

AMENDED SPECIFICATION

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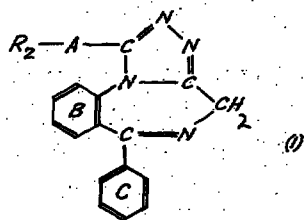


(54) DIAZEPINE DERIVATIVES AND A PROCESS FOR THEIR MANUFACTURE

(71) We, CIBA-GEIGY AG., a body corporate organised according to the laws of Switzerland, of 4002 Basle (R), Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention provides a diazepine derivatives.

The present invention relates to diazepine derivative having the general formula I



wherein
15 R_2 represents a hydroxy group, an alkoxy or alkanoyloxy group having from 1 to 6 carbon atoms, a mono- or di-arylmethoxy group, or a 2-oxacycloalkoxy group having from 5 to 7 ring members, and
20 A represents an alkylene group having from 1 to 3 carbon atoms
and wherein each of the rings B and C, independently of the other, may be unsubstituted or substituted by one substituent selected from halogen atoms up to and including the atomic number 35, trifluoromethyl groups, and alkyl and alkoxy groups having from 1 to 6 carbon atoms. The present invention also provides the 5-oxide of such a diazepine deriv-

ative as well as an acid addition salt, especially a physiologically tolerable acid addition salt, of said diazepine derivative.

As the alkoxy group, R_2 is, e.g. the n-propoxy, isopropoxy, n-butoxy, isobutoxy, n-pentyloxy, isopentyloxy, n-hexyloxy or isohexyloxy group, preferably, however, the methoxy or ethoxy group; as the alkanoyl group, R_2 is, e.g. the formyloxy, acetoxy, propionyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy, pivaloyloxy, or hexanoyloxy group; and as the monoarylmethoxy group, R_2 is, e.g. the benzyloxy, o-, m- or p-chlorobenzyloxy, o-, m- or p-methylbenzyloxy, o-, m- or p-methoxybenzyloxy or 3,4,5-trimethoxybenzyloxy group; as the diarylmethoxy group, R_2 is, especially, the diphenylmethoxy group. As the 2-oxacycloalkoxy group, R_2 is, e.g. the tetrahydrofuran - 2 - yloxy group (2 - oxa - cyclopentyloxy group), the 2 - oxocycloheptyloxy group and, especially, the tetrahydropyran - 2 - yloxy group. By an alkylene group A is meant any bivalent, saturated aliphatic hydrocarbon radical having 1 to 3 carbon atoms, i.e. the methylene, ethylidene, 1 - methylethylidene, ethylene, propylene or trimethylene group; of especial importance amongst these groups is the methylene group.

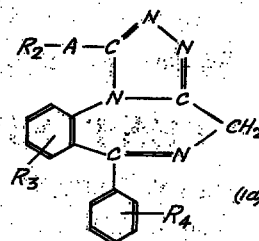
Halogen atoms as substituents of the rings B and C are fluorine, chlorine or bromine atoms, whilst suitable alkyl groups or alkoxy groups having 1 to 6 carbon atoms are, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert.butyl, n-pentyl, isopentyl, 2,2 - dimethylpropyl, n-hexyl or isohexyl groups; or methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, n-pentyloxy, isopentyloxy, 2,2-dimethylpropoxy, n-hexyloxy or isohexyloxy groups. A substituent of the ring

B is, especially, in the 8-position, and is preferably fluorine, bromine, the trifluoromethyl group, and especially chlorine. The ring B is preferably unsubstituted, or substituted by fluorine, chlorine or bromine in any desired position, especially, however, by fluorine or chlorine in the *o*-position.

The compounds of the general formula I, their 5-oxides and the corresponding physiologically tolerable acid addition salts possess useful pharmacological properties. They have a central depressant action, e.g. an anticonvulsive and antiaggressive action; they also inhibit somatic reflexes. The anticonvulsive effectiveness can be determined, e.g. in the electroshock test on the mouse with dosages of from ca. 2.0 mg/kg orally; in the strychnine-spasm test on the mouse with dosages of from ca. 1.5 mg/kg orally; and in the pentetrazole test on the mouse with dosages of from ca. 0.05 mg/kg orally. The antiaggressive effectiveness is evident from the suppression of the fighting reaction of the mouse after oral administration of dosages of from ca. 0.3 mg/kg, whilst the general suppression of the central nervous system is shown, e.g. from the anaesthetic-potentiating action after oral administration to the mouse; as well as from observation tests. Because of these and other properties, which can be assessed by selected standard tests [cp. W. Theobald and H. A. Kunz, *Arzneimittelforsch.* 13, 122 (1963), as well as W. Theobald et al., *Arzneimittelforsch.* 17, 561 (1967)], a compound of the general formula I or 5-oxide thereof, or a physiologically tolerable acid addition salt of a compound of the general formula I with an inorganic or organic acid is suitable as active substance for tranquillisers and for anticonvulsants, which may be used e.g. for the treatment of states of tension and agitation, as well as for the treatment of epilepsy.

Of especial importance are compounds of the general formula I wherein R_2 represents a hydroxy group especially compounds where R_2 represents a hydroxyl group and A represents a methylene group; amongst these compounds there should especially be mentioned those having a chlorine atom in the 8-position, particularly 6-phenyl-8-chloro-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-methanol, as well as 6-(*o*-fluorophenyl)- and 6-(*o*-chlorophenyl)-8-chloro-4H-s-triazolo[4,3-a][1,4]benzodiazepine-1-methanol.

Of especial interest are compounds of the general formula Ia



wherein

R_2 represents a hydroxy group, an alkoxy or alkanoyloxy group having from 1 to 6 carbon atoms or a mono- or di-arylmethoxy group,

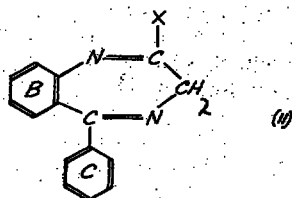
R_3 and R_4 , independently of each other, represent a hydrogen atom, a halogen atom up to and including the atomic number 35, a trifluoromethyl group or an alkyl or alkoxy group having from 1 to 6 carbon atoms, and A represents an alkylene group having from 1 to 3 carbon atoms; and 5-oxides thereof.

Preferred compounds of the general formula Ia are those compounds in which R_2 represents a hydroxy group or an alkanoyloxy group having from 1 to 6 carbon atoms, for example, compounds in which R_2 represents a hydroxy group and A represents a methylene group, and those compounds in which R_2 represents a di-arylmethoxy group or, preferably, a mono-arylmethoxy group, especially those in which A represents a methylene group. Amongst such groups of compounds there should especially be mentioned those in which R_3 represents a chlorine atom in the 8-position and R_4 has the meaning given above, but especially represents a hydrogen atom or a chlorine or fluorine atom in the ortho position.

Also of importance are the 5-oxides of preferred compounds of formulae I and Ia and acid addition salts, especially physiologically tolerable acid addition salts, of preferred compounds of formula I.

Diazepine derivatives of the general formula I and 5-oxides and acid addition salts thereof generally are useful as intermediates in the production of pharmaceutically active products. Especially, compounds wherein R_2 represents a mono- or di-aryl-methoxy group or a 2-oxacycloalkoxy group preferably having 5 to 7 ring members, especially the tetrahydropyran-2-yloxy group, are important, apart from the fact that they are themselves pharmacologically effective, as intermediates for the preparation of corresponding compounds wherein R_2 represents a hydroxyl group. Amongst these compounds

there are preferred, for example, those wherein A represents a methylene group, especially such in which, at the same time, ring B is substituted in the 8-position by a chlorine atom whilst preferably the ring C carries no substituent, or is substituted in the o-position by a fluorine or chlorine atom. 5-Oxides of compounds of the general formula I also have pharmacological activity, but their importance lies especially in their applicability as intermediates for the production of further pharmacologically effective substances. The present invention also provides a process for the preparation of a diazepine derivative of the general formula I wherein R_2 , R_3 , R_4 , A, B and C have the meanings given above with the exception that R_2 may not represent an alkanoyloxy group, or a 5-oxide thereof or an acid addition salt of such a derivative which comprises condensing the corresponding compound having the general formula II



wherein

X represents a mercapto group, an alkoxy or alkylthio group having 1 or 2 carbon atoms which may be activated by a substituent, or an unsubstituted or mono- or di-substituted amino group, and the rings B and C may be substituted as specified above, with a compound having the general formula III



wherein R_2' has the meaning given for R_2 above with the exception that it may not represent an alkanoyloxy group and A has the meaning given above.

An alkylthio or alkoxy group represented by X is the methylthio or ethylthio group, or the methoxy or ethoxy group. These groups may be activated by a substituent. Such activated groups are, e.g. the o- or p-nitrobenzylthio or the o- or p-nitrobenzyloxy group.

Suitable monosubstituted amino groups represented by X are, especially alkylamino groups having at most 3 carbon atoms e.g. the methylamino group, and aralkylamino groups e.g. the benzylamino group. A suitable disubstituted amino group represented by X is, especially a lower dialkylamino group having at most 4 carbon atoms, for example the dimethylamino group.

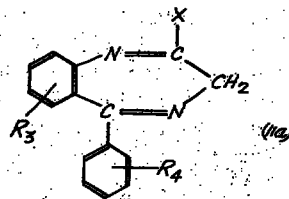
In addition to the foregoing, a diazepine

derivative having the formula I wherein R_2 represents a hydroxy group, or a 5-oxide thereof, or an acid addition salt thereof, may be prepared, in accordance with the present invention, by splitting the corresponding compound having the general formula I wherein R_2 represents a monoarylmethoxy, or diarylmethoxy group or a 2-oxacycloalkoxy group.

The present invention also provides a process for the production of a diazepine derivative having the general formula I wherein R_2 represents an alkanoyloxy group having from 1 to 6 carbon atoms, or a 5-oxide thereof or an acid addition salt thereof, which comprises acylating the corresponding compound having the general formula I wherein R_2 represents a hydroxy group.

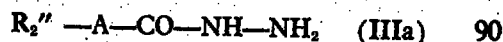
Starting materials wherein R_2 represents a hydroxy group may be prepared, e.g. according to any of the processes described herein.

Especially, the present invention provides a process for the preparation of a diazepine derivative having the general formula Ia or its 5-oxide which comprises condensing the corresponding compound having the general formula IIa



wherein

R_3 and R_4 have the meanings given above and X represents a mercapto or an alkoxy or alkylthio group having 1 to 2 carbon atoms which may be activated by a substituent, with a compound having the general formula IIIa



wherein

R_2'' represents a hydroxy group, an alkoxy group having from 1 to 6 carbon atoms or a mono- or di-arylmethoxy group, and A has the meaning given above,

when required splitting a diazepine derivative having the general formula Ia thus obtained wherein R_2 represents a mono- or di-arylmethoxy group, to produce a diazepine derivative having the general formula Ia wherein R_2 represents a hydroxy group, or acylating a diazepine derivative having the general formula Ia thus produced wherein R_2 represents a hydroxy group, to produce a diazepine derivative having the general formula Ia wherein R_2 represents an alkanoyloxy group having from 1 to 6 carbon atoms, and when required, oxidising a diazepine derivative having the general formula Ia thus obtained to produce its 5-oxide.

In the formula IIa X preferably represents a methoxy, ethoxy, methylthio, ethylthio, o- or p-nitrobenzylthio or o- or p-nitrobenzyloxy group. In the formula IIIa preferably R₂ represents a hydroxy group, an alkoxy group having from 1 to 6 carbon atoms or a monoarylmethoxy group.

Starting materials of the general formulae II and IIa are described in the literature, see, amongst others, L. H. Sternbach and E. Reeder, *J. Org. Chem.* 26, 1111 (1961). S. C. Bell et al., *J. Med. Chem.* 5, 63 (1962) and G. A. Archer and L. H. Sternbach, *J. Org. Chem.* 29, 231 (1964). Also described are compounds of the general formula III, such as, e.g. 2-benzyloxyacetic acid hydrazide and glycolic acid hydrazide [cp. Th. Curtius and N. Schwan, *J. prakt. Chem.* [2] 51, 364 (1895)]. Further compounds of the general formulae II, IIa, III and IIIa may be produced in analogous manner to known compounds. For example, starting materials of the general formula II having an unsubstituted or substituted amino group may be obtained by reduction of the corresponding 4-oxides described in the literature.

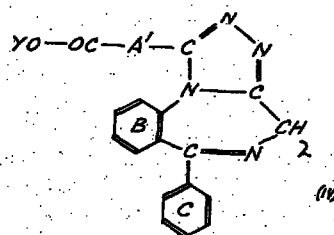
The above condensation reactions are preferably performed at a temperature in the range of from 80 to 180°C in an inert solvent. Suitable inert solvents are, for example, hydrocarbons e.g. toluene or xylenes, halogenated hydrocarbons e.g. chlorobenzene, ethers, e.g. diethylene glycol dimethyl ether, diethylene glycol diethyl ether or dioxane, amides, especially N,N,N',N'',N''',N''''-hexamethylphosphoric acid triamide, or N,N-dimethylacetamide, sulphoxides e.g. dimethylsulphoxide, and alcohols e.g. n-butanol. The reaction times are preferably in the range of from one hour to 24 hours.

The splitting of monoarylmethoxy or diarylmethoxy groups is preferably performed with the aid of hydrochloric acid, hydriodic acid, or especially hydrobromic acid. It is advantageous to use the hydrohalic acids in a solvent. Suitable solvents are carboxylic acids such, for example, as acetic acid. The reaction temperature is preferably in the range of from 20 to 150°C. The splitting of a 2-oxacycloalkoxy group, such as, e.g. the tetrahydropyran-2-yloxy group, is effected likewise by the action of acids, such as, e.g. hydrohalic acids, but usually under milder conditions. Splitting is performed, for example, by the action of diluted aqueous hydrochloric acid to which is added a water miscible organic solvent, such as, e.g. methanol, at a temperature in the range of from 50 to 100°C or at the boiling temperature of the reaction mixture. The starting materials for this process may be obtained e.g. according to the first described process for the production of compounds of the formula I.

The acylation of a compound wherein R₂ represents a hydroxy group may be carried

out, for example, by the reaction of the free hydroxy compound with an acid halide or acid anhydride derived from an aliphatic carboxylic acid having 1 to 6 carbon atoms. Acylation is preferably performed in an inert solvent, in the presence of a tertiary organic base such as, e.g. pyridine or triethylamine. Suitable as solvents are hydrocarbons such, for example, as benzene or toluene, halogenated hydrocarbons such, for example, as carbon tetrachloride or chloroform, or excess tertiary organic base. The reaction is suitably carried out at a temperature in the range of from 0 to 80°C.

According to a further aspect of the present invention there is provided a process for the preparation of a diazepine derivative having the general formula I wherein R₂ represents a hydroxy group and A represents a methylene, ethylene, trimethylene or propylene group, or a 5-oxide thereof, or an acid addition salt of such a derivative, which comprises reducing, by means of a complex hydride in an ethereal solvent, the corresponding compound having the general formula IV



wherein

Y represents a hydrocarbon radical having at most 8 carbon atoms, A' represents a direct bond or a methylene, ethylidene or ethylene group, and the rings B and C may be substituted as specified above.

In the compounds of the general formula IV, Y preferably represents an alkyl group having at most 4 carbon atoms.

The complex hydride employed in this reduction process is, e.g. lithium aluminium hydride, and the ethereal solvent is, e.g. tetrahydrofuran or diethyl ether. The reduction is performed, e.g. at a temperature in the range of from -15° to +20°C, preferably at ca. 0°.

Starting materials of the general formula IV may be produced in analogous manner to compounds of the general formula I by condensation of compounds of the general formula II with aliphatic dicarboxylic acid ester hydrazides, e.g. with oxalic acid methyl ester hydrazide or oxalic acid ethyl ester hydrazide, instead of with compounds of the general formula III.

A 5-oxide of a diazepine derivative may be prepared by oxidation of the diazepine derivative itself.

Suitable oxidising agents are preferably hydrogen peroxide or peroxy acids and the oxidation is effected e.g. at a temperature of from 0 to 70°. Suitable peroxy acids are, e.g. peroxyacetic acid or benzoperoxy acids such as benzoperoxy acid or, especially, m-chlorobenzoperoxy acid. The oxidising agent is preferably used in a solvent, e.g. peroxyacetic acid in acetic acid and benzoperoxy acid in a halogenated hydrocarbon such as methylene chloride or chloroform.

The compound of the general formula I obtained by the processes according to the invention may, if desired, be converted, in the usual manner, into an addition salt thereof within an inorganic or organic acid. For salt formation are used, e.g. hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, perchloric acid, methanesulphonic acid, ethanesulphonic acid or citric acid, preferably in the presence of a solvent such as, e.g. acetone, methanol, ethanol, ether, or mixtures thereof.

The compound of the general formula I or its 5-oxide, or the corresponding physiologically tolerable acid addition salt, is preferably administered orally or rectally. The daily dosage may vary between 0.01 and 2 mg/kg for warm-blooded animals. Suitable dosage units, such as dragées, tablets or suppositories, preferably contain from 0.5 to 25 mg of an active substance according to the invention, i.e. of a compound of the general formula I, of the 5-oxide thereof, or of a physiologically tolerable acid addition salt of the compound of formula I. The said dosage units may be prepared by the combination of the active substance with a solid pulverulent carrier such as lactose, saccharose, sorbitol, mannitol; a starch such as potato starch, maize starch or amylopectin, also laminaria powder or citrus pulp powder; cellulose derivative or gelatine, optionally with the addition of a lubricant such as magnesium stearate or calcium stearate, or a polyethylene glycol, to form tablets or dragée cores. The latter are coated e.g. with a concentrated sugar solution which may also contain, e.g. gum arabic, talcum and/or titanium dioxide, or with a lacquer dissolved in readily volatile organic solvents or solvent mixtures. A dyestuff may be added to these coatings, e.g. for identification of the various dosages of active substance. Further suitable dosage units for oral administration are hard gelatine capsules, as well as soft closed capsules made from gelatine and a softener such as glycerin. The former contain the active substance preferably as a granulate in admixture with lubricant such as talcum or magnesium stearate, and, optionally, stabiliser such as sodium metabisulphite or ascorbic acid.

The following directions serve to illustrate further the production of tablets, dragées and suppositories:

a) An amount of 50.0 g of 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]-benzodiazepine - 1 - methanol is mixed with 550 g of lactose and 292 g of potato starch; the mixture is moistened with an alcoholic solution of 8 g of gelatine, and granulated through a sieve. After the drying of the granulate, 60 g of potato starch, 60 g of talcum, 10 g of magnesium stearate and 20 g of highly dispersed silicon dioxide are mixed in, and the obtained mixture is pressed to form 10,000 tablets each weighing 105 mg, and each containing 5 mg of active substance. If required, the tablets can be provided with grooves to give a more precise adjustment of the dosage amount.

b) An amount of 2.5 g of 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]-benzodiazepine - 1 - methanol is well mixed with 16 g of maize starch and 6 g of highly dispersed silicon dioxide; the mixture is then moistened with a solution of 2 g of stearic acid, 6 g of ethylcellulose and 6 g of stearin in ca. 70 ml of isopropyl alcohol, and the whole granulated through a sieve III (Ph. Helv. V). The granulate is dried for ca. 14 hours, and then put through sieve III—IIIa. It is afterwards mixed with 16 g of maize starch, 16 g of talcum and 2 g of magnesium stearate, and the mixture pressed to obtain 1000 dragée cores. These are coated with a concentrated syrup of 2 g of lacca, 7.5 g of gum arabic, 0.15 g of dyestuff, 2 g of highly dispersed silicon dioxide, 25 g of talcum and 53.35 g of sugar, and then dried. The obtained dragées each weigh 162.5 mg and each contain 2.5 mg of active substance.

c) 10 g of 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4] - benzodiazepine - 1 - methanol and 1990 g of finely ground suppository foundation material (e.g. cocoa butter) are thoroughly mixed and then melted. 1000 Suppositories each weighing 2 g are poured from the melt maintained homogeneous by stirring. The suppositories each contain 10 mg of active substance.

It is also possible to use as the active substance for tablets, dragées and suppositories the same amount of 6 - (o - fluorophenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4] - benzodiazepine - 1 - methanol.

In accordance with the foregoing the present invention also provides a pharmaceutical preparation comprising a diazepam derivative, 5-oxide or physiologically tolerable acid addition salt according to the invention in admixture or conjunction with a pharmaceutically suitable carrier.

The following Examples further illustrate the production of the compounds of the general formula I as well as of starting materials not hitherto known. Temperatures are given in degrees Centigrade. The petroleum ether employed is one having a boiling range of 40 to 65°C.

Example 1.

- a) A solution of 30 g of 2 - (methylthio) - 5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine [cp. G. A. Archer et al., J. Org. Chem. 29, 231 (1964)] and 19.8 g of 2 - benzyloxyacetic acid hydrazide [cp. Th. Curtius and N. Schwan, J.prakt. Chem. [2] 57, 353 (1895)] in 160 ml of hexamethylphosphoric acid triamide is heated for 8 hours at 140°. The solvent is then distilled off in vacuo, and the residue distributed between methylene chloride and water. The organic phase is separated, washed with saturated aqueous sodium chloride solution, dried over sodium sulphate, and concentrated by evaporation. 1 - (Benzyloxymethyl) - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine crystallises out; it melts at 163—165°.
- b) In an analogous manner is obtained, with the use of 26.6 g of 2 - (methylthio) - 5 - phenyl - 3H - 1,4 - benzodiazepine: 1 - (benzyloxymethyl) - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, M.P. 167—168° (from ethyl acetate/petroleum ether).

Example 2.

- a) A solution of 7.8 g of 2 - (methylthio) - 5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine and 3.5 g of 3 - hydroxypropionic acid hydrazide in 70 ml of abs. hexamethylphosphoric acid triamide is heated for 9 hours at 140°C. The solvent is then distilled off in vacuo. The residue is taken up in methylene chloride; the methylene chloride solution is washed with water and then with saturated sodium chloride solution, dried over sodium sulphate, and concentrated by evaporation. The residue is crystallised from methylene chloride/ethyl acetate/petroleum ether, and 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - ethanol, M.P. 227—231°, is obtained.

- If, instead of hydracrylic acid hydrazide, 6.5 g of 3 - benzyloxypropionic acid hydrazide are used, and the crude product is then purified by chromatography on aluminium oxide (eluting agent: ethyl acetate), and subsequent crystallisation from ethyl acetate/petroleum ether, then 1 - (2 - benzyloxyethyl) - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, M.P. 115—117°, is obtained.

- b) An amount of 96.5 g of 3 - benzyloxypropionic acid methyl ester [cp. J. J. Bloomfield, J.Org.Chem. 27, 2742 (1962)] is dissolved in 1000 ml of abs. ethanol; to the solution are then added 49.6 g of hydrazine hydrate, and the whole is allowed to stand for 65 hours at 25°. The reaction mixture is then concentrated in vacuo, the residue distilled at ca. 150°/0.005 Torr, and 3 - benzyloxypropionic acid hydrazide obtained as colourless oil.

An amount of 16.7 g of 3-benzyloxypropionic acid hydrazide is dissolved in 200 ml of abs. ethanol; the solution is then hydrogenated, after the addition of 2.0 g of palladium charcoal catalyst (5% Pd), at 20—25° and 760 Torr for 61 hours. The reaction mixture is afterwards filtered through kieselguhr, and the filtrate concentrated by evaporation to ca. 50 ml. After the addition of petroleum ether, hydracrylic acid hydrazide precipitates and is filtered off, M.P. 94—95°.

Example 3.

A solution of 10.0 g of 2 - (methylthio) - 5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine and 4.85 g of 2 - methoxy - acetic acid hydrazide (cp. E. J. Browne and J. B. Polya, J.Chem.Soc. 1962, 5149—5152) in 70 ml of abs. hexamethyl-phosphoric acid triamide is heated for 11 hours at 140°. The solvent is then distilled off in vacuo. The residue is taken up in methylene chloride; the solution is washed with water and then with saturated sodium chloride solution, dried over sodium sulphate, and concentrated by evaporation. Crystallisation of the concentration residue from ethyl acetate/petroleum ether yields 1 - (methoxymethyl) - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, M.P. 185—191°. After chromatography of the mother liquor on 100 g of silica gel "Merck" (Trade Mark), a further amount of final product of the same melting point can be isolated.

In an analogous manner is obtained, with the use of 5.5 g of 2 - ethoxyacetic acid hydrazide [cp. Curtius, J.prakt. Chem. [2] 95, 171 (1917)]: 1 - (ethoxymethyl) - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, M.P. 161—165° (from ethyl acetate/petroleum ether).

In an analogous manner is likewise obtained, by reaction, with 9 hours' reaction time, of 8.95 g of 2 - (methylthio) - 5 - phenyl - 3H - 1,4 - benzodiazepine and 4.85 g of 2 - methoxy - acetic acid hydrazide: 1 - (methoxymethyl) - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, M.P. 153—154° (from ethyl acetate/petroleum ether).

Example 4.

a) A solution of 6.0 g of 2 - (methylthio) - 5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine and 3.44 g of 3 - ethoxy - propionic acid hydrazide in 60 ml of abs. hexamethyl - phosphoric acid triamide is heated for 5 hours at 140°. After processing analogous to that described in Example 1 and crystallisation from ethyl acetate/petroleum ether, 1 - (2 - ethoxyethyl) - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, M.P. 128—132°, is obtained.

The 3-ethoxypropionic acid hydrazide used as starting material is prepared as follows:

b) An amount of 30 g of 3-ethoxypropionic

acid methyl ester [cp. C. E. Rehberg et al., J. Am. Chem. Soc. 68, 544—546 (1946)] is dissolved in 800 ml of abs. ethanol; to this solution are then added 22.7 g of hydrazine-hydrate, and the whole is allowed to stand for 3 days at 25°. The reaction mixture is concentrated in vacuo, and the residue distilled in a bulb tube at 120°/10⁻³ Torr. In this manner is obtained colourless 3-ethoxypropionic acid hydrazide, M.P. 34°.

Example 5.

a) A solution of 15.0 g 2 - (methylthio) - 5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine [cf. G. A. Archer et al., J. Org. Chem. 29, 231 (1964) and 11.5 g 2 - (p - methoxybenzyloxy) - acetic acid - hydrazide in 100 ml hexamethyl-phosphoric acid triamide is heated for 10 hours at 140°. The reaction mixture is worked up analogously to Example 1. The crude product is crystallised from ethyl acetate-petrol ether, whereby 1 - [(p - methoxybenzyloxy) - methyl] - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine M.P. 157—159° is obtained.

Analogously is obtained on using 16.7 g 2 - (methylthio) - 5 - (o - chlorophenyl) - 7 - chloro - 3H - 1,4 - benzodiazepine, 1 - [(p - methoxybenzyloxy) - methyl] - 6 - (o - chlorophenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine M.P. 200—203° from ethyl acetate.

Also analogously, but with a reaction time of 14 hours, there are obtained on using 15.9 g 2 - (methylthio) - 5 - (o - fluoro - phenyl) - 7 - chloro - 3H - 1,4 - benzodiazepine, 1 - [(p - methoxybenzyloxy) - methyl] - 6 - (o - fluoro - phenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4] - benzodiazepine M.P. 163.5—165° from ethyl acetate-petrol ether;

on using 14.0 g 2 - (methylthio) - 5 - phenyl - 7 - methyl - 3H - 1,4 - benzodiazepine, 1 - [(p - methoxybenzyloxy) - methyl] - 6 - phenyl - 8 - methyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine;

on using 17.3 g 2 - (methylthio) - 5 - phenyl - 7 - bromo - 3H - 1,4 - benzodiazepine, 1 - [(p - methoxybenzyloxy) - methyl] - 6 - phenyl - 8 - bromo - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, and

on using 16.5 g 2 - (methylthio) - 5 - (o - methoxyphenyl) - 7 - chloro - 3H - 1,4 - benzodiazepine, 1 - [(p - methoxybenzyloxy) - methyl] - 6 - (o - methoxyphenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine.

The substituted 2 - (methylthio) - 5 - phenyl - 3H - 1,4 - benzodiazepines required as starting compounds for the above-named end products can be prepared from the corresponding substituted 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepine - 2 - thiones des-

cribed in J. Org. Chem. 29, analogously to the preparation of 2 - (methylthio) - 5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine which is described therein.

Further, there are obtained analogously to the above example, with a reaction time of 14 hours,

from 14.2 g 2 - (methylthio) - 5 - phenyl - 7 - fluoro - 3H - 1,4 - benzodiazepine, 1 - [(p - methoxybenzyloxy) - methyl] - 6 - phenyl - 8 - fluoro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine;

from 15.7 g 2 - (methylthio) - 5 - (o - tolyl) - 7 - chloro - 3H - 1,4 - benzodiazepine, 1 - [(p - methoxybenzyloxy) - methyl] - 6 - (o - tolyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine;

from 14.8 g 2 - (methylthio) - 5 - phenyl - 7 - methoxy - 3H - 1,4 - benzodiazepine, 1 - [(p - methoxybenzyloxy) - methyl] - 6 - phenyl - 8 - methoxy - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine.

from 16.7 g 2 - (methylthio) - 5 - phenyl - 7 - (trifluoromethyl) - 3H - 1,4 - benzodiazepine, 1 - [(p - methoxybenzyloxy) - methyl] - 6 - phenyl - 8 - (trifluoromethyl) - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine,

from 16.7 g 2 - (methylthio) - 5 - (α,α,α - trifluoro - o - tolyl) - 3H - 1,4 - benzodiazepine, 1 - [(p - methoxybenzyloxy) - methyl] - 6 - (α,α,α - trifluoro - o - tolyl) - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine;

from 20.1 g 2 - (methylthio) - 5 - (α,α,α - trifluoro - o - tolyl) - 7 - (trifluoromethyl) - 3H - 1,4 - benzodiazepine, 1 - [(p - methoxybenzyloxy) - methyl] - 6 - (α,α,α - trifluoro - o - tolyl) - 8 - (trifluoromethyl) - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, and

from 18.4 g 2 - (methylthio) - 5 - (α,α,α - trifluoro - o - tolyl) - 7 - chloro - 3H - 1,4 - benzodiazepine 1 - [(p - methoxybenzyloxy) - methyl] - 6 - (α,α,α - trifluoro - o - tolyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4] - benzodiazepine.

b) The substituted 2 - (methylthio) - 5 - phenyl - 3H - 1,4 - benzodiazepines used as starting compounds are obtained from the correspondingly substituted 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepine - 2 - ones, whereas those compounds which contain a trifluoromethyl group are described in the U.S. patent specification 3,341,392 and, partly also in Helv. Chim. Acta 45, 2226 (1962). The three other compounds are described in J. Org. Chem. 27, 3788 (1962). These compounds are converted into the corresponding 2-thiones and the latter are reacted with dimethyl sulphate in methanolic sodium hydroxide solution analogously to the process described in J. Org. Chem. 29, 231 (1964).

c) 2 - (p - Methoxybenzyloxy) - acetate hydrazide, used in all cases as second reaction component, is obtained by reacting 58 g 2 - (p - methoxybenzyloxy) - acetic acid ethyl

ester [cf. A. Viout and H. Gault, *Compt. rend.* 237, 1162 (1953)] with 22.7 g hydrazine hydrate analogously to Example 4b).

Example 6.

5 A solution of 1.5 g 2 - (methylamino) - 5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine [cf. L. H. Sternbach et al, *J. Org.-Chem.* 26, 1111 (1961)] and 2 g of 2 - benzyloxy - acetic acid hydrazide in 10 ml
10 abs. hexamethyl-phosphoric acid triamide is heated 24 hours at 160° and a further 4 hours at 170°. Then, the reaction mixture is evaporated in vacuo and the residue is distributed between ethyl acetate and water. The
15 organic phase is separated, washed with saturated aqueous sodium chloride solution dried over sodium sulphate and evaporated. Chromatography of the residue on silica gel, using ethyl acetate-isopropanol (7:1) as eluent and crystallisation from ethyl acetate-ether-petrol
20 ether yields 1 - (benzyloxymethyl) - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4] - benzodiazepine, M.P. 163—165°.

Analogously, the same product is obtained on using the following starting compounds instead of 2 - (methylamino) - 5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine:

25 1.44 g 2 - Amino - 5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine [cf. S. C. Bell et al., *J. Med.Chem.* 5, 63 (1962)] or 1.90 g 2 - (benzylamino) - 5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine [obtainable according to British Patent Specification 1,023,793
30 or from the 4-oxide described by S. C. Bell et al., loc.cit. analogously to the method of L. H. Sternbach et al., loc.cit] or

35 1.56 g 2 - (dimethylamino) - 5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine [cf. British Patent Specification 1,023,753].

40 Also in an analogous manner are obtained on using 1.60 g 2 - amino - 5 - phenyl - 7 - (trifluoromethyl) - 3H - 1,4 - benzodiazepine, 1 - (benzyloxymethyl) - 6 - phenyl - 8 - (trifluoromethyl) - 4H - s - triazolo
45 [4,3 - a][1,4]benzodiazepine, on using 1.42 g 2 - amino - 5 - phenyl - 7 - methoxy - 3H - 1,4 - benzodiazepine, 1 - (benzyloxymethyl) - 6 - phenyl - 8 - methoxy - 4H - s - triazolo
50 [4,3 - a][1,4]benzodiazepine, and on using 1.34 g 2 - amino - 5 - phenyl - 7 - methyl - 3H - 1,4 - benzodiazepine, 1 - (benzyloxy-methyl) - 6 - phenyl - 8 - methyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine.

55 The three starting compounds mentioned above are obtained e.g. according to the process of deutsche Offenlegungsschrift 1.933.986, Chemical Abstracts 72, 100772 h (1970), or analogously to the 2 - amino - compound named before.

Example 7.

60 A solution of 8.0 g of 2 - (methylthio) - 5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine and 4.1 of 3 - hydroxybutyric acid

hydrazide [cp. *J. Biol. Chem.* 60, 180 (1924)] in 70 ml of abs. hexamethylphosphoric acid triamide is heated for 9 hours at 140°. After processing analogous to that described in Example 1 crystallisation from ethyl acetate/ether, α - methyl - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - ethanol, M.P. 182—184°, is obtained.

70 From 4.1 g of 2 - methyl-lactic acid hydrazide [cp. R. Metzger and W. Kort, *Chem. Ber.* 91, 417 (1958)] there is obtained, after a reaction time of 23 hours with otherwise the same procedure, α, α - dimethyl - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol, M.P. 234—236° (from ethyl acetate/petroleum ether).

Example 8.

80 Crude 1 - [(diphenylmethoxy) - methyl] - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine is obtained, analogously to Example 1, starting with 15.0 g of 2 - (methylthio) - 5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine and 14.1 g of 2 - (diphenylmethoxy) - acetic acid hydrazide in 100 ml of hexamethylphosphoric acid triamide, the reaction time being 12 hours. The crude product is purified by chromatography on silica gel with employment of benzene/ethyl acetate (1:1) as the eluting agent, and crystallisation of the homogeneous fractions from ethyl acetate/petroleum ether. The pure substance melts at 202—203°.

95 The hydrazide required as starting material is obtained from 2 - (diphenylmethoxy) - acetic acid methyl ester [cp. C. Djerassi and C. R. Scholz, *J. Org. Chem.* 13, 830 (1948)] and hydrazine hydrate, analogously to Example 4b), as an oil.

Example 9.

105 From 15.0 g of 2 - (methylthio) - 5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine and 9.6 g of 2 - (tetrahydropyran - 2 - yloxy) - acetic acid hydrazide in 80 ml of hexamethylphosphoric acid triamide is obtained analogously to Example 1, but with a reaction duration of 24 hours, crude 1 - [(tetrahydropyran - 2 - yloxy) - methyl] - 6 - phenyl - 8 - chloro - 4H - s - triazolo
110 [4,3 - a][1,4]benzodiazepine. This is purified by chromatography on silica gel with the use of benzene/isopropanol (95:5) as the eluting agent, and subsequent crystallisation of the homogeneous fractions from ethyl acetate/petroleum ether. The pure substance melts at 159—161°.

The hydrazide required as starting material is produced as follows:

120 a) 84 g of 3,4 - dihydro - 2H - pyran and 132 g of glycolic acid n-butyl ester are dissolved at room temperature. To this solution are added 0.5 ml of concentrated hydrochloric acid, whereupon the temperature immediately rises to 90°. The solution is cooled to room

temperature and stirred for 2 hours. After the addition of 1 g of sodium bicarbonate, the crude product is distilled under 17 Torr to obtain 2 - (tetrahydropyran - 2 - yloxy) - acetic acid n-butyl ester, B.P. 127°/17 Torr.

- 5 b) 10.81 g of the above ester and 5 g of hydrazine hydrate are dissolved in 50 ml of abs. ethanol, the solution being then stirred for 20 hours at 60°. The solution is concentrated in vacuo, and the residue distilled in a ball tube. 2 - (Tetrahydropyran - 2 - yloxy) - acetic acid hydrazide passes over under 0.08 Torr at ca. 150° and is in the form of a colourless oil, which soon crystallises, M.P. 55—78°.

Example 10.

- a) An amount of 25 g of 1 - (benzyloxy-methyl) - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine is dissolved in 200 ml of glacial acetic acid; to this solution are then added 170 ml of 48% aqueous hydrobromic acid. The mixture is heated for 90 minutes at 80°, and afterwards cooled to 5°; the pH-value of the mixture is adjusted with concentrated sodium hydroxide solution to 6, whilst stirring is maintained, and water and also methylene chloride are then added. The organic phase is separated, washed with saturated aqueous sodium chloride solution, dried over sodium sulphate, and concentrated by evaporation. The residue is dissolved in ethyl acetate/methanol (9:1), the solution filtered through a column of 150 g of silica gel (Merck Trade Mark), particle size 0.05—0.2 mm), and the column eluted with ethyl acetate/methanol (9:1) to (7:3). The eluate is concentrated by evaporation and the residue crystallised from ethyl acetate/ether. In this manner is obtained 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol, M.P. 210—211°.

- b) In an analogous manner is obtained, starting with 5 g of 1 - (benzyloxymethyl) - 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine in 40 ml of glacial acetic acid and 35 ml of 48% aqueous hydrobromic acid with a reaction time of 105 minutes: 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol, M.P. 205—206° (from ethyl acetate/petroleum ether).

- c) In a likewise analogous manner is obtained, with application of the acid amounts stated in the second paragraph and with a reaction time of 120 minutes, from 5 g of 1 - (benzyloxymethyl) - 6 - phenyl - 8 - (trifluoromethyl) - 3H - 1,4 - benzodiazepine:— 6 - phenyl - 8 - (trifluoromethyl) - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol;

from 5 g of 1 - (benzyloxymethyl) - 6 - phenyl - 8 - methoxy - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine:— 6 - phenyl - 8 - methoxy - 4H - s - triazolo[4,3 - a][1,4] -

benzodiazepine - 1 - methanol; and from 5 g of 1 - (benzyloxymethyl) - 6 - phenyl - 8 - methyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine:— 6 - phenyl - 8 - methyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol.

Example 11.

To a solution of 3.0 g 1 - [(p - methoxybenzyloxy) - methyl] - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine in 30 ml of glacial acetic acid is added at 25° 24 ml 48% aqueous hydrobromic acid. The reaction mixture is stirred for 20 minutes, neutralised with 30% sodium hydroxide solution and extracted with methylene chloride. The organic phase is separated, washed with water, dried over sodium sulphate and evaporated to dryness. The crystallisation of the residue from acetate-ether-petrol ether yields 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol, M.P. 209—211°.

Analogously are obtained from 3.23 g 1 - [(p - methoxybenzyloxy) - methyl] - 6 - (o - chlorophenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine at a reaction temperature of 20° and 55 minutes reaction time 6 - (o - chlorophenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol, M.P. 235—237° (from ethyl acetate-petrol ether);

from 3.12 g 1 - [(p - methoxybenzyloxy) - methyl] - 6 - (o - fluorophenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine at a reaction temperature of 20° and a reaction time of 15 minutes 6 - (o - fluorophenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol M.P. 195—197° (from ethyl acetate-petrol ether).

Also analogously are obtained at 20° with a reaction of 75 minutes;

from 2.86 g 1 - [(p - methoxybenzyloxy) - methyl] - 6 - phenyl - 8 - methyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, 6 - phenyl - 8 - methyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol;

from 3.32 g 1 - [(p - methoxybenzyloxy) - methyl] - 6 - phenyl - 8 - bromo - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, 6 - phenyl - 8 - bromo - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol;

from 3.20 g 1 - [(p - methoxybenzyloxy) - methyl] - 6 - (o - methoxyphenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, 6 - (o - methoxyphenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol;

from 3.12 g [(p - methoxybenzyloxy) - methyl] - 6 - phenyl - 8 - fluoro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, 6 - phenyl - 8 - fluoro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol;

from 3.10 g 1 - [(p - methoxybenzyloxy) - methyl] - 6 - (o - tolyl) - 8 - chloro - 4H -

- 19
- s - triazolo[4,3 - a][1,4]benzodiazepine, 6 - (o - tolyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol; from 2.98 g 1 - [(p - methoxybenzyloxy) - methyl] - 6 - phenyl - 8 - methoxy - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, 6 - phenyl - 8 - methoxy - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol; from 3.23 g 1 - [(p - methoxybenzyloxy) - methyl] - 6 - phenyl - 8 - (trifluoromethyl) - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, 6 - phenyl - 8 - (trifluoromethyl) - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol;
- 15 from 3.23 g 1 - [(p - methoxybenzyloxy) - methyl] - 6 - (α,α,α - trifluoro - o - tolyl) - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, 6 - (α,α,α - trifluoro - o - tolyl) - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol;
- 20 from 3.70 g 1 - [(p - methoxybenzyloxy) - methyl] - 6 - (α,α,α - trifluoro - o - tolyl) - 8 - (trifluoromethyl) - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, 6 - (α,α,α - trifluoro - o - tolyl) - 8 - trifluoromethyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol, and
- 25 from 3.46 g 1 - [(p - methoxybenzyloxy) - methyl] - 6 - (α,α,α - trifluoro - o - tolyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, 6 - (α,α,α - trifluoro - o - tolyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol.

Example 12.

- 35 A solution of 100 mg of 1 - [(diphenylmethoxy) - methyl] - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine in 10 ml of glacial acetic acid and 8 ml of 48% hydrobromic acid is stirred for 45 minutes at 25°. The reaction mixture is then neutralised with 30% aqueous sodium hydroxide solution, and extracted with ethyl acetate. The organic phase is washed with saturated sodium chloride solution, dried over sodium sulphate, and concentrated by evaporation. Crystallisation of the residue from ethyl acetate/ether/petroleum ether yields: 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol, M.P. 210—211°.

Example 13.

- 55 An amount of 10 ml of 1 - N - hydrochloric acid is added to a solution of 200 mg of 1 - [(tetrahydropyran - 2 - yloxy) - methyl] - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine in 3 ml of methanol; the whole is then stirred for 1 1/2 hours at 70—80°. The reaction mixture is diluted with ethyl acetate, and extracted with aqueous sodium bicarbonate solution. The organic phase is washed with water and saturated sodium chloride solution, dried over sodium sulphate, and concentrated by

evaporation. Crystallisation of the residue from ethyl acetate/ethyl/petroleum ether yields: 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol, M.P. 210—211°.

Example 14.

An amount of 7.0 g of 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol is dissolved in 50 ml of absolute pyridine; to the solution are added 2.4 ml of acetic anhydride, and the whole is then allowed to stand for 17 hours at 25°. The reaction mixture is afterwards concentrated in vacuo. The residue is dissolved in methylene chloride, and the solution washed with water and saturated sodium chloride solution, dried over sodium sulphate, and concentrated by evaporation. After crystallisation of the residue from ethyl/acetate is obtained 1 - (acetoxymethyl) - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine, M.P. 210—212°.

In an analogous manner are obtained:

from 7.44 g of 6 - (o - fluorophenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol:— 1 - (acetoxymethyl) - 6 - (o - fluorophenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine; and

from 7.74 g of 6 - (o - chlorophenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol:— 1 - (acetoxymethyl) - 6 - (o - chlorophenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine.

Example 15.

A solution of 3.11 g of m - chloroperoxybenzoic acid in 40 ml of methylene chloride is added dropwise at 0—5° in the course of 10 minutes, with stirring, to a solution of 3.0 g of 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol in 80 ml of methylene chloride. The reaction mixture is stirred, in a melting ice bath, for a further 16 hours. It is then concentrated in vacuo, and to it are added ether and petroleum ether. The precipitated crystals are filtered off under suction, and recrystallised twice from methanol/ethyl acetate/ether. The obtained 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol - 5 - oxide melts at 267—269°.

The following are obtained in an analogous manner:

starting with 3.84 g of 1 - (benzyloxy - methyl) - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine is obtained:— 1 - (benzyloxymethyl) - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 5 - oxide, M.P. 189—193° (from ether);

starting with 3.13 g of 1 - (methoxy - methyl) - 6 - phenyl - 8 - chloro - 4H - s -

triazolo[4,3 - a][1,4]benzodiazepine is obtained:— 1 - (methoxymethyl) - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 5 - oxide, M.P. 244—248° (from dioxan);

starting with 3.16 g of 6 - (o - fluorophenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol is obtained:— 6 - (o - fluorophenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol - 5 - oxide; and

starting with 3.32 g of 6 - (o - chlorophenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol is obtained:— 6 - (o - chlorophenyl) - 8 - chloro - 4H - s - triazolo[4,3][1,4]benzodiazepine - 1 - methanol - 5 - oxide.

Example 16.

a) A solution of 0.37 g of 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - carboxylic acid ethyl ester in 5 ml of absolute tetrahydrofuran is added dropwise in the course of 15 minutes, with ice cooling and with stirring, to a suspension of 0.078 g of lithium aluminium hydride in 5 ml of absolute tetrahydrofuran. After a further 45 minutes of stirring at 0—5°, 0.40 ml of 1 - N sodium hydroxide solution are added dropwise. The inorganic salts are filtered off, the filtrate is concentrated in vacuo, and the residue dissolved in 10 ml of chloroform. The solution is washed with 1-N sodium hydroxide solution and then with water, dried over sodium sulphate, and concentrated by evaporation. The residue is recrystallised from ethyl acetate/petroleum ether to obtain 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol, M.P. 210—211°.

The following are obtained in an analogous manner:

from 0.33 g of 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - carboxylic acid ethyl ester is obtained:— 6 - phenyl - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol, M.P. 205—206° (from ethyl acetate/petroleum ether);

from 0.38 g of 6 - (o - fluorophenyl) - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - carboxylic acid ethyl ester is obtained:— 6 - (o - fluorophenyl) - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol, M.P. 195—197° (from ethyl acetate/petroleum ether); and

from 0.40 g of 6 - (o - chlorophenyl) - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - carboxylic acid ethyl ester is obtained:— 6 - (o - chlorophenyl) - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol, M.P. 235—237° (from ethyl acetate/petroleum ether).

The ethyl ester required as starting material for the first mentioned reduction is produced as follows:

b) A solution of 3.0 g of 2 - (methylthio) - 5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine [cp. G. A. Archer et al., J. Org. Chem. 29, 231 (1964)] and 4.0 g of oxalic acid monoethyl ester hydrazide in 100 ml of n - butanol is refluxed for 8 hours. The solvent is then evaporated off in vacuo, and the residue distributed between methylene chloride and water. The organic phase is separated, washed with saturated aqueous sodium chloride solution, dried with anhydrous potassium carbonate solution, and concentrated by evaporation. The residue is chromatographed on 300 g of silica gel with the use of a mixture of ethyl acetate and hexane (3:2) as solvent and eluting agent. The fractions are concentrated by evaporation, the homogeneous residues combined and recrystallised from ethyl acetate/hexane to thus obtain 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - carboxylic acid ethyl ester, M.P. 233—235°.

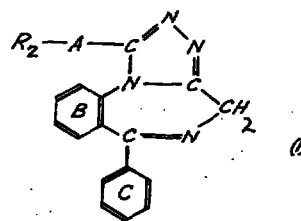
The further ethyl esters employed as starting materials are obtained in an analogous manner.

Example 17.

An amount of 0.13 ml of 70% perchloric acid is added at 25° to a solution of 0.5 g of 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol in 1 ml of methanol and 1 ml of acetone. The mixture is allowed to stand for 16 hours at 0°; the precipitated crystals are filtered off under suction, and recrystallised from methanol/acetone. The obtained 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4]benzodiazepine - 1 - methanol - perchlorate melts at 247—250°. The crystals contain an equimolar amount of acetone.

WHAT WE CLAIM IS:—

1. A diazepine derivative having the general formula I



wherein

R₂ represents a hydroxy group, an alkoxy or an alkanoyloxy group having from 1 to 6 carbon atoms or a mono- or di-arylmethoxy group, and

A represents an alkylene group having from 1 to 3 carbon atoms

and wherein each of the rings B and C, independently of the other, may be unsubstituted or substituted by one substituent selected from



triazo[4,3 - a][1,4]benzodiazepine is obtained:— 1 - (methoxymethyl) - 6 - phenyl - 8 - chloro - 4H - s - triazo[4,3 - a][1,4]benzodiazepine - 5 - oxide, M.P. 244—248° (from dioxan);

starting with 3.16 g of 6 - (o - fluorophenyl) - 8 - chloro - 4H - s - triazo[4,3 - a][1,4]benzodiazepine - 1 - methanol is obtained:— 6 - (o - fluorophenyl) - 8 - chloro - 4H - s - triazo[4,3 - a][1,4]benzodiazepine - 1 - methanol - 5 - oxide; and

starting with 3.32 g of 6 - (o - chlorophenyl) - 8 - chloro - 4H - s - triazo[4,3 - a][1,4]benzodiazepine - 1 - methanol is obtained:— 6 - (o - chlorophenyl) - 8 - chloro - 4H - s - triazo[4,3 - a][1,4]benzodiazepine - 1 - methanol - 5 - oxide.

Example 16.

a) A solution of 0.37 g of 6 - phenyl - 8 - chloro - 4H - s - triazo[4,3 - a][1,4]benzodiazepine - 1 - carboxylic acid ethyl ester in 5 ml of absolute tetrahydrofuran is added dropwise in the course of 15 minutes, with ice cooling and with stirring, to a suspension of 0.078 g of lithium aluminium hydride in 5 ml of absolute tetrahydrofuran. After a further 45 minutes of stirring at 0—5°, 0.40 ml of 1 - N sodium hydroxide solution are added dropwise. The inorganic salts are filtered off, the filtrate is concentrated in vacuo, and the residue dissolved in 10 ml of chloroform. The solution is washed with 1-N sodium hydroxide solution and then with water, dried over sodium sulphate, and concentrated by evaporation. The residue is recrystallised from ethyl acetate/petroleum ether to obtain 6 - phenyl - 8 - chloro - 4H - s - triazo[4,3 - a][1,4]benzodiazepine - 1 - methanol, M.P. 210—211°.

The following are obtained in an analogous manner:

from 0.33 g of 6 - phenyl - 4H - s - triazo[4,3 - a][1,4]benzodiazepine - 1 - carboxylic acid ethyl ester is obtained:— 6 - phenyl - 4H - s - triazo[4,3 - a][1,4]benzodiazepine - 1 - methanol, M.P. 205—206° (from ethyl acetate/petroleum ether);

from 0.38 g of 6 - (o - fluorophenyl) - 4H - s - triazo[4,3 - a][1,4]benzodiazepine - 1 - carboxylic acid ethyl ester is obtained:— 6 - (o - fluorophenyl) - 4H - s - triazo[4,3 - a][1,4]benzodiazepine - 1 - methanol, M.P. 195—197° (from ethyl acetate/petroleum ether); and

from 0.40 g of 6 - (o - chlorophenyl) - 4H - s - triazo[4,3 - a][1,4]benzodiazepine - 1 - carboxylic acid ethyl ester is obtained:— 6 - (o - chlorophenyl) - 4H - s - triazo[4,3 - a][1,4]benzodiazepine - 1 - methanol, M.P. 235—237° (from ethyl acetate/petroleum ether).

The ethyl ester required as starting material for the first mentioned reduction is produced as follows:

b) A solution of 3.0 g of 2 - (methylthio) - 5 - phenyl - 7 - chloro - 3H - 1,4 - benzodiazepine [cp. G. A. Archer et al., J. Org. Chem. 29, 231 (1964)] and 4.0 g of oxalic acid monoethyl ester hydrazide in 100 ml of n - butanol is refluxed for 8 hours. The solvent is then evaporated off in vacuo, and the residue distributed between methylene chloride and water. The organic phase is separated, washed with saturated aqueous sodium chloride solution, dried with anhydrous potassium carbonate solution, and concentrated by evaporation. The residue is chromatographed on 300 g of silica gel with the use of a mixture of ethyl acetate and hexane (3:2) as solvent and eluting agent. The fractions are concentrated by evaporation, the homogeneous residues combined and recrystallised from ethyl acetate/hexane to thus obtain 6 - phenyl - 8 - chloro - 4H - s - triazo[4,3 - a][1,4]benzodiazepine - 1 - carboxylic acid ethyl ester, M.P. 233—235°.

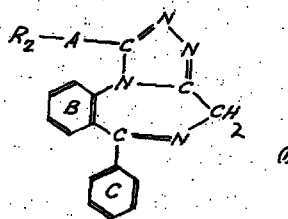
The further ethyl esters employed as starting materials are obtained in an analogous manner.

Example 17.

An amount of 0.13 ml of 70% perchloric acid is added at 25° to a solution of 0.5 g of 6 - phenyl - 8 - chloro - 4H - s - triazo[4,3 - a][1,4]benzodiazepine - 1 - methanol in 1 ml of methanol and 1 ml of acetone. The mixture is allowed to stand for 16 hours at 0°; the precipitated crystals are filtered off under suction, and recrystallised from methanol/acetone. The obtained 6 - phenyl - 8 - chloro - 4H - s - triazo[4,3 - a][1,4]benzodiazepine - 1 - methanol - perchlorate melts at 247—250°. The crystals contain an equimolar amount of acetone.

WHAT WE CLAIM IS:—

1. A diazepine derivative having the general formula I



wherein

R₂ represents a hydroxy group, an alkoxy or an alkanoyloxy group having from 1 to 6 carbon atoms or a mono- or di-arylmethoxy group, and

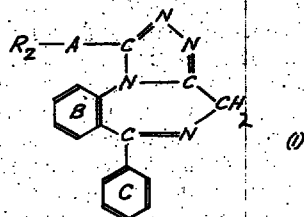
A represents an alkylene group having from 1 to 3 carbon atoms

and wherein each of the rings B and C, independently of the other, may be unsubstituted or substituted by one substituent selected from

halogen atoms up to and including the atomic number 35, trifluoromethyl groups, and alkyl and alkoxy groups having from 1 to 6 carbon atoms.

- 5 2. A 5-oxide of a diazepine derivative as claimed in claim 1.

3. A diazepine derivative having the general formula I



- 10 wherein
 R₂ represents a 2-oxacycloalkoxy group having from 5 to 7 ring members, and
 A represents an alkylene group having from 1 to 3 carbon atoms, and wherein each of the rings B and C, independently of the other, may be unsubstituted or substituted by one substituent selected from halogen atoms up to and including the atomic number 35 trifluoromethyl groups, and alkyl and alkoxy groups having from 1 to 6 carbon atoms.

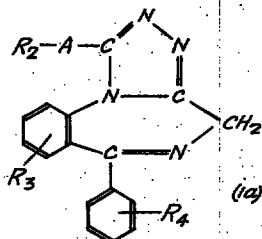
- 20 4. A diazepine derivative as claimed in claim 3 wherein R₂ represents a tetrahydropyran-2-yloxy group.

- 25 5. A diazepine derivative as claimed in claim 4 wherein A represents a methylene group.

6. A diazepine derivative as claimed in claim 5 having a chlorine atom in the 8-position.

- 30 7. The 5-oxide of a diazepine derivative as claimed in any one of claims 3 to 6.

8. A diazepine derivative having the general formula Ia



- 35 wherein
 R₂ represents a hydroxy group, an alkoxy or alkanoyloxy group having from 1 to 6 carbon atoms or a monoarylmethoxy group,
 R₃ and R₄, independently of each other, represent a hydrogen atom, a halogen atom up to and including the atomic number 35, a trifluoromethyl group or an alkyl or alkoxy group having from 1 to 6 carbon atoms; and
 A represents an alkylene group having from 1 to 3 carbon atoms.

9. The 5-oxide of an azepine derivative as claimed in claim 8.

10. A diazepine derivative as claimed in claim 8 wherein R₂ represents a hydroxy group or an alkanoyloxy group having from 1 to 6 carbon atoms.

11. A diazepine derivative as claimed in claim 10 wherein R₂ represents a hydroxy group.

12. A diazepine derivative as claimed in claim 11 wherein A represents a methylene group.

13. A diazepine derivative as claimed in claim 12 wherein R₃ represents a chlorine atom in the 8-position.

14. A diazepine derivative as claimed in claim 13 wherein R₄ represents a hydrogen atom or a chlorine or fluorine atom in the ortho position.

15. A diazepine derivative as claimed in claim 8 wherein R₂ represents a mono-aryl-methoxy group.

16. A diazepine derivative as claimed in claim 15 wherein A represents a methylene group.

17. A diazepine derivative as claimed in claim 16 wherein R₃ represents a chlorine atom in the 8-position.

18. A diazepine derivative as claimed in claim 17 wherein R₄ represents a hydrogen atom or a chlorine or fluorine atom in the ortho position.

19. The 5-oxide of a diazepine derivative as claimed in any one of claims 10 to 14.

20. The 5-oxide of a diazepine derivative as claimed in any one of claims 15 to 18.

21. An acid addition salt of a diazepine derivative as claimed in claim 1 or claim 8.

22. An acid addition salt of a diazepine derivative as claimed in any one of claims 3 to 6.

23. An acid addition salt of a diazepine derivative as claimed in any one of claims 10 to 18.

24. An acid addition salt as claimed in any one of claims 21 to 23 being a physiologically tolerable acid addition salt.

25. 6 - Phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4] - benzodiazepine - 1 - methanol.

26. 6 - (o - Fluorophenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4] - benzodiazepine - 1 - methanol.

27. 6 - (o - Chlorophenyl) - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4] - benzodiazepine - 1 - methanol.

28. 1 - (Benzyloxymethyl) - 6 - phenyl - 8 - chloro - 4H - s - triazolo[4,3 - a][1,4] - benzodiazepine.

29. A diazepine derivative as claimed in claim 1, and described in any one of the Examples herein.

30. The 5-oxide of the diazepine derivative as claimed in claim 25.



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31. The 5-oxide of a diazepine derivative as claimed in claim 26;

32. The 5-oxide of the diazepine derivative claimed in claim 27.

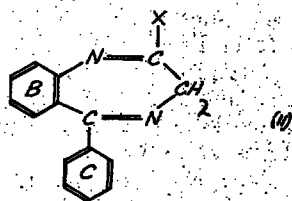
5 33. The 5-oxide of the diazepine derivative as claimed in claim 28.

34. The 5-oxide of a diazepine derivative as claimed in claim 29.

10 35. An acid addition salt of a diazepine derivative as claimed in any one of claims 25 to 29.

36. A physiologically tolerable acid addition salt of a diazepine derivative as claimed in any one of claims 25 to 29.

15 37. A process for the production of a diazepine derivative having the general formula I as defined in claim 1 or claim 3 but wherein R_2 may not represent an alkanoyloxy group, or a 5-oxide thereof, or an acid addition salt of such a derivative which comprises condensing the corresponding compound having the general formula II



wherein

25 X represents a mercapto group, an alkoxy or alkylthio group having 1 or 2 carbon atoms, which may be activated by a substituent, or an unsubstituted mono- or di-substituted amino group

30 and the rings B and C may be substituted according to the definition given in claim 1, with a compound having the general formula III



35 wherein R_2' has the meaning given for R_2 in claim 1 or 3 with the exception that it may not represent an alkanoyloxy group and A has the meaning given in claim 1.

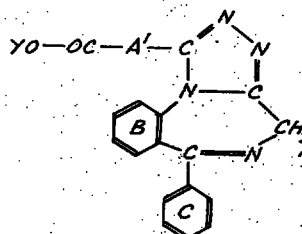
40 38. Process as claimed in claim 37 wherein X represents a methoxy, ethoxy, methylthio, ethylthio, o- or p-nitrobenzylthio, o- or p-nitrobenzyloxy or mercapto group.

45 39. A process as claimed in claim 37 wherein X represents, a methylamino, benzylamino, dimethylamino or amino group.

40 A process as claimed in any one of claims 37 to 39 wherein the condensation is effected at a temperature in the range of from 80 to 180°C in an inert solvent.

50 41. A process for the production of a diazepine derivative having the general formula I as defined in claim 1 wherein R_2 represents a hydroxy group and A represents a methylene, ethylene, trimethylene or propyl-

ene group, or a 5-oxide thereof, or an acid addition salt of such a derivative which comprises reducing, by means of a complex hydride in an ethereal solvent, the corresponding compound having the general formula IV



wherein

Y represents a hydrogen radical having at most 8 carbon atoms,

A' represents a direct bond or a methylene, ethylidene or ethylene group, and the rings B and C may be substituted as stated in claim 1.

42. A process as claimed in claim 41 wherein Y represents an alkyl group having at most 4 carbon atoms.

43. A process as claimed in claim 41 or claim 42 wherein the complex hydride is lithium aluminium hydride.

44. A process as claimed in any one of claims 41 to 43 wherein the reduction is effected at a temperature in the range of from -15 to +20°C.

45. A process for the production of a diazepine derivative having the general formula I as defined in claim 1 wherein R_2 represents a hydroxy group, or a 5-oxide thereof, or an acid addition salt of such a derivative which comprises splitting the corresponding compound of the general formula I wherein R_2 represents a monoarylmethoxy, diarylmethoxy or 2-oxacycloalkoxy group by a known method.

46. A process as claimed in claim 45 wherein, in the starting material, R_2 represents a mono- or di-arylmethoxy group and the splitting is effected in the presence of a hydrohalic acid at a temperature in the range of from 20 to 150°C.

47. A process as claimed in claim 45 wherein, in the starting material, R_2 represents a 2-oxacycloalkoxy group and the splitting is effected in the presence of a hydrohalic acid at a temperature in the range of from 50 to 100°C.

48. A process as claimed in any one of claims 45 to 47 wherein the starting material is prepared by a process as claimed in any one of claims 37 to 40.

49. A process for the production of a diazepine derivative having the general formula I as defined in claim 1 wherein R_2 represents an alkanoyloxy group having from 1 to 6 carbon atoms, or a 5-oxide thereof, or an acid addition salt of such a derivative,



which comprises acylating the corresponding compound having the general formula I wherein R_2 represents a hydroxy group.

50. A process as claimed in claim 49 wherein the starting material is prepared by a process as claimed in any one of claims 37 to 48.

51. A process as claimed in any one of claims 37 to 50 wherein a diazepine derivative thus obtained is oxidised to produce its 5-oxide.

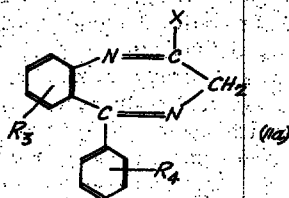
52. A process as claimed in claim 51 wherein the oxidation is effected by employing hydrogen peroxide or a peroxy acid at a temperature of from 0 to 70°C.

53. A process as claimed in claim 52 wherein the peroxy acid is peroxyacetic acid, benzoperoxy acid or m-chlorobenzoperoxy acid.

54. A process as claimed in any one of claims 37 to 50 wherein a diazepine derivative thus obtained is converted into an acid addition salt thereof.

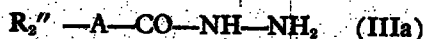
55. A process as claimed in any one of claims 37 to 50 wherein a diazepine derivative thus obtained is converted into physiologically tolerable acid addition salt thereof.

56. A process for the production of a diazepine derivative having the general formula Ia as defined in claim 8 or a 5-oxide thereof which comprises condensing the corresponding compound having the general formula IIa



wherein R_3 and R_4 have the meanings given in claim 8 and

X represents a mercapto or an alkoxy or alkylthio group having 1 or 2 carbon atoms, which may be activated by a substituent, with a compound having the general formula IIIa



wherein

R_2'' represents a hydroxy group an alkoxy group having from 1 to 6 carbon atoms or a mono- arylmethoxy group

when required splitting a diazepine derivative having the general formula Ia thus obtained wherein R_2 represents a mono- arylmethoxy group to produce a diazepine derivative having the general formula Ia wherein R_2 represents a hydroxy group, or acylating a diazepine derivative having the general formula Ia thus produced wherein R_2 represents a hydroxy group to produce a diazepine deriv-

ative having the general formula Ia wherein R_2 represents an alkanoyloxy group having from 1 to 6 carbon atoms, and when required, oxidising a diazepine derivative having the general formula Ia thus obtained to produce its 5-oxide.

57. A process as claimed in claim 56 wherein X represents a methoxy, ethoxy, methylthio, ethylthio, o- or p-nitrobenzylthio or o- or p-nitrobenzyloxy group.

58. A process as claimed in claim 56 or claim 57 wherein R_2'' represents a hydroxy group, an alkoxy group having from 1 to 6 carbon atoms or a mono- arylmethoxy group.

59. A process as claimed in any one of claims 56 to 58 wherein the condensation is effected at a temperature in the range of from 80 to 180°C in an inert solvent.

60. A process as claimed in claim 37, carried out substantially as described in any one of Examples 1b, 2 to 9, 10b, 10c and 11 to 17 herein.

61. A process as claimed in claim 37, carried out substantially as described in Example 1a or Example 10a herein.

62. A diazepine derivative as claimed in claim 1 or claim 3, or 5-oxide thereof, whenever prepared by a process as claimed in any one of claims 37 to 55 and 60.

63. A diazepine derivative as claimed in claim 1, or 5-oxide thereof, whenever prepared by a process as claimed in any one of claims 56, 57 and 59.

64. A diazepine derivative as claimed in claim 1 or claim 3, or 5-oxide thereof, whenever prepared by a process as claimed in claim 58 or claim 61.

65. An acid addition salt of a diazepine derivative as claimed in claim 1, or claim 3, whenever prepared by a process as claimed in any one of claims 37 to 50 and 54 to 61.

66. A physiologically tolerable acid addition salt of a diazepine derivative as claimed in claim 1, or claim 3, whenever prepared by a process as claimed in any one of claims 37 to 50 and 54 to 61.

67. A pharmaceutical preparation comprising a diazepine derivative, 5-oxide or physiologically tolerable acid addition salt as claimed in any one of claims 1 to 7, 24, 26, 27, 29, 31, 32, 34, 36, 62, and 66, in admixture or conjunction with a pharmaceutically suitable carrier.

68. A pharmaceutical preparation comprising a diazepine derivative or 5-oxide thereof as claimed in any one of claims 8, 9, 15 to 18, 20 and 63, in admixture or conjunction with a pharmaceutically suitable carrier.

69. A pharmaceutical preparation comprising a diazepine derivative or 5-oxide thereof as claimed in any one of claims 10 to 14, 19, 25, 28 and 64, in admixture or conjunction with a pharmaceutically suitable carrier.

70. A pharmaceutical preparation comprising a diazepine derivative 5-oxide as claimed



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in claim 30 or claim 33, in admixture or conjunction with a pharmaceutically suitable carrier.

or conjunction with a pharmaceutically suitable carrier.

- 5 71. A pharmaceutical preparation comprising a diazepam derivative or 5-oxide as claimed in claim 15 or claim 20 in admixture

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