

AMENDED SPECIFICATION

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PATENT SPECIFICATION

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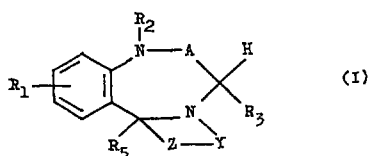


(54) BENZODIAZEPINE DERIVATIVES

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

The present invention relates to benzodiazepine derivatives. More particularly it is concerned with tricyclic benzodiazepine derivatives and with the manufacture thereof.

The tricyclic benzodiazepine derivatives provided by the present invention can be generically formulated thus:



wherein A represents the group $-\text{CH}_2-$ or



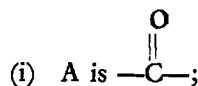
Z represents $-\text{O}-$ or



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in which R_6 represents hydrogen, lower alkyl or lower acyl, R_1 represents hydrogen, halogen, nitro, trifluoromethyl, lower alkyl, lower alkylmercapto or lower alkoxy, R_2

represents hydrogen, lower alkyl, lower cycloalkyl or hydroxy-(lower alkyl), R_3 represents hydrogen or lower alkyl, Y represents a di- or trimethylene group which may be substituted by R_4 , R_4 representing lower alkyl or $-\text{CH}_2\text{X}$ in which X represents chlorine, bromine, (lower alkoxy)-(lower alkyl) or di(lower alkyl)amino, and R_5 represents hydrogen, lower alkyl, pyridyl, phenyl or phenyl substituted by halogen, nitro, trifluoromethyl or lower alkyl, with the proviso that R_2 does not represent hydrogen when



(ii) Y is a dimethylene or trimethylene group which may optionally be substituted by lower alkyl;

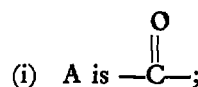
(iii) Z is $-\text{O}-$;

(iv) R_5 is phenyl or phenyl substituted by lower alkyl, halogen, nitro or trifluoromethyl; and

(v) R_1 is lower alkyl, lower alkoxy, halogen, nitro or trifluoromethyl;

and that

R_2 does not represent lower alkyl when



(ii) Y is a dimethylene or trimethylene

group which may optionally be substituted by lower alkyl;

- (iii) Z is —O—;
 (iv) R₃ is hydrogen;
 5 (v) R₅ is phenyl or phenyl substituted by lower alkyl, halogen, nitro or trifluoromethyl; and
 (vi) R₁ is lower alkyl, lower alkoxy, halogen, nitro or trifluoromethyl.

- 10 As used in this description and in the accompanying claims, the term "lower alkyl", either alone or in combination such as in di(lower alkyl)amino, comprehends straight-chain or branched-chain alkyl groups containing from 1 to 7 carbon atoms, preferably 1 to 4 carbon atoms, such as methyl, ethyl, propyl and isopropyl. The term "lower cycloalkyl" encompasses cycloalkyl groups containing from 3 to 6 carbon atoms such as cyclopropyl, cyclobutyl and cyclopentyl. The term "lower acyl" encompasses an organic radical derived by removal of a hydroxyl group from an organic acid such as an alkanolic acid containing from 2 to 7 carbon atoms, for example propionyl. The term "lower alkoxy" comprehends an alkoxy group containing from 1 to 7 carbon atoms such as methoxy, ethoxy and propoxy. The term "halogen" means fluorine, chlorine, bromine and iodine.
 20 One particular aspect of the present invention relates to tricyclic benzodiazepine derivatives of formula I wherein Z represents the group



- 35 in which R₆ represents hydrogen, lower alkyl or acyl and R₁, R₂, R₃, R₅, Y and A have the significance given earlier.

- A further particular aspect of the present invention relates to tricyclic benzodiazepine derivatives of formula I wherein A represents the group —CH₂— and R₁, R₂, R₃, R₅, Y and Z have the significance given earlier.

- A still further particular aspect of the present invention relates to tricyclic benzodiazepine derivatives of formula I wherein A represents the group



- 50 Z represents —O—, R₁, R₃, R₅ and Y have the significance given earlier and R₂ represents hydroxy-(lower alkyl) or A represents



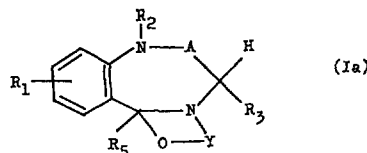
Z represents —O—, R₁, R₂, R₃ and R₅ have the significance given earlier and Y represents

a di- or trimethylene group substituted by CH₂X in which X represents chlorine, bromine, (lower alkoxy)-(lower alkyl) or di(lower alkyl) amino or A represents



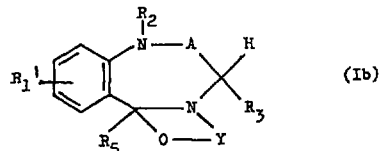
Z represents —O—, R₁, R₂, R₃ and Y have the significance given earlier and R₅ represents hydrogen, lower alkyl or pyridyl.

A preferred group of tricyclic benzodiazepine derivatives of formula I are those in which Z represents —O— i.e. tricyclic benzodiazepine derivatives of the general formula



wherein A, R₁, R₂, R₃, R₅ and Y have the significance given earlier.

A particularly preferred embodiment of the present invention comprises tricyclic benzodiazepine derivatives of formula I in which Z represent —O— and R₁ represents hydrogen, halogen, nitro, trifluoromethyl or lower alkyl, i.e. tricyclic benzodiazepine derivatives of the general formula



wherein R₁' represents hydrogen, halogen, nitro, trifluoromethyl or lower alkyl and A, Y, R₂, R₃ and R₅ have the significance given earlier, with the proviso that R₂ does not represent hydrogen when

(i) A is —C(=O)—;

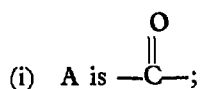
(ii) Y is a dimethylene or trimethylene group which may optionally be substituted by lower alkyl;

(iii) R₅ is phenyl or phenyl substituted by lower alkyl, halogen, nitro or trifluoromethyl; and

(iv) R₁' is lower alkyl, halogen, nitro or trifluoromethyl;

and that

R₂ does not represent lower alkyl when



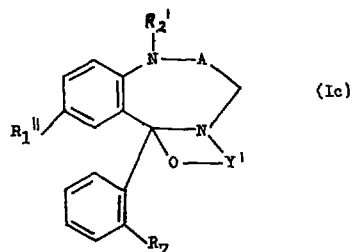
(ii) Y is a dimethylene or trimethylene group which may optionally be substituted by lower alkyl;

(iii) R_3 is hydrogen;

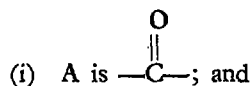
(iv) R_3 is phenyl or phenyl substituted by lower alkyl, halogen, nitro or trifluoromethyl; and

(v) R_1' is lower alkyl, halogen, nitro or trifluoromethyl.

A still more preferred embodiment of the present invention comprises tricyclic benzodiazepine derivatives of formula I in which Z represents —O— , R_1 represents hydrogen or halogen (especially chlorine) in the 7-position of the benzodiazepine moiety, R_2 represents hydrogen, lower alkyl (especially methyl) or hydroxy-(lower alkyl) (especially β -hydroxy-ethyl), R_3 represents hydrogen, Y represents a di- or trimethylene group which may be substituted by lower alkyl (preferably methyl) or chloromethyl and R_5 represents phenyl or phenyl substituted in the *ortho*-position by halogen (especially fluorine), i.e. tricyclic benzodiazepine derivatives of the general formula



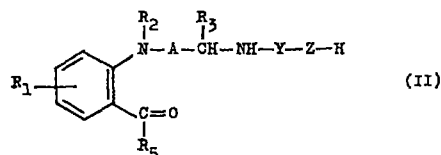
wherein R_1'' represents hydrogen or halogen, A has the significance given earlier, R_2' represents hydrogen, lower alkyl or hydroxy-(lower alkyl), Y' represents a di- or trimethylene group which may be substituted by lower alkyl or chloromethyl and R_7 represents hydrogen or halogen, with the proviso that R_2' does not represent hydrogen or lower alkyl when



(ii) Y' is a di- or trimethylene group which may be substituted by lower alkyl.

Most preferred among the tricyclic benzodiazepine derivatives of formula I are those of formula (Ic) above in which R_1'' represents chlorine, R_2' represents hydrogen, methyl or β -hydroxy-ethyl, Y' represents a dimethylene group which may be substituted by methyl or chloromethyl and R_7 represents hydrogen or fluorine.

According to one process provided by the present invention, the tricyclic benzodiazepine derivatives of formula I hereinbefore are manufactured by cyclizing a compound of the general formula

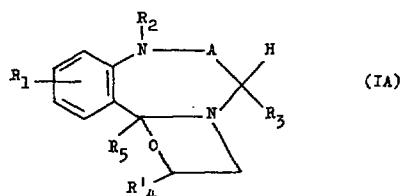


wherein R_1 , R_2 , R_3 , R_5 , A, Y and Z have the significance given for formula I, and, if a tricyclic benzodiazepine derivative of formula I in which Z represents —NH— is obtained and it is desired to produce a tricyclic benzodiazepine derivative of formula I in which Z represents



R_6' representing lower alkyl or lower acyl, alkylating or acylating the said —NH— group, or if a mixture of epimeric tricyclic benzodiazepine derivatives of formula (I) is obtained, separating the mixture into its components, if desired.

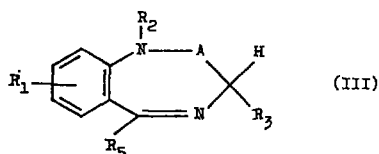
Another process provided by the invention, for the manufacture of tricyclic benzodiazepine derivatives of the general formula



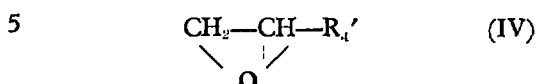
wherein R_1 represents hydrogen, halogen, nitro, trifluoromethyl, lower alkyl, lower alkyl mercapto or lower alkoxy; R_2 represents hydrogen; lower alkyl, lower cycloalkyl or hydroxy-(lower alkyl); R_3 represents hydrogen or lower alkyl; R_5 represents hydrogen, lower alkyl, pyridyl, phenyl or phenyl-substituted by halogen, nitro, trifluoromethyl or lower alkyl; A represents the group $\text{—CH}_2\text{—}$ or



and R_4' represents hydrogen, lower alkyl or CH_2X in which X represents chlorine, bromine, (lower alkoxy)-(lower alkyl) or di-(lower-alkyl) amino, comprises reacting a 4,5-unsaturated 1,4-benzodiazepine of the general formula

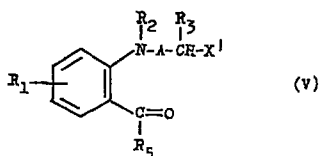


wherein R_1 , R_2 , R_3 , R_5 and A have the significance given above, with an epoxide of the general formula



wherein R_4' has the significance given above, in the presence of an acidic agent and, if a mixture of epimeric tricyclic benzodiazepine derivatives of formula I is obtained separating the mixture into its components if desired.

Thus, as described above in one aspect of the process of the present invention, tricyclic benzodiazepine derivatives of formula I are manufactured by cyclization of a compound of formula II. The compounds of formula II which are used as starting materials in this aspect of the process are conveniently prepared by reacting a corresponding 2-(substituted amino)-phenyl ketone of the general formula



wherein R_1 , R_2 , R_3 , R_5 and A have the significance given for formula (I) and X' represents chlorine, bromine or iodine, with a diamine or aminoalkanol of the general formula



wherein Y and Z have the significance given for formula (I).

The 2-(substituted amino)-phenyl ketones of formula V and diamines and aminoalkanols of formula VI are readily prepared in a known manner. The reaction between a 2-(substituted amino)-phenyl ketone of formula V and a diamine or aminoalkanol of formula VI is conducted in a reaction medium containing a base and an inert organic solvent. Suitable bases for this purpose are inorganic bases such as sodium acetate and organic bases such as the tertiary amines (for example, trialkylamines, with triethylamine and pyridine being preferred). A variety of organic solvents are useful in this reaction. Among the suitable solvents are lower alkanols such as methanol, ethanol and pro-

panol, with ethanol being preferred, aromatic hydrocarbons such as benzene, toluene and xylene, high boiling ethers such as tetrahydrofuran and dioxane and amides such as dimethylformamide and diethylformamide. If, in the 2-(substituted amino)-phenyl ketones of formula V, X' represents chlorine or bromine, the reaction mixture may also contain sodium iodide in order to replace the chlorine or bromine atom X' by the more reactive iodine atom. Examples of useful diamines and aminoalkanols of formula VI are 2-aminoethanol, ethylenediamine and 3-aminopropanol.

The compounds of general formula II thus formed need not be isolated from the reaction mixture since they readily cyclize to the desired tricyclic benzodiazepine derivatives of formula I and, in a preferred embodiment, such compounds are not isolated but are permitted to cyclize in the reaction medium in which they are prepared by conducting the reaction between the 2-(substituted amino)-phenyl ketones of formula V and the diamines or aminoalkanols of formula VI at a temperature in the range of from about 25°C to the reflux temperature of the reaction medium, preferably at about the reflux temperature. However, by using less energetic reaction conditions (e.g. by conducting the reaction at about or below room temperature) the compounds of formula II can be isolated and subsequently cyclized to the desired tricyclic benzodiazepine derivatives (e.g. by heating in pyridine, ethanol or xylene).

Tricyclic benzodiazepine derivatives in which Z represents $-\text{NH}-$ of formula I thus obtained can be converted into the corresponding tricyclic benzodiazepine derivatives of formula I in which Z represents



R_6' representing lower alkyl or lower acyl, by conventional alkylation or acylation procedures. By controlling the conditions, alkylation or acylation can be accomplished on the nitrogen of the heterocyclic ring without affecting other vulnerable positions on the benzodiazepine moiety.

In accordance with a further and particularly important aspect of the process of the present invention, tricyclic benzodiazepine derivatives of formula I in which Z represents $-\text{O}-$ and Y represents a dimethylene group which may be substituted by R_4 , i.e. tricyclic benzodiazepine derivatives of formula IA, are manufactured by reacting a 4,5-unsaturated 1,4-benzodiazepine of formula III with an epoxide of formula IV in the presence of an acidic agent such as, for example, an aprotic acid (e.g., aluminium chloride, ferric chloride, zinc chloride, titanium tetrachloride or boron trifluoride) or *p*-toluene sulfonic acid or benzene

sulfonic acid. The most preferred acidic agent for the purposes of this invention is aluminium chloride. Examples of epoxides of formula IV useful in this aspect of the invention include ethylene oxide, propylene oxide and 1-chloro-2,3-epoxy propane.

The reaction of a 4,5-unsaturated 1,4-benzodiazepine of formula III with an epoxide of formula IV to yield a tricyclic benzodiazepine derivative of formula IA is conveniently conducted in the presence of an anhydrous inert organic solvent. Suitable inert organic solvents for this purpose include, for example, aromatic hydrocarbons such as benzene, toluene and xylene, ethers such as tetrahydrofuran and diethyl ether or carbon disulfide. This reaction may be carried out at a temperature in the range of from about minus 10°C to the reflux temperature of the reaction medium, most preferably from 10°C to the reflux temperature. The selection of temperature is not critical for the purposes of the present invention and will, of course, depend upon the characteristics of the reagents used, the solvent medium employed and the nature of the acidic agent used.

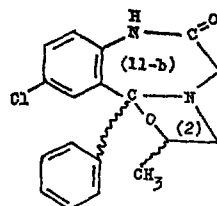
It would appear that when a 4,5-unsaturated 1,4-benzodiazepine of formula III is reacted with an epoxide of formula IV in which R₄' represents other than hydrogen, the R₄'-bearing carbon atom can be attached relative to the benzodiazepine ring in one of two positions depending upon the point where the epoxide ring cleaves during the reaction. However, experiment has shown that the epoxide ring evidences a propensity to favour cleavage between the oxygen and the unsubstituted carbon atom. Thus, when cleavage occurs at this point, the carbon atom bearing the R₄' substituent is bonded to the oxygen atom in the heterocyclic ring.

It should be noted that epoxides of formula IV may, in addition to forming the heterocyclic ring between the 4- and 5-positions of the benzodiazepine moiety upon reaction with a 4,5-unsaturated 1,4-benzodiazepine of formula III, also react with the nitrogen atom in the 1-position of the 4,5-unsaturated 1,4-benzodiazepines of formula III when the nitrogen atom is unprotected, that is, when R₂ represents hydrogen. Thus, the reaction of a 4,5-unsaturated 1,4-benzodiazepine of formula III in which R₂ represents hydrogen with an epoxide of formula IV can result in a mixture of products, the first showing no substitution

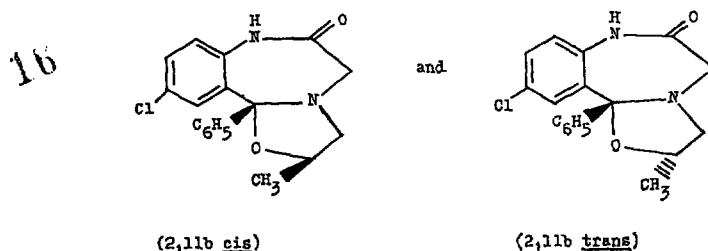
on the 1-nitrogen atom and the second being correspondingly substituted on the 1-nitrogen atom. For example, if a 4,5-unsaturated 1,4-benzodiazepine of formula III in which R₂ represents hydrogen is reacted with an epoxide of formula IV in which R₄' represents hydrogen (i.e. ethylene oxide) one is able to isolate from the reaction mixture both the corresponding tricyclic benzodiazepine derivative of formula IA in which R₂ represents hydrogen and the corresponding tricyclic benzodiazepine derivative of formula IA in which R₂ represents β-hydroxy-ethyl. Experiment has shown that, by controlling the reaction conditions, substitution at the 1-nitrogen atom can be avoided.

Many of the 4,5-unsaturated 1,4-benzodiazepines of formula III required as starting materials in the last-mentioned aspect of the process of this invention are claimed *per se* in the specification of our Letters Patents Nos. 948,888, 972,968, 1,000,507, 1,012,260, 1,017,276, 1,039,372, 1,100,675, 1,102,534, 1,106,039, 1,124,245 and 1,192,729.

It will be appreciated that in the following both the epoxide method of involving the reaction between 4,5-unsaturated 1,4-benzodiazepines of formula III and epoxides of formula IV and the cyclization method discussed earlier for the manufacture of the tricyclic benzodiazepine derivatives of formula I, the product obtained in many cases will be a mixture of epimers which can be separated into its components by known methods. Thus, for example, in the manufacture of a tricyclic benzodiazepine derivative of the formula



by for example the epoxide method, it has been noted that the mixture of two epimers showing a difference in configuration at the 2- and 11-b positions of the molecule is obtained. Upon separating the mixture into its two components, the following *cis* and *trans* isomers were obtained:



If a solution containing either of the isolated epimers is permitted to stand, a mixture containing both the *cis* and *trans* epimers results. Epimerization can also be effected by means of boron trifluoride etherate for example.

Examples of tricyclic benzodiazepine derivatives of and obtainable by the present invention are:

- 10 10 - Chloro - 2,3,5,11b - tetrahydro - 11b-phenyloxazolo[3,2 - d][1,4]benzodiazepin-6(7H) - one;
- 15 10 - Chloro - 2,3,5,11b - tetrahydro - 7-(2 - hydroxyethyl) - 11b - phenyloxazolo[3,2-d][1,4]benzodiazepin - 6 - (7H) - one;
- 20 10 - Chloro - 11b - (2 - fluorophenyl)-2,3,5,11b - tetrahydro - oxazolo[3,2 - d][1,4]benzodiazepin - 6 - (7H) - one;
- 25 10 - Chloro - 11b - (2 - fluorophenyl)-2,3,5,11b - tetrahydro - 7 - (2 - hydroxyethyl)-oxazolo[3,2 - d][1,4]benzodiazepin - 6 - (7H) - one;
- 30 10 - Chloro - 2,3,5,11b - tetrahydro - 7-methyl - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepin - 6 - (7H) - one;
- 35 10 - Chloro - 2,3,5,11b - tetrahydro - 2,7-dimethyl - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepin - 6 - (7H) - one (2,11b *cis*);
- 40 10 - Chloro - 2 - chloromethyl - 2,3,5,11b-tetrahydro - 7 - methyl - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepin - 6(7H) - one;
- 45 10 - Chloro - 2,3,5,6,7,11b - hexahydro-7 - methyl - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepine;
- 50 10 - Chloro - 1,2,3,5,7,11b - hexahydro-7 - methyl - 11b - phenyl - 6H - imidazo[1,2 - d][1,4]benzodiazepin - 6 - one;
- 11 - Chloro - 3,4,6,7,8,12b - hexahydro-8 - methyl - 12b - phenyl - 2H [1,3]oxazino[3,2 - d] [1,4]benzodiazepine;
- 10 - Chloro - 2,3,5,6,7,11b - hexahydro-7 - methyl - 11b - phenyl - 1H - imidazo[1,2 - d] [1,4]benzodiazepine;
- 10 - Chloro - 2,3,5-11b - tetrahydro - 2-methyl - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepin - 6(7H) - one (2,11b *cis*);
- 10 - Chloro - 2,3,5,11b - tetrahydro - 2-methyl - 11b - phenyloxazolo [3,2 - d][1,4]benzodiazepin - 6(7H) - one (2,11b *trans*);
- 10 - Chloro - 2,3,5 - 11b - tetrahydro - 3-methyl - 11b - phenyloxazolo [3,2 - d][1,4]benzodiazepin - 6(7H) - one (3,11b *cis*).

The tricyclic benzodiazepine derivatives of and obtainable by the invention are useful as pharmaceuticals and are characterized by activity as sedative, muscle relaxant and anti-convulsant agents.

The pharmacological activity of a series of tricyclic benzodiazepine derivatives of the present invention was determined in standard screening tests. Tricyclic benzodiazepine derivatives which were employed in these experiments were as follows:

- 10 - chloro - 2,3,5 - tetrahydro - 7- (2-hydroxyethyl) - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepin - 6 - (7H) - one (DERIVATIVE A)
- 10 - chloro - 11b - (2 - fluorophenyl)-2,3,5,11b - tetrahydro - 7 - (2 - hydroxyethyl) oxazolo[3,2 - d][1,4]benzodiazepin - 6 - (7H) - one (DERIVATIVE B)
- 10 - chloro - 11b - (2 - fluorophenyl)-2,3,5,11b - tetrahydro - oxazolo[3,2 - d][1,4]benzodiazepin - 6 - (7H) - one (DERIVATIVE C)
- 10 - chloro - 2,3,5,11b - tetrahydro - 11b-phenyloxazolo - [3,2 - d][1,4]benzodiazepin-6 - (7H) - one (DERIVATIVE D)
- 10 - chloro - 2,3,5,11b - tetrahydro - 7-methyl - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepin - 6 - (7H) - one (DERIVATIVE E)
- 10 - chloro - 2,3,5,11b - tetrahydro - 2,7-dimethyl - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepin - 6 - (7H) - one (DERIVATIVE F)
- 10 - chloro - 2 - chloromethyl - 2,3,5,11b-tetrahydro - 7 - methyl - 11b - phenyloxazolo [3,2 - d][1,4]benzodiazepin - 6 - (7H) - one (DERIVATIVE G)
- 10 - chloro - 2,3,5,6,7,11b - hexahydro - 7-methyl - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepine (DERIVATIVE H)

The tests employed in this experiment were the following:

Foot Shock

This test is a screen for compounds having muscle relaxant and/or anti-anxiety (tranquilizer) activity. A pair of mice is confined under a one liter beaker placed on a grid which presents shock to the feet. At least 5 fighting

episodes are elicited in a two-minute period. Pairs of mice are marked and pretreated by oral dosage 1 hour prior to a second shocking. Logarithmic dose intervals are utilized up to a maximum of 100 mg/kg. At the 100 per cent blocking dose, 3 out of 3 pairs must be blocked from fighting.

Inclined Screen

The test is useful in determining muscle relaxant and/or sedative activity. Groups of 6 male mice are given the test compound (maximum dose of 500 mg/kg) and then are left on the inclined screen at least four hours for observation of paralyzing effects severe enough to cause them to slide off the screen. If activity is observed, additional doses are tested until at least two are reached at which some, but not all the animals slide off the screen. Doses at which mice fall off the screen due to toxicity or excitation are not included in the calculation of PD_{50} . The PD_{50} is determined from a graph on which dose is plotted against per cent of mice paralyzed. This PD_{50} value is defined as the dose in mg/kg which can be expected to cause 50 per cent of mice to slide off the screen.

Unanesthetized Cat

Cats are treated orally and observed for minimum symptoms, usually ataxia. One cat is used at a dose of 50 mg/kg. If activity is present, up to three cats per dose are used. Results are given as minimum effective dose. This test is useful in determining muscle relaxant activity.

Antimetrazol

This test determines anticonvulsant and/or sedative activity of compounds in mice. The test compound is administered orally to groups of four mice at various dose levels. One hour later, metrazol (at a dose level previously determined to be sufficient to induce convulsive seizures in all test animals — approximately 125 mg/kg) is administered subcutaneously and the animals are observed for protection from convulsive seizures. Results are recorded as the number of animals protected against convulsions. The dose at which 50 per cent of the animals are protected from convulsive seizures is expressed as the ED_{50} .

The test results from the foregoing tests using the indicated tricyclic benzodiazepine derivatives of the present invention are summarized in Table I hereinafter.

TABLE I

Derivative	Footshock 100% Blocking Dose	Inclined Screen PD_{50}	Unanesthetized Cat MED	Antimetrazol ED_{50}
Derivative A	20 mg/kg	50 mg/kg	5 mg/kg	—
Derivative B	4 mg/kg	15 mg/kg	5 mg/kg	2.034 mg/kg
Derivative C	1 mg/kg	8 mg/kg	25 mg/kg	0.075 mg/kg
Derivative D	10 mg/kg	20 mg/kg	—	—
Derivative E	100 mg/kg	300 mg/kg	—	—
Derivative F	80 mg/kg	250 mg/kg	—	—
Derivative G	100 mg/kg	300 mg/kg	10 mg/kg	24 mg/kg
Derivative H	—	500 mg/kg	—	—

The tricyclic benzodiazepine derivatives of the invention can be made up in the form of conventional pharmaceutical preparations; for example, they can be mixed with conventional organic or inorganic, inert pharmaceutical carriers suitable for parenteral or enteral administration such as, for example, water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oil, gums, polyalkylene glycols or petroleum jelly. They can be administered in

conventional pharmaceutical forms (e.g., solid forms such as tablets, dragees, capsules or suppositories) or in liquid forms (for example, solutions, suspensions or emulsions). Moreover, the pharmaceutical preparations can be subjected to conventional pharmaceutical operations such as sterilization and can contain conventional pharmaceutical excipients such as preservatives, stabilizing agents, wetting agents, emulsifying agents, salts for the adjustment of

osmotic pressure, or buffers. The pharmaceutical preparations can also contain other therapeutically active materials.

A suitable pharmaceutical dosage unit can contain from about 1 to 500 mg of the tricyclic benzodiazepine derivatives of the invention, with a dosage range of from about 1 mg to 100 mg being the preferred oral administration and a dosage range of from about 1 mg to 50 mg being preferred for parenteral administration. However, for any particular subject, the specific dosage regimen should be adjusted according to individual need and the professional judgement of the person administering or supervising the administration of the tricyclic benzodiazepine derivatives. It will be appreciated that the dosages set forth herein are given by way of example only and that they do not, to any extent, limit the scope or practice of this invention.

The term "dosage unit" employed in this specification refers to pharmaceutically discrete units suitable as unitary dosages for mammalian subjects each containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier or vehicle.

It will be appreciated that the invention also includes within its scope pharmaceutical preparations containing a tricyclic benzodiazepine derivative of the invention in association with a compatible pharmaceutical carrier.

The following Examples illustrate the process provided by the invention. All temperatures given are in degrees Centigrade, unless indicated otherwise.

Example 1.

To 5 g (18.5 mmole) of 7 - chloro - 1,3-dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one in 90 ml of dry benzene were added 5.0 g (37 mmole) of aluminium chloride. The reaction mixture was stirred for 6 hours at reflux, cooled to room temperature and treated with 4.4 g (0.1 mole) of ethylene oxide. The reaction mixture was stirred for 18 hours, the benzene was then removed and the residue was treated with aqueous ammonium hydroxide and 100 ml of methylene chloride. The resulting precipitate was removed by filtration. The organic layer was then separated, washed with aqueous sodium chloride, dried and the solvent evaporated to yield a residue which was crystallized from ether and recrystallized from a mixture of methylene chloride and hexane to give 10-chloro - 2,3,5,11b - tetrahydro - 11b - phenyl-oxazolo[3,2 - d][1,4] - benzodiazepine - 6-(7H) - one as colourless prisms; m.p. 125°—135°; resetting at 173°—177°.

The foregoing filtrates were dissolved in methylene chloride and chromatographed over silica gel (200 g) with methylene chloride (300 ml) and with 700 ml of ethyl acetate. The

ethyl acetate fraction was evaporated to dryness and crystallized from ether. Recrystallization from a mixture of methylene chloride and hexane gave 10 - chloro - 2,3,5,11b-tetrahydro - 7 - (2 - hydroxyethyl) - 11b-phenyloxazolo[3,2 - d][1,4]benzodiazepin-6 - (7H) - one as colourless prisms; m.p. 134°—137°.

Example 2.

To 15 g (51.9 mmole) of 7 - chloro - 5-(2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4-benzodiazepin - 2 - one in 150 ml of dry benzene, 9 g (67.7 mmole) of aluminium chloride were added and the mixture was stirred for 15 minutes. The reaction mixture was cooled in an ice-bath and 8.8 g (0.2 mole) of ethylene oxide were added dropwise. After stirring for 18 hours at room temperature, the reaction mixture was heated to 40° for 1 hour and then cooled to room temperature and treated with 5 g (37.6 mmole) of aluminium chloride, followed by 4.4 g (0.1 mole) of ethylene oxide. The reaction mixture was heated for 4 hours at 45°—50° and then evaporated to dryness. Methylene chloride, ice and ammonium hydroxide were added and the solid was removed by filtration. The filtrate was separated and the organic phase reduced to dryness *in vacuo*. The residue was dissolved in dilute hydrochloric acid and the pH of the solution adjusted to 5 with ammonium hydroxide. The acidic solution was washed with ether, made basic and extracted with methylene chloride. The organic phase was washed with aqueous sodium chloride, dried and evaporated to dryness. Recrystallization from a mixture of methylene chloride and hexane gave 10-chloro - 11b - (2 - fluorophenyl) - 2,3,5,11b-tetrahydrooxazolo[3,2 - d][1,4]benzodiazepin-6 - (7H) - one as colourless rods; m.p. 183°—184°.

The ether wash of the said solution at pH 5 was evaporated to dryness, dissolved in methylene chloride and chromatographed over 200 g of silica gel with methylene chloride and ethyl acetate. The methylene chloride and ethyl acetate fractions were combined and the solvents removed to give a crude product. Recrystallizations from a mixture of methylene chloride and petroleum ether gave 10 - chloro - 11b - (2 - fluorophenyl)-2,3,5,11b - tetrahydro - 7 - (2 - hydroxyethyl) - oxazolo[3,2 - d][1,4]benzodiazepin-6(7H) - one as colourless plates; m.p. 147°—151°.

Example 3.

A mixture of 100 ml of dried benzene and 5.0 g of aluminium chloride under a condenser filled with dry-ice and acetone was stirred and treated with 10.0 g (35 mmole) of 7-chloro - 1,3 - dihydro - 1 - methyl - 5-phenyl - 2H - 1,4 - benzodiazepin - 2 - one giving a yellow solid. Stirring was continued for 20 minutes and, after the addition of 35

ml of hexane, the mixture was cooled in an ice-bath. Upon the addition of 7 ml of ethylene oxide, the yellow solid dissolved. The reaction mixture was warmed to room temperature and was stirred overnight. The benzene solution was repartitioned between methylene chloride and iced aqueous ammonium hydroxide. Filtration removed a large portion of the aluminium salts and the organic layer was separated, washed with water, dried and evaporated. The resulting residue was washed with ether to give 10 - chloro - 2,3,5,11b - tetrahydro - 7 - methyl - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepin - 6 - (7H) - one as colourless crystals; m.p. 179°—184°. Two recrystallizations from a mixture of methylene chloride and hexane gave colourless rods; m.p. 182—184°.

Example 4.

A mixture of 10.0 g (35 mmole) of 7-chloro - 1,3 - dihydro - 1 - methyl - 5-phenyl - 2H - 1,4 - benzodiazepin - 2 - one, 6.7 g of aluminium chloride, 300 ml of benzene and 30 ml of hexane was chilled in an ice-bath and was treated with 10 ml of propylene oxide. The reaction mixture was warmed to room temperature and was stirred overnight. Working-up as described in Example 3 yielded a mixture of the epimers of 10 - chloro - 2,3,5,11b - tetrahydro - 2,7-dimethyl - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepin - 6(7H) - one. A solution of 1.0 g of this mixture was stirred overnight at 80° in 25 ml of boron trifluoride etherate. The mixture was poured carefully into ice-water and made basic with ammonium hydroxide. The mixture was extracted with chloroform, washed with water, dried and concentrated to a solid residue. Three recrystallizations from a mixture of methylene chloride and hexane gave the 2,11b *cis* isomer of the aforementioned derivative; m.p. 142°—143°.

Example 5.

A mixture of 10 g (35 mmole) of 7 - chloro - 1,3 - dihydro - 1 - methyl - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one, 10 g of aluminium chloride and 200 ml of dried benzene was treated with 30 ml of 1 - chloro 2,3-epoxypropane in 100 ml of benzene. The reaction mixture was stirred overnight. Working-up as described in Example 3, gave 32 g of a crude oil. The oil was dissolved in benzene, filtered over activated magnesium silicate, the filtrate evaporated to dryness and the residue crystallized from a mixture of ether and petroleum ether to give 10 - chloro - 2 - chloromethyl - 2,3,5,11b - tetrahydro - 7 - methyl - 11b - phenyloxazolo - [3,2 - d][1,4]benzodiazepin - 6(7H) - one as colourless needles; m.p. 140°—142°.

Example 6.

A mixture of 12.5 g (46 mmole) of 7-chloro - 2,3 - dihydro - 1 - methyl - 5-

phenyl - 1H - 1,4 - benzodiazepine hydrochloride, 5.0 g of aluminium chloride, 200 ml of benzene and 30 ml of hexane was stirred for 20 minutes, chilled in an ice-bath and then treated with 7.0 ml of ethylene oxide. The reaction mixture was warmed to room temperature and stirred overnight. The benzene was removed by evaporation and the residue was partitioned between methylene chloride and dilute ammonium hydroxide. The solid was removed by filtration and the organic layer washed with water, dried and evaporated to give an orange oil. Upon standing, the oil crystallized and the resulting solid was recrystallized from hexane to give 10 - chloro - 2,3,5,6,7,11b - hexahydro - 7 - methyl - 11b-phenyloxazolo[3,2 - d][1,4]benzodiazepine. An analytical sample was obtained as colourless prisms (m.p. 109°—110°) by recrystallization from ether.

Example 7.

A solution of 5.6 g (18.2 mmole) of 5-chloro - 2 - (2 - chloroethylmethylamino) benzophenone, 5.0 g of sodium iodide, 50 ml of 2-aminoethanol, 50 ml of triethylamine and 100 ml of ethanol was heated at reflux for 17 hours. The mixture was poured into ice-water and was extracted with methylene chloride. The organic phase was washed with water, dried and evaporated to an oil. The oil was cooked out with petroleum ether and 10-chloro - 2,3,5,6,7,11b - hexahydro - 7 - methyl - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepine crystallized from the solvent; m.p. 107°—109°.

Example 8.

A solution of 6.4 g (20 mmole) of 2 - (2-chloro - N - methylacetamido) - 5 - chlorobenzophenone, 12.0 g (0.2 mole) of ethylenediamine, 50 ml of triethylamine and 250 ml of ethanol was heated at reflux for 20 hours. The reaction mixture was concentrated to a residue which was partitioned between ether and water. The ether layer was washed with water, dried and concentrated to a small amount of liquid which was treated with a small amount of ethanol to give, upon standing 10 - chloro - 1,2,3,5,7,11b - hexahydro - 7 - methyl - 11b - phenyl - 6H - imidazo[1,2 - d][1,4]benzodiazepin - 6 - one as colourless crystals; m.p. 164°—167°.

Example 9.

A solution of 5.0 g (16 mmole) of 5-chloro - 2 - (2 - chloroethylmethylamino)benzophenone, 3.75 g (50 mmole) of 3-aminopropanol, 50 ml of triethylamine and 250 ml of ethanol was stirred at reflux for 48 hours. The reaction mixture was then evaporated to a residue which was washed with water, dissolved in methylene chloride and chromatographed over a column of activated magnesium silicate. The first fraction yielded 2.7 g of starting material. Elution

with acetone, ethanol, methanol and finally with methanol to which concentrated ammonium hydroxide had been added gave a compound of very low Rf on fluorescent silica eluted with ethanol. Crystallization from acetone and recrystallizations from a mixture of ether and petroleum ether gave 11-chloro-3,4,6,7,8,12b - hexahydro - 8 - methyl - 12b-phenyl - 2H - [1,3]oxazino[3,2 - d][1,4]benzodiazepine as colourless prisms; m.p. 142°—144°.

Example 10.

A solution of 5.0 g (16 mmole) of 5-chloro-2 - (2 - chloroethylmethylamino)benzophenone, 3.0 g (50 mmole) of ethylenediamine, 50 ml of triethylamine and 250 ml of ethanol was stirred at reflux for 48 hours. The solvents were removed by evaporation and the residue containing starting material and the product was washed with water, chromatographed over activated magnesium silicate and recrystallized from petroleum ether to give 10 - chloro-2,3,5,6,7,11b - hexahydro - 7 - methyl - 11b-phenyl - 1H - imidazo[1,2 - d][1,4]benzodiazepine as yellow prisms; m.p. 100°—102°.

The following Example is given to show how a mixture of two epimers obtained can be isolated into the cis and trans forms:

Example 11.

A solution of 67 g (0.19 mole) of 2 - (2-bromoacetamido) - 5 - chloro benzophenone, 500 ml of xylene, 15.7 g (0.21 mole) of 1-amino - 2 - propanol and 25 ml of triethylamine was stirred at reflux for 20 hours. The reaction mixture was concentrated *in vacuo* to a residue which was partitioned between methylene chloride and water. The organic layer was washed with water, dried and concentrated to an oil which was crystallized from ethyl acetate to give 18.3 g of a colourless solid; m.p. 181°—184°. Thin layer chromatography on alumina plates with an eluant of 3 parts of hexane and 2 parts of ethyl acetate revealed the presence of two compounds. The product was dissolved in chloroform and chromatographed over neutral alumina. A mixture concentrated in the 2,11b *trans* isomer of 10 - chloro - 2,3,5,11b - tetrahydro - 2-methyl - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepin - 6(7H) - one (the faster of the two compounds) was collected in a mixture of 30% ethyl acetate and 70% hexane. Recrystallizations from methylene chloride gave colourless prisms; m.p. 188°—189°.

A 1.0 g sample (0.3 mmol) of the two compound mixture obtained earlier was stirred for 17 hours at 80° in a solution of 25 ml of boron trifluoride etherate. The mixture was poured over 200 g of ice and was carefully treated with ammonium hydroxide to a pH of 8. The resulting solid was removed by filtration and was air-dried to give 10 - chloro-2,3,5,11b - tetrahydro - 2 - methyl - 11b-

phenyloxazolo[3,2 - d][1,4]benzodiazepin-6(7H) - one (2,11b *cis*). Two recrystallizations from a mixture of chloroform and hexane gave colourless prisms; m.p. 172°—174°.

Example 12.

A solution of 5.4 g (20 mmol) of 7-chloro-1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and 20 ml of stannic chloride in 300 ml of dry benzene was treated with 60 mmol of propylene oxide and stirred under dry nitrogen for 22 hours at 80°. The reaction mixture was concentrated *in vacuo* to a residue which was partitioned between methylene chloride and ammonia. The organic phase was washed with water, dried and concentrated to give a crystalline residue. Recrystallization from ethyl acetate gave colourless prisms (m.p. 178°—183°) of a mixture of 10 - chloro - 2,3,5,11b - tetrahydro - 2-methyl - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepin - 6(7H) - one (2,11b *cis*) and 10 - chloro - 2,3,5,11b - tetrahydro - 2-methyl - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepin - 6(7H) - one (2,11b *trans*).

This reaction was also effected in benzene solution using aluminium trichloride, titanium tetrachloride or boron trifluoride etherate as catalyst.

Following the procedures set forth in Example 11, the mixture thus obtained can be separated in order to isolate 10 - chloro-2,3,5,11b - tetrahydro - 2 - methyl - 11b-phenyloxazolo[3,2 - d][1,4]benzodiazepin-6(7H) - one (2,11b *cis*) and 10 - chloro-2,3,5,11b - tetrahydro - 2 - methyl - 11b-phenyloxazolo[3,2 - d][1,4]benzodiazepin-6(7H) - one (2,11b *trans*).

The following Example illustrates pharmaceutical preparations containing the tricyclic benzodiazepine derivatives provided by the invention:

Example.

DERIVATIVE C hereinbefore, 10 - chloro-11b - (2 - fluorophenyl) - 2,3,5,11b - tetrahydrooxazolo[3,2 - d][1,4]benzodiazepin-6(7H) - one, was made up in the form of several pharmaceutical preparations as follows:

A) Suppository Formulation

	Per 1.3 g Suppository	
10 - Chloro - 11b - (2 - fluorophenyl) - 2,3,5,11b-tetrahydrooxazolo[3,2 - d][1,4]benzodiazepin - 6(7H)-one	0.010 g	115
Cocoa butter (m.p. 36°—37°)	1.245 g	120
Carnauba wax	0.045 g	

Procedure:

The cocoa butter and the carnauba wax

were melted in a suitable size glass-lined container (stainless steel may also be used), mixed well and cooled to 45°. The 10 - chloro-11b - (2 - fluorophenyl) - 2,3,5,11b - tetrahydrooxazolo[3,2 - d][1,4]benzodiazepin-6(7H)-one, which had been reduced to a fine powder with no lumps, was added and stirred until completely and uniformly dispersed in the mixture. The mixture was poured into 10 suppository moulds to yield suppositories having an individual weight of 1.3 g. The suppositories were cooled and removed from the moulds. They were then individually wrapped in wax paper for packaging (foil may also be used).

B) Capsule Formulation

	Per Capsule
10 - Chloro - 11b - (2-fluorophenyl)-2,3,5,11b-tetrahydrooxazolo[3,2 - d][1,4]-benzodiazepin - 6(7H) - one	10 mg
Lactose	165 mg
Corn starch	30 mg
Talc	5 mg
Total Weight	210 mg

Procedure:

10 - Chloro - 11b - (2 - fluorophenyl)-2,3,5,11b - tetrahydrooxazolo[3,2 - d][1,4]-benzodiazepin - 6(7H) - one, lactose and corn starch were mixed in a suitable mixer. The mixture was further blended by passing it through a comminuting machine. The blended powder was returned to the mixer, the talc added and blended thoroughly. The mixture was filled into hard shell gelatin capsules on a capsulating machine.

C) Parenteral Formulation

	Per ml
10 - Chloro - 11b - (2-fluorophenyl) - 2,3,5,11b-tetrahydrooxazolo[3,2 - d][1,4]benzodiazepin-6(7H)-one	5.0 mg
Propylene glycol	0.4 ml
Benzyl alcohol (benzaldehyde free)	0.015 ml
Ethanol (95 per cent)	0.10 ml
Sodium benzoate	48.8 mg
Benzoic acid	1.2 mg
Water for injection q.s.	1.0 ml

Procedure (For 10,000 ml):

50 g of 10 - chloro - 11b - (2 - fluorophenyl) - 2,3,5,11b - tetrahydrooxazolo[3,2 - d][1,4]benzodiazepin - 6(7H) - one were dissolved in 150 ml of benzyl alcohol and 4,000 ml of propylene glycol and 1,000 ml of ethanol were added. 12 g of benzoic

acid were dissolved in the resulting mixture. 488 g of sodium benzoate dissolved in 3,000 ml of water for injection were added. The solution was brought up to the final volume of 10,000 ml with water for injection. The solution was filtered through a candle filter, filled into suitable size ampoules, gassed with nitrogen and sealed. The ampoules were then autoclaved at 0.7 atmospheres for 30 minutes.

D) Tablet Formulation

	Per Tablet
10 - Chloro - 11b - (2-fluorophenyl) - 2,3,5,11b-tetrahydrooxazolo[3,2 - d][1,4]benzodiazepin-6(7H)-one	25.00 mg
Dicalcium phosphate dihydrate (unmilled)	175.00 mg
Corn starch	24.00 mg
Magnesium stearate	1.00 mg
Total Weight	225.00 mg

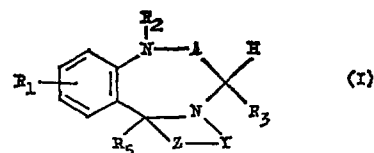
Procedure:

10 - Chloro - 11b - (2 - fluorophenyl)-2,3,5,11b - tetrahydrooxazolo[3,2 - d][1,4]-benzodiazepin - 6(7H) - one and corn starch were mixed together and passed through a comminuting machine. This premix was then mixed with dicalcium phosphate and one-half of the magnesium stearate, passed through a comminuting machine and slugged. The slugs were passed through a comminuting machine and the remaining magnesium stearate was added. The mixture was mixed and compressed.

The foregoing formulations were repeated using DERIVATIVE B, 10 - chloro - 11b - (2 - fluorophenyl) - 2,3,5,11b - tetrahydro-7 - (2 - hydroxyethyl)oxazolo[3,2 - d][1,4]-benzodiazepin - 6(7H) - one, and DERIVATIVE D, 10 - chloro - 2,3,5,11b - tetrahydro-11b - phenyloxazolo[3,2 - d][1,4]benzodiazepin - 6(7H) - one.

WHAT WE CLAIM IS:—

1. A tricyclic benzodiazepine derivative of the general formula



wherein A represents the group $-\text{CH}_2-$ or



Z represents $-\text{O}-$ or

were melted in a suitable size glass-lined container (stainless steel may also be used), mixed well and cooled to 45°. The 10 - chloro-11b - (2 - fluorophenyl) - 2,3,5,11b - tetrahydrooxazolo[3,2 - d][1,4]benzodiazepin-6(7H)-one, which had been reduced to a fine powder with no lumps, was added and stirred until completely and uniformly dispersed in the mixture. The mixture was poured into suppository moulds to yield suppositories having an individual weight of 1.3 g. The suppositories were cooled and removed from the moulds. They were then individually wrapped in wax paper for packaging (foil may also be used).

B) Capsule Formulation

Per Capsule

10 - Chloro - 11b - (2-fluorophenyl)-2,3,5,11b-tetrahydrooxazolo[3,2 - d][1,4]-benzodiazepin - 6(7H) - one	10 mg
Lactose	165 mg
Corn starch	30 mg
Talc	5 mg

Total Weight 210 mg

Procedure:

10 - Chloro - 11b - (2 - fluorophenyl)-2,3,5,11b - tetrahydrooxazolo[3,2 - d][1,4]-benzodiazepin - 6(7H) - one, lactose and corn starch were mixed in a suitable mixer. The mixture was further blended by passing it through a comminuting machine. The blended powder was returned to the mixer, the talc added and blended thoroughly. The mixture was filled into hard shell gelatin capsules on a capsulating machine.

C) Parenteral Formulation

Per ml

10 - Chloro - 11b - (2-fluorophenyl) - 2,3,5,11b-tetrahydrooxazolo[3,2 - d][1,4]benzodiazepin-6(7H)-one	5.0 mg
Propylene glycol	0.4 ml
Benzyl alcohol (benzaldehyde free)	0.015 ml
Ethanol (95 per cent)	0.10 ml
Sodium benzoate	48.8 mg
Benzoic acid	1.2 mg
Water for injection q.s.	1.0 ml

Procedure (For 10,000 ml):

50 g of 10 - chloro - 11b - (2 - fluorophenyl) - 2,3,5,11b - tetrahydrooxazolo[3,2 - d][1,4]benzodiazepin - 6(7H) - one were dissolved in 150 ml of benzyl alcohol and 4,000 ml of propylene glycol and 1,000 ml of ethanol were added. 12 g of benzoic

acid were dissolved in the resulting mixture. 488 g of sodium benzoate dissolved in 3,000 ml of water for injection were added. The solution was brought up to the final volume of 10,000 ml with water for injection. The solution was filtered through a candle filter, filled into suitable size ampoules, gassed with nitrogen and sealed. The ampoules were then autoclaved at 0.7 atmospheres for 30 minutes.

D) Tablet Formulation

Per Tablet

10 - Chloro - 11b - (2-fluorophenyl) - 2,3,5,11b-tetrahydrooxazolo[3,2 - d][1,4]benzodiazepin-6(7H)-one	25.00 mg
Dicalcium phosphate dihydrate (unmilled)	175.00 mg
Corn starch	24.00 mg
Magnesium stearate	1.00 mg

Total Weight 225.00 mg

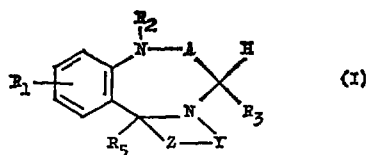
Procedure:

10 - Chloro - 11b - (2 - fluorophenyl)-2,3,5,11b - tetrahydrooxazolo[3,2 - d][1,4]-benzodiazepin - 6(7H) - one and corn starch were mixed together and passed through a comminuting machine. This premix was then mixed with dicalcium phosphate and one-half of the magnesium stearate, passed through a comminuting machine and slugged. The slugs were passed through a comminuting machine and the remaining magnesium stearate was added. The mixture was mixed and compressed.

The foregoing formulations were repeated using DERIVATIVE B, 10 - chloro - 11b - (2 - fluorophenyl) - 2,3,5,11b - tetrahydro-7 - (2 - hydroxyethyl)oxazolo[3,2 - d][1,4]-benzodiazepin - 6(7H) - one, and DERIVATIVE D, 10 - chloro - 2,3,5,11b - tetrahydro-11b - phenyloxazolo[3,2 - d][1,4]benzodiazepin - 6(7H) - one.

WHAT WE CLAIM IS:—

1. A tricyclic benzodiazepine derivative of the general formula



wherein A represents the group $-\text{CH}_2-$ or



Z represents $-\text{O}-$ or





5 in which R_6 represents hydrogen, lower alkyl or lower acyl, R_1 represents hydrogen, halogen, nitro, trifluoromethyl, lower alkyl, lower alkylmercapto or lower alkoxy, R_2 represents hydrogen, lower alkyl, lower cycloalkyl or hydroxy-(lower alkyl), R_3 represents hydrogen or lower alkyl, Y represents a di- or trimethylene group which may be substituted by R_4 , R_4 representing lower alkyl or $-CH_2X$ in which X represents chlorine, bromine, (lower alkoxy)-(lower alkyl) or di-(lower alkyl)amino and R_5 represents hydrogen, lower alkyl, pyridyl, phenyl or phenyl substituted by halogen, nitro, trifluoromethyl or lower alkyl, with the proviso that R_2 does not represent hydrogen when

- 20 (i) A is $\begin{array}{c} O \\ || \\ -C- \end{array}$;
 (ii) Y is a dimethylene or trimethylene group which may optionally be substituted by lower alkyl;
 (iii) Z is $-O-$;
 (iv) R_5 is phenyl or phenyl substituted by lower alkyl, halogen, nitro or trifluoromethyl; and
 25 (v) R_1 is lower alkyl, lower alkoxy, halogen, nitro or trifluoromethyl;

and that

R_2 does not represent lower alkyl when

- 30 (i) A is $\begin{array}{c} O \\ || \\ -C- \end{array}$;
 (ii) Y is a dimethylene or trimethylene group which may optionally be substituted by lower alkyl;
 (iii) Z is $-O-$;
 35 (iv) R_3 is hydrogen;
 (v) R_5 is phenyl or phenyl substituted by lower alkyl, halogen, nitro or trifluoromethyl; and
 40 (vi) R_1 is lower alkyl, lower alkoxy, halogen, nitro or trifluoromethyl.

2. A tricyclic benzodiazepine derivative according to claim 1, wherein Z represents



45 in which R_6 represents hydrogen, lower alkyl or lower acyl and R_1 , R_2 , R_3 , R_5 , Y and A have the significance given in claim 1.

3. A tricyclic benzodiazepine derivative according to claim 1, wherein A represents

$-CH_2-$ and R_1 , R_2 , R_3 , R_5 , Y and Z have the significance given in claim 1.

4. A tricyclic benzodiazepine derivative according to claim 1, wherein A represents



Z represents $-O-$, R_2 represents hydroxy-(lower alkyl) and R_1 , R_3 , R_5 and Y have the significance given in claim 1.

5. A tricyclic benzodiazepine derivative according to claim 1, wherein A represents



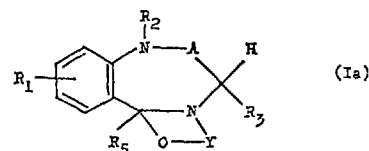
Z represents $-O-$, Y represents a di- or trimethylene group substituted by CH_2X in which X represents chlorine, bromine, (lower alkoxy)-(lower alkyl) or di(lower alkyl)amino and R_1 , R_2 , R_3 and R_5 have the significance given in claim 1.

6. A tricyclic benzodiazepine derivative according to claim 1, wherein A represents



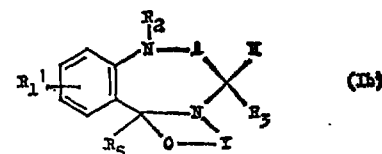
Z represents $-O-$, R_5 represents hydrogen, lower alkyl or pyridyl and R_1 , R_2 , R_3 and Y have the significance given in claim 1.

7. A tricyclic benzodiazepine derivative according to claim 1 of the general formula



wherein A , R_1 , R_2 , R_3 , R_5 and Y have the significance given in claim 1.

8. A tricyclic benzodiazepine derivative of the general formula



wherein R_1' represents hydrogen, halogen, nitro, trifluoromethyl or lower alkyl and A , Y , R_2 , R_3 and R_5 have the significance given in claim 1, with the proviso that R_2 does not represent hydrogen when

- (i) A is $\begin{array}{c} O \\ || \\ -C- \end{array}$;

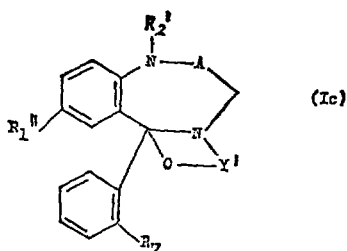
- (ii) Y is a dimethylene or trimethylene group which may optionally be substituted by lower alkyl;
 (iii) R₅ is phenyl or phenyl substituted by lower alkyl, halogen nitro or trifluoromethyl; and
 (iv) R₁' is lower alkyl, halogen, nitro or trifluoromethyl;

and that

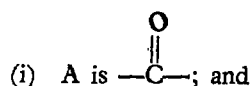
- 10 R₂ does not represent lower alkyl when

- (i) A is $\text{—}\overset{\text{O}}{\parallel}\text{C—}$;
 (ii) Y is a dimethylene or trimethylene group which may optionally be substituted by lower alkyl;
 (iii) R₃ is hydrogen;
 (iv) R₅ is phenyl or phenyl substituted by lower alkyl, halogen, nitro or trifluoromethyl; and
 (v) R₁' is lower alkyl, halogen, nitro or trifluoromethyl.

9. A tricyclic benzodiazepine derivative of the general formula



- wherein R₁'' represents hydrogen or halogen, R₂' represents hydrogen, lower alkyl or hydroxy-(lower alkyl), Y' represents a di- or trimethylene group which may be substituted by lower alkyl or chloromethyl, R₇ represents hydrogen or halogen and A has the significance given in claim 1, with the proviso that R₂' does not represent hydrogen or lower alkyl when



- (ii) Y' is a di- or trimethylene group which may be substituted by lower alkyl.

10. A tricyclic benzodiazepine derivative according to claim 9, wherein R₁'' represents chlorine, R₂' represents hydrogen, methyl or β -hydroxy-ethyl, Y' represents a dimethylene group which may be substituted by methyl

or chloromethyl and R₇ represents hydrogen or fluorine.

11. 10 - Chloro - 2,3,5,11b - tetrahydro-7 - (2 - hydroxyethyl) - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepine - 6 - (7H) - one.

12. 10 - Chloro - 11b - (2 - fluorophenyl)-2,3,5,11b - tetrahydro - 7 - (2 - hydroxyethyl)oxazolo[3,2 - d][1,4]benzodiazepin - 6 - (7H)-one.

13. 10 - Chloro - 2 - chloromethyl-2,3,5,11b - tetrahydro - 7 - methyl - 11b-phenyloxazolo[3,2 - d][1,4]benzodiazepin-6 - (7H) - one.

14. 10 - Chloro - 2,3,5,6,7,11b - hexahydro-7 - methyl - 11b - phenyloxazolo[3,2 - d][1,4]benzodiazepine.

15. 10 - Chloro - 1,2,3,5,7,11b - hexahydro-7 - methyl - 11b - phenyl - 6H - imidazo[1,2 - d][1,4]benzodiazepin - 6 - one.

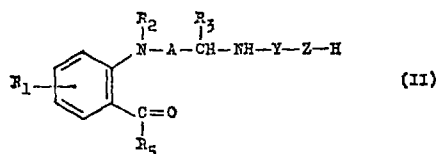
16. 11 - Chloro - 3,4,6,7,8,12b - hexahydro-8 - methyl - 12b - phenyl - 2H - [1,3]-oxazino[3,2 - d][1,4]benzodiazepine.

17. 10 - Chloro - 2,3,5,6,7,11b - hexahydro-7 - methyl - 11b - phenyl - 1H - imidazo[1,2 - d][1,4]benzodiazepine.

18. A pharmaceutical preparation comprising a tricyclic benzodiazepine as claimed in claim 1 in association with a compatible pharmaceutical carrier.

19. A process for the manufacture of the tricyclic benzodiazepine derivatives claimed in claim 1, which process comprises

cyclizing a compound of the general formula



wherein R₁, R₂, R₃, R₅, A Y and Z have the significance given in claim 1,

and, if a tricyclic benzodiazepine derivative of formula I in claim 1 in which Z represents

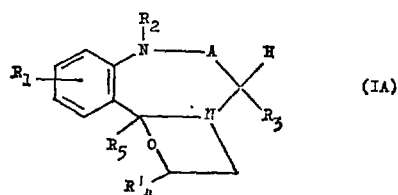
—NH— is obtained and it is desired to produce a tricyclic benzodiazepine derivative of formula I in claim 1 in which Z represents



(R₆' representing lower alkyl or lower acyl), alkylating or acylating the said —NH— group, or if a mixture of epimeric tricyclic benzodiazepine derivatives of formula (I) in claim 1 is obtained, separating the mixture into its components if desired.

20. A process for the manufacture of tricyclic benzodiazepine derivatives of the general formula

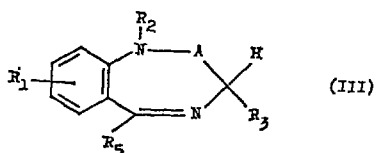




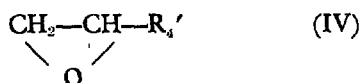
wherein R_1 represents hydrogen, halogen, nitro, trifluoromethyl, lower alkyl, lower alkyl mercapto or lower alkoxy; R_2 represents hydrogen, lower alkyl, lower cycloalkyl or hydroxy-(lower alkyl); R_3 represents hydrogen or lower alkyl; R_4 represents hydrogen, lower alkyl, pyridyl, phenyl or phenyl-substituted by halogen, nitro, trifluoromethyl or lower alkyl; A represents the group $-\text{CH}_2-$ or



and R_4' represents hydrogen, lower alkyl or CH_2X in which X represents chlorine, bromine, (lower-alkoxy)-(lower alkyl) or di-(lower alkyl)amino, which process comprises reacting a 4,5-unsaturated 1,4-benzodiazepine of the general formula

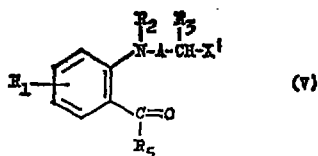


wherein R_1 , R_2 , R_3 , R_4 and A have the significance given in above, with an epoxide of the general formula

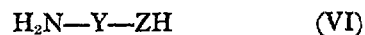


wherein R_4' has the significance given earlier in this claim, in the presence of an acidic agent, and, if a mixture of epimeric tricyclic benzodiazepine derivatives of formula IA is obtained, separating the mixture into its components if desired.

21. A process as claimed in claim 19, wherein the 4,5-unsaturated 1,4-benzodiazepine starting material of formula II is prepared by reacting a corresponding 2-(substituted amino)-phenyl ketone of the general formula



wherein R_1 , R_2 , R_3 , R_4 and A have the significance given in claim 1 and X' represents chlorine, bromine or iodine, with a diamine or aminoalkanol of the general formula



wherein Y and Z have the significance given in claim 1, in the presence of a base.

22. A process as claimed in claim 19 or claim 21, wherein Z represents



in which R_6 represents hydrogen, lower alkyl or lower acyl and R_1 , R_2 , R_3 , R_4 , Y and A have the significance given in claim 1.

23. A process as claimed in claim 19 or claim 21, wherein A represents $-\text{CH}_2-$ and R_1 , R_2 , R_3 , R_4 , Y and Z have the significance given in claim 1.

24. A process as claimed in claim 19 or claim 21, wherein A represents



Z represents $-\text{O}-$, R_2 represents hydroxy-(lower alkyl) and R_1 , R_3 , R_4 and Y have the significance given in claim 1.

25. A process as claimed in claim 19 or claim 21, wherein A represents



Z represents $-\text{O}-$, Y represents a di- or trimethylene group substituted by CH_2X in which X represents chlorine, bromine, (lower alkoxy)-(lower alkyl) or di(lower alkyl)amino and R_1 , R_2 , R_3 and R_4 have the significance given in claim 1.

26. A process as claimed in claim 19 or claim 21, wherein A represents



Z represents $-\text{O}-$, R_4 represents hydrogen, lower alkyl or pyridyl and R_1 , R_2 , R_3 and Y have the significance given in claim 1.

27. A process as claimed in claim 19 or claim 21, wherein Z represents $-\text{O}-$ and A , R_1 , R_2 , R_3 , R_4 and Y have the significance given in claim 1.

28. A process as claimed in claim 27, wherein R_1 represents hydrogen, halogen, nitro, trifluoromethyl or lower alkyl.

29. A process as claimed in claim 28,

wherein R_1 represents hydrogen or halogen which is joined to the benzene ring in the *para*-position with respect to the



5 group, R_2 represents hydrogen, lower alkyl or hydroxy-(lower alkyl), R_3 represents hydrogen, Y represents a di- or trimethylene group which may be substituted by lower alkyl or chloromethyl and R_4 represents phenyl or phenyl substituted in the *ortho*-position by halogen.

10 30. A process as claimed in claim 29, wherein R_1 represents chlorine, R_2 represents hydrogen, methyl or β -hydroxy-ethyl, Y represents a dimethylene group which may be substituted by methyl or chloromethyl and R_3 represents phenyl or *o*-fluorophenyl.

15 31. A process as claimed in claim 20, wherein 7 - chloro - 1,3 - dihydro - 5-phenyl - 2H - 1,4 - benzodiazepin - 2 - one and ethylene oxide are used as the starting materials.

20 32. A process as claimed in claim 20, wherein 7 - chloro - 5 - (2 - fluorophenyl)-1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one and ethylene oxide are used as the starting materials.

25 33. A process as claimed in claim 20, wherein 7 - chloro - 1,3 - dihydro - 1-methyl - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and ethylene oxide are used as the starting materials.

30 34. A process as claimed in claim 20, wherein 7 - chloro - 1,3 - dihydro - 1 - methyl-5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and propylene oxide are used as the starting materials.

35 35. A process as claimed in claim 20, wherein 7 - chloro - 1,3 - dihydro - 1-methyl - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and 1 - chloro - 2,3-epoxypropane are used as the starting materials.

40 36. A process as claimed in claim 20, wherein 7 - chloro - 2,3 - dihydro - 1-methyl - 5 - phenyl - 1H - 1,4 - benzodiazepine and ethylene oxide are used as the starting materials.

45 37. A process as claimed in claim 21, wherein 5 - chloro - 2 - (2 - chloroethyl-methylamino)benzophenone and 2-amino-ethanol are used as the starting materials.

50 38. A process as claimed in claim 21, wherein 2 - (2 - chloro - N - methylacetamido)-5 - chlorobenzophenone and ethylenediamine are used as the starting materials.

55 39. A process as claimed in claim 21, wherein 5 - chloro - 2 - (2 - chloroethyl-methylamino)benzophenone and 3-amino-propanol are used as the starting materials.

40. A process as claimed in claim 21, wherein 5 - chloro - 2 - (2 - chloroethyl-methylamino)benzophenone and ethylenediamine are used as the starting materials.

65 41. A process as claimed in claim 20, wherein 7 - chloro - 1,3 - dihydro - 5-phenyl - 2H - 1,4 - benzodiazepin - 2 - one and propylene oxide are used as the starting materials.

70 42. A process as claimed in any one of claims 19, 22 to 30 inclusive, or 39, wherein the compound of formula II is cyclized by heating.

75 43. A process as claimed in claim 42, wherein the heating is effected in pyridine, ethanol or xylene.

80 44. A process as claimed in any one of claims 21 to 30 inclusive, or 37 to 40 inclusive, wherein the reaction between a 2-(substituted amino)-phenyl ketone of formula V and a diamine or aminoalkanol of formula VI is effected in an inert organic solvent in the presence of a base.

85 45. A process as claimed in claim 44, wherein the said solvent is a lower alkanol, an aromatic hydrocarbon, a high boiling point ether or an amide.

90 46. A process as claimed in claim 44, wherein the said base is a trialkylamine or pyridine.

95 47. A process as claimed in any one of claims 21 to 30 inclusive, or 37 to 40 inclusive, wherein the reaction between a 2-(substituted amino)-phenyl ketone of formula V and a diamine or aminoalkanol of formula VI is conducted at a temperature of from about 25°C to the reflux temperature of the reaction medium to produce a tricyclic benzodiazepine derivative of formula I without isolating a compound of formula II.

100 48. A process as claimed in any one of claims 21 to 30 inclusive, or 39 wherein the reaction between a 2-(substituted amino)-phenyl ketone of formulae V and a diamine or aminoalkanol of formula VI conducted at about or below room temperature to produce a compound of formula II which is subsequently cyclized to yield a tricyclic benzodiazepine derivative of formula I.

105 49. A process as claimed in claim 20, wherein A in the formulae represents $-\text{CH}_2-$ and R_1 , R_2 , R_3 , R_5 and R_4' have the significance given in claim 20.

110 50. A process as claimed in claim 20, wherein A in the formulae represents



R_2 represents hydroxy-(lower alkyl) and R_1 , R_3 , R_5 and R_4' have the meanings given in claim 20.

115 51. A process as claimed in claim 20, wherein A represents





5 R_4' represents CH_2X in which X has the significance given in claim 20, and R_1 , R_2 , R_3 and R_5 also have the meaning given in claim 20.

52. A process as claimed in claim 20, wherein A in the formulae represents



10 R_5 represents hydrogen, lower alkyl or pyridyl and R_1 , R_2 , R_3 and R_4' have the significance given in claim 20.

15 53. A process as claimed in claim 20, wherein the formulae, R, represents hydrogen, halogen, nitro, trifluoromethyl or lower alkyl, and the symbols A, R_2 , R_3 , R_5 and R_4' have the meanings given in claim 20.

20 54. A process as claimed in claim 53, wherein R_1 represents hydrogen or halogen which is joined to the benzene ring in the *para* position with respect to the



25 group, R_2 represents hydrogen, lower alkyl or hydroxy-(lower alkyl), R_3 represents hydrogen, R_4' represents lower alkyl or chloromethyl and R_5 represents phenyl or phenyl substituted in the *ortho*- position by halogen.

30 55. A process as claimed in any one of claims 20, 31—36, 41 and 49—54, wherein the reaction between a 4,5-unsaturated 1,4-benzodiazepine of formula III and an epoxide

of formula IV is conducted in an anhydrous inert organic solvent in the presence of an acidic agent.

56. A process as claimed in claim 55, wherein the said reaction is carried out at a temperature in the range of from about -10°C to the reflux temperature of the reaction medium. 35

57. A process as claimed in claim 55, wherein the said solvent is an aromatic hydrocarbon, an ether or carbon disulfide. 40

58. A process as claimed in claim 55, wherein the said acidic agent is aluminium chloride, ferric chloride, zinc chloride, titanium tetrachloride, boron trifluoride, *p*-toluene sulfonic acid or benzene sulfonic acid. 45

59. A process for the manufacture of tricyclic benzodiazepine derivatives according to claim 19 or 20, and substantially as hereinbefore described with reference to Examples 1 to 15. 50

60. Tricyclic benzodiazepine derivatives as set forth in claim 1, when manufactured by the process claimed in claim 19 or 21.

61. Tricyclic benzodiazepine derivatives whenever manufactured by the process as claimed in claim 20. 55

62. A pharmaceutical preparation comprising a tricyclic benzodiazepine when prepared by the process as claimed in any one of claims 19, 21 to 48 and 59, in association with a compatible pharmaceutical carrier. 60

63. A pharmaceutical preparation comprising a tricyclic benzodiazepine when prepared by the process as claimed in any one of claims 20 and 49 to 59, in association with a compatible pharmaceutical carrier. 65

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