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PATENT SPECIFICATION

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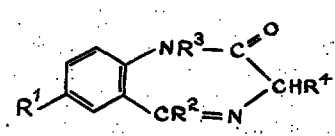
Int. Cl.:—C 07 d 53/06

COMPLETE SPECIFICATION Benzodiazepine Derivatives

We, ETABLISSEMENTS CLIN-BYLA, a French Body Corporate, of 20 rue des Fossés Saint-Jacques, Paris, France, 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:—

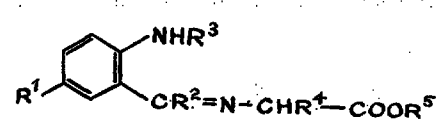
This invention relates to benzodiazepine derivatives. The invention includes an improved process for the production of benzodiazepine derivatives as well as some new compounds made available by the improved process.

In accordance with the present invention there is provided a process for producing a substituted benzodiazepine having the general formula:



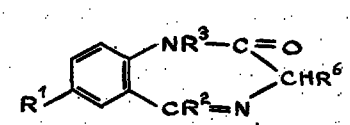
in which R¹ is a hydrogen or halogen atom, a trifluoromethyl group, an alkyl or alkoxy group having 1 to 7 carbon atoms or a nitro or amino group, R² is a phenyl group which may be substituted by a halogen atom or by a trifluoromethyl or nitro group or by an alkyl or alkoxy group having 1 to 7 carbon atoms, or R² is an alkyl group having 1 to 7 carbon atoms or a cycloalkyl group having 5 to 7 carbon atoms or a furyl or thienyl group, R³ is a hydrogen atom or an alkyl group having 1 to 7 carbon atoms, R⁴ is a hydrogen atom, an alkyl group having 1 to 7 carbon atoms, an alkylthioalkyl group having 2 to 7 carbon atoms, a carbalkoxy group having 1 to 7 carbon atoms in the alkoxy group, a

carbamoyl group, an alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group having 1 to 7 carbon atoms in the alkyl group or in each of the alkyl groups, or is a group having the formula —COOCat in which Cat is the cation of an alkali metal or semication of an alkaline earth metal, which comprises treating an orthoaminoarylketimine having the general formula:



in which R¹, R², R³ and R⁴ are as above defined, but excluding the case in which R⁴ is —COOCat, and R⁵ is an alkyl group having 1 to 7 carbon atoms, with an anhydrous alkanoid acid having up to 7 carbon atoms or with an anhydrous mineral acid, or treating an orthoaminoarylketimine having the above general formula in which R¹, R² and R³ are as above defined, R⁴ is —COOCat and R⁵ is —Cat, with a dilute aqueous solution of an acid salt in substantially equimolar proportions or with an aqueous solution of a weak acid. The mineral acid may be gaseous hydrogen chloride.

The new substituted benzodiazepines, in accordance with the invention, have the general formula

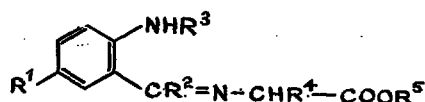


(II)

in which R^1 is a hydrogen or halogen atom, a trifluoromethyl group, an alkyl or alkoxy group having 1 to 7 carbon atoms or a nitro or amino group, R^2 is a phenyl group which may be substituted by a halogen atom or by a trifluoromethyl or nitro group or by an alkyl or alkoxy group having 1 to 7 carbon atoms, or R^2 is an alkyl group having 1 to 7 carbon atoms or a cycloalkyl group having 5 to 7 carbon atoms or a furyl or thienyl group, R^3 is a hydrogen atom or an alkyl group having 1 to 7 carbon atoms, R^4 is a carbalkoxy group having 1 to 7 carbon atoms in the alkoxy group, a carbamoyl group, an alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group having 1 to 7 carbon atoms in the alkyl group or in each of the alkyl groups, or is a group having the formula $-\text{COOCat}$ in which Cat is the cation of an alkali metal or semication of an alkaline earth metal.

In the present specification the alkyl groups, including those present in alkoxy groups, have 1 to 7 carbon atoms in a straight or branched chain; for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, amyl and hexyl groups.

We have found that the action of an anhydrous alkanic acid having up to 7 carbon atoms, in particular glacial acetic acid, on either of the two stereoisomeric forms of the N-substituted imines having the general formula



(I)

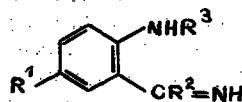
in which R^1 , R^2 , R^3 , R^4 and R^5 are as hereinbefore defined other than the case in which R^4 is $-\text{COOCat}$ and R^5 is Cat, as well as on mixtures of these two forms lead almost exclusively to the corresponding benzodiazepine. Heating for from several minutes to one hour is desirable; after removal of the acid reagent in vacuo and dilution with a suitable solvent, in particular diethyl ether or diisopropyl ether, the benzodiazepine derivative is obtained directly in crystalline state. The said N-substituted imines, as well as those in which R^4 is $-\text{COOCat}$ and R^5 is Cat, are described and claimed in our copending application No. 51366/67, Serial No. 1,117,063.

R^3 may be a hydrogen atom or a methyl group and R^1 a chlorine atom or a nitro group. Thus 7-chloro-5-phenyl-2-oxo-2,3-dihydro-1H-benzo[f]-1,4-diazepine (hereinafter named compound A) which has already been described by L. H. Sternbach and E. Reeder (Journal of Organic

Chemistry 1961, Volume 26, page 4936) may be prepared in two stages, giving an overall yield of 80%, from (2-amino-5-chlorophenyl)-phenylmethane imine without having to separate the two stereoisomeric forms of the intermediate substituted imine 1-phenyl-1-(2-amino-5-chlorophenyl)-4-oxo-5-oxa-2-aza-1-heptane; the N-methyl derivative (B) of compound A, which is already known (see above reference) is obtained in a practically quantitative yield by subjecting 1-phenyl-1-(2-methylamino-5-chlorophenyl)-4-oxo-5-oxa-2-aza-1-heptene for several minutes to the action of glacial acetic acid.

Employing the same technique, the derivatives of compound A substituted on the 3-carbon atom are also obtained. For this purpose, it is sufficient first to react, according to the process of the invention, the free (2-amino-5-chlorophenyl)-phenylmethane imine with the hydrochloride of a suitably selected α -amino acid ester and, without isolating the intermediate substituted imine, proceed with the acetic acid treatment in question. For example, using the hydrochlorides of the alkyl esters of alanine, leucine and methionine having 1 to 7 carbon atoms in the alkyl group as reagents, one obtains the 3-methyl, 3-isobutyl and 3-methylthioethyl derivatives respectively of 7-chloro-5-phenyl-2-oxo-2,3-dihydro-1H-benzo[f]-1,4-diazepine (compounds C, D, E). The yields vary but are always much higher than those indicated in the chemical literature for the same substances (Sternbach, Fryer, Metlesics, Reeder, Sachs, Saucy and Stempel, Journal of Organic Chemistry 1962, Volume 27, page 3788).

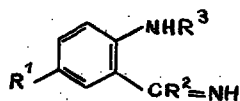
This method has been extended to the preparation of new benzodiazepines carrying a carbalkoxy group having 2 to 8 carbon atoms on the 3-carbon atom. For this purpose, it is sufficient to treat the ketimines having as the substituent R^4 a carbalkoxy group with an anhydrous alkanic acid; these derivatives, obtained by the action of a free imine having the general formula



(III)

on the hydrochloride of a dialkyl aminomalonate, may or may not be isolated. However, the yield is particularly high when crystalline substituted imines (I) are reacted in acetic acid. The imines having the general formula (III) are described and claimed in our copending application No. 42698/67, Serial No. 1,117,062.

We have also found an advantageous modification for the preparation of benzodiazepines (II) without isolation of the N-substituted imines (I), which modification is particularly recommended in those cases in which the group R^2 in the general formula (II) denotes a phenyl or substituted phenyl group, R^3 is a hydrogen atom and R^4 is a carbalkoxy group. Although these substances are easily obtained by the process described above, starting from ketimines having the general formula



in which R^1 , R^2 and R^3 are as above defined, such as (2-amino-5-chlorophenyl)-phenylmethane imine, the yields are somewhat low and the results are difficult to reproduce if the quantity of reactants used is increased, whilst complete purification of the products by crystallisation is, in some cases, laborious. According to this modification, the N-substituted imine (I) such as 1-phenyl-1-(2-amino-5-chlorophenyl)-4-oxo-5-oxa-2-aza-1-heptene is formed by the action of the hydrochloride of a dialkyl amino-malonate on the free imine (III) such as (2-amino-5-chlorophenyl)-phenylmethane imine, the reaction being carried out in a hydrocarbon solvent, preferably benzene or toluene, whilst hydrogen chloride gas is passed through the reaction medium to control the cyclisation without first isolating the intermediate compound. The resulting benzodiazepine derivative is then isolated in the form of the hydrochloride which can subsequently be decomposed into the practically pure benzodiazepine.

This improvement is suitable for the preparation of other benzodiazepines having the general formula (II), in particular those mentioned in Table I which may or may not be substituted on the carbon atom in position 3 in the heterocycle. All that is necessary is to replace the hydrochloride of diethyl amino-malonate by the hydrochloride of an alkyl glycinate such as ethyl glycinate which may or may not be substituted on the α -carbon atom by an alkyl or alkylthioalkyl group having up to 7 carbon atoms.

This procedure is recommended for the synthesis in large quantities of 7-chloro-5-cyclohexyl-2-oxo-2,3-dihydro-1H-benzo[f]-1,4-diazepine (formula (II) in which R^2 is cyclohexyl, R^3 is H and R^4 is H). The use of the substituted or unsubstituted amino-malonic esters or amino-acetic esters is not limited to the ethyl ester.

The structure of the new 3-carbalkoxybenzodiazepines (II) is obtained not only from the elementary analysis of these com-

pounds but also from a study of their infra red spectra and the results of hydrolysis. The infra red spectra of 3-carbalkoxybenzodiazepines (II) dissolved in methylene chloride have the following features. Vibration bands of the N—H bond of the lactam group without substituent (if this is the case): namely a fine line (free N—H) in the region 3400 cm^{-1} and a wide band in the region of 3200 cm^{-1} . In potassium bromide, the absorption due to N—H is often more complex and may result in the presence of various bands between 3100 and 3400 cm^{-1} ; characteristic bands of the ester group at 1730—1755 ($>\text{C}=\text{O}$) and in the region of 1200 cm^{-1} ($\text{C}-\text{O}-\text{C}$); a characteristic band of a secondary amide at 1660—1700 cm^{-1} (absence of the acrylic secondary amide band between 1510 and 1550 cm^{-1}); a band at 1590—1610 cm^{-1} (aromatic $>\text{C}=\text{C}<$ and $>\text{C}=\text{N}<$) flanked by a less intense band at 1560—1580 cm^{-1} for compounds having two phenyl groups conjugated to $>\text{C}=\text{N}<$.

The treatment of 3-carbalkoxybenzodiazepines (II) with a saponifying agent (for example, an alkali metal hydroxide, preferably aqueous or alcoholic potash) and then with a dilute acid reagent (for example, acetic acid), gives rise to hydrolysis and decarboxylation and finally leads to benzodiazepines which are unsubstituted on the 3-carbon atom and, for example, to compound A if 7-chloro-3-carbethoxy-5-phenyl-2-oxo-2,3-dihydro-1H-benzo-[f]-1,4-diazepine is used, which completely demonstrates the proposed structure.

By the treatment of the 3-carbalkoxybenzodiazepines (II) in which R^3 is a hydrogen atom with an alkali metal hydroxide, such as aqueous or alcoholic potash, to produce a dialkali metal salt, then with an alkylating agent such as dimethyl sulphate and thereafter with a dilute acid such as acetic acid, there are obtained the 1-alkylbenzodiazepines which are unsubstituted in the 3-position, for example, compound B (diazepam) when 7-chloro-3-carbethoxy-5-phenyl-2-oxo-2,3-dihydro-1H-benzo-[f]-1,4-diazepine is used. Instead of using the 3-carbalkoxybenzodiazepines (II) the di-salts obtainable by the action of an alkali on the compounds (II) may be treated with an alkylating agent.

The action of ammonia or of a primary or secondary amine at room temperature in a suitable solvent such as methanol converts the 3-carbalkoxybenzodiazepines (II) into benzodiazepines carrying an amide function, with or without substituent, in the 3-position. Thus treatment of the 3-carbalkoxybenzodiazepines with ammonia, an alkylamine, a dialkylamine or a dialkylaminoalkylamine leads to those benzodiazepines having as a

substituent in the 3-position a carbamoyl, alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group.

- 5 Nitration of 3-carbethoxy-5-phenyl-2-oxo-2,3-dihydro-1H-benzo[f]-1,4-diazepine in sulphuric acid leads to the derivative nitrated in the 7-position (cf. 4353 CB); the structure is determined by elementary analysis, by the infra-red spectrum (nitro bands at 1530 and 1350 cm⁻¹ determined in a potassium bromide disc) and by its hydrolysis accompanied by decarboxylation which leads to 7-nitro-5-phenyl-2,3-dihydro-1H-dibenzo[f]-1,4-diazepine which is already known and has been described by Sternbach, Fryer, Keller, Metlesics, Sachs and Steiger in Journal of Medicinal Chemistry 1963, volume 6, page 261. Similarly mononitration of those benzodiazepines in which R¹ is a hydrogen atom and R⁴ is a carbalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group leads to benzodiazepines in which R¹ is a nitro group and R⁴ is as just set forth.

25 Reduction of the nitro derivatives, e.g. of 7-nitro-3-carbethoxy-5-phenyl-2-

oxo-2,3-dihydro-1H-benzo[f]-1,4-diazepine, for example by catalytic means, leads to the corresponding amino compound carrying a 7-amino group (cf. 4354 CB). Reduction of those compounds in which R¹ is a nitro group and R⁴ is a carbalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group with a reagent known to be capable of reducing an aromatic nitro group to a primary amino group gives the 7-amino-2-oxo-2,3-dihydro-1H-benzodiazepines having as a substituent in the 3-position a carbalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group.

The 3-carbalkoxybenzodiazepines (II) generally have a higher melting point than the corresponding benzodiazepines which are unsubstituted on the 3-carbon atom; their solubility in organic solvents is relatively slight.

Table I includes a number of new benzodiazepines (those indicated by a number) carrying a substituent in the 3-position which are obtainable by the process of this invention.

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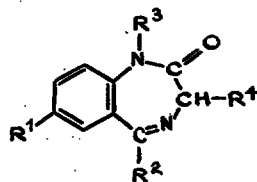
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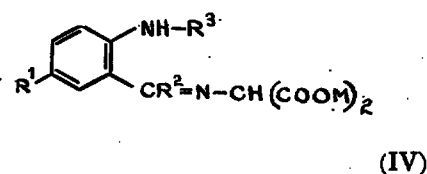
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TABLE I



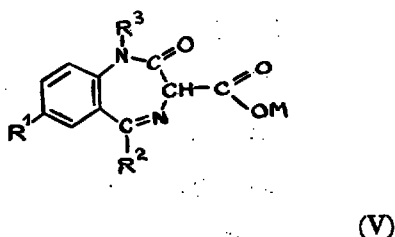
Name	R ¹	R ²	R ³	R ⁴	Example
A	Cl	C ₆ H ₅	H	H	1, 2, 3 and 29
B	Cl	C ₆ H ₅	CH ₃	H	3 and 30
C	Cl	C ₆ H ₅	H	CH ₃	4
D	Cl	C ₆ H ₅	H	CH ₂ —CH (CH ₃) ₂	5
E	Cl	C ₆ H ₅	H	CH ₂ —CH ₂ —S CH ₃	6
4279 CB	Cl	C ₆ H ₅	H	COO C ₂ H ₅	7, 8 and 26
4347 CB	Cl	C ₆ H ₅	H	COO CH ₃	9
4366 CB	Cl	C ₆ H ₅	CH ₃	COO C ₂ H ₅	10
4348 CB	Cl	C ₆ H ₅	H	CO NH ₂	11
4367 CB	Cl	C ₆ H ₅	H	CO NH—CH ₃	12
4368 CB	Cl	C ₆ H ₅	H	CO—N (CH ₃) ₂	13
4369 CB	Cl	C ₆ H ₅	H	CO—NH—CH ₂ —CH ₂ —N(C ₂ H ₅) ₂	14
4352 CB	H	C ₆ H ₅	H	COO C ₂ H ₅	15 and 27
F	CH ₃	C ₆ H ₅	H	H	16
4327 CB	CH ₃	C ₆ H ₅	H	COO C ₂ H ₅	17
4353 CB	NO ₂	C ₆ H ₅	H	COO C ₂ H ₅	18
4354 CB	NH ₂	C ₆ H ₅	H	COO C ₂ H ₅	19
4190 CB	Cl	C ₆ H ₁₁ (cyclo- hexyl)	H	H	20 and 28
4370 CB	Cl	C ₆ H ₁₁ (cyclo- hexyl)	H	COO C ₂ H ₅	21

We have further found that the metal salts having the general formula



- 5 in which R^1 , R^2 and R^3 are as previously defined and M is an alkali metal or one equivalent of an alkaline earth metal may, under carefully controlled conditions, be converted into benzodiazepine derivatives (V) carrying on the 3-carbon atom a carboxylic acid function salified by the original cation.

10 These compounds have the general formula



- 15 To bring about this reaction, it is sufficient to treat an aqueous solution of the starting material used with an aqueous solution of an acid salt at room temperature (that is to say an amount of acid which is just sufficient to liberate one of the two carboxylic functions), preferably potassium dihydrogen phosphate, or with an aqueous solution of a weak acid, which may be carbon dioxide. The

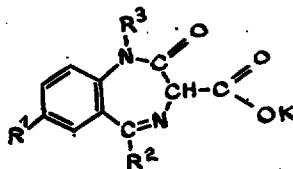
monopotassium salts (V) as a rule crystallise readily provided crystallisation is carried out in a sufficiently concentrated solution since they are less soluble in water than the compounds from which they are derived. They are obtainable in high yield.

The formulae of the compounds V having been established by elementary analysis, their structure is obtained from the study of their infra-red spectra and their chemical properties. The infra-red spectra (determined in a potassium bromide disc) agree with the structure (V) and show a strong band in the region of 1690 cm^{-1} due to the $\text{C}=\text{O}$ of the cyclic amide; also to be noted is the absence of an amide band between 1510 and 1550 cm^{-1} which is characteristic of a cyclic secondary amide. Only the nitro group, if present, gives a band in this region. Moreover, the vibration of the NH bond of the lactam group manifests itself by two very wide bands in the regions of 3400 cm^{-1} and 3100 cm^{-1} . Lastly, an intense and complex band in the region of $1600\text{--}1620\text{ cm}^{-1}$ may be attributed to the vibrations of the aromatic $>\text{C}=\text{C}<$ group, the $>\text{C}=\text{N}-$ group and the $>\text{C}=\text{O}$ group of the carboxyl ion.

Aqueous solutions of compounds (V) generally have a pH in the neutral region, and compounds (V) are less stable in aqueous solution than the compounds (IV) having two carboxyl groups from which they are derived. The aqueous solutions liberate the corresponding benzodiazepine derivatives unsubstituted on the 3-carbon atom after standing for several hours at room temperature or rapidly upon boiling or in the presence of acetic acid at or above room temperature.

Several potassium benzodiazepine-3-carboxylates (V) are shown in Table II to illustrate this aspect of the invention.

TABLE II



No.	R^1	R^2	R^3	Example
4311 CB	Cl	C_6H_5	H	22
4338 CB	H	C_6H_5	H	23
4373 CB	CH_3	C_6H_5	H	24
4336 CB	NO_2	C_6H_5	H	25

The following examples illustrate the invention; the melting points are designated by M.pt._K or M.pt._X according to whether they are measured on a Kofler block or on a Maquenne block.

EXAMPLE 1

7 - Chloro - 5 - phenyl - 2 - oxo -
2,3 - dihydro - 1H - benzo[f] - 1,4 -
diazepine (A).

10 A mixture of 27.6 g (0.12 mol) of (2 - amino - 5 - chlorophenyl) - phenylmethane imine and 20.7 g (0.15 mol) of the hydrochloride of ethyl glycinate in 150 ml of methanol is stirred at room temperature for
15 2.5 hours. A suspension of a pale yellow solid is obtained which consists of a mixture of imine and ammonium chloride formed in the reaction. The solvent is evaporated under reduced pressure and the residue taken
20 up in 150 ml of acetic acid and heated under reflux for 30 minutes. The acetic acid is evaporated until a dry residue is obtained, 250 ml of diisopropyl ether and 250 ml of water are added and the mixture then stirred.
25 A yellowish solid separates which is dried, then washed with ether and recrystallised from methyl ethyl ketone.

Pale yellow crystals are obtained.

First crop 23.4 g M.pt._K: 214—216°C

30 Second crop 2.3 g M.pt._K: 214—216°C.

Yield: about 80% from the unsubstituted imine. The product is identical with the product described by Sternbach and Reeder, Journal of Organic Chemistry 1961, volume
35 26, page 4936).

EXAMPLE 2.

7 - Chloro - 5 - phenyl - 2 - oxo -
2,3 - dihydro - 1H - benzo[f] - 1,4 -
diazepine (A).

40 Acetic acid is added to a solution of 0.409 g (0.001 mol) of the dipotassium salt of [2 - phenyl - 2 - (2 - amino - 5 - chlorophenyl) - 1 - aza - vinyl] - malonic acid in 4 ml of distilled water to adjust the solution to pH 4.
45 The solution is heated on a water bath for 15 minutes; a solid precipitates which is separated, washed with water and dried; weight: 0.216 g; M.pt._K: 214—216°C; yield 80%. This product is identical with
50 the product obtained in Example 1.

EXAMPLE 3.

7 - Chloro - 1 - methyl - 5 - phenyl -
2 - oxo - 2,3 - dihydro - 1H - benzo-
[f] - 1,4 - diazepine (B)

55 6 g of 1 - phenyl - 1 - (2 - methylamino - 5 - chlorophenyl) - 4 - oxo - 5 - oxo - 2 - aza - heptene are heated under reflux for 15 minutes in 25 ml of acetic acid. The acetic acid is removed in vacuo and the residue is taken up in water and a little ether. A
60 yellowish solid separates; M.pt._K: 130°C;

the yield is substantially quantitative. It is recrystallised from diisopropyl ether. Yellowish crystals are obtained (4.4 g); M.pt._K: 132°C; yield 85% in the first batch. The product is identical with the known product (see reference above in Example 1).

EXAMPLE 4.

7 - Chloro - 3 - methyl - 5 - phenyl -
2 - oxo - 2,3 - dihydro - 1H - benzo-
[f] - 1,4 - diazepine (C)

A mixture of 6.9 g (0.03 mol) of 2 - amino - 5 - chlorophenyl - phenylmethane imine and 5.1 g (0.033 mol) of the hydrochloride of the ethyl ester of DL - alanine in 40 cc of absolute alcohol is heated under reflux for one hour. It is evaporated to dryness and the residue taken up in methylene chloride and a 10% sodium carbonate solution. The organic layer is separated, washed with water and dried over sodium sulphate. The solvent is evaporated and the residue taken up in 40 cc of acetic acid. It is heated under reflux for 5 minutes and the solvent then evaporated under reduced pressure. Diisopropyl ether is added and the product allowed to crystallise; clear yellow crystals are obtained (5.15 g), M.pt._K: 224°C. Yield: 60% in the first crop. The product is identical with that described in Journal of Organic Chemistry 1962, volume 27, page 3788.

EXAMPLE 5.

7 - Chloro - 3 - isobutyl - 5 - phenyl -
2 - oxo - 2,3 - dihydro - 1H -
benzo[f] - 1,4 - diazepine (D).

The procedure is the same as described in Example 4 except that the hydrochloride of the ethyl ester of DL - alanine is replaced by the hydrochloride of the ethyl ester of DL - leucine in equimolecular quantity. Compound (D) is obtained in a yield of 48%; M.pt._K: 213°C (ethyl acetate). The product is identical with the product described in the chemical literature (reference given above in Example 4).

EXAMPLE 6.

7 - Chloro - 3 - (3 - thiabutyl) - 5 -
phenyl - 2 - oxo - 2,3 - dihydro -
1H - benzo[f] - 1,4 - diazepine (E).

This product is obtained utilising the procedure described in Example 4, the hydrochloride of the ethyl ester of DL - alanine being replaced by that of the ethyl ester of DL - methionine (50% in excess of the theoretical quantity).

Employing the same treatment after crystallisation from ethyl acetate, 7 - chloro - 3 - (3 - thiabutyl) - 5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo[f] - 1,4 - diazepine (M.pt._K: 184°C) is obtained in a yield of 50%. The product is identical with the product described in the chemical literature (reference given above in Example 4).

EXAMPLE 7.

7 - Chloro - 3 - carbethoxy - 5 -
phenyl - 2 - oxo - 2,3 - dihydro -
1H - benzo[f] - 1,4 - diazepine
(4279 CB).

This compound is obtained by the procedure described in Example 3, the azahexane used in that example being replaced by an equimolecular quantity of diethyl [2-phenyl - 2 - (2 - amino - 5 - chlorophenyl) - 1 - aza - vinyl]malonate. Shiny, colourless crystals are obtained; M.pt._x: 244°C (ethyl acetate). Yield: 74% in the first crop.

EXAMPLE 8.

7 - Chloro - 3 - carbethoxy - 5 -
phenyl - 2 - oxo - 2,3 - dihydro -
1H - benzo - [f] - 1,4 - diazepine
(4279 CB).

A mixture of 9.2 g (0.04 mol) of (2-amino - 5 - chlorophenyl) - phenylmethane imine, 10.6 g (0.05 mol) of the hydrochloride of diethyl amino-malonate and 5 g (0.05 mol) of triethylamine in 45 ml of absolute ethyl alcohol is heated under reflux for one hour. The solvent is evaporated under reduced pressure and the residue taken up in water and ether. The ethereal layer is separated, washed with water and dried over sodium sulphate. After evaporation of the solvent, the residue is dissolved in 45 ml of acetic acid and heated under reflux for 15 minutes. The product is evaporated to dryness under reduced pressure and taken up in ether. A solid separates which is filtered by suction and recrystallised from ethyl acetate. Brilliant, colourless crystals are obtained (6.4 g); M.pt._x 244°C; yield: 47%. The product is identical with that obtained in Example 7.

EXAMPLE 9.

7 - Chloro - 3 - methoxycarbonyl -
5 - phenyl - 2 - oxo - 2,3 - dihydro -
1H - benzo[f] - 1,4 - diazepine
(4347 CB).

A solution of 9.2 g (0.04 mol) of (2-amino - 5 - chlorophenyl) - phenylmethane imine in 20 ml of methanol is added dropwise, in the course of one hour 30 minutes, to a boiling solution of 9.2 g (0.05 mol) of the hydrochloride of dimethyl aminomalonate in 30 ml of methanol. When this is completed, heating under reflux is continued for 30 minutes and the product then concentrated to dryness under reduced pressure. The residue is taken up in water and ether, the ethereal layer separated, the product washed with water and dried over sodium sulphate. The solvent is evaporated under reduced pressure. The residue cannot be obtained in the crystalline state. It is dissolved in 25 ml of acetic acid, heated under reflux for 15 minutes, the product evaporated to dryness and the residual oil taken up in ether. A colourless solid separates which is filtered

by suction and recrystallised from methanol. Colourless crystals are obtained (4.7 g); M.pt._x: 226°C. A second crop (1.5 g) is obtained on concentration of the mother liquor; M.pt._x: 222°C; total quantity 6.2 g, corresponding to a yield of 47%.

EXAMPLE 10.

7 - Chloro - 3 - carbethoxy - 1 -
methyl - 5 - phenyl - 2 - oxo - 2,3 -
dihydro - 1H - benzo[f] - 1,4 -
diazepine (4366 CB).

This product is prepared by the method described in Example 9; the dimethyl aminomalonate hydrochloride and the ketimine used therein being respectively replaced by diethyl aminomalonate hydrochloride and (2-methylamino - 5 - chlorophenyl) - phenylmethane imine in equimolecular quantities. Light yellow crystals are obtained; M.pt._x: 180°C (ethyl alcohol); yield: 45%.

EXAMPLE 11.

7 - Chloro - 3 - carbamoyl - 5 -
phenyl - 2 - oxo - 2,3 - dihydro -
1H - benzo[f] - 1,4 - diazepine
(4348 CB).

10 g of 7 - chloro - 3 - methoxycarbonyl - 5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo[f] - 1,4 - diazepine and 200 ml of a 13.6% solution of ammonia in methanol are left together overnight at room temperature. The solid rapidly dissolves and after several hours a precipitate gradually forms which increases in quantity with passage of time. The precipitate which separates is filtered by suction and washed with methanol. An additional small quantity of the same product is obtained by concentrating the solution to dryness. The two crops are combined and recrystallised from methanol. Colourless crystals are obtained (7 g); M.pt._m: 255—256°C; yield: 74%.

EXAMPLE 12.

7 - Chloro - 3 - methylaminocarbonyl -
5 - phenyl - 2 - oxo - 2,3 - dihydro -
1H - benzo[f] - 1,4 - diazepine
(4367 CB).

This product is prepared by the method of Example 11, the solution of ammonia in methanol being replaced by the equivalent quantity of a solution of methylamine in methanol. Colourless crystals are obtained (ethyl alcohol); M.pt._m: 294°C; yield: 90%.

EXAMPLE 13.

7 - Chloro - 3 - dimethylamino-
carbonyl - 5 - phenyl - 2 - oxo -
2,3 - dihydro - 1H - benzo[f] -
1,4 - diazepine (4368 CB).

This compound is obtained as in Example 11, the solution of ammonia in methanol being replaced by the equivalent quantity of

a solution of dimethylamine in methanol. Colourless crystals are obtained; M.pt._x = 297°C.

EXAMPLE 14.

7 - Chloro - 3 - (2 - diethylamino - ethylaminocarbonyl) - 5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo[f] - 1,4 - diazepine (4369 CB).

This compound is obtained by the procedure employed in Example 11, the solution of ammonia in methanol being replaced by a solution of 2 - diethylamino - ethylamine (three times the calculated quantity) in 20 times its volume of methanol. Colourless crystals are obtained; M.pt._x: 220°C (ethyl acetate); yield: 90%.

EXAMPLE 15.

3 - Ethoxycarbonyl - 5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo[f] - 1,4 - diazepine (4352 CB).

This compound is obtained by the method employed in Example 3, the azaheptene used therein being replaced by an equimolecular quantity of diethyl [2 - phenyl - 2 - (2 - aminophenyl) - 1 - aza - vinyl]malonate. Colourless crystals are obtained; M.pt._x: 226°C (ethyl acetate); yield: 70% in the first crop.

EXAMPLE 16.

7 - Methyl - 5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo[f] - 1,4 - diazepine (F).

The procedure described in Example 3 is employed, the aza - heptene used therein being replaced by an equivalent quantity of 1 - phenyl - 1 - (2 - amino - 5 - methylphenyl) - 4 - oxo - 5 - oxa - 2 - aza - 1 - heptene.

Yellowish crystals are obtained; M.pt._x: 208°C (ethyl acetate); yield: 44%. This product is identical with that described in the literature (see reference in Example 4).

EXAMPLE 17.

7 - Methyl - 3 - ethoxycarbonyl - 5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo[f] - 1,4 - diazepine (4327 CB).

This compound is obtained by the procedure described in Example 9, the hydrochloride of dimethyl aminomalonate and (2 - amino - 5 - chlorophenyl) - phenylmethane imine being replaced by the equivalent quantities of, respectively, the hydrochloride of diethyl aminomalonate and (2 - amino - 5 - methyl - phenyl) - phenyl - methane - imine.

Yellowish crystals are obtained; M.pt._x: 260°C; yield 25%.

EXAMPLE 18.

7 - Nitro - 3 - ethoxycarbonyl - 5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo[f] - 1,4 - diazepine (4353 CB).

12.3 g (0.04 mol) of the finely powdered compound obtained in Example 15 are added slowly, with stirring, to 50 ml of concentrated sulphuric acid (66° Be) in such a manner that the temperature does not rise above 25°C. 4.8 g (0.048 mol) of powdered potassium nitrate is then gradually added to the resulting solution at a rate such that the temperature remains below 25°C. When this is completed, the mixture is stirred for 2 hours 30 minutes at room temperature. The reaction mixture is then poured on to a mixture of crushed ice and ether and allowed to stand for 0.5 hours. The solid which separates is filtered by suction, washed with water and with ether. It is recrystallised from a large volume of ethyl acetate. Pale yellow crystals are obtained (7.7 g); M.pt._x: 271°C; yield 55%.

EXAMPLE 19.

7 - Amino - 3 - ethoxycarbonyl - 5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo[f] - 1,4 - diazepine (4354 CB).

A solution of 4.48 g (0.0133 mol) of the product obtained in Example 18 dissolved in 80 ml of dimethylformamide and 120 ml of ethyl alcohol is hydrogenated at ordinary temperature and pressure in the presence of Raney nickel. The theoretical absorption of hydrogen requires about 3 hours.

After filtration of the catalyst and evaporation of the solvents under reduced pressure, a solid residue is obtained which is recrystallised from a mixture of dimethylformamide and ethyl alcohol. Pale yellow crystals are obtained (3.9 g); M.pt._x: 305°C (decomposition); yield: 90%.

EXAMPLE 20.

7 - Chloro - 5 - cyclohexyl - 2 - oxo - 2,3 - dihydro - 1H - benzo[f] - 1,4 - diazepine (4190 CB).

This product is prepared by the procedure described in Example 4, (2 - amino - 5 - chlorophenyl) - phenylmethane imine and the hydrochloride of the ethyl ester of DL - alanine being respectively replaced by equimolecular quantities of cyclohexyl - (2 - amino - 5 - chlorophenyl) - methane imine and the hydrochloride of ethyl glycinate. Yellowish crystals are obtained; M.pt._x: 210°C (n - propyl alcohol); yield: 71% from the imine. In this case, the intermediate

product viz. 1 - cyclohexyl - 1 - (2' - amino - 5' - chlorophenyl) - 4 - oxo - 5 - oxa - 2 - aza - 1 - heptene cannot be isolated in the crystalline state.

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EXAMPLE 21.

7 - Chloro - 3 - ethoxycarbonyl - 5 - cyclohexyl - 2 - oxo - 2,3 - dihydro - 1H - benzo[f] - 1,4 - diazepine (4370 CB).

10 This product is prepared by the procedure described in Example 9, the dimethyl aminomalonate hydrochloride and (2 - amino - 5 - chlorophenyl) - phenylmethane imine being respectively replaced by the stoichiometric quantities of diethyl aminomalonate hydrochloride and cyclohexyl - (2 - amino - 5 - chlorophenyl) - methane imine.

15 Colourless crystals are obtained, M.pt._K: 208°C (ethyl acetate); yield: 40%. It should be noted that in this case, the intermediate diethyl [2 - cyclohexyl - 2 - (2 - amino - 5 - chlorophenyl) - 1 - azavinyl] - malonate cannot be isolated in the crystalline state.

EXAMPLE 22.

25 Potassium salt of 3 - [7 - chloro - 5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo - [f] - 1,4 - diazepine] - carboxylic acid (4311 CB).

30 2.1 g (0.005 mol) of dipotassium [2 - phenyl - 2 - (2 - amino - 5 - chlorophenyl) - 1 - azavinyl]malonate and 0.68 g (0.005 mol) of monopotassium phosphate are dissolved at room temperature in 18 ml of water. Solution proceeds rapidly and then colourless platelets slowly precipitate. The product is filtered by suction, washed first with chilled water and then with absolute alcohol. The product is dried at room temperature for 12 hours and then in a high vacuum. 1.8 g of colourless crystals completely soluble in water are obtained. The aqueous solution has a substantially neutral reaction; yield: 80%. This product is decarboxylated within a few minutes by heating an aqueous solution thereof, compound A being obtained in the crystalline state.

EXAMPLE 23.

50 Potassium salt of 3 - [5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo[f] - 1,4 - diazepine] - carboxylic acid (4338 CB).

55 This compound is obtained by the procedure described in Example 22, the potassium salt used in that example being replaced by an equivalent quantity of dipotassium [2 - phenyl - 2 - (2 - aminophenyl) - 1 - azavinyl]malonate and the volume of water used being reduced by one-half. It is a colourless powder which dissolves in water, giving a substantially neutral reaction; yield: 74%.

EXAMPLE 24.

Potassium salt of 3 - [7 - methyl - 5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo [f] - 1,4 - diazepine] - carboxylic acid (4373 CB).

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The same procedure is employed as in Example 22 but the potassium salt used is replaced by dipotassium [2 - phenyl - 2 - (2 - amino - 5 - methylphenyl) - 1 - azavinyl]malonate in stoichiometric quantity and the volume of water used is reduced by one-half.

70 It is a colourless solid completely soluble in water; yield: 45%.

EXAMPLE 25.

Potassium salt of 3 - [7 - nitro - 5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo[f] - 1,4 - diazepine] - carboxylic acid (4336 CB).

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80 This product is prepared by the method of Example 22, the potassium salt used in that example being replaced by a stoichiometric quantity of dipotassium [2 - phenyl - 2 - (2 - amino - 5 - nitrophenyl) - 1 - azavinyl]malonate, and the water used is reduced to one-half the volume.

85 It is a light yellow powder which dissolves in water to give a practically neutral solution; yield: 79%.

EXAMPLE 26.

90 7 - Chloro - 3 - carbethoxy - 5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo[f] - 1,4 - diazepine (4279 CB).

95 423.5 g (2 mols) of the hydrochloride of diethyl aminomalonate and 1250 ml of dry benzene are placed in a reaction vessel equipped with stirrer, condenser, dropping funnel and inlet tube for the introduction of gaseous hydrogen chloride. The reaction mixture is heated under reflux and a solution of 460 g (2 mols) of (2 - amino - 5 - chlorophenyl)phenylmethane imine in 1250 ml of dry benzene is added during the course of 50 minutes. Precipitation of the hydrochloride of (- 2 - amino - 5 - chlorophenyl) - phenylmethane imine in the form of orange-red crystals is observed to begin at the commencement of the introduction of the ketimine. Heating under reflux is continued until the suspended precipitate becomes discoloured (ammonium chloride), which takes about 2 hours, and a rapid current of gaseous hydrogen chloride is then bubbled through the reaction mixture for 2 hours while the mixture is kept boiling. The hydrochloride of 7 - chloro - 3 - carbethoxy - 5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo[f] - 1,4 - diazepine precipitates progressively in the form of an orange powder. The crystals (hydrochloride of 4279 CB and ammonium chloride) are cooled, filtered by suction and rinsed with benzene and ether. To liberate

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the base, the product is treated with a sodium carbonate solution in the presence of methylene chloride. The organic layer is separated, dried, the solvent evaporated and the residue treated with ether. A practically pure white product is thus obtained (441.5 g; yield 63.5%), M.pt._x=243—244°C.

EXAMPLE 27.

3 - Ethoxycarbonyl - 5 - phenyl - 2 -
 10 oxo - 2,3 - dihydro - 1H - benzo-
 [f] - 1,4 - diazepine (4352 CB).
 423.5 g (2 mols) of the hydrochloride of diethyl aminomalonate and 1250 ml of benzene are introduced into an apparatus identical with that used in Example 26. The mixture is heated under reflux and a solution of 391 g (2 mols) of (2 - amino - phenyl) - phenyl - methane - imine in 1250 ml of dry benzene is added during the course of 50 minutes. From the commencement of addition of the latter, the hydrochloride of (2 - aminophenyl)phenylmethane imine precipitates in the form of deep red crystals. To facilitate the condensation reaction, 62.5 ml of methanol, i.e. 2.5% of the total solvent used, are added. The reaction mixture is heated under reflux for 4 hours until decolorisation of the precipitate has occurred. The precipitate at the end of the reaction consists solely of ammonium chloride. Methanol is removed by azeotropic distillation (methanol - benzene) and a fast current of gaseous hydrogen chloride is then bubbled through the mixture for two hours whilst the reaction mixture is kept boiling. The hydrochloride of 3 - carbethoxy - 5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo[f] - 1,4 - diazepine progressively precipitates in the form of an orange powder. The reaction mixture is cooled, the crystals of the hydrochloride of the benzodiazepine and ammonium chloride are filtered by suction, washed with benzene and with ether. To liberate the base, the hydrochloride is treated in the manner described in Example 26 for the hydrochloride of the compound 4279 CB. 416 g of practically pure compound 4352 CB are obtained in this way. Yield: 67.5%; M.pt._x=224—225°C.

EXAMPLE 28

7 - Chloro - 5 - cyclohexyl - 2 -
 10 oxo - 2,3 - dihydro - 1H - benzo-
 [f] - 1,4 - diazepine (4190 CB).
 The procedure according to Example 26 is employed, the hydrochloride of diethyl aminomalonate being replaced by the stoichiometric quantity of the hydrochloride of ethyl glycinate, the (2 - amino - 5 - chlorophenyl) - phenylmethane imine being replaced by the stoichiometric quantity of cyclohexyl - (2 - amino - 5 - chlorophenyl) - methane imine and benzene by an equal volume of toluene. The benzodiazepine is finally obtained by de-

composition of its orange-red hydrochloride, giving a yield of 66.5%; M.pt._x=280°C.

EXAMPLE 29.

7 - Chloro - 5 - phenyl - 2 - oxo -
 2,3 - dihydro - 1H - benzo - [f] -
 1,4 - diazepine (A).

A suspension of 6.68 g (0.02 mol) of the product of Example 7 in an aqueous solution of potassium hydroxide, 4.5 g of potassium hydroxide in 45 ml of water) is heated with stirring on a water bath until completely dissolved. There is obtained a strongly yellow coloured solution which clears after a few minutes. The hot solution is treated with 6 ml of acetic acid which causes a pasty product to separate accompanied by evolution of carbon dioxide. Decarboxylation is completed by heating to reflux for a short time. After the reaction is complete the desired product crystallises; it is centrifuged, washed with water and dried at 100°C in vacuo. M.pt._x=212°C. The yield is practically quantitative. A pure product can be obtained by crystallisation as described in Example 1.

Instead of an aqueous solution of potassium hydroxide, a solution of potassium hydroxide in ethyl alcohol, for example a 95 per cent by volume alcohol, may be used, the hot solution being treated with acetic acid as described above.

EXAMPLE 30.

7 - Chloro - 1 - methyl - 5 - phenyl -
 2 - oxo - 2,3 - dihydro - 1H -
 benzo - [f] - 1,4 - diazepine (B).

An aqueous solution prepared by dissolving 7 g of potassium hydroxide in 15 ml of water is added to an aqueous solution of 3 g of dipotassium [2 - phenyl - 2 - (2 - amino - 5 - chlorophenyl) - 1 - azavinyl]malonate, then 1 g of dimethyl sulphate is gradually added (about 5 minutes) with stirring, care being taken that the temperature does not rise above 25°C. After the addition is ended, the mixture is left for 2 hours at room temperature then acidified with acetic acid. A pasty product separates which is covered with diisopropyl ether, and the suspension thus formed is heated to boiling for a few minutes; evolution of carbon dioxide takes place. The product is cooled, diluted with ether and the aqueous phase is separated. Upon evaporation of the solvent, there is obtained a residue which is crystallised from diisopropyl ether. Yield 80%; M.pt._x=132°C. The product is identical with the product obtained according to Example 3.

Some of the compounds described in the present application have been studied with regard to their action on the central nervous system, as psycholeptics, myorelaxants and tranquilisers. In addition, the acute toxicity

has been determined for a number of these compounds.

The study of certain compounds of known pharmacodynamic and clinical activity, such as diazepam and chlordiazepoxide, has been undertaken under the same experimental conditions, with the same tests and with animals of the same origin as for the new compounds. It has thereby been possible to make quantitative comparisons of the activity of the different compounds for the different tests employed.

In the series of tests briefly described hereinafter, each compound was tested with the use of five or six scaled doses on batches of 10 or 20 animals for each dose; it was thereby possible to determine with sufficient exactitude by the method of probits the 50% effective dose (ED_{50}), that is to say the dose for which half the animals are protected and react in a predetermined manner according to a particular action.

Tests employed.

The following tests were employed:

25 1) Traction test (mice).

This consists in observing when the treated animals are capable of retrieving a rod grasped by the front paws only. Inability to carry this out was interpreted as a sign of myorelaxant activity.

2) Balance test: rotating rod (mice).

This test consists in observing whether the treated animals are capable of maintaining their balance on a horizontal rod kept in rotation.

Numerous neuroleptic compounds or tranquillisers disturb the equilibration reflex.

3) Anti-convulsant activity (anti-pentetrazole) (mice).

Pentetrazole injected intraperitoneally in a dose of 125 mg/kg produces fatal convulsions in 100% of the animals.

Certain compounds exert a protective action preventing convulsions and permitting survival.

4) Anti-convulsant activity (electric shock) (mice).

The test consists in determining the intensity of the electric current required to produce a fatal shock in a batch of test animals.

Certain preventively administered compounds effectively protect a certain percentage of animals subjected to an electric current of an intensity which is fatal to untreated animals.

5) Exploration test (mice).

This extremely simple test consists in placing a mouse at the centre of a floor pierced with holes and in noting how many holes

the mouse explores in 5 minutes. This test is carried out in a room in which complete silence is observed and which contains no person except the experimenter who is seated and still. It appeals to the curiosity of the animals. The doses of the compounds employed are, however, very small and considerably less than those required to impair movement. This simple test makes it possible to observe whether the compounds examined produce a more or less pronounced lack of interest in the environment and it gives information which is interesting from the clinical point of view with regard to the treatment of anxiety and restlessness.

6) Spontaneous motor activity in the rat and mouse and provoked motor activity.

The effect of drugs on voluntary movements of animals can be studied statistically by methods the details of which will not be discussed here. The mouse, which is an extremely lively animal and moves about a great deal, is particularly suitable for this type of experiment.

Moreover, this spontaneous mobility can be increased by administration to the animals of certain substances such as 1-phenyl-2-aminopropane, mescaline and methyl α -phenyl- α -(piperidyl-2)acetate.

The experimental results obtained by these methods give valuable information for clinical purposes with regard to the treatment of ambulatory psychomotor crises.

7) Anti-strychnine activity.

This test demonstrates the activity of drugs against a medullary excitant.

8) Morphine excitation.

In the cat, morphine produces a specific state of excitation with hallucinations which can be attenuated or suppressed by certain psycholeptic drugs.

In the mouse, the action of morphine is different but also manifested by marked central excitation.

9) Aggressiveness (cat/mouse).

In general, 75 to 80% of cats are aggressive when confronted with white mice. Psycholeptics and tranquillisers may make the cat indifferent and sometimes even amiable to the mouse. Similarly, in the case of cats that are furious and aggressive in relation to humans, diminution or suppression of the instinctive fear and establishment of a climate of confidence are observed.

10) Combativeness.

It is possible to make a male rat aggressive towards another male rat enclosed in the same cage by passing an electric current of more or less high voltage through the floor of the cage.

This test, like the preceding one, can obviously give information of clinical value for the treatment of aggression diseases.

11) Conditioning test.

5 The test used consists in educating rats to avoid an electric current passed through the floor of a cage of two compartments when they change compartments. The animal is first warned by a lamp which lights up in the compartment through which the current is passing while the other is in relative darkness.

10 This test, which requires more or less daily training at the rate of 50 times for each rat, makes it possible to follow the animals and note their progress. The performances realised at the end of a certain time (3 weeks to one month of training) are fairly constant, the percentage of errors made by adequately gifted subjects being less than

15 10 and very often even zero.
20 One would imagine the disturbances produced in these performances which call upon

the memory of animals would be of great importance for the choice of new medication. A deconditioning drug of sufficient intensity could have the result of partly depriving the patient of the idea of danger and would consequently require special surveillance of the sick persons.

12) Potentiation of narcosis.

Most psycholeptics are hypnotics in large doses but many of them can in small doses, without themselves producing any hypnosis, either prolong the time of sleep obtained with a true hypnotic (for example a barbiturate) or appreciably lower the dose of barbiturate required to obtain sleep.

In the following Table are summarised all the results obtained in the different tests briefly recorded above with certain compounds described in the present application, compared with various reference substances of known clinical activity.

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TABLE

Recapitulating the Activities

M = mouse
R = rat
C = cat

(The figures in the table indicate the 50%
PO = per os; IP = intraperitoneal;

	Acute toxicity (M) LD ₅₀	Traction (M)	Equilibration (M)	Anti-pentetrazole (M)	Electric shock (M)	Exploration (M)	Spontaneous motor activity (R)	Spontaneous motor activity (M)	1-Phenyl-2-aminopropane provoked motor activity (R)
Diazepam (compound B)	720 PO; 220 IP 800 SC	1.60 PO	4.4 PO	1.7 PO	5 PO	6 PO	25 PO	5 PO	100 PO
Nor-diazepam (compound A)		3.5 PO	8.6 PO	2.9 PO	9 PO	7.8 PO	50 PO	50 PO	100 PO
Chlorodiazepoxide	200 PO; 80 IP	3 PO	13 PO	5 PO	17 PO	20 PO			>100 PO
4279 CB		8 PO	50 PO	10 PO	25 PO	25 PO	100 PO	100 PO	>100 PO
4369 CB		>25 PO	>50 PO	>50 PO	>20 PO	>20 PO		>10 PO	
4311 CB	870 PO 310 IP 450 SC 220 IV	1.35 PO 1.75 IP	5 PO 4.5 IP	1.65 PO 2.9 IP	2.6 IP	5 IP	50 PO 25 IP	10 PO 10 IP	50 PO
4336 CB	800 PO	0.28 PO	1.5 PO	0.31 PO	3 PO	6 PO	50 PO	5 PO	
4338 CB		5 PO	>10 PO	>10 PO	>10 PO	>10 PO		>10 PO	

Obtained with Different Tests

SC = subcutaneous; IV intravenous)

[illegible]

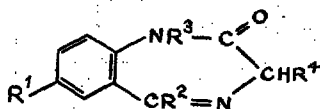
From an examination of the figures given in the Table it is found that

1) The nitro derivative of Example 25 is extremely active in different tests, especially as a myorelaxant and as an anticonvulsant in the test for curiosity; on the other hand, it appears to have less effect on the faculties of displacement. Lastly, it has a marked effect in diminishing aggressiveness (test for combativeness).

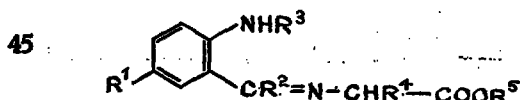
2) Compound 4311 CB (see Example 22) is highly active and compares favourably with diazepam. Its activity is slightly less when administered parenterally than when administered orally.

WHAT WE CLAIM IS:—

1. A process for producing a substituted benzodiazepine having the general formula:



in which R¹ is a hydrogen or halogen atom, a trifluoromethyl group, an alkyl or alkoxy group having 1 to 7 carbon atoms or a nitro or amino group, R² is a phenyl group which may be substituted by a halogen atom or by a trifluoromethyl or nitro group or by an alkyl or alkoxy group having 1 to 7 carbon atoms, or R² is an alkyl group having 1 to 7 carbon atoms or a cycloalkyl group having 5 to 7 carbon atoms or a furyl or thienyl group, R³ is a hydrogen atom or an alkyl group having 1 to 7 carbon atoms, and R⁴ is a hydrogen atom, an alkyl group having 1 to 7 carbon atoms, an alkylthioalkyl group having 2 to 7 carbon atoms, a carbalkoxy group having 1 to 7 carbon atoms in the alkoxy group, a carbamoyl group, an alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group having 1 to 7 carbon atoms in the alkyl group or in each of the alkyl groups, or is a group having the formula —COOCat in which Cat is the cation of an alkali metal or semication of an alkaline earth metal, which comprises treating an orthoaminoarylketimine having the general formula:



in which R¹, R², R³ and R⁴ are as above defined, but excluding the case in which R⁴ is —COOCat, and R⁵ is an alkyl group having 1 to 7 carbon atoms, with an anhydrous alkanoic acid having up to 7 carbon atoms or with an anhydrous mineral acid, or treating an orthoaminoarylketimine having the above general formula in which R¹, R² and R³ are as above defined, R⁴ is —COOCat

and R⁵ is —Cat, with a dilute aqueous solution of an acid salt in substantially equimolar proportions or with an aqueous solution of a weak acid.

2. A process as claimed in claim 1 in which the mineral acid is gaseous hydrogen chloride.

3. A process as claimed in either of claims 1 or 2, in which R³ is a hydrogen atom or a methyl group and R¹ is a chlorine atom or a nitro group.

4. A process according to any of claims 1—3 in which R⁴ is a carbalkoxy group and the product is thereafter treated with ammonia or with an alkylamine, a dialkylamine or a dialkylaminoalkylamine having 1 to 7 carbon atoms in the alkyl group or in each of the alkyl groups to give a 2-oxo-2,3-dihydro-1H-benzodiazepine having as a substituent in the 3-position a carbamoyl, alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group.

5. A process according to any of claims 1—3 in which R⁴ is a carbalkoxy group and the product is thereafter saponified and then treated with a dilute acid reagent to effect decarboxylation to give a 2-oxo-2,3-dihydro-1H-benzodiazepine which is unsubstituted in the 3-position.

6. A process according to any of claims 1—3 in which R³ is a hydrogen atom and R⁴ is a carbalkoxy group and the product is treated with an aqueous solution of an alkali metal hydroxide in order to produce a dialkali metal salt and the said dialkali metal salt is thereafter treated with an alkylating agent and then with a dilute acid to give a 1-alkyl-2-oxo-2,3-dihydro-1H-benzodiazepine which is unsubstituted in the 3-position.

7. A process according to claim 1 or claim 2 in which R¹ is a hydrogen atom and R⁴ is a carbalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group and the product is then mononitrated with a nitrating agent to give a 7-nitro-2-oxo-2,3-dihydro-1H-benzodiazepine having as a substituent in the 3-position a carbalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl.

8. A process according to claim 7 in which the mono-nitro-benzodiazepine thus produced is reduced with a reagent known to be capable of reducing an aromatic nitro group to a primary amino group to give a 7-amino-2-oxo-2,3-dihydro-1H-benzodiazepine having as a substituent in the 3-position a carbalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group.

9. A process for producing a benzodiazepine according to claim 1, claim 4, claim 5, claim 6, claim 7 or claim 8 and sub-



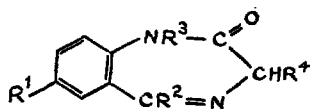
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1) The nitro derivative of Example 25 is extremely active in different tests, especially as a myorelaxant and as an anticonvulsant in the test for curiosity; on the other hand, it appears to have less effect on the faculties of displacement. Lastly, it has a marked effect in diminishing aggressiveness (test for combativeness).

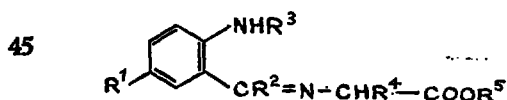
2) Compound 4311 CB (see Example 22) is highly active and compares favourably with diazepam. Its activity is slightly less when administered parenterally than when administered orally.

WHAT WE CLAIM IS:—

1. A process for producing a substituted benzodiazepine having the general formula:



in which R¹ is a hydrogen or halogen atom, a trifluoromethyl group, an alkyl or alkoxy group having 1 to 7 carbon atoms or a nitro or amino group, R² is a phenyl group which may be substituted by a halogen atom or by a trifluoromethyl or nitro group or by an alkyl or alkoxy group having 1 to 7 carbon atoms, or R² is an alkyl group having 1 to 7 carbon atoms or a cycloalkyl group having 5 to 7 carbon atoms or a furyl or thienyl group, R³ is a hydrogen atom or an alkyl group having 1 to 7 carbon atoms, and R⁴ is a hydrogen atom, an alkyl group having 1 to 7 carbon atoms, an alkylthioalkyl group having 2 to 7 carbon atoms, a carbalkoxy group having 1 to 7 carbon atoms in the alkoxy group, a carbamoyl group, an alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group having 1 to 7 carbon atoms in the alkyl group or in each of the alkyl groups, or is a group having the formula —COOCat in which Cat is the cation of an alkali metal or semication of an alkaline earth metal, which comprises treating an orthoaminoarylketimine having the general formula:



in which R¹, R², R³ and R⁴ are as above defined, but excluding the case in which R⁴ is —COOCat, and R⁵ is an alkyl group having 1 to 7 carbon atoms, with an anhydrous alkanic acid having up to 7 carbon atoms or with an anhydrous mineral acid, or treating an orthoaminoarylketimine having the above general formula in which R¹, R² and R³ are as above defined, R⁴ is —COOCat

and R⁵ is —Cat, with a dilute aqueous solution of an acid salt in substantially equimolar proportions or with an aqueous solution of a weak acid.

2. A process as claimed in claim 1 in which the mineral acid is gaseous hydrogen chloride.

3. A process as claimed in either of claims 1 or 2, in which R³ is a hydrogen atom or a methyl group and R¹ is a chlorine atom or a nitro group.

4. A process according to any of claims 1—3 in which R⁴ is a carbalkoxy group and the product is thereafter treated with ammonia or with an alkylamine, a dialkylamine or a dialkylaminoalkylamine having 1 to 7 carbon atoms in the alkyl group or in each of the alkyl groups to give a 2-oxo-2,3-dihydro-1H-benzodiazepine having as a substituent in the 3-position a carbamoyl, alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group.

5. A process according to any of claims 1—3 in which R⁴ is a carbalkoxy group and the product is thereafter saponified and then treated with a dilute acid reagent to effect decarboxylation to give a 2-oxo-2,3-dihydro-1H-benzodiazepine which is unsubstituted in the 3-position.

6. A process according to any of claims 1—3 in which R³ is a hydrogen atom and R⁴ is a carbalkoxy group and the product is treated with an aqueous solution of an alkali metal hydroxide in order to produce a dialkali metal salt and the said dialkali metal salt is thereafter treated with an alkylating agent and then with a dilute acid to give a 1-alkyl-2-oxo-2,3-dihydro-1H-benzodiazepine which is unsubstituted in the 3-position.

7. A process according to claim 1 or claim 2 in which R¹ is a hydrogen atom and R⁴ is a carbalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group and the product is then mononitrated with a nitrating agent to give a 7-nitro-2-oxo-2,3-dihydro-1H-benzodiazepine having as a substituent in the 3-position a carbalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl.

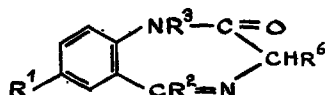
8. A process according to claim 7 in which the mono-nitro-benzodiazepine thus produced is reduced with a reagent known to be capable of reducing an aromatic nitro group to a primary amino group to give a 7-amino-2-oxo-2,3-dihydro-1H-benzodiazepine having as a substituent in the 3-position a carbalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl or dialkylaminoalkylcarbamoyl group.

9. A process for producing a benzodiazepine according to claim 1, claim 4, claim 5, claim 6, claim 7 or claim 8 and sub-



stantially as hereinbefore described with reference to any appropriate example.

10. A substituted benzodiazepine having the general formula



in which R¹ is a hydrogen or halogen atom, a trifluoromethyl group, an alkyl or alkoxy group having 1 to 7 carbon atoms or a nitro or amino group, R² is a phenyl group which may be substituted by a halogen atom, by a trifluoromethyl or nitro group or by an alkyl or alkoxy group having 1 to 7 carbon atoms or R² is an alkyl group having 1 to 7 carbon atoms or a cycloalkyl group having 5 to 7 carbon atoms or a furyl or thienyl group, R³ is a hydrogen atom or an alkyl group having 1 to 7 carbon atoms, R⁶ is a carbalkoxy group having 1 to 7 carbon atoms

in the alkoxy group, a carbamoyl, alkyl-carbamoyl, dialkylcarbamoyl or dialkylamino-alkylcarbamoyl group having 1 to 7 carbon atoms in the alkyl group or in each of the alkyl groups, or is a group having the formula —COOCat in which Cat is the cation of an alkali metal or semication of an alkaline earth metal.

11. The potassium salt of 3 - [7 - chloro - 5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo - [f] - 1,4 - diazepine]carboxylic acid.

12. The potassium salt of 3 - [7 - nitro - 5 - phenyl - 2 - oxo - 2,3 - dihydro - 1H - benzo - [f] - 1,4 - diazepine]carboxylic acid.

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Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to patent Nos. 948,888 and 972,968.