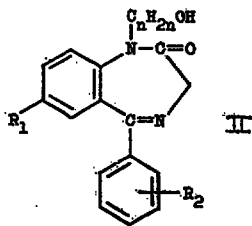
tative of substituted heterocyclic acids suitable for the proposes of the present invention are (lower alkoxy)-nicotinic acids (e.g. 2-methoxy-nicotinic acid), halo-nicotinic acids (e.g. 2-, 4- or 5-bromonicotinic acid and 3-(lower alkyl)-isonicotinic acids. The term "aryl-(lower alkanoyl)" is illustrated by phenyl-acetyl. By the expression, "a monoacyl moiety of a dibasic acid" as utilized herein, there is intended the monoacyl moiety of a C_6-C_7 dibasic alkenoic acid such as acid succinyl and the monoacyl moiety of a C_4-C_7 dibasic alkenoic acid such as acid maleyl and acid glutaconoyl. Salts of the latter can be formed with any suitable base such as an alkali metal alkoxide (e.g. sodium methoxide). A carbamate moiety i.e. a group of the formula $-\text{CONH}-(\text{lower alkyl})$, can be provided by utilizing a (lower alkyl) isocyanate such as methyl isocyanate when esterifying a compound of formula II hereinafter. R as the phosphate grouping or a sulfate group can be conveniently provided by esterifying a compound of formula II with polyphosphoric acid, phosphorus oxychloride, ethyl thiophosphate or concentrated sulfuric acid.

In formula I, R_1 preferably represents nitro or halogen, most suitably, chlorine. If R_2 represents other than hydrogen, it preferably represents halogen, most suitably, fluorine or chloride in the 2-position of the 5-phenyl ring. In a further preferred aspect, n is 2. In another preferred embodiment R_1 represents chlorine, R_2 represents fluorine in the 2-position n is 2 and R represents an aroyl group, preferably



an aryl-(lower alkanoyl) group, a carbamate moiety or the moiety of a dibasic acid.

According to the process provided by the present invention, the benzodiazepine derivatives aforesaid are manufactured by treating a compound of the general formula

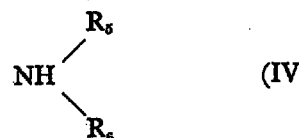


wherein R_1 , R_2 and n have the significance given earlier, with an acid agent containing a halo-(lower alkanoyl), (lower alkoxy)-(lower alkanoyl), aroyl or aryl-(lower alkanoyl) group or a monoacyl moiety of a dibasic acid, an

acyl moiety of a lower alkenoic acid, a carbamate, sulfate or phosphate moiety or with a diol of the general formula



wherein m has the significance given earlier, if desired, treating a compound obtained wherein R represents a halo-(lower alkanoyl) group with a compound of the general formula



wherein R_1 and R_2 have the significance given earlier, and, if desired, transforming a product obtained into a salt.

The compounds of formula II in which R_1 represents hydrogen or halogen are claimed per se in the specification of our Letters Patent No. 972,968. The compound of formula II in which R_1 represents chlorine, R_2 represents hydrogen and the 2-hydroxy-propyl group is present in the 1-position is claimed per se in the specification of our Letters Patent No. 1,102,934. The compound of formula II in which R_1 represents chlorine, R_2 represents hydrogen and the 3-hydroxy-propyl group is present in the 1-position is claimed per se in the specification of our Letters Patent No. 1,106,039. The compound of formula II in which R_1 represents chlorine, R_2 represents fluorine in the 2-position of the 5-phenyl ring and a 2-hydroxy-ethyl group is present in the 1-position is claimed per se in the specification of our copending Application for Letters Patent No. 1,192,729.

Examples of acid agents suitable for effecting the esterification of compounds of formula II include isonicotinoyl chloride, benzoyl chloride, 4-methyl benzoyl chloride, 3,4,5-trimethoxybenzoyl chloride, succinic anhydride, isonicotinic acid, picolinic acid, maleic anhydride, glutaconic acid anhydride, methyl isocyanate, ethyl isocyanate, strong inorganic acids such as acid phosphates, e.g. polyphosphoric acid, ethyl thiophosphate, phosphorus oxychloride and acid sulfates such as concentrated sulfuric acid.

As is evident from the foregoing, also suitable as acid agents are organic acids which are substituted with halogen, lower alkyl or lower alkoxy. Representative of these are haloacetic acids such as chloroacetic acid, (lower alkoxy)-acetic anhydrides such as methoxyacetic anhydride and ethoxyacetic anhydride, 4-(lower alkyl)-benzoyl chlorides such as 4-methylbenzoyl chloride and 3,4,5-trimethoxybenzoyl chloride, 2-, 4- or 5-halonicotinic acids such as 5-bromonicotinic acid and 2-, 4- or 5-(lower alkoxy)-nicotinic acids such as 2-methoxynicotinic acid.

The esterification with any of the acid agents specified earlier is conducted in accordance with procedures conventional in the art and well documented in the literature.

For example, with an acid agent such as an acid anhydride or with an acyl halide (e.g. a benzoyl halide such as 3,4,5-trimethoxy benzoyl chloride) or with a nicotinoyl 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.

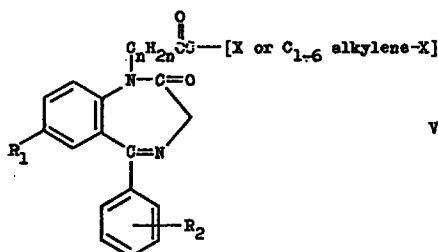
As is evident from the foregoing, the particular conditions for esterifying a compound of formula II are not critical and can be selected by one of ordinary skill in the art depending upon the acid agent utilized, particularly when viewing the esterification desired in the light of the prior art on the subject. By a cursory perusal of the literature, one can readily ascertain a myriad of suitable reagents capable of functioning efficaciously in the formation of the esters of formula I.

If a terminal free acid group is present in position-1 in a compound of formula I (when a dibasic acid or a derivative thereof is utilized as the acyl group providing agent), it can be converted by treatment with a suitable base such as sodium hydroxide or potassium hydroxide, potassium carbonate or an alkali metal alkoxide such as sodium methoxide into the corresponding compound of formula I bearing a COOA grouping at the end of the side chain in position-1 wherein A represents the cation of the base utilized. Preferably, A connotes sodium or potassium.

The esterification, as is evident from the foregoing, can be conducted in any conventional organic solvent such as dimethylformamide, pyridine or a hydrocarbon such as toluene. However, it is preferred to effect the esterification where possible in the presence of pyridine. Moreover, it has been found that in the case where an acid anhydride is used as the acyl group providing agent, such acid anhydride can itself serve as the esterification medium in addition to being participant in the esterification. 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 acid agent utilized.

Especially preferred esters are those which evidence particularly high water solubility. Those esters which contain, as the R group in formula I, nicotinoyl, succinoyl or the phosphate radical have been found to be particularly useful because of their high solubility in water when in pharmaceutically acceptable salt forms. Thus, particularly desirable esters are those which are formed from compounds of formula II utilizing as the esterification agent an acid agent containing a nicotinoyl moiety, a succinoyl moiety or a phosphate moiety.

The reaction of a compound of formula I wherein R represents a halo-(lower alkanoyl) group, i.e., a compound of the formula



wherein n, R₁ and R₂ have the significance given earlier and X represents halogen, preferably chlorine or bromine, with a compound of formula IV is preferably conducted in an inert organic solvent medium utilizing one or more inert organic solvents such as acetone, methyl ethyl ketone, lower alkanols such as methanol and ethanol, dimethylformamide, benzene, nitromethane and N - methyl - pyrrolidone. Temperature and pressure are not critical and thus the reaction can be carried out at or below room temperature and at atmospheric pressure, or at elevated temperatures and/or elevated pressures. However, elevated temperatures, e.g. about the reflux temperature of the reaction mixture, are preferred. If desired, the reaction can proceed in the presence of an alkali metal halide, e.g. sodium iodide.

Any primary or secondary amine of formula IV can be suitably employed. If a secondary amine is utilized, the two carbon atoms joined to the nitrogen atom of the amine can respectively form a part of a group which exists independently of the other group. Therefore, such carbon atoms can individually comprise a part of a straight or branched chain lower alkyl group such as methyl, ethyl, propyl or isopropyl. Alternatively, such carbon atoms can comprise part of a divalent group and such groups can be combined with each other directly or through an oxygen atom or a nitrogen atom to form a group such as pentamethylene, tetramethylene, ethyleneoxaethylene and ethyleneazaethylene, which may be substituted or unsubstituted.

Thus, R₁ and R₂ when taken together with the nitrogen atom and, at the most, one further nitrogen atom or an oxygen atom can represent a 4 - (lower alkyl) - 1 - piperazinyl, 4 - [hydroxy - (lower alkyl)] - 1 - piperazinyl, 4 - [(lower alkoxy) - (lower alkyl)] - piperazinyl, 1-pyrrolidinyl, 1-piperazinyl, morpholino or piperidino group.

Compounds of formula I wherein R represents the group C_mH_{2m}OH can be prepared by reacting a compound of formula II with a diol of formula III. In a preferred aspect, this reaction is effected utilizing the diol as the

solvent medium. Thus, by the convenient expedient of utilizing the diol in excess, there can be provided to the reaction zone a reaction participant as well as the medium in which the reaction may be effected. Temperature is not a critical aspect of this embodiment of the process and thus the reaction can be effected at room temperature or elevated temperatures. However, it is preferred to utilize elevated temperatures, e.g. from about 70° to 180°, more preferably from about 130° to 180°, most suitably at about the reflux temperature of the reaction mixture. Conveniently, a promoter may be present in the reaction system. Examples of such promoters are concentrated hydrochloric acid, polyphosphoric acid and thionyl chloride.

Examples of suitable diols are ethylene glycol, 1,3-propylene glycol, 1,4-butyleneglycol, 1,3-dihydroxy butane and 1,2-dihydroxy propane.

The compounds of formula I are useful as sedatives in view of their capability of inducing sleep. Said compounds and their pharmaceutically acceptable 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 dragées according to conventional pharmaceutical procedures. Accordingly, it will be appreciated that the invention also includes within its scope pharmaceutical preparations comprising a compound of formula I or a pharmaceutically acceptable salt thereof in association with a compatible pharmaceutical carrier.

The compounds of formula I form pharmaceutically acceptable salts (depending of course, on the nature of the substituent in position-1) with both inorganic and organic pharmaceutically acceptable acids and bases such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, succinic acid, methanesulfonic acid, para-toluenesulfonic acid; ammonia; amines such as tertiary amines, e.g. triethylamine, alkali metal hydroxides such as sodium and potassium hydroxide and alkali metal alkoxides such as sodium methoxide. Such salts can be formed quite readily by those skilled in the art with the prior art and the nature of the compound to be placed in salt form in view.

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

EXAMPLE 1

A solution of 5 g (0.0151 M) of 7-chloro-5 - (2 - fluorophenyl) - 1 - (2 - hydroxyethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin-2-one [prepared as described in the

Specification of our copending Application No. 1,192,729] in 60 ml of dry toluene was treated with 2.95 g (0.0302 M) of maleic anhydride and the resulting mixture was refluxed with stirring for 5 hours. The reaction mixture was cooled and poured into 40 ml of ether and 100 ml of dilute ammonium hydroxide. The layers were separated and the basic layer was acidified with acetic acid. The crude product was extracted with 2×100 ml of dichloromethane and evaporated to dryness. The residual oil was dissolved in 100 ml of dichloromethane which was washed with 2×100 ml of water and 100 ml of saturated brine, dried over anhydrous sodium sulfate and evaporated to dryness.

The product was crystallized from isopropanol and then recrystallized twice from a mixture of dichloromethane and hexane to give 2 - [7 - chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin-1-yl]ethyl maleate as pale yellow prisms melting at 153—157°.

EXAMPLE 2

A solution of 1.6 g (0.00371 M) of crude 2 - [7 - chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin-1-yl]ethyl maleate in 10 ml of methanol was treated with 0.7 ml (0.00328 M) of 4.69 N sodium methoxide in methanol and the solution was evaporated to dryness. The residual oil was triturated with ether and the residue was crystallized from a mixture of ethanol and ether. Recrystallization from a mixture of methanol and ether gave 2-[7-chloro-5(2-fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin - 1 - yl]ethyl maleate sodium salt as pale yellow prisms melting at 143—7°. It was found that this sample retained methanol at 100°, but on recrystallization from a mixture of methanol and acetone the product was obtained methanol free as pale yellow prisms melting at 220—222°.

EXAMPLE 3

A solution of 4 g (0.0121 M) of 7-chloro-5 - (2 - fluorophenyl) - 1 - (2 - hydroxyethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin-2-one in 40 ml of dry pyridine was treated with 8.2 g (0.0362 M) of 3,4,5-trimethoxybenzoyl chloride and the mixture was allowed to stand at room temperature for 16 hours. Solvent was removed by distillation and the residue was dissolved in 100 ml of dichloromethane. The solution was washed with 100 ml of 5 per cent potassium carbonate solution and 50 ml of saturated brine, dried over anhydrous sodium sulfate and evaporated to dryness. Recrystallization of the residue from methanol and then from a mixture of dichloromethane and hexane gave 2-[7-chloro-5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin - 1 - yl]ethyl

3,4,5-trimethoxy-benzoate as white prisms melting at 161—163°.

EXAMPLE 4

A solution of 4 g (0.012 M) of 7-chloro-5-(2 - fluorophenyl) - 1 - (2 - hydroxyethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2-one in 15 ml of dry pyridine was treated with 20 ml of methyl isocyanate and the reaction mixture was warmed on a steam bath for 2 hours. Solvents were removed under reduced pressure and the residue was dissolved in 50 ml of dichloromethane. The solution was washed with 50 ml of dilute ammonium hydroxide and 25 ml of saturated brine, dried over anhydrous sodium sulfate and evaporated to dryness giving N - methyl - 2 - [7 - chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin - 1 - yl] - ethyl carbamate as an oil.

The resulting oil was dissolved in 10 ml of ethanol and an excess of ethanolic hydrogen chloride was added. The solution was evaporated to dryness and the residue was crystallized first from a mixture of isopropanol and ether, and then from a mixture of methanol and ether to give the hydrochloride as pale yellow prisms melting at 175—180° in a sealed tube.

EXAMPLE 5

In a 2 liter flask equipped with a thermometer, stirrer, reflux condenser, drying tube, nitrogen inlet tube and a dropping funnel were added 100 g (0.346 M) of 7-chloro-5-(2-fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one hydrochloride and 400 ml of dry N,N-dimethylformamide. The solution was stirred under a slow stream of nitrogen and 33.2 g (0.692 M) of a 50 per cent dispersion of sodium hydride in mineral oil were added. After 30 minutes the solution was cooled in an ice bath to 5° and 130 g (1.04 M) of 2-bromoethanol in 100 ml of dry N,N-dimethylformamide were added dropwise over a 20 minute period. The nitrogen was turned off, the reaction mixture was heated to 100° for 5 hours, then rinsed into a 3 liter flask with benzene and distilled to dryness under reduced pressure. The so-obtained 7-chloro - 5 - (2 - fluorophenyl) - 1 - (2 - hydroxyethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin-2-one was transferred to a 3 liter 3-necked flask with 750 ml of benzene, 100 ml (0.719 M) of triethylamine and 100 g (1.0 M) of succinic anhydride were added and the reaction mixture was stirred for 16 hours at room temperature. The reaction mixture was rinsed into a 3 liter flask with benzene and evaporated to dryness under a vacuum. The dark oil was dissolved in 750 ml of benzene which was then treated with 450 ml of water with shaking or stirring, and then with a mixture of 550 ml of ice and water to bring the temperature down to approxi-

mately 10°. The solution was made basic (about pH 8.5) with 175 ml of a 50 per cent (w/v) potassium carbonate solution with stirring to avoid foaming over. After transferring to a separatory funnel the layers were separated and the water layer was extracted with 3×600 ml of benzene. The benzene solutions were combined and washed with 200 ml of a saturated brine solution, dried over anhydrous sodium sulfate and evaporated to dryness under a vacuum to give an oil containing 2 - [7 - chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin - yl]ethylsuccinate potassium salt.

EXAMPLE 6

A solution of 5 g (0.0151 M) of 7-chloro-1 - (2 - hydroxyethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one hydrochloride in 60 ml of pyridine was treated with 8 g (0.044 M) of nicotinoyl chloride hydrochloride and the solution was heated on a steam bath, with stirring, for 2 hours. Pyridine was removed under a vacuum. The residue was dissolved in 100 ml of dichloromethane, washed with 10 percent potassium carbonate solution (2×75 ml) and 75 ml of a saturated brine solution, dried over anhydrous sodium sulfate and evaporated to dryness.

The oil was crystallized from ether and then recrystallized from methanol to give 1-(2 - nicotinoyloxyethyl) - 7 - chloro - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin-2-one as white prisms melting at 138—140°.

EXAMPLE 7

A solution of 0.5 g (0.00151 M) of 7-chloro-5 - (2 - fluorophenyl) - 1 - (2 - hydroxyethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one in 15 ml of ethylene glycol was treated with 2 drops of concentrated sulfuric acid. The reaction mixture was heated at 160° for 4 hours with stirring, then cooled, poured into 100 ml of ice-water and filtered to remove tarry material. The filtrates were extracted with 100 ml of dichloromethane, which was then washed with 100 ml of water, dried over anhydrous sodium sulfate and evaporated to dryness yielding 7 - chloro - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 1 - [2 - (2 - hydroxyethyl) - oxyethyl] - 2H - 1,4 - benzodiazepin - 2-one. The residue was dissolved in 10 ml of ethanol, 1 ml of 7.8N ethanolic hydrogen chloride was added and the solution was evaporated to dryness. The 7-chloro-5-(2-fluorophenyl) - 1,3 - dihydro - 1 - [2 - (2 - hydroxyethyl)oxyethyl] - 2H - 1,4 - benzodiazepin - 2-one hydrochloride was crystallized from a mixture of ethanol and ether and recrystallized from a mixture of methanol and ether to give the product as pale yellow prisms melting at 180—185° (decomposition) (sealed tube).

EXAMPLE 8

A solution of 10 g (0.03 M) of 7-chloro-5-(2-fluorophenyl)-1-(2-hydroxyethyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one in 100 ml of benzene was treated with 4 g of succinic anhydride and 4 ml of triethylamine. After 18 hours at room temperature, solvents were removed under reduced pressure. The residue was dissolved in 100 ml of dilute potassium carbonate solution, washed with 100 ml of ether and the aqueous layer was acidified with acetic acid. The liquid was decanted and the residual oil was dissolved in 100 ml of dichloromethane. The solution was washed with 100 ml of water, dried over anhydrous sodium sulfate and evaporated to dryness. 2-[7-chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-1H-1,4-benzodiazepin-1-yl]-ethyl succinate crystallized from ether. Upon recrystallization from a mixture of methanol and ether, the product was obtained as white prisms melting at 152—156°.

EXAMPLE 9

A solution of 15 g (0.045 M) of 7-chloro-5-(2-fluorophenyl)-1-(2-hydroxyethyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one in 200 ml of xylene was treated with 12.8 g (0.135 M) of chloroacetic acid and the solution was heated under reflux for 4 hours using a Dean-Stark trap. The reaction mixture was cooled, washed with 10% potassium carbonate solution (3×75 ml) and water (3×75 ml), dried over anhydrous sodium sulfate and evaporated to dryness. The residue was dissolved in dichloromethane (50 ml) and filtered over 100 g of activated magnesium silicate using 500 ml of ether as the eluant. The solvent was evaporated and the residue was recrystallized twice from a mixture of dichloromethane and petroleum ether to give 7-chloro-1-(2-chloroacetoxyethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one as white prisms melting at 135—137°.

EXAMPLE 10

A solution of 3.0 g (0.00733 M) of 7-chloro-1-(2-chloroacetoxyethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one in 25 ml of benzene was treated with 5 ml of diethylamine and the solution was heated under reflux for 12 hours. Solvent was removed under reduced pressure and the residue was triturated with a mixture of ether and petroleum ether. The precipitate was recrystallized from a mixture of dichloromethane, ether and petroleum ether to give 7-chloro-1-(2-diethylaminoacetoxyethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one as white prisms melting at 84.5—88°.

EXAMPLE 11

A solution of 15 g (0.045 M) of 7-chloro-

5-(2-fluorophenyl)-1-(2-hydroxyethyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one in 170 ml of xylene was treated with 11.1 g (0.09 M) of isonicotinic acid and the solution was heated under reflux for 36 hours using a Dean-Stark trap. The reaction mixture was cooled, washed with 100 ml of 10% potassium carbonate solution and then with 100 ml of water. The xylene solution was extracted with 1N hydrochloric acid (2×75 ml). The acid layers were combined, washed with 100 ml of ether 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 oil was crystallized from ether and recrystallized from a mixture of dichloromethane and petroleum ether to give 7-chloro-5-(2-fluorophenyl)-1-(2-isonicotinoyloxyethyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one as white plates melting at 138—142°.

EXAMPLE 12

A solution of 5 g (0.0122 M) of 7-chloro-1-(2-chloroacetoxyethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one in 75 ml of benzene was treated with 1.8 g (0.0305 M) of propylamine and heated under reflux for 20 hours. The mixture was cooled, treated with 75 ml of water and enough hydrochloric acid to adjust the pH to 5. The acid layer was separated, made basic with ammonium hydroxide and extracted with 100 ml of dichloromethane. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and evaporated to dryness yielding 7-chloro-5-(2-fluorophenyl)-1-(2-propylaminoacetoxyethyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one. A solution of 3 g of the residue in 10 ml of ethanol was treated with 1 equivalent of ethanolic hydrogen chloride (0.6 ml of a 7.8N solution) and the solution was evaporated to dryness. The monohydrochloride was crystallized from isopropanol and recrystallized from a mixture of methanol and ether to give 7-chloro-5-(2-fluorophenyl)-1-(2-propylaminoacetoxyethyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one hydrochloride as white prisms melting at 219—222° (decomposition) (sealed tube).

EXAMPLE 13

4 g (12.0 mmol) of 7-chloro-5-(2-fluorophenyl)-1-(2-hydroxyethyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one were dissolved in 21 ml of anhydrous pyridine and 150 ml of dry ether and the solution was cooled to -10°. A second solution of 1.2 ml of phosphorus oxychloride in 75 ml of ether was added from a pressure-equilibrated dropping funnel over a half-hour period with stirring. The temperature was kept below 0° for

another two hours, and then allowed to rise to ambient. After one additional hour, 300 ml of ice slush and 150 ml of ether were added and, after one hour, the layers were separated.

- 5 The aqueous portion was concentrated in vacuo at 30°, care being taken to avoid splashing, and the pH adjusted downward to 3.2. The organic derivative was adsorbed into 100 ml of a 30% aqueous suspension of acid-washed amorphous carbon. The liquid phase was removed and the carbon washed with four bed volumes of water adjusted to the mildly acid pH of the original solution. The phosphate was then desorbed with a 1:1 mixture of ethanol/water containing 0.3% concentrated ammonia in 5×100 ml batches.

- 10 The combined filtrates were concentrated to a highly hygroscopic oil, reconcentrated once with absolute ethanol and finally triturated with several batches of diethyl ether. The resultant powder was kept in a vacuum desiccator, yielding 7-chloro-1-(2-hydroxyethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one O-phosphoric acid diammonium salt (MW 447.1—2.7 mM).

EXAMPLE 14

- A solution containing 4.4 g (0.0131 M) of 7-chloro-5-(2-fluorophenyl)-1-(2-hydroxyethyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one and 2.0 g (0.0131 M) of 2-methoxynicotinic acid in 100 ml of xylene was heated under reflux for 58 hours using a Dean Stark trap. The reaction mixture was cooled and washed with 75 ml of 1N hydrochloric acid which was then extracted with 50 ml of ether. The ether was combined with the xylene fraction and washed with 100 ml of dilute ammonium hydroxide and 50 ml of saturated brine, dried over anhydrous sodium sulfate and distilled to dryness under a vacuum giving 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-1-(2-methoxynicotinoyloxyethyl)-2H-1,4-benzodiazepin-2-one.
- 30 The oil was dissolved in 100 ml of benzene, 5 ml (0.039 M) of a 7.8N ethanolic hydrogen chloride solution were added and the solution was distilled to dryness under a vacuum. The residue was crystallized from a mixture of acetone and ether and then recrystallized from a mixture of methanol and ether to give 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-1-(2-methoxynicotinoyloxyethyl)-2H-1,4-benzodiazepin-2-one dihydrochloride as pale yellow prisms melting at 154—158° (sealed tube).

EXAMPLE 15

- A solution of 3.3 g (0.01 M) of 7-chloro-5-(2-fluorophenyl)-1-(2-hydroxyethyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one and 2.0 g (0.01 M) of 5-bromonicotinic acid in 100 ml of xylene was heated under reflux for 48 hours using a Dean-Stark trap.

The reaction mixture was cooled and washed with 75 ml of 1N hydrochloric acid to remove unreacted starting material. The aqueous layer was extracted with 50 ml of ether which was combined with the xylene solution, washed with 100 ml of dilute ammonium hydroxide and 50 ml of saturated brine, dried over anhydrous sodium sulfate and evaporated to dryness under a vacuum. The residue was crystallized from ether and recrystallized from a mixture of dichloromethane and hexane to give 7-chloro-1-(5-bromonicotinoyloxyethyl)-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one as white prisms melting at 140—143°.

EXAMPLE 16

A solution of 10 g (0.030 M) of 7-chloro-5-(2-fluorophenyl)-1-(2-hydroxyethyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one in 100 ml of dry benzene was treated with 6 ml (0.0428 M) of triethylamine and 6.3 g (0.033 M) of ethoxyacetic anhydride. After 18 hours at room temperature, the solvents were removed under a vacuum and the residue was dissolved in 100 ml of dichloromethane which was washed with 100 ml of 10% potassium carbonate solution and 50 ml of saturated brine, dried over anhydrous sodium sulfate and evaporated to dryness yielding 7-chloro-1,3-dihydro-1-(2-ethoxyacetoxyethyl)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one as an oil. The oil was dissolved in 100 ml of benzene which was treated with 6 ml (0.0468 M) of a solution of 7.8N ethanolic hydrogen chloride and then evaporated to dryness. The residue was recrystallized from a mixture of acetone and ether to give 7-chloro-1,3-dihydro-1-(2-ethoxyacetoxyethyl)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one hydrochloride as pale yellow prisms melting at 154—158° (sealed tube).

EXAMPLE 17

A solution of 0.332 g (1 mM) of 7-chloro-5-(2-fluorophenyl)-1-(2-hydroxyethyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one in 6 ml of dry pyridine was mixed with 0.795 g (5 mM) of sulfur trioxide/pyridine adduct and the suspension shaken at room temperature overnight. The residue left after removal of the solvent in vacuo at 25° was dissolved in water and adjusted to pH 7 with saturated barium hydroxide solution. An equal volume of ethanol was added and the barium sulphate removed by centrifuging. The supernatant and a 50 percent ethanol wash of the precipitate were combined, concentrated in vacuo to dryness and the residue dissolved in 95 percent ethanol. After centrifuging to remove some insoluble material, the ethanol solution was evaporated and the residue dissolved in 1 ml of water. Chromatography was carried out on a

DEAE-cellulose (bicarbonate) column, 2×20 cm, using a linear gradient of H₂O—0.3 M pH 7 TEABIC (triethylammonium bicarbonate) of 1500 ml total volume. Fractions 161—235 contained 7 - chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin-1-ethyl hydrogen sulfate triethylamine salt and fractions 201—235 were evaporated to give the product as a yellow glass with a $\lambda_{\max}^{\text{EtOH}}=311 \text{ m}\mu$; $E_{211}=400 \text{ O.D.}$, corresponding to $\sim 0.18 \text{ mM}$ (based on E_{2200}).

EXAMPLE 18

A quantity of 300 mg (2 mMoles) of dilithium S-(ethyl) phosphorothioate was converted to its pyridinium salt by passage over DOWEX—50 (pyridinium)—the word "DOWEX" is a Registered Trade Mark. The pyridinium salt was rendered anhydrous with frequent high vacuum concentration using anhydrous pyridine. To the dry residue were added 332 mg (1 mMole) of 7-chloro-5-(2-fluorophenyl) - 1 - (2 - hydroxyethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one, 800 mg (4 mM) of dicyclohexylcarbodiimide and 10 ml of anhydrous pyridine. The reaction mixture was shaken in the dark for 24 hours. 3 ml of water were added and the reaction mixture was left standing overnight. The dicyclohexylurea was filtered off and washed with aqueous pyridine. The filtrate was concentrated to remove the pyridine, the residue dissolved in water (2 ml) and the pH adjusted to 8 with dilute ammonium hydroxide. The solution was applied to a 4×40 cm column of DEAE-cellulose DE—23 (bicarbonate form) and the column washed with a linear gradient consisting of 2 liters of triethylammonium bicarbonate in the reservoir (0.2 M, pH 7.2) and 2 liters of water in the mixing vessel. Fractions of 20 ml were collected at a flow rate of 3 ml/minute.

Fraction 100—220 contained the product as shown by paper chromatography (70 parts acetonitrile, 30 parts 0.1 N ammonium chloride pH 9, ascending). The fractions were pooled, concentrated to an oily residue and dissolved in 10 ml of water. A solution containing 1.2 g of iodine in acetone (10 ml) was added and the mixture left standing for 3 hours. The solution was extracted with 6×30 ml of ether, the aqueous portion was concentrated and the pH adjusted to 3.2. Activated amorphous carbon (70 ml of a 30 percent suspension) was added and the mixture left at 0° for 15 minutes. The carbon was filtered and washed with water. The product was desorbed twice with a mixture of 100 ml of water, 100 ml of ethanol and 0.6 ml of concentrated ammonia. The filtrate was concentrated and reconcentrated with ethanol to an oil. 7 - Chloro - 1 - (2 - hydroxyethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one O-phosphoric

acid diammonium salt as a yellowish powder was obtained upon triturating with ether.

The following Examples illustrate pharmaceutical preparations containing the benzodiazepine derivatives provided by the invention:

EXAMPLE A

A tablet formulation containing the following ingredients:

	Per Tablet	
2 - [7 - Chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin - 1 - yl]ethyl succinate	25.00 mg	75
Dicalcium Phosphate Dihydrate, Unmilled	175.00 mg	80
Corn Starch	24.00 mg	
Magnesium Stearate	1.00 mg	
Total Weight	225.00 mg	

was prepared as follows:

2 - [7 - Chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin-1-yl]ethyl succinate 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.

EXAMPLE B

A capsule formulation containing the following ingredients

	Per Capsule	
2 - [7 - Chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin - 1 - yl]ethyl succinate	10 mg	105
Lactose	165 mg	
Corn Starch	30 mg	
Talc	5 mg	
Total Weight	210 mg	110

was prepared as follows:

2 - [7 - Chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin-1-yl]ethyl succinate, lactose and 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 C

- 5 A parenteral formulation containing the following ingredients.

	Per ml
2 - [7 - Chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin - 1 - yl] - ethyl succinate	10.2 mg
Diethanolamine	2.904 mg
Benzyl Alcohol	0.01 ml
Hydrochloric Acid 1N	
15 q.s. to pH 7.3	
Water for Injection q.s.	1.00 ml

were prepared (for 10 liters) as follows:

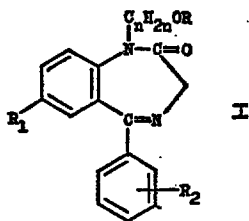
- 20 The 29.04 g of diethanolamine and 100 ml of benzyl alcohol were dissolved in 8 liters of water for injection. The 102 g of 2-[7-chloro-5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin - 1 - yl]ethyl succinate were added and the mixture was stirred until the drug was completely dissolved.

25 A 1N preparation of HCl was added slowly, dropwise, with constant stirring to a pH of 7.3. The solution was brought up to final volume of 10 liters with water for injection.

- 30 The solution was filtered through a filter candle, filled into suitable size amber ampoules, gassed with N₂ and sealed. The sealed ampoules were then autoclaved at 0.7 atm. for 30 minutes.

35 WHAT WE CLAIM IS:—

1. Compounds of the general formula



- wherein R₁ represents hydrogen, halogen, nitro or trifluoromethyl, R₂ represents hydrogen, halogen or nitro and R represents halo-(lower alkanoyl), (lower alkoxy)-(lower alkanoyl), aroyl, aryl-(lower alkanoyl), the monoacyl moiety of a dibasic acid, the acyl moiety of a lower alkenoic acid, a carbamate moiety, a sulfate moiety or a phosphate moiety, the

group $-\text{CO}-[\text{C}_{1-6} \text{ alkylene}]-\text{N} \begin{matrix} \text{R}_5 \\ \text{R}_6 \end{matrix}$ or the group $-\text{C}_m\text{H}_{2m}\text{OH}$, R₅ and R₆ represent

hydrogen or lower alkyl or taken together with the nitrogen atom a heterocyclic moiety containing at the most one additional nitrogen or oxygen atom and n and m are integers from 2—7, and salts thereof.

2. Derivatives according to claim 1, wherein R₁ represents nitro or halogen.

3. Derivatives according to claim 1, wherein R₁ represents chlorine.

4. Derivatives according to any one of claims 1 to 3, wherein R₂ represents halogen.

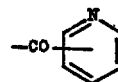
5. Derivatives according to claim 4, wherein R₂ is in the 2-position of the 5-phenyl ring and represents fluorine or chlorine.

6. Derivatives according to any one of claims 1 to 5 inclusive, wherein n is 2.

7. Derivatives according to any one of claims 1 to 6 inclusive, wherein R₁ is chlorine and R₂ is fluorine in the 2'-position.

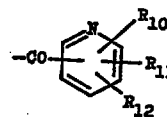
8. Derivatives according to claim 7, wherein R₁ represents aroyl, aryl-(lower alkanoyl), the monoacyl moiety of a C₃—C₇ dibasic acid or a carbamate moiety.

9. Derivatives according to claim 8, wherein the aroyl moiety is a



moiety.

10. Derivatives according to claim 7, wherein R is a



moiety

wherein R₁₀, R₁₁ and R₁₂ represent hydrogen, lower alkoxy, methyl or halogen.

11. Derivatives according to claim 10, wherein R₁₁ and R₁₂ are hydrogen.

12. Derivatives according to any one of claims 1 to 9 inclusive, wherein R represents a nicotinoyl or succinoyl moiety.

13. Derivatives according to any one of claims 1 to 7 inclusive, wherein R is a phosphate moiety.

14. 2 - [7 - Chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin-1-yl]ethyl maleate or the sodium salt thereof.

15. N - Methyl - 2 - [7 - chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin-1-yl]ethyl carbamate.

16. 1 - (2 - Nicotinoyloxyethyl) - 7 - chloro - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin-2-one.

17. 2 - [7 - Chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin-1-yl]ethyl-succinate,



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9

1,208,541

9

The mixture was filled into hard shell gelatin capsules on a capsulating machine.

EXAMPLE C

5 A parenteral formulation containing the following ingredients.

	Per ml
2 - [7 - Chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin - 1 - yl]-ethyl succinate	10.2 mg
Diethanolamine	2.904 mg
Benzyl Alcohol	0.01 ml
Hydrochloric Acid 1N	
15 q.s. to pH 7.3	
Water for Injection q.s.	1.00 ml

were prepared (for 10 liters) as follows:

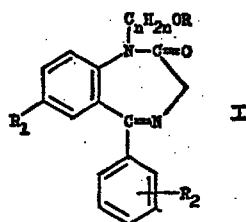
20 The 29.04 g of diethanolamine and 100 ml of benzyl alcohol were dissolved in 8 liters of water for injection. The 102 g of 2-[7-chloro-5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin - 1 - yl]ethyl succinate were added and the mixture was stirred until the drug was completely dissolved.

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30 The solution was filtered through a filter candle, filled into suitable size amber ampoules, gassed with N₂ and sealed. The sealed ampoules were then autoclaved at 0.7 atm. for 30 minutes.

35 WHAT WE CLAIM IS:—

1. Compounds of the general formula



wherein R₁ represents hydrogen, halogen, nitro or trifluoromethyl, R₂ represents hydrogen, halogen or nitro and R represents halo-(lower alkanoyl), (lower alkoxy)-(lower alkanoyl), aroyl, aryl-(lower alkanoyl), the monoacyl moiety of a dibasic acid, the acyl moiety of a lower alkenoic acid, a carbamate moiety, a sulfate moiety or a phosphate moiety, the

group $-\text{CO}-[\text{C}_{1-6} \text{ alkylene}]-\text{N} \begin{matrix} \nearrow \text{R}_5 \\ \searrow \text{R}_6 \end{matrix}$ or the group $-\text{C}_m\text{H}_{2m}\text{OH}$, R₅ and R₆ represent

hydrogen or lower alkyl or taken together with the nitrogen atom a heterocyclic moiety containing at the most one additional nitrogen or oxygen atom and n and m are integers from 2—7, and salts thereof.

2. Derivatives according to claim 1, wherein R₁ represents nitro or halogen.

3. Derivatives according to claim 1, wherein R₁ represents chlorine.

4. Derivatives according to any one of claims 1 to 3, wherein R₂ represents halogen.

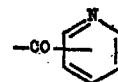
5. Derivatives according to claim 4, wherein R₂ is in the 2-position of the 5-phenyl ring and represents fluorine or chlorine.

6. Derivatives according to any one of claims 1 to 5 inclusive, wherein n is 2.

7. Derivatives according to any one of claims 1 to 6 inclusive, wherein R₁ is chlorine and R₂ is fluorine in the 2'-position.

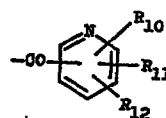
8. Derivatives according to claim 7, wherein R₁ represents aroyl, aryl-(lower alkanoyl), the monoacyl moiety of a C₂—C₇ dibasic acid or a carbamate moiety.

9. Derivatives according to claim 8, wherein the aroyl moiety is a



moiety.

10. Derivatives according to claim 7, wherein R is a



moiety

wherein R₁₀, R₁₁ and R₁₂ represent hydrogen, lower alkoxy, methyl or halogen.

11. Derivatives according to claim 10, wherein R₁₁ and R₁₂ are hydrogen.

12. Derivatives according to any one of claims 1 to 9 inclusive, wherein R represents a nicotinoyl or succinoyl moiety.

13. Derivatives according to any one of claims 1 to 7 inclusive, wherein R is a phosphate moiety.

14. 2 - [7 - Chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin-1-yl]ethyl maleate or the sodium salt thereof.

15. N - Methyl - 2 - [7 - chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin-1-yl]ethyl carbamate.

16. 1 - (2 - Nicotinoyloxyethyl) - 7 - chloro - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin-2-one.

17. 2 - [7 - Chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin-1-yl]ethyl-succinate.



18. 7 - Chloro - 1 - (2 - hydroxyethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one O-phosphoric acid.

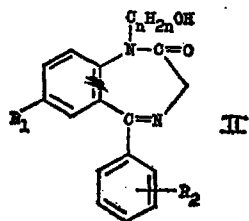
19. 7 - Chloro - 5 - (2 - fluorophenyl) - 1 - (2 - propylaminoacetoxyethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin-2-one.

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

21. 7 - Chloro - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 1 - [2 - (hydroxyethyl) - oxyethyl] - 2H - 1,4 - benzodiazepin - 2 - one.

22. A pharmaceutical preparation comprising a compound as formulated in claim 1 or a pharmaceutically acceptable salt thereof in association with a compatible pharmaceutical carrier.

23. A process for the manufacture of the derivatives claimed in claim 1, which process comprises treating a compound of the general formula

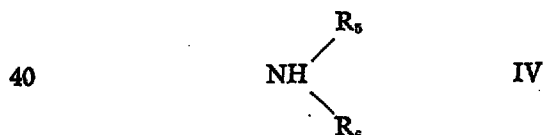


wherein R₁ and R₂ have the meanings given in claim 1,

with an acid agent containing a halo-(lower alkanoyl), (lower alkoxy)-(lower alkanoyl), aroyl or aryl-(lower alkanoyl) group or a monoacyl moiety of a dibasic acid, an acyl moiety of a lower alkenoic acid, a carbamate, sulfate or phosphate moiety, or with a diol of the general formula



wherein m has the significance given in claim 1, if desired, treating a compound obtained wherein R represents a halo-(lower alkanoyl) group with a compound of the general formula



wherein R₅ and R₆ have the significance given in claim 1, and, if desired, transforming a product obtained into a salt.

24. A process according to claim 23, wherein R₁ represents nitro or halogen.

25. A process according to claim 23, wherein R₁ represents chlorine.

26. A process according to any one of claims 23 to 25 inclusive, wherein R₂ represents halogen.

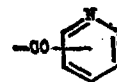
27. A process according to any one of claims 23 to 26 inclusive, wherein R₂ represents fluorine or chlorine in the 2-position of the 5-phenyl ring.

28. A process according to any one of claims 23 to 27 inclusive, wherein n is 2.

29. A process according to any one of claims 23 to 28 inclusive, wherein R₁ is chlorine and R₂ is fluorine in the 2'-position.

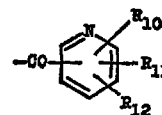
30. A process according to claim 29, wherein 7 - chloro - 5 - (2 - fluorophenyl) - 1 - (2 - hydroxyethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin-2-one is treated with an acid agent containing an aroyl, aryl-(lower alkanoyl) or carbamate moiety or the moiety of a C₃-C₇ dibasic acid and, if desired, a product obtained is transformed into a salt.

31. A process according to claim 30, wherein the aroyl moiety is a



moiety.

32. A process according to claim 29, wherein R is a



moiety

wherein, R₁₀, R₁₁ and R₁₂ represent hydrogen, lower alkoxy, methyl or halogen.

33. A process according to claim 32, wherein R₁₁ and R₁₂ are hydrogen.

34. A process according to any one of claims 23 to 31 inclusive, wherein R represents a nicotinoyl or succinoyl moiety.

35. A process according to any one of claims 23 to 29 inclusive, wherein R represents a phosphate moiety.

36. A process according to any one of claims 23 to 30 inclusive, wherein 2-[7-chloro-5-(2-fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin - 1 - yl]ethyl maleate or the sodium salt thereof is prepared.

37. A process according to any one of claims 23 to 30 inclusive, wherein N-methyl-2-[7-chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin - 1 - yl]ethyl carbamate is prepared.

38. A process according to any one of claims 23 to 31 inclusive or claim 34, wherein 1-(2-nicotinoyloxyethyl) - 7 - chloro - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin-2-one is prepared.

39. A process according to any one of claims 23 to 31 inclusive or claim 34, wherein 2-[7-chloro - 5 - (2 - fluorophenyl) - 2,3 - dihydro - 2 - oxo - 1H - 1,4 - benzodiazepin - 1 - yl]-ethyl-succinate is prepared. 5
40. A process according to any one of claims 23 to 29 inclusive or claim 35, wherein 7-chloro - 1 - (2 - hydroxyethyl) - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin-2-one O-phosphoric acid is prepared. 10
41. A process according to any one of claims 23 to 29 inclusive, wherein 7-chloro-5-(2-fluorophenyl) - 1 - (2 - propylaminoacetoxyethyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin-2-one is prepared. 15
42. A process according to any one of claims 23 to 29 inclusive, wherein 7-chloro-1-(2-diethylaminoacetoxyethyl) - 5 - (2 - fluoro-phenyl) - 1,3 - dihydro - 2H - 1,4 - benzo- diazepin-2-one is prepared. 20
43. A process according to any one of claims 23 to 29 inclusive, wherein 7-chloro-5-(2-fluorophenyl) - 1,3 - dihydro - 1 - [2 - (hydroxyethyl) - oxyethyl] - 2H - 1,4 - benzo- diazepin-2-one is prepared. 25
44. A process for the manufacture of the benzodiazepine derivatives claimed in claim 1, substantially as hereinbefore described with reference to the foregoing Examples 1 to 17. 30
45. Benzodiazepine derivatives as set forth in claim 1, when manufactured by the process claimed in any one of claims 23 to 44 inclusive.

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