

1099,749



PATENT SPECIFICATION

NO DRAWINGS

1099,749

Date of Application and filing Complete Specification: July 12, 1966.
No. 31134/66.

Application made in Switzerland (No. 9799) on July 13, 1965.

Application made in Switzerland (No. 10446) on July 26, 1965.

Complete Specification Published: Jan. 17, 1968.

© Crown Copyright 1968.

Index at acceptance: —C2 C(1G5A, 1G6A3, 2A3, 2A5, 2A6, 2A8, 2A9, 2A14, 2R16, 2R17, 3A10E3A4, 3A10E3D1, 3A10E5A, 3A10E5E, 3A10E5F1C, 3A10E5F1E, 3A10E5F2A, 3A10E5F3D, 3A13A3A4, 3A13A3B1, 3A13A3C, 3A13A3H1, 3A13A3K, 3A13A3L, 3A13C1C, 3A13C10H, 3A14A3C, 3A14A7A, B4A1, B4A2, B4A4, B4M)

Int. Cl.: —C 07 d 41/08, C 07 d 57/00

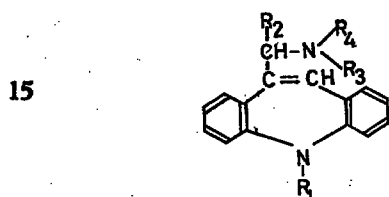
COMPLETE SPECIFICATION

New Azepine Derivatives and their Production

We J. R. GRIGY A.G. a body corporate organised according to the laws of Switzerland, of 215, Schwarzwaldallee, 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 invention concerns new azepine derivatives, processes for the production thereof, medicaments which contain the new compounds and the use thereof.

Azepine derivatives of the general formula I



(I)
wherein R₁ represents an alkyl radical containing at most 4 carbon atoms,
R₂ represents hydrogen or the methyl radical,
20 R₃ and R₄ represent hydrogen or alkyl radicals, each alkyl radical containing at most 4 carbon atoms, or
NR₃(R₄) represents a saturated heterocyclic radical of 5—7 ring members having, optionally, the imino group,
25 an alkylimino, or hydroxyalkylimino group, the two latter groups each containing at most 4 carbon

atoms or an alkanoyloxyalkylimino group containing at most 10 carbon atoms as ring member,

and their addition salts with inorganic or organic acids, have not been known hitherto.

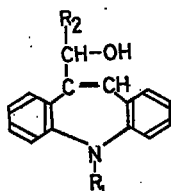
It has now been found that such compounds have valuable central and peripheral pharmacological properties. On oral, rectal or parenteral administration, they have a sedative, anticonvulsive and anaesthesia-potentiating action; they inhibit monosynaptic and polysynaptic reflexes, and they antagonise medicaments which have a depressant action on the central nervous system e.g. tetrabenzazine. They also have spasmolytic, histaminolytic and norepinephrine-potentiating activity. These pharmacological properties characterise the new compounds as suitable for the treatment of conditions of tension and agitation which are caused, e.g., by neuroses or depressions.

In the compounds of general formula I, R₁, R₂ and R₄ as alkyl radicals are, for example, the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.butyl and tert.butyl group, or R₃ and R₄, together with the adjacent nitrogen, form, as a heterocyclic radical, the 1-pyrrolidinyl, piperidino, hexahydro-1H-azepin-1-yl, 1-piperazinyl, 4-methyl-1-piperazinyl, 4-(2-hydroxyethyl)-1-piperazinyl, 4-(2-acetoxyethyl)-1-piperazinyl, 4-(2-pivaloyloxyethyl)-1-piperazinyl, hexahydro-1H-1,4-diazepin-1-yl, 4-methyl-hexahydro-1H-1,4-diazepin-1-yl or the 4-(2-hydroxyethyl)-hexahydro-1H-1,4-diazepin-1-yl radical.

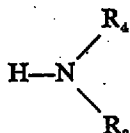
The compounds of general formula I are

[Price 4s. 6d.]

produced according to the invention by reacting a reactive ester of a hydroxyl compound of the general formula II



- 5 wherein R_1 and R_2 have the meanings given in formula I, with a compound of the general formula III



- 10 wherein R_3 and R_4 or $NR_3(R_4)$ have the meanings given in formula I, or with an N-acyl derivative of piperazine or hexahydro-1H-1,4-diazepine, or with a metal compound of an N-acyl derivative of an alkylamine containing at most 4 carbon atoms, if necessary
15 subjecting the reaction product to hydrolysis to remove any acyl radical bound to a nitrogen atom of the side chain, if desired, treating a compound of general formula I having the imino group as ring member with an alkylene oxide containing at most 4 carbon atoms, with a reactive monoester of an alkane diol containing at most 4 carbon atoms or with a reactive ester of an alkanoyloxy-
20 alkanol containing at most 10 carbon atoms, if desired, acylating a compound of the general formula I which contains a hydroxyalkylimino group having at most 4 carbon atoms as ring member into one containing an alkanoyloxy-alkylimino group, having at most 10 carbon atoms, and, if desired, converting a compound of general formula I into an addition salt with an inorganic or organic acid.

- 25 The halides, particularly the bromides, are used as reactive esters of hydroxyl compounds of general formula II. Other derivatives of this type are sulphonic acid esters such as tosyl esters or mesyl esters.

- 30 Reactions of reactive esters of compounds of the general formula II with amines of general formula III are performed, e.g., in inert solvents, whereby an excess of amine can serve as acid binding agent and, optionally also as sole reaction medium. Suitable inert solvents are, e.g. hydrocarbons such as benzene or toluene, alkanols such as methanol or ethanol, alkanones such as acetone or methyl-
45 ethyl ketone, and also water. The reaction is more or less exothermic depending on the meaning of R_1 , R_2 , R_3 and R_4 ; if necessary, it is completed by heating the reaction mixture. The reactive ester of compounds of general formula II can be reacted, for example, with

dimethylamine, methylethylamine, diethylamine, dipropylamine, dibutylamine, methylamine, ethylamine, propylamine, isopropylamine, sec. butylamine, ammonia, pyrrolidine, piperidine, hexahydro - 1H - 1,4 - diazepine, 1 - methyl - piperazine, 1 - (β - hydroxyethyl) - piperazine, 1 - (2 - acetoxyethyl) - piperazine, 1 - (2 - pivaloyloxyethyl) - piperazine or 1 - methyl - hexahydro - 1H - 1,4 - diazepine.

The reaction of a reactive ester of a compound of general formula II with an N-acyl derivative of piperazine or hexahydro-1H - 1,4 - diazepine, e.g. an N - formyl, N - acetyl, N - phenoxycarbonyl, N - phenoxithiocarbonyl, N - methoxycarbonyl, N - ethoxycarbonyl, N - methylthiocarbonyl or an N - ethylthiocarbonyl derivative, or with a metal compound of an N - acyl derivative of an alkylamine, the latter containing at most 4 carbon atoms, such as the sodium compound of an N - formyl-, N - methoxycarbonyl, N - ethoxycarbonyl, N - phenoxy-
75 carbonyl, N - methoxythiocarbonyl, N - ethoxythiocarbonyl or N - phenoxithiocarbonyl - alkylamine, is performed, e.g., in an inert organic solvent under anhydrous conditions. Suitable solvents are, e.g. hydrocarbons such as benzene or toluene. The piperazine or hexahydro - 1H - 1,4 - diazepine compounds mentioned can be reacted in the presence of an acid binding medium, preferably in the presence of an excess of the original base.

The acyl radical of the reaction product obtained, which radical is bound to a nitrogen atom of the side chain, can subsequently be removed by heating the reaction product with an alkali metal hydroxide such as potassium hydroxide in an organic solvent. Suitable reaction media are, e.g., solvents containing hydroxyl groups such as ethylene glycol or diethylene glycol, their methyl or ethyl or alkanols such as methanol or ethanol. These alkanols are preferably used in a closed vessel. In addition, the hydrolysis can also be performed by boiling with alkanolic hydrochloric acid.

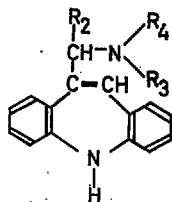
Hydroxyalkyl radicals containing at most 4 carbon atoms or alkanoyloxyalkyl radicals containing at most 10 carbon atoms are introduced into the free imino group of compounds of general formula I wherein $NR_3(R_4)$ represents a heterocyclic radical containing an imino group as ring member, by treating such compounds, particularly 1 - piperazinyl or hexahydro - 1H - 1,4 - diazepin - 1 - yl compounds with, for example, ethylene oxide, propylene oxide, 2 - bromoethanol, 2 - (*p* - tolylsulphonyloxyethanol) or with (2 - bromoethyl) - acetate. The reaction is preferably performed in a solvent, to which an acid binding agent is added if the reaction proceeds with removing 1 mol equivalent of acid. Suitable solvents are, e.g., hydrocarbons such as

benzene or toluene, alkanones such as acetone or methylethyl ketone, and suitable acid binding agents are alkali metal carbonates such as potassium carbonate.

- 5 The hydroxyl groups of compounds of general formula I wherein NR_1 (R_1) represents a heterocyclic radical containing hydroxyalkylimino group containing at most 4 carbon atoms as ring member, particularly the hydroxyl groups of 4 - hydroxyalkyl - 1 - piperazinyl or 4 - hydroxyalkylhexahydro - 1H - 1,4 - diazepin - 1 - yl compounds, are acylated by heating these, for example, in the anhydride of alkanolic acid containing at most 6 carbon atoms such as acetic acid, propionic acid, butyric acid or pivalic acid or treating with a corresponding acid halide in a tertiary nitrogen base such as pyridine. Also, the sodium derivatives of such hydroxyalkyl compounds can be reacted with corresponding acid halides.

- Starting materials of the general formula II are, e.g. 10 - bromomethyl - or 10 - (α - bromoethyl) - 5 - alkyl - 5H - dibenz[b,f] azepines. Surprisingly, these compounds can be produced, e.g. by bromination with N-bromosuccinimide, from 10 - methyl - or 10 - ethyl - 5 - alkyl - dibenz[b,f] azepines.

- According to a second process of the invention to produce the compounds of general formula I, compounds of the general formula IV



(IV)

- wherein R_2 , R_3 and R_4 have the meanings given in formula I, or $[\text{NR}_1(\text{R}_1)]'$ represents a saturated heterocyclic radical having 5-7 ring members with optionally, the imino group, an alkylimino group containing at most 4 carbon atoms or an alkanoyloxyalkylimino group containing at most 10 carbon atoms, are alkylated, preferably in the presence of solvents and basic condensing agents, with reactive esters of alkanols of the general formula V

- 45 R_1-OH (V) wherein R_1 has the meaning given in formula I, and, optionally, the compounds obtained are converted into their addition salts with inorganic or organic acids.

- 50 Some of the starting materials of general formula IV are described in the literature. Other compounds of this type are produced analogously. As second reaction component, reactive esters of alkanols of general formula

III are used, the radical R_1 of which has the meanings given for this radical following formula I. As reactive esters, for example, halides such as chlorides, bromides or iodides, sulphonic acid esters such as methane sulphonic acid ester, benzene sulphonic acid ester, *o*- and *p*-toluene sulphonic acid ester of 2,4-dinitrobenzene sulphonic acid ester as well as sulphuric acid esters such as dimethyl or diethyl sulphate, can be used.

The reaction can take place in the presence or absence of an inert organic solvent. Suitable inert organic solvents are, e.g. hydrocarbons such as benzene, toluene, xylene, cumol or tetralin, ethereal liquids such as dioxan, alkanones such as acetone or methyl ethyl ketone, carboxylic acid amides such as dimethyl formamide, or sulfoxides such as dimethyl or diethyl sulfoxide. Suitable basic condensing agents are, e.g. alkali metals such as sodium, potassium or lithium, alkali metal hydroxides such as sodium or potassium hydroxide, alkali metal carbonates such as potassium carbonate, alkali metal amides such as sodium, potassium or lithium amide, alkali metal hydrides such as sodium or lithium hydride, alkali metal alkanolates such as sodium methylate, sodium ethylate or sodium tert.butylate or alkyl and aryl lithium compounds such as butyl or phenyl lithium.

The compounds of general formula I obtained by the processes according to the invention are then converted, if desired, into their addition salts in the usual way 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 general formula I in an organic solvent. Preferably organic solvents in which the salt formed is difficultly soluble are chosen for the reaction so that the salt can be isolated by filtration. Such solvents are, e.g., methanol, methanol/diethyl ether or ethanol/diethyl ether.

These acid addition salts can be used as medicaments instead of free bases, i.e. salts with those acids the anions of which are pharmaceutically acceptable in the usual dosages. It is also of advantage if the salts to be used as medicaments crystallise well and are not, or are only slightly, hygroscopic. For example, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, β -hydroxyethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenyl acetic acid, mandelic acid and embonic acid can be used for salt formation with compounds of the general formula I.

As mentioned above, the new active substances are administered orally, rectally and parenterally. The daily dosages of the free

bases or of pharmaceutically acceptable salts thereof vary between 10 and 800 mg for adult patients. Suitable dosage units such as dragées (sugar coated tablets), tablets, suppositories or ampoules, preferably contain 5—50 mg of an active substance according to the invention or of a pharmaceutically acceptable salt thereof. Also corresponding amounts of forms not made up into single dosages such as syrups, aerosols, ointments or powders can be applied.

Dosage units for oral administration preferably contain between 1—90% of a compound of general formula I or a pharmaceutically acceptable salt thereof as active substance. 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 of lubricants such as magnesium or calcium stearate or polyethylene glycols (Carbowaxes) of suitable molecular weights to form tablets or dragée cores. The latter 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 dosages or active substance.

Examples of dosage units for rectal administration are suppositories which consist of a combination of an active substance or a suitable acid addition salt thereof and a neutral fatty foundation, or also gelatine rectal capsules which contain a combination of the active substance or a suitable acid addition salt thereof and polyethylene glycols (Carbowaxes) of suitable molecular weight.

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

The following prescription further illustrates the production of tablets and dragées:

a) 250 g of 5 - methyl - 10 - dimethylaminomethyl - 5H - dibenz[b,f]azepine hydrochloride are mixed 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 and granulated through a sieve. After drying, 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 into 10,000 tablets each weighing 100 mg and containing 25 mg of active substance. If desired, the tablets can be grooved for better adaptation of the dosage.

b) A granulate is produced from 250 g of 5 - methyl - 10 - dimethylaminomethyl - 5H - dibenz[b,f]azepine hydrochloride, 175.90 g of lactose and an alcoholic solution of 10 g of stearic acid. After drying, 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 pressed into 10,000 dragées cores. These are then coated with a concentrated syrup 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 dragées obtained each weigh 120 mg and contain 25 mg of active substance.

The following examples illustrate the production of the new compounds of general formula I and of hitherto undescribed intermediate products but they in no way limit the scope of the invention thereto. The temperatures are given in degrees Centigrade.

EXAMPLE 1.

a) 15 g of 5 - methyl - 10 - bromoethyl - 5H - dibenz[b,f]azepine are dissolved in 50 ml of abs. benzene and the solution is added to a solution of 10 g of dimethylamine in 100 ml of abs. benzene. The reaction mixture is then stirred for 1 hour at 40—50° whereupon the organic phase is washed well with water and extracted with 2N hydrochloric acid. The acid extracts are made phenolphthalein alkaline with concentrated aqueous ammonia and shaken with diethyl ether. The ethereal solution is washed with water, dried over potassium carbonate and evaporated in vacuo. The residue, which is boiled under high vacuum, boils at 140—144°/0.01 Torr. The free base obtained, 5 - methyl - 10 - dimethylaminomethyl - 5H - dibenz[b,f]azepine, is converted into the hydrochloride with abs. ethanolic hydrochloric acid; M.P. 225—228° from abs. ethanol.

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

b) 37.5 g of 5,10 - dimethyl - 5H - dibenz[b,f]azepine are dissolved in 375 ml of carbon tetrachloride and 30.5 g of N-bromosuccinimide are added all at once. The reaction mixture is heated to 70° while stirring and exposed to two 200 watt lamps. The temperature is kept for 3—5 minutes at 70° by slight cooling. The reaction mixture is then cooled to 20° and the succinimide is drawn off under suction and washed with carbon tetrachloride. The filtrate is extracted with water and the organic phase is dried over sodium sulphate and concentrated in vacuo at 40°. The residue is recrystallised from cyclohexane whereupon the compound obtained melts at 109—111°.

EXAMPLE 2

The following compounds are obtained analogously to Example 1 a) from 5-methyl-10-bromomethyl-5H-dibenz[b,f]azepine:

- 5 a) with methylamine, 5 - methyl - 10 - methylaminomethyl - 5H - dibenz[b,f]azepine, B.P. 147—149°/0.05 Torr; hydrochloride M.P. 175—177° (from abs. ethanol/diethyl ether);
- 10 b) with 1 - (β - hydroxyethyl) - piperazine 1 - (β - hydroxyethyl) - 4 - (5 - methyl - 5H - dibenz[b,f]azepine - 10 - ylmethyl) - piperazine; M.P. of dihydrochloride 214—217° (from abs. methanol/diethyl ether);
- 15 c) with diethylamine, 5 - methyl - 10 - diethylaminomethyl - 5H - dibenz[b,f]azepine, B.P. 147—150°/0.04 Torr; fumarate M.P. 148—149° (from abs. ethanol);
- 20 d) with 4 - methyl - piperazine, 5 - methyl - 10 - (4 - methyl - 1 - piperazinyl - methyl) - 5H - dibenz[b,f]azepine (crude product); dihydrochloride M.P. 224—229° (from ethanol, with decomposition);
- 25 e) with 1 - (2 - acetoxy - ethyl) - piperazine, 1 - (2 - acetoxy - ethyl) - 4 - (5 - methyl - 5H - dibenz[b,f]azepine - 10 - ylmethyl) - piperazine.

EXAMPLE 3

- 30 a) The following end products are produced analogously to Example 1 a) from 5 - ethyl - 10 - bromomethyl - 5H - dibenz[b,f]azepine:

- a¹) with dimethylamine, 5 - ethyl - 10 - (dimethylaminomethyl) - 5H - dibenz[b,f]azepine, B.P. 150—152°/0.04 Torr; hydrochloride M.P. 247—249° (from abs. ethanol);
- 35 a²) with pyrrolidine, 5 - ethyl - 10 - (1 - pyrrolidinylmethyl) - 5H - dibenz[b,f]azepine, M.P. 92° (from pentane); hydrochloride M.P. 170—172° (from abs. ethanol).

- 40 b) The necessary starting compound, 5 - ethyl - 10 - bromomethyl - 5H - dibenz[b,f]azepine (crude product) is produced analogously to 5 - methyl - 10 - bromomethyl - 5H - dibenz[b,f]azepine described in Example 1, starting from 5 - ethyl - 10 - methyl - 5H - dibenz[b,f]azepine, M.P. 143—145° (from ethanol). Analogously to the preparation of 5,10 - dimethyl - 5H - dibenz[b,f]azepine described in the literature, the 5 - ethyl - 10 - methyl - 5H - [b,f]azepine is produced starting from 10 - methoxy - 5H - dibenz[b,f]azepine, M.P. 124°, by way of the following intermediate products:

- 55 5 - ethyl - 10 - methoxy - 5H - dibenz[b,f]azepine, M.P. 186—188° (from ethanol),
- 5 - ethyl - 5H - dibenz[b,f]azepine - 10(11H) - one, M.P. 126—128° (from ethanol), and
- 60 5 - ethyl - 10 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 10 - ol (crude product).

EXAMPLE 4

A suspension of 13.8 g of sodium amide in 30 ml of abs. toluene is added dropwise within 15 minutes to 72 g of 10 - dimethyl - aminomethyl 5H - dibenz[b,f]azepine in 720 ml of abs. toluene while stirring and the reaction mixture is then refluxed for 1 hour. It is cooled to 50° and, within 90 minutes, 45 g of methyl iodide are added dropwise while maintaining a temperature of 50—52°. The reaction mixture is then stirred, first for 16 hours at between 50 and 52° and then for 1 hour at between 85 and 95° whereupon it is cooled to 20°. 100 ml of water are added and the organic phase is separated and extracted with 2N hydrochloric acid. The free base is precipitated from the hydrochloric acid extract with concentrated sodium hydroxide solution and it is extracted with diethyl ether. The ethereal solution is washed with water, dried over potassium carbonate and concentrated in vacuo. Distillation of the residue under high vacuum yields 5 - methyl - 10 - dimethylamino - methyl - 5H - dibenz[b,f]azepine which boils at 140—144°/0.01 Torr. The free base is converted with ethanolic hydrochloric acid into the hydrochloride which, when recrystallised from abs. ethanol, melts at 225—228°.

EXAMPLE 5

The following compounds are obtained analogously to Example 4:

- 95 a) 5 - methyl - 10 - (1 - pyrrolidinyl - methyl) - 5H - dibenz[b,f]azepine, B.P. 160—164°/0.01 Torr, from 10 - (1 - pyrrolidinylmethyl) - 5H - dibenz[b,f]azepine and methyl iodide. The hydrochloride melts at 130—132° (from isopropanol).

- 100 b) 5 - methyl - 10 - piperidinomethyl - 5H - dibenz[b,f]azepine, B.P. 172—175°/0.01 Torr, from 10 - piperidinomethyl - 5H - dibenz[b,f]azepine and methyl iodide. The hydrochloride melts at 171—174° (from isopropanol).

- 105 c) 5 - methyl - 10 - (α - dimethylamino - ethyl) - 5H - dibenz[b,f]azepine B.P. 145—149°/0.04 Torr, from 10 - (α - dimethyl - aminoethyl) - 5H - dibenz[b,f]azepine and methyl iodide. The hydrochloride melts at 156—160° (from abs. ethanol/diethyl ester), and

- 115 d) 5 - methyl - 10 - [α - (1 - pyrrolidinyl) - ethyl] - 5H - dibenz[b,f]azepine B.P. 168—172°/0.03 Torr from 10 - [α - (1 - pyrrolidinyl) - ethyl] - 5H - dibenz[b,f]azepine and methyl iodide. The hydrochloride melts at 193—196° (from abs. ethanol).

EXAMPLE 6

a) 15 g of crude 5 - methyl - 10 - (1 - piperazinylmethyl) - 5H - dibenz[b,f]azepine dissolved in 150 ml of toluene are refluxed for 4 hours with 70 g of potassium carbonate and 12.5 g of β -bromoethanol. 100 ml of

18 g of the residue, 4 - (5 - methyl - 5H - dibenz[b,f]azepin - 10 - ylmethyl) - piperazine - 1 - carboxylic acid ethyl ester and a solution of 18 g of potassium hydroxide in 72 ml of abs. ethanol are refluxed for 8 hours. The cooled reaction mixture is then poured into water and taken up in ether. The ether solution is extracted with 2N hydrochloric acid and the acid extract is made phenolphthalein alkaline with concentrated ammonia. The precipitated crude base is taken up in ether and the ether solution is washed with water, dried over potassium carbonate and concentrated. Crude 5 - methyl - 10 - (1 - piperazinylmethyl) - 5H - dibenz[b,f]azepine is obtained which, in acetone solution with ethanolic hydrochloric acid, yields the dihydrochloride. The latter melts at 184—189° (from ethanol).

The starting material, 5 - methyl - 10 - (1 - piperazinylmethyl) - 5H - dibenz[b,f]azepine, is produced according to Example 6 b).

33.6 g. of 1 - (β - hydroxyethyl) - 4 - (5 - methyl - 5H - dibenz[*b,f*]azepin - 10 - ylmethyl) - piperazine and 101 g. of acetic acid anhydride are refluxed for 3 hours. The excess acetic acid anhydride is then distilled off in vacuo and concentrated ammonia is added to the residue. The base which precipitates is extracted with diethyl ether and the ethereal solution is washed with water, dried over sodium sulphate and concentrated in vacuo. The residue is dissolved in acetone and neutralised with abs. ethanolic hydrochloric acid, whereupon 1 - (2 - acetoxyethyl) - 4 - (5 - methyl - 5H - dibenz[*b,f*]azepin - 10 - ylmethyl) - piperazine dihydrochloride crystallises out.

R1C(=C(R2)N(R3)R4)c1-c1ccccc1

$\text{NR}_3(\text{R}_4)$ represents a saturated heterocyclic radical having 5-7 ring members with, optionally, the imino group, an alkylimino, or hydroxyalkylimino group, the two latter groups each containing at most 4 carbon atoms, or an alkanoyloxyalkylimino group containing at most 10 carbon atoms as ring member.

R2C(R4)N(R3)C(=CH)c1ccccc1N(R)Cc2ccccc2

wherein R_1 represents an alkyl radical containing at most 4 carbon atoms.



water are then added to the cooled reaction mixture and the organic phase is removed and is extracted with 2N hydrochloric acid. The hydrochloric acid extract is made alkaline with 4N sodium hydroxide solution whereupon the crude base precipitates. It is taken up in ether and the ether solution is washed with water, dried over potassium carbonate and concentrated. Ethanolic hydrochloric acid is added to the concentrated solution until the pH is 4—5 whereupon the 1 - (β - hydroxy - ethyl) - 4 - (5 - methyl - 5H - dibenz[b,f]azepin - 10 - ylmethyl) - piperazine dihydrochloride precipitates. It melts at 214—217° (from methanol/abs. ether).

The starting material, 5 - methyl - 10 - (1 - piperazinylmethyl) - 5H - dibenz[b,f]azepine, can be produced analogously to Example 1 a) or as follows:

b) 17.0 g of piperazine - 1 - carboxylic acid ethyl ester are dissolved while stirring in 100 ml of abs. benzene. 15 g of 5 - methyl - 10 - bromomethyl - 5H - dibenz[b,f]azepine in 75 ml of abs. benzene are added dropwise to this solution and the mixture is refluxed for 1 hour. It is then cooled and the organic phase is washed with water, dried over potassium carbonate and concentrated in vacuo.

18 g of the residue, 4 - (5 - methyl - 5H - dibenz[b,f]azepin - 10 - ylmethyl) - piperazine - 1 - carboxylic acid ethyl ester and a solution of 18 g of potassium hydroxide in 72 ml of abs. ethanol are refluxed for 8 hours. The cooled reaction mixture is then poured into water and taken up in ether. The ether solution is extracted with 2N hydrochloric acid and the acid extract is made phenolphthalein alkaline with concentrated ammonia. The precipitated crude base is taken up in ether and the ether solution is washed with water, dried over potassium carbonate and concentrated. Crude 5 - methyl - 10 - (1 - piperazinylmethyl) - 5H - dibenz[b,f]azepine is obtained which, in acetone solution with ethanolic hydrochloric acid, yields the dihydrochloride. The latter melts at 184—189° (from ethanol).

EXAMPLE 7

7 g of ethylene oxide are introduced into a solution of 5 - methyl - 10 - (1 - piperazinylmethyl) - 5H - dibenz[b,f]azepine in 250 ml of ethanol and the mixture is refluxed for 2 hours. The cooled reaction mixture is concentrated in vacuo and the calculated amount of methanolic hydrochloric acid is added to the residue whereupon 1 - (β - hydroxyethyl) - 4 - (5 - methyl - 5H - dibenz[b,f]azepin - 10 - ylmethyl) - piperazine dihydrochloride precipitates. It melts at 214—217° (from methanol/absolute ether).

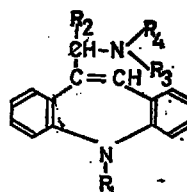
The starting material, 5 - methyl - 10 - (1 - piperazinylmethyl) - 5H - dibenz[b,f]azepine, is produced according to Example 6 b).

EXAMPLE 8

33.6 g of 1 - (β - hydroxyethyl) - 4 - (5 - methyl - 5H - dibenz[b,f]azepin - 10 - ylmethyl) - piperazine and 101 g of acetic acid anhydride are refluxed for 3 hours. The excess acetic acid anhydride is then distilled off in vacuo and concentrated ammonia is added to the residue. The base which precipitates is extracted with diethyl ether and the ethereal solution is washed with water, dried over sodium sulphate and concentrated in vacuo. The residue is dissolved in acetone and neutralised with abs. ethanolic hydrochloric acid, whereupon 1 - (2 - acetoxy - ethyl) - 4 - (5 - methyl - 5H - dibenz[b,f]azepin - 10 - ylmethyl) - piperazine dihydrochloride crystallises out.

WHAT WE CLAIM IS:—

1. Azepine derivatives of the general formula I



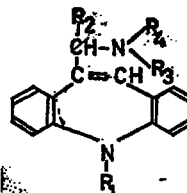
(I)

wherein R₁ represents an alkyl radical containing at most 4 carbon atoms, R₂ represents hydrogen or the methyl radical,

R₃ and R₄ represent hydrogen or alkyl radicals, each alkyl radical containing at most 4 carbon atoms or NR₅(R₆) represents a saturated heterocyclic radical having 5—7 ring members with, optionally, the imino group, an alkylimino, or hydroxyalkylimino group, the two latter groups each containing at most 4 carbon atoms, or an alkanoyloxyalkylimino group containing at most 10 carbon atoms as ring member,

as well as their addition salts with inorganic or organic acids.

2. Azepine derivatives of the general formula I

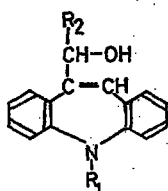


(I)

wherein R₁ represents an alkyl radical containing at most 4 carbon atoms,

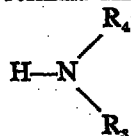


- R_2 represents hydrogen or the methyl radical,
 R_3 and R_4 represent alkyl radicals containing at most 4 carbon atoms or
5 $NR_3(R_4)$ represents a saturated heterocyclic radical having 5—7 ring members,
as well as their addition salts with inorganic or organic acids.
- 10 3. Azepine derivatives of the general formula I, given in claim 1, wherein R_1 , R_2 , R_3 , R_4 and $NR_3(R_4)$ are as defined in claim 1 and R_2 represents hydrogen and their acid addition salts with inorganic or organic acids.
- 15 4. Azepine derivatives of the general formula I, given in claim 1, wherein R_1 , R_2 , R_3 , R_4 and $NR_3(R_4)$ are as defined in claim 1, and R_2 represents the methyl radical and their acid addition salts with inorganic or organic acids.
- 20 5. Azepine derivatives of the general formula I, given in claim 1, wherein R_1 , R_3 and R_4 are as defined in claim 1, and R_2 represents hydrogen and their acid addition salts with inorganic or organic acids.
- 25 6. Azepine derivatives of the general formula I, given in claim 1, wherein R_1 , R_3 and R_4 are as defined in claim 1, and R_2 represents the methyl radical, and their acid addition salts with inorganic or organic acids.
- 30 7. Azepine derivatives of the general formula I, given in claim 1, wherein R_1 , R_3 and R_4 are as defined in claim 1, and R_2 represents an alkyl radical having at most 4 carbon atoms, and their acid addition salts with inorganic or organic acids.
- 35 8. Azepine derivatives of the general formula I, given in claim 1, wherein R_1 , R_3 and R_4 are as defined in claim 1, and R_2 represents hydrogen, and their acid addition salts with inorganic or organic acids.
- 40 9. Azepine derivatives of the general formula I, given in claim 1, wherein R_1 and R_2 are as defined in claim 1, and $NR_3(R_4)$ represents a saturated heterocyclic radical having 5—7 ring members with, optionally, the imino group, an alkylimino, or hydroxyalkylimino group, the two latter groups each containing at most 4 carbon atoms, or an alkanoyloxyalkylimino group containing at most 10 carbon atoms as ring member, and their acid addition salts with inorganic or organic acids.
- 50 10. 5 - Methyl - 10 - dimethylamino - methyl - 5H - dibenz[b,f] azepine.
- 55 11. The hydrochloride salt of 5 - methyl - 10 - dimethylaminomethyl - 5H - dibenz[b,f]azepine.
- 60 12. 5 - Methyl - 10 - methylaminomethyl - 5H - dibenz[b,f] azepine.
13. The hydrochloride salt of 5 - methyl - 10 - methylaminomethyl - 5H - dibenz[b,f] azepine.
14. 4 - (5 - Methyl - 5H - dibenz[b,f] azepine - 10 - ylmethyl) - piperazine - 1 - ethanol.
15. The dihydrochloride salt of 4 - (5 - methyl - 5H - dibenz[b,f]azepine - 10 - ylmethyl) - piperazine - 1 - ethanol.
16. 5 - Methyl - 10 - diethylaminomethyl - 5H - dibenz[b,f]azepine.
17. The fumarate salt of 5 - methyl - 10 - (diethylaminomethyl) - 5H - dibenz[b,f] azepine.
18. 5 - Ethyl - 10 - (dimethylamino - methyl) - 5H - dibenz[b,f]azepine.
19. The hydrochloride salt of 5 - ethyl - 10 - (dimethylaminomethyl) - 5H - dibenz[b,f]azepine.
20. 5 - Methyl - 10 - (4 - methyl - 1 - piperazinylmethyl) - 5H - dibenz[b,f]azepine.
21. The dihydrochloride salt of 5 - methyl - 10 - (4 - methyl - 1 - piperazinylmethyl) - 5H - dibenz[b,f]azepine.
22. 5 - Methyl - 10 - (1 - pyrrolidinyl - methyl) - 5H - dibenz[b,f]azepine.
23. The hydrochloride salt of 5 - methyl - 10 - (1 - pyrrolidinylmethyl) - 5H - dibenz[b,f]azepine.
24. 5 - Methyl - 10 - piperidinomethyl - 5H - dibenz[b,f]azepine.
25. The hydrochloride salt of 5 - methyl - 10 - piperidinomethyl - 5H - dibenz[b,f] azepine.
26. 5 - Methyl - 10 - (α - dimethylamino - ethyl) - 5H - dibenz[b,f]azepine.
27. The hydrochloride salt of 5 - methyl - 10 - (α - dimethylaminoethyl) - 5H - dibenz[b,f]azepine.
28. 5 - Methyl - 10 - [α - (1 - pyrrolidinyl) - ethyl] - 5H - dibenz[b,f]azepine.
29. The hydrochloride salt of 5 - methyl - 10 - [α - (1 - pyrrolidinyl) - ethyl] - 5H - dibenz[b,f]azepine.
30. 5 - Ethyl - 10 - (1 - pyrrolidinyl - methyl) - 5H - dibenz[b,f]azepine.
31. The hydrochloride salt of 5 - ethyl - 10 - (1 - pyrrolidinylmethyl) - 5H - dibenz[b,f]azepine.
32. Compounds of the general formula I, defined in claim 1, and salts thereof with inorganic or organic acids substantially as herein described with reference to and as illustrated in either of the Examples 1 and 2.
33. Compounds of the general formula I, defined in claim 1, and salts thereof with inorganic or organic acids substantially as herein described with reference to and as illustrated in either of Examples 4 and 5.
34. Compounds of the general formula I, defined in claim 1, and salts thereof with inorganic or organic acids substantially as herein described with reference to and as illustrated in any of Examples 3, 6, 7 and 8.
35. A process for the production of azepine derivatives according to claim 1, characterised by reacting a reactive ester of a compound of the general formula II



(II)

wherein R_1 and R_2 have the meanings given in formula I of claim 1, with a compound of the general formula III



(III)

wherein R_3 and R_4 , or $NR_3(R_4)$ have the meanings given in formula I of claim 1, or with a metal compound of an N-acyl derivative of an alkylamine containing at most 4 carbon atoms, if necessary, subjecting the reaction product to hydrolysis to remove any acyl radical bound to a nitrogen atom in the side chain, if desired, treating a compound of the general formula I having the imino group as ring member, with an alkylene oxide containing at most 4 carbon atoms, a reactive monoester of an alkane diol containing at most 4 carbon atoms or with a reactive ester of an alkanoyloxyalkanol containing at most 10 carbon atoms, if desired, acylating a compound of the general formula I having a hydroxyalkylimino group having at most 4 carbon atoms as ring member into one having an alkanoyloxyalkylimino group having at most 10 carbon atoms and, if desired, converting a compound of general formula I into an addition salt with an inorganic or organic acid.

36. A process as claimed in claim 35 in which the compound of formula II is reacted with an N-acyl derivative of piperazine or hexahydro - 1H - 1,4 - diazepine instead of the metal compound of an N-acyl derivative of an alkylamine having at most 4 carbon atoms.

37. A process as claimed in claim 35 or 36 in which the reaction is carried out in the presence of an inert solvent.

38. A process as claimed in any of claims 35 to 37 in which the reactive ester of a compound of the general formula II is a bromide.

39. A process as claimed in any of claims 35 to 38 in which R_1 , R_2 , R_3 , R_4 and $NR_3(R_4)$ have the meanings given in claim 3.

40. A process as claimed in any of claims 35 to 38, in which the R_1 , R_2 , R_3 , R_4 and $NR_3(R_4)$ have the meanings given in claim 4.

41. A process as claimed in any of claims 35 to 38, in which the R_1 , R_2 , R_3 and R_4 have the meanings given in claim 5.

42. A process as claimed in any of claims

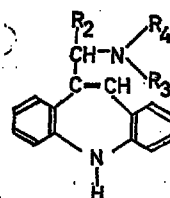
35 to 38, in which R_1 , R_2 , R_3 and R_4 have the meanings given in claim 6.

43. A process as claimed in any of claims 35 to 38, in which R_1 , R_2 , R_3 and R_4 have the meanings given in claim 7.

44. A process as claimed in any of claims 35 to 38, in which R_1 , R_2 , R_3 and R_4 have the meanings given in claim 8.

45. A process as claimed in any of claims 35 to 38, in which R_1 , R_2 and $NR_3(R_4)$ have the meanings given in claim 9.

46. A process for the production of azepine derivatives of the general formula I defined in claim 1, characterised by alkylating compounds of the general formula IV



(IV)

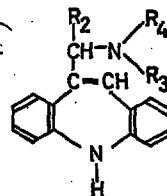
wherein R_2 , R_3 and R_4 have the meanings given in formula I of claim 1, or $[NR_3(R_4)]'$ represents a saturated heterocyclic radical having 5-7 ring members, with optionally, the imino group, an alkylimino group having at most 4 carbon atoms or an alkanoyloxyalkylimino group having at most 10 carbon atoms as ring member, with reactive esters of alkanols of the general formula V



(V)

wherein R_1 has the meaning given in formula I of claim 1, and, optionally, converting the compounds obtained into their addition salts with inorganic or organic acids.

47. Process for the production of azepine derivative of the general formula I defined in claim 2 which comprises alkylating compounds of the general formula IV



(IV)

in which R_2 , R_3 , R_4 and $NR_3(R_4)$ are as defined in claim 2, with reactive esters of alkanols of the general formula V



(V)

in which R_1 is as defined in claim 2, and, optionally, converting the compounds obtained into their addition salts with inorganic or organic acids.

48. Process as claimed in claim 46 or 47 which is carried out in the presence of inert organic solvents and basic condensing agents.

49. A process as claimed in claim 48 in

which the basic condensing agent is sodium amide.

50. A process as claimed in any of claims 46 to 49, in which the R_1 , R_2 , R_3 and R_4 have the meanings given in claim 7.

51. A process as claimed in claim 35 substantially as hereinbefore described in Example 1 or 2.

52. A process as claimed in claim 35 or 36 substantially as hereinbefore described in Examples 3, 6, 7 or 8.

53. A process as claimed in claim 47 substantially as hereinbefore described in Example 4 or 5.

54. A pharmaceutical preparation in dosage unit form comprising a compound claimed in claim 1 and at least one inert pharmaceutical carrier.

W. P. THOMPSON & CO.
12, Church Street, Liverpool, 1.
Chartered Patent Agents.

Leamington Spa: Printed for Her Majesty's Stationery Office by the Courier Press.—1968.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

