

# PATENT SPECIFICATION

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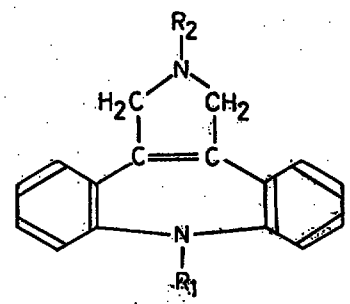
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### (54) NEW AZEPINE DERIVATIVES, PROCESSES FOR THEIR PRODUCTION AND MEDICAMENTS CONTAINING SAME

(71) CIBA-GEIGY A.G., a body corporate organised according to the laws of Switzerland, of CH-4002, 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:—  
The present invention relates to new azepine derivatives, processes for the production thereof, medicaments containing the new compounds and their use.  
Azepine derivatives of the formula I



(I)

wherein  
R<sub>1</sub> represents hydrogen, the methyl, ethyl or n-propyl group and  
R<sub>2</sub> represents hydrogen, a straight chain low alkyl group having maximally 4 carbon atoms, an isopropyl or an allyl group,  
as well as their pharmaceutically acceptable addition salts with inorganic or organic acids, have not been known hitherto.  
It has now been found that such compounds, especially compounds of which the radical R<sub>2</sub> represents a straight chain lower alkyl group containing maximally 4 carbon atoms as well as the pharmaceutically acceptable acid addi-

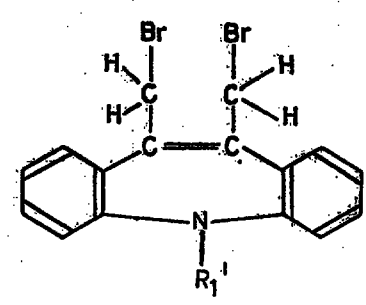
[Price 25p]

tion salts of such compounds, possess valuable pharmacological properties and a high therapeutic index. In the case of oral, rectal and parental administration they have a central depressant activity, e.g. they reduce motility, potentiate the action of anaesthetics, counteract the effect of amphetamine, exhibit a positive action in the "test de la traction", have an antiemetic, serotonin-antagonistic activity on the rat's paw, an analgesic activity on the extension test and lower the body temperature. Furthermore, they exhibit antihistamine activity.

These properties, which are determined by selected standard tests [cp. R. Domenjoz and W. Theobald, Arch. Int. Pharmacodyn. 120, 450 (1959), W. Theobald et al., Arzneimittelforsch. 17, 561 (1967) and W. Theobald and R. Domenjoz, Arzneimittelforsch. 8, 18 (1958)], characterise the compounds as being suitable for the treatment of states of tension and agitation.

As straight chain alkyl group in the compounds of the general formula I, R<sub>2</sub> is the methyl, ethyl, n-propyl or n-butyl group.

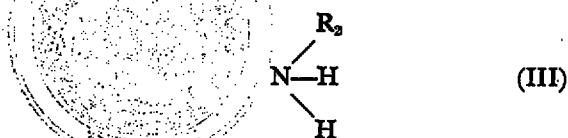
Compounds of the formula I and their pharmaceutically acceptable acid addition salts are produced, according to the invention, by reacting a compound of the general formula II,



(II)

wherein

$R_1'$  represents a methyl, ethyl or n-propyl group or a group which can be replaced by a hydrogen atom by hydrolysis, with a compound having the formula III,



wherein  $R_2$  has the meaning given under formula I, hydrolysing a compound thus obtained wherein  $R_1'$  is other than a methyl, ethyl or n-propyl group and when required converting an azepine derivative having the formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof or converting an acid addition salt of an azepine derivative having the formula I thus obtained into the free base or into another, pharmaceutically acceptable acid addition salt thereof.

Compounds of the formula II above are described and claimed in our copending Application No. 24840/72 (Serial No. 1295679)

The bis-bromomethyl compounds of the formula II are preferably reacted with the free bases of the formula III in the presence of a solvent. Suitable solvents are those which are inert under the reaction conditions, e.g. hydrocarbons such as benzene or toluene, halogenated hydrocarbons such as chloroform, lower alkanols containing maximally 6 carbon atoms such as methanol or ethanol, ether-like solvents such as ether or dioxane, as well as lower alkanones containing maximally 6 carbon atoms such as acetone, methylethyl ketone or diethyl ketone.

In the reaction, according to the invention of one molar equivalent of the bis-bromomethyl compound with one molar equivalent of the free base, two molar equivalents of hydrogen bromide are split off and preferably bound by the use of excess base of the general formula III.

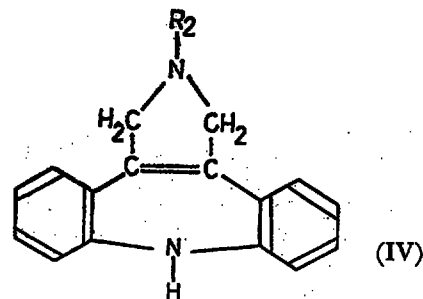
Radicals  $R_1'$ , which are convertible by hydrolysis into the hydrogen atom, are, for example, acyl radicals, e.g. lower alkanoyl groups containing maximally 5 carbon atoms such as the acetyl group, arylcarbonyl groups such as the benzoyl group, and radicals of monofunctional derivatives of carbonic acid such as, e.g. the methoxycarbonyl, ethoxycarbonyl or the phenoxycarbonyl group. The hydrolysis can be performed with the aid of an alkali metal hydroxide, e.g. potassium or sodium hydroxide, preferably at the boiling temperature, either in a higher boiling organic solvent containing hydroxyl groups such as, e.g. ethylene glycol or diethylene glycol, or in a lower monoalkyl ether of such a glycol containing maximally 5 carbon atoms in the alkyl moiety and, in particular, in a lower alkanol containing maximally 6 carbon atoms,

e.g. methanol or ethanol. Moreover, the hydrolysis can be carried out, e.g. in acid medium, e.g. in alkanolic hydrochloric acid, or with the aid of hydrogen bromide in water or glacial acetic acid.

One starting material of the formula II, the 5-methyl-10,11-bis-bromomethyl-5H-dibenz[b,f]azepine, is obtained, for example, as follows: Starting with 5-methyl-5,11-dihydro-10H-dibenz[b,f]azepin-10-one, this is converted with sodium amide into the 11-sodium derivative. The sodium derivative is methylated with methyl iodide to give the 5,11-dimethyl-5,11-dihydro-10H-dibenz[b,f]azepin-10-one. The methylation product yields with magnesium iodide, according to the Grignard reaction, the 5,10,11-trimethyl-10,11-dihydro-5H-dibenz[b,f]azepin-10-ol, which is dehydrated, using polyphosphoric acid, to obtain the 5,10,11-trimethyl-5H-dibenz[b,f]azepine. Finally, the reaction product is brominated with N-bromosuccinimide.

A group of starting materials of the formula II are compounds which are substituted in the 5-position by an acyl radical, e.g. the acetyl group, the methoxycarbonyl or ethoxycarbonyl group. The 5-acetyl-10,11-bis-bromomethyl-5H-dibenz[b,f]azepine is obtained, e.g. if the 10,11-dimethyl-5H-dibenz[b,f]azepine (cp. Geigy A.G. USA Patent No. 3,130,191) is acetylated with acetyl chloride to the 5-acetyl-10,11-dimethyl-5H-dibenz[b,f]azepine and the reaction product brominated with N-bromosuccinimide. Further 5-acyl derivatives of the general formula II can be produced analogously.

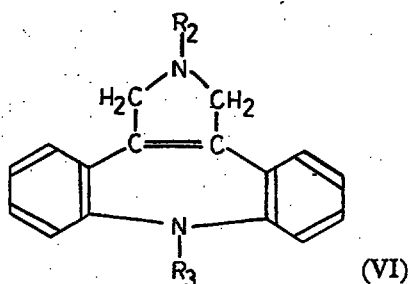
A second process according to the invention for the production of compounds of the formula I but wherein  $R_1$  may not represent a hydrogen atom and their pharmaceutically acceptable acid addition salts which comprises reacting compound of the formula IV



wherein  $R_2$  has the meaning given in claim 1, with a reactive ester of methanol, ethanol or n-propanol preferably in the presence of a solvent and a basic condensing agent, and, when required converting the azepine derivative having the formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof with an inorganic or organic acid.

Starting materials of the formula V are prepared by the first process in which 5 - acyl - 10,11 - bis - bromomethyl - 5H - dibenz[b,f]azepine compounds of the general formula II are reacted with an amine of the general formula III and the acyl compounds thus obtained subsequently hydrolysed.

A third process for the preparation of compounds of the formula I defined above but wherein  $R_1$  may not represent a hydrogen atom, and their pharmaceutically acceptable addition salts comprises reducing a compound of the general formula VI



wherein  $R_2$  has the meaning given under formula I and  $R_3$  represents a formyl, acetyl or propionyl group, with diborane in an ethereal solution and, when required, converting an azepine derivative having the formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof with an inorganic or organic acid.

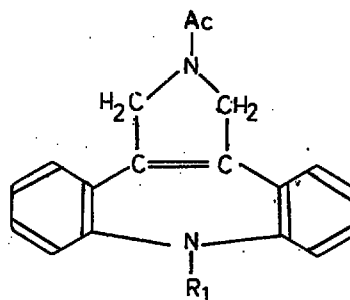
Suitable as reaction media are, for example, tetrahydrofuran, dioxane, methyleneglycoldimethylether or diethyleneglycolmethylether. The reaction temperature is preferably between room temperature and about 100° and reaction time preferably between about 30 minutes and 25 hours. The diborane is prepared, for example, from borontrifluoride-etherate and sodium borohydride ether in situ or in a separate apparatus and subsequently added to the reaction mixture.

The starting materials of the formula VI may be prepared analogously to the first process described for the preparation of compounds of formula I, e.g. by reacting a 5 - alkanoyl - 10,11 - bis - bromo - methyl - 5H - dibenz[b,f]azepine compound of the general formula II but wherein  $R_1'$  represents a formyl, acetyl or propionyl group with an amine of the general formula III.

The 5 - alkanoyl - 10,11 - bis - bromomethyl - 5H - dibenz[b,f]azepine compound of the formula II is obtained for example, by acylating 10,11 - dimethyl - 5H - dibenz[b,f]azepine (cf. Geigy A.G., U.S. Patent No. 3,130,191) with an alkanoyl chloride to give a 5 - alkanoyl - 10,11 - dimethyl - 5H - dibenz[b,f]azepine and then brominating the reaction product with N-bromosuccinimide.

A fourth process for the preparation of

compounds of the formula I defined above but wherein  $R_1$  may represent a hydrogen atom only and their pharmaceutically acceptable acid addition salts comprises hydrolysing a compound having the formula VII



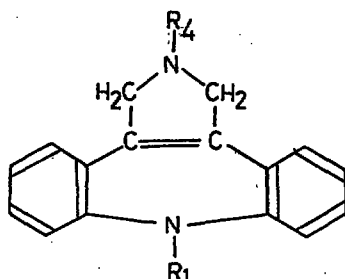
in which  $R_1$  has the meaning given under formula I and Ac represents the acyl radical of an organic acid or a cyano group and, when required, converting an azepine derivative having the formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof or converting an acid addition salt of an azepine derivative having the formula I thus obtained into the free base or into, or into another, pharmaceutically acceptable acid addition salt thereof.

In the starting material of the general formula VII Ac represents in particular a cyano group or the acyl radical of chloroformic acid, a carbonic acid- or thiocarbonic acid monoester, a low alkanic acid containing maximally 5 carbon atoms or an arene carboxylic acid. Examples of acyl radicals as Ac are the chlorocarbonyl-, methoxycarbonyl-, ethoxycarbonyl-, tert.butoxycarbonyl-, phenoxy carbonyl-, benzyloxycarbonyl-, methoxythiocarbonyl-, methylthio - thiocarbonyl, acetyl- and the benzoyl group.

The hydrolysis of compounds of the formula VII is carried out, for example, by heating such compounds for several hours in an alkanolic or aqueous/alkanolic solution of an alkali metal hydroxide, for example, by boiling in a mixture of potassium or sodium hydroxide with ethanol or methanol and a little water. Apart from alkanols, other solvents containing an hydroxyl group may be used, such as ethylene glycol and monoalkyl ethers thereof. Furthermore, compounds of the general formula VII, in particular those in which Ac represents CN, can be hydrolysed by heating with a mineral acid in an organic/ aqueous or aqueous medium, for example, by boiling for several hours in a mixture of 85% phosphoric acid and formic acid or by heating for several hours in 48% hydrobromic acid at 60 to 70° C.

The starting material of the formula VII

is itself prepared, for example, from a compound of the formula VIII



(VIII)

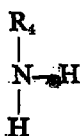
wherein

- 5  $R_1$  has the meaning given under formula I and

$R_4$  represents a low alkyl group containing maximally 5 carbon atoms, the allyl- or benzyl group,

- 10 by reacting the latter compound with a cyanogenhalide, in particular, a cyanogenbromide, or with phosgene, or with an organic acyl halide e.g. a chloroformic acid alkyl ester, the chloroformic acid-phenyl ester or -benzyl ester,
- 15 or the chloride or bromide of a low alkanic acid containing maximally 5 carbon atoms or benzoic acid, in particular acetyl chloride, acetylbromide or benzoyl-chloride, at room temperature or a raised temperature, whereby according to the von Braun reaction, the desired acylation occurs with the splitting off of the
- 20 group  $R_4$  to give the corresponding alkyl, allyl or benzyl halide. The reaction is carried out in an inert organic solvent such as, for example, chloroform or benzene or, if desired, also in an excess of an acylhalide suitable as reaction
- 25 medium.

The starting material of the formula VIII is prepared analogously to the first process by reacting a compound of the formula II with an amine of the formula IX



(IX)

in which

$R_4$  represents a low alkyl group containing maximally 5 carbon atoms, the allyl or the benzyl group.

- 35 The compounds of the formula I, obtained by the process according to the invention, are then optionally converted, in the usual manner, into their addition salts with inorganic and organic acids. For example, the acid desired as salt component, or a solution thereof, is added to a solution of a compound of the
- 40 formula I in an organic solvent. For the reaction, solvents are preferably chosen in which the formed salt is not readily soluble, so

that it can be separated by filtration. Such solvents are, e.g. methanol, acetone, methyl-ethyl ketone, acetone/ethanol, methanol/ether or ethanol/ether.

It is possible to use as medicaments, instead of free bases, pharmaceutically acceptable acid addition salts, i.e. salts with such acids, the anions of which are not toxic in the case of the dosages in question. Furthermore, it is of advantage if the salts to be used as medicaments easily crystallise and are not, or only slightly, hygroscopic. For salt formation with compounds of the formula I it is possible to use, e.g. hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid,  $\beta$ -hydroxy-ethanesulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, mandelic acid and embonic acid.

In a further aspect, therefore, the present invention provides a pharmaceutical composition comprising an azepine derivative of formula I defined above or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable diluent or carrier therefor.

The new active substances, as mentioned above, are administered orally, rectally or parenterally. The dosage depends on the manner of administration, the species, the age and on the individual condition. The daily dosages of the free bases or of pharmaceutically acceptable salts thereof vary between 0.1 mg/kg and 10.5 mg/kg for warm-blooded animals. Suitable dosage units such as dragées, tablets, suppositories or ampoules, preferably contain 5—200 mg of an active substance, according to the invention, or of a pharmaceutically acceptable salt thereof.

Dosage units for oral administration preferably contain, as active substance, between 1 and 10% of a compound of the formula I or of a pharmaceutically acceptable acid addition salt thereof. They are produced by combining the active substance with, e.g. solid pulverulent carriers such as lactose, saccharose, sorbitol, mannitol; starches such as potato starch, maize starch or amylopectin, also laminaria powder or citrus pulp powder; cellulose derivatives or gelatine, optionally with the addition or lubricants, such as magnesium or calcium stearate or polyethylene glycols, to form tablets or dragée cores. The dragée cores are coated, e.g. with concentrated sugar solutions which can also contain, e.g. gum arabic, talcum and/or titanium dioxide, or with a lacquer dissolved in easily volatile organic solvents or mixtures of solvents. Dyestuffs can be added to these coatings, e.g. to distinguish between varying dosage of active substance.

Other 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 hard capsules preferably contain the active substance as a granulate, e.g. in admixture with fillers such as maize starch, and/or lubricants such as talcum or magnesium stearate and, optionally, stabilisers such as sodium metabisulphite ( $\text{Na}_2\text{S}_2\text{O}_5$ ) or ascorbic acid. In soft capsules, the active substance is preferably dissolved or suspended in suitable liquids such as liquid polyethylene glycols, whereby stabilisers can also be added.

Suitable dosage units for rectal administration are, e.g. suppositories consisting of a combination of an active substance, or of a suitable pharmaceutically acceptable acid addition salt thereof, with a suppository foundation substance. Suitable as a suppository foundation substance are, e.g. natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. Also suitable are gelatine rectal capsules consisting of a combination of the active substance, or of a suitable pharmaceutically acceptable acid addition salt thereof, and a foundation substance. Suitable as a foundation substance are, e.g. liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Ampoules for parenteral administration, particularly intramuscular administration, preferably contain a pharmaceutically acceptable water soluble acid addition salt of an active substance in a concentration of preferably 0.5—5%, optionally together with suitable stabilising agents and buffer substances, in aqueous solution.

The following prescriptions further illustrate the production of tablets, dragées, capsules, suppositories and ampoules:

a) 250 g of 2 - ethyl - 1,2,3,8 - tetrahydro-dibenzo[b,f]pyrrolo[3,4 - d]azepine hydrochloride are mixed together with 175.80 g of lactose and 169.70 g of potato starch. The mixture is moistened with an alcoholic solution of 10 g of stearic acid, granulated through a sieve and dried. 160 g of potato starch, 200 g of talcum, 2.50 g of magnesium stearate and 32 g of colloidal silicon dioxide are mixed in and the mixture is pressed to form 10,000 tablets each weighing 100 mg and each containing 25 mg of active substance. Optionally, the tablets can be provided with grooves for finer adjustment of the dosage amount.

b) A granulate is produced from 250 g of 2 - ethyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine hydrochloride, 175.90 g of lactose and the alcoholic solution of 10 g of stearic acid. After being dried, the granulate is mixed with 56.60 g of colloidal silicon dioxide, 165 g of talcum, 20 g of potato starch and 2.50 g of magnesium stearate, and the mixture is pressed into 10,000 dragée cores. These are subsequently coated with a concentrated syrup made from 502.28 g of crystallised saccharose, 6 g of shellac, 10 g

of gum arabic, 0.22 g of dyestuff and 1.5 g of titanium dioxide, and dried. The obtained dragées, each weight 120 mg and each contain 25 mg of active substance.

c) To produce 1000 capsules each containing 25 mg of active substance, 25 g of 2 - n - propyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine - hydrochloride are mixed with 248.0 g of lactose. The mixture is evenly moistened with an aqueous solution of 2.0 g of gelatine and is then granulated through a suitable sieve (e.g. Seive No. III according to Ph. Helv. V). The granulate is mixed with 10.0 g of dried maize starch and 15.0 g of talcum. The obtained mixture is uniformly filled into 1000 hard gelatine capsules, size 1.

d) A suppository foundation mixture is prepared from 2.5 g of 2 - n - propyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine - hydrochloride and 167.5 g of adeps solidus and from this mixture are filled 100 suppositories, each containing 25 mg of active substance.

e) A solution of 25 g of 2 - ethyl - 8 - methyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[2,3 - d]azepine - hydrochloride in one litre of water is filled into 1000 ampoules and sterilized. An ampoule contains a 2.5% solution of 25 mg of active substance.

The following examples further illustrate the production of the new compounds of the general formula I and of intermediate products not described hitherto, but the examples in no way limit the scope of the invention. The temperatures are given in degrees Centigrade.

#### Example 1

a) 35 g of 5 - acetyl - 10,11 - bis - bromomethyl - 5H - dibenz[b,f]azepine are dissolved in 250 ml of anhydrous benzene. The obtained solution is added dropwise within one hour at 5—15° to a solution of 20 g of methylamine in 180 ml of anhydrous benzene. The reaction mixture is stirred for a further hour at 40°, cooled to 20° and 25 ml of water are added all at once. The organic phase is separated, dried over potassium carbonate and completely concentrated by evaporation in a rotary evaporator. The residue, 2 - methyl - 8 - acetyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine, is a viscous oil which, as crude product, is further processed.

b) 23 g of 2 - methyl - 8 - acetyl - 1,2,3,8 - tetrahydrodibenzo[b,f]pyrrolo[3,4 - d]azepine (crude product) are refluxed with 115 ml of 20% ethanolic potassium hydroxide solution for 2 hours. The mixture is then cooled to 20° and the precipitated crude product is filtered with suction. The obtained 2 - methyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine melts, after recrystallisation from benzene, at 233—234°; 14 g of the

obtained base are stirred into 80 ml of anhydrous acetone and the hydrochloride is precipitated with 11.3 ml of 5N anhydrous ethanolic hydrochloric acid; M.P. of the hydrochloride after recrystallisation from ethanol is 233—236°.

The starting material, the 5 - acetyl - 10, 11 - bis - bromomethyl - 5H - dibenz[b,f]azepine, is produced as follows:

c) 39.5 g of acetyl chloride are added dropwise within 30 minutes, whilst stirring to a solution of 98 g of 10,11 - dimethyl - 5H - dibenz[b,f]azepine (cp. Geigy A.G., USA Patent No. 3,130,191) M.P. 131—132°, in 295 ml of toluene. The reaction mixture is afterwards refluxed for 5 hours, concentrated by evaporation in vacuo and the residue dissolved in ether. The ethereal solution is washed with water, dried over sodium sulphate and concentrated by evaporation. The residue, which is recrystallised from petroleum ether, yields 5 - acetyl - 10,11 - dimethyl - 5H - dibenz[b,f]azepine M.P. 109—111°.

d) 101 g of 5 - acetyl - 10,11 - dimethyl - 5H - dibenz[b,f]azepine are dissolved in one litre of carbon tetrachloride and to the solution are added 138 g of N-bromosuccinimide. By exposure to two 200 watt lamps or to a UV-lamp, the mixture is heated, while being stirred, to boiling. The mixture is kept boiling until all the N-bromosuccinimide is converted. The reaction mixture is cooled to 0° and 200 ml of water are added. The precipitated crystalline 5 - acetyl - 10,11 - bis - bromomethyl - 5H - dibenz[b,f]azepine, M.P. 175—176°, is filtered off with suction.

#### Example 2

Analogously to Example 1a and b) are produced the following intermediate products and final products:

a) from 23 g of 5 - acetyl - 10,11 - bis - bromomethyl - 5H - dibenz[b,f]azepine and 15 g of ethylamine in 135 ml of anhydrous benzene is obtained the intermediate product: 2 - ethyl - 8 - acetyl - 1,2,3 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine (crude product); and by subsequent saponification is obtained the final product:

2 - ethyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine, M.P. 209—211° (from benzene); hydrochloride M.P. 260—264° (from ethanol);

b) from 37.5 g of 5 - acetyl - 10,11 - bis - bromomethyl - 5H - dibenz[b,f]azepine and 15 g of n - propylamine in 135 ml of anhydrous benzene is obtained the intermediate product:

2 - n - propyl - 8 - acetyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine (crude product); and by subsequent saponification is obtained the final product:

2 - n - propyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine, M.P.

181—182° (from benzene); hydrochloride, M.P. 253—256° (from ethanol);

c) from 37.5 g of 5 - acetyl - 10,11 - bis - bromomethyl - 5H - dibenz[b,f]azepine and 15 g of allylamine in 135 ml of anhydrous benzene is obtained the intermediate product:

2 - allyl - 8 - acetyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine (crude product); and by subsequent saponification is obtained the final product:

2 - allyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine, M.P. 174—176° (from benzene); hydrochloride, M.P. 245—249° (from ethanol); and

d) From 25 g of 5 - acetyl - 10,11 - bis - bromomethyl - 5H - dibenz[b,f]azepine and 26 g of n-butylamine in 150 ml of anhydrous benzene, the intermediate product 2 - n - butyl - 8 - acetyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine (crude product); and by subsequent saponification, the end product 2 - n - butyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine, M.P. 156—157° (from ethanol); hydrochloride, M.P. 230—234° (from ethanol).

e) From 39.5 g of 5 - acetyl - 10,11 - bis - bromomethyl - 5H - dibenz[b,f]azepine and 22 g of isopropylamine in 150 ml of anhydrous benzene, the intermediate product 2 - isopropyl - 8 - acetyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine (crude product); and by subsequent saponification, the end product 2 - isopropyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine, M.P. 197—198° (from benzene); methanesulphonate, M.P. 282—285° (from ethanol).

#### Example 3

a) 14 g of 5 - methyl - 10,11 - bis - bromomethyl - 5H - dibenz[b,f]azepine are dissolved in 60 ml of anhydrous benzene and the solution is added dropwise within one hour at 32—34°, whilst stirring is maintained, to a solution of 30 g of methylamine in 270 ml of methanol. The reaction mixture is stirred for a further one hour at 50° and the solvent and excess methylamine are then distilled off. 50 ml of water are added to the residue and the suspension is extracted with ether. The ethereal solution is washed with water and extracted with 2N hydrochloric acid. The acid aqueous extract is rendered alkaline to phenolphthalein with concentrated ammonia water and the precipitated base extracted with ether. The ethereal solution is washed with water, dried over potassium carbonate and concentrated by evaporation. The residue, 2,8 - dimethyl - 1,2,3,8 - tetrahydrodibenzo[b,f]pyrrolo[3,4 - d]azepine, is recrystallised from petrol and melts at 120—121°; oxalate, M.P. 230—232°.

The starting material, the 5 - methyl - 10,11 - bisbromomethyl - 5H - dibenz[b,f]azepine, is produced as follows:

b) A suspension of 43 g of sodium amide

in 120 ml of toluene is added dropwise within one hour at 65—75°, whilst vigorous stirring is maintained, to a solution of 223 g of 5 - methyl - 5,11 - dihydro - 10H - dibenzo[b,f]azepin - 10 - one in 1.5 litres of anhydrous benzene. The reaction mixture is subsequently refluxed for 2 hours. The suspension is afterwards cooled to 45—50°, 221 g of methyl iodide are added dropwise within 2 hours at this temperature and stirring is maintained for a further 16 hours at 45—50°. The reaction mixture is cooled to 5—10° and to it are carefully added 250 ml of water. The organic phase is separated, washed with water, dried over sodium sulphate and concentrated to ca. 400 ml. To this concentrated solution are added 200 ml of petroleum ether, whereupon 5,11 - dimethyl - 5,11 - dihydro - 10H - dibenz[b,f]azepin - 10 - one, M.P. 128—130°, crystallises out;

c) A solution of 228 g of 5,11 - dimethyl - 5,11 - dihydro - 10H - dibenz[b,f]azepin - 10 - one in 950 ml of anhydrous benzene is added dropwise within 1 1/2 hours, with vigorous stirring, to a Grignard solution consisting of 47 g of magnesium, 273 g of methyl iodide and 540 ml of absolute ether, whereby a reaction temperature of -5 to 0° is maintained. The suspension is subsequently heated to 50° and stirring proceeds for a further 20 hours at this temperature. The reaction mixture is cooled to 0° and then poured on to a mixture of one litre of 2N hydrochloric acid and 500 g of ice. The organic phase is separated and the aqueous phase again extracted with benzene. The combined organic solutions are washed with water, dried over sodium sulphate and concentrated by evaporation in vacuo. The residue, which is recrystallised from petrol, yields 5,10,11 - trimethyl - 10,11 - dihydro - 5H - dibenz[b,f]azepin - 10 - ol, M.P. 102—104°;

d) A mixture of 89 g of 5,10,11 - trimethyl - 10,11 - dihydro - 5H - dibenz[b,f]azepin - 10 - ol and 890 g of polyphosphoric acid is well stirred for one hour at 95—100°. The reaction mixture is cooled to 60—70° and slowly poured on to 3 litres of water at 40°, so that the reaction temperature does not exceed 60—70°. The precipitated product is filtered off with suction at 20°, one litre of 2N ammonia solution is added and the liberated base is extracted with benzene. The benzene solution is washed with water, dried over potassium carbonate and concentrated by evaporation. The residue, which is recrystallised from petrol, yields 5,10,11 - trimethyl - 5H - dibenz[b,f]azepine, M.P. 109—111°;

e) 23.5 g of 5,10,11 - trimethyl - 5H - dibenz[b,f]azepine are dissolved in 300 ml of carbon tetrachloride and to the solution are added 36 g of N-bromosuccinimide. Whilst being stirred and exposed to two 200 watt lamps, or to a UV-lamp, the mixture is heated to boiling. The mixture is maintained

boiling until all the N-bromosuccinimide is converted. The reaction mixture is then cooled to 20° and 50 ml of water are added. The organic phase is separated, washed with water, dried over sodium sulphate and concentrated by evaporation at 40° in vacuo. The residue is dissolved in 50 ml of ether, the solution cooled to 0°, whereupon 5 - methyl - 10,11 - bis - bromomethyl - 5H - dibenz[b,f]azepine, M.P. 127—130°, crystallises out;

#### Example 4.

The following end products are prepared analogously to Example 3a).

a) From 16 g of 5 - methyl - 10,11 - bis - bromomethyl - 5H - dibenz[b,f]azepine and 25 g of ethylamine in 150 ml of methanol, 2 - ethyl - 8 - methyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]azepine (crude product); oxalate M.P. 208—210° (from methanol).

b) From 39.5 g of 5 - methyl - 10 - 11 - bis - bromomethyl - 5H - dibenz[b,f]azepine and 28.5 g of allylamine in 100 ml of methanol, 2 - allyl - 8 - methyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine, M.P. 137—139° (from anhydrous ethanol). methanesulfonate, M.P. 194—196° (from anhydrous ethanol).

#### Example 5.

a) 7.8 g of 2 - ethyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine are stirred into 40 ml of dimethyl formamide and 0.8 g of sodium hydride are added to the suspension thus produced at a temperature of 25—35°.

The reaction mixture is then stirred for a further hour at 80°, cooled to 20° and at this temperature a solution of 5.1 g of n-propyliodide is added dropwise within 30 minutes. The reaction mixture is then stirred for 18 hours between 50 and 55°, cooled to 20° and water and ether then added. The organic phase is separated and extracted with 2N hydrochloric acid.

The free base is precipitated out from the hydrochloric acid extract with concentrated ammonia water and taken up with ethyl ether. The ethereal solution is washed with water, dried over potassium carbonate and completely evaporated in a rotary evaporator. The residue yields, after recrystallisation from ethanol, 2 - ethyl - 8 - n - propyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine, M.P. 105—107°. 2 g of the obtained base are dissolved in 20 ml of acetone and a solution of 0.87 g of oxalic acid in 5 ml of anhydrous ethanol is added, whereupon the oxalate crystallises out, M.P. (after recrystallisation from ethanol) 192—194°.

#### Example 6

a) 0.64 g of diborane, freshly prepared from 2.6 g of sodiumborohydride and 13 g of boron-trifluoride-etherate (G. Zweifel and H. C.

Brown, Organic Reactions, Vol. XIII, page 32) are introduced with nitrogen into a solution of 13.5 g of 2 - ethyl - 8 - acetyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine in 70 ml of anhydrous tetrahydrofuran, whilst the temperature is maintained between 0 and 5° by ice cooling. The mixture was then stirred for one hour at 0—5° and a further hour at 20—25°. 30 ml of 10% sodium phosphate solution are then added dropwise and the tetrahydrofuran then evaporated in a rotary evaporator. The residue is heated to boiling under reflux for one hour with 300 ml of 4N hydrochloric acid, after cooling to 20° made alkaline to phenolphthalein with concentrated sodium hydroxide and the precipitated base extracted with ether. The ethereal solution is washed with water, dried over potassium carbonate and concentrated to a small volume, whereupon 2,8 - diethyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine crystallises out. The crude product is recrystallised from ethanol, M.P. 100—102°. 5.8 g of the obtained base are dissolved in 40 ml of anhydrous acetone and 4 ml of 5N anhydrous ethanolic hydrogen chloride solution are added, whereupon the hydrochloride crystallises out; M.P. after recrystallisation from isopropanol, 267—271° (decomposition).

#### Example 7.

a) 22 g of 2 - allyl - 8 - methyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine are dissolved in 250 ml of anhydrous benzene and boiled under reflux. A solution of 9.5 g of ethyl chloroformate in 10 ml of anhydrous benzene is added dropwise to the reaction mixture within 30 minutes and the allyl chloride formed simultaneously distilled off. After the end of the dropwise addition, the mixture is boiled for a further hour under reflux, then cooled to room temperature.

The benzene solution is washed with 2N hydrochloric acid and then with water, dried over sodium sulphate and concentrated in vacuo to a small volume, whereupon 2 - carbethoxy - 8 - methyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine, M.P. 129—131°, crystallises out.

b) 18 g of 2 - carbethoxy - 8 - methyl - 1,2,3,8 - tetrahydrodibenzo[b,f]pyrrolo[3,4 - d]azepine are boiled for six hours under reflux with a solution of 18 g of potassium hydroxide in 180 ml of anhydrous ethanol. The ethanol is then distilled off from the reaction mixture in a rotary evaporator. The residue is taken up with 200 ml of water and ether. The ethereal solution is stirred with 100 ml of 2N hydrochloric acid, whereupon 8 - methyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine hydrochloride precipitates. After filtering under suction and washing with 2N hydrochloric acid, the crude product is dried in a vacuum cabinet and then recrystallised

from ethanol, M.P. 274—278° (decomposition).

#### Example 8.

Analogously to Example 7 a) and b), the following intermediate product and end product are prepared.

a) From 13.8 g of 2 - allyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine and 5.5 g of ethyl chloroformate, the intermediate product 2 - carbethoxy - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine (crude product; and by subsequent saponification the ends product 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine, M.P. 222—224° (from benzene); hydrochloride, M.P. 261—265° (decomposition) (from ethanol).

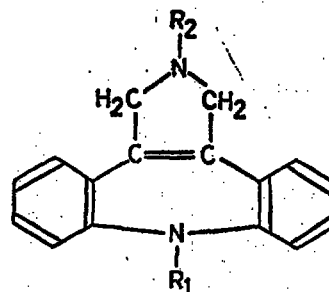
#### Example 9

10 g of 2 - ethyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine and 100 ml of 99% of formic acid are boiled under reflux for 2 hours with stirring.

The excess formic acid is then evaporated in vacuo from the reaction mixture. The residue is dissolved in water, and the base precipitated by the addition of concentrated ammonia and taken up in ether. The ethereal solution is washed with water, dried over potassium carbonate and evaporated. The residue, 2 - ethyl - 8 - formyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine is a viscous oil as crude product. 10 g of the obtained base are dissolved in 30 ml of absolute acetone and 6.9 ml of 5N anhydrous ethanolic hydrogen chloride are added, whereupon the hydrochloride crystallises out. After recrystallisation from methanol, the substance melts at 245—250° (decomposition).

#### WHAT WE CLAIM IS:—

1. Azepine derivatives having the formula



(I)

wherein

R<sub>1</sub> represents a hydrogen atom or a methyl, ethyl or n-propyl group, and

R<sub>2</sub> represents a hydrogen atom, a straight-chain low alkyl group having maximally 4 carbon atoms, an isopropyl or an allyl group.

2. Azepine derivatives having the formula



Brown, Organic Reactions, Vol. XIII, page 32) are introduced with nitrogen into a solution of 13.5 g of 2 - ethyl - 8 - acetyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine in 70 ml of anhydrous tetrahydrofuran, whilst the temperature is maintained between 0 and 5° by ice cooling. The mixture was then stirred for one hour at 0—5° and a further hour at 20—25°. 30 ml of 10% sodium phosphate solution are then added dropwise and the tetrahydrofuran then evaporated in a rotary evaporator. The residue is heated to boiling under reflux for one hour with 300 ml of 4N hydrochloric acid, after cooling to 20° made alkaline to phenolphthalein with concentrated sodium hydroxide and the precipitated base extracted with ether. The ethereal solution is washed with water, dried over potassium carbonate and concentrated to a small volume, whereupon 2,8 - diethyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine crystallises out. The crude product is recrystallised from ethanol, M.P. 100—102°. 5.8 g of the obtained base are dissolved in 40 ml of anhydrous acetone and 4 ml of 5N anhydrous ethanolic hydrogen chloride solution are added, whereupon the hydrochloride crystallises out; M.P. after recrystallisation from isopropanol, 267—271° (decomposition).

#### Example 7.

a) 22 g of 2 - allyl - 8 - methyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine are dissolved in 250 ml of anhydrous benzene and boiled under reflux. A solution of 9.5 g of ethyl chloroformate in 100 ml of anhydrous benzene is added dropwise to the reaction mixture within 30 minutes and the allyl chloride formed simultaneously distilled off. After the end of the dropwise addition, the mixture is boiled for a further hour under reflux, then cooled to room temperature.

The benzene solution is washed with 2N hydrochloric acid and then with water, dried over sodium sulphate and concentrated in vacuo to a small volume, whereupon 2 - carboxy - 8 - methyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine, M.P. 129—131°, crystallises out.

b) 18 g of 2 - carboxy - 8 - methyl - 1,2,3,8 - tetrahydrodibenzo[b,f]pyrrolo[3,4 - d]azepine are boiled for six hours under reflux with a solution of 18 g of potassium hydroxide in 180 ml of anhydrous ethanol. The ethanol is then distilled off from the reaction mixture in a rotary evaporator. The residue is taken up with 200 ml of water and ether. The ethereal solution is stirred with 100 ml of 2N hydrochloric acid, whereupon 8 - methyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine hydrochloride precipitates. After filtering under suction and washing with 2N hydrochloric acid, the crude product is dried in a vacuum cabinet and then recrystallised

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#### Example 8.

Analogously to Example 7 a) and b), the following intermediate product and end product are prepared.

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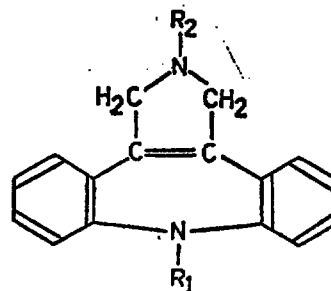
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(I)

wherein

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R<sub>2</sub> represents a hydrogen atom, a straight-chain low alkyl group having maximally 4 carbon atoms, an isopropyl or an allyl group.

2. Azepine derivatives having the formula

I as defined in claim 1 but wherein  $R_1$  may represent a hydrogen atom or methyl group only.

3. The pharmaceutically acceptable acid addition salts of an azepine derivative as claimed in claim 1.

4. The pharmaceutically acceptable acid addition salts of an azepine derivative as claimed in claim 2.

5. 2 - Methyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine and its pharmaceutically acceptable acid addition salts.

6. 2 - Ethyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine and its pharmaceutically acceptable acid addition salts.

7. 2 - n - Propyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine and its pharmaceutically acceptable acid addition salts.

8. 2 - Allyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine and its pharmaceutically acceptable acid addition salts.

9. 2 - n - Butyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine and its pharmaceutically acceptable acid addition salts.

10. 2 - Isopropyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine and its pharmaceutically acceptable acid addition salts.

11. 2,8 - Dimethyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine and its pharmaceutically acceptable acid addition salts.

12. 2 - Ethyl - 8 - methyl 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine and its pharmaceutically acceptable acid addition salts.

13. 2 - Allyl - 8 - methyl 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine and its pharmaceutically acceptable acid addition salts.

14. 2 - Ethyl - 8 - n - propyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine and its pharmaceutically acceptable acid addition salts.

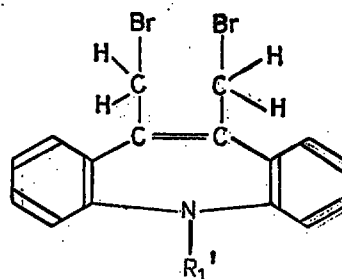
15. 2,8 - Diethyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine and its pharmaceutically acceptable acid addition salts.

16. 8 - Methyl - 1,2,3,8 - tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine and its pharmaceutically acceptable acid addition salts.

17. 1,2,3,8 - Tetrahydro - dibenzo[b,f]pyrrolo[3,4 - d]azepine and its pharmaceutically acceptable acid addition salts.

18. Process for the production of azepine derivatives having the formula I as defined in claim 1 and their pharmaceutically acceptable

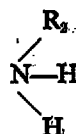
acid addition salts, which comprises reacting a compound having the formula II



(II)

wherein

$R_1$  represents a methyl, ethyl or n-propyl group or a group which can be replaced by a hydrogen atom by hydrolysis with a compound having the formula III



(III)

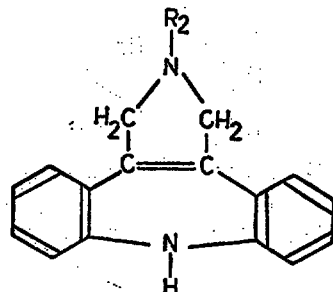
wherein  $R_2$  has the meaning given in claim 1, hydrolysing a compound thus obtained wherein  $R_1$  is other than a methyl-ethyl or n-propyl group and when required converting an azepine derivative having the formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof or converting an acid addition salt of an azepine derivative having the formula I thus obtained into the free base or into another, pharmaceutically acceptable acid addition salt thereof.

19. Process as claimed in claim 18, wherein  $R_1$  represents a methyl group or a group which can be replaced by a hydrogen atom by hydrolysis whereby an azepine derivative as claimed in claim 2, or a pharmaceutically acceptable acid addition salt thereof, is obtained.

20. Process for the production of azepine derivatives having the formula I as defined in claim 1 but wherein  $R_1$  may not represent a hydrogen atom and their pharmaceutically acceptable acid addition salts, which com-



prises reacting a compound having the formula IV

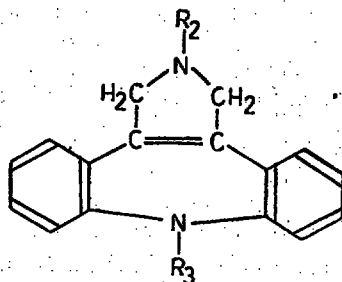


(IV)

wherein  $R_2$  has the meaning given in claim 1, with a reactive ester of methanol, ethanol or n-propanol, and, when required, converting an azepine derivative having the formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

21. Process as defined in claim 22 wherein the reaction is effected in the presence of a solvent and a basic condensing agent.

22. Process for the production of azepine derivatives having the formula I as defined in claim 1 but wherein  $R_1$  may not represent a hydrogen atom, and their pharmaceutically acceptable addition salts, which comprises reducing a compound having the formula VI

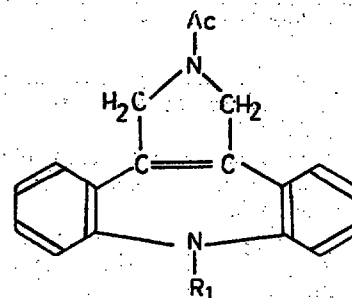


(VI)

wherein  $R_3$  has the meaning given in claim 1 and

$R_3$  represents a formyl, acetyl or propionyl group, with diborane in an ethereal solution and, when required, converting an azepine derivative having the formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

23. Process for the production of azepine derivatives having the formula I as defined in claim 1 but wherein  $R_2$  may represent a hydrogen atom only and their pharmaceutically acceptable acid addition salts, which comprises hydrolysing a compound having the formula VII



(VII)

wherein

$R_1$  has the meaning given in claim 1 and AC represents the acyl radical of an organic acid or a cyano group

and when required converting an azepine derivative having the formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof or converting an acid addition salt of an azepine derivative having the formula I thus obtained into the free base or into, or into another, pharmaceutically acceptable acid addition salt thereof.

24. Process as claimed in claim 19 substantially as hereinbefore described with reference to any one of the foregoing Examples 1, 2 parts (a) to (d) and 4 part (b).

25. Process as claimed in any one of claims 18 to 23 substantially as hereinbefore described with reference to any one of the foregoing Examples.

26. An azepine derivative or pharmaceutically acceptable acid addition salt thereof, whenever prepared by a process as claimed in claim 19 or 24.

27. An azepine derivative or pharmaceutically acceptable acid addition salt thereof, whenever prepared by a process as claimed in any one of claims 18, 20 to 23 or 25.

28. A pharmaceutical composition, comprising an azepine derivative as claimed in claim 1, or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable diluent or carrier therefor.

29. A pharmaceutical composition, comprising an azepine derivative as claimed in claim 2, or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable diluent or carrier therefor.

30. A pharmaceutical composition as claimed in claim 29 substantially as hereinbefore described with reference to any one of the foregoing prescriptions (a) to (e).

W. P. THOMPSON & CO.,  
12 Church Street, Liverpool L1 3AB,  
Chartered Patent Agents.

