

PATENT SPECIFICATION

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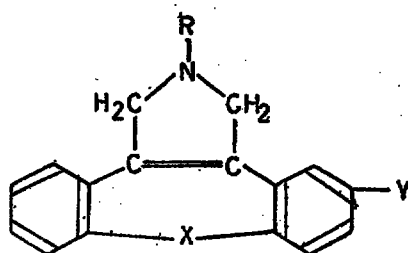


(54) THIEPIN AND OXEPIN DERIVATIVES, PROCESSES
 FOR THEIR PRODUCTION AND MEDICAMENTS
 CONTAINING SAME

(71) We, CIBA GEIGY A.G., a Swiss Company, of CH-4002, Basle, Switzerland (R), 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 thiepin and oxepin derivatives, processes for the production thereof, medicaments containing the new compounds and their use.

Thiepin and oxepin derivatives of the general formula I,



(I)

15 wherein

X represents oxygen or sulphur,
 Y represents hydrogen, chlorine, or the methyl, methoxy or methylthio group and

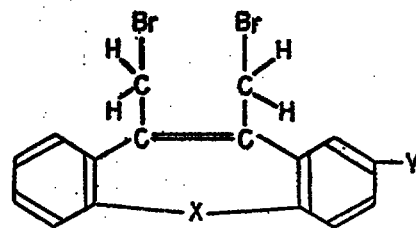
20 R represents hydrogen, a straight chain low alkyl group with 1—6 carbon atoms, the isopropyl or the allyl groups
 as well as their pharmaceutically acceptable acid addition salts, have not been known hitherto.

It has now been found that such compounds, especially those the radical R of which represents a straight chain lower alkyl group, as

[Price 25p]

well as the pharmaceutically acceptable additions salts of such compounds, possess valuable pharmacological properties and a high therapeutic index. In the case of oral, rectal and parenteral administration they exhibit a central depressant activity, e.g. they reduce motility, potentiate the action of analgesics and anaesthetics, counteract the effect of amphetamine, exhibit a positive action in the "test de la traction", have an antiemetic, serotonin-antagonistic action and lower the body temperature. Furthermore, they exhibit an antihistaminic activity. These properties, which may be determined by selected standard tests [cp. R. Domenjoz and W. Theobald, Arch.Int.Pharmacodyn. 120, 450 (1959), G. Raynaud, Produits Pharm. 16, 99 (1961) and W. Theobald and R. Domenjoz, Arzneimittelforschung 8, 18 (1958)], characterise the compounds as being suitable for the treatment of states of tension and agitation.

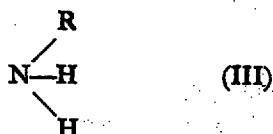
According to the present invention, compounds of the general formula I in which R is not a hydrogen atom, are produced by reacting a compound of the general formula II,



(II)

wherein X and Y have the meanings given under formula I, with an amine of the general formula III,

55



wherein R has the meaning given under formula I except that it may not represent a hydrogen atom, and optionally converting the obtained reaction product into a pharmaceutically acceptable acid addition salt with an inorganic or organic acid. Compounds of general formula II above and described, and claimed in our co-pending Application, No. 24841/72 (Serial No. 1,297,387).

The bis-bromomethyl compounds of the general formula II are reacted with the free bases of the general formula III optionally 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, ethereal liquids such as ether or dioxane, as well as lower alkanones containing maximally 6 carbon atoms such as acetone, methyl ethyl ketone or diethyl ketone.

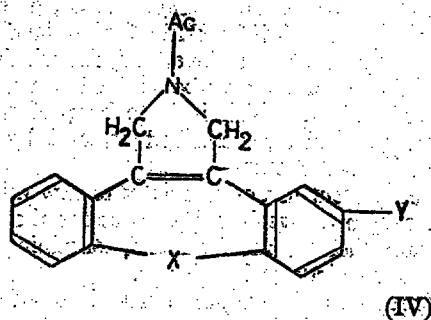
In the reaction, according to the invention, of one molar equivalent of the bis-bromomethyl compounds with one molar equivalent of free base, two molar equivalents of hydrogen bromide are split off. The hydrogen bromide is preferably bound by the use of excess base of the general formula III.

One of the starting materials, e.g. 2-methoxy - 10,11 - bis - bromomethyl - dibenzo - [b,f]thiepin, embraced by the general formula II, can be produced by the following process:

The starting compound is 8-methoxy-dibenzo-[b,f]thiepin-10(11H)-one (cp. Spofa, French patent specification No. 1,484,332) which, with methyl iodide in the presence of sodium amide, yields the 8-methoxy-11-methyl-dibenzo[b,f]thiepin-10(11H)-one. This intermediate product is reacted according to the Grignard reaction with methyl iodide, in the presence of magnesium, to give the 8-methoxy - 10,11 - dimethyl - 10,11 - dihydro - dibenzo[b,f]thiepin-10-ol which, after boiling with dilute hydrochloric acid and then with potassium hydroxide is converted, with the splitting off of water, into the 2-methoxy-10,11 - dimethyl - dibenzo[b,f]thiepin. The obtained dimethyl compound is finally brominated with N-bromosuccinimide in the presence of dibenzyl-peroxide. Further thiepin or oxepin derivatives of the general formula II are to be produced analogously, to the above process, e.g. the 10,11-bis-bromomethyl-dibenzo[b,f]thiepin, by bromination of 10,11-dimethyl - dibenzo[b,f]thiepin [cp. M.M. Urberg and E.T. Kaiser, J.Am.Chem.Soc. 89, 5931 (1967)]. Also the 2-chloro-10,11-bis-bromomethyl - dibenzo[b,f]thiepin can be

produced starting with 8 - chloro - dibenzo - [b,f]thiepin - 10(11H) - one (cp. Geigy D.A.S. No. 1,228,272) by way of the intermediate products 8 - chloro - 10,11 - dimethyl - 10,11 - dihydro - dibenzo[b,f]thiepin - 10 - ol and 2 - chloro - 10,11 - dimethyl-dibenzo[b,f]thiepin, as well as the 10,11 - bis - bromomethyl - dibenz[b,f]oxepin, starting with dibenz[b,f]oxepin - 10(11H)-one [cp. R.H.F. Manske and A.E. Ledingham, J.Am.Chem.Soc. 72, 4797 (1950)] by way of the intermediate products 11 - methyl - dibenz[b,f]oxepin - 10(11H) - one, 10,11 - dimethyl - 10,11 - dihydro - dibenz[b,f]oxepin - 10 - ol and 10,11 - dimethyl-dibenz[b,f]oxepin.

Compounds of the general formula I in which R represents hydrogen can be prepared by a second process which comprises hydrolysing a compound of the general formula IV



wherein

X and Y have the meanings given under formula I and

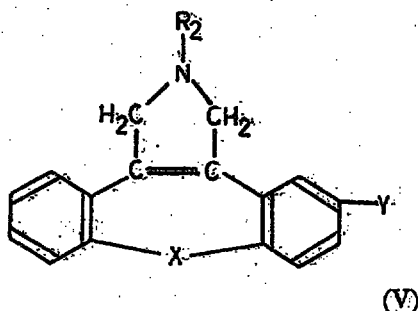
Ac represents the acyl radical of an organic acid or a cyano group; and,

if desired, converting a compound of the general formula I thus obtained into a pharmaceutically acceptable acid addition salt with an inorganic or organic acid.

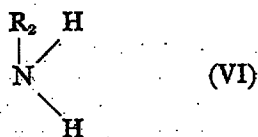
In the starting material of the general formula IV Ac represents particularly the cyano group, or the acyl radical of chloroformic acid, a carbonic or thiocarbonic acid monoester, a low alkanolic carboxylic acid containing maximally 5 carbon atoms or an arene carboxylic acid. Examples of acyl radicals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

The hydrolysis of compounds of the general formula IV 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. Instead of alkanols other solvents containing a hydroxyl group may be used, such as ethylene glycol and monoalkylethers thereof.

- Furthermore, compounds of the general formula IV, 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—70°C.
- The starting material of the general formula IV is prepared, for example, from a compound of the general formula V



- wherein:
- X and Y have the meanings given under formula I and
- R₂ represents a low alkyl group containing maximally 6 carbon atoms, or the allyl or benzyl group, by reacting the compound with
- a cyanohalide, in particular a cyanogenbromide, or with phosgene, or with an acyl halide, for example chloroformic acid-phenylester or -benzylester, the chloride or bromide of a low alkanolic acid containing maximally 6 carbon atoms or benzoic acid, particularly acetylchloride, acetylbromide or benzoylchloride, at room temperature or at raised temperature, whereby according to the von Braun-reaction the desired cyanation or acylation occurs with the splitting off of the group R₂ 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 medium.
- The starting material of the general formula V is in its turn prepared analogously to the first process, by reacting a compound of the general formula II with an amine of the general formula VI



- wherein
- R₂ represents a low alkyl containing maximally 6 carbon atoms, the allyl or the benzyl group.
- The preparation of the starting compound,

of the general formula II used in connection with the first process is fully described in the literature.

The compounds of the general formula I, obtained according to the invention, may optionally be converted, in the usual manner, into their pharmaceutically acceptable addition salts with inorganic and organic acids. For example, the acid desired as salt component, or a solution of the acid, is added to a solution of a compound of the general formula I in an organic solvent. For the reaction, it is preferable to use organic solvents, in which the salt formed 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.

For use as medicaments it is possible to use, instead of the free bases, pharmaceutically acceptable acid addition salts, i.e. salts with such acids, the anions of which are non-toxic at the required dosage levels. Furthermore, it is of advantage if the salts to be used as medicaments readily crystallise and are not, or are only slightly hygroscopic. For salt formation with compounds of the general formula I it is possible to use, e.g. hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, β-hydroxyethanesulphonic 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.

The new active substances, as mentioned above, may be administered orally, rectally or parenterally. The dosage depends on the form of administration, the species, the age and on the individual condition. The daily dosages of the free bases or of pharmaceutically acceptable acid addition salts thereof, vary between 0.1 mg/kg. and 10 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 90% of a compound of the general formula I or of a pharmaceutically acceptable 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 of lubricants, such as magnesium stearate 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 dosages 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 salt thereof, with a fatty foundation substance. Also suitable are gelatine rectal capsules containing a combination of the active substance, or of a suitable salt thereof with polyethylene glycol.

Ampoules for parenteral, especially intramuscular administration, preferably contain a water-soluble 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-methyl-2,3-dihydro-1H-dibenzo[2,3:6,7]thiepine[4,5 - c]pyrrole-methanesulphonate are mixed with 175.80 g of lactose and 169.70 g of potato starch. The mixture is moistened with an ethanolic 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. The mixture is then pressed into 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-2,3-dihydro-1H-dibenzo[2,3:6,7]thiepine[4,5 - c]pyrrolmethane-sulphonate, 175.90 g of lactose and an ethanolic 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 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 dye-

stuff and 1.5 g of titanium dioxide, and dried. The obtained dragées each weigh 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-methyl-2,3-dihydro-1H-dibenzo[2,3:6,7]thiepine[4,5 - c]pyrrolmethanesulphonate are mixed with 248 g of lactose. The mixture is evenly moistened with an aqueous solution of 2 g of gelatine and is granulated through a suitable sieve (e.g. sieve No. III according to Ph.Helv. V). The granulate is mixed with 10 g of dried maize starch and 15 g of talcum. The obtained mixture is uniformly filled into 1000 hard gelatine capsules, size 1.

d) A suppository base mixture is prepared from 2.5 g of 2-ethyl-5-methoxy-2,3-dihydro-1H-dibenzo[2,3:6,7]thiepine[4,5 - c]pyrrolmethanesulphonate and 167.5 g of adeps solidus. From this mixture are then filled 100 suppositories each containing 25 mg of active substance.

e) A solution of 25 g of 2-ethyl-2,3-dihydro-1H-dibenzo[2,3:6,7]thiepine[4,5 - c]pyrrolmethanesulphonate in one litre of water is filled into 1000 ampoules and sterilised. 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) 25.0 g of 10,11-bis-bromomethyl-dibenzo[b,f]thiepin are dissolved in 150 ml of anhydrous benzene. This solution is added dropwise within one hour at 40° to a solution of 75.0 g of methylamine in 425 ml of methanol. The reaction mixture is stirred for a further two hours at 50° and the solvent and the excess methylamine are then distilled off. 100 ml of water are added to the residue and a suspension is obtained which is extracted with ether. The ethereal solution is washed with water, dried over potassium carbonate and concentrated by evaporation. The residue, which is recrystallised from ethanol, yields 2-methyl-2,3-dihydro-1H-dibenzo[2,3:6,7]thiepine[4,5-c]pyrrole, M.P. 109—110°.

12.5 g of the obtained base are dissolved in 25 ml of anhydrous acetone and 4.5 g of methanesulphonic acid are carefully added, whereupon the methanesulphonate crystallises. After recrystallisation from anhydrous ethanol, the methane-sulphonate melts at 238—243°.

The starting material, i.e. the 10,11-bis-bromomethyl-dibenzo[b,f]thiepin, is produced as follows:

b) 38.5 g of 10-11-dimethyl-dibenzo[b,f]-

thiepin [cp. M.M. Urberg and E.T. Kaiser, J. Am. Chem. Soc. 89, 5931 (1967)] are dissolved in 385 ml of carbon tetrachloride. To this solution are added 58.0 g of N-bromosuccinimide and 1.1 g of dibenzoylperoxide. By exposure to two 200 watt lamps or to a UV-lamp, the mixture is heated, while stirring, to boiling. The mixture is kept boiling until all the N-bromosuccinimide, lying on the bottom of the vessel, has been converted into succinimide which separates out as an upper phase. The reaction mixture is then cooled to 20° and the succinimide is separated by filtration. The filtrate is washed with water, dried over sodium sulphate and completely concentrated by evaporation in a rotary evaporator. The residue, which is recrystallised from benzene, yields 10,11-bis-bromomethyl-dibenzo[b,f]thiepin, M.P. 150—151°.

Example 2

The following end products are produced analogously to Example 1 a):

- a) from 20.0 g of 10,11-bis-bromomethyl-dibenzo[b,f]thiepin and 17.5 g of ethylamine in 100 ml of methanol is produced 2-ethyl-2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepin[4,5-c]pyrrole, M.P. 83—85° (from petroleum ether); methanesulphonate, M.P. 220—223° (from anhydrous ethanol); and
- b) from 20.0 g of 10,11-bis-bromomethyl-dibenzo[b,f]thiepin and 33.0 g of n-butylamine in 150 ml of methanol is obtained 2-n-butyl - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepin[4,5-c]pyrrole, M.P. 69—70° (from petroleum ether); the free base is converted with ethanolic hydrochloric acid into the hydrochloride, M.P. 220—224° (from anhydrous ethanol/anhydrous ether);
- c) from 13.2 g of 10,11-bis-bromomethyl-dibenzo[b,f]thiepin and 30.3 g of n-hexylamine in 100 ml of methanol is produced 2 - n - hexyl - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepin[4,5-c]pyrrole crude product; methanesulphonate, M.P. 185—187°C (from acetone);
- d) from 13.2 g of 10,11-bis-bromomethyl-dibenzo[b,f]thiepin and 19.7 g of isopropylamine in 100 ml of methanol is produced 2 - isopropyl - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepin[4,5-c]pyrrole, crude product; methanesulphonate, M.P. 282—284° (from anhydrous ethanol);
- e) from 20.0 g of 10,11-bis-bromomethyl-dibenzo[b,f]thiepin and 28.5 g of allylamine in 100 ml of methanol is produced 2-allyl-2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepin[4,5-c]pyrrole, crude product; methanesulphonate, M.P. 255—258°C (from anhydrous ethanol).

Example 3

- a) 21.5 g of 2-chloro-10,11-bis-bromomethyl-dibenzo[b,f]thiepin are dissolved in

100 ml of absolute benzene and added dropwise at 40°, within one hour, to a solution of 35.0 g of methylamine in 200 ml of methanol. The reaction mixture is stirred for a further two hours at 50° and the solvent and the excess methylamine are subsequently distilled off. 100 ml of water are added to the residue and the obtained suspension is extracted with ether. The ethereal solution is washed with water, dried over potassium carbonate and concentrated by evaporation. The residue, which is recrystallised from ethanol, yields 2-methyl - 5 - chloro - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepin[4,5-c]pyrrole, M.P. 123—124°.

The obtained base is converted with methanesulphonic acid into the methanesulphonate, M.P. 251—254° (from anhydrous ethanol).

The starting material, i.e. the 2-chloro-10,11 - bis - bromomethyl - dibenzo[b,f]thiepin, is produced as follows:

- b) A solution of 37.0 g of 8-chloro-11-methyl - dibenzo[b,f]thiepin - 10(11H) - one, M.P. 113° (cp. Geigy D.A.S. 1,288,272), in 80 ml of benzene is added dropwise within one hour, while stirring well, to a Grignard solution prepared from 6.6 g of magnesium, 38.5 g of methyl iodide and 70 ml of ether, while a reaction temperature of -5 to 0° is maintained. The reaction mixture is subsequently heated to 45° and is further stirred for 15 hours at this temperature. The mixture is then cooled to 0° and is stirred into a solution of 85.0 g of ammonium chloride in 250 ml of ice water. The organic phase is separated and the aqueous phase extracted with benzene. The combined organic solutions are washed with water, dried over sodium sulphate and concentrated by evaporation in vacuo. As residue is obtained 8-chloro-10,11-dimethyl-10,11 - dihydro - dibenzo[b,f]thiepin - 10 - ol (crude product) in the form of a yellowish-brown oil;

- c) 39.0 g of the hydroxy compound, obtained according to b), are refluxed for 10 hours, while stirring, in 200 ml of 4N hydrochloric acid. The mixture is cooled to 20°, extracted with ether, the organic phase washed with water, dried over potassium carbonate and concentrated by evaporation. The residue is dissolved in 200 ml of anhydrous ethanol, 40.0 g of potassium hydroxide are added to this solution and the mixture is then refluxed for 5 hours. The reaction mixture is poured in to water and extracted with ether. The organic phase is washed with water, dried over potassium carbonate and concentrated by evaporation. The residue, 2 - chloro - 10,11 - dimethyl-dibenzo[b,f]thiepin, melts after crystallisation from ether/petroleum ether at 99—102°;

- d) 26.0 g of the thiepin, obtained according to c), are dissolved in 260 ml of carbon tetrachloride and to this solution are added 34.5

g. of N-bromosuccinic and 0.6 g. of dibenzoyl-peroxide. The mixture is brought to boiling, while stirring, by exposure to two 200 watt lamps or to a UV-lamp. The mixture is kept boiling until all the N-bromosuccinimide, lying on the bottom of the vessel, has been converted into succinimide which separates on an upper phase. The reaction mixture is thereupon cooled to 20° and the succinimide separated by filtration. The filtrate is washed with water, dried over sodium sulphate and completely concentrated by evaporation in a rotary evaporator. The residue, which is recrystallised from benzene, yields 2-chloro-10,11-bis-bromomethyl-dibenzo[b,f]thiepin, M.P. 131—133°.

Example 4

From 14.0 g of 2-chloro-10,11-bis-bromomethyl-dibenzo[b,f]thiepin and 23.0 g of ethylamine in 140 ml of methanol is produced, analogously to Example 3 a), 2-ethyl-5-chloro-2,3-dihydro-1H-dibenzo[2,3:6,7]thiepin[4,5-c]pyrrole, M.P. 71—74° (from petroleum/ether); yield 8.0 g, 80% of theoretical value; methane-sulphonate, M.P. 261—264° (from absolute ethanol);

b) from 20 g 2-chloro-10,11-bis-bromomethyl-dibenzo[b,f]thiepin and 26 g of allylamine in 90 ml of methanol is produced 2-allyl-5-chloro-2,3-dihydro-1H-dibenzo[2,3:6,7]thiepin[4,5-c]pyrrole, crude product; methane-sulphonate, M.P. 235—237° (from anhydrous ethanol).

Example 5

a) 21.3 g of 2-methoxy-10,11-bis-bromomethyl-dibenzo[b,f]thiepin are dissolved in 200 ml of anhydrous benzene and added dropwise, within one hour at 40°, to a solution of 35.0 g of methylamine in 200 ml of methanol. The reaction mixture is stirred for a further two hours at 50° and the solvent and the excess methylamine are subsequently distilled off. 100 ml of water are added to the residue and the obtained suspension is extracted with ether. The ethereal solution is washed with water, dried over potassium carbonate and concentrated by evaporation. The residue, which is recrystallised from petrol yields 2-methyl-5-methoxy-2,3-dihydro-1H-dibenzo[2,3:6,7]thiepin[4,5-c]pyrrole, M.P. 127—129°.

The obtained base is converted with methane-sulphonic acid into the methane-sulphonate, M.P. 223—226° (from anhydrous ethanol).

The starting material, 2-methoxy-10,11-bis-bromomethyl-dibenzo[b,f]thiepin, is produced as follows:

b) A suspension of 13.5 g of sodium amide in 35 ml of anhydrous toluene is added dropwise at 50—60° over a period of 30 minutes to a solution of 80.0 g of 8-methoxy-dibenzo[b,f]thiepin-10(11H)-one, M.P. 97—98° (cp. Spofa, French patent specification No.

1,484,332), in 800 ml of anhydrous benzene and the mixture is then refluxed for two hours. The obtained suspension is cooled to 45° and, over a period of one hour, 54.5 g of methyl iodide are added dropwise, while the temperature is maintained between 40° and 45°. The reaction mixture is stirred for 14 hours at this temperature and a further 20.0 g of methyl iodide are added. The mixture is further stirred for 24 hours at 55—60° and subsequently refluxed for 24 hours. The suspension is then cooled to 10° and 150 ml of water are added dropwise. The organic phase is separated, washed with water, dried over sodium sulphate and completely concentrated by evaporation in a rotary evaporator. The residue, which is recrystallised from petrol, yields 8-methoxy-11-methyl-dibenzo[b,f]thiepin-10(11H)-one, M.P. 105—107°;

c) The ketone, obtained according to b); is subsequently converted, analogously to Examples 3 b—d), into the following intermediate products:

c¹ 8-methoxy-10,11-dimethyl-10,11-dihydro-dibenzo[b,f]thiepin-10-one, M.P. 143—146° (from ethyl acetate);

c² 8-methoxy-10,11-dimethyl-dibenzo[b,f]thiepin (crude product);

c³ 8-methoxy-10,11-bis-bromomethyl-dibenzo[b,f]thiepin, M.P. 118—120° (from benzene).

Example 6

a) From 11.0 g of 2-methoxy-10,11-bis-bromomethyl-dibenzo[b,f]thiepin and 22.0 g of ethylamine in 130 ml of methanol, 2-ethyl-5-methoxy-2,3-dihydro-1H-dibenzo[2,3:6,7]thiepin[4,5-c]pyrrole (crude product) is produced analogously to Example 5 a); methane-sulphonate, M.P. 209—213° (from isopropyl-ethanol);

b) Similarly from 21 g of 2-methoxy-10,11-bis-bromomethyl-dibenzo[b,f]thiepin and 28.5 g of allylamine in 100 ml of methanol, 2-allyl-5-methoxy-2,3-dihydro-1H-dibenzo[2,3:6,7]thiepin[4,5-c]pyrrole, (crude product) is produced.

Example 7

a) 15 g of 2-methyl-10,11-bis-bromomethyl-dibenzo[b,f]thiepin are dissolved in 50 ml of anhydrous benzene and added dropwise at 40° and within one hour, to a solution of 22 g of methylamine in 130 ml of methanol. The reaction mixture is then stirred for a further two hours at 50° and the solvent and the excess methylamine subsequently distilled off. The residue is mixed with 70 ml of water and the suspension thus obtained is extracted with ether. The ethereal solution is washed with water, dried over potassium carbonate and evaporated. The residue, 2,5-dimethyl-2,3-dihydro-1H-dibenzo[2,3:6,7]thie-

pino[4,5-c]pyrrole is a viscous oil; 9 g of the crude base obtained are dissolved in 40 ml of anhydrous acetone and 3.1 g of methane sulphonic acid are cautiously added to the solution, whereupon the methane sulphonate crystallises, which, after recrystallisation from isopropanol, melts at 240—242°.

The starting material, 2-methyl-10,11-bis-bromomethyl-dibenzo[b,f]thiepin is prepared as follows:

- 10 b) A suspension of 33.5 g of sodium amide in 91 ml of anhydrous toluene is added dropwise at 50—60° and within 30 minutes, to a solution of 180 of 8-methyl-dibenzo[b,f]thiepin-10(11H)-one, M.P. 68—69° Spofa, French Patent No. 1,484,332 in 1750 ml of anhydrous benzene and the mixture is then boiled under reflux for two hours. The suspension thus obtained is cooled to 45° and 169 g of methyl iodide are added dropwise within one hour during which time the temperature is maintained between 40 and 45°. The reaction mixture is then stirred for 14 hours at this temperature and a further 60 g of methyl iodide are then added. This mixture is then stirred for 24 hours at 55—60° and for a further 24 hours under reflux. The suspension is then cooled to 10° and 400 ml of water are added dropwise. The opposite phase is separated, washed with water, dried over sodium sulphate and completely evaporated in a rotary evaporator. The residue, which is recrystallized from methanol, produces 8,11-dimethyl - dibenzo[b,f]thiepin - 10(11H) - one, M.P. 80—82°;
- 15 20 25 30 35

c) The ketone obtained from b) is converted into the following intermediate products analogously to Example 3 b)—d):

- 40 c¹ 8,10,11 - trimethyl - 10,11 - dihydro - dibenzo[b,f]thiepin-10-ol, crude product;
c² 2,10,11 - trimethyl - dibenzo[b,f]thiepin, M.P. 87—88° (from methanol);
c³ 2 - methyl - 10,11 - bis - bromomethyl - dibenzo[b,f]thiepin, M.P. 122—124° (from cyclohexane).
- 45

Example 8

Analogously to Example 7 a) are prepared:

- 50 a) from 15 g of 2-methyl-10,11-bis-bromomethyl-dibenzo[b,f]thiepin and 33 g of ethylamine in 145 ml of methanol, 2-ethyl-5-methyl - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepin[4,5-c]pyrrole, crude product; methanesulphonate M.P. 218—221° (from isopropanol);
- 55 b) From 20.5 g of 2-methyl-10,11-bis-bromomethyl-dibenzo[b,f]thiepin and 28.5 g of allylamine in 100 ml of methanol, 2-allyl-5 - methyl - 2,3 - dihydro - 1H - dibenzo - [2,3;6,7]pyrrole crude product, methanesulphonate, M.P. 223—225° (from anhydrous ethanol).
- 60

Example 9

- a) 3.95 g of 2-methylthio-10,11-bis-bromo-

methyl-dibenzo[b,f]thiepin are dissolved in 20 ml of anhydrous benzene and added dropwise at 40° and within half an hour to a solution of 10 g of ethylamine in 65 ml of methanol. The reaction mixture is stirred for a further 2 hours at 50° and the solvent and the excess ethylamine are subsequently distilled off. The residue is mixed with water and the obtained suspension is extracted with ether. The ethereal solution is washed with water, dried over potassium carbonate and concentrated to a small volume, whereupon 2 - ethyl - 5 - methylthio - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepin[4,5 - c]pyrrole crystallises out, M.P. 111—113°, after recrystallisation from petrol; 1.9 g of the obtained base are dissolved in 10 ml of anhydrous acetone and 0.56 g of methane sulfonic acid are added whereupon the methane sulphonate crystallises out, which, after recrystallisation from anhydrous ethanol melts at 215—218°;

65 70 75 80 85

b) The starting material, 2-methylthio-10,11 - bis - bromomethyl - dibenzo[b,f] - thiepin is prepared from 36 g of 8-methylthio-dibenzo[b,f]thiepin - 10(11H) - one Spofa French Patent No. 1,484,338, M.P. 88—90°, through the following intermediates analogously to Examples 5 b) and 3 b)—d):

90

b¹ 8 - methylthio - 11 - methyl - dibenzo - [b,f]thiepin-10(11H)-one, M.P. 111—113° (from ethyl acetate);

95

b² 8 - methylthio - 10,11 - dimethyl - 10,11 - dihydro - dibenzo[b,f]thiepin - 10-ol, M.P. 115—117° (from ethanol);

b³ 2 - methylthio - 10,11 - dimethyl - dibenzo[b,f]thiepin, B.P. 150°, 0.02 Torr;

100

b⁴ 2 - methylthio - 10,11 - bis - bromo - methyl-dibenzo[b,f]thiepin, M.P. 126—130°, crude product.

Example 10

105

a) 15 g of 10,11-bis-bromomethyl-dibenz - [b,f]oxepin are dissolved in benzene and then added dropwise at 40° and within one hour to a solution of 35.5 g of ethylamine in 150 ml of methanol. The reaction mixture is stirred for a further hour at 50° and the solvent and excess ethylamine are subsequently distilled off. The residue is mixed with water and the resulting suspension is extracted with ether. The ethereal solution is washed with water, dried over potassium carbonate and completely evaporated. The residue is dissolved in petroleum ether and cooled to 0°, whereupon 2 - ethyl - 2,3 - dihydro - 1H - dibenz[2,3:6,7]oxepino[4,5-c]pyrrole, M.P. 51—52°, crystallises out. 6.5g of the obtained base are dissolved in 25 ml of absolute acetone and 2.38 g of methanesulphonic acid are added, whereupon the methane-sulphonate crystallises out which, after recrystallisation from anhydrous ethanol melts at 181—184°;

110 115 120 125

b) The starting material 10,11-bis-bromomethyl - dibenz[b,f]oxepin is prepared analogously to Examples 5 b) and 3 b)—d) through the following intermediates starting with dibenz[b,f]oxepin-10(11H)-one R.H.F. Manske and A.E. Ledingham, J.Am.Chem. Soc. 72, 4797 (1950), M.P. 51—52°:

- 5
10
15
b¹ 11 - methyl - dibenz[b,f]oxepin - 10 - (11H)-one, B.P. 156°, 0.01 Torr;
b² 10,11 - dimethyl - 10,11 - dihydro - dibenz[b,f]oxepin-10-ol, M.P. 96—98° (from pentane);
b³ 10,11 - dimethyl - dibenz[b,f]oxepin, M.P. 59—60° (from pentane);
b⁴ 10,11 - bis - bromomethyl - dibenz - [b,f]oxepin, M.P. 110—112° (from diethylether).

Example 11

- 20 Analogously to Example 10 a) is prepared:
a) From 23.5 g 10,11-bis-bromomethyl-dibenz[b,f]oxepin and 38.5 g of methylamine in 230 ml of methanol, 2-methyl-2,3-dihydro-1H - dibenz[2,3:6,7]oxepino[4,5 - c]pyrrole, M.P. 110—111° (from petroleum ether);
25 methanesulphonate, M.P. 190—193° (from anhydrous ethanol).

Example 12

- 30 Analogously to Example 10 a) is prepared:
a) from 20.7 g of 2-chloro-10,11-bis-bromomethyl-dibenz[b,f]oxepin and 31 g of methylamine in 186 ml of methanol, 2-methyl-5-chloro - 2,3 - dihydro - 1H - dibenz[2,3:6,7] - oxepino[4,5-c]pyrrole, M.P. 104—106° (from acetone); methanesulphonate, M.P. 179—182° (from anhydrous ethanol);
35 b) The starting material, 2-chloro-10,11-bis-bromomethyl-dibenz[b,f]oxepin is prepared analogously to Examples 5 b) and 3 b)—d) through the following intermediates starting with 8-chloro-dibenz[b,f]oxepin-10-(11H)-one Rhone-Poulenc, S.A. NE. 68.06854, M.P. 84°:

- 40
45
50
55
b¹ 8 - chloro - 11 - methyl - dibenz[b,f] - oxepin-10(11H)-one, M.P. 55—58° (from methanol);
b² 8 - chloro - 10,11 - dimethyl - 10,11 - dihydro-dibenz[b,f]oxepin-10-ol, crude product;
b³ - 2 - chloro - 10,11 - dimethyl - dibenz - [b,f]oxepin, M.P. 106—108° (from methanol); and
b⁴ 2 - chloro - 10,11 - bis - bromomethyl - dibenz[b,f]oxepin, M.P. 118—120° (from cyclohexane).

Example 13

- 60 Analogously to Example 12 a) is prepared:
from 20.7 g of 2-chloro-10,11-bis-bromomethyl-dibenz[b,f]oxepin and 45 g of ethylamine in 200 ml of ethanol, 2-ethyl-5-chloro-2,3 - dihydro - 1H - dibenz[2,3:6,7]oxepino -

[4,5-c]pyrrole, M.P. 94—97° (from acetone); methanesulphonate, M.P. 189—192° (from anhydrous ethanol).

Example 14

- 65 Analogously to Example 10 a) is prepared:
a) From 26 g of 2-methoxy-10,11-bis-bromomethyl-dibenz[b,f]oxepin and 57 g of ethylamine in 250 ml of methanol;
2 - ethyl - 5 - methoxy - 2,3 - dihydro - 1H - dibenz[2,3:6,7]oxepino[4,5 - c]pyrrole, crude product: yield 14 g: methanesulphonate, M.P. 195—198° (from anhydrous ethanol);
70
75 b) The starting material, 2-methoxy-10,11-bis - bromomethyl - dibenz[b,f]oxepin is prepared analogously to Example 3 b)—d) through the following intermediates starting with 2 - methoxy - 11 - methyl - dibenz - [b,f]oxepin-10(11H)-one, B.P. 163—165°/0.015 Torr:
80

- b¹ 2 - methoxy - 10,11 - dimethyl - 10,11 - dihydro-dibenz[b,f]oxepin-10-ol, crude product;
b² 2 - methoxy - 10,11 - dimethyl - dibenz - [b,f]oxepin, B.P. 123—126°/0.06 Torr; and
b³ 2 - methoxy - 10,11 - bis - bromo - methyl-dibenz[b,f]oxepin (crude product).

Example 15

- 90 a) 72 g of 2-allyl-2,3-dihydro-1H-dibenzo-[2,3:6,7]thiepino[4,5-c]pyrrole are dissolved in 525 ml of anhydrous benzene and heated to boiling with stirring. Within one hour a solution of 31 g of ethyl chloroformate in 525 ml of anhydrous benzene is added dropwise, and the allyl chloride thus formed is simultaneously distilled off. When the addition is completed, the mixture is boiled under reflux for a further hour and then cooled to room temperature. The benzene solution is washed with 2-N hydrochloric acid and, then with water, dried over sodium sulphate and concentrated to a small volume in vacuo whereupon 2 - carbethoxy - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole, M.P. 121—123° crystallises out;
95
100 b) 60 g of 2-carbethoxy-2,3-dihydro-1H-dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole are boiled for 6 hours under reflux with a solution of 60 g of potassium hydroxide in 600 ml of anhydrous ethanol. The ethanol is then distilled off from the mixture in a rotary evaporator. The residue is mixed with 600 ml of water and the resulting suspension is extracted with ether. The ethereal solution is washed with water, dried over potassium carbonate and concentrated. The residue is 2,3-dihydro-1H-dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole as crude product. 35 g of the obtained base are dissolved in 100 ml of anhydrous acetone and 10.4 g of methane sulphonate is cautiously added, whereupon the methane sulphonate cry-
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120

stallises out, which, after recrystallisation from anhydrous methanol melts at 220—223°.

Example 16

- 5 Analogously to Example 15 a) and b) are prepared the following intermediates and end-product respectively: from 13 g of 2-allyl-5-chloro - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and 4.5 g of ethyl chloroformate the intermediate 2-carbethoxy-5 - chloro - 2,3 - dihydro - 1H - dibenzo - 10 [2,3:6,7]thiepino[4,5-c]pyrrole, M.P. 161—164° (from ethanol) and by subsequent saponification, the end product, 5-chloro-2,3-dihydro - 1H - dibenzo[2,3:6,7]thiepino - 15 [4,5-c]pyrrole; methane-sulphonate, M.P. 252—255° (from methanol).

Example 17

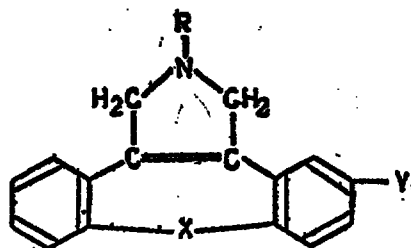
- 20 Analogously to Example 15 a) and b) are prepared the following intermediate and end-product respectively: from 15 g of 2-allyl-5-methyl - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and 4.8 g ethyl chloroformate the intermediate 2-carbethoxy-5 - methyl - 2,3 - dihydro - 1H - dibenzo - 25 [2,3:6,7]thiepino[4,5-c]pyrrole, M.P. 124—126° (from ethanol); and by subsequent saponification, the end-product, 5-methyl-2,3-dihydro - 1H - dibenzo[2,3:6,7]thiepino - 30 [4,5-c]pyrrole, M.P. 84—86° (from ethyl acetate); methanesulphonate, M.P. 212—215° (from anhydrous ethanol).

Example 18

- 35 Analogously to Example 15 a) and b) are prepared the following intermediate and end products, respectively: from 15 g 2-allyl-5-methoxy - 2,3 - dihydro - 1H - dibenzo - [2,3:6,7]thiepino[4,5-c]pyrrole and 5 g of ethyl chloroformate ester the intermediate 2-carbethoxy - 5 - methoxy - 2,3 - dihydro - 40 1H - dibenzo[2,3:6,7]thiepino[4,5 - c]pyrrole, M.P. 119—120° (from methanol) and by subsequent saponification, the end-product, 5-methoxy - 2,3 - dihydro - 1H - dibenzo - 45 [2,3:6,7]thiepino[4,5 - c]pyrrole; hydrochloride, M.P. 271—274° (from ethanol).

WHAT WE CLAIM IS:—

1. Thiepin and oxepin derivatives of the general formula I



(I)

- wherein 50
X represents oxygen or sulphur,
Y represents hydrogen, chlorine, or the methyl, methoxy or methylthio group and
R represents hydrogen, a straight chain low alkyl group with 1—6 carbon atoms, the isopropyl or the allyl group 55
as well as their pharmaceutically acceptable acid addition salts.
2. 2 - Methyl - 2,3 - dihydro - 1H - 60 dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.
3. 2 - Ethyl - 2,3 - dihydro - 1H - dibenzo - 65 [2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.
4. 2 - n - butyl - 2,3 - dihydro - 1H - 70 dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.
5. 2 - n - Hexyl - 2,3 - dihydro - 1H - 75 dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.
6. 2 - Isopropyl - 2,3 - dihydro - 1H - 80 dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.
7. 2 - Allyl - 2,3 - dihydro - 1H - dibenzo - 85 [2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.
8. 2 - Methyl - 5 - chloro - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5 - c]pyrrole and its pharmaceutically acceptable acid addition salts. 90
9. 2 - Ethyl - 5 - chloro - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5 - c]pyrrole and its pharmaceutically acceptable acid addition salts.
10. 2 - Allyl - 5 - chloro - 2,3 - dihydro - 95 1H - dibenzo[2,3:6,7]thiepino[4,5 - c]pyrrole and its pharmaceutically acceptable acid addition salts.
11. 2 - Methyl - 5 - methoxy - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino - 100 [4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.
12. 2 - Ethyl - 5 - methoxy - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino - 105 [4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.
13. 2 - Allyl - 5 - methoxy - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5 - c]pyrrole and its pharmaceutically acceptable acid addition salts.
14. 2,5 - dimethyl - 2,3 - dihydro - 1H - 110 dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.
15. 2 - Ethyl - 5 - methyl - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5 - c]pyrrole and its pharmaceutically acceptable acid addition salts.
16. 2 - Allyl - 5 - methyl - 2,3 - dihydro -

stallises out, which, after recrystallisation from anhydrous methanol melts at 220—223°.

Example 16

- 5 Analogously to Example 15 a) and b) are prepared the following intermediates and end-product respectively: from 13 g of 2-allyl-5-chloro - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and 4.5 g of ethyl chloroformate the intermediate 2-carbethoxy-10 5 - chloro - 2,3 - dihydro - 1H - dibenzo - [2,3:6,7]thiepino[4,5-c]pyrrole, M.P. 161—164° (from ethanol) and by subsequent saponification, the end product, 5-chloro-2,3-dihydro - 1H - dibenzo[2,3:6,7]thiepino - 15 [4,5-c]pyrrole; methane-sulphonate, M.P. 252—255° (from methanol).

Example 17

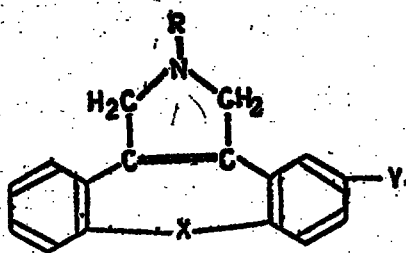
- 20 Analogously to Example 15 a) and b) are prepared the following intermediate and end-product respectively: from 15 g of 2-allyl-5-methyl - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and 4.8 g ethyl chloroformate the intermediate 2-carbethoxy-25 5 - methyl - 2,3 - dihydro - 1H - dibenzo - [2,3:6,7]thiepino[4,5-c]pyrrole, M.P. 124—126° (from ethanol); and by subsequent saponification, the end-product, 5-methyl-2,3-dihydro - 1H - dibenzo[2,3:6,7]thiepino - 30 [4,5-c]pyrrole, M.P. 84—86° (from ethyl acetate); methanesulphonate, M.P. 212—215° (from anhydrous ethanol).

Example 18

- 35 Analogously to Example 15 a) and b) are prepared the following intermediate and end products, respectively: from 15 g 2-allyl-5-methoxy - 2,3 - dihydro - 1H - dibenzo - [2,3:6,7]thiepino[4,5-c]pyrrole and 5 g of ethyl chloroformate ester the intermediate 2-carbethoxy - 5 - methoxy - 2,3 - dihydro - 40 1H - dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole, M.P. 119—120° (from methanol) and by subsequent saponification, the end-product, 5-methoxy - 2,3 - dihydro - 1H - dibenzo - [2,3:6,7]thiepino[4,5-c]pyrrole; hydro - 45 chloride, M.P. 271—274° (from ethanol).

WHAT WE CLAIM IS:—

1. Thiopin and oxepin derivatives of the general formula I



(I)

wherein

X represents oxygen or sulphur,
Y represents hydrogen, chlorine, or the methyl, methoxy or methylthio group and

R represents hydrogen, a straight chain low alkyl group with 1—6 carbon atoms, the isopropyl or the allyl group as well as their pharmaceutically acceptable acid addition salts.

2. 2 - Methyl - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.

3. 2 - Ethyl - 2,3 - dihydro - 1H - dibenzo - [2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.

4. 2 - n - butyl - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.

5. 2 - n - Hexyl - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.

6. 2 - Isopropyl - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.

7. 2 - Allyl - 2,3 - dihydro - 1H - dibenzo - [2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.

8. 2 - Methyl - 5 - chloro - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.

9. 2 - Ethyl - 5 - chloro - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.

10. 2 - Allyl - 5 - chloro - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.

11. 2 - Methyl - 5 - methoxy - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino - [4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.

12. 2 - Ethyl - 5 - methoxy - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino - [4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.

13. 2 - Allyl - 5 - methoxy - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.

14. 2,5 - dimethyl - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.

15. 2 - Ethyl - 5 - methyl - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole and its pharmaceutically acceptable acid addition salts.

16. 2 - Allyl - 5 - methyl - 2,3 - dihydro -



1H - dibenzo[2,3:6,7]thiepine[4,5 - c]pyrrole and its pharmaceutically acceptable acid addition salts.

17. 2 - Ethyl - 5 - methylthio - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepine[4,5 - c]pyrrole and its pharmaceutically acceptable acid addition salts.

18. 2 - Ethyl - 2,3 - dihydro - 1H - dibenz[2,3:6,7]oxepino[4,5 - c]pyrrole and its pharmaceutically acceptable acid addition salts.

19. 2 - Methyl - 2,3 - dihydro - 1H - dibenz[2,3:6,7]oxepino[4,5 - c]pyrrole and its pharmaceutically acceptable acid salts.

20. 2 - Methyl - 5 - chloro - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]oxepino[4,5 - c]pyrrole and its pharmaceutically acceptable acid addition salts.

21. 2 - Ethyl - 5 - chloro - 2,3 - dihydro - 1H - dibenz[2,3:6,7]oxepino[4,5 - c]pyrrole and its pharmaceutically acceptable acid addition salts.

22. 2 - Ethyl - 5 - methoxy - 2,3 - dihydro - 1H - dibenz[2,3:6,7]oxepino[4,5 - c]pyrrole and its pharmaceutically acceptable acid addition salts.

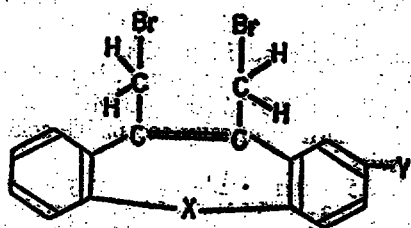
23. 2,3 - Dihydro - 1H - dibenzo[2,3:6,7] - thiepine[4,5 - c]pyrrole and its pharmaceutically acceptable acid addition salts.

24. 5 - Chloro - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepine[4,5 - c]pyrrole and its pharmaceutically acceptable acid addition salts.

25. 5 - Methyl - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepine[4,5 - c]pyrrole and its pharmaceutically acceptable acid addition salts.

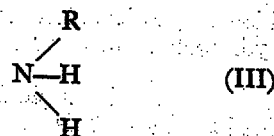
26. 5 - Methoxy - 2,3 - dihydro - 1H - dibenzo[2,3:6,7]thiepine[4,5 - c]pyrrole and its pharmaceutically acceptable acid addition salts.

27. Process for the production of thiepin and oxepin derivatives of the general formula I as defined in claim 1 but wherein R may not represent a hydrogen atom, as well as their pharmaceutically acceptable acid addition salts, which comprises reacting a compound of the general formula II



(II)

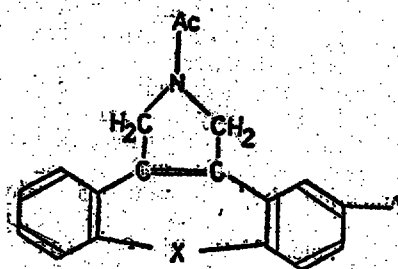
50 wherein X and Y have the meanings given in claim 1 with an amine of the general formula III



(III)

wherein R has the meaning given in claim 1 except that it may not represent a hydrogen atom and, when required, converting a compound of the general formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

28. Process for the production of thiepin and oxepin derivatives of the general formula I as defined in claim 1, but wherein R may represent a hydrogen atom only, and their pharmaceutically acceptable acid addition salts, which comprises hydrolysing a compound of the general formula IV



(IV)

wherein

X and Y have the meanings given in claim 1 and

Ac represents the acyl radical of an organic acid or a cyano group,

and, when required, converting a compound of the general formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

29. Thiepin and oxepin derivatives having the formula I as illustrated in claim 1 wherein X represents oxygen or sulphur,

Y represents hydrogen or chlorine, the methoxy or methylthio group, and

R represents a straight chain low alkyl group with 1-6 carbon atoms, the isopropyl or the allyl group,

as well as their pharmaceutically acceptable acid addition salts.

30. Process as defined in claim 27 wherein X, Y and R have the meanings given in claim 29, whereby a thiepin or oxepin derivative or pharmaceutically acceptable acid addition salt thereof as claimed in claim 29 is obtained.

31. Process as defined in claim 27 or 28 substantially as hereinbefore described with reference to any one of the accompanying Examples.

32. Process as defined in claim 30 substantially as hereinbefore described with refer-



ence to any one of the accompanying Examples 1, 2 excluding parts (c) to (e), 3, 4 excluding part (b), 5 and 6 excluding part (b).

33. Thiopin and oxepin derivatives as claimed in claim 1 and their pharmaceutically acceptable acid addition salts as hereinbefore described with reference to any one of the accompanying Examples.

34. Thiopin and oxepin derivatives as claimed in claim 29 and their pharmaceutically acceptable acid addition salts as hereinbefore described with reference to any one of the accompanying Examples 1, 2 excluding parts (c) to (e), 3, 4 excluding part (b), 5 and 6 excluding part (b).

35. Thiopin and oxepin derivatives and their pharmaceutically acceptable acid addition salts whenever prepared by a process as claimed in claim 27 or 28.

36. Thiopin and oxepin derivatives and their pharmaceutically acceptable acid addition salts whenever prepared by a process as claimed in claim 30.

37. A pharmaceutical composition comprising a thiopin or oxepin derivative as claimed in claim 1 or a pharmaceutically acceptable acid addition salt thereof together with a pharmaceutically acceptable diluent or carrier therefor.

38. A pharmaceutical composition comprising a thiopin or oxepin derivative as claimed in claim 29 or a pharmaceutically acceptable acid addition salt thereof together with a pharmaceutically acceptable diluent or carrier therefor.

39. A pharmaceutical composition as claimed in claim 27 substantially as hereinbefore described with reference to any one of the foregoing prescriptions a) to e).

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