

PATENT SPECIFICATION

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NO DRAWINGS

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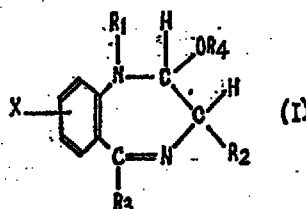
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(54) NOVEL BENZODIAZEPINES

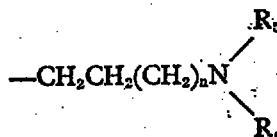
(71) We, SCHERICO LTD., of Topferstrasse 5, Lucerne, Switzerland, a body corporate constituted under the laws of Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel 1-substituted-2-oxy-2,3-dihydro-5-aryl-1H-1,4-benzodiazepines, to processes for their preparation and to compositions containing such compounds.

The compounds of this invention are 1,4-benzodiazepines of the general formula I



and pharmaceutically acceptable salts thereof, wherein X is hydrogen, halogen, trifluoromethyl, nitro, hydroxy, lower alkyl or lower alkoxy; R₁ is lower alkyl, polyfluoro-lower alkyl, phenyl-lower alkyl, lower cycloalkyl, lower cycloalkyl-lower alkyl, lower alkenyl or amino-lower alkyl the amino group of which may be substituted by one or more lower alkyl groups; R₂ is hydrogen, lower alkyl, hydroxy or lower alkanoyloxy; R₃ is phenyl, X-substituted phenyl, naphthyl, thienyl or pyrrolyl and R₄ is lower alkyl or



(wherein n is 0 or 1 and R₅ and R₆ are hydrogen or lower alkyl) and may additionally be hydrogen when X is hydroxy and/or R₁ is polyfluoro-lower alkyl, phenyl-lower alkyl, lower cycloalkyl-lower alkyl, lower alkenyl or amino-lower alkyl the amino group of which may be substituted by one or more lower alkyl groups and/or R₂ is lower alkyl, hydroxy or lower alkanoyloxy. (The term "pharmaceutically acceptable salts" as used herein includes the 4-oxides of the compounds of formula I). The term "lower alkyl" refers to both straight and branched-chain saturated hydrocarbon radicals having up to six carbon atoms. Preferred are groups such as methyl, ethyl, propyl, isopropyl, n-butyl and t-butyl.

[Price 25p]

Price 33p

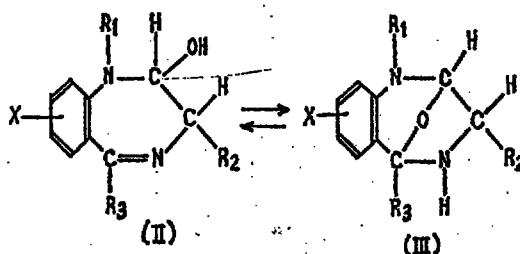
"Lower alkenyl" similarly refers to straight and branched-chain olefinic hydrocarbon radicals having up to six carbon atoms and may be exemplified by 1-propenyl, 2-isopropenyl, 2-butenyl, 3-butenyl and 2-isopentenyl. The terms "lower cycloalkyl" and "lower cycloalkyl-lower alkyl" are limited similarly and may be exemplified by cyclopentyl, cyclohexyl and cyclopropylmethyl. Similarly the term "phenyl-lower alkyl" may be illustrated by phenethyl and benzyl. By "lower alkoxy" is meant ether radicals wherein the lower alkyl moiety is as defined for "lower alkyl" above, such as for example, methoxy, ethoxy, propoxy and the like. By "lower alkanoyloxy" is meant those acid radicals derived from alkanolic acids having up to 6 carbon atoms, and therefore comprises such radicals as formyl, acetyl, propionyl, butyryl, valeryl, hexanoyl and the branched-chain isomers thereof. The term "halogen" as used herein comprehends all four halogens, although chloro is the preferred halogen species of this invention.

In a preferred embodiment of this invention X is a 7-chloro substituent.

The term "polyfluoro-lower alkyl" refers to lower alkyl radicals substituted with more than one fluorine atom and includes such moieties as 2,2,2-trifluoroethyl, trifluoromethyl, 2,2,3,3,3-pentafluoropropyl and the like. In a preferred embodiment of this invention the polyfluoro-lower alkyl moiety has two α -hydrogen atoms, i.e. R_1CH_2- wherein R_1 is polyfluoroalkyl. Most preferably, R_1 is trifluoromethyl, as in the 1-(2,2,2-trifluoroethyl) substituted compounds.

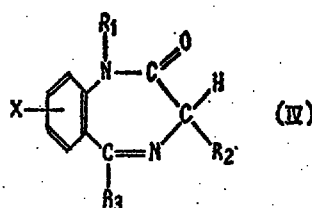
The pharmaceutically acceptable salts include those formed with both inorganic and organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, acetic acid, formic acid, succinic acid, maleic acid, p-toluenesulfonic acid and the like. Further pharmaceutically acceptable salts are the 4-oxides of the compounds of formula I.

In solution the 2-hydroxy compounds of this invention can best be represented by the structure as indicated in formula II, an equilibrium existing between this 2-hydroxy form and the bridged 2,5-oxy form (III)



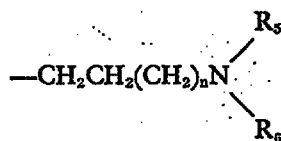
In the solid state, the equilibrium may be in the direction of the bridged 2,5-oxy form. In any event, compounds of the formulae II and III will hereinafter be understood when the 2-hydroxy compounds of this invention are referred to.

The compounds of this invention may advantageously be prepared by the process disclosed and claimed in our copending Application No. 33498/72 (Serial No. 1297630). This process comprises, when applied to the production of the compounds of the present invention, reducing at the keto group, a compound of the general formula IV



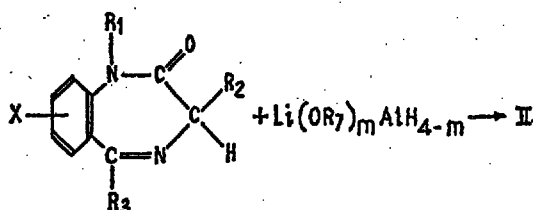
wherein X, R_1 , R_2 and R_3 are as defined herein in relation to formula I. The so-obtained compound of formula I having a free hydroxy group in position 2 may then, if desired,

be etherified to the corresponding compound of formula I in which R_4 is lower alkyl or



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A preferred embodiment of this process comprises adding a lithium aluminium hydride in a suitable inert solvent such as tetrahydrofuran or ether to the corresponding 2,3-dihydro-2-oxo-5-aryl-1H-1,4-benzodiazepine at reduced temperatures, e.g. about 0°C. The reaction may be illustrated by the following reaction scheme:

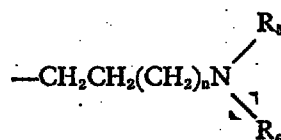


wherein R_1 , R_2 , R_3 and X are as previously defined, R_4 is lower alkyl; and m has a value of 0, 1, 2 or 3.

The reduction of the keto group may also be performed electrolytically or by means of an amalgam, preferably sodium amalgam, as a reducing agent.

If in the above reaction X represents a nitro group, this group will also, at least to a certain extent, be attacked by the reduction. This will reduce the yield of the desired compound.

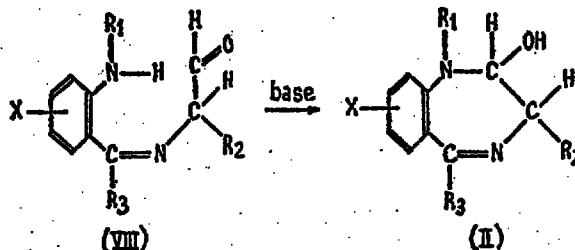
The corresponding 2-ethers can readily be prepared by reaction of the corresponding 2-hydroxy compounds of formula II with the appropriate alcohol ($R_4\text{OH}$), R_4 representing lower alkyl or the grouping



wherein n, R_5 and R_6 are as hereinbefore defined.

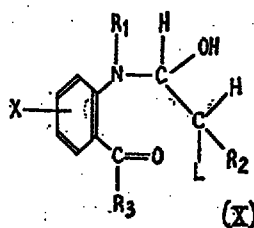
The starting compounds of general formula IV are well known and may for example be obtained according to the processes described in the Austrian Patent No. 275,528 and in the Belgian Patent No. 692,621.

The compounds of the present invention may also be prepared by a process which comprises treating an aldehyde of formula VIII (below) with a base as illustrated in the following reaction scheme:



In the above formulae R_1 , R_2 , R_3 and X are as previously defined.

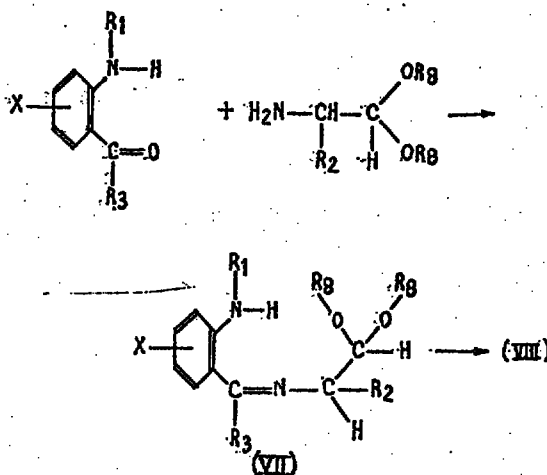
A further possibility is the intramolecular condensation of a compound of the general formula X



wherein R_1 , R_2 , R_3 and X are as previously defined, and L is a free amino group or a blocked amino group, such as a salfied amino group, for example $\text{—NH}_2 \cdot \text{HCl}$, benzyl-oxy carbonyl amino group, phthalimido group, acetamido group and the like.

For the preparation of those compounds having an etherified hydroxy group in position 2, the compounds of formula II obtained above are subjected to an etherification reaction. This reaction may often be carried out simply by dissolving the hydroxy compound in the appropriate alcohol and allowing the ether to crystallize.

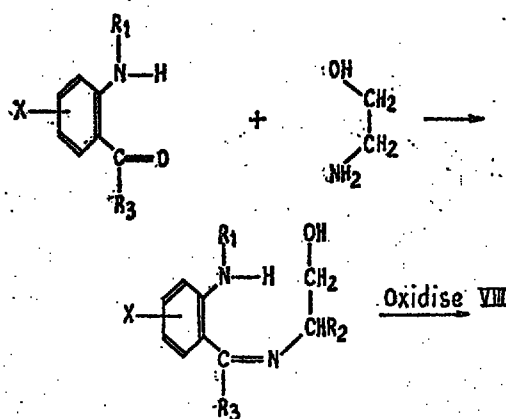
The starting compounds of the general formula VIII may be prepared according to the following reaction scheme:



wherein R_8 is lower alkyl.

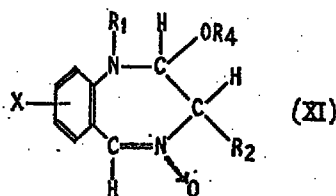
The conversion of the Schiff base VII into the aldehyde is effected by means of an acid, preferably a Lewis acid such as BF_3 .

The starting compounds of formula VIII may also be obtained by a reaction according to the following reaction scheme:



The compounds of this invention may also be prepared by reacting a benzo-diazepine-4-oxide of the general formula

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wherein R_1 , R_2 , R_4 and X are as previously defined except that R_4 is desirably other than hydrogen, with a Grignard reagent of the general formula XII



wherein R_3 is as previously defined and Hal represents a halogen atom. By hydrolysis and dehydration of the so-formed complex a compound of the general formula I is obtained.

This process may for example be performed analogously to the process described in the Belgian Patent No. 711 409.

The following examples illustrate the preparation of representative compounds of this invention and of intermediates useful in the preparation thereof:

Example 1

Preparation of 7-chloro-1-(2,2,2-trifluoroethyl)-2-hydroxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine

0.64 Grams (0.017 moles) lithium aluminium hydride are added to a stirred solution of 5.6 grams (0.016 mole) of 7-chloro-1-(2,2,2-trifluoroethyl)-1,3-dihydro-2-oxo-5-phenyl-2H-1,4-benzodiazepine in 80 ml. of dry tetrahydrofuran cooled to 0°C. After the addition is completed, the mixture is stirred a further 5 minutes, and then quenched with wet ether. The solution is filtered, dried over sodium sulfate, and concentrated under reduced pressure. The solution is then treated with a small amount of hexane and 3.0 grams of the title compound in the form of white needles (m.p. 130—131°C.) are collected.

If in the above Example 1-(2,2,2-trifluoroethyl)-1,3-dihydro-2-oxo-5-phenyl-2H-1,4-benzodiazepine is used as a starting compound the 1-(2,2,2-trifluoroethyl)-2-hydroxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine is obtained. (M.p. 123°C.—125°C.).

Example 2

Preparation of 7-chloro-1-(2,2,2-trifluoroethyl)-2-methoxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine

2.5 Grams (0.0071 moles) of 7-chloro-1-(2,2,2-trifluoroethyl)-2-hydroxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine are dissolved in 10 ml. methanol and allowed to stand at 0°C. until crystallization occurs. 2.2 Grams of the title compound (m.p. 145°C.—146°C.) are collected.

If in the above Example the methanol is replaced by ethanol, the corresponding 2-ethoxy compound is obtained (m.p. 135°C.—136°C.).

Example 3

Preparation of 7-chloro-1-methyl-2-hydroxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine

1.2 Grams (0.032 mole) of lithium aluminium hydride are added to a stirred solution of 7.0 grams (0.025 mole) of 7-chloro-1,3-dihydro-1-methyl-2-oxo-5-phenyl-2H-1,4-benzodiazepine in 150 ml. of dry tetrahydrofuran cooled to 0°C. After the addition is completed, the mixture is stirred a further 5 minutes, and then quenched with wet ether. The solution is filtered, dried over sodium sulfate, and concentrated under reduced pressure. The mixture is then triturated with ether-petroleum ether and 2.8 grams of the title compound (m.p. 125°C.—126°C.) are collected.

Similarly, one can prepare other compounds of this invention by substituting the corresponding 1,3-dihydro-2-oxo-5-aryl-2H-1,4-benzodiazepine of formula IV to produce the desired 2-hydroxy-2,3-dihydro-5-aryl-1H-1,4-benzodiazepine, as for example:

- 1-(2,2,2-trifluoroethyl-2-hydroxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine;
 7 - chloro - 1 - (2,2,2 - trifluoroethyl) - 2 - hydroxy - 2,3 - dihydro - 5 - (2 -
 pyrrol-1H-1,4-benzodiazepine;
 7 - chloro - 1 - diethylaminoethyl - 2 - hydroxy - 5 - (o - fluorophenyl) - 2,3 -
 dihydro-1H-1,4-benzodiazepine;
 6 - trifluoromethyl - 1 - (2 - isopentenyl) - 2,3 - dihydro - 2 - hydroxy - 3 -
 methyl-5-(p-chlorophenyl)-1H-1,4-benzodiazepine;
 7 - nitro - 1 - trifluoromethyl - 2 - hydroxy - 2,3 - dihydro - 5 - (p - tolyl) - 1H -
 1,4-benzodiazepine;
 1 - (2,2,2 - trifluoroethyl) 2 - hydroxy - 2,3 - dihydro - 5 - phenyl - 1H - 1,4 -
 benzodiazepine;
 7 - hydroxy - 1 - isopropyl - 2 - hydroxy - 2,3 - dihydro - 5 - (p - hydroxyphenyl) -
 1H-1,4-benzodiazepine;
 7 - methoxy - 1 - allyl - 2 - hydroxy - 2,3 - dihydro - 5 - (1 - naphthyl) - 1H -
 1,4-benzodiazepine;
 8 - bromo - 1 - (1,2,2,2 - tetrafluoroethyl) - 2 - hydroxy - 2,3 - dihydro - 3 -
 acetoxy-5-(2-thienyl)-1H-1,4-benzodiazepine;
 9 - fluoro - 1 - phenethyl - 2 - hydroxy - 2,3 - dihydro - 5 - (m - nitrophenyl) -
 1H-1,4-benzodiazepine.

20 By reaction with the appropriate alcohol (e.g. methanol, ethanol, dimethylamino-
 ethanol etc.) one can similarly produce the corresponding ethers, as for example: 20

- 7 - chloro - 1 - cyclopropylmethyl - 2 - methoxy - 2,3 - dihydro - 5 - phenyl -
 1H-1,4-benzodiazepine;
 7-chloro-1-methyl-2-methoxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine;
 7 - chloro - 1 - methyl - 2 - ethoxy - 3 - acetoxy - 2,3 - dihydro - 5 - phenyl -
 1H-1,4-benzodiazepine;
 7 - chloro - 1 - methyl - 2 - (2 - N,N - dimethylaminoethoxy) - 2,3 - dihydro -
 5-phenyl-1H-1,4-benzodiazepine;
 1,8-dimethyl-2-ethoxy-2,3-dihydro-5-(o-methoxyphenyl)-1H-1,4-benzodiazepine;
 2 - isopropoxy - 1 - methyl - 3 - propionyloxy - 2,3 - dihydro - 5 - (p - trifluoro-
 methylphenyl)-1H-1,4-benzodiazepine;
 1 - methyl - 2 - (3 - aminopropoxy) - 2,3 - dihydro - 5 - (o - fluorophenyl) - 1H -
 1,4-benzodiazepine.

Example 4

35 Preparation of 7-chloro-1-(2,2,2-trifluoroethyl)-2-hydroxy-2,3-
 dihydro-5-phenyl-1H-1,4-benzodiazepine 35

A mixture of 3.1 grams (0.01 mole) of 2-(2,2,2-trifluoroethylamino)-5-chloro-
 benzophenone and 25 ml. of aminoacetaldehyde dimethyl acetal is refluxed for 3 hours.
 The mixture is cooled, poured onto water, and the material that separates is collected.
 This material is added to 50 ml. of 0.1N hydrochloric acid and the mixture is basified
 with a saturated aqueous solution of sodium bicarbonate and extracted with chloro-
 form. The chloroform layer is dried (Na₂SO₄) and evaporated almost to dryness. It is
 then triturated with a small amount of hexane and the product collected, m.p. 130°C.—
 131°C.

45 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
 tranquilizer or anti-anxiety agents. Additionally they exhibit valuable anti-convulsant
 and muscle relaxant properties. In pharmacological testing there has been observed
 significant differentials between tranquilizing and muscle-relaxing doses and doses which
 cause neurological impairment, e.g. ataxia. The therapeutic ratio is generally higher in
 the compounds of this invention than that observed in analogous compounds presently
 known in the art. By way of further advantage, it has been found that test animals do
 not develop a tolerance to the tangible embodiments on repeated treatment in anti-
 convulsant evaluation.

55 The compounds of this invention have greater water solubility than their corres-
 ponding 2-oxo-precursors. They have a more favourable distribution constant between
 organic and aqueous layers. This factor is important in effecting greater absorption into
 the mammalian blood stream when orally administered.

60 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, Syn-
 ward, E. A. et al., J. Pharm. and Exp. Ther., Vol. 106, pg. 319 (1952) for anti-con-

vulsant activity, the Central Nervous System Activity and Acute Toxicity, Irwin, Science 136, pg. 123 (1962) for muscle relaxant and sedative-hypnotic activities, and Antagonism of Foot-Shock Induced Fighting in Mice, Tedeschi, et al., J. Pharm. and Exp. Ter., 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 0.1—5 mg/kg. of body weight per day, preferably administered orally in divided dosages. When used as an anti-convulsant the dosage range is about 2—30 mg/kg. of body weight per day, preferably orally administered in divided doses. When used as a muscle relaxant the dosage range is about 0.1—1.5 mg/kg. of body weight per day, preferably orally administered in divided doses. When used as a sedative-hypnotic the dosage range is about 3—10 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, ointments, creams and the like.

In the formulations of pharmaceutical preparations there can be employed such pharmaceutically acceptable diluents, as for example, water, gelatine, lactose, starches, magnesium stearate, talc, vegetable oils, gums and petroleum jelly.

The following examples show typical tablet and capsule formulations incorporating the compounds of this invention. The formulations are illustrative merely and no limitation is intended.

Tablet Formulations

I. Formula and Method of Manufacture for 7-chloro-1-(2,2,2-trifluoroethyl)-2-hydroxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine

Coated Tablets:		mg/core
7-Chloro-1-(2,2,2-trifluoroethyl)-2-hydroxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine		100.0
Lactose, USP		123.0
Dicalcium Phosphate		70.0
Sodium Lauryl Sulfate		15.0
Polyvinylpyrrolidone		15.0
Water 50 ml/1000 cores		
Corn Starch		30.0
Dry		
Sodium Lauryl Sulfate		3.0
Magnesium Stearate		3.0
Tablet Weight		359.0

Procedure:

The 7-chloro-1-(2,2,2-trifluoroethyl)-2-hydroxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine 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 containing 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 to 14 hours. Reduce 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 desired shade is obtained. After drying the coated tablets are polished to give the tablets an even gloss.

II. Capsule Formulations

Formula:

		mg/capsule	
5	7-Chloro-1-(2,2,2-trifluoroethyl)-2-hydroxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine	100.0	
	Sodium Lauryl Sulfate	20.0	5
	Lactose	279.0	
	Magnesium Stearate	101.0	
	Capsule Weight	500.0	

Procedure:

- 10 Mix together 7 - chloro - 1 - (2,2,2 - trifluoroethyl) - 2 - hydroxy - 2,3 - dihydro - 5-phenyl-1H-1,4-benzodiazepine, sodium lauryl sulfate and lactose. Pass through a No. 80 screen. Add magnesium stearate, mix and encapsulate into the proper size 2 piece gelatin capsule. 10

III. Suppository

Formula:

		mg/2 gs.	
15	7-Chloro-1-(2,2,2-trifluoroethyl)-2-hydroxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine, micronized	100	15
	Theobromo Oil, Pharm. Grade to make	2 gms.	

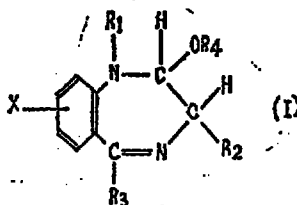
Method of Preparation:

- 20 Prepare a slurry of the 7-chloro-1-(2,2,2-trifluoroethyl)-2-hydroxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine with a portion of the melted theobroma oil and then add the rest of the oil to bring the batch to final weight. Pour the melted mix, while maintaining uniformity, into appropriately prepared molds and allow to cool. 20

- 25 Numerous variations of the above compositions of matter and processes for the manufacture will be apparent to one skilled in the art within the scope of the present invention. In particular, other active ingredients within the definition of the invention may be substituted for the active ingredients specified in formulations I to III. 25

Having regard to the provisions of Section 9 of the Patents Act, 1949, attention is directed to Patent Nos. 1,179,125; 1,179,124; and 972,968.

- 30 WHAT WE CLAIM IS:— 30
1. A 1,4-benzodiazepine of the general formula I



- 35 or a pharmaceutically acceptable salt thereof, wherein X is hydrogen, halogen, trifluoro-methyl, nitro, lower alkyl, hydroxy or lower alkoxy; R₁ is lower alkyl, polyfluoro-lower alkyl, phenyl-lower alkyl, lower cycloalkyl, lower cycloalkyl-lower alkyl, lower alkenyl or amino-lower alkyl the amino group of which may be substituted by one or more lower alkyl groups; R₂ is hydrogen, lower alkyl, hydroxy or lower alkanoyloxy; R₃ is phenyl, X-substituted phenyl, naphthyl, thienyl or pyrrolyl; and R₄ is lower alkyl, or the grouping 35

- 40
$$-\text{CH}_2 \cdot \text{CH}_2 \cdot (\text{CH}_2)_n \cdot \text{N} \begin{matrix} \text{R}_5 \\ \text{R}_6 \end{matrix}$$
 40

wherein n is 0 or 1 and R₅ and R₆ are hydrogen or lower alkyl, and may additionally be hydrogen when X is hydroxy and/or R₁ is polyfluoro-lower alkyl, phenyl-lower alkyl, lower cycloalkyl-lower alkyl, lower alkenyl or amino-lower alkyl the amino group of

II. Capsule Formulations

Formula:		mg/capsule	
5	7-Chloro-1-(2,2,2-trifluoroethyl)-2-hydroxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine	100.0	5
	Sodium Lauryl Sulfate	20.0	
	Lactose	279.0	
	Magnesium Stearate	101.0	
	Capsule Weight	500.0	

Procedure:

- 10 Mix together 7-chloro-1-(2,2,2-trifluoroethyl)-2-hydroxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine, sodium lauryl sulfate and lactose. Pass through a No. 80 screen. Add magnesium stearate, mix and encapsulate into the proper size 2 piece gelatin capsule. 10

III. Suppository

Formula:		mg/2 gs.	
15	7-Chloro-1-(2,2,2-trifluoroethyl)-2-hydroxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine, micronized	100	15
	Theobromo Oil, Pharm. Grade to make	2 gms.	

Method of Preparation:

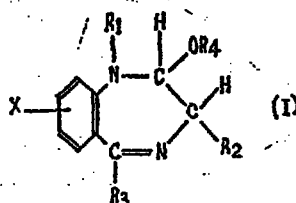
- 20 Prepare a slurry of the 7-chloro-1-(2,2,2-trifluoroethyl)-2-hydroxy-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine with a portion of the melted theobroma oil and then add the rest of the oil to bring the batch to final weight. Pour the melted mix, while maintaining uniformity, into appropriately prepared molds and allow to cool. 20

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- 30 WHAT WE CLAIM IS:— 30

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



- 35 or a pharmaceutically acceptable salt thereof, wherein X is hydrogen, halogen, trifluoro-methyl, nitro, lower alkyl, hydroxy or lower alkoxy; R₁ is lower alkyl, polyfluoro-lower alkyl, phenyl-lower alkyl, lower cycloalkyl, lower cycloalkyl-lower alkyl, lower alkenyl or amino-lower alkyl the amino group of which may be substituted by one or more lower alkyl groups; R₂ is hydrogen, lower alkyl, hydroxy or lower alkanoyloxy; R₃ is phenyl, X-substituted phenyl, naphthyl, thienyl or pyrrolyl; and R₄ is lower alkyl, or the grouping 35

- 40
$$-\text{CH}_2 \cdot \text{CH}_2 \cdot (\text{CH}_2)_n \cdot \text{N} \begin{matrix} \text{R}_5 \\ \text{R}_6 \end{matrix}$$
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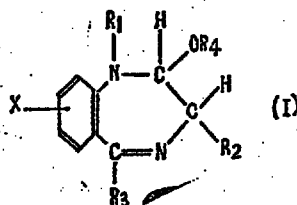
wherein n is 0 or 1 and R₅ and R₆ are hydrogen or lower alkyl, and may additionally be hydrogen when X is hydroxy and/or R₁ is polyfluoro-lower alkyl, phenyl-lower alkyl, lower cycloalkyl-lower alkyl, lower alkenyl or amino-lower alkyl the amino group of



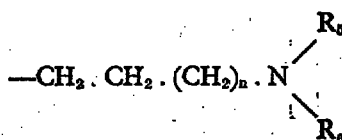


which may be substituted by one or more lower alkyl groups and/or R_2 is lower alkyl, hydroxy or lower alkanoyloxy.

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

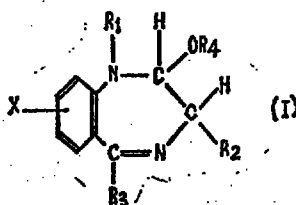


or a pharmaceutically acceptable salt thereof, wherein X is hydrogen, halogen, trifluoromethyl, nitro, lower alkyl, or lower alkoxy; R_1 is lower alkyl, polyfluoro-lower alkyl, phenyl-lower alkyl, lower cycloalkyl or lower alkenyl; R_2 is hydrogen, lower alkyl, hydroxy or lower alkanoyloxy; R_3 is phenyl, X-substituted phenyl, naphthyl, thienyl or pyreryl; and R_4 is lower alkyl, or the grouping



wherein n is 0 or 1 and R_5 and R_6 are hydrogen or lower alkyl, and may additionally be hydrogen when R_1 is polyfluoro-lower alkyl, phenyl-lower alkyl, or lower alkenyl and/or R_2 is lower alkyl, hydroxy or lower alkanoyloxy.

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



or a pharmaceutically acceptable salt thereof, wherein X is hydrogen, halogen, trifluoromethyl, nitro, lower alkyl, or lower alkoxy; R_1 is polyfluoro-lower alkyl; R_2 is hydrogen, lower alkyl, hydroxy or lower alkanoyloxy; R_3 is phenyl, X-substituted phenyl, naphthyl, thienyl or pyreryl; and R_4 is hydrogen.

4. A compound according to claim 1, wherein R_1 is polyfluoro-lower alkyl.

5. A compound according to claim 4 wherein R_1 is 2,2,2-trifluoroethyl.

6. A compound according to any one of claims 1, 4 and 5, wherein X is a 7-chloro-substituent.

7. A compound according to any one of claims 1 and 4 to 6, wherein R_3 is phenyl.

8. A compound according to any one of claims 1 and 4 to 7, wherein R_4 is methyl.

9. 7 - Chloro - 1 - (2,2,2 - trifluoroethyl) - 2 - hydroxy - 2,3 - dihydro - 5 - phenyl-1H-1,4-benzodiazepine.

10. 7 - Chloro - 1 - (2,2,2 - trifluoroethyl) - 2 - methoxy - 2,3 - dihydro - 5 - phenyl-1H-1,4-benzodiazepine.

11. A 1,4-benzodiazepine as claimed in claim 1 or a pharmaceutically acceptable salt thereof, substantially as hereinbefore described.

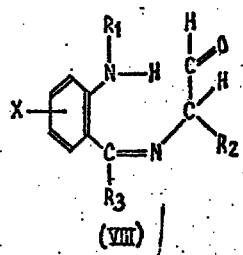
12. Process for the preparation of a 1,4-benzodiazepine claimed in claim 1 or of a salt thereof which process comprises treating a compound of the general formula VIII



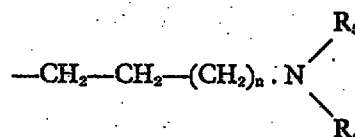
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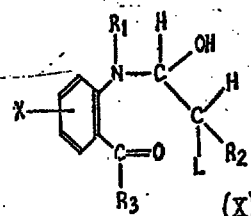


wherein R_1 , R_2 , R_3 , and X are as defined in claim 1 with a base whereby the ring is closed and a 2-hydroxy compound of formula I set forth in claim 1 is obtained; and for the preparation of those compounds of formula I in which R_4 is lower alkyl or the grouping

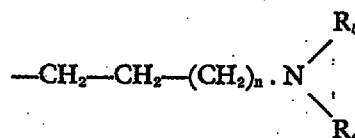


n , R_5 and R_6 being as defined in claim 1, etherifying the 2-hydroxy compound accordingly and, if desired, transforming a compound obtained by any of the previous steps into a pharmaceutically acceptable salt.

13. Process for the preparation of a 1,4-benzodiazepine claimed in claim 1 or of a salt thereof which process comprises subjecting a compound of the general formula X

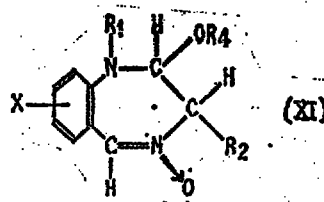


wherein R_1 , R_2 , R_3 and X are as defined in claim 1 and L is a free or protected amino group, to an intramolecular condensation whereby a 2-hydroxy compound of formula I is obtained, and for the preparation of those compounds of formula I set forth in claim 1 in which R_4 is lower alkyl or the grouping



n , R_5 and R_6 being as defined in claim 1, etherifying the 2-hydroxy compound accordingly; and, if desired, transforming a compound obtained by any of the previous steps into a pharmaceutically acceptable salt.

14. Process for the preparation of a 1,4-benzodiazepine claimed in claim 1 or of a salt thereof, which process comprises reacting a compound of the general formula XI



wherein R_1 , R_2 , R_3 and X are as defined in claim 1, with a Grignard reagent of the general formula XII



wherein R_3 is as defined in claim 1 and Hal represents a halogen atom; hydrolysing and dehydrating the so-formed complex to a compound of general formula I set forth in claim 1 and, if desired, transforming the compound obtained into a pharmaceutically acceptable salt.

15. A process according to any one of claim 12 to 14 and substantially as hereinbefore described and exemplified.

16. A 1,4-benzodiazepine having the general formula I set forth in claim 1 or a pharmaceutically acceptable salt thereof, whenever prepared by a process according to any one of claims 12 to 15.

17. A pharmaceutical composition comprising a compound as defined in any one of claims 1, 4 to 10 and 16 as an active ingredient in admixture with a suitable pharmaceutically acceptable carrier.

18. A composition according to claim 17, in the form of a solid shaped dosage unit.

19. A composition according to claim 18, wherein the dosage unit is a tablet.

20. A composition according to claim 18, wherein the dosage unit is a capsule.

21. A composition according to claim 17 in the form of a liquid solution or suspension.

22. A composition according to claim 21, wherein the liquid is sterile, for use as an injectable.

23. A pharmaceutical composition according to claim 17 and substantially as hereinbefore described and exemplified.

24. Process for the preparation of a pharmaceutical composition which comprises admixing a compound as claimed in any one of claims 1, 4 to 10 and 16 with a suitable therapeutical carrier.

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