

PATENT SPECIFICATION

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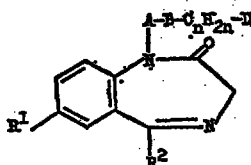
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(54) BENZODIAZEPINE DERIVATIVES AND A PROCESS FOR THE MANUFACTURE THEREOF

- (71) We, F. HOFFMANN - LA ROCHE & CO., AKTIENGESellschaft, a Swiss Company of 124-184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—
 10 The present invention is concerned with benzodiazepine derivatives and a process for the manufacture thereof.
 15 The benzodiazepine derivatives provided by the present invention are compounds of the general formula



(I)

“carbalkoxy” or “allylcarbamoil” means straight-chain or branched-chain, saturated, aliphatic hydrocarbon groups containing up to 5 carbon atoms such as methyl, ethyl, propyl and isopropyl. The methyl and ethyl groups are preferred. When R¹ represents an alkyl group, the methyl group is excluded. In this case, the ethyl group is preferred. The term “alkanoyl” relates in a similar manner to acyl groups derived from aliphatic carboxylic acids containing up to 5 carbon atoms such as formyl, acetyl and propionyl. The acetyl group is preferred. The term “halogen” includes chlorine, bromine, iodine and fluorine. When R¹ represents a halogen atom, chlorine and iodine are preferred. The term “isopropylene” includes both isomeric forms, i.e. both



and



- wherein A represents an ethylene, propylene or isopropylene group, B represents —O—, —S— or —NR³—, D represents a carbalkoxy, cyano, carbamoil, monoalkylcarbamoil or dialkylcarbamoil group, R¹ represents a halogen atom, a nitro or trifluoromethyl group, an alkyl group containing 2 to 5 carbon atoms or an alkanoyl group, R² represents a phenyl, o-halophenyl, o,o'-dihalophenyl or 2-pyridyl group, R³ represents a hydrogen atom or an alkyl group and n stands for 1 or 2, 4-oxides thereof and salts of said compounds and of those 4-oxides which are basic.

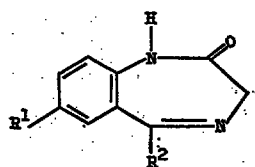
As used in this description and in the accompanying claims, the term “alkyl” when taken alone or in combination such as in

When R² represents a 2-pyridyl group, R¹ preferably represents a bromine atom. When R² represents an o-halophenyl group, the halogen atom is preferably a fluorine or chlorine atom. Fluorine atoms are the preferred halogen atoms in o,o'-dihalophenyl groups.

Apart from the preferred substituents within the general terms mentioned hereinbefore, the cyano group and the carbamoil group are preferred values for D. In addition, B preferably represents —O—, —NH— or —N(CH₃)—.

According to the process provided by the present invention, the benzodiazepine derivatives aforesaid (that is to say, the compounds of formula I, 4-oxides thereof and salts of said compounds and of those 4-oxides which are basic) are manufactured by

(a) reacting a compound of the general formula



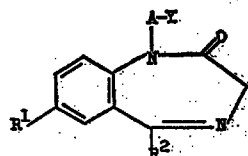
(II)

5 wherein R¹ and R² have the significance given earlier,
or a 4-oxide thereof, with a compound of the general formula



10 wherein X represents a halogen atom or a leaving group and A, B, D and n have the significance given earlier provided that R² represents an alkyl group or a protecting group,
15 and, if necessary, removing the protecting group, or

(b) reacting a compound of the general formula



(IV)

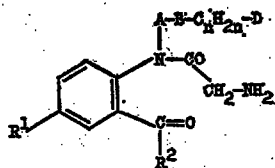
20 or a 4-oxide thereof, with a compound of the general formula



25 in which formulae R¹, R², A, B, D and n have the significance given earlier and one of the symbols Y and Z stands for a hydroxy, mercapto, amino or alkyl-amino group and the other symbol stands for a halogen atom or a leaving group,

or

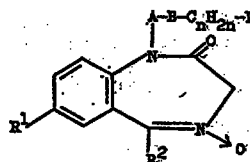
30 (c) cyclising a compound of the general formula



(VI)

wherein R¹, R², A, B, D and n have the significance given earlier,
or

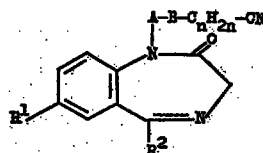
(d) deoxygenating an N-oxide of the general formula



(VII)

wherein R¹, R², A, B, D and n have the significance given earlier,
or

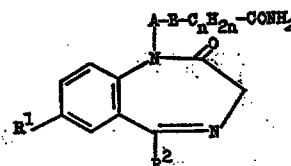
(e) transforming a nitrile of the general formula



(VIII)

wherein R¹, R², A, B, and n have the significance given earlier,
or a 4-oxide thereof, into the corresponding amide, or

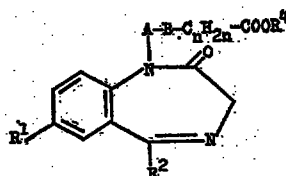
(f) transforming an amide of the general formula



(IX)

wherein R¹, R², A, B, and n have the significance given earlier,
or a 4-oxide thereof, into the corresponding nitrile, or

(g) transforming an ester of the general formula

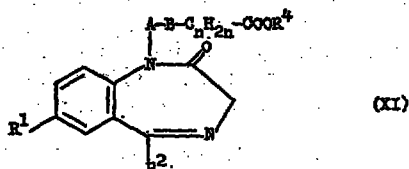


(X)

wherein R¹, R², A, B, and n have the significance given earlier and R⁴ represents an alkyl group,

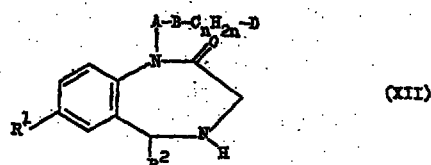
or a 4-oxide thereof, into the corresponding amide (the amide function of which can be mono- or di-substituted by alkyl), or

- (h) saponifying an ester of the general formula



- wherein R^1 , R^2 , R^4 , A and B and n have the significance given earlier, or a 4-oxide thereof, to the corresponding acid and transforming said acid into the corresponding amide (the amide function of which can be mono- or di-substituted by alkyl), or

- (i) oxidising or dehydrogenating a compound of the general formula



wherein R^1 , R^2 , A, B, D and n have the significance given earlier, at the 4,5-bond, and

- (j) converting a basic product obtained into a salt if desired.

Embodiment (a) of the process provided by the present invention can be described as an alkylation at the nitrogen atom in the 1-position of the benzodiazepine molecule. Such alkylations are known per se. In carrying out the alkylation, it is of advantage if a starting material of formula II or a 4-oxide thereof is reacted in the form of an alkali derivative with a compound of formula III. This is expediently achieved by carrying out the reaction in the presence of a strong alkali-containing base; for example an alkali methylate such as sodium methylate, an alkali amide such as sodium amide, an alkali hydride such as sodium hydride or an alkali hydroxide such as sodium hydroxide.

The reaction of a compound of formula II or a 4-oxide thereof with a compound of formula III is expediently carried out in the presence of an inert organic solvent. Suitable inert organic solvents are, for ex-

ample, dimethylformamide, dimethyl sulphoxide, ethyl acetate and alkanols such as isopropanol. Many other solvents and solvent mixtures are likewise suitable and their selection does not present any difficulties with regard to the solubility properties and their inert behaviour in the reaction. The reaction temperature is variable within rather wide limits. As a rule, it will lie between room temperature and the boiling temperature of the reaction mixture. In general, however, temperatures above 120°C should be avoided. Preferred reaction temperatures lie between 60°C and 80°C . The application of pressure is not necessary in this reaction, but is also not of fundamental disadvantage.

In the compounds of formula III the symbol X can represent, besides a halogen atom (especially chlorine or bromine), a leaving group; for example, an arylsulphonyloxy group such as the tosyloxy group or an alkylsulphonyloxy group such as the mesyloxy group. Quaternary ammonium groups such as the trimethyl ammonium group can also serve as effective leaving groups.

When it is desired to manufacture a compound of formula I or a 4-oxide thereof in which B represents the $-\text{NH}-$ group, the amino group in the compound of formula III must be protected by a protecting group which is cleaved off after the reaction with a compound of formula II or a 4-oxide thereof. Especially suitable protecting groups are the benzyloxycarbonyl group and the benzyl group; it being expedient to replace a benzyl group by a benzyloxycarbonyl group before carrying out the cleavage. The cleavage of such a group can be carried out in a known manner by solvolysis or hydrogenolysis.

In the reaction between a compound of formula IV or a 4-oxide thereof with a compound of formula V in accordance with embodiment (b) of the process of this invention, either the compound of formula IV can carry a halogen atom (especially a chlorine or bromine atom) or a leaving group on group A and the compound of formula V can carry a hydroxy, mercapto, amino or alkylamino group, or vice versa. As regards the leaving group, this can be a leaving group of the kind described hereinbefore. Since acid is released in the reaction, it is expedient to carry out the reaction in the presence of an acid-binding agent. Suitable acid-binding agents are, for example, tertiary organic bases such as trialkylamines (especially triethylamine or ethyldiisopropylamine) and alkali carbonates (especially potassium hydrogen carbonate). For the manufacture of ethers and thioethers of formula I (B representing $-\text{O}-$ or $-\text{S}-$), stronger bases such as alkali hydroxides (e.g. sodium hydroxide) and alkali hydrides (e.g. sodium hydride) can also be employed.

The reaction of a compound of formula

IV or a 4-oxide thereof with a compound of formula V can be carried out in an inert organic solvent. Suitable inert organic solvents are, for example, hydrocarbons such as benzene and toluene, ethers such as dioxan, dimethyl sulphoxide and dimethylformamide. The selection of the inert solvent can be varied within a very wide scope. However, attention should be paid that the solvent is inert under the conditions of the reaction to be carried out. Thus, for example, it is also possible to use simple ketones such as methyl ethyl ketone as the solvent. However, such solvents will be avoided when one reaction partner is present as the free amine. The reaction temperature can vary within a wide range. Generally, however, the reaction is carried out at a temperature between room temperature and about 150°C depending upon the solvent chosen. The use of pressure is possible, but in view of the technical complications caused thereby it is normally avoided.

The cyclisation of a compound of formula VI in accordance with embodiment (c) of the present process is effected almost spontaneously. It can, if desired, be accelerated by prolonged standing and/or by the application of heat. It can be carried out in a neutral, alkaline or acidic medium, but an alkaline medium is, however, preferred. It is expedient to carry out the cyclisation in an inert organic solvent; for example, a hydrocarbon such as benzene or toluene, a chlorinated hydrocarbon such as chloroform or methylene chloride, an ether such as dioxan, glacial acetic acid or dimethylformamide. As mentioned hereinbefore, the temperature is not a critical parameter in the carrying out of the cyclisation. Temperatures in the range between room temperature and about 150°C (regard being paid to the solvent employed) are appropriate. The cyclisation can be carried out under pressure, but this is, however, not essential.

The deoxidation of a compound of formula VII in accordance with embodiment (d) of the present process can be carried out, for example, by means of a phosphorus trihalide, especially phosphorus trichloride. This deoxidation is expediently carried out in the presence of an inert organic solvent; for example, a hydrocarbon such as benzene or a chlorinated hydrocarbon such as chloroform or methylene chloride. The temperature advantageously lies at between room temperature and about 80°C to 100°C. The deoxidation of a compound of formula VII can also be carried out by hydrogenation in the presence of Raney-nickel, likewise in an inert organic solvent; for example, an alkanol such as ethanol, an ether such as dioxan, or ethyl acetate. This deoxidation is advantageously carried out at a temperature in the vicinity of room temperature.

Embodiments (e), (f), (g) and (h) of the process in accordance with the invention relate to modification of the terminal function in the side-chain of a compound of formula I or a 4-oxide thereof.

Embodiment (e) involves the hydrolysis of a cyano group to the corresponding amide group. This can be carried out in a conventional manner by strong acids, especially hydrobromic acid, in an inert solvent, especially in glacial acetic acid. This embodiment is expediently carried out at about room temperature.

Embodiment (f) is the reverse of embodiment (e), namely the transformation of an amide group into a cyano group. The dehydration necessary for this can be achieved in a manner known per se by means of phosphorus pentoxide or phosphorus oxychloride. Suitable solvents for this dehydration are, for example, chlorinated aliphatic hydrocarbons such as chloroform, methylene chloride and carbon tetrachloride. The transformation of the amide group into a cyano group can also be carried out by treatment with arylsulphonyl chlorides such as benzenesulphonyl chloride or toluenesulphonyl chloride in the presence of a pyridine base.

The ammonolysis or aminolysis of an ester in accordance with embodiment (g) can be carried out in a manner known per se by treatment of the ester with ammonia or a primary or secondary alkylamine. In this case it is expedient to carry out the treatment in an inert organic solvent; for example, an alkanol such as ethanol, a hydrocarbon such as benzene or a chlorinated hydrocarbon such as chloroform. Aqueous solutions of ammonia or of the amine can also be employed if desired. The temperature at which the treatment is carried out generally lies between room temperature and about 150°C and is dependent on the solvent used, unless one works under pressure which likewise has to be taken into consideration.

The saponification of an ester to the acid in accordance with the first step of embodiment (h) of the present process can be carried out in a manner known per se both by basic and by acidic saponification. Suitable acidic agents are, for example, dilute hydrochloric acid or dilute sulphuric acid. In this case, the temperature advantageously lies at about 60°C to 100°C. The basic saponification is expediently carried out using aqueous alkali (e.g. caustic soda) at a temperature between room temperature and about 60°C and yields the corresponding salt.

The transformation of an acid into an amide in accordance with the second step of embodiment (h) of the present process can be carried out directly in a manner known per se by reaction of the free acid with ammonia or a primary or secondary alkylamine. It is advantageous to carry out this

transformation in two stages by first converting the acid into an acid halide, especially the acid chloride, or into a reactive acid anhydride, whereupon this acid chloride or acid anhydride is subsequently reacted or is reacted in situ with ammonia or the alkylamine. The conversion into an acid chloride can be effected, for example, by treatment with phosphorus pentachloride or thionyl chloride. The reaction is expediently carried out in the absence of a solvent or in the presence of an inert organic solvent such as a chlorinated hydrocarbon (e.g. methylene or chloroform) at a temperature in the vicinity of room temperature (e.g. between -20° and $+30^{\circ}\text{C}$). For the preparation of the acid anhydride, the acid is expediently reacted with a chlorocarbonic acid alkyl ester (e.g. the ethyl ester). In this case, the reaction is advantageously carried out in the presence of a tertiary organic base (e.g. a trialkylamine such as triethylamine). The reaction temperature expediently lies between -5°C and room temperature. An inert organic solvent such as chloroform, toluene, tetrahydrofuran or dimethylformamide can serve as the reaction medium.

The reaction of the acid chloride or acid anhydride formed with ammonia or a primary or secondary alkylamine is advantageously carried out at a temperature between -5°C and room temperature and in a solvent such as water, chloroform, toluene, tetrahydrofuran, dimethylformamide and mixtures thereof.

Tetrahydrocompounds of formula XII can be oxidised or dehydrogenated in accordance with embodiment (i) of the present process in a known manner; for example, by reaction with bromine, chlorine or azodicarboxylic acid esters such as the ethyl ester. The reaction is expediently carried out using an inert organic solvent such as a halogenated hydrocarbon (e.g. carbon tetrachloride, methylene chloride or chloroform), an ether (e.g. dioxan or tetrahydrofuran) and the like. The reaction is expediently carried out at a temperature between about -30°C and 100°C .

The compounds of formula I hereinbefore and those 4-oxides thereof which are basic form acid addition salts with inorganic or organic acids such as hydrochloric acid, phosphoric acid, hydrobromic acid, citric acid, sulphuric acid, acetic acid, formic acid, succinic acid, maleic acid, p-toluenesulphonic acid and the like.

The starting materials of formulae II, III, IV and V hereinbefore are generally and specifically known in many individual cases. Those compounds which are not yet described in the literature can be prepared without difficulty in analogous manner to the methods of preparation employed for known compounds.

The starting materials of formula VI are claimed in our Copending Application No.

25144/73 (Serial No. 1357548), which also describes their preparation.

Starting materials of formula VIII, IX, X and XI can be prepared according to the process embodiments (a), (b), (c) and (d) hereinbefore. An especially suitable route for the preparation of starting materials of formula VII comprises the N_1 -substitution of corresponding compounds of formula VII which are unsubstituted in the 1-position in accordance with process embodiment (a) hereinbefore.

The starting materials of formula XII are new. They can be prepared from the corresponding compounds which are unsubstituted in the 1-position in accordance with the procedure described under embodiment (a) hereinbefore. In this case, it is expedient to protect the nitrogen function in the 4-position of the 1-unsubstituted compound, advantageously with a carbobenzoxy group. After the N_1 -substitution, the protecting group is removed in a manner known per se by solvolysis or hydrogenolysis.

It will be appreciated that the starting materials, especially those of formula VI, need not necessarily be employed in the present process in an isolated state, but can be employed without isolation from the mixture in which they have been prepared.

The compounds of formula I hereinbefore, 4-oxides thereof and pharmaceutically acceptable salts of said compounds and of those 4-oxides which are basic can be used as anticonvulsants, muscle relaxants, sedatives and anxiolytics. The anticonvulsant activity is demonstrated when mice to which said compounds, 4-oxides or salts have been administered are subjected to the pentamethylene-tetrazole test. For example, when testing for anticonvulsant activity in the pentetrazole test according to the method of Orloff (Proc. Soc. Exptl. Biol. Med. 70 254-257 1949), 1 - [2 - (carbamoylmethoxy) - ethyl] - 7 - chloro - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one, which displays an LD_{50} of greater than 1250 mg/kg (p.o.), exhibits an APR 2.0 of 0.76 mg/kg (p.o.) [by APR 2.0 there is meant that dosage in mg/kg of an anticonvulsant which brings about double the pentetrazole consumption in comparison to the untreated control group]. In contrast thereto, phenobarbital, a well-known anticonvulsant, exhibits an APR 2.0 of 30 mg/kg. The muscle relaxant activity can be demonstrated in the rotating rod test. For example, in this test the aforementioned benzodiazepine derivative exhibits an HD_{50} of 0.2 mg/kg (p.o.).

The compounds of formula I hereinbefore, 4-oxides thereof and pharmaceutically acceptable salts of said compounds and of those 4-oxides which are basic can accordingly be used as medicaments; for example, in the form of pharmaceutical preparations which

contain them in association with a compatible pharmaceutical carrier. This carrier can be an organic or inorganic inert carrier material which is suitable for enteral or parenteral administration; for example, water, gelatin, lactose, starches, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols, petroleum jelly etc. The pharmaceutical preparations can be made up in solid form (e.g. as tablets, dragées, suppositories or capsules) or in liquid form (e.g. as solutions, suspensions or emulsions). They may be sterilised and/or may contain adjuvants such as preserving, stabilising, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They can also contain other therapeutically valuable substances. The dosage follows individual requirements, but a dosage of 0.01 mg/kg to 1 mg/kg/day is preferred.

The following Examples illustrate the process provided by the invention: all temperatures are stated in degrees centigrade and are corrected.

Example 1

A solution of 11.3 g (0.037 mol) of 7-chloro - 5 - (o - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one in 100 ml of dimethylformamide is treated at 0°—5° with a solution of 2.06 g (0.090 mol) of sodium in 20 ml of methanol. The mixture is subsequently stirred at room temperature for 15 minutes, 8.4 g (0.045 mol) of 2 - (N - methyl - 2 - chloroethylamino) - acetamide hydrochloride are added and the mixture is heated at 60° for 6 hours. After concentration under reduced pressure, the residue is partitioned between water and methylene chloride, the organic phase washed with a saturated aqueous solution of sodium chloride, dried over sodium sulphate and evaporated. The remaining oil crystallises on trituration with ether. The crude product is recrystallised once from ethanol and once from methylene chloride/ether. There is obtained 1 - {2 - [(carbamoylmethyl)methylamino]ethyl} - 7 - chloro - 5 - (o - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one of melting point 152°—154°. The different mother liquors are combined, concentrated to dryness, taken up in methylene chloride and chromatographed on 200 g of silica gel. The column is initially eluted with methylene chloride/ethyl acetate (1:1), whereby starting material is recovered. The column is subsequently washed out with methanol. Concentration of the eluate and recrystallisation of the residue (once from ethanol and once from methylene chloride/ether) gives an additional amount of the desired product of melting point 152°—154°.

Example 2

In accordance with the procedure described in Example 1, from 10.8 g of 7 - chloro -

5 - (o - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one and 8.4 g of 2 - (N - methyl - 2 - chloroethylamino) - acetamide hydrochloride there is obtained a solid product which, after recrystallisation from acetonitrile, yields 1 - {2 - [(carbamoylmethyl)methylamino]ethyl} - 7 - chloro - 5 - (o - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one of melting point 130°—132°. Chromatography of the different mother liquors and recrystallisation of the uniform fractions yields, besides starting material, an additional amount of the desired product of melting point 130°—132°.

Example 3

In accordance with the procedure described in Example 1, from 10 g of 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and 8.4 g of 2 - (N - methyl - 2 - chloroethylamino) - acetamide hydrochloride there is obtained a solid product which, after recrystallisation from acetone, yields 7.8 g of 1 - {2 - [(carbamoylmethyl)methylamino]ethyl} - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 146°—148°. Chromatography of the different mother liquors and recrystallisation of the uniform fractions yields, besides starting material, an additional amount of the desired product of melting point 146°—148°.

Example 4

In accordance with the procedure described in Example 1, from 10.4 g of 1,3 - dihydro - 7 - nitro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and 8.4 g of 2 - (N - methyl - 2 - chloroethylamino) - acetamide hydrochloride there is obtained a solid crude product which, after repeated recrystallisation from acetonitrile, yields 2.5 g of 1 - {2 - [(carbamoylmethyl)methylamino]ethyl} - 1,3 - dihydro - 7 - nitro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 215°—218° (decomposition). Chromatography of the different mother liquors and recrystallisation of the uniform fractions yields, besides unreacted starting material, an additional amount of the desired product of melting point 215°—218° (decomposition).

Example 5

In accordance with the procedure described in Example 1, from 11.1 g of 5 - (o - fluorophenyl) - 1,3 - dihydro - 7 - nitro - 2H - 1,4 - benzodiazepin - 2 - one and 8.4 g of 2 - (N - methyl - 2 - chloroethylamino) - acetamide hydrochloride there is obtained an oily crude product which is directly chromatographed on 500 g of silica gel using methylene chloride/ethyl acetate (1:1) as the eluting agent. The uniform fractions give unreacted starting material. By washing out the

column with methanol, evaporation of the eluate and recrystallisation of the residue from ethanol there is obtained 1 - {2 - [(carbamoylmethyl)methylamino]ethyl} - 5 - (o - fluorophenyl) - 1,3 - dihydro - 7 - nitro - 2H - 1,4 - benzodiazepin - 2 - one of melting point 187°—189°.

Example 6

In accordance with the procedure described in Example 1, from 11.7 g of 7 - bromo - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one and 8.4 g of 2 - (N - methyl - 2 - chloroethylamino)acetamide hydrochloride there is obtained a solid crude product which, after recrystallisation from ethanol yields 7 - bromo - 1 - {2 - [(carbamoylmethyl)methylamino] - ethyl} - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one of melting point 176°—178°. Chromatography of the different mother liquors and recrystallisation of the uniform fractions gives, besides unreacted starting material, an additional amount of the desired product of melting point 176°—178°.

Example 7

In an analogous manner to that described in Example 1, from 10 g of 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and 9.45 g of 2 - (N - ethyl - 2 - chloroethylamino)acetamide hydrochloride (which can be obtained in analogy to the known preparation of the corresponding N-methyl derivative and which melts at 130°—131°) there is obtained a solid crude product which after recrystallisation from acetonitrile, yields 6.6 g of 1 - {2 - [(carbamoylmethyl)ethylamino]ethyl} - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 116°—118°.

Example 8

In an analogous manner to that described in Example 1, from 10 g of 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and 8.15 g of 2 - (N - methyl - 2 - chloroethylamino)propionitrile hydrochloride there is obtained an oily crude product which is directly chromatographed on 500 g of silica gel using methylene chloride/ethyl acetate (1:1) as the eluting agent. The uniform fractions crystallise from ether and yield 1 - {2 - [(cyanoethyl)methylamino] - ethyl} - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 82°—83°. By treatment, in the usual manner, with methanolic hydrochloric acid there can be obtained a dihydrochloride which can be readily crystallised from ethanol/ether and which melts at above 200° with decomposition.

Example 9

5.0 g of 1 - {2 - [(cyanoethyl)methylamino]ethyl} - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one are shaken with 100 ml of a solution of 33% hydrobromic acid in glacial acetic acid for 4 hours at room temperature. The clear solution obtained is poured onto 600 ml of ether and allowed to stand in an ice-bath for 0.5 hour. The hydrobromide which precipitates is separated off, rapidly washed with ether, and immediately dissolved in ice-water. With the addition of ice, the aqueous solution is made alkaline with 2-N caustic soda and extracted with methylene chloride. The extracts are dried over sodium sulphate and evaporated, and the residue is crystallised from hexane/ether, whereby there is obtained 1 - {2 - [(carbamoyl)ethyl)methylamino] - ethyl} - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 140°—143°. One recrystallisation from ethanol increases the melting point to 143°—145°.

Example 10

8.2 g (0.02 M) of 7 - chloro - 1,3 - dihydro - 1 - [2 - (methylamino)ethyl] - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one dihydrochloride are dissolved in 50 ml of ice-water, treated with 20 ml of 2-N caustic soda and extracted four times with 50 ml of methylene chloride each time. The organic phase is dried over sodium sulphate, evaporated and the residual oil base taken up in 20 ml of methylene chloride. This solution is then added to a mixture of 30 ml of methyl ethyl ketone, 1.5 g (0.02 M) of chloroacetonitrile, 3.1 g (0.02 M) of sodium iodide and 2.8 g (0.022 M) of N-ethyldiisopropylamine and boiled at reflux for 6 hours. After concentration under reduced pressure, the residue is partitioned between water and methylene chloride, the organic phase washed with a saturated aqueous solution of sodium chloride, dried over sodium sulphate and concentrated to dryness. The residual oil is chromatographed on 200 g of silica gel using ethyl acetate as the eluting agent. The uniform fractions are combined, evaporated and crystallised from ether. 7 - Chloro - 1 - {2 - [(cyanomethyl)methylamino]ethyl} - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 108°—110° is obtained. Recrystallisation from methylene chloride/ether does not increase the melting point.

The starting material can be prepared as follows:

A solution of 20 g (0.074 M) of 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one in 200 ml of dimethylformamide is treated at 0°—5° with a solution of 4.12 g (0.18 M) of sodium in 40 ml of methanol. The mixture is subse-

quently stirred for 15 minutes at room temperature, 3.0 g of sodium iodide and 20 g (0.090 M) of N - (2 - chloro - ethyl) - N - methylbenzylamine hydrochloride are added and the resulting mixture is heated at 60° for 6 hours. After concentration under reduced pressure, the oily residue is partitioned between water and methylene chloride, the organic phase is washed with a saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated to dryness. The residual oil is dissolved in 100 ml of benzene and treated dropwise at 20°—25° with 30.9 g (0.2 M) of chloroformic acid benzyl ester. It is subsequently boiled at reflux for 3 hours. After evaporation, the oily residue is taken up in 500 ml of ether, decanted off from the precipitate and treated with 100 ml of 1-N methanolic hydrochloric acid. The precipitated hydrochloride is filtered off by suction, washed with ether and briefly boiled up in 200 ml of acetone. There is obtained 1 - {2 - [(benzyloxycarbonyl)methylamino]ethyl} - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one hydrochloride which can be employed for the next step without further purification. An analytically pure product melting at 176°—180° with decomposition is obtained by crystallisation from acetone.

26.6 g of 1 - {2 - [(benzyloxycarbonyl)methylamino]ethyl} - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one hydrochloride are dissolved in 75 ml of glacial acetic acid, 150 ml of a solution of 33% hydrobromic acid in glacial acetic acid are added, the mixture is allowed to stand at room temperature with occasional thorough shaking for 3 hours and poured onto 1000 ml of ether. The precipitate is decanted off and immediately partitioned between 1000 ml of ice-water and 1000 ml of methylene chloride. With the addition of ice, it is made alkaline with 2-N caustic soda, the organic phase is separated off and the aqueous phase is extracted with methylene chloride. The extracts are dried over sodium sulphate, evaporated, the oily residue is dissolved in ca 30 ml of methanol and treated with an excess of 2-N methanolic hydrochloric acid. The salt which precipitates in crystalline form is filtered off and washed with ether. There is obtained 7 - chloro - 1,3 - dihydro - 1 - [2 - (methylamino)ethyl] - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one dihydrochloride of melting point 220°—223° (decomposition). Crystallisation from methanol/ether does not increase the melting point.

60 Example 11

0.9 g of 1 - {2 - [(cyanomethyl)methylamino] - ethyl} - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one are shaken with 25 ml of a solution of

33% hydrobromic acid in glacial acetic acid for 7 hours, there being obtained a clear solution. The working up is effected in the manner described in Example 9. There is obtained a crude product of melting point 143°—146°. Recrystallisation from acetone gives 1 - {2 - [(carbamoylmethyl)methylamino]ethyl} - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 146°—148°.

Example 12

A solution of 10 g (0.029 M) of 7 - chloro - 1 - (3 - chloropropyl) - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one in 50 ml of methyl ethyl ketone is treated with 4.4 g of sodium iodide and 5.3 g (0.058 M) of 2-methylaminoacetamide and boiled at reflux for 20 hours. After concentration under reduced pressure, the residue is partitioned between water and methylene chloride, the organic phase washed with a saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated to dryness. The residual oil is chromatographed on 300 g of silica gel, first using ethyl acetate and subsequently using ethyl acetate/methanol (1:1) as the eluting agent. The first fractions eluted with ethyl acetate give some unreacted starting material. The subsequent fractions eluted with ethyl acetate/methanol (1:1) yield, after evaporation, an oil which is crystallised from ether and, after recrystallisation from methylene chloride/ether, yields 1 - {3 - [(carbamoylmethyl) - methylamino] - propyl} - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 136°—138°.

Example 13

In an analogous manner to that described in Example 1, from 10.6 g of 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one 4-oxide and 8.4 g of 2 - (N - methyl - 2 - chloroethylamino)acetamide hydrochloride there is obtained a solid crude product which, for purification, is first shaken with a solution of 10 g of succinic acid in 200 ml of water for 0.5 hour. Unreacted starting material is recovered by filtering off under suction. The filtrate is adjusted to pH 7—8 with 2-N ammonium hydroxide and shaken out with methylene chloride. The extracts are dried over sodium sulphate, evaporated and the residue is crystallised from ether. Two recrystallisations from acetonitrile yield 1 - {2 - [(carbamoylmethyl)methylamino]ethyl} - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one 4-oxide of melting point 162°—164° (decomposition).

Example 14

A solution of 2 g of 1 - {2 - [(carbamoylmethyl)methylamino]ethyl} - 7 - chloro - 1,

3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one 4-oxide in 15 ml of chloroform is treated with 1 ml of phosphorus trichloride and boiled at reflux for 5 hours. The mixture is thereupon poured onto ice, shaken with an excess of 40% caustic soda, the organic phase is separated off, dried over sodium sulphate and evaporated. The residual oil is taken up in ethyl acetate and chromatographed on 60 g of silica gel, initially using ethyl acetate and subsequently using ethyl acetate/methanol (1:1) as the eluting agent. The uniform fractions eluted with ethyl acetate/methanol are evaporated and the residual oil is crystallised from ether. Recrystallisation from acetone yield 1 - {2 - [(carbamoylmethyl)methylamino]ethyl} - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 146°—148°.

Example 15

A solution of 10 g (0.037 M) of 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one in 70 ml of dimethylformamide is treated at 0°—5° with a solution of 1.03 g (0.045 M) of sodium in 10 ml of methanol. The mixture is subsequently stirred at room temperature for 30 minutes and, after the addition of 6.3 g (0.053 M) of 2-chloroethoxyacetonitrile, heated at 60° for 6 hours. After concentration under reduced pressure, the residue is partitioned between water and methylene chloride, the organic phase washed with a saturated aqueous sodium chloride solution, dried over sodium sulphate and evaporated. The oil remaining behind is chromatographed over 150 g of aluminium oxide (neutral, activity III) with benzene. The homogeneous fractions are combined, concentrated, taken up in about 30 ml of methanol and treated with excess 2-N methanolic hydrochloric acid. The salt which precipitates in crystalline form after the addition of ether is filtered off, washed with ether and recrystallised from methanol/ether. There are obtained 5.4 g of 1 - [2 - (cyanomethoxy)ethyl] - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one hydrochloride which melts at above 220° with decomposition.

Example 16

1.5 g of 1 - [2 - (cyanomethoxy)ethyl] - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one hydrochloride are treated with 15 ml of a solution of 33% hydrobromic acid in glacial acetic acid and allowed to stand at room temperature for 2 hours. The mixture is worked up according to the procedure described in Example 1 and there is obtained a crude product which is recrystallised from acetonitrile. 1 - [2 - Carbamoylmethoxyethyl] - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H -

1,4 - benzodiazepin 2 - one of melting point 97°—100° is obtained.

Example 17

In accordance with the procedure described in Example 15, from 11.7 g of 7 - bromo - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one and 6.3 g of 2-chloroethoxyacetonitrile there is obtained an oily crude product which is chromatographed on 200 g of silica gel, first using a mixture of methylene chloride/ethyl acetate (1:1) and subsequently using ethyl acetate. The homogeneous fractions eluted with methylene chloride/ethyl acetate yield with oil which crystallises from ether. After recrystallisation from ethanol, there is obtained 7 - bromo - 1 - [2 - (cyanomethoxy)ethyl] - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one of melting point 126°—128°. The subsequent fractions eluted with ethyl acetate yield unreacted starting material.

Example 18

A solution of 10 g (0.035 M) of 7 - chloro - 5 - (o - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one in 65 ml of dimethylformamide is cooled to 0°—5° and, with stirring, treated with a solution of 0.95 g (0.041 M) of sodium in 9.5 ml of methanol. The mixture is subsequently stirred at room temperature for 30 minutes, then a solution of 11.9 g (1.0 M) of 2-chloroethoxyacetonitrile in 10 ml of dimethylformamide is added and the mixture is heated at 60° for 6 hours. It is thereupon evaporated under reduced pressure and the residue partitioned between water and methylene chloride. The organic phase is washed with a saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated. The residual oily crude product is then directly treated with 50 ml of a solution of 33% hydrobromic acid in glacial acetic acid and allowed to stand at room temperature for 2 hours. The crude solution is poured onto 200 ml of ether and left to stand in an ice-bath for 0.5 hour. The precipitate is decanted off and immediately partitioned between 200 ml of ice-water and 100 ml of methylene chloride. With the addition of ice, it is made alkaline with 2-N caustic soda, the organic phase is separated off and the aqueous phase is exhaustively extracted with methylene chloride. The extracts are dried over sodium sulphate, evaporated, the residue is taken up in 40 ml of methylene chloride and chromatographed on 200 g of silica gel. For the elution, there are successively used 250 ml of methylene chloride/ethyl acetate (1:1), 1000 ml of ethyl acetate and 1000 ml of methanol/acetone (1:1). After recrystallisation from ether, the first fractions eluted with methylene chloride/ethyl acetate and

with ethyl acetate give starting material. From the subsequent fractions eluted with methanol/acetone there is obtained, after crystallisation from ethanol, 1 - [2 - (carbamoylmethoxy)ethyl] - 7 - chloro - 5 - (o - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one of melting point 187°—189°.

Example 19

In accordance with the procedure described in Example 18, from 10.6 g of 7 - chloro - 5 - (o - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one and 11.9 g of 2-chloroethoxyacetoneitrile there is obtained a crude product which is directly reacted with hydrobromic acid in glacial acetic acid. By working up in an analogous manner to that described in Example 18 there is obtained, besides starting material, 1 - [2 - (carbamoylmethoxy)ethyl] - 7 - chloro - 5 - (o - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one of melting point 198°—200°.

Example 20

2.25 g (0.041 M) of sodium methylate are added with stirring at room temperature to a solution of 10 g (0.035 M) of 7 - chloro - 5 - (o - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one in 70 ml of dimethylformamide. After the mixture has been stirred for a further 30 minutes, a solution of 7.0 g (0.051 M) of 2-chloroethoxyacetamide in 5 ml of dimethylformamide is added and the resulting mixture is heated at 70° for 6 hours. After concentration under reduced pressure, this residue is partitioned between water and methylene chloride, the organic phase is washed with a saturated aqueous sodium chloride solution, dried over sodium sulphate and evaporated. The residual oil is taken up in 40 ml of methylene chloride and chromatographed on 200 g of silica gel according to the procedure described in Example 18. Besides unreacted starting material, there is obtained 1 - [2 - (carbamoylmethoxy)ethyl] - 7 - chloro - 5 - (o - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one of melting point 187°—189°.

The 2-chloroethoxyacetamide starting material can be prepared as follows:

90 ml of concentrated sulphuric acid are added at 0°—5° with stirring to 119.5 g of 2-chloroethoxyacetoneitrile. The temperature is then allowed to rise by itself and, by means of occasional cooling, is first held at 5°—10° for 30 minutes and subsequently, until cessation of the exothermic reaction (ca 2 hours), at 35°—45°. The mixture is thereupon allowed to stand at room temperature overnight and then poured onto 450 g of ice-water. It is shaken at 0° for 2 hours and the clear solution obtained is shaken out six times with 500 ml of methylene chloride

each time. The organic phase is washed with sodium sulphate, concentrated and the crystalline residue triturated with ether and filtered off by suction. There are obtained 115 g of 2-chloroethoxyacetamide of melting point 75°—77°. An analytically pure product of melting point 76°—77° is obtained by crystallisation from methylene chloride/ether.

Example 21

In an analogous manner to that described in Example 20, by reaction of 11.0 g of 7 - bromo - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one with 7.0 g of 2-chloroethoxyacetamide there is obtained, besides starting material, 7 - bromo - [2 - (carbamoylmethoxy)ethyl] - 1,3 - dihydro - 5 - (2 - pyridyl) - 2H - 1,4 - benzodiazepin - 2 - one which melts at 143°—144° after recrystallisation from ethanol.

Example 22

In an analogous manner to that described in Example 15, from 10 g of 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one and 8.1 g of 2 - chloroethoxyacetic acid methyl ester there is obtained an oily crude product which is purified by chromatography on 150 g of aluminium oxide (neutral, activity III) using benzene as the eluting agent. Conversion into the hydrochloride in a conventional manner yields 1.5 g of 7 - chloro - 1,3 - dihydro - 1 - [2 - [(methoxycarbonyl)methoxy]ethyl] - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one hydrochloride which melts at 179°—182° with decomposition after repeated recrystallisation from ethanol/ether.

Example 23

10 g (0.029 M) of 7 - chloro - 1 - (3 - chloropropyl) - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one, 3.8 g (0.03 M) of N - ethyl - diisopropylamine, 5.3 g (0.058 M) of 2-mercaptoacetamide (freshly prepared) and 4.4 g of sodium iodide are dissolved in 50 ml of methyl ethyl ketone and heated to reflux for 17 hours. The working up is effected in an analogous manner to that described in Example 12. There is obtained an oily crude product which is chromatographed on 200 g of silica gel using ethyl acetate as the eluting agent. The homogeneous fractions yield an oil which crystallises from ether. After recrystallisation from ethanol, there is obtained 1 - {3 - [(carbamoyl)methylthio]propyl} - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 135°—137°.

Example 24

2.3 g (0.042 M) of sodium methylate are added with stirring at room temperature to a solution of 10 g (0.037 M) of 7 - chloro -

1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one in 70 ml of dimethylformamide. The resulting mixture is stirred for a further 30 minutes, then treated with a solution of 8.05 g (0.053 M) of 2 - chloroethoxy - N - methylacetamide in 5 ml of dimethylformamide, heated at 60° for 6 hours, and concentrated under reduced pressure. The residue is partitioned between water and methylene chloride and the organic phase is washed with a saturated aqueous solution of sodium chloride, dried over sodium sulphate and evaporated. The residual oil is chromatographed on 250 g of silica gel, initially with ethyl acetate and subsequently with a 1:1 mixture of ethyl acetate and acetone. The fractions eluted with ethyl acetate chiefly contain unreacted starting material. The subsequent homogeneous fractions eluted with ethyl acetate/acetone give an oil which crystallizes from ether. Recrystallization from methylene chloride/ether yields 1 - [2 - (N - methyl - carbamoyl-methoxy)ethyl] - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 140°—142°.

The 2 - chloroethoxy - N - methyl - acetamide starting material can be prepared as follows:

A solution of 27.6 g (0.2 M) of 2-chloroethoxy-acetic acid and 20.4 g (0.2 M) of triethylamine in 500 ml of tetrahydrofuran is cooled to -5° and, with stirring, treated with a solution of 23.8 g (0.22 M) of ethyl chloroformate in 40 ml of tetrahydrofuran. After 5 minutes, 42 ml of a 30% aqueous methylamine solution are added dropwise and the resulting mixture is further stirred at room temperature for 1 hour. The tetrahydrofuran is then removed in vacuo and the residue taken up in benzene. The benzene solution is dried over sodium sulphate and evaporated. The residual crude product is fractionated in vacuo to yield 2 - chloroethoxy - N - methylacetamide of boiling point 102°—104°/0.4 mm Hg.

Example 25

By reaction of 10 g of 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one with 8.8 g of 2 - chloroethoxy - N,N - dimethylacetamide in accordance with the procedure described in the first paragraph of Example 24 there is obtained 1 - [2 - (N,N - dimethylcarbamoyl - methoxy) - ethyl] - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one which melts at 120°—122° after recrystallization from methylene chloride/ether.

The 2 - chloroethoxy - N,N - dimethylacetamide starting material can be prepared by analogy with the procedure described in the final paragraph of Example 24 from 27.6 g of 2 - chloroethoxy - acetic acid, 20.4 g of triethylamine, 23.8 g of ethyl chloro-

formate and 40 ml of a 45% aqueous dimethylamine solution. After distillation in vacuo there is obtained 2 - chloroethoxy - N,N - dimethylacetamide having a boiling point of 96°—98°/0.5 mm Hg.

Example 26

By reaction of 11.3 g of 7 - chloro - 5 - (o - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one with 8.8 g of 2 - chloroethoxy - N - ethyl - acetamide in accordance with the procedure described in the first paragraph of Example 24 there is obtained 1 - [2 - (N - ethyl - carbamoyl - methoxy) - ethyl] - 7 - chloro - 5 - (o - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one which melts at 136°—138° after recrystallization from methylene chloride/ether.

The 2 - chloroethoxy - N - ethylacetamide starting material can be prepared by analogy with the procedure described in the final paragraph of Example 24 from 27.6 g of 2 - chloroethoxy - acetic acid, 20.4 g of triethylamine, 23.8 g of ethyl chloroformate and 26 ml of a 70% aqueous ethylamine solution. After distillation in vacuo there is obtained 2 - chloroethoxy - N - ethylacetamide of boiling point 95°—97°/0.2 mm Hg.

Example 27

A solution of 12.6 g (0.04 M) of 7 - chloro - 1,3 - dihydro - 1 - (2 - hydroxyethyl) - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one in 100 ml of tetrahydrofuran is treated at room temperature with 2.4 g (0.05 M) of a 50% sodium hydride dispersion in oil. The resulting mixture is subsequently stirred for 1 hour, cooled to 5°—10° and treated over the course of about 1 hour with a solution of 8.3 g (0.05 M) of ethyl bromoacetate in 20 ml of tetrahydrofuran. The resulting yellowish suspension is stirred at room temperature for a further 20 hours, then concentrated under reduced pressure. The residue is partitioned between water and methylene chloride and the organic phase is washed with a saturated aqueous sodium chloride solution, dried over sodium sulphate and evaporated. The oily residue is chromatographed on 280 g of silica gel using ethyl acetate as eluant. The uniform fractions are combined and concentrated. The residual oily 1 - [2 - [(ethoxycarbonyl) - methoxy] - ethyl] - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one can be used for the next step without further purification.

A solution of 10.0 g (0.025 M) of 1 - [2 - [(ethoxycarbonyl) - methoxy] - ethyl] - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one in 75 ml of methanol is treated with 25 ml of 1.0-N sodium hydroxide solution, stirred at room temperature for 2.5 hours and carefully acid-

fied with acetic acid. The methanol is removed under reduced pressure and the residue is basified with 2-N ammonium hydroxide, extracted with ether, re-acidified with acetic acid and extracted with methylene chloride. The methylene chloride extract is dried over sodium sulphate and concentrated. The residual viscous oil is dissolved in 35 ml of acetone and treated with 7 g of p-toluenesulphonic acid. After the addition of 90 ml of ether there separates out an oil which soon crystallizes. The salt thus formed is purified by dissolving in acetone/methanol (7:1) and reprecipitating with ether. The resulting crystalline powder of 1 - [2 - (carboxymethoxy) - ethyl] - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one p-toluenesulphonate melts at 179°—181° (with decomposition).

A solution of 5.45 g (0.01 M) of 1 - [2 - (carboxymethoxy) - ethyl] - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one p-toluenesulphonate and 2.05 g (0.02 M) of triethylamine in 25 ml of tetrahydrofuran is cooled to -5°C and, with stirring, treated with a solution of 1.2 g (0.01 M) of ethyl chloroformate in 3 ml of tetrahydro-furan. After 5 minutes, 2 ml of a 30% aqueous methylamine solution are added dropwise and the mixture is subsequently stirred at room temperature for a further 1 hour. The turbid solution is then concentrated to dryness under reduced pressure and the residual oil partitioned between methylene chloride and water. The organic phase is washed with a saturated aqueous solution of sodium chloride, dried over sodium sulphate and evaporated. The residue crystallizes after the addition of ether, and is recrystallized from methylene chloride/ether to yield 1 - [2 - (N - methyl - carbamoyl - methoxy) - ethyl] - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 140°—142°.

Example 28

A solution of 4.4 g (0.01 M) of 1 - [2 - [(ethoxycarbonyl) - methoxy] - ethyl] - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one in 20 ml of methanol is treated with 4.2 ml of a 30% aqueous methylamine solution, allowed to stand at room temperature for 3 days, and concentrated. The residual oil is taken up in methylene chloride and the resulting solution is washed with water, dried over sodium sulphate and evaporated to dryness. The oily residue is chromatographed on silica gel, initially with ethyl acetate and subsequently with a 1:1 mixture of ethyl acetate and acetone. The uniform fractions eluted with ethyl acetate/acetone yield an oil which crystallizes from ether. Recrystallization from methylene chloride/ether gives 1 - [2 - (N -

methyl - carbamoyl - methoxy) - ethyl] - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 140°—142°.

Example 29

In a manner analogous to that described in the first paragraph of Example 10, from 8.2 g (0.02 M) of 7 - chloro - 1,3 - dihydro - 1 - (2 - methylamino - ethyl) - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one dihydrochloride, 3.0 g (0.02 M) of N - methyl - bromoacetamide, 3.1 g (0.02 M) of sodium iodide and 2.8 g (0.022 M) of N - ethyl - diisopropylamine there is obtained an oily crude product which is chromatographed on 200 g of silica gel with ethyl acetate/ethanol (9:1). Evaporation of the uniform fractions yields an oil which is crystallized from ether and recrystallized from acetonitrile/ether to give 1 - [2 - [(N - methyl - carbamoylmethyl) - methylamino] - ethyl] - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 111°—113°.

Example 30

A suspension of 1.95 g (0.005 M) of 1 - [2 - (carbamoylmethoxy) - ethyl] - 7 - chloro - 5 - (o - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one in 5 ml of pyridine is treated with 1.05 g (0.006 M) of benzenesulphonyl chloride and heated at 100° for 30 minutes, a clear solution being formed. The residue obtained after concentrating under reduced pressure is partitioned between water and methylene chloride and the organic phase is washed with a saturated aqueous solution of sodium chloride, dried over sodium sulphate and evaporated. The residual oil is chromatographed on 60 g of silica gel with ethyl acetate as eluant. The uniform fractions are evaporated and the residual oil is crystallized from ether to yield 1 - [2 - (cyanomethoxy) - ethyl] - 7 - chloro - 5 - (o - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one of melting point 100°—101°. Recrystallization from ether/heptane does not increase the melting point.

Example 31

2 - [2 - (N,N - dimethyl - carbamoyl - methoxy) - ethylamino] - 5 - chloro - benzophenone is prepared as described in the Example of our Copending Application No. 25144/73 (Serial No. 1357548).

A solution of 7.2 g (0.02 M) of 2 - [2 - (N,N - dimethyl - carbamoyl - methoxy) - ethylamino] - 5 - chloro - benzophenone in 20 ml of chloroform is treated at room temperature with 3.0 g (0.025 M) of azidocetyl chloride, stirred at room temperature for 2 hours, diluted with 200 ml of methylene chloride, washed with 2-N sodium carbonate

10 solution and water, dried over sodium sulphate and concentrated. The residual yellow oil is dissolved in 12 ml of acetone and treated dropwise at room temperature with 28
5 ml of a solution of 33% hydrogen bromide in glacial acetic acid. The resulting mixture is stirred at room temperature for a further hour, then is poured onto 300 ml of ether. The precipitate is separated off by
10 decantation and immediately partitioned between ice-water and methylene chloride. The mixture is made alkaline with 2-N sodium carbonate, then the organic phase is separated off and the aqueous phase is repeatedly extracted with methylene chloride. After drying over sodium sulphate, the combined extracts are concentrated and the oily residue is chromatographed on 250 g of silica gel with ethyl acetate/ethanol (9:1). The homogeneous fractions give an oil which crystallizes from ether to yield 1 - [2 - (N,N - dimethyl - carbamoylmethoxy) - ethyl] - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 120°—121°. Recrystallization from methylene chloride/ether does not increase the melting point.

Example 32

30 In accordance with the procedure described in the first paragraph of Example 24, by reaction of 10 g of 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2 H- 1,4 - benzodiazepin - 2 - one with 12.7 g of methyl 2 - (N - benzyl - 2 - chloroethylamino) - acetate there is obtained 1 - {2 - [N - benzyl - N - (methoxycarbonylmethyl) - amino] - ethyl} - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one which melts at 145°—147° after recrystallization from methanol.

40 12 g of 1 - {2 - [N - benzyl - N - (methoxycarbonylmethyl) - amino] - ethyl} - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one in 50 ml of toluene are treated with 7.5 g of benzyl chloroformate, heated at reflux for 20 hours and evaporated. The oily residue is dissolved in 25 ml of glacial acetic acid. 75 ml of a solution of 33% hydrobromic acid in glacial
50 acetic acid are added and the mixture is allowed to stand at room temperature for 2 hours with occasional thorough shaking, then is poured onto 6000 ml of ether. The precipitate is filtered off and immediately partitioned between ice-water and methylene chloride. With addition of ice, the mixture is made alkaline with 2-N sodium carbonate, then the organic phase is separated off and the aqueous phase is repeatedly extracted with methylene chloride. The extracts are combined, dried over sodium sulphate and chromatographed on 400 g of silica gel, initially with ethyl acetate and subsequently with
60 ethyl acetate/acetone (1:1). The fractions

eluted with ethyl acetate chiefly contain un- 65 reacted starting material. The homogeneous fractions subsequently eluted with ethyl acetate/acetone give an oil which is taken up in 30 ml of acetone. The resulting solution is treated with 1.5 g of p-toluenesulphonic acid and subsequently gradually with 60 ml of ether; crystallization occurs. 1 - {2 - [Methoxycarbonyl - methyl] - amino] - ethyl} - 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one 70 p-toluenesulphonate of melting point 147°—150° (with decomposition) is obtained; recrystallization from acetone/ether does not increase the melting point.

The methyl 2 - (N - benzyl - 2 - chloro- 80 ethylamino) - acetate starting material can be prepared as follows:

A stirred suspension of 20.6 g (0.1 M) of N - (2 - chloroethyl) - benzylamine hydrochloride in 200 ml of glacial acetic acid is treated at 5°—10° with 9 g (0.3 M) of paraformaldehyde and 19.5 g (0.3 M) of potassium cyanide. The resulting mixture is heated to 50° over the course of 30 minutes and maintained at this temperature for 5 hours. After cautious removal of hydrocyanic acid and of acetic acid, the oily residue is triturated with 500 ml of ice-water, adjusted to pH 7 with 2-N ammonia solution and extracted with methylene chloride. The extract is dried over sodium sulphate and concentrated to dryness. The residual oil is dissolved in 100 ml of methanol and 40 ml of concentrated hydrochloric acid, and the solution is saturated with hydrogen chloride at 0°—10°, heated to boiling for 15 minutes, and heated to reflux for 4 hours while introducing further hydrogen chloride. After distilling off the methanol, the resulting aqueous suspension is neutralized, while cooling, with sodium bicarbonate and extracted with ether. The extract is dried over sodium sulphate and concentrated. The residual crude product is fractionated in vacuo to give methyl 2 - (N - benzyl - 2 - chloroethylamino) - acetate of boiling point 130—132°/0.5 mm Hg. 100 105 110

Example 33

A solution of 1.56 g (0.004 M) of 1 - [2 - (carbamoylmethoxy) - ethyl] - 7 - chloro - 5 - (o - fluorophenyl) - 1,3,4,5 - tetrahydro - 2H - 1,4 - benzodiazepin - 2 - one in 20 ml of chloroform is treated dropwise at -10° with 16 ml (0.5 M) of bromine in chloroform, stirred at 0°—5° for 30 minutes, treated with 20 ml of 2-N sodium hydroxide solution, and stirred for a further 15 minutes at the same temperature. The organic phase is then separated off, washed with a saturated solution of sodium chloride, dried over sodium sulphate and evaporated to dryness. The semi-solid residue is chromatographed on 80 g of silica gel with acetone/ethyl acetate (1:1) as eluting agent to yield 1 - [2 - (carbamoyl- 115 120 125

methoxy) - ethyl] - 7 - chloro - 5 - (o - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one of melting point 187°—189°.

5 The 1 - [2 - (carbamoylmethoxy) - ethyl] - 7 - chloro - 5 - (o - fluorophenyl) - 1,3,4,5 - tetrahydro - 2H - 1,4 - benzodiazepin - 2 - one starting material can be prepared in the following manner:

10 57 g (0.2 M) of 7 - chloro - 5 - (o - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one are dissolved in 400 ml of glacial acetic acid and, after the addition of 0.75 g of platinum dioxide, hydrogenated under normal conditions. The hydrogenation comes to a standstill after the uptake of the theoretical amount of hydrogen. The catalyst is filtered off and the filtrate evaporated under reduced pressure. The solid residue is triturated with methanol and filtered off to yield 7 - chloro - 5 - (o - fluorophenyl) - 1,3,4,5 - tetrahydro - 2H - 1,4 - benzodiazepin - 2 - one of melting point 215°.

25 A suspension of 29 g (0.1 M) of 7 - chloro - 5 - (o - fluorophenyl) - 1,3,4,5 - tetrahydro - 2H - 1,4 - benzodiazepin - 2 - one in 200 ml of dimethylformamide is treated at room temperature with 34 g (0.2 M) of benzyl chloroformate. The resulting mixture is stirred until a clear solution is obtained, then is treated dropwise with 20 g (0.2 M) of triethylamine, stirred at room temperature for a further 15 hours and poured onto ice-water. The aqueous phase is separated off and further extracted with ether. The combined ether extracts are washed with ice-water, dried over magnesium sulphate and evaporated to dryness. The residue is chromatographed on 1000 g of silica gel with ethyl acetate as eluant. After recrystallization from ethyl acetate/hexane, the uniform fractions yield 25 g of 4 - benzyloxycarbonyl - 7 - chloro - 5 - (o - fluorophenyl) - 1,3,4,5 - tetrahydro - 2H - 1,4 - benzodiazepin - 2 - one of melting point 169°—170°.

14.9 g (0.035 M) of 4 - benzyloxycarbonyl - 7 - chloro - 5 - (o - fluorophenyl) - 1,3,4,5 - tetrahydro - 2H - 1,4 - benzodiazepin - 2 - one are reacted with 7.0 g of 2 - chloroethoxy - acetamide in a manner analogous to that described in the first paragraph of Example 20. After chromatography on silica gel with ethyl acetate as eluant, there is obtained, in addition to unreacted starting material, 4 - benzyloxycarbonyl - 1 - [2 - (carbamoylmethoxy)ethyl] - 7 - chloro - 5 - (o - fluorophenyl) - 1,3,4,5 - tetrahydro - 2H - 1,4 - benzodiazepin - 2 - one in the form of a viscous oil which can be employed for the next step without further purification.

100 g of crude 4 - benzyloxycarbonyl - 1 - [2 - (carbamoylmethoxy) - ethyl] - 7 - chloro - 5 - (o - fluorophenyl) - 1,3,4,5 - tetrahydro - 2H - 1,4 - benzodiazepin - 2 -

one are dissolved in 100 ml of methylene chloride, 20 ml of a solution of 33% hydrobromic acid in glacial acetic acid are added, and the mixture is stirred at room temperature for 2 hours, then poured onto 200 ml of ice-water. The aqueous phase is separated off, made alkaline at 0°—5° with a saturated solution of sodium carbonate, and extracted with methylene chloride. The extract is washed with a saturated aqueous solution of sodium chloride, dried over sodium sulphate and concentrated to dryness. The residue crystallizes on trituration with ether. Recrystallization from ethanol yields 1 - [2 - (carbamoylmethoxy) - ethyl] - 7 - chloro - 5 - (o - fluorophenyl) - 1,3,4,5 - tetrahydro - 2H - 1,4 - benzodiazepin - 2 - one of melting point 168°—170°.

Example 34

Tablets with the following composition are manufactured:

	per tablet	
1 - {2 - [(carbamoylmethyl)-methylamino] - ethyl} - 7 - chloro - 5 - (o - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one	10 mg	90
corn starch	53 mg	95
lactose	150 mg	
gelatine (10% solution)	6 mg	

The active substance, the corn starch and the lactose are thickened with a 10% gelatine solution. The paste is comminuted; the granulate is brought into a suitable pan and dried at 43°. The dried granulate is passed through a comminuting machine and mixed in a mixer with the following ingredients:

talc	6 mg	105
magnesium stearate	6 mg	
corn starch	9 mg	

then compressed to tablets of 240 mg.

Example 35

Suppositories are manufactured with the following ingredients:

	per 1 g suppository	
1 - {2 - [(carbamoylmethyl)-methylamino] - ethyl} - 7 - chloro - 5 - (o - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one	10 mg	115
hydrogenated coconut oil	975 mg	120
carnauba wax	15 mg	

The hydrogenated coconut oil and the carnauba wax are melted in a suitable vessel fitted with glass liner and cooled to 45°.

The active substance is added with stirring and stirred until complete dispersion is obtained. The mixture is then poured into suppository moulds which ensure a suppository weight of 1 g.

Example 36

A parenteral form of presentation is manufactured with the following ingredients:

		per ml
10	1 - {2 - [(carbamoylmethyl) - methylamino]ethyl} - 7 - chloro - 5 - (o - fluoro-phenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin -	
15	2 - one	5 mg
	dimethylacetamide	10%
	propylene glycol	50%
	benzyl alcohol	1.5%
	ethanol	10%
20	water for injection	to 1 ml

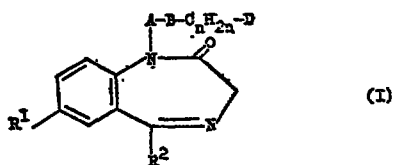
The active substance is dissolved in dimethylacetamide and treated with benzyl alcohol, propylene glycol, ethanol and water. The resulting solution is filtered through a candle filter, filled into suitable ampoules, sealed and sterilised.

Example 37

Tablets and suppositories and a parenteral form of presentation are manufactured according to the data in Examples 34, 35 and 36 respectively, 1 - [2 - (carbamoylmethoxy)ethyl] - 7 - chloro - 5 - (o - fluoro-phenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one or 1 - [2 - (carbamoylmethoxy)ethyl] - 7 - chloro - 5 - (o - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one being used as the active substance.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



wherein A represents an ethylene, propylene or isopropylene group, B represents —O—, —S— or —NR³—, D represents a carbalkoxy, cyano, carbamoyl, monoalkylcarbamoyl or dialkylcarbamoyl group, R¹ represents a halogen atom, a nitro or trifluoromethyl group, an alkyl group containing 2 to 5 carbon atoms or an alkanoyl group, R² represents a phenyl, o-halophenyl, o,o'-dihalophenyl or 2-pyridyl group, R³ represents a

hydrogen atom or an alkyl group and n stands for 1 or 2,

4-oxides thereof and salts of said compounds and of those 4-oxides which are basic.

2. Benzodiazepine derivatives according to claim 1 insofar as R¹ represents a halogen atom, wherein said halogen atom is a chlorine or iodine atom or, where R² represents a 2-pyridyl group, a bromine atom.

3. Benzodiazepine derivatives according to claim 1 insofar as R¹ represents an alkyl group containing 2 to 5 carbon atoms, wherein said alkyl group is the ethyl group.

4. Benzodiazepine derivatives according to claim 1 insofar as R¹ represents an alkanoyl group, wherein said alkanoyl group is the acetyl group.

5. Benzodiazepine derivatives according to any one of claims 1 to 4 inclusive insofar as R² represents a o-halophenyl group, wherein said o-halophenyl group is the o-fluorophenyl or o-chlorophenyl group.

6. Benzodiazepine derivatives according to any one of claims 1 to 5 inclusive, wherein D signifies a cyano or carbamoyl group.

7. Benzodiazepine derivatives according to any one of claims 1 to 6 inclusive, wherein B represents the group —O—, —NH— or —N(CH₃)—.

8. 1 - {2 - [(Carbamoylmethyl)methylamino]ethyl} - 7 - chloro - 5 - (o - fluoro-phenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

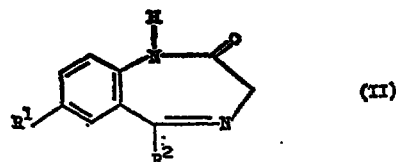
9. 1 - [2 - (Carbamoylmethoxy)ethyl] - 7 - chloro - 5 - (o - fluoro-phenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

10. 1 - [2 - (Carbamoylmethoxy)ethyl] - 7 - chloro - 5 - (o - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

11. A pharmaceutical preparation comprising a compound of formula I in claim 1, a 4-oxide thereof or a pharmaceutically acceptable acid addition salt of such a compound or of a 4-oxide which is basic in association with a compatible pharmaceutical carrier.

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

(a) reacting a compound of the general formula



wherein R¹ and R² have the significance given in claim 1,

The active substance is added with stirring and stirred until complete dispersion is obtained. The mixture is then poured into suppository moulds which ensure a suppository weight of 1 g.

Example 36

A parenteral form of presentation is manufactured with the following ingredients:

		per ml
10	1 - {2 - [(carbamoylmethyl)-methylamino]ethyl} - 7 - chloro - 5 - (o - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one	5 mg
15	dimethylacetamide	10%
	propylene glycol	50%
	benzyl alcohol	1.5%
	ethanol	10%
20	water for injection	to 1 ml

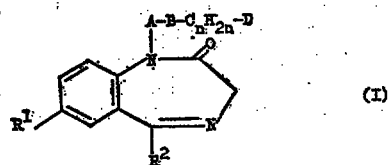
The active substance is dissolved in dimethylacetamide and treated with benzyl alcohol, propylene glycol, ethanol and water. The resulting solution is filtered through a candle filter, filled into suitable ampoules, sealed and sterilised.

Example 37

Tablets and suppositories and a parenteral form of presentation are manufactured according to the data in Examples 34, 35 and 36 respectively, 1 - [2 - (carbamoylmethoxy)ethyl] - 7 - chloro - 5 - (o - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one or 1 - [2 - (carbamoylmethoxy)ethyl] - 7 - chloro - 5 - (o - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one being used as the active substance.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



wherein A represents an ethylene, propylene or isopropylene group, B represents —O—, —S— or —NR³—, D represents a carbalkoxy, cyano, carbamoyl, monoalkylcarbamoyl or dialkylcarbamoyl group, R¹ represents a halogen atom, a nitro or trifluoromethyl group, an alkyl group containing 2 to 5 carbon atoms or an alkanoyl group, R² represents a phenyl, o-halophenyl, o,o'-dihalophenyl or 2-pyridyl group, R³ represents a

hydrogen atom or an alkyl group and n stands for 1 or 2,

4-oxides thereof and salts of said compounds and of those 4-oxides which are basic.

2. Benzodiazepine derivatives according to claim 1 insofar as R¹ represents a halogen atom, wherein said halogen atom is a chlorine or iodine atom or, where R² represents a 2-pyridyl group, a bromine atom.

3. Benzodiazepine derivatives according to claim 1 insofar as R¹ represents an alkyl group containing 2 to 5 carbon atoms, wherein said alkyl group is the ethyl group.

4. Benzodiazepine derivatives according to claim 1 insofar as R¹ represents an alkanoyl group, wherein said alkanoyl group is the acetyl group.

5. Benzodiazepine derivatives according to any one of claims 1 to 4 inclusive insofar as R² represents a o-halophenyl group, wherein said o-halophenyl group is the o-fluorophenyl or o-chlorophenyl group.

6. Benzodiazepine derivatives according to any one of claims 1 to 5 inclusive, wherein D signifies a cyano or carbamoyl group.

7. Benzodiazepine derivatives according to any one of claims 1 to 6 inclusive, wherein B represents the group —O—, —NH— or —N(CH₃)—.

8. 1 - {2 - [(Carbamoylmethyl)methylamino]ethyl} - 7 - chloro - 5 - (o - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

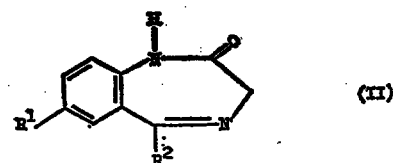
9. 1 - [2 - (Carbamoylmethoxy)ethyl] - 7 - chloro - 5 - (o - fluorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

10. 1 - [2 - (Carbamoylmethoxy)ethyl] - 7 - chloro - 5 - (o - chlorophenyl) - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one.

11. A pharmaceutical preparation comprising a compound of formula I in claim 1, a 4-oxide thereof or a pharmaceutically acceptable acid addition salt of such a compound or of a 4-oxide which is basic in association with a compatible pharmaceutical carrier.

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

(a) reacting a compound of the general formula



wherein R¹ and R² have the significance given in claim 1,





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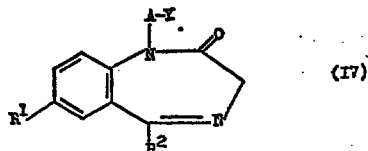
or a 4-oxide thereof, with a compound of the general formula



5 wherein X represents a halogen atom or a leaving group and A, B, D and n have the significance given in claim 1 provided that R³ represents an alkyl group or a protecting group,

10 and, if necessary, removing the protecting group, or

(b) reacting a compound of the general formula

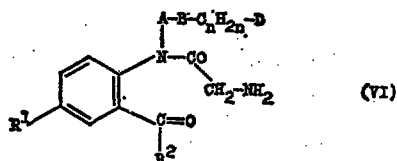


15 or a 4-oxide thereof, with a compound of the general formula



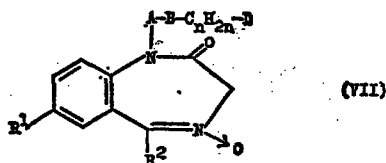
20 in which formulae R¹, R², A, B, D and n have the significance given in claim 1 and one of the symbols Y and Z stands for a hydroxy, mercapto, amino or alkyl-amino group and the other symbol stands for a halogen atom or a leaving group, or

25 (c) cyclising a compound of the general formula



wherein R¹, R², A, B, D and n have the significance given in claim 1, or

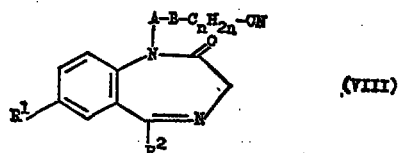
30 (d) deoxygenating an N-oxide of the general formula



wherein R¹, R², A, B, D and n have the significance given in claim 1,

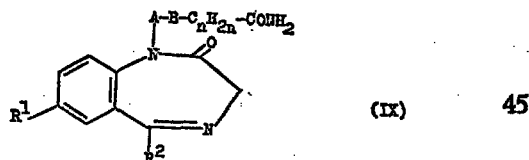
35 or

(e) transforming a nitrile of the general formula



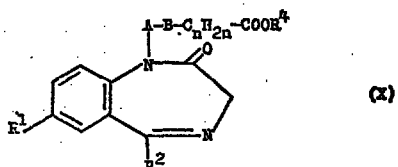
wherein R¹, R², A, B and n have the significance given in claim 1, or a 4-oxide thereof, into the corresponding amide, or

(f) transforming an amide of the general formula



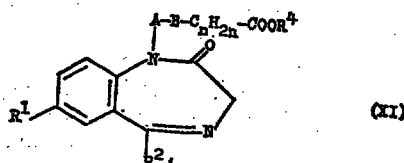
wherein R¹, R², A, B and n have the significance given in claim 1, or a 4-oxide thereof, into the corresponding nitrile, or

(g) transforming an ester of the general formula



wherein R¹, R², A, B and n have the significance given in claim 1 and R⁴ represents an alkyl group, or a 4-oxide thereof, into the corresponding amide (the amide function of which can be mono- or di-substituted by alkyl), or

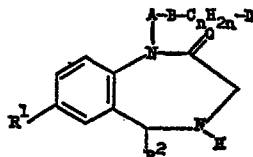
(h) saponifying an ester of the general formula



wherein R¹, R², A, B and n have the significance given in claim 1 and R⁴ has

the significance given earlier in this claim, or a 4-oxide thereof, to the corresponding acid and transforming said acid into the corresponding amide (the amide function of which can be mono- or di-substituted by alkyl), or

(i) oxidising or dehydrogenating a compound of the general formula



wherein R^1 , R^2 , A, B, D and n have the significance given in claim 1, at the 4,5-bond, and

(j) converting a basic product obtained into a salt if desired.

13. A process according to claim 12, wherein any one of embodiments (a) to (h) is carried out and, if desired, a basic product obtained is converted into an acid addition salt.

14. A process according to claim 12 or claim 13 insofar as R^1 represents a halogen atom, wherein said halogen atom is a chlorine or iodine atom or, where R^2 represents a 2-pyridyl group, a bromine atom.

15. A process according to claim 12 or claim 13 insofar as R^1 represents an alkyl group containing 2 to 5 carbon atoms, wherein said alkyl group is the ethyl group.

16. A process according to claim 12 or claim 13 insofar as R^1 represents an alkanoyl group, wherein said alkanoyl group is the acetyl group.

17. A process according to any one of claims 12 to 16 inclusive insofar as R^2 represents an o-halophenyl group, wherein said o-halophenyl group is the o-fluorophenyl or o-chlorophenyl group.

18. A process according to any one of claims 12 to 17 inclusive, wherein D represents a cyano or carbamoyl group.

19. A process according to any one of claims 12 to 18 inclusive, wherein B represents $-O-$, $-NH-$ or $-N(CH_3)-$.

20. Process according to claims 12, 13, 14, 17, 18 and 19, wherein R^1 represents a chlorine atom R^2 represents the o-fluorophenyl group, A represents an ethylene group, B represents the group $-N(CH_3)-$, n stands for 1 and D represents the carbamoyl group and wherein the nitrogen atom in the 4-position of the benzodiazepine molecule does not carry an oxygen atom.

21. A process according to claims 12, 13, 14, 17, 18 and 19, wherein R^1 represents a chlorine atom, R^2 represents the o-fluorophenyl group, A represents an ethylene group, B represents $-O-$, n stands for 1 and D represents the carbamoyl group and wherein the nitrogen atom in the 4-position of the benzodiazepine molecule does not carry an oxygen atom.

22. A process according to claims 12, 13, 14, 17, 18 and 19, wherein R^1 represents a chlorine atom, R^2 represents the o-chlorophenyl group, A represents an ethylene group, B represents $-O-$, n stands for 1 and D represents the carbamoyl group and wherein the nitrogen atom in the 4-position of the benzodiazepine molecule does not carry an oxygen atom.

23. A process as claimed in claim 12 for the manufacture of the benzodiazepine derivatives set forth in claim 1, substantially as hereinbefore described with reference to Examples 1 to 33.

24. Benzodiazepine derivatives as claimed in claim 1, when manufactured by the process claimed in any one of claims 12 to 23 inclusive.

25. Compounds of formula XII in claim 12.

For the Applicants,
CARPMAELS & RANSFORD,
Chartered Patent Agents,
43 Bloomsbury Square,
London, WC1A 2RA.

