

PATENT SPECIFICATION

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NO DRAWINGS

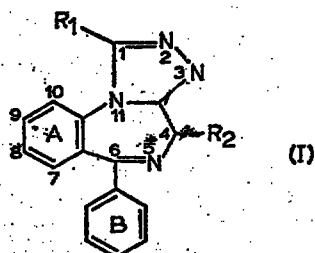
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(54) BENZODIAZEPINE DERIVATIVES

(71) We, TAKEDA YAKUHIN KOGYO KABUSHIKI KAISHA, also known as TAKEDA CHEMICAL INDUSTRIES LTD., of 27, 2-chome, Doshomachi, 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)



wherein R_1 is hydrogen or a hydrocarbon residue, R_2 is hydrogen or C_1-C_6 alkyl and the rings A and B are unsubstituted, or substituted by one or more of halogen or nitro, trifluoromethyl, alkyl or alkoxy groups which can be the same or different, and their 5-oxides.

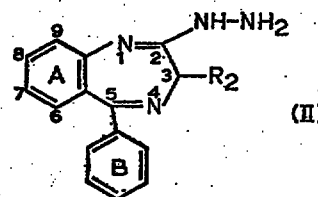
This invention relates also to a novel and useful process for producing the benzodiazepine derivatives (I).

Referring to the general formula (I), as the hydrocarbon residue represented by R_1 , there are generally mentioned those having 1 to 8 carbon atoms, which include alkyl up

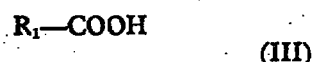
[Price 25p]

to six carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, amyl, hexyl or tert-butyl), aralkyl (e.g. benzyl or phenethyl) and aryl (e.g. phenyl). The alkyl represented by R_2 is exemplified by methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, amyl or hexyl. Both 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 or iodine), alkyl such as C_1-C_6 alkyl (e.g. methyl, ethyl or propyl) and alkoxy such as C_1-C_6 alkoxy (e.g. methoxy or ethoxy).

The benzodiazepine derivatives (I) can be produced by allowing 2-hydrazinobenzodiazepine derivatives of the general formula (II):



(wherein the symbols have the meaning given above) or their 4-oxides to react with carboxylic acids of the general formula (III):

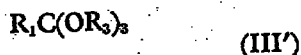


(wherein R_1 has the meaning given above) or their reactive derivatives. The reactive derivatives derived from the carboxylic acids (III) are exemplified by esters (e.g. alkyl esters such as methyl and ethyl esters, or activated esters such as *p*-nitrophenyl ester), anhydrides,

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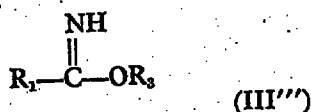
halides (e.g. chloride or bromide), amides (e.g. formamide, dimethylformamide or acetamide), orthoesters, iminoethers and amidines.

The orthoesters are shown by the general formula (III'):



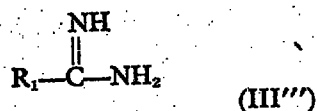
(wherein R_1 has the meaning given above and R_3 is C_1-C_2 alkyl i.e. methyl or ethyl).

The iminoethers are shown by the general formula (III''):



(wherein the symbols have the meaning given above).

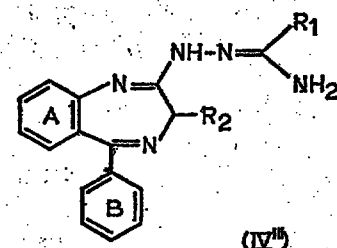
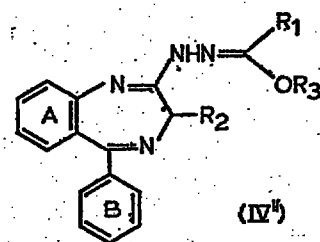
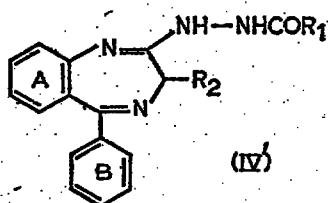
The amidines are shown by the general formula (III'''):



(wherein R_1 has the meaning given above).

The carboxylic acids (III) or their reactive derivatives are employed generally in an amount of 1 to 10 moles, in practice in an amount of 2 to 5 moles per mole of the 2-hydrazinobenzodiazepine (II). The reaction is preferably carried out in the presence of a solvent and an acid catalyst at a temperature of from 0°C to 300°C , but the conditions vary with the reagents used. The solvent is exemplified by methanol, ethanol, chloroform, methylene chloride, dimethylformamide and mixtures thereof. The acid catalyst is exemplified by inorganic acids (e.g. hydrochloric acid, sulphuric acid, phosphoric acid or polyphosphoric acid), organic carboxylic acids (e.g. acetic acid or propionic acid) and organic sulphonc acids (e.g. benzenesulphonic acid or *p*-toluenesulphonic acid). The amount of the acid catalyst is generally 2 moles to 10 moles per mole of the 2-hydrazinobenzodiazepine derivative (II).

In this reaction, acylhydrazino compounds (IV'), their enol derivatives (IV'') or α -aminoalkylidene (or aralkylidene) compounds (IV''') of the following general formulae:



(wherein the symbols have the meanings given above, including the case in which the nitrogen atom at the 4-position carries an oxygen atom) are produced at intermediates. These intermediates together with a process for their preparation are claimed in our copending divisional application No. 30424/72 and (Serial No. 1298366) can be cyclised to the compounds (I) under somewhat drastic conditions. In the present method, the compounds (I) may be synthesised in one step without isolating the intermediates, or alternatively, may be synthesised in two steps which comprise producing and isolating the intermediate and then allowing them to cyclise to the compounds (I).

For instance, when amidines are used under mild conditions, e.g. in a solvent and around room temperature, the intermediate (IV''') can be isolated. The intermediate (IV''') can be cyclised on heating at 140°C to 250°C to the compounds (I) with the evolution of ammonia. Therefore, for one step synthesis of the compounds (I), the 2-hydrazinobenzodiazepine derivatives (II) and amidines (III''') are desirably allowed to react with each other at a relatively high temperature, e.g. 140°C to 250°C . This reaction proceeds either in the presence or the absence of a solvent. Generally, a fusion method, especially in the presence of 2-methylimidazole, gives good results.

Also, in the case of esters, amides, anhydrides and halides the intermediate, i.e. acylhydrazinobenzodiazepine derivatives (IV') can be isolated, if the reaction is conducted under mild conditions, e.g. in a solvent and around room temperature. The separated acylhydrazinobenzodiazepine derivatives (IV') are easily cyclised to the compounds (I) on heating at 130°C to 250°C . The cyclising can, if

necessary, be accelerated by using a catalyst such as polyphosphoric acid. This cyclising is conducted either in the presence or the absence of a solvent. The solvent is exemplified by pyridine, dimethylformamide, xylene or tetralin. As to the intermediate (IV'), the above-mentioned matters are similarly applicable.

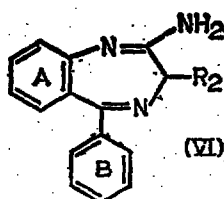
The benzodiazepine derivatives (I) can be isolated in the form of a free base or in the form of a suitable acid addition salt (e.g. chloride, sulphate or acetate) in conventional ways. For example, the reaction mixture may be neutralised with a saturated aqueous solution of sodium bicarbonate and extracted with a suitable solvent (e.g. methylene chloride or chloroform) followed by distillation of the solvent, whereby the benzodiazepine derivatives (I) are obtained.

The structure of the benzodiazepine derivatives (I) is determined from the results of X-ray analysis of 8-chloro-6-phenyl-4H-s-triazolo [4,3-a] [1,4] benzodiazepine.

When the benzodiazepine derivatives (I) carry an oxygen atom at the 5-position (i.e. 5N-oxides), the 5N-oxides can, if necessary, be reduced to the corresponding benzodiazepine derivatives (I) wherein the nitrogen atom at the 5-position carries no oxygen atom. The reduction can be conducted by conventional means, which are exemplified by catalytic hydrogenation and by the reduction using halogenophosphorus compounds (e.g. phosphorus trichloride). The hydrogenation is usually carried out in a suitable solvent such as methanol or ethanol around room temperature and under atmospheric pressure. The reduction using halogenophosphorus compounds can be usually effected on heating in a suitable solvent such as chloroform or methylene chloride.

The 2-hydrazinobenzodiazepine derivatives (II) to be employed as the starting material of the above ring closure reaction and their method of preparation are described and claimed in our copending divisional Application No. 20561/72 (Serial No. 1298365).

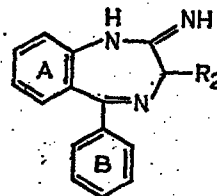
Thus, the compounds of general formula (II) can be produced by a process which comprises allowing a 2-aminobenzodiazepine of the general formula (VI):



(wherein the symbols have the same meaning as defined above) or its 4-oxide to react with hydrazine.

Referring to the above general formula, the

2- amino - α - benzodiazepine derivatives (VI) may have the following isomeric form:



which can also be used in this process.

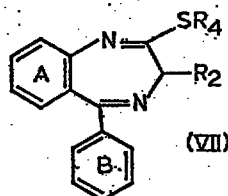
The compounds of the formula (VI) may be prepared, for example, in the manner described in Journal of Organic Chemistry 26, 1111 (1961), or by a method which comprises reacting 2-aminobenzophenone derivatives with an alkylamine to produce 2-amino - α - phenylbenzylidene alkylamine derivatives, reacting the resulting 2 - amino - α - phenylbenzylidene alkylamine derivatives with an aminoacetonitrile derivative and subjecting the resulting 2- amino - α - phenylbenzylidene-aminoacetonitrile derivatives to cyclisation in the presence of an acid or alkali.

The reaction between the 2-aminobenzodiazepine derivatives (VI) and hydrazine is preferably conducted in the presence of a suitable solvent and an acid at an appropriate temperature of from 0°C to 150°C. The solvents employable are exemplified by methanol, ethanol, pyridine, dimethylformamide, mixtures thereof and their aqueous mixtures. The acids employable are exemplified by inorganic acids (e.g. hydrochloric acid, sulphuric acid or phosphoric acid), and organic acids (e.g. acetic acid or *p*-toluenesulphonic acid, etc). The acids can be added in the form of salts with amines which are exemplified by pyridine, trialkylamines or 2-methylimidazole. It is to be noted that both or either of the hydrazine and 2-aminobenzodiazepine derivatives (VI) can be put into use in the form of their acid addition salts, and in such a case it is not always necessary to add further acid or its salt with amine to the reaction system. The amounts of hydrazine and the acid to be used are generally from one mole to five moles per mole of the 2-aminobenzodiazepine derivative (VI), but may be varied, if required.

The 2-hydrazinobenzodiazepine derivatives (II) produced above can be subjected to subsequent ring closure reaction with or without isolation from the reaction mixture. The isolation of the 2-hydrazinobenzodiazepine derivatives (II) can be effected by conventional means, for example, by adding water to the reaction mixture and extracting the mixture with a suitable solvent (e.g. methylene chloride or chloroform) followed by evaporation of the solvent.

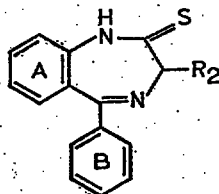
The 2-hydrazinobenzodiazepine derivatives (II) wherein the nitrogen atom at the 4-position carries no oxygen can also be produced

by a process which comprises allowing a compound of the general formula (VII):



- 5 (wherein R_4 means hydrogen, alkyl or aralkyl and other symbols have the meanings given above) to react with hydrazine.

Referring to the above general formula, when R_4 is hydrogen, the compounds may have the following isomeric form:



which can also be used in this process.

- 15 The compound of the formula (VII) may be prepared, for example, according to the method described in Journal of Organic Chemistry 29, 231 (1964).

- The alkyl represented by R_4 is preferably exemplified by lower alkyls having up to six carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, amyl or hexyl. The aralkyl represented by R_4 is exemplified by benzyl or phenethyl.

- The reaction is generally conducted in the presence of a solvent (e.g. methanol, ethanol and aqueous mixtures thereof) around room temperature or with heating, if necessary around the boiling point of the solvent used. The amount of the hydrazine to be employed is from one to ten moles per mole of the compounds (VII) for practical purposes.

- 30 The 2-hydrazinobenzodiazepine derivatives (II) thus produced can be isolated by conventional means, for example, by evaporation of the solvent from the reaction mixture.

- 35 The benzodiazepine derivatives (I) of the present invention which are novel compounds, show muscle relaxant, anticonvulsant, sedative and taming effects and therefore are useful as muscle relaxants, anticonvulsants, sedatives and tranquilising agents.

- 40 The benzodiazepine derivatives (I) as well as their acid addition salts are orally or parenterally administrable *per se* or in a suitable form such as powder, granules, tablets or injectable solutions admixed with a pharmaceutically acceptable carrier or diluent. The

dose of the benzodiazepine derivatives (I) or their acid addition salts to be administered varies depending on the kinds of the benzodiazepine derivatives (I), 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 a human adult per day.

The invention is illustrated by the following Examples in which parts are by weight unless otherwise specified and the relationship between parts by weight and parts by volume corresponds to that between grams and millilitres.

Example 1

To a suspension of 8.1 parts of 2-amino-7-chloro-5-phenyl-3H-1,4-benzodiazepine in 180 parts by volume of methanol are added 3.6 parts of 2-methylimidazole hydrochloride and 2.25 parts by volume of 80% hydrazine hydrate. The suspension is stirred at room temperature for 1.5 hours and then 25 parts of ethyl orthoformate are added. To the mixture are added dropwise with stirring 60 parts by volume of ethanol containing 10% hydrogen chloride. After stirring for a further hour, the mixture is warmed for a while so as to complete the reaction. After evaporation of the solvent, an aqueous solution of sodium bicarbonate is added to the residue to neutralise. The mixture is then extracted with methylene chloride. The methylene chloride layer is washed with water and dried over sodium sulphate, followed by evaporation of the solvent. The residue is recrystallised from a mixture of acetone and *n*-hexane to give 8-chloro-6-phenyl-4H-s-triazolo [4,3-a][1,4] benzodiazepine as colourless flakes. Melting point: 226°C to 227°C.

Elementary analysis $C_{18}H_{11}ClN_4$

Calculated	C 65.20,	H 3.76,	N 19.01
Found	C 65.30,	H 3.48,	N 19.03

Example 2

To a solution of 2.8 parts of 7-chloro-2-hydrazino-5-phenyl-3H-1,4-benzodiazepine and 7.4 parts of ethyl orthoformate in 80 parts by volume of chloroform are added with stirring 2 parts of concentrated sulphuric acid. The mixture is stirred at room temperature for 30 minutes, followed by addition of saturated aqueous sodium bicarbonate to neutralise the mixture. The chloroform layer is washed with water and dried over anhydrous sodium sulphate, followed by evaporation of the solvent. The residue is recrystallised from a mixture of acetone and *n*-hexane to give 8-chloro-6-phenyl-4H-s-triazolo [4,3-a][1,4] benzodiazepine as colourless flakes. Melting point: 226°C to 227°C.

The product obtained is identical with the product prepared in Example 1.

Example 3

- 5 To a solution of 2.85 parts of 7 - chloro - 2 - hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine in 100 parts by volume of methanol are added 7.4 parts of ethyl orthoformate and 20 parts by volume of methanol saturated with hydrogen chloride. The mixture is stirred for 2 hours and refluxed gently for 30 minutes. The solvent is distilled off under reduced pressure. To the residue is added saturated aqueous sodium bicarbonate so as to make the mixture alkaline, followed by extraction with chloroform. The chloroform extract is washed with water and dried over anhydrous sodium sulphate, followed by evaporation of the solvent. The residue is recrystallised from ethyl acetate to give 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3 - a] [1,4] benzodiazepine as colourless flakes. Melting point: 226°C to 227°C.

The product obtained is identical with the product prepared in Examples 1 and 2.

Example 4

- 25 A solution of 2.8 parts of 7 - chloro - 2 - hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine in 20 parts by volume of formic acid is left standing overnight. The solution is diluted with water, neutralised with an aqueous solution of sodium bicarbonate and extracted with chloroform. The chloroform extract is washed with water, dried over anhydrous sodium sulphate, and the solvent is evaporated. The residue is recrystallised from a mixture of acetone and *n*-hexane to give 8 - chloro - 6 - phenyl - 4H - s - triazolo flakes. Melting point: 226 to 227°C.

- 40 The product obtained is identical with the product prepared in Examples 1, 2 and 3.

Example 5

- 45 To a suspension of 2.8 parts of 7 - chloro - 2 - hydrazino 5 - phenyl - 3H - 1,4 - benzodiazepine in 40 parts by volume of formamide is added 1 part by volume of concentrated sulphuric acid. The resulting solution is left standing for 6 hours and then warmed on a boiling water bath for 30 minutes. The solution is diluted with water, neutralised with sodium bicarbonate and extracted with chloroform. The chloroform extract is washed with water and dried over anhydrous sodium sulphate, followed by evaporation of the solvent. The residue is recrystallised from ethyl acetate to give 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3 - a] [1,4] benzodiazepine as colourless flakes. Melting point 226°C to 227°C.

- 60 The product obtained is identical with the product prepared in Examples 1, 2, 3 and 4.

Example 6

A mixture of 2.8 parts of 7 - chloro - 2 - hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine, 2.4 parts of formamide hydrochloride and 2.5 parts of 2-methylimidazole is fused at 160°C for 10 minutes. Water is added to the mixture, followed by extraction with methylene chloride. The methylene chloride layer is washed with water, dried over sodium sulphate and the solvent is evaporated, whereby 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine is yielded. Recrystallisation from ethyl acetate yields colourless flakes melting at 226°C to 227°C.

The product obtained is identical with the product prepared in Examples 1 to 5.

Example 7

To a suspension of 1.35 parts of 2 - amino - 7 - chloro - 5 - phenyl - 3H - 1,4 - benzodiazepine in 25 parts by volume of methanol are added 0.6 part of 2-methylimidazole hydrochloride and 6 parts by volume of a 1 molar methanol solution of hydrazine hydrate. The mixture is stirred at room temperature for 1.5 hours, followed by the addition of 4.8 parts of ethyl orthoacetate and 10 parts by volume of ethanol containing 10% hydrogen chloride. The mixture is refluxed for 30 minutes, followed by evaporation of the solvent. The residue is neutralised with saturated aqueous sodium bicarbonate and extracted with methylene chloride. The methylene chloride extract is washed with water and dried over sodium sulphate, followed by evaporation of the solvent. The residue is purified by means of silica gel column-chromatography to give 8 - chloro-1-methyl-6 - phenyl - 4H - s - triazolo [4,3 - a] [1,4] benzodiazepine. Recrystallisation from a mixture of acetone and *n*-hexane affords colourless needles. Melting point: 225°C to 226°C.

Elementary analysis $C_{17}H_{13}ClN_5$.

Calculated	C 66.13, H 4.24, N 18.15	
Found	C 66.39, H 4.08, N 18.07	105

Example 8

To a solution of 2.84 parts of 7 - chloro - 2 - hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine in 50 parts by volume of chloroform are added 10 parts of ethyl orthoacetate and 4 parts of *p*-toluenesulphonic acid. The solution is left standing at room temperature for 6 hours and heated for a while on a water-bath to complete the reaction. The mixture is washed with saturated aqueous sodium bicarbonate, then with water and dried over anhydrous sodium sulphate. After evaporation of the solvent, the residue is treated in a similar manner to Example 7 to give 8-chloro-1 - methyl - 6 - phenyl - 4H - s - triazolo

[4,3a][1,4] benzodiazepine as colourless needles. Melting point: 224°C. to 225°C.

The product obtained is identical with the product prepared in Example 7.

5

Example 9

To a suspension of 2.84 parts of 7-chloro-2-hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine in 50 parts by volume of acetic anhydride is added 1 part by volume of concentrated sulphuric acid. The resulting solution is left standing at room temperature for 1 hour, poured in ice-water, neutralised with sodium bicarbonate and extracted with methylene chloride. The methylene chloride extract is washed with water and dried over anhydrous sodium sulphate, followed by evaporation of the solvent. The residue is recrystallised from a mixture of acetone and *n*-hexane to give 8 - chloro - 1 - methyl - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benbodiazepine as colourless needles. Melting point: 224°C to 225°C.

10

The product obtained is identical with the product prepared in Examples 7 and 8.

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Example 10

To a solution of 2.84 parts of 7 - chloro - 2-hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine in 60 parts by volume of chloroform are added 2.46 parts of ethyl acetimidate hydrochloride. The mixture is stirred for 8 hours, and then aqueous sodium bicarbonate is added so as to neutralise the mixture. The chloroform layer is separated, washed with water and dried over anhydrous sodium sulphate, followed by evaporation of the solvent. The residue is recrystallised from ethyl acetate to give 8 - chloro - 1 - methyl - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine as colourless needles. Melting point: 225°C to 226°C.

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The product obtained is identical with the product prepared in Examples 7, 8 and 9.

25

Example 11

A mixture of 2.8 parts of 7 - chloro - 2-hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine, 2.8 parts of acetamidine hydrochloride and 2.5 parts of 2-methylimidazole is fused with heating at 160°C, for 10 minutes. Water is added to the mixture, followed by extraction with methylene chloride. The methylene chloride layer is washed with water and dried over sodium sulphate. The solvent is evaporated, whereby 8-chloro-1-methyl-6-phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine is yielded. Recrystallisation from ethyl acetate yields colourless needles melting at 223°C to 225°C.

30

The product obtained is identical with the product prepared in Examples 7 to 10.

35

Example 12

A mixture of 2.8 parts of 7 - chloro - 2-

hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine; 2.8 parts of acetamidine hydrochloride, 2.5 parts of 2-methylimidazole and 100 parts by volume of chloroform is stirred at room temperature for 24 hours. The chloroform layer is washed with water, dried over sodium sulphate and the solvent is evaporated. After treating the residue with diethyl ether, the resulting crystals are subjected to extraction with hot methanol. Evaporation of the methanol gives 2 - (α - aminoethylidene) hydrazino - 7 - chloro - 5 - phenyl - 3H - 1,4-benzodiazepine as crystals. Recrystallisation from acetone yields pale yellow needles melting at 203°C to 205°C (effervescence).

65

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Elementary analysis $C_{17}H_{16}ClN_5$

Calculated	C 62.67,	H 4.95,	N 21.50
Found	C 62.99,	H 4.84,	N 21.53

3.5 Parts of the 2 - (α - aminoethylidene) hydrazino - 7 - chloro - 5 - phenyl - 3H - 1,4-benzodiazepine thus prepared is heated on an oil bath at 200°C. for 10 minutes, whereby it melts with foaming and is then solidified. Recrystallisation from ethyl acetate yields 8-chloro - 1 - methyl - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine as colourless needles melting at 225.5°C to 226.5°C.

80

85

The product obtained is identical with the product prepared in Examples 7 to 11.

90

Example 13

To a solution of 1.4 parts of 7 - chloro - 2-hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine in 30 parts by volume of chloroform is added with stirring 0.47 part by volume of acetic anhydride. The mixture is stirred for 1 hour and washed with a saturated aqueous solution of sodium bicarbonate and then with water. The chloroform layer is dried over sodium sulphate and the solvent is evaporated. Addition of methanol yields 2-(2-acetylhydrazino) - 7 - chloro - 5 - phenyl - 3H - 1,4 - benzodiazepine as white crystals. Recrystallisation from a mixture of chloroform and methanol yields powdery crystals melting at 202°C to 204°C (effervescence).

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100

105

Elementary analysis $C_{17}H_{16}ClN_4O$

Calculated	C 62.48,	H 4.63,	N 17.15
Found	C 62.38,	H 4.44,	N 17.23

110

3.3 Parts of the 2 - (2 - acetylhydrazino) - 7 - chloro - 5 - phenyl - 3H - 1,4 - benzodiazepine thus prepared is heated at 215°C for 10 minutes under mildly reduced pressure. The fused substance is recrystallised from ethyl acetate to yield 8 - chloro - 1 - methyl - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine as colourless needles melting at 225°C to 226°C.

115

The product obtained is identical with the product prepared in Examples 7 to 12.

120

Example 14

A suspension of 3.3 parts of 2 - (2 - acetylhydrazino) - 7 - chloro - 5 - phenyl - 3H - 1,4-benzodiazepine prepared as an intermediate in Example 13 in 20 parts by volume of pyridine is refluxed, whereby the crystals are gradually dissolved. After 2 hours the solvent is evaporated under reduced pressure. The residue is recrystallised from a mixture of acetone and *n*-hexane to yield 8 - chloro - 1-methyl - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine as colourless needles melting at 224°C to 225°C.

The product obtained is identical with the product prepared in Examples 7 to 13.

Example 15

To a mixture of 1.4 parts of 7 - chloro - 2-hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine (prepared in Example 1 of copending divisional application No. 20561/72) (Serial No. 1298365), 50 parts by volume of ethanol and 4 parts by volume of ethyl orthopropionate is added 0.5 part by volume of concentrated sulphuric acid. The mixture is stirred for 30 minutes at room temperature and then treated in a similar manner to Example 3, whereby 8 - chloro - 1 - ethyl - 6-phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine is yielded as crystals. Recrystallisation from acetone yields colourless prisms melting at 229°C. to 230°C.

Elementary analysis $C_{18}H_{15}ClN_4$

Calculated C 66.97, H 4.68, N 17.36
Found C 67.18, H 4.48, N 17.53

Example 16

To a solution of 1.4 parts of 7 - chloro - 2-hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine (prepared in Example 1 of copending divisional application No. 20561/72) (Serial No. 1298365) in 30 parts by volume of chloroform is added with stirring 0.65 part by volume of propionic anhydride. The mixture is stirred for 1 hour, washed with a saturated aqueous solution of sodium bicarbonate then with water, and dried over sodium sulphate. After evaporation of the chloroform, methanol is added to the residue, whereby 7 - chloro - 5 - phenyl - 2 - (2 - propionylhydrazino) - 3H - 1,4 - benzodiazepine is yielded as crystals. Recrystallisation from a mixture of chloroform and methanol yields colourless prisms melting at 186°C. to 187°C. (effervescence).

Elementary analysis $C_{18}H_{17}ClN_4O$

Calculated C 63.43, H 5.03, N 16.44
Found C 63.54, H 4.88, N 16.70

Under mildly reduced pressure, 3.4 parts of the 7 - chloro - 5 - phenyl - 2 - (2 - propionylhydrazino) - 3H - 1,4 - benzodiazepine thus prepared are heated at 195°C for 15 minutes.

The fused substance is recrystallised from acetone to yield 8 - chloro - 1 - ethyl - 6-phenyl - 4H - s - triazolo[4,3 - a][1,4] benzodiazepine as colourless prisms melting at 229°C to 230°C.

The product obtained is identical with the product prepared in Example 15.

Example 17

To a mixture of 2.85 parts of 7 - chloro - 2-hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine, 50 parts by volume of chloroform and 2 parts by volume of triethylamine, a solution of 1.6 parts of enanthyl chloride in 20 parts by volume of diethyl ether is gradually added with ice-cooling. The mixture is stirred for a while to complete the reaction. After evaporation of the solvent under reduced pressure, the residue is treated with methanol to yield 7 - chloro - 2 - (2 - enanthylhydrazino) - 5 - phenyl - 3H - 1,4 - benzodiazepine as crystals. Recrystallisation from a mixture of dimethylformamide and water yields colourless needles melting at 205°C. to 206°C. (effervescence).

Elementary analysis $C_{22}H_{23}ClN_4O$

Calculated C 66.57, H 6.35, N 14.12
Found C 66.43, H 6.24, N 14.29

A mixture of 1.98 parts of 7 - chloro - 2-(2 - enanthylhydrazino) - 5 - phenyl - 3H - 1,4 - benzodiazepine thus prepared and 30 parts of polyphosphoric acid is heated at 170°C to 180°C for 2 hours. 200 parts by volume of ice-water are added to the mixture and the resulting solution is neutralised with concentrated aqueous ammonia with ice-cooling, followed by extraction with chloroform. The chloroform layer is washed with water, dried over sodium sulphate and the solvent is evaporated. The residue is recrystallised from aqueous acetone to yield 8 - chloro - 1 - hexyl-6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine as colourless plates melting at 75°C to 78°C. (sintering).

Elementary analysis $C_{22}H_{23}ClN_4 \cdot 2H_2O$

Calculated C 63.68, H 6.56, N 13.50
Found C 63.71, H 6.15, N 13.60

The product obtained is further dried under reduced pressure to yield the compound containing $1/4H_2O$ sintered at 61°C. to 63°C.

Example 18

A suspension of 4 parts of 7 - chloro - 2-(2 - enanthylhydrazino) - 5 - phenyl - 3H - 1,4-benzodiazepine prepared as intermediate in Example 17 in 20 parts by volume of pyridine is refluxed for about 3 hours. After evaporation of pyridine, water is added to the residue, whereby 8 - chloro - 1 - hexyl - 6-phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine is yielded at crystals. Re-

crystallisation from aqueous acetone yields colourless flakes melting at 75°C. to 78°C. (sintering).

- 5 The product obtained is identical with the product prepared in Example 17.

Example 19

- 10 To a solution of 1.4 parts of 7 - chloro - 2 - hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine, (prepared in Example 1 of copending application No. 20561/72) (Serial No. 1298365); in 25 parts by volume of tetrahydrofuran is added 0.62 part by volume of benzoyl chloride, and the mixture is stirred at room temperature for 2 hours to complete the reaction. The reaction mixture is neutralised with a saturated aqueous solution of sodium bicarbonate. The resulting white precipitate is separated, washed with water and then with methanol, and dried, whereby 20 2 - (2 - benzoylhydrazino) - 7 - chloro - 5 - phenyl - 3H - 1,4 - benzodiazepine is yielded as crystals. Recrystallisation from a mixture of chloroform and methanol yields white needles melting at 207°C to 208°C (effervescence). 25

Elementary analysis $C_{22}H_{17}ClN_4O$

Calculated C 67.95, H 4.41, N 14.41
Found C 67.87, H 4.20, N 14.49

- 30 A mixture of 38.8 parts of 2 - (2 - benzoylhydrazino) - 7 - chloro - 5 - phenyl - 3H - 1,4 - benzodiazepine thus prepared and 400 parts of polyphosphoric acid is heated at 150°C for 1.5 hours. The mixture is treated in a similar manner to Example 17, whereby 35 8 - chloro - 1,6 - diphenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine is yielded as crystals. Recrystallisation from ethyl acetate yields colourless needles melting at 191°C. to 192°C.

40 Elementary analysis $C_{22}H_{17}ClN_4$

Calculated C 71.25, H 4.08, N 15.11
Found C 71.11, H 4.10, N 14.98

Example 20

- 45 Under mildly reduced pressure 3.9 parts of 2 - (2 - benzoylhydrazino) - 7 - chloro - 5 - phenyl - 3H - 1,4 - benzodiazepine as prepared as an intermediate in Example 19 are fused with heating at 215°C. for about 15 minutes until foaming has ceased. Recrystallisation of the fused substance from ethyl acetate yields 8 - chloro - 1,6 - diphenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine as colourless needles melting at 193°C. to 194°C. 50

- 55 The product obtained is identical with the product prepared in Example 19.

Example 21

A solution of 1.4 parts of 7 - chloro - 2 - hydrazino - 5 - phenyl - 3H - 1,4 - benzo-

diazepine and 1.8 parts of ethyl benzimidate hydrochloride in 30 parts by volume of chloroform is stirred at room temperature for 24 hours and then washed with water. The chloroform layer is dried over sodium sulphate and the solvent is evaporated. Treatment of the residue with diethyl ether yields 8 - chloro - 1,6 - diphenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine as crystals. Recrystallisation from a mixture of ethyl acetate and *n*-hexane yields colourless needles melting at 192°C. to 193.5°C. 60 65 70

The product obtained is identical with the product prepared in Examples 19 and 20.

Example 22

In a similar manner to Example 17, a solution of 0.85 part of phenylacetyl chloride in 10 parts by volume of diethyl ether is added to a mixture of 1.4 parts of 7 - chloro - 2 - hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine, 1 part by volume of triethylamine and 25 parts by volume of chloroform. The whole mixture is stirred for 45 minutes, whereby 7 - chloro - 2 - (2 - phenylacetylhydrazino) - 5 - phenyl - 3H - 1,4 - benzodiazepine is yielded as crystals. Recrystallisation from a mixture of dimethylformamide and water yields colourless fine prisms melting at 220°C. to 221°C. (effervescence). 75 80 85

Elementary analysis $C_{23}H_{19}ClN_4O$

Calculated C 68.57, H 4.75, N 13.91
Found C 68.72, H 4.79, N 13.71 90

A mixture of 4 parts of 7 - chloro - 2 - (2 - phenylacetylhydrazino) - 5 - phenyl - 3H - 1,4 - benzodiazepine thus prepared and 50 parts of polyphosphoric acid is heated at 180°C. for 2 hours. The mixture is treated in a similar manner to Examples 21 and 24, whereby 95 1 - benzyl - 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine is yielded. Recrystallisation from ethyl acetate yields colourless pillars melting at 190°C. to 192°C. 100

Elementary analysis $C_{23}H_{19}ClN_4$

Calculated C 71.78, H 4.45, N 14.56
Found C 72.07, H 4.34, N 14.74

Recrystallisation from methanol yields colourless needles melting at 101°C to 103°C. (effervescence). 10

Elementary analysis $C_{23}H_{19}ClN_4 \cdot CH_3OH$

Calculated C 69.14, H 5.08, N 13.44
Found C 69.31, H 5.02, N 13.59 11

Example 23

4 Parts of 7 - chloro - 2 - (2 - phenylacetylhydrazino) - 5 - phenyl - 3H - 1,4 - benzodiazepine prepared as intermediate in Example 22 are fused with heating at 230°C. for 10 minutes under mildly reduced pressure until 11

foaming has ceased. Recrystallisation of the fused substance from ethyl acetate yields 1-benzyl - 8 - chloro - 6 - phenyl - 4H - s-triazolo [4,3-a][1,4] benzodiazepine as colourless prisms melting at from 191°C. to 192°C.

The product obtained is identical with the product prepared in Example 22.

Example 24

- 10 To a suspension of 1.6 parts of 7-chloro-2-hydrazino - 5 - (p - methoxyphenyl) - 3H-1,4-benzodiazepine (prepared in Example 2 of copending divisional application No. 20561/72) (Serial No. 1298365) in 50 parts by volume of ethanol are added 3.0 parts by volume of ethyl orthoformate and 0.5 part by volume of concentrated sulphuric acid is then added dropwise with stirring. The mixture is stirred for a while and then neutralised with an aqueous solution of sodium bicarbonate, followed by evaporation of the solvent. Water is added to the residue, whereby 8 - chloro - 6 - (p - methoxyphenyl) - 4H - s - triazolo [4,3-a][1,4] benzodiazepine is yielded as crystals. Recrystallisation from acetone and then from ethyl acetate yields pale yellow flakes melting at 216°C to 217°C.

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

- 30 Calculated C 62.87, H 4.03, N 17.25
Found C 62.98, H 3.95, N 17.57

Example 25

- 35 To a mixture of 2.1 parts of 7 - chloro - 2-hydrazino - 5 - (p - methoxyphenyl) - 3H-1,4-benzodiazepine, (prepared in Example 2 of copending divisional application No. 20561/72) (Serial No. 1298365), 4.33 parts of ethyl orthoacetate and 60 parts by volume of ethanol is added dropwise 0.75 part by volume of concentrated sulphuric acid. The mixture is stirred for about 15 minutes. After completion of the reaction, the reaction mixture is neutralised with a saturated aqueous solution of sodium bicarbonate, whereby 8-chloro - 1 - methyl - 6 - (p - methoxyphenyl)-4H - s - triazolo[4,3 - a][1,4]benzodiazepine is yielded as crystals. Recrystallisation from a mixture of methanol and chloroform yields colourless needles melting at 268°C. to 269°C.

Elementary analysis $C_{18}H_{15}ClN_4O$

- 50 Calculated C 63.81, H 4.46, N 16.54
Found C 63.76, H 4.31, N 16.58

Example 26

- 55 To a mixture of 1 part of 2 - hydrazino - 5-phenyl - 3H - 1,4 benzodiazepine, (prepared in Example 3 of copending divisional application No. 20561/72) (Serial No. 1298365), 2 parts by volume of ethyl orthoformate and 20 parts by volume of ethanol, 0.44 part by volume of concentrated sulphuric acid is added dropwise with ice-cooling. The mixture is

stirred at room temperature for 30 minutes and neutralised with saturated aqueous sodium bicarbonate. The resulting oily substance is extracted with methylene chloride. The methylene chloride layer is washed with water and dried over sodium sulphate and the solvent is evaporated, whereby 6 - phenyl-4H - s - triazolo [4,3 - a][1,4] benzodiazepine is yielded as crystals. Recrystallisation from a mixture of acetone and n-hexane yields colourless needles melting at 195°C. to 196°C.

Elementary analysis $C_{16}H_{12}N_4$

Calculated C 73.83, H 4.65, N 21.53
Found C 73.71, H 4.37, N 21.21

The compound may be obtained as polymorphic pillars melting at 201°C. to 202°C. by recrystallisation from the same solvent and its elementary analytical data coincide with the calculated value for $C_{16}H_{12}N_4$.

Example 27

The same procedure as in Example 26 is repeated except that 4 parts by volume of ethyl orthoacetate are employed instead of ethyl orthoformate, whereby 1 - methyl - 6-phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine is yielded. Recrystallisation from a mixture of methanol and ethyl acetate yields colourless prisms melting at 226°C. to 227°C.

Elementary analysis $C_{17}H_{14}N_4$

Calculated C 74.43, H 5.14, N 20.43
Found C 74.70, H 5.17, N 20.41

Example 28

To a mixture of 3.2 parts of 2-hydrazino-5 - phenyl - 7 - trifluoromethyl - 3H - 1,4-benzodiazepine (prepared in Example 4 of copending divisional application No. 20561/72) (Serial No. 1298365), 8.5 parts of ethyl orthoformate and 50 parts by volume of chloroform are added dropwise 7.6 parts of p-toluenesulphonic acid at a temperature below 10°C. The mixture is stirred at room temperature for 2.5 hours. After completion of the reaction, the reaction mixture is neutralised with a saturated aqueous solution of sodium bicarbonate. The chloroform layer is separated, washed with water and dried over sodium sulphate. Evaporation of the solvent yields 6 - phenyl - 8 - trifluoromethyl - 4H-s - triazolo [4,3 - a][1,4] benzodiazepine as crystals. The crystals are dissolved in ethanol and the insoluble material is removed by filtration. The filtrate is concentrated and recrystallised from ethyl acetate to give colourless flakes. Melting point: 258°C. to 260°C.

Elementary analysis $C_{17}H_{11}F_3N_4$

Calculated C 62.19, H 3.38, N 17.07
Found C 61.99, H 3.46, N 16.89

Example 29

To a mixture of 9.5 parts of 2-hydrazino-5-phenyl-7-trifluoromethyl-3H-1,4-benzodiazepine (prepared in Example 4 of copending divisional application No. 20561/72) (Serial No. 1298365), 29 parts of ethyl orthoacetate and 150 parts by volume of chloroform are added dropwise 23 parts of *p*-toluenesulphonic acid with stirring under ice-cooling below 10°C and then the mixture is stirred at room temperature for 7 hours. After completion of the reaction, the reaction mixture is neutralised with a saturated aqueous solution of sodium bicarbonate and the chloroform layer is separated, washed with water and dried over sodium sulphate. After evaporation of the solvent, the residue is treated with a mixture of benzene and isopropyl ether, whereby 1-methyl-6-phenyl-8-trifluoromethyl-4H-s-triazolo [4,3-a][1,4] benzodiazepine is yielded as crystals containing benzene of crystallisation. Recrystallisation from a mixture of benzene and *n*-hexane yields colourless needles melting at 129°C. to 130°C (sintering), 133°C. to 134°C (effervescence).

Elementary analysis $C_{15}H_{12}F_3N_4 \cdot 1/3C_6H_6$

Calculated C 65.21, H 4.10, N 15.21
Found C 65.26, H 4.20, N 14.81

Recrystallisation from aqueous acetone yields colourless needles containing 1/5H₂O and melting at 112°C. to 113°C. (sintering).

Elementary analysis $C_{18}H_{13}F_3N_4 \cdot 1/5H_2O$

Calculated C 62.49, H 3.90, N 16.20
Found C 62.53, H 4.08, N 16.42

Example 30

To a mixture of 5.3 parts of 2-hydrazino-7-methyl-5-phenyl-3H-1,4-benzodiazepine (prepared in Example 5 of copending divisional application No. 20561/72) (Serial No. 1298365), 14.8 parts of ethyl orthoformate and 150 parts by volume of ethanol are added dropwise, 4 parts of concentrated sulphuric acid under ice-cooling. The whole mixture is stirred for about 30 minutes and neutralised with a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The chloroform layer is washed with water and dried over sodium sulphate. After evaporation of the solvent, the residue is treated with *n*-hexane, whereby 8-methyl-6-phenyl-4H-s-triazolo [4,3-a][1,4] benzodiazepine is yielded as crystals. Recrystallisation from ethyl acetate yields pale yellow prisms melting at 177°C. to 178°C.

Elementary analysis $C_{17}H_{14}N_4$

Calculated C 74.43, H 5.14, N 20.43
Found C 74.30, H 5.15, N 20.14

Example 31

The same procedure as Example 30 is repeated except that 16.2 parts of ethyl orthoacetate are employed instead of ethyl orthoformate, whereby 1,8-dimethyl-6-phenyl-4H-s-triazolo [4,3-a][1,4] benzodiazepine is yielded as crystals. Recrystallisation from ethyl acetate yields colourless needles melting at 211°C. to 211.5°C.

Elementary analysis $C_{18}H_{16}N_4$

Calculated C 74.97, H 5.59, N 19.43
Found C 74.93, H 5.42, N 19.73

Example 32

To a mixture of 2.8 parts of 2-hydrazino-7-methoxy-5-phenyl-3H-1,4-benzodiazepine (prepared in Example 6 of copending divisional application No. 20561/72) (Serial No. 1298365), 7.4 parts of ethyl orthoformate and 100 parts by volume of ethanol are added 2 parts of concentrated sulphuric acid with stirring and ice-cooling. The mixture is stirred at room temperature for about 45 minutes to complete the reaction. After evaporation of the solvent under reduced pressure, the residue is neutralised with a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The chloroform layer is washed with water and dried over sodium sulphate. Evaporation of the solvent under reduced pressure leaves 8-methoxy-6-phenyl-4H-s-triazolo [4,3-a][1,4] benzodiazepine as crystals. Recrystallisation from ethyl acetate yields pale yellow prisms melting at 209°C. to 210°C.

Elementary analysis $C_{17}H_{14}N_4O$

Calculated C 70.33, H 4.86, N 19.30
Found C 70.23, H 4.93, N 19.15

Example 33

The same procedure as Example 32 is repeated except that 8 parts of ethyl orthoacetate are employed instead of the ethyl orthoformate, whereby 1-methyl-8-methoxy-6-phenyl-4H-s-triazolo [4,3-a][1,4] benzodiazepine is yielded as crystals. Recrystallisation from ethyl acetate yields pale yellow prisms melting at 196°C. to 197°C.

Elementary analysis $C_{18}H_{16}N_4O$

Calculated C 71.03, H 5.30, N 18.41
Found C 71.16, H 5.44, N 18.21

Example 33

2-Hydrazino-7-nitro-5-phenyl-3H-1,4-benzodiazepine prepared from 5.6 parts of 2-amino-7-nitro-5-phenyl-3H-1,4-benzodiazepine (in a similar manner to Example 7 of copending application No. 20561/72) (Serial No. 1298365), is dissolved in a mixture of 20 parts by volume of ethyl orthoformate and 100 parts by volume of chloroform, followed by the addition of 10

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parts of *p*-toluenesulphonic acid. The whole mixture is left standing at room temperature for 1 hour with occasional shaking. After completion of the reaction, the solution is washed with a saturated aqueous solution of sodium bicarbonate, then with water, and dried over sodium sulphate. After evaporation of the solvent, the residue is treated with ethyl acetate, whereby 8 - nitro - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine is yielded as crystals. Recrystallisation from tetrahydrofuran yields pale yellow needles melting at 271°C to 272°C.

Elementary analysis $C_{16}H_{11}N_5O_2$
15 Calculated C 62.94, H 3.63, N 22.94
Found C 63.07, H 3.75, N 23.39

Example 34

The same procedure as Example 33 is repeated except that 20 parts by volume of ethyl orthoacetate are employed instead of the ethyl orthoformate, whereby 1 - methyl - 8 - nitro - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine is yielded as yellow crystals. Recrystallisation from acetone yields yellow prisms melting at 227°C. to 229°C.

Elementary analysis $C_{17}H_{13}N_5O_2$
Calculated C 63.94, H 4.10, N 21.93
Found C 64.11, H 4.00, N 21.69

Example 35

To a mixture of 1.7 parts of 7 - chloro - 2 - hydrazino - 3 - isobutyl - 5 - phenyl - 3H - 1,4-benzodiazepine (prepared in Examples 8 and 11 of our copending application No. 20561/72) (Serial No. 1298365), 3.7 parts of triethyl orthoformate and 40 parts by volume of ethanol is added 1 part of concentrated sulphuric acid with stirring and ice-cooling. The mixture is stirred for about 20 minutes at room temperature. After completion of the reaction, the mixture is neutralised with sodium bicarbonate, followed by extraction with chloroform. The chloroform layer is washed with water and dried over sodium sulphate. After evaporation of the solvent, the residue is treated with *n*-hexane, whereby 8 - chloro - 4 - isobutyl - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine is yielded as pale yellow crystals. Recrystallisation from a mixture of benzene and *n*-hexane yields colourless needles melting at 140.5°C. to 141.5°C.

Elementary analysis $C_{20}H_{19}ClN_4$
Calculated C 68.47, H 5.46, N 15.97
Found C 68.56, H 5.30, N 16.11

Example 36

To a solution of 3 parts of 7 - chloro - 2 - hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N-oxide, prepared in Example 12 of our copending application No. 20561/72,

(Serial No. 1298365), in 60 parts by volume of chloroform are added 7.4 parts of ethyl orthoformate and then 1.1 parts by volume of concentrated sulphuric acid are added dropwise. The resulting mixture is stirred for 20 minutes, followed by neutralisation with saturated aqueous sodium bicarbonate. The chloroform layer is washed and dried over sodium sulphate. Evaporation of the solvent leaves 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine 5N-oxide as crystals. Recrystallisation from a mixture of methanol and chloroform (1:1 by volume) yields colourless needles melting at 267°C to 268°C (decomposition).

Elementary analysis $C_{16}H_{11}ClN_5O$
Calculated C 61.74, H 3.57, N 18.03
Found C 61.87, H 3.26, N 17.92

Example 37

To a mixture of 3 parts of 7 - chloro - 2 - hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N-oxide as prepared in Example 12 of copending application No. 20561/72 (Serial No. 1298365) and 20 parts by volume of formamide are added dropwise 1.1 parts by volume of concentrated sulphuric acid and the mixture is stirred for 4 hours. After completion of the reaction, the mixture is neutralised with a saturated aqueous solution of sodium bicarbonate. The resulting crystals of 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine 5N-oxide are separated by filtration and recrystallised from chloroform to give colourless needles melting at 267°C. to 269°C. (decomposition).

The product obtained is identical with the product prepared in Example 36.

Example 38

A solution of 3 parts of 7 - chloro - 2 - hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N-oxide as prepared in Example 12 of copending application No. 20561/72 (Serial No. 1898365) in 20 parts by volume of 99% formic acid is allowed to stand overnight at room temperature and the solvent is distilled off. Neutralisation with saturated aqueous sodium bicarbonate yields 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine 5N-oxide as crystals. Recrystallisation from chloroform yields colourless crystals, melting at 268°C. to 269°C. (decomposition).

The product obtained is identical with the product prepared in Examples 44 and 45.

Example 39

To a suspension of 3 parts of 7 - chloro - 2 - hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N-oxide, prepared in Example 12 of copending application No. 20561/72 (Serial No. 1298365) and 8 parts of ethyl orthoacetate in 100 parts by volume of ethanol

- are added dropwise 1.1 parts by volume of concentrated sulphuric acid. The mixture is stirred for 15 minutes at room temperature, followed by evaporation of the solvent. The residue is neutralised with saturated aqueous sodium bicarbonate, whereby 8 - chloro - 1 - methyl - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine 5N-oxide is obtained as crystals. Recrystallisation from a mixture of methanol and diethyl ether yields colourless needles melting at 272°C. to 273°C. (decomposition).

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

- Calculated C 62.87, H 4.03, N 17.25
Found C 63.04, H 4.04, N 17.26

Example 40

- To a solution of 3 parts of 7 - chloro - 2 - hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N-oxide in 100 parts by volume of ethanol are added 2.5 parts of ethyl acetimidate hydrochloride. The mixture is refluxed for 30 minutes, followed by evaporation of the solvent. The residue is neutralised with a saturated aqueous solution of sodium bicarbonate, whereby 8 - chloro - 1 - methyl - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine 5N-oxide is obtained as crystals. Recrystallisation from a mixture of methanol and diethyl ether yields colourless needles melting at 268°C. to 269°C. (decomposition).

The product obtained is identical with the product prepared in Example 39.

Example 41

- A mixture of 3 parts of 7 - chloro - 2 - hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N-oxide, 4 parts of acetimidine hydrochloride and 5 parts of 2 - methylimidazole is fused with heating at 175°C. for 10 minutes. After cooling, water is added to the mixture, followed by extraction with chloroform. The chloroform layer is washed with water and dried over sodium sulphate. Evaporation of the solvent, followed by the addition of methanol to the residue yields 8 - chloro - 1 - methyl - 6 - phenyl - 4H - s - triazolo[4,3-a][1,4] benzodiazepine 5N-oxide as crystals. Recrystallisation from methanol yields colourless needles melting at 268°C. to 270°C. (decomposition).

The product obtained is identical with the product prepared in Examples 39 and 40.

Example 42

- 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 -

acetylhydrazino) - 7 - chloro - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N-oxide is yielded as crystals. Recrystallisation from a mixture of dimethylformamide and water yields fine needles melting at 256°C. to 258°C. (decomposition).

Elementary analysis $C_{17}H_{13}ClN_4O_2$

- 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 - acetylhydrazino) - 7 - chloro - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N-oxide thus prepared 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).

The product obtained is identical with the product prepared in Examples 39 to 41.

Example 43

To a suspension of 3 parts of 7 - chloro - 2 - hydrazino - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N-oxide, prepared in Example 12 of copending application No. 20561/72 (Serial No. 1298365) and 8.8 parts of ethyl orthopropionate in 100 parts by volume of ethanol are added dropwise 1.1 parts by volume of concentrated sulphuric acid. The whole mixture is stirred for 20 minutes, followed by evaporation of the solvent. The residue is neutralised with a saturated aqueous solution of sodium bicarbonate, whereby 8 - chloro - 1 - ethyl - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine 5N-oxide is crystallised out. Recrystallisation from methanol yields colourless flakes melting at 273°C. to 274°C. (decomposition).

Elementary analysis $C_{19}H_{15}ClN_4O$

- Calculated C 63.81, H 4.46, N 16.54
Found C 63.60, H 4.20, N 16.34

Example 44

To a suspension of 1.55 parts of 2 - hydrazino - 7 - nitro - 5 - phenyl - 3H - 1,4 - benzodiazepine 4N-oxide, prepared in Example 13 of copending application No. 20561/72 (Serial No. 1298365) 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 first 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]

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benzodiazepine 5N-oxide is yielded as yellow crystals. Recrystallisation from aqueous dimethylformamide yields yellow crystals melting at 274°C. to 275°C. (decomposition).

- 5 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

Example 45

- 10 A mixture of 3.1 parts of 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine 5N-oxide, prepared in Examples 36 to 38, 200 parts by volume of chloroform and 5.3 parts by volume of phosphorus trichloride is refluxed for 1 hour. After evaporation of the solvent, saturated aqueous bicarbonate is added to the residue, followed by extraction with chloroform. The chloroform layer is washed with water and dried over sodium sulphate. Evaporation of the solvent leaves 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine as crystals. Recrystallisation from ethyl acetate yields colourless flakes melting at 223.5°C. to 224.5°C.

- 25 The product obtained is identical with the product prepared in Examples 1 to 6.

Example 46

- 30 To 200 parts by volume of methanol are added 3.1 parts of 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine 5N-oxide and 1 part by volume of Raney nickel. The mixture is subjected to catalytic hydrogenation. After absorption of 1 mole equivalent of hydrogen, the catalyst is removed by filtration and the filtrate is concentrated to dryness. Recrystallisation of the residue from ethyl acetate yields 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine as colourless flakes melting at 222°C. to 223°C.

- 40 The product obtained is identical with the product prepared in Example 45.

Example 47

- 45 A mixture of 3.4 parts of 8 - chloro - 1 - ethyl - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine 5N-oxide, prepared in Example 43, 200 parts by volume of chloroform and 5.3 parts by volume of phosphorus trichloride is refluxed for 1.5 hours and the solvent is then evaporated. The residue is neutralised with a saturated aqueous solution of sodium bicarbonate and extracted with chloroform. The chloroform layer is washed with water and dried over sodium sulphate.
- 50 After evaporation of the solvent, the residue is treated with a mixture of acetone and petroleum ether, whereby 8 - chloro - 1 - ethyl - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine is obtained as crystals. Recrystallisation from acetone yields colourless granules melting at 229°C. to 230°C.
- 60

The product obtained is identical with the product prepared in Examples 15 and 16.

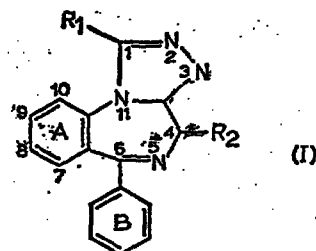
Example 48

To a suspension of 3.2 parts of 8 - nitro - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine 5N-oxide in 600 parts by volume of chloroform are added 20 parts by volume of phosphorus trichloride. The mixture is refluxed for 16 hours, followed by evaporation of the solvent. The residue is neutralised with a saturated aqueous solution of sodium bicarbonate and extracted with chloroform. The chloroform layer is washed with water, dried over sodium sulphate. After evaporation of the solvent, the residue is treated with ethanol, whereby 8 - nitro - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine is yielded as crystals. Recrystallisation from tetrahydrofuran yields pale yellow needles melting at 266°C. to 267°C.

The product obtained is identical with the product prepared in Example 33.

WHAT WE CLAIM IS:—

1. A compound of the general formula (I):



wherein R_1 is hydrogen or a hydrocarbon residue, R_2 is hydrogen or C_1 to C_6 alkyl and the rings A and B are unsubstituted, or substituted by one or more, identical or different, of halogen or nitro, trifluoromethyl, alkyl or alkoxy groups, the 5-oxide of the compound

and a pharmaceutically acceptable acid addition salt thereof.

2. A compound as claimed in claim 1 wherein R_1 is hydrogen, methyl, ethyl, hexyl, phenyl or benzyl.

3. A compound as claimed in claim 1 wherein R_2 is hydrogen or isobutyl.

4. 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine.

5. 8 - chloro - 1 - methyl - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine.

6. 8 - chloro - 1 - ethyl - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine.

7. 8 - chloro - 1 - hexyl - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine.

8. 8 - chloro - 1,6 - diphenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine.

9. 1 - benzyl - 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine.



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benzodiazepine 5N-oxide is yielded as yellow crystals. Recrystallisation from aqueous dimethylformamide yields yellow crystals melting at 274°C. to 275°C. (decomposition).

- 5 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

Example 45

- 10 A mixture of 3.1 parts of 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3 - a] [1,4] benzodiazepine 5N-oxide, prepared in Examples 36 to 38, 200 parts by volume of chloroform and 5.3 parts by volume of phosphorus trichloride is refluxed for 1 hour. After evaporation of the solvent, saturated aqueous bicarbonate is added to the residue, followed by extraction with chloroform. The chloroform layer is washed with water and dried over sodium sulphate. Evaporation of the solvent leaves 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3 - a] [1,4] benzodiazepine as crystals. Recrystallisation from ethyl acetate yields colourless flakes melting at 223.5°C. to 224.5°C.

- 25 The product obtained is identical with the product prepared in Examples 1 to 6.

Example 46

- 30 To 200 parts by volume of methanol are added 3.1 parts of 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3 - a] [1,4] benzodiazepine 5N-oxide and 1 part by volume of Raney nickel. The mixture is subjected to catalytic hydrogenation. After absorption of 1 mole equivalent of hydrogen, the catalyst is removed by filtration and the filtrate is concentrated to dryness. Recrystallisation of the residue from ethyl acetate yields 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3 - a] [1,4] benzodiazepine as colourless flakes melting at 222°C. to 223°C.

- 40 The product obtained is identical with the product prepared in Example 45.

Example 47

- 45 A mixture of 3.4 parts of 8 - chloro - 1 - ethyl - 6 - phenyl - 4H - s - triazolo [4,3 - a] [1,4] benzodiazepine 5N-oxide, prepared in Example 43, 200 parts by volume of chloroform and 5.3 parts by volume of phosphorus trichloride is refluxed for 1.5 hours and the solvent is then evaporated. The residue is neutralised with a saturated aqueous solution of sodium bicarbonate and extracted with chloroform. The chloroform layer is washed with water and dried over sodium sulphate.
- 50 After evaporation of the solvent, the residue is treated with a mixture of acetone and petroleum ether, whereby 8 - chloro - 1 - ethyl - 6 - phenyl - 4H - s - triazolo [4,3 - a] [1,4] benzodiazepine is obtained as crystals. Recrystallisation from acetone yields colourless granules melting at 229°C. to 230°C.

The product obtained is identical with the product prepared in Examples 15 and 16.

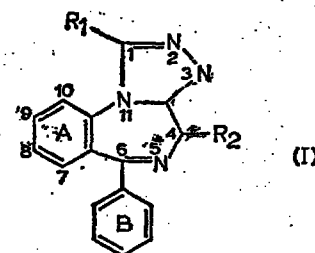
Example 48

- To a suspension of 3.2 parts of 8 - nitro - 6 - phenyl - 4H - s - triazolo [4,3 - a] [1,4] benzodiazepine 5N-oxide in 600 parts by volume of chloroform are added 20 parts by volume of phosphorus trichloride. The mixture is refluxed for 16 hours, followed by evaporation of the solvent. The residue is neutralised with a saturated aqueous solution of sodium bicarbonate and extracted with chloroform. The chloroform layer is washed with water, dried over sodium sulphate. After evaporation of the solvent, the residue is treated with ethanol, whereby 8 - nitro - 6 - phenyl - 4H - s - triazolo [4,3 - a] [1,4] benzodiazepine is yielded as crystals. Recrystallisation from tetrahydrofuran yields pale yellow needles melting at 266°C. to 267°C.

The product obtained is identical with the product prepared in Example 33.

WHAT WE CLAIM IS:—

1. A compound of the general formula (I):

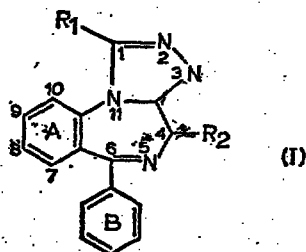


- wherein R_1 is hydrogen or a hydrocarbon residue, R_2 is hydrogen or C_1 to C_6 alkyl and the rings A and B are unsubstituted, or substituted by one or more, identical or different, of halogen or nitro, trifluoromethyl, alkyl or alkoxy groups, the 5-oxide of the compound and a pharmaceutically acceptable acid addition salt thereof.

2. A compound as claimed in claim 1 wherein R_1 is hydrogen, methyl, ethyl, hexyl, phenyl or benzyl.
3. A compound as claimed in claim 1 wherein R_2 is hydrogen or isobutyl.
4. 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3-a] [1,4] benzodiazepine.
5. 8 - chloro - 1 - methyl - 6 - phenyl - 4H - s - triazolo [4,3 - a] [1,4] benzodiazepine.
6. 8 - chloro - 1 - ethyl - 6 - phenyl - 4H - s - triazolo [4,3-a] [1,4] benzodiazepine.
7. 8 - chloro - 1 - hexyl - 6 - phenyl - 4H - s - triazolo [4,3-a] [1,4] benzodiazepine.
8. 8 - chloro - 1,6 - diphenyl - 4H - s - triazolo [4,3-a] [1,4] benzodiazepine.
9. 1 - benzyl - 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3-a] [1,4] benzodiazepine.

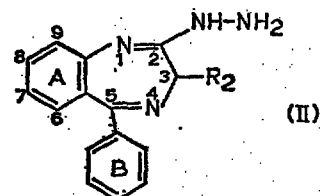


10. 8 - chloro - 6 - (p - methoxyphenyl)-4H-s-triazolo [4,3-a][1,4] benzodiazepine.
11. 8 - chloro - 1 - methyl - 6 - (p-methoxyphenyl) - 4H - s - triazolo [4,3-a][1,4] benzodiazepine.
- 5 12. 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine.
13. 1 - methyl - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine.
- 10 14. 6 - phenyl - 8 - trifluoromethyl - 4H-s-triazolo [4,3-a][1,4] benzodiazepine.
15. 1 - methyl - 6 - phenyl - 8 - trifluoromethyl - 4H - s - triazolo [4,3 - a][1,4] benzodiazepine.
- 15 16. 8 - methyl - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine.
17. 1,8 - dimethyl - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine.
18. 8 - methoxy - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine.
- 20 19. 1 - methyl - 8 - methoxy - 6 - phenyl-4H-s-triazolo [4,3-a][1,4] benzodiazepine.
20. 8 - nitro - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine.
- 25 21. 1 - methyl - 8 - nitro - 6 - phenyl-4H-s-triazolo [4,3-a][1,4] benzodiazepine.
22. 8 - chloro - 4 - isobutyl - 6 - phenyl-4H-s-triazolo [4,3-a][1,4] benzodiazepine.
23. 8 - chloro - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine 5N-oxide.
- 30 24. 8 - chloro - 1 - methyl - 6 - phenyl-4H - s - triazolo [4,3 - a][1,4] benzodiazepine 5N-oxide.
- 35 25. 8 - chloro - 1 - ethyl - 6 - phenyl - 4H-s-triazolo [4,3-a][1,4] benzodiazepine 5N-oxide.
26. 8 - nitro - 6 - phenyl - 4H - s - triazolo [4,3-a][1,4] benzodiazepine 5N-oxide.
- 40 27. A process for producing a compound of the general formula (I):

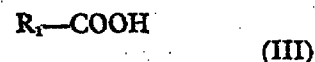


- 45 wherein R₁ is hydrogen or a hydrocarbon residue, R₂ is hydrogen or C₁-C₆ alkyl and the rings A and B are unsubstituted, or substituted by one or more, identical or different, of halogen or nitro, trifluoromethyl, alkyl or alkoxy groups, or its 5-oxide
- 50

which comprises allowing a compound of the general formula (II):

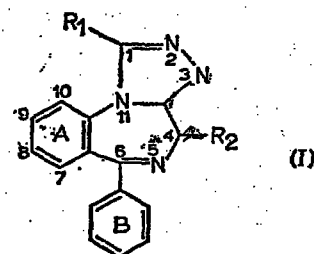


wherein R₂, A and B have the meanings given above, or its 4-oxide, to react with a carboxylic acid of the general formula (III):



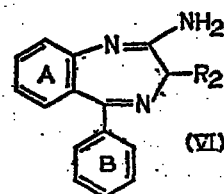
wherein R₁ has the meaning given above, or its reactive derivative, and, if required, subjecting the resulting compound (I) to reduction when the compound (I) carries an oxygen atom at the 5-position.

28. A process for producing a compound of the general formula (I):



wherein R₁ is hydrogen or a hydrocarbon residue, R₂ is hydrogen or C₁-C₆ alkyl and the rings A and B are unsubstituted, or substituted by one or more, identical or different, of halogen or nitro, trifluoromethyl, alkyl or alkoxy groups, or its 5-oxide

which comprises allowing a compound of the general formula (VI):



wherein R₂, A and B have the meanings given above, or its 4-oxide

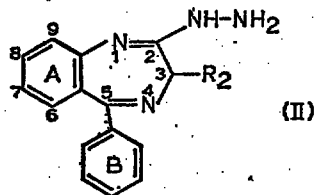


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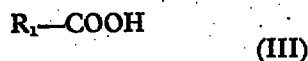
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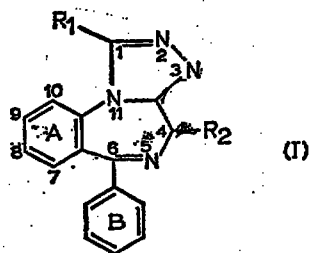
to react with hydrazine, whereby a compound of the general formula (II):



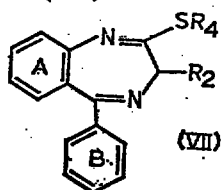
- 5 wherein R_2 , A and B have the meanings defined above, or its 4-oxide is produced, and allowing the compound (II) to react with a carboxylic acid of the general formula (III):



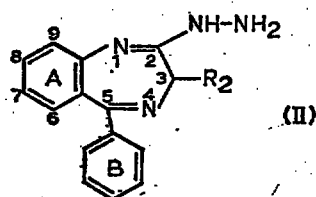
- 10 wherein R_1 has the meaning defined above, or its reactive derivative.
29. A process for producing a compound of the general formula (I):



- 15 wherein R_1 is hydrogen or a hydrocarbon residue and R_2 is hydrogen or C_1-C_6 alkyl, and the rings A and B are unsubstituted or substituted by one or more identical or different, of halogen or nitro, trifluoromethyl, alkyl or alkoxy groups,
20 which comprises allowing a compound of the general formula (VII):



- 25 wherein R_2 , A and B have the same meanings defined above, and R_4 is hydrogen, alkyl or aralkyl, to react with hydrazine, whereby a compound of the general formula (II):

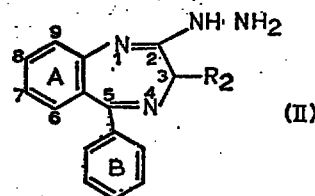


wherein R_2 , A and B have the meanings defined above, is produced, and allowing the compound (II) to react with a carboxylic acid of the general formula (III):

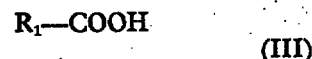


wherein R_1 has the meaning defined above, or its reactive derivative.

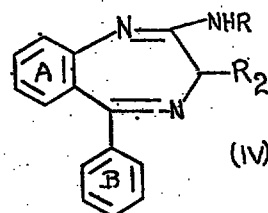
30. A process as claimed in any of claims 27 to 29 for preparing a compound of the general formula (I) as defined in claim 1 or the 5-oxide of a compound (I) wherein a 2-hydrazinobenzodiazepine derivative of the general formula (II):



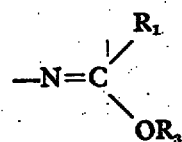
in which R_2 , A and B are as defined in claim 1, or its 4-oxide is reacted with a carboxylic acid of the general formula (III):



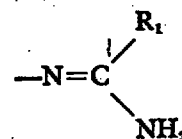
in which R_1 is hydrogen or a hydrocarbon residue, or its reactive derivative, wherein a compound of the general formula (IV)



in which R represents



or



in which R_3 is C_1 to C_2 alkyl and R_1 , R_2 , A and B are as defined in claim 1, or its 4-



oxide is isolated and then subjected to a ring-closure reaction to produce a compound of formula I or its 5-oxide.

5 31. A process for preparing a compound of the general formula (I) as defined in claim 1 wherein a compound of the general formula (IV) as defined in claim 30 subjected to a ring closure reaction.

10 32. A compound of the general formula (I) as defined in claim 1 substantially as herein described with reference to any of the specific examples and pharmaceutically acceptable acid addition salts thereof.

15 33. A process according to claim 27 substantially as herein described with reference

to any of the specific examples.

34. Compounds (I) as defined in claim 1 when made by a process as claimed in any of claims 27 to 31 and 33.

35. A pharmaceutical composition comprising a compound (I), its 5-oxide or a pharmaceutically acceptable acid addition salt thereof as claimed in any of claims 1 to 26, 32 and 34 together with a pharmaceutically acceptable carrier or diluent therefor.

ELKINGTON & FIFE,
Chartered Patent Agents,
52-54 High Holborn,
London, W.C.1.
Agents for the Applicants.

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ERRATUM

SPECIFICATION NO 1298364

Page 1, line 15, and page 13, line 87, Formula (I) should read

