

PATENT SPECIFICATION

NO DRAWINGS

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International Classification:—C 07 d 53/06

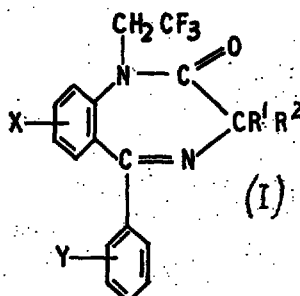
COMPLETE SPECIFICATION

Novel Benzodiazepines and process for their Manufacture

We, SCHERICO LTD., of Topferstrasse 5, Lucerne, Switzerland (formerly of Winkelriedstrasse 56, 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 substituted benzodiazepines, processes for their production and compositions containing these compounds.

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



wherein X and Y are independently selected from hydrogen, halogen, trifluoromethyl, nitro, alkyl and alkoxy; R¹ and R² are independently selected from hydrogen and alkyl, or one is hydrogen and the other free or esterified hydroxy; and the 4-oxides thereof when R¹ and R² are independently selected from hydrogen and alkyl.

Any esterified hydroxy group preferably is an alkanoyloxy group. The alkyl, alkoxy and alkanoyloxy substituents when present are preferably lower alkyl, lower alkoxy and lower alkanoyloxy respectively. The term lower alkyl means radicals, having up to 6 carbon atoms, including straight and branched chains. In like manner, lower alkoxy has a similar range of up to 6 carbon atoms, including straight and branched chain isomers. Lower alkanoyloxy means radicals having up to 6 carbon atoms. Among these are: methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, methoxy, ethoxy, acetoxy, propionyloxy, isobutyroxy and capryloxy. The term halogen covers all four members, namely fluorine, chlorine, bromine and iodine. However, of particular value are those wherein X represents chloro or bromo and Y represents fluoro or chloro.

Of particular interest are those compounds in which R¹ is hydrogen R² is hydrogen, alkyl, hydroxy or alkanoyloxy, X is halogen, preferably chloro attached to the 7-position, and Y is hydrogen.

The compounds of this invention exert an effect upon the central nervous system and as such are useful as muscle relaxants, sedatives, anti-convulsants and anti-anxiety agents.

The present N-trifluoroethylated 1,4-benzodiazepines and 4-oxides may be prepared in any convenient way, such as by methods suitable for the preparation of the

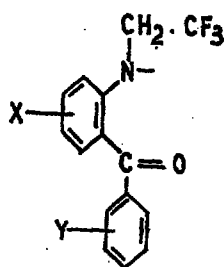
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corresponding compounds without the 1-trifluoroethyl substituent, the corresponding 1-unsubstituted or 1-methyl-substituted compounds. They may be very advantageously prepared from intermediates already bearing the desired trifluoroethyl radical, or by trifluoroethylation of the corresponding 1-unsubstituted compounds. When it is desired to prepare the present N-trifluoroethylated compounds from the corresponding 1-unsubstituted compounds several trifluoroethylation procedures may be utilized, such as methods making use of a compound of the formula $\text{CF}_3\text{—CH}_2\text{—A}$, wherein A is a reactive grouping, such as a reactive organic or inorganic ester grouping. Alternatively, for example, a grouping $\text{C(Hal)}_3\text{—CH}_2\text{—}$, with Hal representing a halogen other than fluoro, may first be introduced, whereupon Hal is replaced by fluoro, such as by reaction with silver fluoride. In a preferred instance the said 1-unsubstituted compound is subjected to alkylation with a sulfonate ester of trifluoroethanol of the general formula $\text{CF}_3\text{CH}_2\text{OSO}_2\text{Z}$, wherein Z is alkyl, aryl, aralkyl or polyhaloalkyl. Among the sulfonate esters which may be used as 2,2,2-trifluoroethyl methylsulfonate, 2,2,2-trifluoroethyl phenylsulfonate, 2,2,2-trifluoroethyl benzylsulfonate and 2,2,2-trifluoroethyl trichloromethylsulfonate. In effecting this alkylation reaction, the reactants are usually heated together in an anhydrous solvent system at reflux temperatures in the presence of an inorganic base such as potassium carbonate. Among the solvents useful for this reaction are diphenyl ether, diglyme and tetralin. In another convenient embodiment the appropriately X and Y substituted benzodiazepine starting materials are alkylated with 2,2,2-trifluoroethyl bromide, chloride or preferably iodide. The trifluoroethylation reaction with these halides is preferably effected in non-reactive organic solvents such as dimethyl-formamide or aromatic hydrocarbons like benzene, toluene or xylene in the presence of a basic condensing agent according to standard techniques. Among the basic condensing agents which may be used are sodium methoxide, sodium hydride, potassium t-butoxide, and sodium amide. The reaction is usually conducted at temperatures in the range from about 20 to about 110°C., preferably around 65°C., and for a period of time ranging from 1 to 24 hours, preferably about 7 hours, followed by the further addition of trifluoroethyl halide and further reaction for approximately 16 hours.

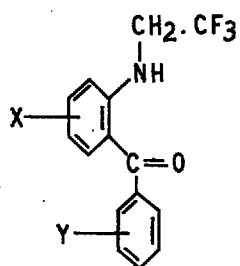
The trifluoroethylated benzodiazepine products may be isolated by filtration of the insoluble salts, evaporation of the filtrate, further isolated by selective solvent extraction techniques, and purified by chromatographic techniques such as by elution from an alumina adsorption column.

When it is desired to prepare the 1-trifluoroethylated 1,4-benzodiazepines according to the invention from intermediates already bearing the trifluoroethyl radical, several routes of synthesis are applicable. Usually, the several routes of synthesis ultimately employ an N-trifluoroethyl-substituted aminobenzophenone of the general partial formula:



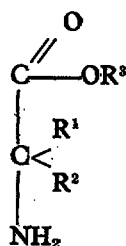
wherein X and Y are as previously defined, which aminobenzophenone through condensation reactions may be transformed into the desired 1,4-benzodiazepine, which, if desired, may be converted into a 4-oxide.

Thus, an aminobenzophenone of the general formula II



(II)

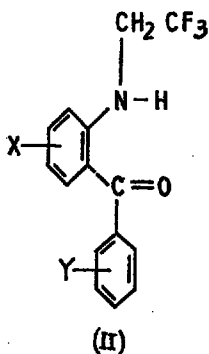
wherein X and Y are as previously defined, may be condensed, preferably by heating in the presence of a solvent, such as pyridine, with a compound having the formula III:



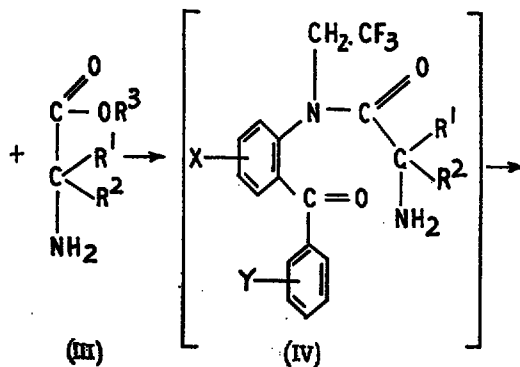
(III)

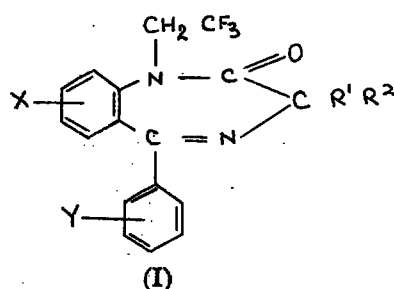
wherein R¹ and R² are as previously defined, and R³ is hydrogen or alkyl, preferably ethyl. Instead of the free acid or the ester, other reactive derivatives such as the halides may be used. The condensation may lead directly to the desired end product, or an intermediate (IV) may first be formed which undergoes further reaction to give the 1,4-benzodiazepine. Reaction scheme A illustrates this condensation:

A:



(II)

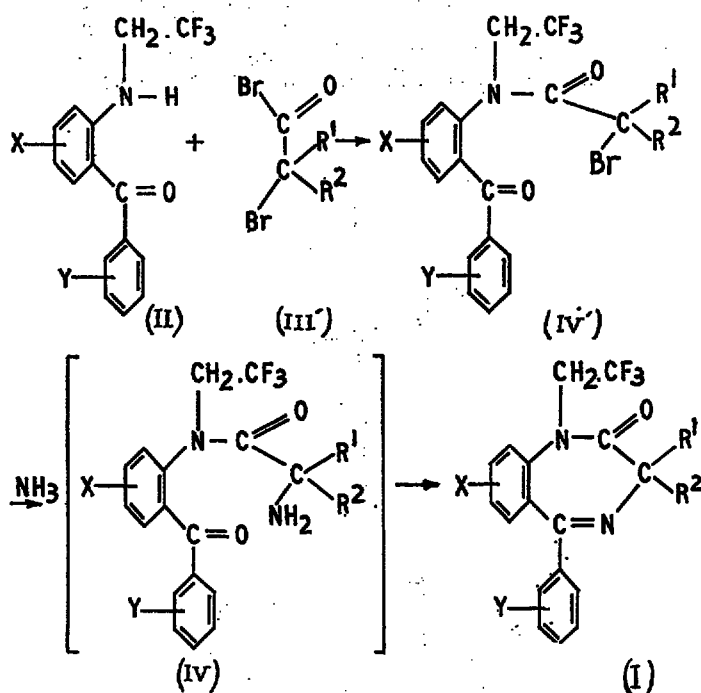




In the above described reaction the amino group preferably is protected, either by substitution or by forming an addition salt. The preferred protecting substituents are acyl groups, such as the carbobenzoxy or the phthaloyl group. Among the addition salts which may be used, the hydrochloride is preferred.

Instead of the aforementioned aminoacetic acid or acid derivatives (III) one can also use the corresponding halo compounds wherein the NH_2 -group is replaced by chloro, iodo or preferably bromo (III'). In the first step the condensation using such a halo compound yields a 2-[N-(2,2,2-trifluoroethyl)- α -haloacetamido]-benzophenone (IV') which is then reacted with ammonia to yield the corresponding 2-[N-(2,2,2-trifluoroethyl)- α -amino-acetamido]-benzophenone, which simultaneously undergoes intramolecular condensation to give a compound of formula I, as illustrated in reaction scheme B.

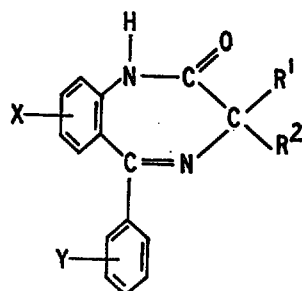
B:



The compounds of formula (IV) may also be used as starting compounds. By intramolecular condensation the desired end product is formed.

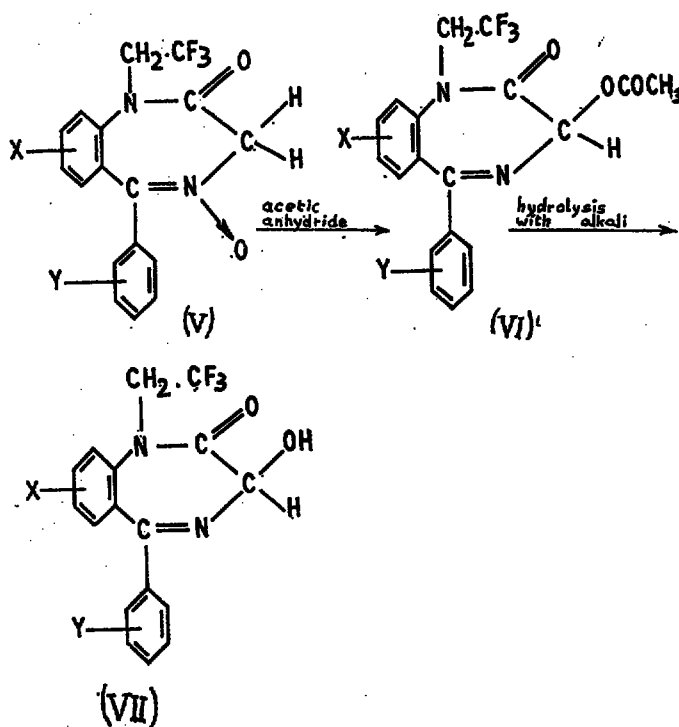
Moreover an intermediate of formula (IV') is a very convenient starting material and can be transformed into the corresponding 1,4-benzodiazepine by treatment according to the last two steps of reaction scheme B.

By subjecting the trifluoroethylated products, wherein R^1 and R^2 represent hydrogen or alkyl to an oxidative treatment, the 4-oxides are obtained. N-oxidation of an intermediate of the formula



wherein R^1 and R^2 represent hydrogen or alkyl, followed by trifluoroethylation as described supra is another way for the preparation of these 4-oxides. The oxidative treatment can be conveniently carried out by means of a peroxy acid such as peracetic acid. The benzodiazepines according to the invention, wherein R^1 or R^2 is free or esterified hydroxy may be prepared by heating the corresponding 1-trifluoroethylated or 1-unsubstituted 4-oxide with an anhydride such as acetic anhydride, followed, if desired, by hydrolysis of the esterified hydroxy group to the free hydroxy group and, if necessary, introduction of a trifluoroethyl substituent in position 1. An example of this transformation is given in reaction scheme C.

C:



The hydroxyl group thus introduced can be converted in the usual manner into other esters, such as with acid chlorides or anhydrides of propionic acid, butyric acid, and valeric acid.

The 1,4-benzodiazepines of this invention exert an effect on the central nervous system as determined by standard pharmacological evaluation and as such are useful as tranquilizer or anti-anxiety agents. In addition the novel compounds exhibit valuable anti-convulsant and muscle relaxant properties. In pharmacological testing there has been observed significant differentials between a tranquilizing dose and one which causes neurological impairment. The therapeutic ratio (ratio of effective dose required to produce neurological impairment to the effective dose required to produce a tranquilizing effect) is significantly higher in the 1,4-benzodiazepines according to the invention than that observed in analogous compounds presently known in the art.

5 In particular, 7-chloro-1,3-dihydro-5-phenyl-1-(2,2,2-trifluoroethyl)-2H-1,4-benzodiazepine-2-one has a therapeutic ratio of about 13 which indicates that the neurological impairment dose is about 13 times greater than that dose required to produce a
5 tranquilizing effect according to accepted pharmacological testing methods. By way of further advantage, it has been found that test animals do not develop a tolerance to the 1,4-benzodiazepines according to the invention on repeated treatment in anti-convulsant evaluation.

10 The 1,4-benzodiazepines of this invention are preferably administered via the oral route and for such are compounded into pharmaceutical dosage forms such as tablets, capsules, elixirs, and solutions. In the compounding, a dosage unit may contain the
10 usual excipients like starches, gums and alcohol bases commonly employed. In addition, the 1,4-benzodiazepines according to the invention may be incorporated into a dosage unit together with another active therapeutic agent. The dosage depends upon the patient and severity of condition being treated. Normally a dose of about 0.1 to 1.0
15 mg. per kg. body weight per day, given in three or four divided doses is sufficient to elicit a therapeutic effect.

The following examples are illustrative of the production of 1,4-benzodiazepines according to the invention.

EXAMPLE 1

20 7-Chloro-1,3-dihydro-5-phenyl-1-(2,2,2-trifluoroethyl)-
2H-1,4-benzodiazepine-2-one

25 Prepare a solution of sodium methylate by dissolving 3.9 grams of sodium metal in 500 ml. of methanol. Add 39.0 grams of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one. Evaporate the reaction mixture to a residue and dissolve the
25 residue in 170 ml. of dimethylformamide. Add 30 grams of 2,2,2-trifluoroethyl iodide and stir at room temperature for 1/2 hour, then heat to 60°—70°C for an additional 7 hours. Add 19 grams of 2,2,2-trifluoroethyl iodide and resume the heating and stirring at 60°—70°C for an additional 16 hours. Filter off the solids and evaporate
30 the filtrate to a residue in vacuo. Triturate the residue with water and extract with ethyl ether. Wash the ethereal extract with water, dry over anhydrous sodium sulfate and evaporate the solvent to a residue. Extract the residue with ethyl ether and filter. Concentrate the ethereal extract to a residue. Dissolve the residue in benzene and chromatograph on 300 grams of alumina contained in a glass column 1.5 inches in
35 diameter to give the crude product. Elute with benzene. Crystallize this product from acetone-petroleum ether to obtain the product of this example.

Alternatively, the compound of this example is prepared as follows:

40 Dissolve 29.5 grams of 2-(2,2,2-trifluoroethyl)-amino-5-chlorobenzophenone and 21.0 grams of glycine ethyl ester hydrochloride in 200 ml. of pyridine. Heat the solution to reflux and maintain the reflux with stirring for 15 hours. During the first
40 4 hours remove approximately 50 ml. of solvent and replace with dry pyridine. Concentrate the solution *in vacuo* to a residue. Triturate the residue in water and extract with ether. Filter off any remaining solids and separate the solvent layers. Adjust the pH of the aqueous solution to 8.0—8.5 and re-extract with ether. Combine
45 the ethereal extracts and wash them with water and dry them over anhydrous sodium sulfate. Chromatograph as described above.

EXAMPLE 2

7-Chloro-1,3-dihydro-5-phenyl-1-(2,2,2-trifluoroethyl)-2H-1,4-
benzodiazepine-2-one-4-oxide

50 Dissolve 50.0 grams of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one in 1250 ml. of acetic acid. Cool the solution slightly and with agitation add 50 ml. of 40% peracetic acid. Maintain this solution at room temperature for 24 hours and precipitate by the addition of 10 liters of water with agitation. Neutralize the suspen-
50 sion with sodium carbonate and filter. Wash the precipitate with water and crystallize 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one-4-oxide from alcohol for use in the next step.

55 Prepare a solution of sodium methylate by dissolving 3.9 g. sodium metal in 500 ml. methanol. Add 39.8 g. of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one-4-oxide with stirring. Evaporate the methanol and dissolve the residue in 170 ml. dimethylformamide. Add 30 grams of 2,2,2-trifluoroethyl iodide and stir
60 at room temperature for 1/2 hour. Heat the mixture to 60°—70°C with stirring for 7 hours. Add 19 grams of 2,2,2-trifluoroethyl iodide and heat with stirring at 60°—70°C for a further 16 hours. Filter off the insoluble and evaporate the filtrate to a residue in *vacuo*. Triturate the residue with water, extract with ether, wash the ethereal

solution with water, dry the solution over anhydrous sodium sulfate and evaporate to a residue. Triturate the residue with ether and filter. Evaporate the ether to a residue, dissolve the residue in benzene and chromatograph on 300 grams of alumina contained in a glass column 1.5 inches in diameter. Elute with benzene to give the product. Crystallize this product from acetone-petroleum ether to give the purified product.

EXAMPLE 3

3-Acetoxy-7-chloro-1,3-dihydro-5-phenyl-1-(2,2,2-trifluoroethyl)-2H-1,4-benzodiazepine-2-one

Suspend 10 grams of 7-chloro-1,3-dihydro-5-phenyl-1-(2,2,2-trifluoroethyl)-2H-1,4-benzodiazepine-2-one-4-oxide in 100 ml. of acetic anhydride. Heat the mixture on the steam bath for 30 minutes with agitation. Cool and collect the product by filtration. Crystallize from acetone-petroleum ether obtaining the product of this example.

EXAMPLE 4

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

Suspend 5.0 grams of the product of Example 3 in 100 ml. of alcohol. Add one equivalent of a 5% sodium hydroxide solution while stirring. Dilute the reaction mixture with water until the product is fully precipitated. Collect the product by filtration, wash with water, air dry and recrystallize from hexane to yield the compound of this example.

EXAMPLE 5

3-Propionyloxy-7-chloro-1,3-dihydro-5-phenyl-1-(2,2,2-trifluoroethyl)-2H-1,4-benzodiazepine-2-one

Suspend 3.7 grams of 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-1-(2,2,2-trifluoroethyl)-2H-1,4-benzodiazepine-2-one in 25 ml. of benzene and add 1 ml. propionyl chloride. Heat the mixture to reflux and maintain for 2 hours. Cool the reaction mixture and dilute with hexane to incipient crystallization. Cool and filter obtaining the product of this example.

EXAMPLE 6

7-Chloro-1,3-dihydro-3-methyl-5-phenyl-1-(2,2,2-trifluoroethyl)-2H-1,4-benzodiazepine-2-one

Dissolve 23.2 grams of 2-amino-5-chloro-benzophenone in 200 ml. of pyridine. Add 22.9 grams alanine ethyl ester hydrochloride and bring the mixture to reflux. Slowly distil from the reaction mixture approximately 40 ml. of solvent. Reflux the mixture for a total of about 15 hours, then cool slightly and concentrate the mixture under reduced pressure to a residue. Add water to the residue and extract with ether. If there are insolubles present, filter the mixture and separate the solvent layers. Adjust the pH of the aqueous layer to 8.0—8.5 and extract with ether. Combine the ether layers, water wash and dry. Filter and concentrate the layers to a crystalline slurry. There is obtained 7-chloro-1,3-dihydro-3-methyl-5-phenyl-2H-1,4-benzodiazepine-2-one which is used in the next step.

Prepare a solution of sodium methylate by dissolving 1.0 gram of sodium metal in 125 ml. methanol. Add 9.8 g. of 7-chloro-1,3-dihydro-3-methyl-5-phenyl-2H-1,4-benzodiazepine-2-one and evaporate the solution to a residue. Dissolve the residue in 45 ml. of dimethylformamide. Add 8 g. of 2,2,2-trifluoroethyl iodide and stir at room temperature for 1/2 hour, then heat to 60°—70°C for an additional 7 hours. Add 5 g. of 2,2,2-trifluoroethyl iodide and resume heating and stirring at 60°—70°C for an additional 16 hours. Filter off the residue and proceed as in Example 1, obtaining the compound of this example.

EXAMPLE 7

1,3-Dihydro-5-phenyl-1-(2,2,2-trifluoroethyl)-2H-1,4-benzodiazepine-2-one

Prepare a solution of sodium methylate by dissolving 2.4 grams of sodium metal in 400 ml. of methanol. Add 23.6 g. of 1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one and evaporate the reaction mixture to a residue. Dissolve the residue in 150 ml. of dimethylformamide and add 25.0 g. of 2,2,2-trifluoroethyl iodide to the mixture. Stir the mixture at room temperature for 1/2 hour, then heat to 60°—70°C for an additional 7 hours. Add 15 g. of 2,2,2-trifluoroethyl iodide and resume the heating and stirring at 60°—70°C for an additional 16 hours. Filter off the solids and evaporate the filtrate to a residue *in vacuo*. Triturate the residue with water and extract with ethyl ether. Wash the ethereal extract with water, dry over anhydrous sodium sulfate and evaporate the solution to a residue. Extract the residue with ethyl ether and filter

off the solids. Concentrate the ethereal extract to a residue and dissolve the residue in benzene and chromatograph on 300 g. of alumina as described in previous examples obtaining the compound of this example.

EXAMPLE 8

5 1,3-Dihydro-5-phenyl-1-(2,2,2-trifluoroethyl)-2H-1,4-
benzodiazepine-2-one-4-oxide 5

Dissolve 5.0 g. of the product of Example 7 in 125 ml. of acetic acid. Cool the solution slightly and add 5.0 ml. of 40% peracetic acid. Maintain this solution at room temperature for 24 hours and precipitate the product by the addition of 1.0 liter of cold water followed by neutralization with sodium carbonate solution. Filter and wash the precipitate with water. Crystallization from alcohol obtaining the N-oxide of this example. 10

EXAMPLE 9

15 7-Chloro-1-(2,2,2-trifluoroethyl)-5-phenyl-1,3-dihydro-2H-1,4-
benzodiazepine-2-one 15

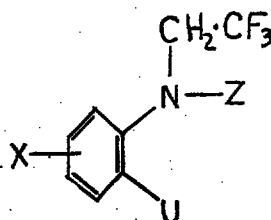
Dissolve 52 gms. of 2-[N-(2,2,2-trifluoroethyl)-2-bromoacetamido]-5-chlorobenzophenone in 1.0 liter of chloroform and bubble ammonia gas through the solution at room temperature for 18 hours. Evaporate the chloroform under reduced pressure, wash the residue with water, extract the residue with ether and wash the ethereal solution with water. Dry the solution over anhydrous sodium sulfate and evaporate the solution to a residue. Crystallize the residue from an acetone-petroleum ether mixture to yield 30 gms. of 7-chloro-1-(2,2,2-trifluoroethyl)-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one melting at 164°—166°C. 20

EXAMPLE 10

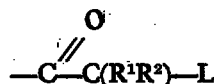
25 7-Chloro-1-(2,2,2-trifluoroethyl)-5-phenyl-1,3-dihydro-2H-1,4-
benzodiazepine-2-one-4-oxide 25

Dissolve 27 gms. of 2-[2-(N-acetoxyacetamido)-N-(2,2,2-trifluoromethyl)-acetamido]-5-chlorobenzophenone in 100 ml. of ethyl alcohol. Add 10 ml. of 15% hydrochloric acid and reflux for 15 minutes. Dilute with water and chill the mixture. Collect the solid by filtration. Wash the solid with water and dry at 50°C. Crystallize the solid from alcohol to yield the product of this example. 30

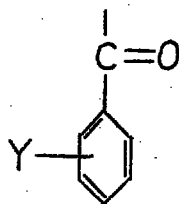
In copending Patent Application No. 46993/69 (Serial No. 1,179,125) there are claimed compounds of the general formula



35 wherein X is hydrogen, halogen, trifluoromethyl, nitro, alkyl or alkoxy; Z is hydrogen or the grouping 35



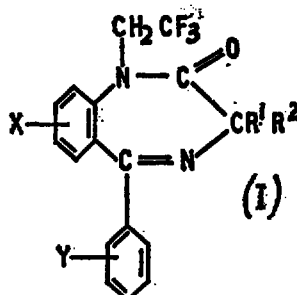
—R¹ and R² being hydrogen or alkyl and L being halogen or a free or protected amino group — and U is the grouping



wherein Y has the same definition as given for X above; and processes for the preparation thereof.

WHAT WE CLAIM IS:—

1. 1,4-Benzodiazepines having the general formula I



wherein X and Y are independently selected from hydrogen, halogen, trifluoromethyl, nitro, alkyl and alkoxy; R¹ and R² are independently selected from hydrogen and alkyl, or one is hydrogen and the other free or esterified hydroxy.

2. Compounds as claimed in Claim 1 in which the esterified hydroxy substituent is alkanoyloxy.

3. Compounds as claimed in Claim 2 in which the alkanoyloxy substituent has from 1 to 6 carbon atoms.

4. 4-oxides of compounds as claimed in Claim 1 wherein R¹ and R² are independently selected from hydrogen and alkyl.

5. Compounds as claimed in any preceding claim in which any alkyl and alkoxy substituents present have from 1 to 6 carbon atoms.

6. Compounds as claimed in any preceding claim in which R¹ is hydrogen.

7. Compounds as claimed in any preceding claim in which X is halogen and Y is hydrogen.

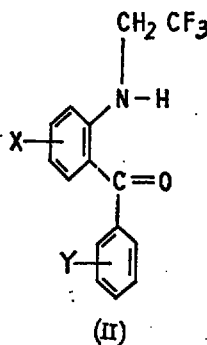
8. Compounds as claimed in Claim 7 in which X is chloro.

9. Compounds as claimed in Claim 1 in which R¹ is hydrogen, R² is hydrogen, alkyl, hydroxy or alkanoyloxy, X is halogen and Y is hydrogen.

10. 4-Oxides of compounds as claimed in Claim 9 in which R² is hydrogen or alkyl.

11. Compounds as claimed in Claim 9 or Claim 10 in which X is chloro attached to the 7-position.

12. Process for the production of a compound of the general formula I claimed in claim 1, wherein R¹ and R² are independently selected from hydrogen and alkyl, which comprises condensing a compound of the general formula II

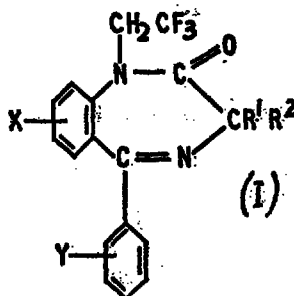


wherein X and Y are as defined in Claim 1 with a compound of the general formula VIII

wherein Y has the same definition as given for X above; and processes for the preparation thereof.

WHAT WE CLAIM IS:—

1. 1,4-Benzodiazepines having the general formula I



wherein X and Y are independently selected from hydrogen, halogen, trifluoromethyl, nitro, alkyl and alkoxy; R¹ and R² are independently selected from hydrogen and alkyl, or one is hydrogen and the other free or esterified hydroxy.

2. Compounds as claimed in Claim 1 in which the esterified hydroxy substituent is alkanoyloxy.

3. Compounds as claimed in Claim 2 in which the alkanoyloxy substituent has from 1 to 6 carbon atoms.

4. 4-oxides of compounds as claimed in Claim 1 wherein R¹ and R² are independently selected from hydrogen and alkyl.

5. Compounds as claimed in any preceding claim in which any alkyl and alkoxy substituents present have from 1 to 6 carbon atoms.

6. Compounds as claimed in any preceding claim in which R¹ is hydrogen.

7. Compounds as claimed in any preceding claim in which X is halogen and Y is hydrogen.

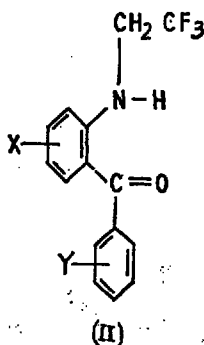
8. Compounds as claimed in Claim 7 in which X is chloro.

9. Compounds as claimed in Claim 1 in which R¹ is hydrogen, R² is hydrogen, alkyl, hydroxy or alkanoyloxy, X is halogen and Y is hydrogen.

10. 4-Oxides of compounds as claimed in Claim 9 in which R² is hydrogen or alkyl.

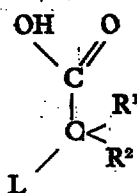
11. Compounds as claimed in Claim 9 or Claim 10 in which X is chloro attached to the 7-position.

12. Process for the production of a compound of the general formula I claimed in claim 1, wherein R¹ and R² are independently selected from hydrogen and alkyl, which comprises condensing a compound of the general formula II



wherein X and Y are as defined in Claim 1 with a compound of the general formula VIII





(VIII)

or with a reactive derivative thereof, wherein R^1 and R^2 are as above defined and L is a free or protected amino group.

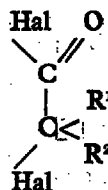
13. A process as claimed in claim 12 in which the reactive derivative of the compound of formula VIII is an alkyl ester.

14. A process as claimed in claim 13, in which the alkyl ester is the ethyl ester.

15. A process as claimed in any one of claims 12 to 14 in which L is an amino group protected by the formation of an addition salt.

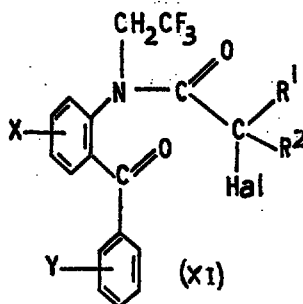
16. A process as claimed in claim 15, in which the addition salt is the hydrochloride.

17. Process for the production of a compound of the general formula I, claimed in claim 1, wherein R^1 , R^2 , X and Y are as defined in claim 12, which comprises condensing the compound of the general formula II, set forth in claim 12 with a compound of the general formula IX



(IX)

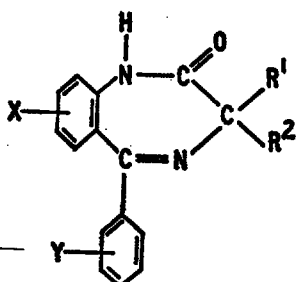
wherein R^1 and R^2 are as above defined and Hal is chloro, bromo or iodo and reacting the so obtained compound of the general formula XI



(XI)

wherein R^1 , R^2 , X and Y and Hal as above defined with ammonia.

18. A process for the production of a compound of the general formula I, claimed in claim 1, or a 4-oxide thereof claimed in claim 4, which comprises trifluoroethylating a compound of the general formula



* C L M S *



wherein R^1 , R^2 , X and Y are as defined in claim 1 or a 4-oxide thereof wherein R^1 , R^2 , X and Y are as defined in claim 4 by reaction with a compound of the general formula



wherein A is a reactive organic or inorganic ester group, and Hal represents halogen, followed, if necessary, by replacement of Hal with fluoro.

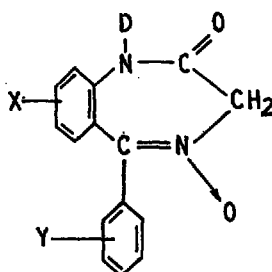
19. A process as claimed in claim 18, in which A is chloro, bromo or iodo.

20. A process as claimed in claim 18, in which A is OSO_2Z , wherein Z is aryl, alkyl, aralkyl or polyhaloalkyl.

21. A process for the production of a 4-oxide claimed in claim 4, which comprises reacting a compound of the general formula I, set forth in claim 1, wherein R^1 and R^2 are independently selected from hydrogen and alkyl with a peroxy acid.

22. A process as claimed in claim 21 in which the peroxy acid is peracetic acid.

23. A process for the production of a compound of formula I, set forth in claim 1, wherein of R^1 and R^2 one is hydrogen and the other free or esterified hydroxy, which comprises heating a compound of the general formula



wherein X and Y are as defined in Claim 1 and D is hydrogen or trifluoroethyl, with an acid anhydride, followed, if necessary, by conversion of D into trifluoroethyl and, if desired, of the esterified hydroxy group into a free hydroxy group, and if desired, by subsequent re-esterification.

24. A process for the production of a 1,4-benzodiazepine claimed in Claim 1 substantially as hereinbefore described and exemplified.

25. A process for the production of a 4-oxide claimed in Claim 4 substantially as hereinbefore described and exemplified.

26. 1,4-Benzodiazepines when produced by a process according to any one of Claims 12 to 20, 23 and 24.

27. A 4-oxide when produced by a process according to Claim 18, 21, 22 or 25.

28. 7 - Chloro - 1,3 - dihydro - 5 - phenyl - 1 - (2,2,2 - trifluoroethyl) - 2H - 1,4-benzodiazepine-2-one and the 4-oxide thereof.

29. 3 - Acetoxy - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 1 - (2,2,2 - trifluoroethyl)-2H-1,4-benzodiazepine-2-one.

30. 7 - Chloro - 1,3 - dihydro - 3 - hydroxy - 5 - phenyl - 1 - (2,2,2 - trifluoroethyl)-2H-1,4-benzodiazepine-2-one.

31. 3 - Propionyloxy - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 1 - (2,2,2 - trifluoroethyl)-2H-1,4-benzodiazepine-2-one.

32. 7 - Chloro - 1,3 - dihydro - 3 - methyl - 5 phenyl - 1 - (2,2,2 - trifluoroethyl)-2H-1,4-benzodiazepine-2-one.

33. 1,3 - Dihydro - 5 - phenyl - 1 - (2,2,2 - trifluoroethyl) - 2H - 1,4 - benzodiazepine-2-one and the 4-oxide thereof.

34. A process for the production of pharmaceutical preparations, which comprises bringing a compound claimed in any one of claims 1 to 11 and 26 to 33 into a form suitable for pharmaceutical administration.

35. Pharmaceutical preparations whenever produced by a process as claimed in claim 4.

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