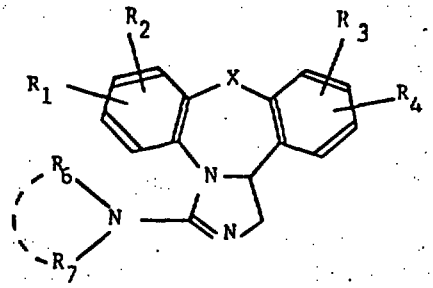
SPECIFICATION

Heterocyclic compounds, processes for their preparation and pharmaceutical compositions containing them

The invention relates to novel heterocyclic compounds, processes for their preparation, pharmaceutical compositions containing the novel heterocyclic compounds and their use in a method of treatment.

It has been found that certain novel heterocyclic compounds have interesting pharmacological activities, in particular, while being of relatively low toxicity, possessing long-lasting antiallergic, antihistaminic and antiserotonic activities as well as inhibiting blood platelet aggregation.

According to one aspect of the present invention we therefore provide compounds of formula I



(I)

[wherein

R_1, R_2, R_3 and R_4, which may be the same or different, each represents a hydrogen or halogen atom or a C_1 to C_6 alkyl or C_1 to C_6 alkoxy group;

R_5 and R_6, which may be the same or different, each represents a hydrogen atom or a C_1 to C_6 alkyl or C_3 to C_6 alkenyl group; or

R_5 and R_6, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino or morpholino group; and

X represents an oxygen or sulfur atom or a methylene group]

and acid addition salts thereof.

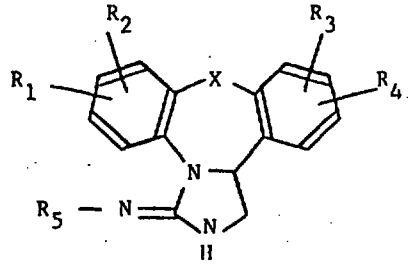
The compounds of the present invention can occur as racemates, as pure enantiomers or as mixtures thereof whether in the form of the free bases or the acid addition salts.

In the compounds of the present invention, the alkyl, alkoxy and alkenyl substituent groups can be straight-chained or branched. Consequently, the substituent alkyl groups may possess the following formulae:-

$-CH_3$, $-C_2H_5$, $-CH_2-CH_2-CH_3$, $-CH(CH_3)_2$, $-(CH_2)_3-CH_3$,
$-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C(CH_2)_4-CH_3$,
$-CH_2-CH_2-CH(CH_3)_2$, $-CH_2-CH(CH_3)-C_2H_5$,
$-CH(CH_3)-CH_2-CH_2-CH_3$, $-CH_2-C(CH_3)_3$, $-C(CH_3)_2-C_2H_5$,
$-CH(CH_3)-CH(CH_3)_2$, $-(CH_2)_5-CH_3$, $-(CH_2)_3-CH(CH_3)_2$,
$-CH_2-CH_2-CH(CH_3)-C_2H_5$, $-CH_2-CH(CH_3)-CH_2-CH_2-CH_3$,
$-CH(CH_3)-(CH_2)_3-CH_3$, $-C(CH_3)_2-CH_2-CH_2-CH_3$,
$-CH_2-C(CH_3)_2-C_2H_5$, $-CH_2-CH_2-C(CH_3)_3$,
$-CH(CH_3)CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH_2-CH(CH_3)_2$,
$-C(CH_3)_2-CH(CH_3)_2$, $-CH(CH_3)-C(CH_3)_3$, $-CH_2-CH(C_2H_5)_2$
and $-CH(C_2H_5)-(CH_2)_2-CH_3$.

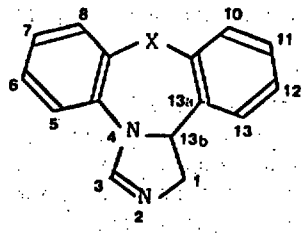
The substituent alkoxy groups may contain the same carbon skeletons.

As cyclic guanidine derivatives the compounds of formula I (if R_6 and, if desired, R_5 represent hydrogen atoms) also may occur in their tautomeric form of formula Ia



(Ia)

The designation of the positions within the molecular structure of the compounds of formulae I and Ia is indicated in formula Ib



(Ib)

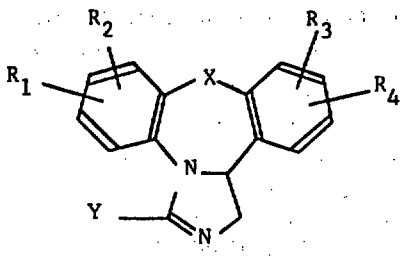
The compounds according to the present invention may advantageously be in the form of physiologically acceptable acid addition salts. Other acid addition salts however may be useful in the preparation of compounds of formulae I or Ia or physiologically acceptable acid addition salts thereof and therefore are deemed to fall within the scope of the present invention.

Preferred compounds according to the present invention by virtue of their pharmacological activities include the following

(a) 3-amino-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine and acid addition salts thereof;
(b) 3-amino-7-chloro-9,13b-dihydro-1H-dibenzo[c,f]imidazo-[1,5-a]azepine and acid addition salts thereof;
(c) 3-amino-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine and acid addition salts thereof;
(d) 3-amino-12-chloro-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine and acid addition salts thereof;
(e) 3-amino-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]thiazepine and acid addition salts thereof;
(f) 3-amino-12-chloro-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]thiazepine and acid addition salts thereof.

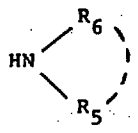
According to a further aspect of the present invention we provide a process for the preparation of compounds of formula I or Ia and acid addition salts thereof which process comprises at least one of the following steps:

(a) reacting a compound of formula II



(II)

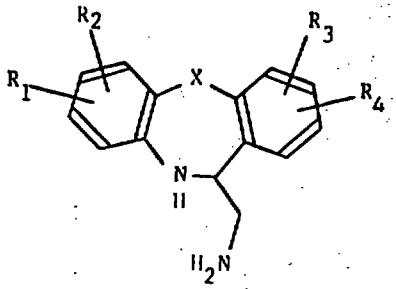
(wherein Y represents a halogen atom, suitably a chlorine atom, or an alkoxy or alkylthio group and R_1, R_2, R_3, R_4 and X are as hereinbefore described) with an amine of formula III



(III)

(wherein R_5 and R_6 are as hereinbefore defined);

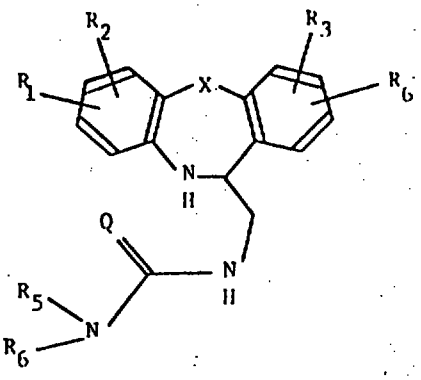
(b) (for the preparation of compounds of formula I or Ia wherein R_5 and R_6 represent hydrogen atoms) reacting a diamine of formula IV



(IV)

(wherein R_1, R_2, R_3, R_4 and X are as hereinbefore defined) with a cyanogen halide, suitable cyanogen bromide;

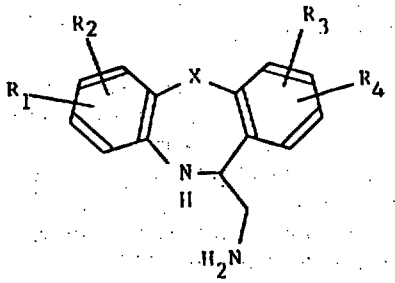
(c) cyclizing of a compound of formula VIII



(VIII)

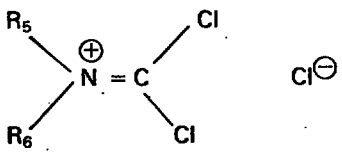
(wherein R_1, R_2, R_3, R_4, R_5, R_6 and X are as hereinbefore defined and Q represents an oxygen or sulfur atom or a group $=NR_7$ [in which R_7 represents a hydrogen atom or an optionally substituted C_1 to C_8 alkyl group, for example a methyl, ethyl, propyl or benzyl group]);

(d) (for the preparation of compounds of formula I wherein R_5 and R_6 represent other than hydrogen atoms) reacting a diamine of formula IV



(IV)

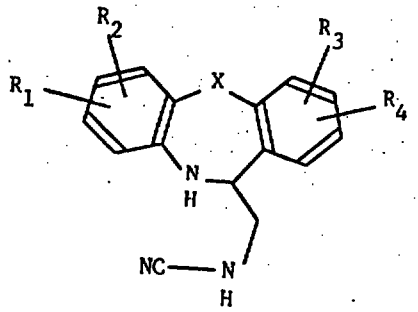
(wherein R_1, R_2, R_3, R_4 and X are as hereinbefore defined) with a N,N-disubstituted-dichloromethyleneiminium salt of formula X



(X)

(wherein R_5 and R_6, which may be the same or different, each represents a C_1 to C_6 alkyl or C_3 to C_6 alkenyl group or R_5 and R_6, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino or morpholino group); and

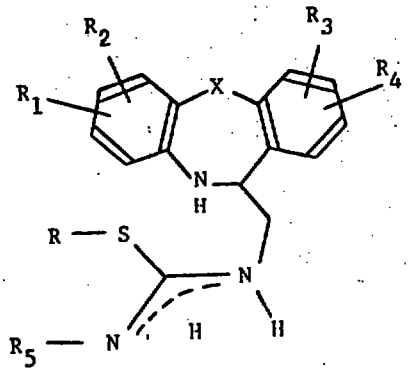
(e) (for the preparation of compounds of formula I or Ia wherein R_5 and R_6 represent hydrogen atoms) cyclizing a compound of formula IVa



(IVa)

(wherein R_1, R_2, R_3, R_4 and X are as hereinbefore defined) by intramolecular reaction;

(f) (for the preparation of compounds of formula I or Ia wherein R_6 represents a hydrogen atom) cyclizing a compound of formula IX



(IX)

(wherein R_1, R_2, R_3, R_4, R_5 and X are as hereinbefore defined and R represents an optionally substituted C_1 to C_8 alkyl group);

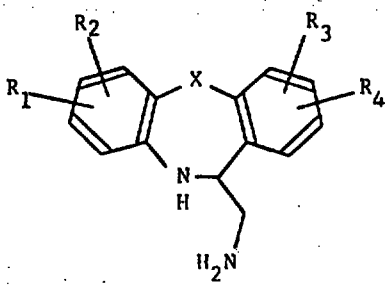
(g) converting a compound of formula I or Ia into an acid addition salt thereof or converting an acid addition salt of a compound of formula I or Ia into the free base; and

(h) separating a racemic mixture of a compound of formula I or Ia or an acid addition salt thereof into its enantiomers, for example by means of conventional techniques for the resolution of racemates.

Reaction (a) may be effected in the melt or with addition of conventional solvents (for example alcohols, ketones, ethers, aliphatic or aromatic hydrocarbons), optionally in an autoclave. In general, reaction step (a) is effected at temperatures up to the boiling point of the solvent.

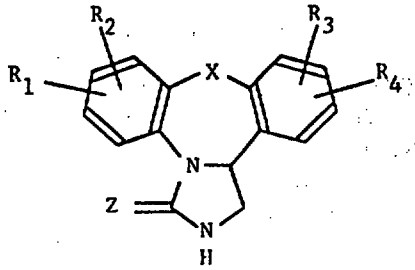
The amines of formula III, reagents in reaction step (a), may also serve as the reaction medium.

The starting materials of formula II used in reaction step (a) may be obtained by methods analogous to the methods known from the literature; where substituent Y represents a halogen atom, the reagents of formula II may be prepared, for example by reacting diamines of formula IV



(IV)

(wherein R_1, R_2, R_3, R_4 and X are as hereinbefore defined) with bifunctional carbonic acid derivatives (such as phosgene, chlorocarbonic acid esters or N,N'-carbonyldiimidazole) to produce the corresponding 3-oxo compounds of formula V

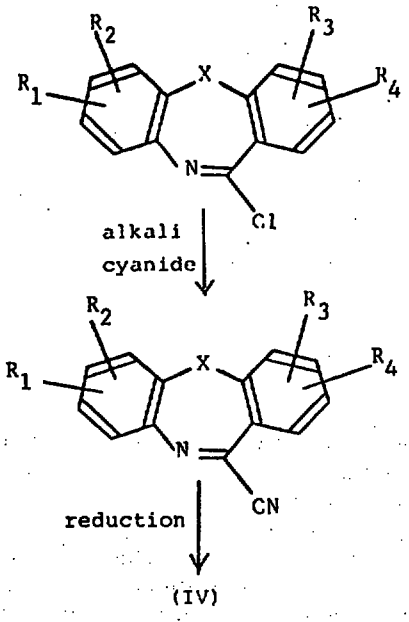


(V)

(wherein Z represents an oxygen atom and R_1, R_2, R_3, R_4 and X are as hereinbefore defined) which subsequently may be halogenated with a suitable inorganic acid haloide, for example an inorganic acid chloride.

The starting materials of formula II, wherein Y represents an alkylthio group, may be prepared, for example, by reacting diamines of formula IV with carbon disulfide, thiophosgene or N,N'-thiocarbonyldiimidazole to product the corresponding 3-thioxo derivatives of formula V (wherein Z represents a sulfur atom) which subsequently may be alkylated with an alkyl halide to produce the compound of formula II wherein Y represents an alkylthio group. The alkyl moiety of the substituent Y (where Y represents alkoxy or alkylthio group) preferably comprises 1 to 8 carbon atoms and also may itself be substituted.

The diamines of formula IV may be obtained according to the reaction scheme:



(VI)

(VII)

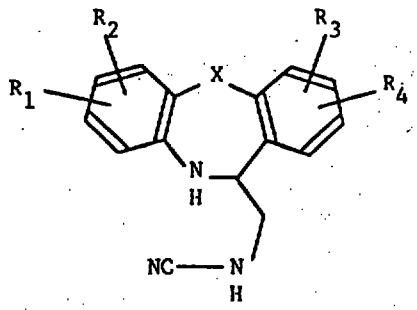
(IV)

(wherein R_1, R_2, R_3, R_4 and X are as hereinbefore defined).

Compounds of formula VI are known [see, for example, Helv. chim. Acta *49/II*, 1433 et seq (1966) or Helv. chim. Acta *50/I*, 245 et seq. (1967)] or may be produced in line with a known process. The reaction of compounds of formula VI with an alkali metal cyanide such as sodium cyanide advantageously is effected in DMSO at temperatures of from ambient temperature up to 60°C. The reduction of the cyano compounds of formula VII preferably is effected with lithium aluminium hydride ($LiAlH_4$) or aluminum hydride (AlH_3) in tetrahydrofuran or diethylether respectively.

While reaction step (b) preferably is effected at ambient temperature in an ethanol/tetrahydrofuran mixture, it can however also be effected in other solvents, such as alcohols, chloroform or hydrocarbons such as toluene and xylene. Reaction step (b) may also, if desired, be effected with the addition of a base (such as for example, potassium carbonate). The reaction temperatures suitable vary to a great extent and may rise up to the boiling temperature of the reaction mixture.

In reaction stem (b), the reaction of the compound IV with the cyanogen halide (for example, cyanogen bromide) may involve the formation of a compound of formula IVa

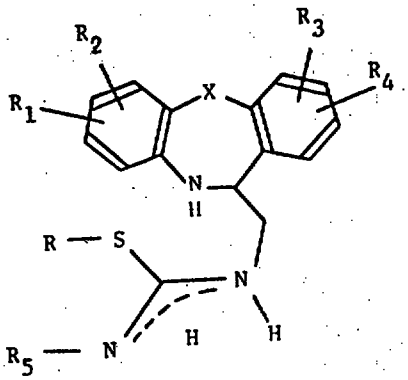


(IVa)

(wherein R_1, R_2, R_3, R_4 and X are as hereinbefore defined) as an intermediate which then provides the true starting material of the cyclization reaction. However, it is not necessary to isolate this intermediate compound as it continues reacting smoothly to produce the desired end product.

In reaction step (c), compounds of formula VIII (wherein Q represents an oxygen or sulfur atom, R_5 represents an alkyl or alkenyl group and R_6 represents a hydrogen atom) can be obtained by reacting diamines of formula IV with alkyl or alkenylisocyanates or alkyl or alkenyl isothiocyanates respectively.

Cyclization by reaction step (c) to the compounds of formula I or Ia of the present invention may be effected by the action of said halides, such as $POCl_3$, optionally in conventional solvents such as toluene. An alternative to this process consists in the S-alkylation of the thiourea derivatives of formula VIII (wherein Q represents a sulfur atom) to produce the corresponding alkylthio compounds of formula IX



(IX)

(wherein R_1, R_2, R_3, R_4, R_5 and X are as hereinbefore defined and R represents an optionally substituted C_1 to C_8 alkyl group) which subsequently are cyclized, for example in a manner known per se by heating in conventional solvents (such as for example alcohols or toluene) or in the melt to form compounds of formula I or Ia.

In reaction step (c), compounds of formula VIII (wherein Q represents the group $=NR_7$) may be obtained, for example by reacting diamines of formula IV with suitable substituted or unsubstituted S-alkyl-isothioureas. The subsequent cyclization to produce the compounds of formula I or Ia preferably is carried out in the melt.

Reaction step (d) advantageously is effected in an inert solvent, for example chloroform, under addition of a base, for example, triethylamine.

The reaction products obtained by means of the various processes may be isolated (e.g. with the aid of known laboratory methods) and, if required, the crude products thus obtained may be purified using methods such as, for example, column chromatography, before being crystallized in the form of the free bases or suitable salts.

Acids particularly suitable for production of physiologically acceptable acid addition salts of the compounds of the invention include for example hydrohalic acids; aliphatic, alicyclic, aromatic or heterocyclic carboxylic acids or sulfonic acids, (such as acetic acid, tartaric acid, malonic acid, citric acid, fumaric acid, salicylic acid, ambonic acid, urethanesulfonic acid and toluenesulfonic acid); and sulfuric acid and phosphoric acids.

The novel compounds according to the invention are therapeutically useful or represent intermediate products for the production of therapeutically useful compounds. While they exhibit a relatively low toxicity, the compounds of the present invention are particularly advantageous in view of their long-lasting antiallergic, antihistaminic and antiserotonic activity, and furthermore their blood platelet aggregation inhibiting activity. The novel compounds may be used therapeutically, for example, in the treatment of reactions provoked by liberation of histamine or serotonin or in bronchial asthma, allergic bronchitis, allergic rhinitis, allergic conjunctivitis or allergic diathesis. The beneficial therapeutic effect of these compounds on oral administration is of special significance for therapeutic purposes and, in compounds according to the invention which have been tested, has been shown to be especially advantageous in comparison to the disodium salt of cromoglycic acid, a commercial product widely used for the treatment of bronchial asthma

and allergic bronchitis.

According to a yet further aspect of the present invention we provide pharmaceutical compositions comprising as active ingredient at least one compound of formula I or Ia or a physiological acceptable acid addition salt thereof togehter with a pharmaceutical carrier or excipient.

According to a still further aspect of the present invention we provide a method of treatment of the human or animal body to combat the effects of histamine or serotonin liberation, bronchial asthma, allergic bronchitis, allergic rhinitis, allergic conjunctivitis or allergic diathesis which method comprises administering to the said body an effective quantity of at least one compound of formula I or Ia or physiologically acceptable acid addition salt thereof, advantageously in the form of a pharmaceutical composition according to the present invention.

The pharmaceutical compositions of the present invention are advantageously in forms suitable for oral, rectal or parenteral administration and conveniently may be in dosage unit form.

In the preparation of the pharmaceutical compositions according to the invention, the compounds according to the invention may be formulated together with excipients and carriers to produce galenic preparations for example in the conventional way, for example to produce capsules, tablets, coated tablets, solutions or suspensions for oral administration; to produce aerosols for pulmonal administration; to produce sterile isotonic aqueous solutions for parenteral administration; and to produce creams, ointments, lotions, emulsions or sprays for topical administration.

The single preferred dose for oral administration amounts to 0.2 to 40, preferably 0.5 to 10 mg in adults. For inhalation it is advantageous that single doses of between 0.05 to 20, preferably 0.2 to 5 mg, are administered, for example in the form of conventional preparations and and especially suitably in the form of metered aerosols or capsules for powder inhalation. If desired, the indicated doses may be administered several times per day.

In order to determine the effect of the compounds according to the invention, these were subjected to numerous pharmacological tests, including tests of the following three categories:

(a) Tests on sensitized rats, performed after passive sensitization of the animals by IgE-antibodies and subsequent antigen challenge. In this manner a passive cutaneous anaphylaxis (GOOSE et al. (1969): Immunology 16, 749) (PCA) and a passive lung anaphylaxis (FARMER et al. (1975): Br. J. Pharmac. *55*, 57) (PLA, experimental asthma) could be provoked.

(b) The antianaphylactic effect was confirmed in dogs by per os administration, showing a hypersensitivity of the skin to ascaris antigen (BOOTH et al. (1970): J. Lab. clin. Med. *76*, 181).

(c) Antihistaminic and antiserotonic activities:
The compounds administered p.o. and i.v. to rats, dogs and monkeys inhibited the histamine swelling induced by intracutaneous injection of histamine. Quantification was achieved by measuring the swelling after extravasation of Evans blue into the skin.
The antiserotonic effect was proved by the activity against serotonin oedema of the rat's paw (DOEPENER et al. (1958): Int. Arch. Allergy *12*, 89).

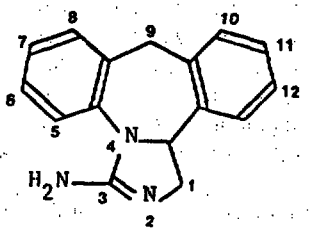
The indications made in the following Table are provided to exemplify the activities of the compounds according to the invention:

Compound	PCA ED_{50} [mg/kg] (rat p.o.)	PLA ED_{50} [mg/kg] (rat i.v.)	LD_{50} [mg/kg] (mouse p.o.)
Example 1	6	0.052	325
Example 1 (a)	0.96	-	-
Example 1 (c)	1.1	-	340
Example 1 (d)	2.5	-	-
Example 1 (i)	3.8	-	-
Example 1 (l)	5.4	-	-

The following Examples illustrate the invention without serving to restrict the scope of protection sought therefor. Temperatures referred to in these Examples are in degrees Celsius unless otherwise stated.

EXAMPLE 1

3-Amino-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine hydrobromide



6.72 g (0.03 mol) of 6-aminomethyl-6,11-dihydro-5H-dibenzo-[b,e]azepine are dissolved in 60 ml of ethanol and a solution of 3.18 g (0.03 mol) of cyanogen bromide in 25 ml of absolute tetrahydrofuran is added dropwise while stirring. The reaction mixture is stirred over night at ambient temperature, admixed with 50 ml of ether and, subsequently, the crystals are suction filtered.

Yield: 8.7 g (78.9% of theory); m.p. 284 - 286° (CH_3OH/ethyl acetate).

The free base liberated from the hydrobromide with aqueous sodium hydroxide solution has a melting point of 205 to 208° (acetonitrile).

For production of the hydrochloride a suspension of the free base in methanol is treated with the calculated quantity of ethereal hydrochloric acid and, subsequently, the hydrochloric is precipitated with addition of ether.

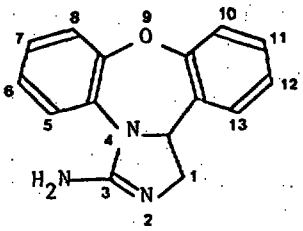
M.p. 272 - 273° (methanol/ether)

Analogously to Example 1, the following compounds can be obtained:

(a) 3-amino-7-chloro-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine hydrochloride; m.p. 325-329° decomp. (alcohol)

(b) 3-amino-6-methyl-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine hydrobromide

(c) 3-amino-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]-oxazepine hydrobromide;



m.p. 261-264° (alcohol/ethylacetate)

(d) 3-amino-12-chloro-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine hydrobromide; m.p. 300° (acetonitrile/ethylacetate)

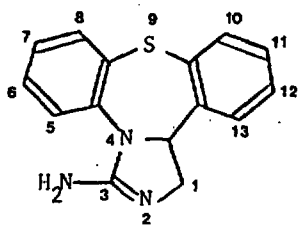
(e) 3-amino-7-chloro-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine hydrobromide; m.p. 297-300° (alcohol/ether)

(f) 3-amino-6-chloro-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine hydrobromide; m.p. 282-284° (methanol/ether)

(g) 3-amino-6-methyl-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine hydrobromide; m.p. 187-189°

(h) 3-amino-12-methyl-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine hydrobromide; m.p. 309-312°

(i) 3-amino-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]thiazepine hydrobromide



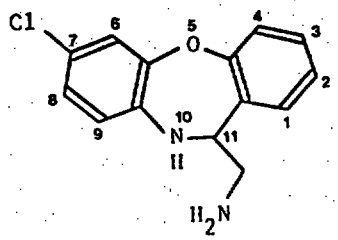
For production of the acid maleate ($C_{15}H_{13}N_3S \times C_4H_4O_4$), the free base liberated in the usual way is dissolved in methanol and admixed with the calculated quantity of maleic acid. The precipitated crystals are recrystallized from methanol under addition of charcoal; m.p. 230° decomp.

(j) 3-amino-6-chloro-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]thiazepine hydrobromide
(k) 3-amino-7-chloro-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]thiazepine hydrobromide
(l) 3-amino-12-chloro-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]thiazepine hydrobromide; m.p. 358-361° decomp. (methanol/ethylacetate)
(m) 3-amino-6-methyl-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]thiazepine hydrobromide
(n) 3-amino-6-methoxy-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]thiazepine hydrobromide

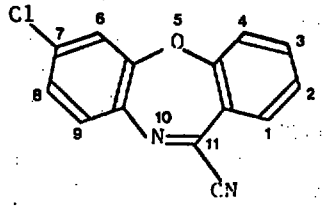
The diamines of formula IV used as starting material may be produced in line with the reaction scheme detailed above, for example:

EXAMPLE α

11-Aminomethyl-7-chloro-10,11-dihydro-dibenzo[b,f][1,4]oxazepine-fumarate



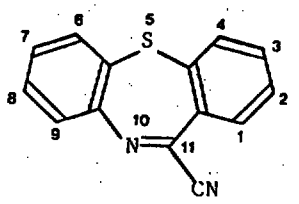
STEP (I): *7-Chloro-11-cyano-dibenzo[b,f],[1,4]oxazepine*



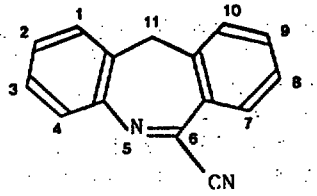
A suspension of 123 g (0.47 mol) of 7,11-dichlorodibenzo-[b,f][1,4]oxazepine and 46 g (0.94 mol) of sodium cyanide in 1400 ml of dimethylsulfoxide is stirred for 3 hours at 50-60°. The reaction mixture is cooled and poured onto 6 l of ice water. After extraction with chloroform and drying with anhydrous sodium sulfate, the organic phase is evaporated in vacuo. The crystalline residue is washed with methanol and dried.
The yield amounts to 74 g (62.4% of theory);
M.p. 185-188°.

The following cyano compounds are produced analogously:

(a) 8-chloro-11-cyano-dibenzo[b,f][1,4]oxazepine;
yield: 69.7%; m.p. 161-163° (acetonitrile)
(b) 2-chloro-11-cyano-dibenzo[b,f][1,4]oxazepine;
yield: 31..4%; the melting point of the crude product is from 126-132°
(c) 11-cyano-dibenzo[b,f][1,4]oxazepine;
yield: 85.7%; m.p. of the crude product 107-114°
(d) 11-cyano-dibenzo[b,f][1,4]thiazepine;



Yield: 100%; m.p. of the crude product 93-100°
(e) 2-chloro-11-cyano-dibenzo[b,f][1,4]thiazepine
Yield: 65.3% m.p. of the crude product 176-182°
(f) 6-cyano-11-H-dibenzo[b,e]azepine;



yield: 73.2% m.p. 98-100° (methanol)

(g) 2-chloro-6-cyano-11H-dibenzo[b,e]azepine;
yield: 67.5%; m.p. of the crude product 163-168°

STEP II: *Reduction of 7-Chloro-11-cyano-dibenzo-[b,f][1,4]oxazepine obtained according to Step (I)*

A solution of aluminium hydride in tetrahydrofuran is produced by the slow dropwise addition while stirring of a solution of 9.8 g (0.1 mol) of 100% sulfuric acid in 40 ml of anhydrous tetrahydrofuran to a suspension of 7.6 g (0.2 mol) of lithium aluminium hydride in 200 ml of absolute tetrahydrofuran. Without separating the lithium sulfate that forms, within 30 minutes a solution of 12.3 g (0.05 mol) of 7-chloro-11-cyano-dibenzo[b,f][1,4]oxazepine in 80 ml of absolute tetrahydrofuran is added. The reaction mixture is stirred for 2 hours at ambient temperature and then the excess of the hydride is decomposed while ice-cooling by the addition of 25 ml of water. The inorganic components are suction filtered and stirred twice with chloroform. The tetrahydrofuran and the chloroform solutions are combined, washed with an aqueous common salt solution, after drying with sodium sulfate, evaporated in vacuo. As a residue there remains 25 g of a dark-red oil. For purification, the oil is dissolved in methanol and converted with the calculated quantity of fumaric acid into the acid fumarate.
Yield: 26 g (71.3% of theory), m.p. 228° decomp.

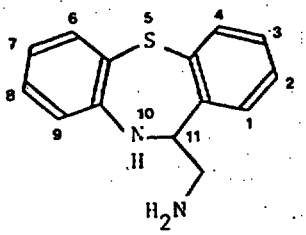
The following diamines were produced in line with the process described for Step (II):

(a) 11-aminomethyl-8-chloro-10,11-dihydro-dibenzo[b,f][1,4]oxazepine fumarate.
Yield: 54.6%, m.p. of the crude product 239-241° decomp.

(b) 11-aminomethyl-2-chloro-10,11-dihydro-dibenzo[b,f][1,4]oxazepine fumarate.
Yield: 54.4%. M.p. of the crude product 228-229° decomp. M.p. of the base: 131-133° (acetonitrile).

(c) 11-aminomethyl-10,11-dihydro-dibenzo[b,f][1,4]oxazepine,
yield: 65.5%. M.p. of the base: 119-122° (acetonitrile).

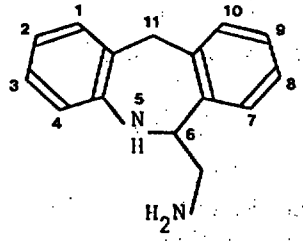
(d) 11-aminomethyl-10,11-dihydro-dibenzo[b,f][1,4]thiazepine fumarate



yield: 61%. M.p. of the crude product 204-206° decomp.

(e) 11-aminomethyl-2-chloro-10,11-dihydro-dibenzo[b,f][1,4]thiazepine fumarate.
Yield: 68.8%. M.p. of the crude product 202° decomp.

(f) 6-aminomethyl-6,11-dihydro-5H-dibenzo[b,e]azepine fumarate.



Yield: 72.3%, m.p. of the crude product 192-193° decomp.

(g) 6-aminomethyl-2-chloro-6,11-dihydro-5H-dibenzo[b,e]azepine fumarate.
Yield: 42.1%. M.p. of the crude product 197-198° decomp.

EXAMPLE 2

3-Morpholino-1,13b-dihydro-dibenzo[b,f]imidazo [1,5-d][1,4]oxazepine fumarate

STEP (I): 3-Methylmercapto-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine hydroiodide

20 g (0.075 mol) of 1,2,3,13b-tetrahydrodibenzo[b,f]-imidazol[1,5-d][1,4]oxazepine-3-thione (m.p. 199-201°C; prepared from 11-aminomethyl-10,11-dihydro-dibenzo[b,f][1,4]oxazepine and carbon disulfide) are admixed with a solution of 21.4 g (0.15 mol) of methyl iodide in 170 ml of methanol and refluxed for three hours. In so doing, a clear solution is obtained, from which crystals gradually separate. After cooling, the precipitate is suction filtered and dried.

Crude yield: 26.6 g (87% of theory). M.p. 219-228° decomp.

Analogously, for example, starting from 6-aminomethyl-6,11-dihydro-5H-dibenzo[b,e]azepine and via 2,3,9,13b-tetrahydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine-3-thione (m.p. 222-224°), the 3-methylmercapto-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine hydroiodide may be obtained (m.p. of the crude product 274-283° decomp.).

The 3-methylmercapto derivatives can be reacted without further purification.

STEP (II):

8.2 g (0.02 mol) of 3-methylmercapto-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine hydroiodide are refluxed with 25 ml of morpholine for two hours while stirring. The light-yellow solution is evaported in vacuo and the residue is distributed between ether and 2 N sodium hydroxide solution. Subsequently, the organic phase is washed with water, dried with sodium sulfate and evaporated. The residue is recrystallized from acetonitrile (m.p. 141-142°). For production of the acid fumarate the free base thus obtained is dissolved in alcohol and admixed with the calculated quantity of fumaric acid. On cooling, there are obtained 5.8 g (66.4% of theory) of 3-morpholino-1,13b-dihydro-dibenzo[b,f]imidazo[1,5] [1,4]oxazepine hydrogen fumarate, m.p. 189-191° decomp.

Analogously to the process of step (II), the following compounds may be produced starting from the corresponding methylmercapto compounds:

(a) 3-n-pentylamino-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine, which may be converted into the hydrochloride in the usual way.
(M.p. of hydrochloride: 204-207° (decomp.)

(b) 3-morpholino-9,13b-dihydro-1H-dibenzo[c,f]imidazo]1,5-a]-azepine hydrochloride; m.p. 204-207° decomp.

EXAMPLE 3

3-Allylamino-9,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine hydrochloride

8.2 g (0.02 mol) of 3-methylmercapto-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine hydroiodide are heated with 3.42 g (0.06 mol) of allylamine for two hours to 70° while stirring. After cooling, the light-yellow oil is admixed with 2 N sodium hydroxide solution and subsequently is extracted with ether. The organic phase is separated, washed with water and dried over anhydrous sodium sulfate. On evaporation in vacuo 5.6 g of crude base are obtained, which are converted in the conventional way with methanolic hydrochloric acid into the hydrochloride.
Yield: 4.1 g (62.6% of theory).
M.p. 189-192° (acetonitrile).

EXAMPLE 4

3-Dimethylamino-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine hydrochloride

3 g (7.4 mmol) of 3-methylmercapto-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine hydroiodide are heated to 130° for three hours with a solution of 15 ml of dimethylamine in 30 ml of ethanol in an autoclave. The resin remaining after evaporation of the reaction solution is taken up in chloroform and shaken with 2 N sodium hydroxide solution. The organic phase is dried with sodium sulfate and the solvent is distilled off in vacuo. 2.6 g of oil (crude base) are obtained which is converted with methanolic hydrochloric acid into the hydrochloride (m.p. 163-167°; acetonitrile/ether). The substance contains 1 mol of water (Karl Fischer titration).

In line with the process described in Example 4, the following compounds may be produced from the corresponding methylmercapto derivatives:

(a) 3-dimethylamino-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine hydrochloride; m.p. 268-271°

(b) 3-dimethylamino-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d[1,4]thiazepine hydrochloride; m.p.: 241-244° (the substance contains 0.5 mol of water).

Under similar reaction conditions the following compounds are obtained by reacting 3-methylmercapto-9,11b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]-azepine hydrochloride with alcoholic solutions of ammonia or of the corresponding amines:

(c) 3-amino-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]-azepine hydrochloride (m.p. 283-286°). The substance is identical to the product obtained according to Example 1.

(d) 3-pyrrolidino-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine hydrochloride; m.p. 158-162 decomp. (alchol/ether). The substance contains 0.25 mol of water.

(e) 3-methylamino-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine hydrochloride; m.p. 234° decomp. (methanol/ether).

(f) 3-ethylamino-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine hydrochloride; m.p. 275-280°.

(g) 3-allylamino-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine hydrochloride; m.p.: 202-205°. (acetonitrile/ethylacetate).

EXAMPLE 5

3-Dimethylamino-7-chloro-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine hydrochloride

To a solution of 6.7 g (0.026 Mol of 6-aminomethyl-2-chloro-6,11-dihydro-5H-dibenzo[b,e]azepine and 5.76 g (0.057 Mol) of triethylamine in 70 ml of chloroform is added dropwise while stirring 4.21 g (0.026 Mol) of dichloromethylene dimethylimmonium chloride. In so doing, a slightly exothermic reaction occurs. The reaction solution then is refluxed for one hour, cooled and shaken successively with 2 N hydrochloric acid and 2 N sodium hydroxide solution. The organic phase is washed with water, dried over anhydrous sodium sulphate and evaporated in vacuo. Subsequently the residue is chromatographed on silica gel. Then impurities are separated with acetone and methanol and the desired product is eluted with a mixture of chloroform/methanol/conc. NH_3 : 65/35/1. When evaporating the chloroform/methanol/conc. NH_3 eluates there are obtained 4.5 g of oil. This crude base is dissolved in ether and, after filtering off the insoluble particles, converted with methanolic hydrochloric acid into the hydrochloride. Yield: 3.7 g (40% of theory) (m.p.: 195-197° decomposition from acetonitrile/ethylacate. The substance contains 0.5 mol of water).

EXAMPLE 6

3-Methylamino-6-chloro-9,13-dihydro-dibenzo[b,f]imidazo [1,5-d][1,4]oxazepine hydrochloride

STEP (I):

A solution of 9.2 g (0.035 mol) of 11-aminoethyl-8-chloro-10,11-dihydro-dibenzo[b,f][1,4]oxazepine and 2.58 g (0.035 mol) of methylisothiocyanate is stirred for two hours at ambient temperature and subsequently is allowed to stand overnight. On evaporation of the reaction solution a crystalline residue of 11.7 g (m.p.: 126-132°) is obtained.

STEP (II):

10 g (0.03 mol) of the thio-urea derivatives thus obtained are dissolved in a methanolic solution of 6.38 g (0.045 mol) of methyl iodide in 80 ml of methanol and the reaction mixture is subsequently refluxed for two hours.

The precipitated N-(8-chloro-10,11-dihydro-dibenzo[b,f][1,4]oxazepin-11-yl)methyl-S-methyl-thiourea hydroiodide (Melting point: 212-215°) is suction filtered and dried.

STEP (III)

To liberate the free base, a suspension in water of 9.7 g of the hydriodide obtained according to Step (II) is admixed with 2 N sodium hydroxide solution and ether and is stirred until 2 clear layers are formed. The organic phase is separated, dried with anhydrous sodium sulphate and evaporated in vacuo. The residue of 7.1 g (0.02 mol of base) is dissolved in 60 ml of xylene and the solution is refluxed for 11 hours. The crystals precipitating when the reaction solution is cooling off (5.6 g) are suction filtered, dissolved in methanol and converted with ethereal hydrochloric acid into the hydrochloride. For further purification the salt is taken up in dilute sodium acetate solution. The aqueous solution formed thereby is shaken with ether, adjusted to alkalinity with sodium hydroxide solution and subsequently extracted with chloroform. The organic phase is dried with anhydrous sodium sulphate and evaporated in vacuo. The remaining free base is converted into the hydrochloride.

Yield: 4.1 g (61% of theory); m.p.: 297-300° (CH_3OH/ether).

Starting from 11-aminoethyl-10,11-dihydro-dibenzo[b,f][1,4]oxazepine analogously to steps (I) and (II) there may be obtained N(10,11-dihydro-dibenzo[b,f][1,4]oxazepin-11-yl)methyl-S-methyl-thiourea-hydroiodide. The free base liberated therefrom is reacted to form 3-methylamino-9,13b-dihydro-dibenzo-[b,f]imidazo[,5-d][1,4] oxazepine by heating for three hours in toluene with splitting of methylmercaptan. The hydrochloride has a melting point of 328-320° decomposition.

EXAMPLE 7

3-Methylamino-7-chloro-9,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine hydrochloride

STEP (I):

N-(7-chloro-10,11-dihydro-dibenzo[b,f][1,4]oxazepin-11-yl)-N-methyl-urea

Into a solution of 11 g (0.042 mol) of 11-aminomethyl-7-chloro-10,11-dihydro-dibenzo[b,f][1,4]oxazepine in 60 ml of toluene is added dropwise while stirring a solution of 2.68 g (0.045 Mol) of methylisocyanate in 40 ml of toluene. After a reaction time of two hours the precipitated crystals are suction filtered and dried. Yield: 10.8 g (80.5% of theory); m.p. 146-149°.

STEP (II)

A suspension of 10.8 g (0.034 Mol) of the urea derivative produced according to Step (I) in 200 ml of toluene is admixed with 10.8 ml of phosphorus oxychloride and the reaction mixture is refluxed for 30 minutes. After evaporation off of the solvent the residue is distributed betwen cold dilute sodium hydroxide solution and chloroform. The organic phase is dried over anhydrous sodium sulphate and evaporated in vacuo.

Yield: 6.2 g (60.9% of theory); m.p. 163-165° (acetonitrile). The hydrochloride produced in the conventional way has a melting point of 298-302° (CH_3/OH/ethylacetate).

Starting from 6-aminomethyl-6,11-dihydro-5H-dibenzo-[b,e]azepine, by reacting with isopropylisocyanate, the corresponding urea derivative may be obtained (m.p. 190-192°), which itself can be converted analogously into 3-isopropylamino-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine. The hydrochloride melts at 241-143° under decomposition.

EXAMPLE 8

(−)3-Amino-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine hydrochloride and (+) 3-amino-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine hydrochloride

36.5 g (0.146 mol) of racemic 3-amino-9,13b-dihydro-dibenzo[c,f]imidazo[1,6-a]azepine free base and 55.1 g (0.164 mol) of dibenzoyl-L(+) tartaric acid are dissolved by heating in a litre of methanol.

On cooling, a precipitate forms which is suction filtered after standing for a while. The crystals obtained are recrystallized up to a constant melting point and spec. rotation from methanol. m.p. 150-152° decomposition: $[\alpha]_D^{25} - 200°$ (c=1; methanol).

The free base, liberated in the conventional way, is dissolved with ethereal hydrochloric acid. m.p. 266-269°; $[\alpha]_D^{25} - 285°$ (c = 1; Alcohol).

Analogously thereto, the (+) enantiomer may be obtained using dibenzoyl-D (−) tartaric acid.

Hydrochloride: m.p. 266-269°; $[\alpha]_D^{25} + 285°$ (c = 1; alcohol).

The following are Examples of pharmaceutical compositions according to the present invention:

EXAMPLE I: *Tablets*

Composition:

active ingredient according to the invention	0.005 g
stearic acid	0.001 g
glucose	0.194 g

Tablets each having the composition indicated above are formulated in a conventional manner.

EXAMPLE II: *Inhalation aerosol*

Composition:

active ingredient according to the invention		1.00 parts
soy lecithin		0.20 "
propellant gas mixture (Frigen 11, 12 and 14) ("Frigen" is a registered Trade Mark)	*ad*	100.00 "

The preparation preferably is filled into aerosol containers with metering valves, the single stroke is adjusted to release a dose of 0.5 mg. For the other dosage-units within the indicated range, it is useful to apply preparations with a higher or lower portion of active ingredient.

EXAMPLE III: *Capsules for Inhalation*

The active substance according to the invention is filled in micronized form (i.e. with a particle size for the most part between 2 and 6 µm), optionally under addition of micronized carriers (for example lactose) into hard gelatin capsules ("micronizer" is a registered Trade Mark). For administration by inhalation conventional devices for powder inhalation are suitable. In each capsule are filled, for example between 0.2 and 20 mg of the active substance and 0 to 40 mg of lactose.

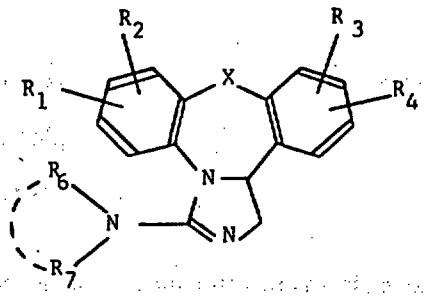
EXAMPLE IV: *Ointment*

Composition:		g/100 g of ointment
active substance according to the invention		2.000
fuming hydrochloric acid		0.011
sodium pyrosulfite		0.050
mixture of equal parts of cetyl alcohol and stearyl alcohol		20.000
white vaseline ("vaseline" is a registered Trade Mark)		5.000
artificial bergamot oil		0.075
distilled water	*ad*	100.000

The components are worked up to an ointment in the conventional way.

CLAIMS

1. Compounds of formula I



(I)

[wherein R_1, R_2, R_3 and R_4, which may be the same or different, each represents a hydrogen or halogen atom or a C_1 to C_6 alkyl or C_1 to C_6 alkoxy group; R_5 and R_6, which may be the same or different, each represents a hydrogen atom or a C_1 to C_6 alkyl or C_3 to C_6 alkenyl group; or R_5 and R_6, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino or morpholino group; and X represents an oxygen or sulfur atom or a methylene group] and acid addition salts thereof.

2. Compounds of formula I as claimed in claim 1 wherein R_6 represents a hydrogen atom, tautomers thereof of formula Ia

The preparation preferably is filled into aerosol containers with metering valves, the single stroke is adjusted to release a dose of 0.5 mg. For the other dosage-units within the indicated range, it is useful to apply preparations with a higher or lower portion of active ingredient.

EXAMPLE III: *Capsules for Inhalation*

The active substance according to the invention is filled in micronized form (i.e. with a particle size for the most part between 2 and 6 μm), optionally under addition of micronized carriers (for example lactose) into hard gelatin capsules ("micronizer" is a registered Trade Mark). For administration by inhalation conventional devices for powder inhalation are suitable. In each capsule are filled, for example between 0.2 and 20 mg of the active substance and 0 to 40 mg of lactose.

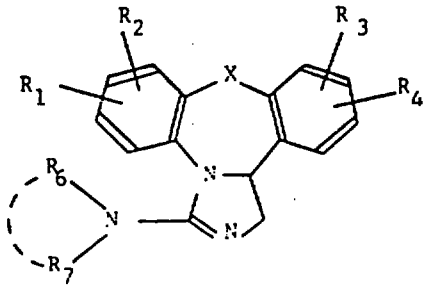
EXAMPLE IV: *Ointment*

Composition:		g/100 g of ointment
active substance according to the invention		2.000
fuming hydrochloric acid		0.011
sodium pyrosulfite		0.050
mixture of equal parts of cetyl alcohol and stearyl alcohol		20.000
white vaseline ("vaseline" is a registered Trade Mark)		5.000
artificial bergamot oil		0.075
distilled water	*ad*	100.000

The components are worked up to an ointment in the conventional way.

CLAIMS

1. Compounds of formula I

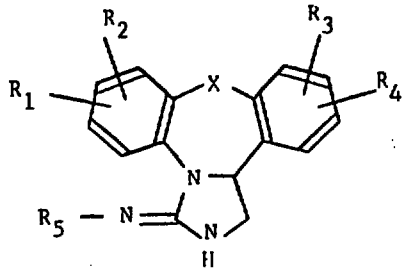


(I)

[wherein R_1, R_2, R_3 and R_4, which may be the same or different, each represents a hydrogen or halogen atom or a C_1 to C_6 alkyl or C_1 to C_6 alkoxy group; R_5 and R_6, which may be the same or different, each represents a hydrogen atom or a C_1 to C_6 alkyl or C_3 to C_6 alkenyl group; or R_5 and R_6, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino or morpholino group; and X represents an oxygen or sulfur atom or a methylene group] and acid addition salts thereof.

2. Compounds of formula I as claimed in claim 1 wherein R_6 represents a hydrogen atom, tautomers thereof of formula Ia

* C L M S



(Ia)

(wherein R_1, R_2, R_3, R_4 and X are as defined in claim 1 and R_5 represents a hydrogen atom of a C_1 to C_6 alkyl or C_3 to C_6 alkenyl group) and acid addition salts of the compounds of formula I and tautomers thereof.

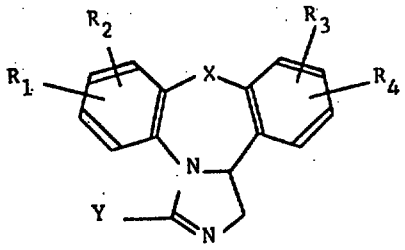
3. A compound as claimed in either of claims 1 and 2 which is:

(a) 3-amino-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine and acid addition salts thereof;
(b) 3-amino-7-chloro-9,13b-dihydro-1H-dibenzo[c,f]imidazo[1,5-a]azepine and acid addition salts thereof;
(c) 3-amino-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine and acid addition salts thereof;
(d) 3-amino-12-chloro-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]oxazepine and acid addition salts thereof;
(e) 3-amino-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]thiazepine and acid addition salts thereof;
(f) 3-amino-12-chloro-1,13b-dihydro-dibenzo[b,f]imidazo[1,5-d][1,4]thiazepine and acid addition salts thereof.

4. Compounds as claimed in either of claims 1 and 2 as herein specifically disclosed with the exception of compounds claimed in claim 3.

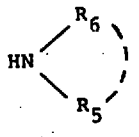
5. A process for the preparation of compounds of formula I or Ia (as defined in claims 1 and 2) and acid addition salts thereof, which process comprises at least one of the following steps:

(a) reacting a compound of formula II



(II)

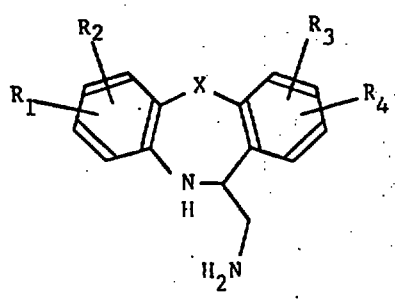
(wherein Y represents a halogen atom or an alkoxy or alkylthio group and R_1, R_2, R_3, R_4 and X are as defined in claim 1) with an amine of formula III



(III)

(wherein R_5 and R_6 are as defined in claim 1);

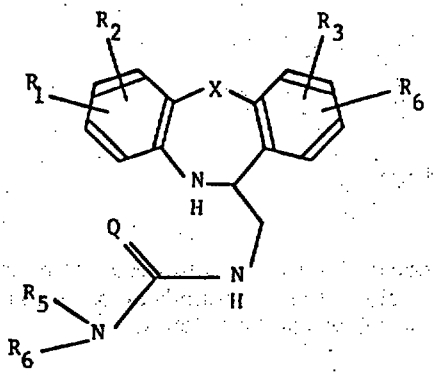
(b) (for the preparation of compounds of formula I or Ia wherein R_5 and R_6 represent hydrogen atoms) reacting a diamine of formula IV



(IV)

(wherein R_1, R_2, R_3, R_4 and X are as defined in claim 1) with a cyanogen halide;

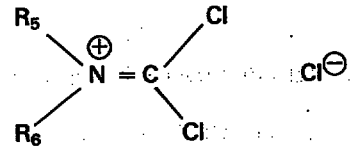
(c) cyclizing a compound of formula VIII



(VIII)

(wherein R_1, R_2, R_3, R_4, R_5, R_6 and X are as defined in claim 1 and Q represents an oxygen or sulphur atom or a group $=NR_7$ [in which R_7 represents a hydrogen atom or an optionally substituted C_1 to C_8 alkyl group]);

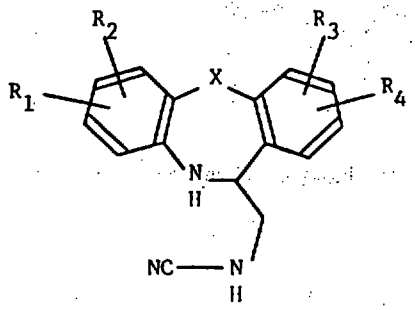
(d) (for the preparation of compounds of formula I wherein R_5 and R_6 represent other than hydrogen atoms) reacting a diamine of formula IV (wherein R_1, R_2, R_3, R_4 and X are as defined in claim 1) with a N,N-distributed dichloromethylene iminium salt of formula X



(X)

(wherein R_5 and R_6, which may be the same or different, each represents a C_1 to C_6 alkyl or C_3 to C_6 alkenyl group or R_5 and R_6, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino or morpholino group);

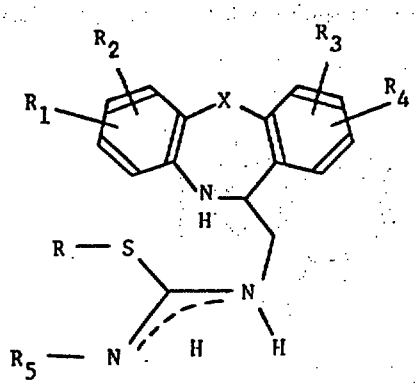
(e) (for the preparation of compounds of formula I or Ia wherein R_5 and R_6 represent hydrogen atoms) cyclizing a compound of formula IVa



(IVa)

(wherein R_1, R_2, R_3, R_4 and X are as defined in claim 1) by intramolecular reaction;

(f) (for the preparation of compounds of formula I or Ia wherein R_6 represents a hydrogen atom) cyclizing a compound of formula IX



(IX)

(wherein R_1, R_2, R_3, R_4, R_5 and X are as defined in claim 1 and R represents an optionally substituted C_1 to C_8 alkyl group);

(g) converting a compound of formula I or Ia into an acid addition salt thereof or converting an acid addition salt of a compound of formula I or Ia into the free base; and

(h) separating a racemic mixture of a compound of formula I or Ia or an acid addition salt thereof into its enantiomers.

6. A process as claimed in claim 5 substantially as herein described in any one of Examples 1 to 8.

7. Pharmaceutical compositions comprising as active ingredient at least one compound of formula I or Ia as defined in claims 1 and 2 or a physiologically acceptable acid addition salt thereof together with a pharmaceutical carrier or excipient.

8. Pharmaceutical compositions as claimed in claim 7 in dosage unit form.

9. Pharmaceutical compositions as claimed in claim 7 substantially as herein described in any one of Examples I to IV.

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