

PATENT SPECIFICATION

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NO DRAWINGS

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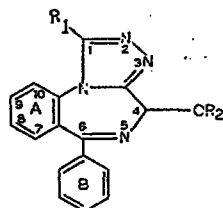
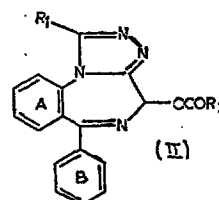
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 624 628 658 671 672 67X 790 79Y ML



(54) BENZODIAZEPINE DERIVATIVES

- (71) We, TAKEDA YAKUHIN KOGYO KABUSHIKI KAISHA (TAKEDA CHEMICAL INDUSTRIES LTD) of 27, Doshomachi 2-chome, Higashi-ku, Osaka, Japan, a body corporate organised under the laws of Japan do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel and useful benzodiazepine derivatives of the general formula (I):



- 15 wherein
 R₁ is hydrogen or a hydrocarbon residue,
 R₂ is hydrogen or lower alkyl,
 the rings A and B are unsubstituted or substituted by one or more nitro, trifluoromethyl, halogen, alkyl or alkoxy groups, which can be the same or different,
 20 and their pharmaceutically acceptable acid addition salts; and also relates to a novel and useful process for producing the benzodiazepine derivatives (I).
 25

- The present invention is further concerned with novel and useful intermediates for the production of the benzodiazepine derivatives (I), which intermediates have the following
 30 general formula (II):

[Price 25p]

wherein

—OCOR₃ is an acyloxy group convertible to a hydroxy or alkoxy group, and the other symbols have the same meanings as given above,

and with a process for the production of the intermediates (II).

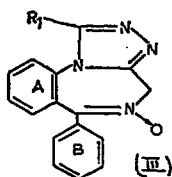
The desired benzodiazepine derivatives (I) of the present invention are useful, for example, as anticonvulsants, sedatives and tranquillising agents without causing undesirable side-effects.

- Referring to the general formula (I), as the hydrocarbon residue represented by R₁, there are generally mentioned those having 1 to 8 carbon atoms, which include alkyl with up to six carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, amyl and hexyl), aralkyl (e.g. benzyl and phenethyl) and aryl (e.g. phenyl). The lower alkyl of R₂ is that having 1 to 4 carbon atoms which is exemplified by methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc. The rings A and B are unsubstituted or substituted by one or more substituents, which are the same or different, selected from nitro, trifluoromethyl, halogen (i.e. chlorine, fluorine, bromine and iodine), alkyl such as lower alkyl (e.g. methyl, ethyl and propyl) and alkoxy such as lower alkoxy (e.g. methoxy and ethoxy).

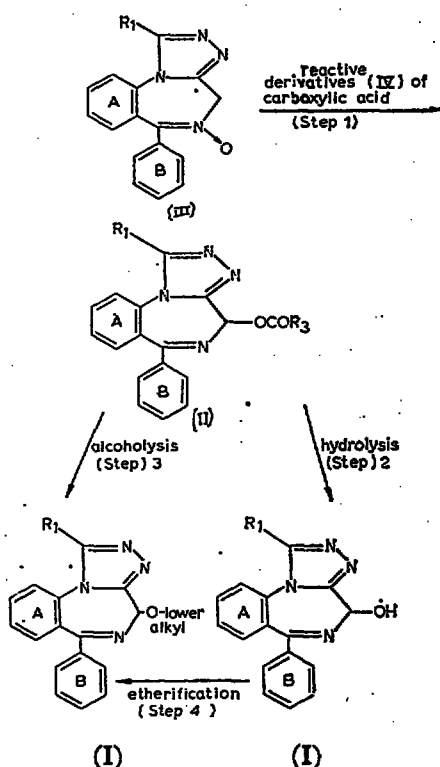
The benzodiazepine derivatives (I) of the

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present invention can be produced by allowing compounds of the general formula (III):



- 5 wherein all the symbols have the same meanings as given above,
to react with reactive derivatives (IV) of
carboxylic acids, the carboxylic acid being
represented by the general formula $R_3\text{COOH}$,
whereby the intermediates (II) can be pro-
10 duced; and then subjecting the intermediates
(II) to hydrolysis or to alcoholysis, and option-
ally subjecting the benzodiazepine derivatives
(I), wherein R_2 is hydrogen, to etherification.
15 The reactions of the present invention are
summarised in the following reaction scheme:



The above steps (1) to (4) will be explained in more detail as follows:

- 20 According to the step (1) of the present invention, the compounds (III) are allowed to react with the reactive derivatives (IV) of carboxylic acids. The compounds (III) may be employed in the form of suitable acid salts (e.g. the hydrochloride). The reactive
25 derivatives (IV) of carboxylic acids are those

derived from carboxylic acids of the general formula $R_3\text{COOH}$, wherein $-\text{OCOR}_3$ is, as mentioned above, an acyloxy group convertible to the hydroxy or alkoxy group. Preferred examples of the group R_3 are hydrocarbons hav-
30 ing 1 to 7 carbon atoms, such as alkyls having 1 to 4 carbon atoms, aryls and aralkyls. Typical examples of the carboxylic acid of the general formula $R_3\text{COOH}$ include acetic
35 acid, propionic acid, butyric acid, benzoic acid, phenylacetic acid, etc.

The reactive derivatives of the carboxylic acid, which are employed in this method, include acid anhydrides, acid halides (e.g. acid
40 chlorides, acid bromides, etc.) and acid sulphides.

The present reaction of the step (I) is generally conducted by allowing the reactive derivatives (IV) of a carboxylic acid to react
45 with the compound (III) in the presence of a suitable solvent with or without heating. The reactive derivative (IV) of the carboxylic acid may take a role as a solvent, when it is in the liquid state. The amount of the reactive derivative (IV) is from 2 to 5 moles
50 per mole of the compound (III).

The intermediates (II) produced are subjected to the step (2) or the step (3) of the present invention with or without the isolation thereof from the reaction mixture. The isolation of the intermediates is conveniently
55 conducted, for example, by evaporating the solvent from the reaction mixture. The intermediates (II) may be obtained in the form of suitable acid salts (e.g. the hydrochloride).

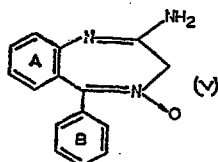
According to the step (2) of the present invention, the intermediates (II) are subjected to hydrolysis. The intermediates (II) may be used in the form of suitable acid salts. The hydrolysis is generally conducted in the pre-
65 sence of alkali (e.g. sodium hydroxide, potassium hydroxide, etc.) in a suitable solvent at room temperature. The reaction can be controlled by suitable cooling or heating, if necessary. In the present step (2), benzodiazepine derivatives (I), wherein R_2 is hydrogen, are produced and are conveniently separated,
70 for example, by evaporating the solvent from the reaction mixture. The benzodiazepine derivatives (I) may be obtained in the form of a suitable acid salt (e.g. the hydrochloride) by conventional means.

According to step (3) of the present invention, the intermediates (II) are subjected to alcoholysis. The intermediates (II) may be
80 employed in the form of acid salts. The alcoholysis is generally conducted by allowing the intermediates (II) to react with alcohols (e.g. methanol, ethanol, propanol, isopropanol, butanol, tert-butanol, etc.) suitable
85 for introduction of the desired alkoxy groups in the presence of acids (e.g. hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, *p*-toluene sulphonic acid, etc.) in suitable solvents (e.g. chloroform, carbon tetra-
90

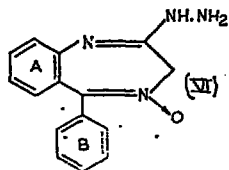
chloride, etc.) in a suitable temperature range between room temperature and the boiling point of the solvent used. The alcohol may take a role as the solvent. The benzodiazepine derivatives (I) produced, wherein R_2 is lower alkyl, are conveniently separated, for example, by evaporating the solvent from the reaction mixture. The benzodiazepine derivatives (I) may be obtained in the form of acid salts.

According to the step (4) of the present invention, the benzodiazepine derivatives (I), wherein R_2 is hydrogen, are subjected to etherification. The etherification is generally conducted by allowing the benzodiazepine derivatives (I), wherein R_2 is hydrogen, to react with an alcohol which is suitable for the introduction of the desired alkoxy groups, in the presence of suitable solvents (e.g. chloroform, carbon tetrachloride, etc.) in a temperature range between room temperature and the boiling point of the solvent used. This reaction is conducted preferably in the presence of acids (e.g. hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, *p*-toluene sulphonic acid, etc.). The benzodiazepine derivatives (I) may be employed in the form of acid salts. The alcohol used for the etherification may take a role as the solvent. The benzodiazepine derivatives (I) produced, wherein R_2 is lower alkyl, are conveniently separated, for example, by evaporating the solvent from the reaction mixture. The benzodiazepine derivatives (I), wherein R_2 is lower alkyl, may be obtained in the form of suitable acid salts (e.g. hydrochlorides).

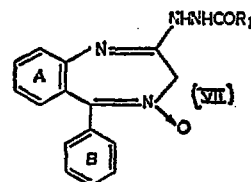
The starting compounds (III) which are employable in the present invention can be prepared, for example, by allowing the compounds of the general formula (V):



wherein all the symbols have the same meanings as given above, to react with hydrazine, whereby the compounds of the general formula (VI):

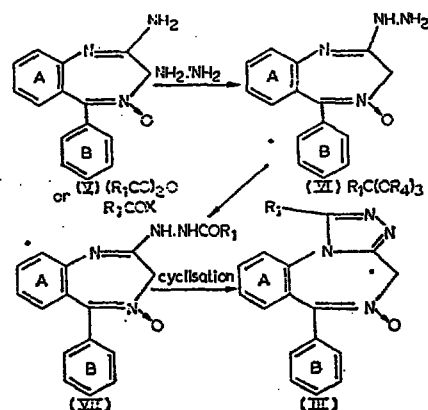


are yielded, and then allowing the resulting compounds (VI) to react with orthoesters of the general formula $RC(OR_4)_3$, wherein R_1 has the same meaning as given above and R_4 represents lower alkyl such as methyl and ethyl. The starting compounds (III) can also be prepared by allowing the compounds (VI) to react with a carboxylic anhydride of the general formula $(R_1-CO)_2O$, or an acyl halide of the general formula R_1-COX (wherein X is halogen), whereby the compounds of the general formula (VII):



are yielded, and then subjecting these compounds (VII) to cyclisation.

The above two reactions for the production of the starting compounds (III) may be shown as follows:



The benzodiazepine derivatives (I) obtained as well as their salts are novel compounds and show anticonvulsant, sedative and taming effects without causing any undesirable side-effects. Therefore, they are useful as anticonvulsants, sedatives and tranquilising agents. For such purposes, the benzodiazepine derivatives (I) as well as their pharmaceutically acceptable acid salts are orally or parenterally administered *per se* or in a suitable form such as powder, granules, tablets or injectable solutions admixed with a non-toxic, pharmaceutically acceptable carrier or diluent. The dose of the benzodiazepine derivatives (I) or their acid salts to be administered, varies depending on the kinds of the compounds, the severity of the disease, etc., and generally falls within the range

of from 1 to 30 milligrams for oral administration, and 0.5 to 10 milligrams for parenteral administration for an adult human per day.

The compound (II) is useful not only as an intermediate for the production of the benzodiazepine derivatives (I) of the present invention, but also as medicine producing similar medicinal effects to those of the benzodiazepine derivatives (I) of the present invention.

For further detailed explanation of the present invention, the following preparative examples and examples are given, wherein the term "part(s)" means "weight part(s)" unless otherwise specified, and the relationship between "part(s)" and "part(s) by volume" corresponds to that between gram(s) and millilitre(s).

PREPARATIVE EXAMPLE 1

To a mixture of 3 parts of 2 - amino - 7 - nitro - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N-oxide and 100 parts by volume of ethanol are added 2.5 parts by volume of 100% hydrazine hydrate and 1.8 parts by volume of acetic acid. The whole mixture is slightly warmed on a water bath for a while to make a solution and stirred at room temperature for about 20 minutes. The precipitated crystals are collected and washed with ethanol and then with diethyl ether, whereby 2 - hydrazino - 7 - nitro - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N - oxide is yielded as yellow needles melting at 176°C (sintering), 226°C (decomposition).

Elementary analysis: $C_{15}H_{13}N_5O_3$
Calculated: C 57.87 H 4.21 N 22.50
Found: C 57.98 H 4.01 N 22.26

To a suspension of 1.55 parts of 2-hydrazino-7 - nitro - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N - oxide in 100 parts by volume of ethanol are added 3.7 parts of ethyl orthoformate, and then 0.6 part by volume of concentrated sulphuric acid, whereby the solid substance is once dissolved and then yellow crystals are precipitated. After stirring for 30 minutes, the mixture is neutralised with a saturated aqueous solution of sodium bicarbonate. The crystals are collected and washed with water, ethanol and then diethyl ether, whereby 8 - nitro - 6 - phenyl - 4H - s - triazolo - [4,3 - a][1,4] - benzodiazepine 5N - oxide is yielded as yellow crystals. Recrystallisation from aqueous dimethyl formamide yields yellow crystals melting at 274°C to 275°C (decomposition).

Elementary analysis: $C_{16}H_{11}N_5O_3$
Calculated: C 59.81 H 3.45 N 21.80
Found: C 59.58 H 3.48 N 21.56

PREPARATIVE EXAMPLE 2

To a suspension of 14.3 parts of 2 - amino - 7 - chloro - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N - oxide in 400 parts by volume of methanol are added 12.5 parts by volume

of 100% hydrazine hydrate and 10 parts by volume of methanol saturated with hydrogen chloride. The mixture is refluxed for 10 minutes and the resulting solution is concentrated to half the initial volume. The concentrate is poured into 500 parts by volume of water and the resulting oily substance is extracted with chloroform. The chloroform layer is dried over sodium sulphate and evaporated. Treatment of the residue with diethyl ether gives 7 - chloro - 2 - hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N - oxide as pale yellow powdery crystals melting at 262°C to 263°C.

Elementary analysis: $C_{15}H_{13}ClN_4O$

Calculated: C 59.90 H 4.36 N 18.63

Found: C 60.05 H 4.13 N 18.41

To a mixture of 1.5 parts of 7 - chloro - 2 - hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N - oxide, 50 parts by volume of tetrahydrofuran and 1 part by volume of triethylamine is added 0.5 part by volume of acetic anhydride with stirring. The whole mixture is stirred for about 1 hour, followed by the addition of water, whereby 2 - (2 - acetyl - hydrazino) - 7 - chloro - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N - oxide is yielded as crystals. Recrystallisation from a mixture of dimethyl formamide and water yields fine needles melting at 256°C to 258°C (decomposition).

Elementary analysis: $C_{17}H_{15}ClN_4O_2$

Calculated: C 59.56 H 4.41 N 16.35

Found: C 59.38 H 4.55 N 16.30

A mixture of 3.4 parts of 2 - (2 - acetyl - hydrazino) - 7 - chloro - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N - oxide and 30 parts by volume of pyridine is refluxed for 4 hours, followed by evaporation of the pyridine under reduced pressure. The residue is recrystallised from methanol, whereby 8 - chloro - 1 - methyl - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine 5N - oxide is yielded as needles melting at 272°C to 274°C (decomposition).

Elementary analysis: $C_{17}H_{15}ClN_4O$

Calculated: C 62.87 H 4.03 N 17.25

Found: C 63.04 H 4.04 N 17.26

The other starting compounds can be prepared in a similar manner to the above preparative examples.

EXAMPLE 1

A mixture of 1.5 parts of 8 - chloro - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine 5N - oxide and 50 parts by volume of acetic anhydride is heated at 90°C for 1.5 hours, followed by evaporation of the solvent under reduced pressure. The residue is treated with diethyl ether, whereby 4 - acetoxy - 8 - chloro - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine is yielded as crystals. Recrystallisation from methanol yields colourless needles melting at 232 to 233°C.

Elementary analysis: $C_{18}H_{18}ClN_4O_2$
 Calculated: C 61.28 H 3.71 N 15.88
 Found: C 61.56 H 3.72 N 15.95

EXAMPLE 2

- 5 A mixture of 1.5 parts of 8 - chloro - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine 5N - oxide and 50 parts by volume of acetyl chloride is heated at 50°C for 10 minutes and then stirred at room temperature for 2 hours, followed by evaporation of the acetyl chloride under reduced pressure. The residue is neutralised with a saturated aqueous solution of sodium bicarbonate, whereby 4 - acetoxy - 8 - chloro - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine is yielded as crystals. Recrystallisation from methanol yields colourless needles melting at 231 to 232°C.
- 20 The compound yielded is identical with that obtained in Example 1.

EXAMPLE 3

- 25 A mixture of 3.25 parts of 8 - chloro - 1 - methyl - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine 5N - oxide and 60 parts by volume of acetic anhydride is heated at 90°C for 2 hours, followed by evaporation of the solvent under reduced pressure. The residue is treated with diethyl ether, whereby 4 - acetoxy - 8 - chloro - 1 - methyl - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine is yielded as crystals. Recrystallisation from a mixture of methanol and petroleum ether yields colourless needles melting at 229 to 230°C (decomposition).
- 35 Elementary analysis: $C_{18}H_{15}ClN_4O_2$
 Calculated: C 62.21 H 4.12 N 15.28
 Found: C 62.23 H 3.83 N 15.42

EXAMPLE 4

- 40 A mixture of 3.3 parts of 8 - chloro - 1 - ethyl - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine 5N - oxide and 100 parts by volume of acetic anhydride is heated at 90°C for 2.5 hours. The solvent is removed by distillation under reduced pressure and water is added to the residue, whereby 4 - acetoxy - 8 - chloro - 1 - ethyl - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine is yielded as an oil. The oil is extracted with chloroform and the chloroform layer is washed with water and dried. After evaporation of the solvent, the residue is dissolved in 50 parts by volume of ethanol, followed by the addition of 5 parts by volume of 4N aqueous sodium hydroxide solution. The mixture is left standing at room temperature for 30 minutes and acidified by the addition of acetic acid. The solvent is evaporated and the residue is treated with an aqueous ethanol, whereby 8 - chloro - 1 - ethyl - 4 - hydroxy - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine is yielded as crystals. Recrystallisation from methanol yields colourless needles melting at 254 to 255°C.

stallisation from methanol yields colourless prisms melting at 254 to 255°C.

Elementary analysis: $C_{18}H_{18}ClN_4O$
 Calculated: C 63.81 H 4.46 N 16.54
 Found: C 63.97 H 4.58 N 16.61

EXAMPLE 5

- 70 A suspension of 3.2 parts of 8 - nitro - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine 5N-oxide in 100 parts by volume of acetic anhydride is heated at 90°C for 3 hours, followed by evaporation of the solvent. Treatment of the residue with diethyl ether gives 4 - acetoxy - 8 - nitro - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine as crystals. Recrystallisation from a mixture of tetrahydrofuran and diethyl ether gives colourless prisms melting at 253 to 254°C (decomposition).
- 80 Elementary analysis: $C_{18}H_{18}N_5O_4$
 Calculated: C 59.50 H 3.61 N 19.28
 Found: C 59.44 H 3.62 N 18.99

EXAMPLE 6

- 85 A mixture of 3.53 parts of 4 - acetoxy - 8 - chloro - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, 50 parts by volume of ethanol and 6 parts by volume of 4N aqueous sodium hydroxide solution is left standing at room temperature for 30 minutes, followed by acidification with acetic acid. The solvent is evaporated from the mixture under reduced pressure and water is added to the residue, whereby 8 - chloro - 4 - hydroxy - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine is yielded as crystals. Recrystallisation from methanol yields colourless prisms melting at 241 to 242°C.
- 95 Elementary analysis: $C_{18}H_{15}ClN_4O$
 Calculated: C 61.84 H 3.57 N 18.03
 Found: C 61.77 H 3.45 N 17.81

EXAMPLE 7

- 105 To a suspension of 3.7 parts of 4-acetoxy-8 - chloro - 1 - methyl - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine in 100 parts by volume of ethanol are added 6 parts by volume of 4N aqueous sodium hydroxide solution. After stirring the mixture for about 15 minutes, the resulting solution is acidified with acetic acid. Evaporation of the solvent and then addition of water to the residue affords 8 - chloro - 4 - hydroxy - 1 - methyl - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine as crystals. Recrystallisation from a mixture of dimethyl formamide and water yields its hemihydrate as colourless needles melting at 245.5°C (decomposition).
- 115 Elementary analysis: $C_{17}H_{18}ClN_4O \cdot \frac{1}{2}H_2O$
 Calculated: C 61.17 H 4.22 N 16.79
 Found: C 61.06 H 4.37 N 16.87

EXAMPLE 8

- 120 To a suspension of 1.2 parts of 4 - acetoxy - 8 - nitro - 6 - phenyl - 4H - s - triazolo

- 5 [4,3 - a][1,4]benzodiazepine in 15 parts by volume of ethanol are added 6.6 parts by volume of 1N aqueous sodium hydroxide solution, the mixture is left standing at room temperature for about 10 minutes. The resulting solution is acidified with acetic acid, whereby 4 - hydroxy - 8 - nitro - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine is yielded as crystals. Recrystallisation from aqueous dimethyl formamide yields yellow crystals melting at 236.5°C (decomposition).

Elementary analysis: $C_{18}H_{11}N_5O_2$

Calculated: C 59.81 H 3.45 N 21.80

Found: C 59.45 H 3.70 N 21.77

15 EXAMPLE 9

- To a suspension of 1.5 parts of 8-chloro-4 - hydroxy - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine in 100 parts by volume of methanol is added 0.5 part by volume of glacial acetic acid, and then the mixture is refluxed for 3.5 hours. Evaporation of the solvent yields 8 - chloro - 4 - methoxy - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine as colourless crystals. Recrystallisation from methanol yields colourless needles melting at 270 to 271°C (decomposition).

Elementary analysis: $C_{17}H_{13}ClN_4O$

Calculated: C 62.87 H 4.03 N 17.25

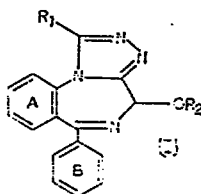
- 30 Found: C 63.06 H 3.88 N 17.12

EXAMPLE 10

- To a suspension of 1.2 parts of 4 - acetoxy - 8 - chloro - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine in 50 parts by volume of methanol is added 0.5 part by volume of glacial acetic acid. The mixture is refluxed for 4 hours and then left standing at room temperature, whereby 8 - chloro - 4 - methoxy - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine is yielded as crystals melting at 269 to 270°C (decomposition). This compound is identical with the compound obtained in Example 9.

WHAT WE CLAIM IS:—

- 45 1. A benzodiazepine derivative of the general formula (I):

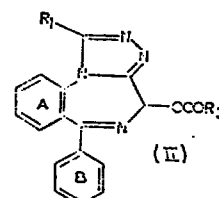


wherein

- 50 R_1 is hydrogen or a hydrocarbon residue,
 R_2 is hydrogen or a lower alkyl group,
the rings A and B are unsubstituted or sub-

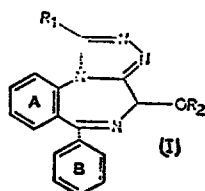
stituted by one or more nitro, trifluoromethyl, halogen, alkyl or alkoxy groups, which can be the same or different, and its pharmaceutically acceptable acid addition salts.

2. 8 - Chloro - 4 - hydroxy - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine.
3. 8 - Chloro - 4 - hydroxy - 1 - methyl - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine.
4. 8 - Chloro - 1 - ethyl - 4 - hydroxy - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine.
5. 4 - Hydroxy - 8 - nitro - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine.
6. 8 - Chloro - 4 - methoxy - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine.
7. A benzodiazepine derivative (I) according to claim 1 substantially as herein described with reference to any of the specific examples 4 and 6 to 10.
8. Pharmaceutically acceptable acid addition salts of any of the compounds claimed in claims 2 to 7.
9. A compound of the general formula (II):



wherein

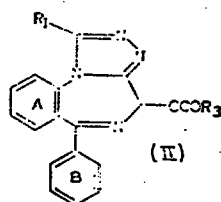
- R_1 is hydrogen or a hydrocarbon residue,
 $-OCOR_3$ is an acyloxy group convertible to a hydroxy or alkoxy group, and
the rings A and B are unsubstituted or substituted by one or more nitro, trifluoromethyl, halogen, alkyl or alkoxy groups, which can be the same or different.
10. The compound as claimed in claim 9, wherein R_3 is a lower alkyl group.
11. 4 - Acetoxy - 8 - chloro - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine.
12. 4 - Acetoxy - 8 - chloro - 1 - methyl - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine.
13. 4 - Acetoxy - 8 - chloro - 1 - ethyl - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine.
14. 4 - Acetoxy - 8 - nitro - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine.
15. Compounds of the formula (II) as defined in claim 9 substantially as herein described with reference to any of the specific examples 1 to 5.
16. A process for the production of a benzodiazepine derivative of the general formula (I):



wherein

R_1 is hydrogen or a hydrocarbon residue,
 R_2 is hydrogen or lower alkyl, and

- 5 the rings A and B are unsubstituted or substituted by one or more nitro, trifluoromethyl, halogen, alkyl or alkoxy groups, which can be the same or different, which comprises subjecting a compound of the
 10 general formula (II):

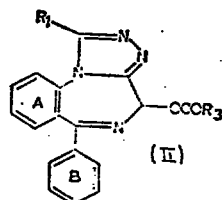


wherein

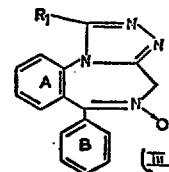
— $OCOR_3$ is an acyloxy group convertible to a hydroxy or alkoxy group, and
 15 the other symbols have the same meanings as given above,

- 20 to hydrolysis or alcoholysis, and optionally subjecting the resulting benzodiazepine derivative (I), wherein R_2 is hydrogen, to etherification.

17. A process as claimed in claim 16, wherein the starting compound of the formula (II):



is prepared by allowing a compound of the
 general formula (III):



wherein

R_1 is hydrogen or a hydrocarbon residue and the rings A and B are unsubstituted or substituted by one or more nitro, trifluoromethyl, halogen, alkoxy or alkyl groups, which can be the same or different, to react with a reactive derivative of a
 carboxylic acid.

18. A process according to claim 16 substantially as herein described with reference to any of the specific examples 4 and 6 to 10.

19. A benzodiazepine (I) as defined in claim 1 when made by a process as claimed in any of claims 16 to 18.

20. A pharmaceutical composition comprising a benzodiazepine (I) or a non-toxic pharmaceutically acceptable acid addition salt thereof as claimed in any of claims 1 to 8 and 19, together with a non-toxic, pharmaceutically acceptable carrier or diluent therefor.

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