



PATENT SPECIFICATION

NO DRAWINGS

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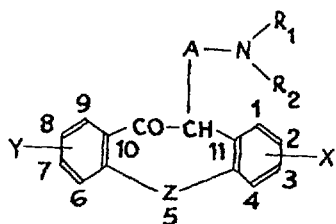
COMPLETE SPECIFICATION

Thiepin and Oxepin Derivatives and process for their production

We, J. R. GEIGY 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 present invention concerns new thiepin and oxepin derivatives and processes for their production.

Compounds of the general formula I (numbering according to Chemical Abstracts)



(I)

wherein Z represents S or O,

X and Y represent hydrogen, halogen up to the atomic number 35, alkyl, alkoxy or alkylthio groups containing at most 4 carbon atoms,

A represents a straight or branched-chain alkylene radical having 2 to 5 carbon atoms,

R₁ and R₂ represent alkyl radicals containing at most 4 carbon atoms, or

R₁ and R₂ together with the adjacent nitrogen and with the optional inclusion of an alkylimino group containing at most 4 carbon atoms as ring member, represent a saturated heterocyclic radical having 5—7 ring members, have not been known up to the present. It has now been found that such compounds and their pharmaceutically acceptable salts with inorganic and organic acids,

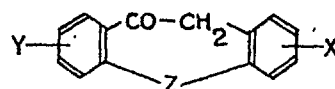
[Price 4s. 6d.]

have valuable central and peripheral pharmacological properties; they antagonise, for example, the action of reserpine and tetra-

The new compounds can be administered, for example for the treatment of mental disorders, orally or, in the form of aqueous solutions of their salts, also parenterally. If desired they can also be combined with other pharmaceuticals.

In the compounds of the general formula I, X and Y, when other than hydrogen, can be in the 1-, 2-, 3- or 4-positions or in the 6-, 7-, 8- or 9-positions, the 2- and 8-positions being preferred. As alkyl radicals they represent, for example, the methyl, ethyl, n-propyl, isopropyl, n-butyl or tert. butyl group. As alkoxy radicals they represent, for example, the methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy or sec. butoxy group, and as alkyl thio radicals they represent, e.g., the methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio or sec. butylthio group. A is, for example, the ethylene, 1-methylethylene, 2-methylethylene, trimethylene, 1-methyltrimethylene, 2-methyltrimethylene or 2-ethyltrimethylene radical. R₁ and R₂ represent, for example, the methyl, ethyl, n-propyl, isopropyl or n-butyl radical. If R₁ and R₂ form a heterocyclic radical with the nitrogen atom then this is, e.g., the 1-pyrrolidinyl, piperidino, hexamethyleneimino, 4-methyl-1-piperazinyl or 4-methyl-1-homopiperazinyl radical.

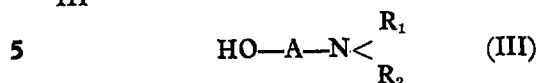
To produce the new compounds of the general formula I, a compound of the general formula II



(II)

wherein X, Y and Z have the meanings given

in formula I, is condensed, in the presence of a basic condensing agent, with a reactive ester of an amino alcohol of the general formula III



wherein A, R₁ and R₂ have the meanings given in formula I. Suitable condensing agents are, in particular, sodium amide, phenyl sodium, lithium amide, potassium amide, sodium, potassium, lithium, butyl lithium, phenyl lithium, sodium or lithium hydride. The reaction can be performed in the presence or absence of an inert organic solvent such as benzene, toluene, xylene, dimethyl formamide or dioxan.

Of the starting materials of the general formula II used according to the invention, dibenzo[b,f]thiepin - 10(11H) - one, dibenzo[b,f]oxepin - 10(11H) - one and 4 - methoxydibenz[b,f]oxepin - 10(11H) - one are known. 2 - Chloro- and 8 - chloro - dibenzo[b,f]thiepin - 10(11H) - one are produced in an analogous manner to these compounds. The former is produced starting from the potassium salt of 2,5 - dichlorobenzoic acid, this is condensed with the sodium salt of thiophenol and the condensation product, potassium 3 - chloro - 6 - (phenylthio)benzoate is hydrolysed to the free 3 - chloro - 6 - (phenylthio)benzoic acid, M.P. 143—153°, from which the ethyl ester (B.P._{0.02} 150°) is produced by esterification. This intermediate product as well as the corresponding known starting material for 8 - chlorodibenzo[b,f]thiepin - 10(11H) - one, *o* - (*p'* - chlorophenylthio)benzoic acid ethyl ester or also the corresponding free carboxylic acids, are reduced with lithium aluminium hydride to form the 3-chloro - 6 - (phenylthio)benzyl alcohol, M.P. 52—54°, or *o* - (*p'* - chlorophenylthio) - benzyl alcohol, B.P._{0.03} 155°, and then these compounds are converted with 48% hydrobromic acid into 2 - ~~bromoethyl~~ - 4 - chlorodiphenyl sulphide, B.P._{0.01} 135°, or into 2 - ~~bromoethyl~~ - 4' - chlorodiphenyl sulphide, M.P. 53°. Potassium cyanide in 95% ethanol, with the bromine compounds, yields 3-chloro-6 - (phenylthio)phenyl acetonitrile, B.P._{0.05} 145°, or *o* - (*p'* - chlorophenylthio) - phenyl acetonitrile which are hydrolysed to form 3-chloro - 6 - (phenylthio)phenyl acetic acid, M.P. 115—118°, or *o* - (*p'* - chlorophenylthio) - phenyl acetic acid, M.P. 97—100°. The carboxylic acids obtained can be cyclised with polyphosphoric acid to form 2 - chloro- or 8 - chloro - dibenzo[b,f]thiepin - 10(11H) - one.

The halides are used in particular as reactive esters of amino alcohols of the general formula III; individually can be named: 2-dimethylamino ethyl chloride, 2 - diethylamino ethyl chloride, 2 - methylethylamino

ethyl chloride, 2 - dimethylamino - propyl chloride, 2 - dimethylamino - 1 - methyl ethyl chloride, 3 - dimethylamino - propyl chloride, 3 - dimethylamino butyl chloride, 4 - dimethylamino butyl chloride, 3 - dimethylamino - 2 - methyl - propyl chloride, 2 - (di-*n* - propylamino) - ethyl chloride, 2 - (methylisopropylamino) - ethyl chloride, 1 - (2' - chloroethyl) - pyrrolidine, 1 - (3' - chloropropyl) - pyrrolidine, 1 - (2' - chloroethyl) - piperidine, 1 - (3' - chloropropyl) - piperidine, 1 - (2' - chloroethyl) - 4 - methyl piperazine, 1 - (3' - chloropropyl) - 4 - methyl piperazine and 1 - (3' - chloropropyl) - 4 - methyl homopiperazine, as well as the corresponding bromides and iodides.

The new compounds of general formula I form salts, most of which are water soluble, with inorganic and organic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane disulphonic acid, β -hydroxyethane sulphonic acid, acetic acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid, phenyl acetic acid and mandelic acid.

The invention also includes pharmaceutical preparations in dosage unit form which comprises a compound of the general formula I together with at least one inert pharmaceutical carrier.

The following examples further illustrate the production of the new compounds of general formula I, but are by no means the sole methods of producing same. The temperatures are given in degrees Centigrade.

EXAMPLE 1

a) 45.2 g of dibenzo[b,f]thiepin - 10(11H) - one are dissolved in 250 ml of abs. benzene and a suspension of 8 g of sodium amide in 24 ml of abs. toluene is added. The mixture is refluxed for 2 hours, then cooled to 50°, 27 g of freshly distilled 3 - dimethylamino propyl chloride are added and the whole is refluxed for 20 hours. The reaction mixture is cooled to 20°, water is added, the organic phase is separated and extracted with 2N hydrochloric acid. The aqueous extract is made alkaline with concentrated sodium hydroxide solution, extracted with ethyl ether, the ether extract is washed with water, dried over potassium carbonate and concentrated in vacuo. To cleave the basic enol ether formed as side product, the residue is heated with 250 ml of 2N hydrochloric acid for 30 minutes at 80—90° and then the reaction solution is cooled with ice whereupon the neutral cleavage produce, dibenzo[b,f]thiepin - 10(11H) - one, crystallises out. The crystals are filtered off, washed with 2N hydrochloric acid and the combined acid filtrates are made alkaline with concentrated sodium hydroxide solution. The alkaline phase is extracted with

bromomethyl

bromomethyl

ethyl ether, the ethereal solution is washed with water, dried over potassium carbonate and concentrated. On distilling the residue in vacuo, 11 - (3' - dimethylaminopropyl)-dibenzo[b,f]thiepin - 10(11H) - one is obtained, B.P._{0.005} 165—168°. The base is converted into the hydrochloride with ethanolic hydrochloric acid, M.P. 122—124°.

b) The following are obtained from dibenzo[b,f]thiepin - 10(11H) - one analogously to process a):

with 2 - dimethylaminoethyl chloride; 11 - (2' - dimethylaminoethyl) - dibenzo[b,f]thiepin - 10(11H) - one, B.P._{0.005} 160—161°, hydrochloride M.P. 206—208° from abs. ethanol;

with 3 - diethylaminopropyl chloride; 11 - (3' - diethylaminopropyl) - dibenzo[b,f]thiepin - 10(11H) - one, B.P._{0.01} 187—189°, hydrochloride, M.P. 197—200° from abs. ethanol;

with 3 - dimethylamino - 2 - methyl propyl chloride; 11 - (3' - dimethylamino - 2' - methylpropyl) - dibenzo[b,f]thiepin - 10(11H) - one, B.P._{0.005} 181—182°, M.P. 85—86° from petroleum ether; and

with 3 - piperidino propyl chloride; 11 - (3' - piperidinopropyl) - dibenzo[b,f]thiepin - 10(11H) - one, B.P._{0.01} 193—196°, hydrochloride M.P. 203—206° from abs. ethanol.

c) 8 - Chlorodibenzo[b,f]thiepin - 10(11H) - one, M.P. 141°, is converted according to process a), with 2 - dimethylaminoethyl chloride, into 8 - chloro - 11 - (2' - dimethylaminoethyl) - dibenzo[b,f]thiepin - 10(11H) - one (M.P. 108—109° from ethyl ether/petroleum ether), and with 3 - dimethylaminopropyl chloride it is converted into 8 - chloro - 11 - (3' - dimethylaminopropyl) - dibenzo[b,f]thiepin - 10(11H) - one, B.P._{0.01} 180—183°, M.P. 62—63° from pentane.

d) The following are further obtained analogously to process a):

3 - chloro - 11 - (2' - dimethylaminoethyl)-dibenzo[b,f]thiepin - 10(11H) - one, M.P. 91—92°;

3 - chloro - 11 - (3' - dimethylaminopropyl)-dibenzo[b,f]thiepin - 10(11H) - one, M.P. 83—84°; and

2 - chloro - 8 - methyl - 11 - (3' - dimethylaminopropyl) - dibenzo[b,f]thiepin - 10(11H) - one, B.P._{0.002} 197—200°, hydrochloride M.P. 168—172°;

EXAMPLE 2

a) 210 g of dibenz[b,f]oxepin - 10(11H) - one are dissolved in 1.70 litres of abs. benzene, a suspension of 23 g of lithium amide in 69 ml of abs. toluene is added to the solution and the whole is refluxed for 2 hours. After cooling the reaction mixture to 50°, 152 g of freshly distilled 3 - dimethylamino - propyl chloride are added and the whole is refluxed for another 20 hours. The mixture is then cooled to 20°, water is added, the organic

phase is removed and extracted with 2N hydrochloric acid. The hydrochloric acid extracts are heated for 30 minutes at 80—90° in order to split the basic enol ether formed as side product. After cooling the reaction mixture to 20°, the neutral cleavage product, dibenz[b,f]oxepin - 10(11H) - one, crystallises out. The crystals are filtered off, washed with 2N hydrochloric acid and the combined acid filtrates are made alkaline with concentrated sodium hydroxide solution. The alkaline phase is extracted with diethyl ether, the ethereal solution is washed with water, dried over potassium carbonate and concentrated. Distillation of the residue under high vacuum yields 11 - (3' - dimethylaminopropyl) - dibenz[b,f]oxepin - 10(11H) - one, B.P. 166—169°/0.01 Torr. The base is converted with ethanolic hydrochloric acid into the hydrochloride, M.P. 191—195° recrystallised from isopropanol.

b) The following compounds are obtained from dibenz[b,f]oxepin - 10(11H) - one analogously to process a):

b¹) with 2 - dimethylamino - ethyl chloride: 11 - (2' - dimethylaminoethyl) - dibenz[b,f]oxepin - 10(11H) - one, B.P. 147—151°/0.002 Torr, hydrochloride M.P. 175—177° from isopropanol/diethyl ether,

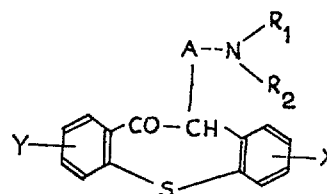
b²) with 3 - diethylamino - propyl chloride: 11 - (3' - diethylaminopropyl) - dibenz[b,f]oxepin - 10(11H) - one, B.P. 155—157°/0.002 Torr, hydrochloride M.P. 131—132° from acetone,

b³) with 3 - piperidino - propyl chloride: 11 - (3' - piperidinopropyl) - dibenz[b,f]oxepin - 10(11H) - one, B.P. 176—180°/0.004 Torr, hydrochloride, M.P. 96—99° from acetone, and

b⁴) with 1 - (3' - chloropropyl) - 4 - methylpiperazine: 11 - [3' - (4'' - methyl - 1'' - piperazinyl) - propyl] - dibenz[b,f]oxepin - 10(11H) - one, M.P. 123—125° from benzene, dihydrochloride M.P. 250—255° from ethanol.

WHAT WE CLAIM IS:—

1. Thiepin derivatives of the general formula Ia



(Ia)

X and Y represent hydrogen, halogen up to the atomic number 35, alkyl groups containing at most 4 carbon atoms, or alkoxy or alkylthio groups containing at most 4 carbon atoms, A represents a straight or branched-chain



ethyl ether, the ethereal solution is washed with water, dried over potassium carbonate and concentrated. On distilling the residue in vacuo, 11 - (3' - dimethylaminopropyl)-

5 dibenzo[b,f]thiepin - 10(11H) - one is obtained, B.P._{0.005} 165—168°. The base is converted into the hydrochloride with ethanolic hydrochloric acid, M.P. 122—124°.

b) The following are obtained from dibenzo-

10 [b,f]thiepin - 10(11H) - one analogously to process a):

with 2 - dimethylaminoethyl chloride; 11 - (2' - dimethylaminoethyl) - dibenzo[b,f]-

15 thiepin - 10(11H) - one, B.P._{0.005} 160—161°, hydrochloride M.P. 206—208° from abs. ethanol;

with 3 - diethylaminopropyl chloride; 11 - (3' - diethylaminopropyl) - dibenzo[b,f]-

20 thiepin - 10(11H) - one, B.P._{0.01} 187—189°, hydrochloride, M.P. 197—200° from abs. ethanol;

with 3 - dimethylamino - 2 - methyl propyl chloride; 11 - (3' - dimethylamino - 2' - methylpropyl) - dibenzo[b,f]thiepin - 10-

25 (11H) - one, B.P._{0.005} 181—182°, M.P. 85—86° from petroleum ether; and

with 3 - piperidino propyl chloride; 11 - (3' - piperidinopropyl) - dibenzo[b,f]thiepin -

30 10(11H) - one, B.P._{0.01} 193—196°, hydrochloride M.P. 203—206° from abs. ethanol.

c) 8 - Chlorodibenzo[b,f]thiepin - 10(11H)-

35 one, M.P. 141°, is converted according to process a), with 2 - dimethylaminoethyl chloride, into 8 - chloro - 11 - (2' - dimethylamino-

ethyl) - dibenzo[b,f]thiepin - 10(11H) - one (M.P. 108—109° from ethyl ether/petroleum

40 ether), and with 3 - dimethylaminopropyl chloride it is converted into 8 - chloro - 11 - (3' - dimethylaminopropyl) - dibenzo[b,f]-

thiepin - 10(11H) - one, B.P._{0.01} 180—183°, M.P. 62—63° from pentane.

d) The following are further obtained analogously to process a):

45 3 - chloro - 11 - (2' - dimethylaminoethyl)-dibenzo[b,f]thiepin - 10(11H) - one, M.P. 91—92°;

3 - chloro - 11 - (3' - dimethylaminopropyl)-dibenzo[b,f]thiepin - 10(11H) - one, M.P. 83—84°; and

50 2 - chloro - 8 - methyl - 11 - (3' - dimethylaminopropyl) - dibenzo[b,f]thiepin - 10-

(11H) - one, B.P._{0.002} 197—200°, hydrochloride M.P. 168—172°;

EXAMPLE 2

55 a) 210 g of dibenz[b,f]oxepin - 10(11H)-one are dissolved in 1.70 litres of abs. benzene, a suspension of 23 g of lithium amide in 69 ml of abs. toluene is added to the solution

and the whole is refluxed for 2 hours. After

60 cooling the reaction mixture to 50°, 152 g of freshly distilled 3 - dimethylamino - propyl chloride are added and the whole is refluxed for another 20 hours. The mixture is then

cooled to 20°, water is added, the organic

phase is removed and extracted with 2N

hydrochloric acid. The hydrochloric acid ex-

tracts are heated for 30 minutes at 80—90°

in order to split the basic enol ether formed

as side product. After cooling the reaction

mixture to 20°, the neutral cleavage product,

dibenz[b,f]oxepin - 10(11H) - one, crystal-

lises out. The crystals are filtered off, washed

with 2N hydrochloric acid and the com-

85 bined acid filtrates are made alkaline with concentrated sodium hydroxide solution. The alkaline phase is extracted with diethyl ether, the ethereal solution is washed with water, dried over potassium carbonate and concentrated. Distillation of the residue under high vacuum yields 11 - (3' - dimethylamino-

propyl) - dibenz[b,f]oxepin - 10(11H) - one, B.P. 166—169°/0.01 Torr. The base is converted with ethanolic hydrochloric acid into the hydrochloride, M.P. 191—195° recrystal-

lised from isopropanol.

b) The following compounds are obtained from dibenz[b,f]oxepin - 10(11H) - one anal-

ogously to process a):

b¹) with 2 - dimethylamino - ethyl chloride:

11 - (2' - dimethylaminoethyl) - dibenz-

90 [b,f]oxepin - 10(11H) - one, B.P. 147—151°/0.002 Torr, hydrochloride M.P. 175—177° from isopropanol/diethyl ether,

b²) with 3 - diethylamino - propyl chloride:

11 - (3' - diethylaminopropyl) - dibenz-

95 [b,f]oxepin - 10(11H) - one, B.P. 155—157°/0.002 Torr, hydrochloride M.P. 131—132° from acetone,

b³) with 3 - piperidino - propyl chloride:

11 - (3' - piperidinopropyl) - dibenz[b,f]-

100 oxepin - 10(11H) - one, B.P. 176—180°/0.004 Torr, hydrochloride, M.P. 96—99° from acetone, and

b⁴) with 1 - (3' - chloropropyl) - 4 - methyl-

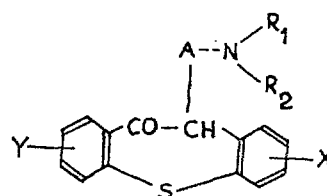
105 piperazine: 11 - [3' - (4'' - methyl - 1'' - piperazinyl) - propyl] - dibenz[b,f]oxepin-

10(11H) - one, M.P. 123—125° from benzene, dihydrochloride M.P. 250—255° from ethanol.

WHAT WE CLAIM IS:—

1. Thiepin derivatives of the general formula

Ia



(Ia)

X and Y represent hydrogen, halogen up to

the atomic number 35, alkyl groups contain-

ing at most 4 carbon atoms, or alkoxy or alkyl-

thio groups containing at most 4 carbon atoms,

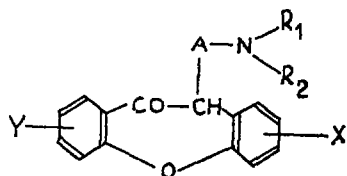
A represents a straight or branched-chain



alkylene radical having 2—5 carbon atoms, R_1 and R_2 represent alkyl radicals containing at most 4 carbon atoms, or

R_1 and R_2 together with the adjacent nitrogen and with the optional inclusion of a alkylimino group containing at most 4 carbon atoms as ring member, represent a saturated heterocyclic ring having 5—7 ring members and their acid addition salts with inorganic or organic acids.

2. Oxepin derivatives of the general formula Ib



(Ib)

X and Y represent hydrogen, halogen up to the atomic number 35, alkyl groups containing at most 4 carbon atoms, or alkoxy or alkylthio groups containing at most 4 carbon atoms,

A represents a straight or branched-chain alkylene radical having 2—5 carbon atoms, R_1 and R_2 represent alkyl radicals containing at most 4 carbon atoms or,

R_1 and R_2 together with the adjacent nitrogen and with the optional inclusion of a alkylimino group containing at most 4 carbon atoms as ring member, represent a saturated heterocyclic ring having 5—7 ring members and their acid addition salts with inorganic or organic acids.

3. Thiepin derivatives of the general formula Ia given in claim 1 wherein A, R_1 and R_2 are as defined in claim 1, and X and Y represent hydrogen and their acid addition salts with inorganic or organic acid.

4. Oxepin derivatives of the general formula Ib given in claim 2 wherein A, R_1 and R_2 are as defined in claim 2, and X and Y represent hydrogen and their acid addition salts with inorganic or organic acids.

5. 11 - (3' - Dimethylaminopropyl) - dibenzo[b,f]thiepin - 10(11H) - one.

6. The hydrochloride salt of 11 - (3' - dimethylaminopropyl) - dibenzo[b,f]thiepin - 10(11H) - one.

7. 11 - (2' - Dimethylaminoethyl) - dibenzo[b,f]thiepin - 10(11H) - one.

8. 11 - (3' - Dimethylamino - 2' - methylpropyl) - dibenzo[b,f] - thiepin - 10(11H) - one.

9. 8 - Chloro - 11 - (3' - dimethylaminopropyl) - dibenzo[b,f]thiepin - 10(11H) - one.

10. 8 - Chloro - 11 - (2' - dimethylaminoethyl) - dibenzo[b,f]thiepin - 10(11H) - one.

11. 11 - (3' - Dimethylaminopropyl) - dibenz[b,f]oxepin - 10(11H) - one.

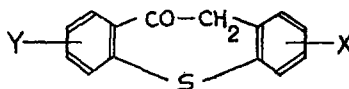
12. The hydrochloride salt of 11 - (3' - di-

methylaminopropyl) - dibenz[b,f]oxepin - 10(11H) - one.

13. Compounds of the formula Ia 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 the foregoing examples.

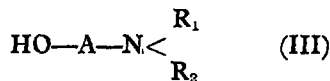
14. Compounds of the formula Ib defined in claim 2 and salts thereof with inorganic or organic acids substantially as herein described with reference to and as illustrated in any of the foregoing examples.

15. A process for the production of thiepin derivatives according to claim 1, which comprises condensing, in the presence of a basic condensing agent, a compound of the general formula IIa



(IIa)

wherein X and Y have the meanings given in claim I, with a reactive ester of an amino alcohol of the general formula III



wherein A, R_1 and R_2 have the meanings given in claim I, and, if desired, converting the compound obtained of the general formula Ia into a salt with an inorganic or organic acid.

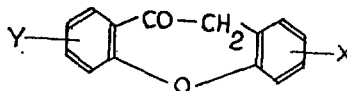
16. A process as claimed in claim 15 in which the reaction is carried out in the presence of an inert solvent.

17. A process as claimed in claim 15 or 16 in which the reactive ester of an amino alcohol of the general formula III is a chloride.

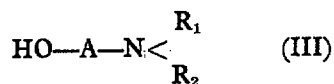
18. A process as claimed in any of claims 15 to 17 in which X, Y, A, R_1 and R_2 have the meanings given in claim 3.

19. A process as claimed in claim 17 substantially as herein before described in Example 1.

20. A process for the production of oxepin derivatives according to claim 2 which comprises condensing, in the presence of a basic condensing agent, a compound of the formula IIb



wherein X and Y have the meanings given in claim 2, with a reactive ester of an amino alcohol of the general formula III



wherein A, R₁ and R₂ have the meanings given in claim 2 and, if desired, converting the compound obtained of the general formula Ib into a salt with an inorganic or organic acid.

21. A process as claimed in claim 20 in which the reaction is carried out in the presence of an inert solvent.

22. A process as claimed in claim 20 or 21 in which the reactive ester of an amino alcohol of the general formula III is a chloride.

23. A process as claimed in any of claims

20 to 22 in which X, Y, A, R₁ and R₂ have the meanings given in claim 4.

24. A process as claimed in claim 20 substantially as herein before described in Example 2.

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

26. A pharmaceutical preparation in dosage unit ~~form~~ comprising a compound claimed in claim 2 and at least one inert pharmaceutical carrier.

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Chartered Patent Agents.

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