

PATENT SPECIFICATION

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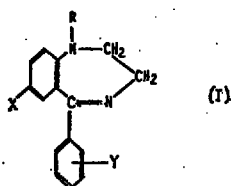
(54) NOVEL 1-POLYFLUOROALKYL-BENZODIAZEPINES AND
 METHODS FOR THEIR PRODUCTION

(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 2,3-dihydro-5-aryl-1H-1,4-benzodiazepine compounds, to the 4-oxides and the pharmaceutically acceptable salts thereof, to processes for making such novel compounds and to pharmaceutical compositions containing them.

The compounds of the invention affect mammalian central nervous systems and in particular, are useful as anti-anxiety agents, sedatives, muscle relaxants and anti-convulsants.

The compounds of this invention are those having the general formula:



and 4-N-oxides and pharmaceutically acceptable salts of such compounds, wherein in the formula X is halogen, trifluoromethyl or nitro; Y represents hydrogen, halogen, trifluoromethyl, nitro, hydroxy, lower alkyl or lower alkoxy; and R is a polyfluoro-lower alkyl group.

As used herein, the term "lower alkyl" refers to both straight and branched-chain alkyl radicals having up to six carbon atoms such as methyl, ethyl propyl, isopropyl, n-butyl, t-butyl and the like. The term "lower alkoxy"

refers to -O-lower alkyl radicals wherein the lower alkyl moiety is as defined above, such as methoxy, ethoxy, propoxy and the like. The term "halogen" as used herein comprehends fluorine, chlorine, bromine and iodine. Chloro is the preferred X substituent and ortho-fluoro is the preferred Y substituent.

The term "polyfluoro-lower alkyl" refers to lower alkyl radicals substituted with more than one fluoro radical 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 alpha hydrogen atoms, i.e. R_1CH_2 —wherein R_1 is polyfluoroalkyl. Most preferably, R_1 is trifluoromethyl, i.e. R represents a 2,2,2-trifluoroethyl group.

The compounds may be used in the form of their therapeutically acceptable acid addition salts. Such salts include those formed in the conventional manner 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.

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

One basic approach for preparing the compounds of this invention comprises subjecting to an intramolecular condensation a starting compound differing from a compound of formula (I) or from a 4-oxide thereof, only in that the diazepine ring is broken at one place only, with each of the ring members adjacent to such break being substituted by an atom or group of atoms capable of being eliminated under the reaction conditions applied so as to close the diazepine ring.

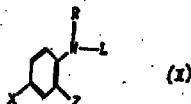
One embodiment of the process outlined

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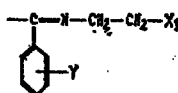
above comprises subjecting a compound of the general formula (II)



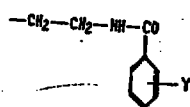
- 5 wherein X represents halogen, trifluoromethyl or nitro; R is a polyfluoro-lower alkyl group; Z is hydrogen, a



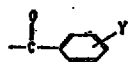
group or a



- 10 group; and, when Z is H, then L is a

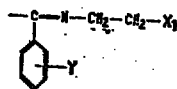


group, and when Z is a



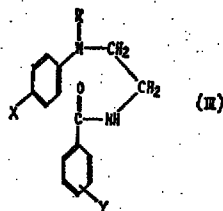
group, then L is a $-\text{CH}_2-\text{CH}_2-\text{R}_4$ group,

- 15 and when Z is a



- 20 group, then L is H (Y being halogen, hydrogen, trifluoromethyl, nitro, hydroxy, lower alkyl or lower alkoxy; R_4 being a free or protected amino group; and X_1 being an atom or group capable of being eliminated, under the reaction conditions applied, together with the hydrogen atom represented by L), to an intramolecular condensation.

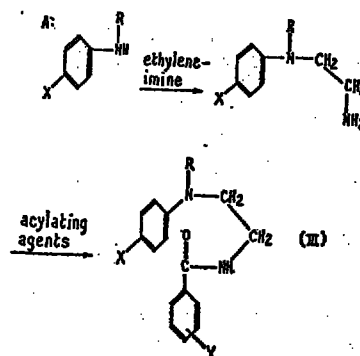
- 25 The preferred starting compounds of the general formula (II) are



wherein X, Y and R are as defined above.

The aroylated diamines of formula (III) can be cyclized to the desired benzodiazepines employing standard dehydration reagents and techniques. A preferred dehydrating agent is a mixture of phosphorus pentoxide and phosphorus oxychloride. Generally, the aroylated diamines and dehydrating agent are maintained in intimate contact for several hours. The desired benzodiazepines of formula (I) can then be recovered by conventional methods and are preferably extracted with an organic solvent.

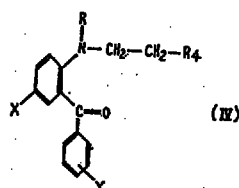
The compounds of formula (III) may be prepared, as illustrated by the following reaction scheme:



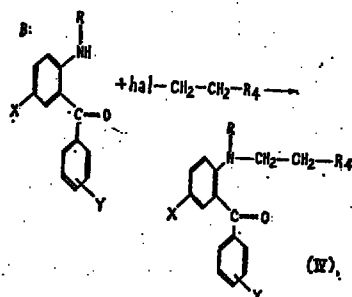
The para-substituted -N-(polyfluorolower alkyl)-anilines of this reaction scheme may be prepared as described in U.S. Patent No. 3,429,874 (see Example 10). The novel diamines may be prepared by the Friedel-Crafts alkylation of the anilines using ethyleneimine employing the usual Friedel-Crafts reaction techniques. Molar amounts of a suitable catalyst such as aluminium chloride or ferric chloride are employed. The resultant complex can be broken up with water, basified, and the organic components extracted with a suitable organic solvent such as methylene chloride. The organic extract is then extracted with aqueous dilute acid. The aqueous extract is then rendered basic and the desired diamines are extracted with a suitable organic solvent such as chloroform.

The diamines are then aroylated using suitable acylating agents in the conventional manner. Generally the desired benzoyl halide, and particularly the chloride is a preferred acylating agent. An organic solvent such as dry ether containing a tertiary amine such as triethylamine is employed for the aroylation. The desired aroylated diamine of formula (III) can then be recovered by conventional work-up.

Further representations of the starting compounds of formula (II) are compounds of the general formula (IV)

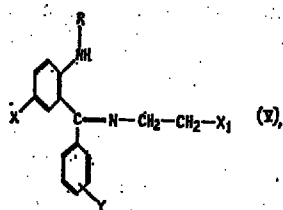


wherein X, Y, R and R₄ are as defined above. Preferably R₄ represents an amino group protected by hydrolysable acid residues, such as benzoyl, phthaloyl, tosyl, lower alkanoyl and the like. The hydrolysis is preferably carried out in acid media, whereby one preferred embodiment is the use of mineral acids, such as sulfuric acid or hydrochloric acid. The reaction can be carried out at room temperature but is preferably accomplished by heating in an inert organic solvent. The starting compounds of the general formula (IV) may be obtained as indicated in the following reaction scheme:



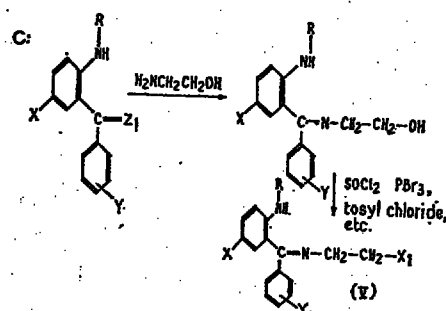
wherein hal represents halogen, preferably bromo. Preferred β-acylaminoethyl reactants are compounds such as β-bromoethylbenzamide, β-bromoethylphthalimide, or β-tosylaminoethyl bromide and β-aminoethyl bromide. The reaction is carried out in an inert organic solvent, such as pyridine at elevated temperatures.

In a further example of the intramolecular condensation process a compound of the general formula (V)



wherein X₁, Y, R and X are as defined above is used as a starting compound. Preferably X₁ represents an inorganic or organic ester moiety, such as halogen, arylsulphonate or alkylsulphonate. The process is preferably carried out at temperatures from 50°C to 150°C.

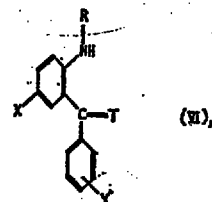
The compounds of the formula (V) may be obtained as illustrated in the reaction scheme:



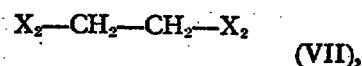
wherein X, Y, R and X₁ are as defined above and Z₁ represents an oxygen atom, an imino group or a N-alkyl group.

Another basic approach for preparing the compounds of this invention comprises condensing a first reactant which contains the benzene moiety and part of the structural elements of the diazepine moiety of the compounds of formula (I), with a second reactant containing those structural elements of the diazepine moiety missing in the first reactant, said first and second reactants having attached to those positions of their molecules where they are to be linked together, atoms or groups of atoms capable of being eliminated, under the reaction conditions applied, so as to form the diazepine ring.

In a preferred embodiment of this process a first reactant of the general formula (VI)



is condensed with a second reactant of the general formula (VII)



whereby in the formulae R, X and Y are as above defined; T is an oxygen atom or an imino group; and when T is an imino group, then each X₂ is an atom or group capable of being eliminated under the reaction conditions applied, together with the N-hydrogen atoms, and when T is oxygen, then both X₂ together represents an imino group.

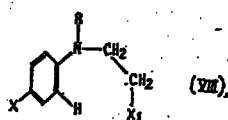
Thus the benzodiazepine ring may be completed by reacting a compound of the general formula (VI) wherein T is NH with a compound of the general formula (VII) wherein each X₂ is a reactive organic or inorganic ester moiety such as halogen, arylsulphonate or alkylsulphonate. Preferably X₂ is bromo, mesyl or

tosyl. An excess of the compound of the general formula (VII) may be used as reaction medium, however the reaction may also be carried out in organic solvents such as halogenated hydrocarbons, ethers, alcohols or aromatic hydrocarbons and in basic solvents such as pyridine, triethylamine or tributylamine which act as a binding agent for the acid formed by the reaction. The atom or groups X_2 in formula (VII) may be the same or different.

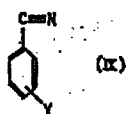
Typical examples for the compounds (VII) are 1 - iodo - 2 - bromoethane, ethylenedibromide and 1 - chloro - 2 - bromoethane. The compound of formula (VI) may be obtained by reacting the corresponding benzophenone with ammonia in the presence of a catalyst such as stannous chloride.

In a further example of the cyclisation reaction a compound of the general formula (VI) wherein T represents an oxygen atom is reacted with ethylenimine as the second reactant. The reaction is preferably carried out at elevated temperatures but may also be effected at room temperature or even below. Temperatures of from about 40°C to about 100°C are most preferred. The reaction is preferably carried out in the presence of an inert organic solvent such as benzene, an ether or the like.

The compounds of the general formula (I) may also be obtained by subjecting a compound of the general formula (VIII)

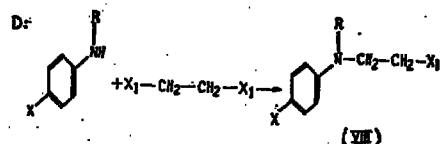


to a condensation reaction with a compound of the general formula (IX)



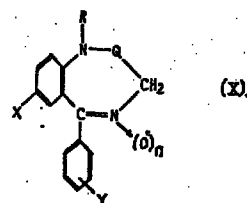
wherein the formulae R, X and Y are as defined above, and X_1 represents an atom or group capable of being eliminated, under the reaction conditions applied, together with the hydrogen atom depicted at the phenyl ring of formula (VIII). Preferably the condensation reaction is carried out in the presence of a Lewis acid such as tin tetrachloride, aluminium chloride, titanium tetrachloride, ferric chloride, boron trifluoride or the like. Most preferred are tin tetrachloride and aluminium chloride. The reaction may be carried out in an inert organic solvent, such as nitrobenzene or in the melt at temperatures from about 50°C to about 200°C. Typical atoms or groups represented by X_1 are halogen, arylsulphonate, alkylsulphonate and hydroxy. Bromo and chloro are most preferred.

The compounds of formula (VIII) may be obtained according to the following reaction scheme



The reactants are heated to reflux temperature in an inert organic solvent for about one day and the desired compound is isolated by known methods.

A further basic approach for preparing the compounds of the general formula (I) comprises reducing a compound of the general formula (X)



wherein R, X and Y are as defined above except that they may not represent substituents which interfere with the reduction process under the conditions of reaction applied, Q is

$-\text{CH}_2-$, $-\text{C}(=\text{S})-$, or $-\text{C}(=\text{O})-$ and when Q is $-\text{CH}_2-$, then n is one, and when Q is $-\text{C}(=\text{S})-$ or $-\text{C}(=\text{O})-$, then n is zero or one; at position 2 and/or 4.

In a preferred embodiment of this process a compound of formula (X) wherein Q is $-\text{C}(=\text{S})-$

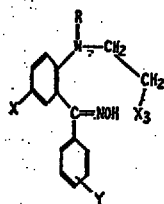
or $-\text{C}(=\text{O})-$ and n is zero is reduced by means of a complex metal hydride or by means of catalytic hydrogenation. When Q represents the

$-\text{C}(=\text{S})-$ grouping the reduction is preferably carried out with hydrogen in the presence of a catalyst such as Raney-nickel and an inert organic solvent, such as acetone, ethanol, dioxane or the like. The reaction can be effected at room temperature or below or with the application of heat. Most preferred is the reflux temperature.

The starting compounds of the general formula (X) wherein Q is the $-\text{C}(=\text{S})-$ grouping may be obtained by the reaction of the corresponding benzodiazepine-2-one compound with

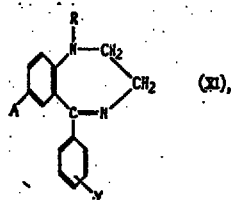
a thiating agent such as phosphorus pentasulfide in an inert organic solvent at elevated temperatures. While the reduction of the 2-thiono compounds is a preferred embodiment of this process for the preparation of the compounds of formula (I), the reduction of the corresponding 2-one compounds is less important, because significant amounts of 2,3,4,5-tetrahydro-1H-1,4-benzodiazepine compounds are formed as by-products which may be dehydrogenated as described below in order to also obtain the desired product.

A further embodiment is the reduction of a compound of formula (X), wherein Q represents a methylene group and n is one. As desoxygenating agent preferably is used phosphorus trichloride and the reaction may be carried out in an inert organic solvent, such as chloroform or methylene chloride at room temperature or with the application of heat, preferably at reflux temperature. The starting compounds may be obtained by controlled oxidation of the corresponding 4-unsubstituted 1,4-benzodiazepines employing, for example, a peracid such as m-chloroperbenzoic acid, or by a cyclisation of a compound of the general formula



wherein X, Y and R are as defined above and X₃ is an atom or group capable of being eliminated under the reaction conditions applied, such as halogen.

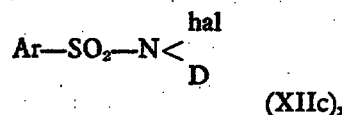
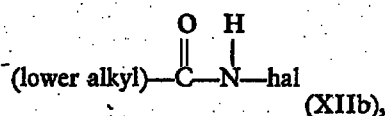
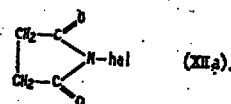
Those compounds of general formula (I) wherein X represents halogen may also be prepared by halogenation in position 7 of compounds of the general formula (XI)



wherein R and Y are as defined above and A represents a hydrogen atom or a —NH₂ group. When A is NH₂ the compound of the formula (XI) is subjected to a diazotisation and to a subsequent Sandmeyer reaction, so as to replace the diazonium grouping by the desired halogen atom. The diazotisation and the Sandmeyer reaction are carried out according to

techniques well known in the art. The starting compounds may be obtained by reducing the corresponding 7-nitro-benzodiazepine compounds in the presence of Raney-nickel or by using starting compounds in the preparation of the diazepine ring which are substituted in the corresponding position with a free or protected amino group.

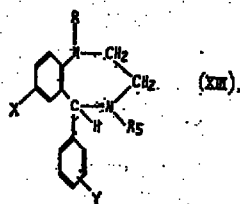
When A represents a hydrogen atom then the compound of formula (XI) is treated with a halogenating agent, preferably one capable of providing halogen cations to obtain a compound of formula (I). Useful halogenating agents are halogen, hypohalogenite esters or compounds containing the group >N-hal, wherein hal represents halogen, preferably bromo or chloro. An example for the hypohalogenite esters is hypohalogenite tert. butyl ester. The >N-hal group containing compounds may be represented by compounds of the general formulae (XIIa), (XIIb) and (XIIc)



wherein hal is halogen; Ar is phenyl or preferably substituted phenyl and D represents hydrogen or lower alkyl. Representatives of such compounds are N-chlorosuccinimide, N-bromosuccinimide, N-chloroacetamide, N-bromoacetamide, N-chlorobenzenesulfonamide, N-chlorotoluenesulfonamide or N-chloro-N-methyltoluenesulfonamide. If the chlorinating agent is a compound containing the >N-hal group, the reaction is preferably carried out in the presence of a catalyst capable of forming free radicals such as azo-bis-lower-alkyl nitriles, di-lower alkyl peroxides, diacyl peroxides, peresters or hydroperoxides. Azo-bis-isobutyronitrile, 2,2'-azo-bis-(2-methylpropionitrile), di-tert.-butyl peroxide, acetyl peroxide, perbenzoic acid tert. butyl ester and tert. butyl hydroperoxide exemplify these catalysts. The preferred catalyst is 2,2'-azo-bis-(2-methylpropionitrile) and the preferred halogenating agent N-chlorosuccinimide. In general the reaction is performed in an inert organic solvent such as weak organic acids or chlorinated hydrocarbons e.g. chlorobenzene, carbon tetrachloride, methylene chloride, chloroform,

acetic acid or formic acid. When an organic acid is used the presence of a buffer would be advantageous. The reaction can be conducted at room temperature or above. In the presence of a catalyst the reaction should be conducted at the temperature at which the catalyst forms free radicals.

- 5
10 A further basic approach for preparing the compounds of formula (I) comprises subjecting a starting compound of the general formula (XIII)



- 15 wherein R, X and Y are as defined above and R₅ represents an atom or grouping of atoms which, under the reaction conditions applied, is removed together with the hydrogen atom at C—5, to an elimination reaction whereby the 4,5-double bond is introduced. Preferably R₅ represents a free or esterified hydroxy group, such as an aryl-SO₃— group, an alkyl-SO₃— group or a lower alkanoyloxy group having up to six carbon atoms or hydrogen.

- 20 The 4-unsubstituted 1H-2,3,4,5-tetrahydro-1,4-benzodiazepines may be applied as starting compounds in that embodiment of the aforementioned process for the preparation of compounds of Formula (I) wherein R₅ in formula (XIII) represents a hydrogen atom. These starting compounds are subjected to a dehydrogenation reaction which may be performed by means of a dialkyl azodicarboxylate such as diethyl azodicarboxylate, a quinone such as 2,3-dichloro-5,6-dicyanobenzoquinone or chloranil, or a metal salt of a hypohalogenous acid such as sodium hypoiodite in an organic solvent such as aliphatic or aromatic hydrocarbons, alkanols, dioxan and the like. When dialkyl azodicarboxylate or a quinone is used as dehydrogenating agent, the preferred solvents are benzene, toluene and xylene, whereas the preferred solvent is methanol when a metal salt of a hypohalogenous acid is applied as dehydrogenating agent. The reaction can be conducted at room temperature or above or below room temperature, but is preferably effected with the application of heat. Temperatures of from about 0°C to about 100°C are suitable and in the presence of a metal salt of hypohalogenous acid room temperature is most preferred.

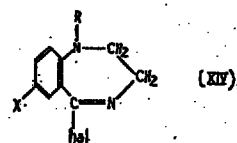
- 50 When R₅ in formula (XIII) represents an esterified hydroxy group, compounds of formula (I) are obtained by the elimination of the acid by means of a base. Alkali metal hydrides e.g. sodium hydride, triethylamine, alkali metal amides e.g. sodium amide, alkali

metal alkoxides e.g. sodium methoxide are preferred agents for the elimination. The reaction can be carried out in an inert organic solvent such as ethers, alkanols, hydrocarbons e.g. ethanol, benzene and toluene or dimethyl formamide at temperatures from about -30°C to about 120°C. The hydroxy groups can be esterified with a carboxylic acid, e.g. an alkanoyl group such as acetyl or an aroyl group such as benzoyl, or with a sulphonic acid, e.g. the tosyl or mesyl group.

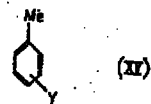
The starting compounds for the aforementioned embodiment may be obtained by reacting the 4-hydroxy compound with the corresponding acid anhydride or acid chloride in the presence of a base and an organic solvent at temperatures from about -30°C to about 100°C.

The compounds of formula (I) may also be obtained by dehydration of a starting compound of formula (XIII) wherein R₅ represents a free hydroxy group. The dehydration can be carried out with a carbodiimide such as dicyclohexylcarbodiimide or an α -alkenylamine. A suitable medium for this reaction is an inert organic solvent such as hydrocarbons, e.g. benzene, toluene, or ethers, e.g. dioxane. The reaction can be conducted at room temperature or above or below room temperature, preferably from about -20°C to about 100°C. The starting compounds may be prepared by the reduction of the corresponding 4-N-oxides with hydrogen in the presence of platinum oxide in an organic solvent such as glacial acetic acid or an alkanol at temperatures from 0°C to 80°C.

Another basic approach for preparing the compounds of the general formula (I) comprises reacting a compound of the general formula (XIV)



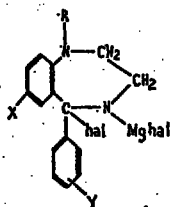
wherein X and R are as defined above and hal represents a halogen atom, with an organometallic compound of the general formula (XV)



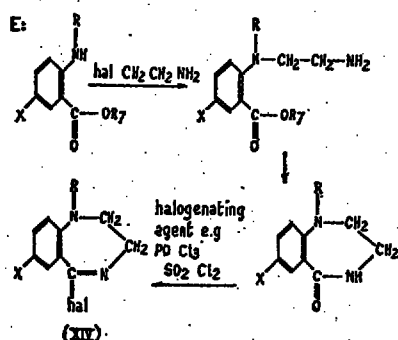
where Y is as defined above and Me represents the metal-containing moiety of the organometallic compound.

Preferred organometallic compounds are the corresponding phenyl magnesium halides and the corresponding phenyl-lithium, sodium or potassium compounds. When a phenyl magnesium halide is used as starting material, inter-

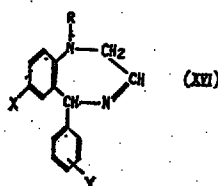
mediates of the general formula given below are formed, which are subsequently transformed into the final product:



- 5 Suitable solvents for the reaction are hydrocarbons such as benzene, toluene or xylene, chlorinated hydrocarbons such as chlorobenzene and ethers such as tetrahydrofuran, diethyl ether, dioxane. The reaction is conducted at temperatures ranging from about -60°C to about 30°C .
- 10 The starting materials may be obtained as illustrated by the following reaction scheme



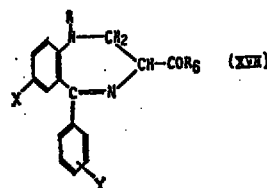
- 15 wherein X, R and hal are as defined above and R₆ represents alkyl or the hydrogen atom.
- A further fundamental approach for preparing the compounds of formula (I) comprises the isomerisation of a compound of formula (XVI)
- 20



- wherein X, R and Y are as defined above, whereby the 3,4-double bond is moved to the position 4,5 of the benzodiazepine ring. The isomerization is preferably performed by subjecting the starting material to treatment with a basic agent such as alkali metal alkoxides, alkali metal hydrides or tertiary organic amines such as sodium methoxide, sodium hydride and triethylamine. The reaction may be carried out in an inert organic solvent such as hydrocarbons, ethers and alkanols at temperatures from about -40°C to about 120°C .
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- 30

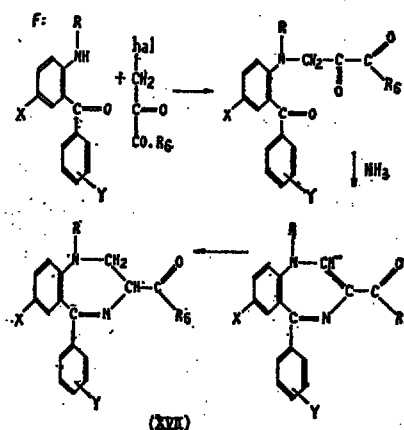
A suitable method for obtaining the starting materials is the separation of a mixture containing the corresponding 3,4- and 4,5-double bond compounds. This mixture may be formed in the process for introducing a double bond in position 4,5 of the diazepine ring by elimination of groups such as esterified hydroxy, e.g. aryl SO_3 —, alkyl- SO_3 — or alkanoyloxy from position 4 together with hydrogen from position 5.

Still another basic approach for preparing the compounds of formula (I) comprises subjecting a compound of the general formula (XVII)



wherein X, R and Y are as defined above and R₆ represents a hydrolysable grouping, to a hydrolysis and decarboxylation reaction. The hydrolysis may be for example carried out by treating the compounds of formula (XVII) with a basic agent such as alkali metal hydroxides, alkaline earth metal hydroxides or tertiary organic amines. Sodium hydroxide, potassium hydroxide and triethylamine are examples thereof. The decarboxylation can be conducted slowly without the application of heat, rapidly with the application of heat or in a strong acid medium.

The starting materials may be obtained, as illustrated by the following reaction scheme:



Obvious equivalents of the afore-described processes are those wherein the corresponding N-1-unsubstituted compounds are first prepared in an analogous manner and are then converted into the compounds of the invention by means of polyfluoroalkylation as described in British Patents Nos. 1,179,124 and

layer with sodium sulphate and concentrate in vacuo. Crystallize the residue from petroleum ether to obtain 7 - nitro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (o - fluorophenyl) - 1H - 1,4 - benzodiazepine.

Example 6

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

10 Add 9 g. of tin tetrachloride to a mixture of 8.2 g. of benzonitrile and 15 g. of N - (2,2,2 - trifluoroethyl) - N - (2 - chloroethyl) - p - chloro - aniline, and heat for three hours at 120°C. After cooling add 80 ml. of ether and 200 ml. of dilute sodium hydroxide solution. Then separate the ether layer, wash with water three times, dry with sodium sulphate, filter, and evaporate the solvent. After crystallisation from petroleum ether obtain 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 1H - 1,4 - benzodiazepine, m.p. 65—67,5°C.

Example 7

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

25 Treat 10 g. of 7 - chloro - 1 - (2,2,2 - trifluoroethyl) - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepine - 2 - thione in 300 ml. of acetone with hydrogen and 10 g. of Raney nickel (washed previously with water, ethanol and finally acetone), and heat the mixture under reflux for two hours. Then cool, filter off the Raney nickel and wash it with ethanol. 35 Evaporate the combined filtrates, dissolve the residue in methylene chloride, wash the resulting solution with water and dry over magnesium sulphate. After evaporation of the solvent dissolve the residue in ether and extract with cold dilute hydrochloric acid. Basify the aqueous solution with dilute sodium hydroxide and extract the product into ether. Wash this extract with water, dry over magnesium sulphate and evaporate the solvent. Crystallize the residue from petroleum ether and obtain 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 1H - 1,4 - benzodiazepine, m.p. 65—67,5°C.

Example 8

Preparation of 7-chloro-2,3-dihydro-1-(2,2,2-trifluoroethyl)-5-(o-fluorophenyl)-1H-1,4-benzodiazepine.

50 To a solution of 1.3 g. of 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (o - fluorophenyl) - 1H - 1,4 - benzodiazepine - 4 - oxide in 20 ml. of chloroform add 2.5 ml. of phosphorus trichloride. Stir the solution for one hour at the reflux temperature, cool the mixture and pour it into a mixture of methylene chloride, excess 50 per cent potassium hydroxide solution and ice. Stir the mixture vigorously and separate the organic layer. After

extracting the aqueous phase three times with methylene chloride, combine the organic layers, wash with water five times and dry over sodium sulphate. Evaporate the solvent and crystallize the residue from petroleum ether to give 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (o - fluorophenyl) - 1H - 1,4 - benzodiazepine, m.p. 81—83°C.

Example 9

Preparation of 7-chloro-2,3-dihydro-1-(2,2,2-trifluoroethyl)-5-(o-chlorophenyl)-1H-1,4-benzodiazepine hydrochloride.

To a cooled (−3° to +5°C), stirred solution of 11.8 g. of 7 - amino - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (o - chlorophenyl) - 1H - 1,4 - benzodiazepine dihydrochloride in 40 ml. of 1N hydrochloric acid add during 10 minutes 40 ml. of 1N aqueous sodium nitrite. Add the diazonium chloride solution formed during 10 minutes to a hot stirred solution of 3.7 g. of cuprous chloride in 70 ml. of concentrated hydrochloric acid diluted with 40 ml. of water. Keep the mixture for ten minutes at 80—90°C., and then cool. Then add ice, water, and an excess of ammonium hydroxide, and extract the reaction product with methylene chloride. Dry the organic layer, concentrate in vacuo to dryness and dissolve the residue in ethanol. Add an excess of ethanolic hydrogen chloride and again concentrate the solution. Add ether to the solution to obtain 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (o - chlorophenyl) - 1H - 1,4 - benzodiazepine hydrochloride, m.p. 188°—198°C.

Example 10

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

Reflux a solution of 120 mg. of 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 1H - 1,4 - benzodiazepine and 65.1 mg. of N-chlorosuccinimide in 4 ml. of methylene chloride under nitrogen for 24 hours. Remove the solvent in vacuo and triturate the residue five times with ether. Filter the combined extracts and wash with water to remove the excess of succinimide. Dry over sodium sulphate and evaporate the solvent. Crystallize the residue from petroleum ether and obtain 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 1H - 1,4 - benzodiazepine, m.p. 65°—67.5°C.

Example 11

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

Add 0.3 g. of sodium hydride, dispersed in mineral oil, to a solution of 3.4 g. of 7 - chloro - 2,3,4,5 - tetrahydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 4 - (p - toluenesulphonyloxy) - 1H - 1,4 - benzodiazepine in 38

ml. of dry N,N-dimethylformamide. Stir the mixture for two hours at room temperature and leave it for 48 hours. Then pour the mixture into 100 ml. of water and extract twice with methylene chloride. Wash the combined extracts with water, dry over sodium sulphate and evaporate the solvent. After crystallisation from petroleum ether obtain 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 1H - 1,4 - benzodiazepine, m.p. 65—67.5°C.

Example 12

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

Reflux 2.2 g of 7 - chloro - 2,3,4,5 - tetrahydro - 1 - (2,2,2 - trifluoroethyl) - 4 - acetoxy - 5 - phenyl - 1H - 1,4 - benzodiazepine in 30 ml. of ethanol with 5 ml. of triethylamine for 30 minutes. Evaporate the solvent in vacuo and chromatograph the residue over silica gel with ether and hexane. Small amounts of 7 - chloro - 1,2 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 5H - 1,4 - benzodiazepine are first eluted, followed by 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 1H - 1,4 - benzodiazepine, m.p. 65°—67.5°C.

Example 13

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

Reflux 0.7 g. of 7 - chloro - 2,3,4,5 - tetrahydro - 1 - (2,2,2 - trifluoroethyl) - 4 - hydroxy - 5 - phenyl - 1H - 1,4 - benzodiazepine and 0.6 g. of dicyclohexylcarbodiimide in 20 ml. toluene for twenty hours. Separate the precipitated dicyclohexylurea and extract the filtrate three times with dilute hydrochloric acid. Then render the extracts alkaline with ammonia and extract with methylene chloride, dry the solution over sodium sulphate and evaporate the solvent. Crystallize from petroleum ether and obtain 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 1H - 1,4 - benzodiazepine, m.p. 65°—67.5°C.

Example 14

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

Add a solution of phenyl magnesium bromide in 250 ml. of tetrahydrofuran to a solution of 4.5 g. of 5,7 - dichloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 1H - 1,4 - benzodiazepine in 75 ml. of tetrahydrofuran, and stir one hour at reflux temperature. Allow to cool, dilute with 400 ml. of ether and acidify the solution with acetic acid. Separate the aqueous layer, make it alkaline with sodium hydroxide and extract three times with ether. Wash the united extracts with water and dry over sodium sulphate. Then evaporate the solvent in vacuo and crystallize the residue from

petroleum ether and obtain 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 1H - 1,4 - benzodiazepine, m.p. 65—67.5°C.

Example 15

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

Stir a mixture of 0.32 g. of 7 - chloro - 1,2 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 5H - 1,4 - benzodiazepine and a solution of 0.1 g of sodium in 10 ml. of ethanol for one hour, neutralize with glacial acetic acid and evaporate the solvent. Take up the residue in a mixture of methylene chloride and sodium hydroxide and separate the organic layer. After evaporating the solvent and crystallizing the residue from petroleum ether obtain 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 1H - 1,4 - benzodiazepine, m.p. 65—67.5°C.

Example 16

Preparation of 7-chloro-2,3-dihydro-1-(2,2,2-trifluoroethyl)-5-(o-fluorophenyl)-1H-1,4-benzodiazepine.

Dissolve 4.1 g. of ethyl 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (o - fluorophenyl) - 1H - 1,4 - benzodiazepine - 3 - carboxylate in 40 ml. of dioxan and stir in the presence of 40 ml. of dilute aqueous sodium hydroxide for six hours at room temperature under nitrogen. Then stir at reflux temperature for four hours. Extract the mixture with methylene chloride, separate the organic layer, wash three times with water, dry over sodium sulphate, and evaporate the organic solvent. Crystallize the residue from petroleum ether and obtain 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (o - fluorophenyl) - 1H - 1,4 - benzodiazepine, m.p. 81—83°C.

Example 17

Preparation of N-(p-chlorophenyl)-N-(2,2,2-trifluoroethyl)-ethylenediamine.

84.0 grams of p - chloro - N - (2,2,2 - trifluoroethyl) - aniline is added slowly to a stirred suspension of 29.3 grams of aluminium chloride and 200 ml. of dry benzene at room temperature. When the addition is complete the mixture is heated under reflux for 20 minutes, the heating is discontinued and 20.6 grams of ethyleneimine is slowly distilled into the reaction vessel. The mixture is left overnight at 50—53°C.

The mixture is cooled and poured onto 500 grams of ice. Potassium hydroxide (100 grams) is added in small portions. The organic layer is separated; the aqueous layer is extracted with methylene chloride. The organic layers are combined, concentrated, and extracted with 5% hydrochloric acid. The acid extract is made basic and extracted with chloroform. After drying with sodium sulfate the solution is evaporated to give the title compound.

Example 18

Preparation of N-(*p*-chlorophenyl)-N-(2,2,2-trifluoroethyl)-N¹-(*o*-fluorobenzoyl)-ethylenediamine.

- 5 10.0 grams N - (*p* - chlorophenyl - N - (2,2,2 - trifluoroethyl) - ethylenediamine in 40 ml. of dry ether containing 4 grams of triethylamine are stirred in an ice-bath. 8.8 grams of *o*-fluorobenzoyl chloride are added slowly to the cold mixture and stirred for two hours. 100 ml methylene chloride is added and the mixture is extracted successively with 5% hydrochloric acid, water, 10% sodium hydroxide and water. The organic layer is separated, dried (with sodium sulphate) and the solvent is removed *in vacuo*. The material is subjected to column chromatography using 300 grams of silica gel and methylene chloride. Fractions of 500 ml. are collected and fraction 2 and 3 are evaporated to yield the product which is crystallized from methylene chloride and hexane to yield the title compound, m.p. 80—82°C.

Example 19

- 25 Preparation of 7-chloro-2,3-dihydro-1-(2,2,2-trifluoroethyl)-5-(*o*-fluorophenyl)-1H-1,4-benzodiazepine-4-oxide.

- 30 0.1 grams of 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (*o* - fluorophenyl) - 1H - 1,4 - benzodiazepine are dissolved in 10 ml. of 1,2-dichloroethane and then 0.06 grams of 85% *m*-chloroperbenzoic acid are added. The mixture is heated, with stirring, at 40—45°C. overnight, 60—65°C. for 4 hours and then refluxed for 3 hours while following the reaction with thin layer chromatography. The reaction mixture is cooled and transferred to a chromatography column containing silica gel with hexane and the mixture is eluted with ether. After all of the yellow colored material is eluted off, the silica gel is poured out, and washed with ethyl acetate. The solvent is removed *in vacuo*. The residue is dissolved in methylene chloride and shaken with saturated sodium bicarbonate solution and water. The methylene chloride solution is separated and dried (sodium sulfate). The solvent is removed to give the title compound, m.p. 160—162°C. which is recrystallized from methylene chloride-hexane to yield 0.08 g., m.p. 163—164.5°C.

Example 20

- 55 Preparation of 7-chloro-2,3-dihydro-1-(2,2,2-trifluoroethyl)-5-(*o*-fluorophenyl)-1H-1,4-benzodiazepine.

- 60 Add 0.9 g. of diethyl azodicarboxylate to a solution of 1.5 g. of 7 - chloro - 2,3,4,5 - tetrahydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (*o* - fluorophenyl) - 1H - 1,4 - benzodiazepine in 20 ml. of benzene, which must be completely free of water, and stir the mixture for one hour at reflux temperature. Filter off the precipitated diethyl hydrazodicarboxylate and evapo-

rate the solvent of the filtrate. Crystallize the residue from petroleum ether and obtain 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (*o* - fluorophenyl) - 1H - 1,4 - benzodiazepine, m.p. 81—83°C.

By substituting analogous starting materials in the processes of the above Examples, one can produce the other compounds in accordance with the invention, and in the case of Examples 17 and 18, other intermediates. For example, by substituting *o*-chlorobenzoyl chloride or benzoyl chloride in place of *o*-fluorobenzoyl chloride in Example 18 one can prepare N - (*p* - chlorophenyl) - N - (2,2,2 - trifluoroethyl) - N¹ - (*o* - chlorobenzoyl) - ethylenediamine and N - (*p* - chlorophenyl) - N - (2,2,2 - trifluoroethyl) - N¹ - benzoyl - ethylenediamine, respectively. By subjecting these two diamines to the cyclization process of Example 1, one can prepare 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (*o* - chlorophenyl) - 1H - 1,4 - benzodiazepine and 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 1H - 1,4 - benzodiazepine, respectively. In the same fashion, by substituting *p*-trifluoromethyl benzoyl chloride and *m*-nitrobenzoyl chloride in the reaction scheme of Examples 1 and 18, one can produce 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (*p* - trifluoromethylphenyl) - 1H - 1,4 - benzodiazepine and 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (*m* - nitrophenyl) - 1H - 1,4 - benzodiazepine, respectively.

Similarly, by substituting *p* - nitro - N - trifluoromethyl aniline in Example 17, one can prepare N - (*p* - nitrophenyl) - N - trifluoromethyl ethylenediamine. By acylation of the latter with *p*-toluyl bromide one can prepare N - (*p* - nitrophenyl) - N - trifluoromethyl - N¹ - (*p* - toluyl) - ethylenediamine which can be cyclized to 7 - nitro - 2,3 - dihydro - 1 - trifluoromethyl - 5 - (*p* - toluyl) - 1H - 1,4 - benzodiazepine. In the same manner, by substituting *p* - trifluoromethyl - N - (2,2,3,3,3 - pentafluoropropyl) - aniline in Example 17, one can prepare N - (*p* - trifluoromethylphenyl) - N - (2,2,3,3,3 - pentafluoropropyl) - phenyl - N - (2,2,3,3,3 - pentafluoropropyl) - ethylenediamine.

Upon acylation of this species with *m*-anisoyl chloride one can prepare *p* - trifluoromethylphenyl - N - (2,2,3,3,3 - pentafluoropropyl) - N¹ - (*m* - anisoyl) - ethylenediamine which yields upon cyclization 7 - trifluoromethyl - 2,3 - dihydro - 1 - (2,2,3,3,3 - pentafluoropropyl) - 5 - (*m* - anisyl) - 1H - 1,4 - benzodiazepine.

The compounds of the general formula (I), their N-oxides and pharmaceutically acceptable salts 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 significantly higher in the compounds of this invention than that observed in analogous compounds presently known in the art.

Based upon standard laboratory investigative procedures such as the Antagonism of Pentylene Tetrazole, Everett and Richard, J. Pharm. and Exp. Ther., Vol. 81, pg. 402 (1944) and Antagonism of Maximal Electro-Shock-Induced Seizures in Mice, Synward, E.A. et al. J. Pharm. and Exp. Ther., Vol. 106, pg. 319 (1962) for anti-convulsant 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. Ther., Vol. 125, pg. 28 (1959) and Taming Activity in Monkeys, Randall, Diseases of the Nervous System, Vol. 21, pg. 7 (1960) for anti-anxiety activity, it is found that when used as an anti-anxiety agent the dosage range is about 0.1—5 mg/kg. of body weight 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 solid, shaped dosage units, for example tablets, capsules or containers comprising a sterile injection liquid, or in the form of syrups, elixirs, suspensions, ointments, creams and the like. In the formulations of pharma-

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

Tablet Formulations

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

Coated Tablets	mg/core	
7-chloro-1-(2,2,2-trifluoroethyl)-2,3-dihydro-5-(o-fluorophenyl)-1H-1,4-benzodiazepine	100.0	80
Lactose, USP	123.0	
Dicalcium Phosphate	70.0	
Sodium Lauryl Sulfate	15.0	
Polyvinylpyrrolidone	15.0	85
Water 50 ml/1000 cores		
Corn Starch	30.0	
Dry	mg/core	
Sodium Lauryl Sulfate	3.0	
Magnesium Stearate	3.0	90
Tablet Weight	359.0	

Procedure:

The 7 - chloro - 1 - (2,2,2 - trifluoroethyl) - 2,3 - dihydro - 5 - (o - fluorophenyl) - 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—14 hours. Reduce dried granulation through a No. 16 screen, add sodium lauryl sulfate and magnesium stearate, 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
7-chloro-1-(2,2,2-trifluoroethyl)-2,3-dihydro-5-(<i>o</i> -fluorophenyl)-1H-1,4-benzodiazepine	100.0
Sodium Lauryl Sulfate	20.0
Lactose	279.0
Magnesium Stearate	101.0
	500.0

10 Procedure:

Mix together 7 - chloro - 1 - (2,2,2 - trifluoroethyl) - 2,3 - dihydro - 5 - (*o* - fluorophenyl) - 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 gelatine capsule.

III. Suppository

Formula:	mg/2gs.
7-chloro-1-(2,2,2-trifluoroethyl)-2,3-dihydro-5-(<i>o</i> -fluorophenyl)-1H-1,4-benzodiazepine, micronized	100
Theobroma Oil, Pharm. Grade to make	2 gms.

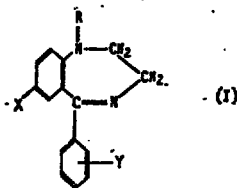
Method of Preparation:

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

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

WHAT WE CLAIM IS:—

1. A 1-polyfluoroalkyl-benzodiazepine having the general formula (I)



wherein X represents halogen, trifluoromethyl or nitro, Y represents hydrogen, halogen, trifluoromethyl, nitro, hydroxy, lower alkyl or lower alkoxy, and R represents a polyfluoro-lower alkyl group.

2. A compound according to claim 1, wherein X represents chloro.

3. A compound according to claim 1 or 2, wherein R represents 2,2,2-trifluoroethyl.

4. A compound according to any one of claims 1 to 3, wherein Y represents hydrogen.

5. A compound according to any one of claims 1 to 3, wherein Y represents fluoro.

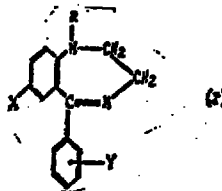
6. A 4-oxide of a 1-polyfluoroalkyl-benzodiazepine as claimed in any one of the claims 1 to 5.

7. A pharmaceutically acceptable salt of a 1 - polyfluoroalkyl - benzodiazepine as claimed in any one of the claims 1 to 5 or of a 4-oxides as claimed in claim 6.

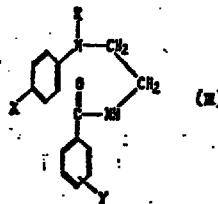
8. 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 1H - 1,4 - benzodiazepine, its 4-oxide or a pharmaceutically acceptable salt of 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 1H - 1,4 - benzodiazepine or of its 4-oxide.

9. 7 - Chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (*o* - fluorophenyl) - 1H - 1,4 - benzodiazepine, its 4-oxide or a pharmaceutically acceptable salt of 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (*o* - fluorophenyl) - 1H - 1,4 - benzodiazepine or of its 4-oxide.

10. Process for the preparation of a benzodiazepine compound having the general formula (I)



or of a 4-oxide thereof; or of a pharmaceutically acceptable salt of said benzodiazepine compound or of said 4-oxide, whereby in the formula X represents halogen, trifluoromethyl or nitro; Y represents halogen, hydrogen, trifluoromethyl, nitro, hydroxy, lower alkyl or lower alkoxy; and R is a polyfluoro-lower alkyl group, characterized in that a compound of the general formula (III)



wherein X, Y and R are as defined above, is subjected to an intramolecular condensation reaction; and that the so obtained compound of formula (I), if desired, is transformed into its 4-oxide; and that the so obtained compound of formula (I) or 4-oxide thereof is isolated as such or in the form of a pharmaceutically acceptable salt.

11. Process according to claim 10, characterized in that the intramolecular condensation or the compound of the general formula

II. Capsule Formulations

	Formula:	mg/capsule
	7-chloro-1-(2,2,2-trifluoroethyl)-2,3-dihydro-5-(<i>o</i> -fluorophenyl)-1H-1,4-benzodiazepine	100.0
5	Sodium Lauryl Sulfate	20.0
	Lactose	279.0
	Magnesium Stearate	101.0
		500.0

10 Procedure:

Mix together 7 - chloro - 1 - (2,2,2 - trifluoroethyl) - 2,3 - dihydro - 5 - (*o* - fluorophenyl) - 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 gelatine capsule.

III. Suppository

	Formula:	mg/2gs.
20	7-chloro-1-(2,2,2-trifluoroethyl)-2,3-dihydro-5-(<i>o</i> -fluorophenyl)-1H-1,4-benzodiazepine, micronized	100
25	Theobroma Oil, Pharm. Grade to make	2 gms.

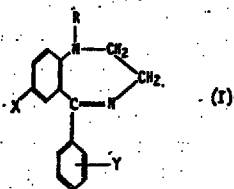
Method of Preparation:

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

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

WHAT WE CLAIM IS:—

1. A 1-polyfluoroalkyl-benzodiazepine having the general formula (I)



wherein X represents halogen, trifluoromethyl or nitro, Y represents hydrogen, halogen, trifluoromethyl, nitro, hydroxy, lower alkyl or lower alkoxy, and R represents a polyfluoro-lower alkyl group.

2. A compound according to claim 1, wherein X represents chloro.

3. A compound according to claim 1 or 2, wherein R represents 2,2,2-trifluoroethyl.

4. A compound according to any one of claims 1 to 3, wherein Y represents hydrogen.

5. A compound according to any one of claims 1 to 3, wherein Y represents fluoro.

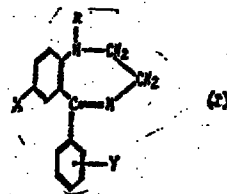
6. A 4-oxide of a 1-polyfluoroalkyl-benzodiazepine as claimed in any one of the claims 1 to 5.

7. A pharmaceutically acceptable salt of a 1 - polyfluoroalkyl - benzodiazepine as claimed in any one of the claims 1 to 5 or of a 4-oxides as claimed in claim 6.

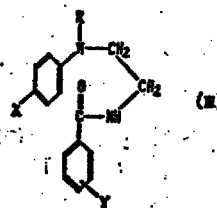
8. 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 1H - 1,4 - benzodiazepine, its 4-oxide or a pharmaceutically acceptable salt of 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - phenyl - 1H - 1,4 - benzodiazepine or of its 4-oxide.

9. 7 - Chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (*o* - fluorophenyl) - 1H - 1,4 - benzodiazepine, its 4-oxide or a pharmaceutically acceptable salt of 7 - chloro - 2,3 - dihydro - 1 - (2,2,2 - trifluoroethyl) - 5 - (*o* - fluorophenyl) - 1H - 1,4 - benzodiazepine or of its 4-oxide.

10. Process for the preparation of a benzodiazepine compound having the general formula (I)



or of a 4-oxide thereof; or of a pharmaceutically acceptable salt of said benzodiazepine compound or of said 4-oxide, whereby in the formula X represents halogen, trifluoromethyl or nitro; Y represents halogen, hydrogen, trifluoromethyl, nitro, hydroxy, lower alkyl or lower alkoxy; and R is a polyfluoro-lower alkyl group, characterized in that a compound of the general formula (III)



wherein X, Y and R are as defined above, is subjected to an intramolecular condensation reaction; and that the so obtained compound of formula (I), if desired, is transformed into its 4-oxide; and that the so obtained compound of formula (I) or 4-oxide thereof is isolated as such or in the form of a pharmaceutically acceptable salt.

11. Process according to claim 10, characterized in that the intramolecular condensation or the compound of the general formula



(II) is performed in the presence of an inorganic dehydrating agent.

12. Process according to claim 11, characterized in that the dehydrating agent is a mixture of phosphorus pentoxide and phosphorus oxychloride.

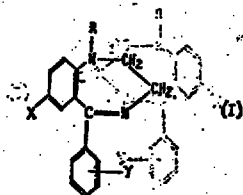
13. Process according to any one of claims 10 to 12, characterized in that the end product of the intramolecular condensation is extracted with an organic solvent.

14. Process according to any one of claims 10 to 13, characterized in that there is used as starting material a compound of the general formula (III), wherein X is chloro.

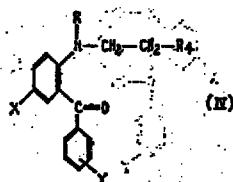
15. Process according to any one of claims 10 to 14, characterized in that there is used as starting material a compound of the general formula (III), wherein R is 2,2,2-trifluoroethyl.

16. Process according to any one of claims 10 to 15, characterized in that there is used as starting material a compound of the general formula (III), wherein Y is hydrogen or fluoro, preferably *o*-fluoro.

17. Process for the preparation of a benzodiazepine compound having the general formula (I)



or of a 4-oxide thereof; or of a pharmaceutically acceptable salt of said benzodiazepine compound or of said 4-oxide, whereby in the formula X represents halogen, trifluoromethyl or nitro; Y represents halogen, hydrogen, trifluoromethyl, nitro, hydroxy, lower alkyl or lower alkoxy; and R is a polyfluoro-lower alkyl group, characterized in that a compound of the general formula (IV)

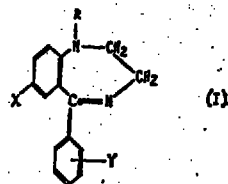


wherein X, Y and R are as defined above, and R₄ is a free or protected amino group, is subjected to an intramolecular condensation reaction, and that the so obtained compound of formula (I), if desired, is transformed into its 4-oxide; and that the so obtained compound of formula (I) or 4-oxide thereof is isolated as such or in the form of a pharmaceutically acceptable salt.

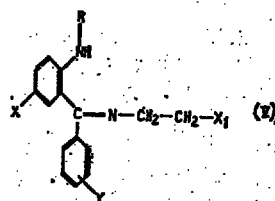
18. Process according to claim 17, characterized in that the intramolecular condensation of the compound of formula (IV) is

carried out at 20°C to 100°C in an inert organic solvent.

19. Process for the preparation of a benzodiazepine compound having the general formula (I)



or of a 4-oxide thereof; or of a pharmaceutically acceptable salt of said benzodiazepine compound or of said 4-oxide, whereby in the formula X represents halogen, trifluoromethyl or nitro; Y represents halogen, hydrogen, trifluoromethyl, nitro, hydroxy, lower alkyl or lower alkoxy; and R is a polyfluoro-lower alkyl group, characterized in that a compound of the general formula (V)

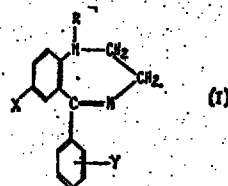


wherein X, Y and R are as defined above, and X₁ is an atom or group capable of being eliminated, under the reaction conditions applied, together with the N-hydrogen atom, is subjected to an intramolecular condensation reaction; and that the so obtained compound of formula (I), if desired, is transformed into its 4-oxide; and that the so obtained compound of formula (I) or 4-oxide thereof is isolated as such or in the form of a pharmaceutically acceptable salt.

20. Process according to claim 19, characterized in that there is used a compound of formula (V) wherein X₁ is an inorganic or organic ester moiety, preferably halogen, arylsulphonate or alkylsulphonate.

21. Process according to claim 19 or 20, characterized in that the intramolecular condensation of the compound of formula (V) is carried out at 50°C to 150°C.

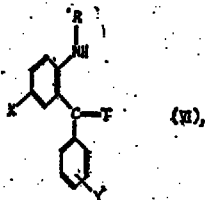
22. Process for the preparation of a benzodiazepine compound having the general formula (I)



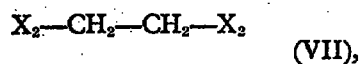
or of a 4-oxide thereof; or of a pharmaceutically acceptable salt of said benzodiazepine compound or of said 4-oxide, where-



by in the formula X represents halogen, trifluoromethyl or nitro; Y represents halogen, hydrogen, trifluoromethyl, nitro, hydroxy, lower alkyl or lower alkoxy; and R is a polyfluoro-lower alkyl group, characterized in that a first reactant of the general formula (VI)



is condensed with a second reactant of the general formula (VII)



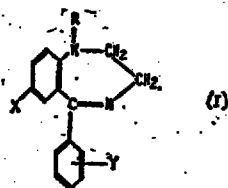
whereby in the formulae R, X and Y are as defined above; T is an oxygen atom or an imino group; and when T is an imino group, then each X_2 is an atom or group capable of being eliminated, under the reaction conditions applied, together with both the N-hydrogen atoms in the imino and amino group and when T is oxygen, then both X_2 together represent an imino group; and that the so obtained compound of formula (I), if desired, is transformed into its 4-oxide; and that the so obtained compound of formula (I) or 4-oxide thereof is isolated as such or in the form of a pharmaceutically acceptable salt.

23. Process according to claim 22, characterized in that as first reactant is used a compound of the general formula (VI) wherein T is =NH, and as second reactant is used a compound of the general formula (VII) wherein each X_2 is a reactive organic or inorganic ester moiety.

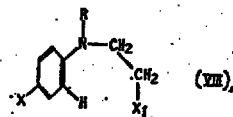
24. Process according to claim 23, characterized in that as second reactant is used a compound of the formula (VII) wherein each X_2 is halogen, preferably bromo.

25. Process according to claim 22, characterized in that as first reactant is used a compound of the general formula (VI) wherein T is O, and as second reactant is used ethyleneimine.

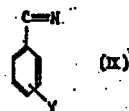
26. Process for the preparation of a benzodiazepine compound having the general formula (I)



or of a 4-oxide thereof; or of a pharmaceutically acceptable salt of said benzodiazepine compound or of said 4-oxide, whereby in the formula X represents halogen, trifluoromethyl or nitro; Y represents halogen, hydrogen, trifluoromethyl, nitro, hydroxy, lower alkyl or lower alkoxy; and R is a polyfluoro-lower alkyl group, characterized in that a compound of the general formula (VIII)



is condensed with a compound of the general formula (IX)

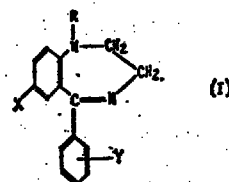


whereby in the formulae R, X and Y are as defined above, and X_1 being an atom or group capable of being eliminated, under the reaction conditions applied, together with the hydrogen atom depicted at the phenyl ring of formula (VIII); and that the so obtained compound of formula (I), if desired, is transformed into its 4-oxide; and that the so obtained compound of formula (I) or 4-oxide thereof is isolated as such or in the form of a pharmaceutically acceptable salt.

27. Process according to claim 26, characterized in that the condensation is carried out in the presence of a Lewis acid, preferably $AlCl_3$ or $SnCl_4$.

28. Process according to claim 26 or 27, characterized in that the reaction is carried out at $50^\circ C$ to $200^\circ C$, preferably at $100^\circ C$ to $150^\circ C$, in an inert organic solvent.

29. Process for the preparation of a benzodiazepine compound having the general formula (I)

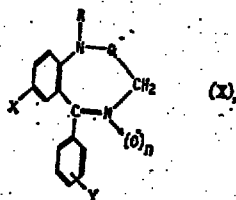


or of a 4-oxide thereof; or of a pharmaceutically acceptable salt of said benzodiazepine compound or of said 4-oxide, whereby in the formula X represents halogen, or trifluoromethyl; Y represents halogen, hydrogen, trifluoromethyl, hydroxy, lower alkyl or

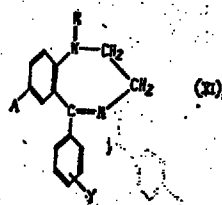




lower alkoxy; and R is a polyfluoro-lower alkyl group, characterized in that a compound of the general formula (X)



lower alkyl or lower alkoxy; and R is a polyfluoro-lower alkyl group, characterized in that a compound of the general formula (XI)



5 wherein R, X and Y are as defined above,

Q is $-\text{CH}_2-$ or $-\text{C}(=\text{S})-$; and when Q is $-\text{CH}_2-$, then n is one, and when Q is $-\text{C}(=\text{S})-$, then n is zero or one, is reduced at

10 position 2 and/or 4; and that the so obtained compound of formula (I), if desired, is transformed into its 4-oxide, and that the so obtained compound of formula (I) or 4-oxide thereof is isolated as such or in the form of a pharmaceutically acceptable salt.

15 30. Process according to claim 29, characterized in that as starting compound is used a compound of the general formula (X) wherein

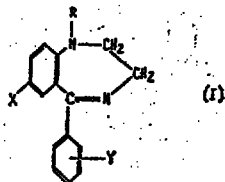
Q is $-\text{C}(=\text{S})-$ and n is zero, and that said starting compound is reduced by means of catalytic hydrogenation.

20 31. Process according to claim 29, characterized in that the reduction is performed by means of LiAlH_4 .

25 32. Process according to claim 29, characterized in that as starting compound is used a compound of the general formula (X) wherein Q is $-\text{CH}_2-$ and n is one.

30 33. Process according to claim 32, characterized in that the reduction is carried out by means of PCl_3 .

34. Process for the preparation of a benzodiazepine compound having the general formula (I)



35 or of a 4-oxide thereof; or of a pharmaceutically acceptable salt of said benzodiazepine compound or of said 4-oxide, whereby in the formula X represents halogen; Y represents halogen, hydro-

40 gen, trifluoromethyl, nitro, hydroxy,

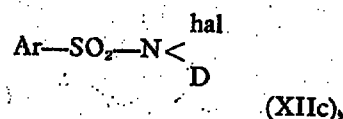
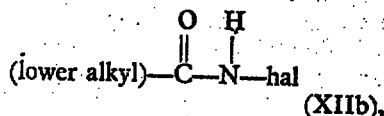
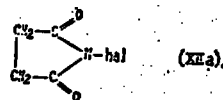
45 wherein R and Y are as defined above, and A represents a hydrogen atom or an NH_2 group, is halogenated in position 7, and that the so obtained compound of formula (I), if desired, is transformed into its 4-oxide; and that the so obtained compound of formula (I) of 4-oxide thereof is isolated as such or in the form of a pharmaceutically acceptable salt.

50 35. Process according to claim 34, characterized in that as starting compound is used a compound of the general formula (XI), wherein A is NH_2 , and that the said starting compound is subjected to a diazotisation and to a subsequent Sandmeyer reaction, so as to replace the diazonium grouping by the desired halogen atom.

60 36. Process according to claim 34, characterized in that as starting compound is used a compound of the general formula (XI) wherein A is hydrogen and that the said starting compound is treated with a halogenating agent.

70 37. Process according to claim 36, characterized in that there is used as halogenating agent, a compound capable of providing halogen cations.

75 38. Process according to claim 37, characterized in that there is used as halogenating agent molecular halogen, a hypohalogenite ester, or preferably a compound containing the group $>\text{N}-\text{hal}$ such as represented by compounds of the general formulae (XIIa), (XIIb) and (XIIc)



80 wherein hal is halogen; Ar is phenyl or preferably substituted phenyl (e.g. tolyl), and D represents hydrogen or lower alkyl.

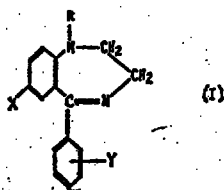
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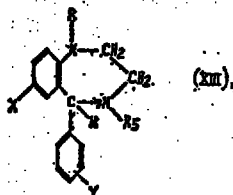
39. Process according to claim 38, characterized in that the halogenation is performed with a compound containing the group $>N-hal$, wherein hal is halogen, in the presence of a catalyst capable of forming free radicals.

40. Process according to claim 39, characterized in that the halogenation is effected using N-chloro-succinimide in the presence of 2,2'-azo-bis-(2-methylpropionitrile).

41. Process for the preparation of benzodiazepine compounds having the general formula (I)



of their 4-oxides, and of the pharmaceutically acceptable salts of both, whereby in the formula X represents halogen, trifluoromethyl or nitro; Y represents halogen, hydrogen, trifluoromethyl, nitro, hydroxy, lower alkyl or lower alkoxy; and R is a polyfluoro-lower alkyl group, which comprises subjecting a starting compound of the general formula (XIII)



wherein R, X and Y are as defined above, and R_s represents an atom or grouping of atoms which, under the reaction conditions applied, is removed together with the hydrogen atom at C-5, to an elimination reaction whereby the 4,5-double bond is introduced; and that the so obtained compound of formula (I), if desired, is transformed into its 4-oxide; and that the so obtained compound of formula (I) or 4-oxide thereof is isolated as such or in the form of a pharmaceutically acceptable salt.

42. Process according to claim 41, characterized in that there is used as starting compound a compound of the general formula (XIII) wherein R_s represents an esterified hydroxy group, such as aryl-SO₂-, alkyl-SO₂- or a lower alkanoyloxy group having up to six carbon atoms, and that the said starting compound is subjected to alkaline conditions so as to remove R_s together with the hydrogen atom at C-5 and to introduce the 4,5-double bond.

43. Process according to claim 42, characterized in that the reaction medium is rendered alkaline with an alkali metal or alkaline earth metal hydroxide, an alkali metal hydride, an alkali metal alkoxide, a trialkylamine or an alkali metal amide.

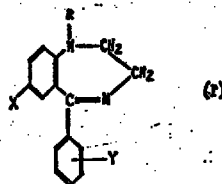
44. Process according to claim 41, characterized in that there is used as starting material a compound of the general formula (XIII), wherein R_s represents a free hydroxy group, and that the said starting compound is subjected to dehydration.

45. Process according to claim 44, characterized in that the dehydration is effected using a carbodiimide, preferably dicyclohexylcarbodiimide, or a α -alkenylamine as dehydrating agent.

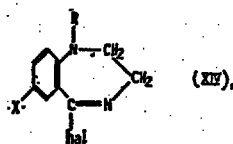
46. Process according to claim 41, characterized in that there is used as starting material a compound of the general formula (XIII) wherein R_s represents a hydrogen atom, and that the said starting compound is subjected to dehydrogenation.

47. Process according to claim 46, characterized in that there is used as dehydrogenating agent a dialkyl azodicarboxylate, a quinone or a metal salt of an hypohalogenous acid.

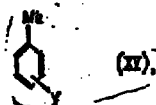
48. Process for the preparation of a benzodiazepine compound having the general formula (I)



or of a 4-oxide thereof; or of a pharmaceutically acceptable salt of said benzodiazepine compound or of said 4-oxide, whereby in the formula X represents halogen, trifluoromethyl or nitro; Y represents halogen, hydrogen, trifluoromethyl, nitro, hydroxy, lower alkyl or lower alkoxy; and R is a polyfluoro-lower alkyl group, characterized in that a compound of the general formula (XIV)



wherein X and R are as defined above and hal represents a halogen atom, is reacted with an organometallic compound of the general formula (XV)

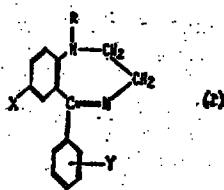


wherein Y is as defined above, and Me represents the metal-containing moiety of the organometallic compound, preferably

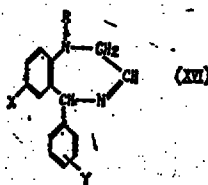
—Mg—hal, Li, Na or K;

- 5 and that the so obtained compound of formula (I), if desired, is transformed into its 4-oxide; and that the so obtained compound of formula (I) or 4-oxide thereof is isolated as such or in the form of a pharmaceutically acceptable salt.

- 10 49. Process for the preparation of a benzodiazepine compound having the general formula (I)



- 15 or of a 4-oxide thereof; or of a pharmaceutically acceptable salt of said benzodiazepine compound or of said 4-oxide, whereby in the formula X represents halogen, trifluoromethyl or nitro; Y represents halogen, hydrogen, trifluoromethyl, nitro, hydroxy, lower alkyl or lower alkoxy; and R is a polyfluoro-lower alkyl group, characterized in that a compound of the general formula (XVI),

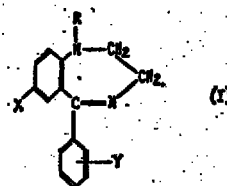


- 25 wherein X, R and Y are as defined above is isomerised whereby the 3,4-double bond is moved to the position 4,5 of the benzodiazepine ring and that the so obtained compound of formula (I), if desired, is transformed into its 4-oxide and that the so obtained compound of the formula (I) or 4-oxide thereof is isolated as such or in the form of a pharmaceutically acceptable salt.

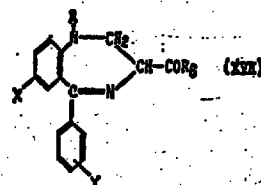
- 30 50. Process according to claim 49, characterized in that the isomerization is performed by subjecting the starting material to alkaline conditions.

- 35 51. Process according to claim 50, characterized in that the reaction medium is rendered alkaline with an alkali metal hydride, an alkali metal alkoxide or a trialkyl amine.

- 40 52. Process for the preparation of a benzodiazepine compound having the general formula (I)



or of a 4-oxide thereof; or of a pharmaceutically acceptable salt of said benzodiazepine compound or of said 4-oxide, whereby in the formula X represents halogen, trifluoromethyl or nitro; Y represents halogen, hydrogen, trifluoromethyl, nitro, hydroxy, lower alkyl or lower alkoxy; and R is a polyfluoro-lower alkyl group, characterized in that a compound of the general formula (XVII)



wherein X, R and Y are as defined above and R₁ represents a hydrolysable grouping, is subjected to a hydrolysis and a decarboxylation reaction, and that the so-obtained compound of formula (I), if desired, is transformed into its 4-oxide, and that the so obtained compound of formula (I) or 4-oxide thereof is isolated as such or in the form of a pharmaceutically acceptable salt.

53. Process according to claim 52, characterized in that the reactions are performed by subjecting the starting material to alkaline conditions.

54. Process according to claim 52 or 53, characterized in that the decarboxylation is carried out with the application of heat.

55. Process according to any one of claims 17 to 54, characterized in that there is used as starting material a compound wherein R is 2,2,2-trifluoroethyl.

56. Process according to any one of claims 17 to 33 and 41 to 55, characterized in that there is used as starting material a compound wherein X represents chloro.

57. Process according to any one of Claims 17 to 56, characterized in that there is used as starting material a compound wherein Y is hydrogen or fluoro, preferably o-fluoro.

58. Process for the preparation of 1-polyfluoroalkyl-benzodiazepines having the general formula (I) their 4-oxides, and the pharmaceutically acceptable salts of said benzodiazepines or of said 4-oxides, substantially as here-



inbefore described, with particular reference to Examples 1 to 16, 19 and 20.

5 59. A 1-polyfluoroalkyl-benzodiazepine having the general formula (I), a 4-oxide thereof or a pharmaceutically acceptable salt of said benzodiazepine or of said 4-oxide, when prepared by a process according to any one of claims 10 to 58.

10 60. A therapeutical composition having central nervous system activity, comprising a compound as defined by any one of claims 1 to 9 as an active ingredient, in admixture with a suitable therapeutical carrier.

15 61. A composition according to claim 60, in the form of a solid shaped dosage unit.

62. The composition of claim 61, wherein the dosage unit is a tablet.

63. The composition of claim 61, wherein the dosage unit is a capsule.

20 64. The composition of claim 61, wherein the dosage unit is a suppository.

65. A composition of claim 61, wherein the

dosage unit is a container comprising a sterile injection liquid.

25 66. Process for preparing a therapeutical composition having central nervous system activity, characterized in that a compound as defined in any one of claims 1 to 9 is brought into a form suitable for therapeutical administration.

30 67. Process according to claim 66, characterized in that the compound as defined in any one of claims 1 to 9 is admixed with a suitable therapeutical carrier.

35 68. A therapeutical composition having central nervous system activity, when prepared by the process of claim 66 or 67.

MATHYS & SQUIRE,
Chartered Patent Agents,
10 Fleet Street,
London, E.C.4.
Agents for the Applicants.

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PATENTS ACT 1949

SPECIFICATION NO 1297206

The following corrections were allowed under Section 76 on 1 May 1975:-

Page 4, line 71, for - CH₂ -, - C^S -, or - C^O - read - CH₂ - or - C^S -

Page 4, line 72, after - C^S - delete or

Page 4, line 73 before then delete - C^O -

Page 4, line 77 before and delete or - C^O -

Page 5, line 2, after elevated delete tem - insert temperatures.

Page 5, lines 3 to 12, delete whole lines

THE PATENT OFFICE
29 May 1975

R 22627/1

