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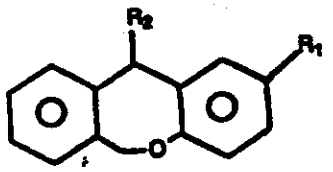
EP 0 214 779 B1

Description

The present invention relates to new chemical compounds which have potent antihistaminic activity, to processes for preparing them and to their use in medicine. Belg. Patent 623 259, Neth. Patent Appl. 6 407 758, Neth. Patent Appl. 6 411 861 and Belg. Patent 641 498 disclose a group of 11-[(dialkylamino)-alkylidene]-6,11-dihydrodibenz[b,e]oxepins as psychotherapeutic agents the most outstanding of which is the compound named, (11-(3-(dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin), and hereinafter referred to by its generic name, doxepin. Doxepin has been accepted as an antidepressant in human clinical chemotherapy and an antipruritic for veterinary use.

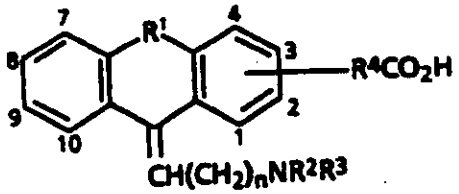
Published European Patent Application No 130 555 discloses compounds of formula:



wherein R_1 represents a cyano group, a 5-tetrazolyl group, a carbamoyl group or $-CO_2R_3$ [wherein R_3 represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms or a 1-(ethoxycarbonyloxy)ethyl group, and R_2 represents a 4-alkylpiperazino group (wherein the alkyl group has 1 to 5 carbon atoms), a 3-quinuclidinylamino group or $-X-(CH_2)_n-NR_4R_5$ (wherein X represents –NH–, –S– or –O–, R_4 and R_5 are same or different and each represents an alkyl group having 1 to 5 carbon atoms and n represents 2 or 3); and the pharmaceutically acceptable acid addition salts or metal salts thereof, which compounds are said to exhibit anti-allergic activity.

We have now discovered that a group of carboxylic acid derivatives of doxepin possess surprisingly potent antihistaminic and antiasthmatic properties. In this invention, compound (Z)-11-(3-(dimethylamino)-propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid exhibits extremely good antihistaminic activity in vivo.

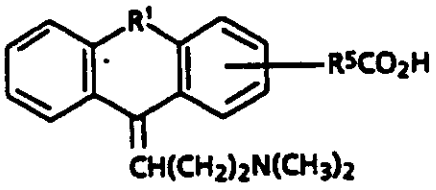
Accordingly this invention provides a compound of the formula (I),



(I)

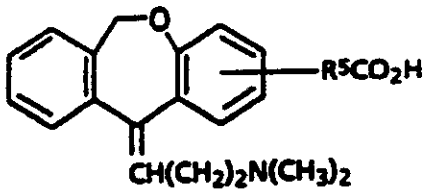
or a salt, ester or amide thereof; wherein R^1 is $-CH_2-O-$ or $-O-CH_2-$;
R^2 and R^3 are the same or different and are each hydrogen, C_{1-4} alkyl or taken together with the nitrogen comprise a nitrogen-containing heterocyclic ring having four to six ring members;
R^4 is a single bond or a C_{1-7} bivalent aliphatic hydrocarbon group and may be joined to the aromatic ring system at the 2, 3, 8 or 9 positions. n is 0 to 3.

Of the compounds of formula (I) those of formula (II), wherein R^1 is as defined herein above, and R^5 is a single bond or -CH=CH-, are preferred.



(II)

The most preferred compounds of formula (II), are those of formula (IIa) wherein R^5 is as defined for formula (II)



(IIA)

Examples of compounds of formula (IIA) include:

(1) (Z)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
(2) (E)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
(3) (E)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-3-carboxylic acid
(4) (Z)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-3-carboxylic acid
(5) (E)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-8-carboxylic acid
(6) (Z)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-8-carboxylic acid
(7) (E)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-9-carboxylic acid
(8) (Z)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-9-carboxylic acid
(9) (E)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-2-acrylic acid
(10) (Z)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-2-acrylic acid

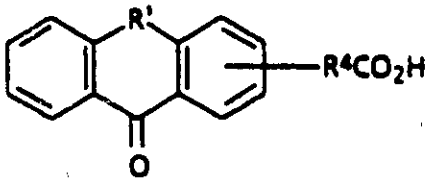
The compounds of the present invention exist in either the cis (Z) or trans (E) isomers (in relation to the bridge oxygen in the case of formula (IIA)). If the compounds of formula (I) or (II) contain a double bond in the acid bearing side chain, i.e. R^4 or R^5, there exists a second possibility of Z and E isomeric forms. All such geometric isomers and the isomeric mixture of these compounds are included within the scope of the present invention. Salts, amides and esters of the compounds of the formula (I) and (II) are included within the scope of the invention. While esters and amides of the compounds of the formulae (I) and (II) have antihistamine activity in their own right, they may also be useful intermediates in the preparation of the carboxy compounds of the formulae (I) and (II). Amides derived from ammonia, primary amines or amino acids, such as glycine, are particularly suitable. Suitable esters include conventional ester groups known to be useful for protecting carboxylic acid groups such as C_{1-6} alkyl esters wherein the alkyl group is straight or branched chain and is optionally substituted by halogen. Alkyl esters (C_{1-4}) are particularly preferred.

Solvates of the compounds of the formulae (I) and (II) are also included within the scope of the present invention. Preferred solvates include hydrates and C_{1-4} alkanolates.

Salts of the compounds of formula (I) may be either acid addition salts or salts formed with the carboxylic acid group. Acid addition salts are preferred but salts formed from the carboxylic acid group may be particularly useful in preparing the corresponding carboxy compound. When used in medicine, the salts of the compounds of formulae (I) and (II) should be both pharmacologically and pharmaceutically acceptable, but non pharmaceutically acceptable salts may conveniently be used to prepare the free active compound or pharmaceutically acceptable salts thereof and are not excluded from the scope of this invention. Such pharmacologically and pharmaceutically acceptable acid addition salts include, but are not limited to, those prepared from the following acids: hydrochloric, sulphuric, nitric, phosphoric, maleic, salicylic, toluene-p-sulphonic, tartaric, citric, methanesulphonic, formic, malonic, isethionic, succinic, naphthalene-2-sulphonic and benzenesulphonic. Also, pharmaceutically acceptable salts can be prepared as ammonium salts, alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group.

The present invention also provides analogous methods for preparing compounds of formula (I), for example:

a) (I) A compound of formula (I) may be prepared via the well known Wittig method (e.g., U.S. Patents 3,354,155 and 3,509,175) by reaction of a compound of formula (III).



(III)

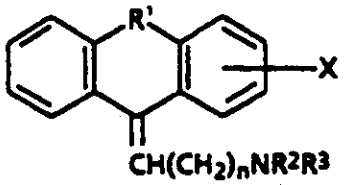
The Wittig reagent, $Ph_3P{=}CH(CH_2)_nNR_2R_3$; i.e., formula (IV), is conveniently

$$(C_6H_5)_3P{=}CH(CH_2)_nNR^2R^3 \qquad (IV)$$

prepared by reacting a compound of the formula $Ph_3PCH_2(CH_2)_nNR_2R_3Br$, with a strong base, such as sodium hydride or C_{1-6} alkyl lithium in a suitable inert solvent, such as tetrahydrofuran or dimethoxyethane at or near room temperature. It will be appreciated by those skilled in the art of organic chemistry that protection of the carboxy group may be desirable or required prior to the Wittig reaction and deprotection after the reaction.

(ii) A compound of formula (I) also may be prepared via the well known Grignard conditions (e.g., Belg. 623 259) in which a Grignard reagent, i.e. $R^2R^3NCH_2CH_2CH_2Mg$ X where X is a halogen atom, is reacted with a compound of formula (III), followed by dehydration with a strong acid.

b) A compound of formula (I) wherein R^4 is a single bond can be prepared by carboxylation of a compound of formula (V)



(V)

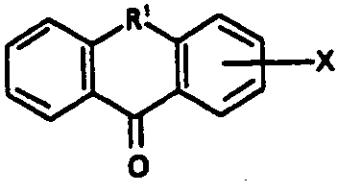
wherein R^1, R^2, R^3 and n are as defined, vide supra and X is a hydrogen or halogen atom (suitably a bromine or chlorine atom attached directly to the ring system in the 2, 3, 8 or 9 positions. For example, a compound of formula (V) can be treated with a metalating agent such as butyl lithium followed by a reaction with carbon dioxide. When X is hydrogen separation of isomers may be required to obtain the desired compound of formula (I). When X is a halogen atom, a compound of formula (V) can be reacted with magnesium in an appropriate solvent followed by reaction with carbon dioxide via the Grignard procedure (The Merck Index, ninth ed., page ONR-38, Merck and Co., Rahway, N.J. (1976).

c) A compound of formula (I) wherein R^4 is other than a single bond can be synthesized by reacting a compound of formula (V) (wherein X is a halogen atom) with a compound of formula (VI),

$$CH_2{=}CH{-}R^6{-}COR^7 \qquad (VI)$$

wherein R^6 is a C_{1-5} bivalent aliphatic hydrocarbon and R^7 is a removable carboxylic acid protecting group such as one derived from a reaction of the carboxylic acid group which has been activated (e.g. converted to an acyl chloride) with an alcohol or amine. In some cases this reaction may need to be facilitated by a palladium catalyst (J. Org. Chem. 42, 3903–3907 (1977)). A variation of this method involves a reaction of a compound of formula (VII) with a compound of formula VI in a similar manner, vide supra, followed by catalytic reduction of the double bond in the carboxylic bearing side chain that followed by the Wittig reaction described in Section a) (i) or (ii), vide supra. The carboxylic acid groups may then be regenerated by deprotection if required.

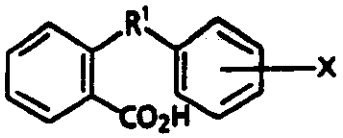
d) When the preparation of a compound of the formula (I) wherein R^4 is CH=CH is required, a compound of the formula (VII)



(VII)

wherein R^1 is as defined, vide supra and X is halogen can be reacted with acrylic acid or an acrylic acid ester, with use of a catalyst if needed, by a method analogous to that described in b), vide supra, followed by a Wittig reaction as described in part a) (i) or (ii), vide supra. The carboxylic acid can be regenerated by deprotection if desired.

A compound of formula (VII) may be prepared by reacting a compound of formula (VIII).



(VIII)

wherein R^1 and X are as defined, vide supra with a dehydrating agent such as $(CF_3CO)_2O/BF_3{\cdot}OEt_2$.

(e) It is possible to convert one compound of the formula (III) to another compound of the formula (III) by methods well known to those skilled in the art, for example the reduction of one or more double bonds or de-esterification of an ester group or hydrolysis of an amide, followed by a Wittig reaction with $Ph_3P{=}CH_2(CH_2)_nNR_2R_3$ as described, vide supra.

(f) A compound of formula (VIII) can be converted to a Grignard reagent or an organolithium reagent by methods well known to those skilled in the art (after protecting the CO_2H group) then reacted with dimethyl formamide to obtain the corresponding aldehyde. Such an aldehyde can be converted to an acid by oxidation or reaction with a trialkyl phosphonium acetate or an equivalent. By methods well known in the art of organic chemistry, after deprotecting such an acid can be dehydrated as described in d), vide supra to give a compound of formula (III).

(g) A compound of the formula (V) where X is halogen can be reacted with a metal (I) cyanide, such as cuprous cyanide to give a corresponding carbonitrile derivative, which can then be converted to compounds of formula (I), eg the carboxylic acid via hydrolysis.

Those intermediates that are novel form an important further aspect of the present invention.

(h) Interconversion of compounds of the formula (I) is possible, e.g., by hydrolysis of esters, amides and by isomerization about the multiple bonds when such bonds are present or by selective reduction of multiple bonds when such bonds are present.

The compounds of this invention having antiallergic activity may be used for the same indications as clinically used antiasthmatic compounds, namely to help to control bronchoconstriction or brochospasm characteristic of allergic asthma and exercise induced asthma and the symptoms of bronchoconstriction and bronchospasm resulting from acute or chronic bronchitis. The compounds are believed to inhibit the release of autacoids (i.e. histamine, serotonin and the like) from mast cells and to inhibit directly the antigen-induced production of histamine. Thus, they may be classified as mast cell stabilizers with antihistaminic action.

The compounds of this invention having antihistamine activity may be used for the same indications as clinically used antihistamines, namely to relieve detrimental symptoms (caused by histamine release) of nasal stuffiness due to colds and vasomotor rhinitis and for the symptomatic control of allergic conditions including nasal allergy, perennial rhinitis, urticaria, angioneurotic oedema, allergic conjunctivitis, food allergy, drug and serum reactions, insect bites and stings and desensitizing reactions. The compound may also be used in conditions responsive to its antipruritic activity including allergic dermatoses, neurodermatitis, anogenital pruritus, and pruritus of non-specific origin such as eczema, and of specific cause such as chickenpox, photosensitivity and sunburn. The present invention therefore provides a method for the symptomatic treatment of allergic conditions by the administration of an effective amount of a compound of formula (I). The present invention also provides a method for the antagonism of endogenously released histamine by the administration of an effective amount of a compound of formula (I). The compounds of formula (I) are substantially free from sedative effects.

The amount of active compound, ie, a compound of formula (I) required for use in the above conditions will vary with the compound chosen, the route of administration and the condition and mammal undergoing treatment, and is ultimately at the discretion of the physician. A suitable oral dose of the active compound for a mammal is in the range of from 0.003 to 1.0 mg per kilogram body weight per day; preferably from 0.04 to 0.24 mg/kg. For example a typical dose for a human recipient of compound (1), (Z)-11-(3-(dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid, as the hydrogen chloride salt (see Example 7 and Table 1, vide infra) is between 0.03 and 0.1 mg/kg body weight per day.

The desired daily dose is preferably presented as from one to six sub- doses administered at appropriate intervals throughout the day as needed. Where three subdoses of compounds of formula (I) are employed, each will preferably lie in the range of from 0.014 to 0.08 mg/kg body weight; for example, a typical sub-dose of such a compound for a human recipient is between 1 and 20 mg, for example 4 or 8 mg.

While it is possible for a compound of formula (I) to be administered alone as the raw chemical, it is preferable to present the compound of formula (I) as a pharmaceutical formulation. Thus, the present invention also provides pharmaceutical formulations, both for veterinary and for human medical use, which comprise a compound of formula (I) together with one or more pharmaceutically acceptable carriers therefor and optionally any other therapeutic ingredients. For example, the active compound may be formulated with a sympathomimetic agent such as the decongestant pseudoephedrine, an antitussive such as codeine, an analgesic, an antiinflammatory, an antipyretic, or an expectorant. The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, rectal, topical, nasal, ophthalmic or parenteral (including subcutaneous, intramuscular and intravenous) administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active compound into association with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier or a finely divided solid carrier or both and then, if necessary, shaping the product into desired formulations.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound (defined herein as a compound of formula (I)); as a powder or granules; or a suspension in an aqueous liquid or nonaqueous liquid such as a syrup, and elixir, an emulsion or a draught. A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, with the active compound being in a free-flowing form such as a powder or granules which is optionally mixed with a binder, disintegrant, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets comprised of a mixture of the powdered active compound with any suitable carrier may be made by molding in a suitable machine.

A syrup may be made by adding the active compound to a concentrated, aqueous solution of a sugar for example sucrose to which may also be added any accessory ingredient(s). Such accessory ingredient(s) may include flavourings, an agent to retard crystallization of the sugar or an agent to increase the solubility of any other ingredient, such as a polyhydric alcohol, for example glycerol or sorbitol, and suitable preservatives.

Formulations for rectal administration may be presented as a suppository with a usual carrier such as cocoa butter, or hydrogenated fats or hydrogenated fatty carboxylic acids.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound which is preferably isotonic with the blood of the recipient.

Nasal spray formulations comprise purified aqueous solutions of the active compound with preservative agents and isotonic agents. Such formulations are adjusted to a pH and isotonic state compatible with the nasal mucous membranes.

Ophthalmic formulations are prepared by a similar method to the nasal spray except that the pH and isotonic factors are adjusted to match that of the eye.

Topical formulations comprise the active compound dissolved or suspended in one or more media such as mineral oil, petroleum, polyhydroxy alcohols or other bases used for topical pharmaceutical formulations. The addition of other accessory ingredients, vide infra, may be desirable.

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavouring agents, binders, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants) and the like.

The present invention also provides the first use of the compounds of formula (I) in medicine.

The following Examples are provided by the way of illustration of the present invention and should in no way be construed as a limitation thereof. All temperatures indicated are in degrees Celsius

Example 1: (E)/(Z)-11-(3-Dimethylamino)propylidene)-6, 11-dihydro-dibenz[b,e]oxepin-2-carboxylic acid

a) 2-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-one

2-Bromo-6, 11-dihydrodibenz[b,e]oxepin-11-one was prepared as described in US Patent 4,282,365, m.p. 132-134°C (Lit. m.p. 136-139°C). pmr (DMSO/d_6) δ: 8.13 (d, J=2.6 Hz, 1H, H_1), 7.48-7.83 (m, 5H, aromatic), 7.07 (d, J=8.8 Hz, 1H, H_4), 5.31 (s, 2H, CH_2O).

Analysis: Calcd. for $C_{14}H_9BrO_2$: C, 58.16; H, 3.14; Br, 27.64. Found: C, 58.20; H, 3.18; Br, 27.73.

b) (E)/(Z)-3-(2-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)-N,N-dimethylpropylamine

Anhydrous 3-(dimethylamino)propyltriphenylphosphonium bromide hydrobromide (39.4 g., 0.08 mole) was suspended in 450 mL of dry tetrahydrofuran and 100 mL of a solution of n-butyl lithium in hexane (1.6 M) was added dropwise at 0°C under a nitrogen atmosphere during a 30 minute period. After an additional 10 minutes, 2-bromo-6, 11-dihydrodibenz[b,e]oxepin-11-one (16.8 g., 0.06 mole) in 150 mL dry tetrahydrofuran was added slowly to the deep red solution and the reaction mixture was then refluxed for 18 hours. The reaction mixture was poured onto ice-water, and the mixture was extracted with diethyl ether. The ether layer was concentrated under reduced pressure and the residue was suspended in water and then acidified with 6N hydrochloric acid. The acidic aqueous layer was washed with hexanes and then was concentrated to give a gummy residue. The residue was crystallized from ethyl acetate/methanol to provide 5.3 g. of pure Z-isomer as its hydrochloride salt, m.p. 201-204°C. The mother liquor was chromatographed on a silica gel column (Waters Associates -Prep. 500) with ethyl acetate/methanol (8:2) to give an additional 2.55 g. of pure Z-isomer as the hydrochloride salt and 2.79 g. of E-isomer as its hydrochlo-

ride salt, m.p. 230-233°C. pmr (Z-isomer) (DMSO/d_6) δ: 7.25-7.44 (m, 6H, aromatic), 6.81 (degenerate d, J=9.1 Hz, 1H, H_4), 5.72 (t, J=7.1 Hz, 1H, CH=), 5.22 (s, 2H, CH_2O), 3.18 (m, 2H, NCH_2), 2.70 (m, 2H, CH_2), 2.66 (s, 6H, NMe_2). pmr (E-isomer) (DMSO/d6) δ: 7.23-7.50 (m, 6H, aromatic), 6.70 (d, J=8.6 Hz, 1H, H4), 6.10 (t, J=7.2 Hz, 1H, CH=) 5.15 (br s, 2H, CH_2O), 3.07 (m, 2H, NCH_2), 2.65 (s, 6H, NMe_2), 2.50 (m overlap with DMSO, 2H, CH_2).

c) (Z)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 1)

A solution of n-butyl lithium in hexane (1.6 M, 3.5 mL) was added dropwise to a solution of 1.8 g. pure (Z)-3-(2-bromo-6, 11-dihydrodibenz[b,e]oxepin-11-ylidene)-N,N-dimethylpropylamine in 100 mL of dry tetrahydrofuran at -70°C under a nitrogen atmosphere. After the yellowish-orange solution was stirred at -70°C for 10 minutes, gaseous carbon dioxide was bubbled through the reaction medium to give a pale yellow solution. The solution was allowed to warm gradually to room temperature and was then concentrated under reduced pressure. The foamy residue was dissolved in water, and the mixture was neutralized with 1N hydrochloric acid and then extracted with chloroform. Concentration of the chloroform and recrystallization of the residue from water gave 0.5 g. pure Z-2-carboxylic acid, m.p. 121-123°C. pmr ($CDCl_3$) δ: 7.87 (d, J≤1 Hz, 1H, H_1), 7.81 (dd, J=7.8, 2.2 Hz, 1H, H_3), 7.25-7.28 (m, 4H, aromatic), 6.82 (degenerate d, J=8.8 Hz, 1H, H_4), 6.45 (br s, 1H, CO_2H), 5.50 (m, 1H, CH=), 5.20 (br s, 2H, CH_2O), 2.92 (m, 4H, NCH_2CH_2), 2.66 (s, 6H, NMe_2).

Analysis: Calcd. for $C_{20}H_{21}NO_3 \cdot 0.55\ H_2O$: C, 72.07; H, 6.68; N, 4.20. Found: C, 72.07; H, 6.69; N, 4.18.

d) (E)-11-(3-(Dimethylamino)propylidine)-6, 11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 2).

Pure (E)-3-(2-bromo-6, 11-dihydrodibenz[b,e]oxepin-11-ylidene)-N,N-dimethylpropylamine (1.55 g., 4.3 mmole), was treated under nitrogen in cold (-70°C) tetrahydrofuran (100 mL) with 4.4 mmole of n-butyl lithium in hexane followed by gaseous carbon dioxide as described for the Z-isomer (Step C).

Isolation of the (E)-2-carboxylic acid was achieved by through chromatography of the crude product on a reverse phase C18 semipreparative column eluted with 20% methanol in water (containing 0.1% triethylamine). Recrystallization of the solid product from water afforded 0.012 g of pure E-2-carboxylic acid, m.p. >200°C (decomp.). pmr ($CDCl_3$) δ: 7.85 (d, J=2.0 Hz, 1H, H_1), 7.06-7.78 (m, 5H, aromatic), 6.47 (d, J=8.5 Hz, 1H, H_4), 6.28 (t, J=4.2 Hz, 1H, CH=), 5.85 (m, 1H, ArCH), 4.70 (m, 1H, ArCH), 2.43 (m, 4H, NCH_2CH_2), 2.28 (s, 6H, NMe_2).

Analysis: Calcd. for $C_{20}H_{21}NO_3 \cdot 0.50\ H_20$: C, 72.27; H, 6.67; N, 4.21. Found: C, 72.15; H, 6.46; N, 4.22.

Example 2: (E)/(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydro-dibenz[b,e]oxepin-3-carboxylic acid

a) Methyl 2-(3-bromophenoxymethyl)benzoate

To a mixture of 3-bromophenol (60 g, 0.35 mole) and potassium carbonate (25 g, 0.18 mole) in 250 mL of N,N-dimethylformamide was added methyl α-bromo-2-toluate (65 g, 0.28 mole). The reaction mixture was stirred at room temperature for 18 hours, then heated on a steam bath for 3 hours. The mixture was poured into ice-water, and the solids were collected by filtration and washed with water to give the crude product. Analytical sample was obtained by recrystallization from methylene chloride/hexanes, m.p. 84-85°C. pmr ($CDCl_3$) δ: 8.0 (m, 1H, H_6), 6.93-7.69 (m, 7H, aromatic H), 5.47 (s, 2H, $ArCH_2O$), 3.89 (s, 3H, CO_2CH_3).

Analysis: Calcd. for $C_{15}H_{13}BrO_3$: C, 56.09; H, 4.08; Br, 24.88. Found: C, 56.20; H, 4.12; Br, 24.77.

b) 2-(3-bromophenoxy)methylbenzoic acid

Methyl 2-(3-bromophenoxy)methylbenzoate (34 g) was refluxed in a mixture of 100 mL of 10% sodium hydroxide and 200 mL of methanol for 3 hours. The reaction mixture was concentrated under reduced pressure and water was added to the residue. The mixture was then acidified with concentrated hydrochloric acid. Extracting the acidic solution with ethyl acetate and then concentration of the organic layer gave the 2-(3-bromophenoxy)methyl benzoic acid (35 g) m.p. 158-159°C. pmr ($CDCL_3$) δ: 8.10 (m, 1H, H6), 6.84-7.74 (m, 7H, aromatic H), 6.16 (br s, 1H, CO_2H), 5.49 (s, 2H, $ArCH_2O$).

Analysis: Calcd. for $C_{14}H_{11}BrO_3$: C, 54.74; H, 3.61; Br, 26.02. Found: C, 54.65; H, 3.61; Br, 26.08.

c) 3-Bromo-6, 11-dihydrodibenz[b,e]oxepin-11-one

A suspension of 2-(3-bromophenoxymethyl)benzoate (35 g, 0.11 mole) in 100 mL of trifluoroacetic anhydride containing 20 drops of boron trifluoride-ether complex was refluxed for 4 hours. The mixture was poured into ice-water and then extracted with diethyl ether. Concentration of ether solution under reduced pressure and chromatography of the residue on a silica gel column (Waters Associates, Prep

500) with hexane/methylene chloride (70:30) gave the pure product (14 g). m.p. 110-112°C. pmr ($CDCl_3$) δ: 8.10 (d, J=9.1 Hz, 1H, H_1), 7.90 (dd, J=1.4, 7.6 Hz, 1H, H_{10}) 7.57 (dt, J=1.4, 7.4, 7.4 Hz, 1H H8), 7.48 (dt, J=1.4, 7.6, 7.6 Hz, 1H, H9), 7.36 (dd, J=1.3, 7.3 Hz, 1H, H_7), 7.27 (d,J=1.8 Hz, 1H, H_4), 7.24 (dd, J=1.8, 9.1 Hz, 1H, H_2), 5.18 (s, 2H, $ArCH_2O$).

Analysis: Calcd. for $C_{14}H_9BrO_2$: C, 58.16; H, 3.14; Br, 27.64. Found: C, 58.13; H, 3.19; Br, 27.72.

d) (E)/(Z)-3-(3-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)-N,N-dimethylpropylamine

Anhydrous 3-(dimethylamino)propyltriphenylphosphonium bromide hydrobromide (24.5 g, 48.0 mmole), 96 mmole of n-butyl lithium in hexane, and 3-bromo-6, 11-dihydrodibenz[b,e]oxepin-11-one (10 g, 34.6 mmole) were reacted in 580 mL dry tetrahydrofuran by the procedure of Example I, step b. This provided an (E)/(Z)-(1:3) isomeric mixture of bromoamines (6.0 g). Recrystallization of half of the mixtures (3.0 g) from ethyl acetate gave 1.45 g of Z-isomer of ≥93% stereoisomeric purity (assayed by ^{1}H-NMR) as a white solid. pmr ($CDCl_3$) δ: 7.23-7.31 (m, 4H, aromatic H), 6.92-7.05 (m, 3H, aromatic H), 5.91 (t, 1H, CH=, 7% E-isomer), 5.60 (t, 1H, CH=, 93% Z-isomer) 5.15 (very br s, 2H, $ArCH_2O$), 3.12 (m, 2H, CH_2), 2.99 (m, 2H, NCH_2), 2.78 (s, 6H, NMe_2, 93% Z-isomer), 2.71 (s, 6H, NMe_2, 3% E-isomer).

Analysis: Calcd. for $C_{19}H_{20}BrNO \cdot 1.0$ HCl: C, 57.81; H, 5.36; N, 3.55. Found: C, 57.62; H, 5.33; N, 3.54.

e) (E)/(Z)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-3-carboxylic acid (Compounds 3/4)

An isomeric mixture E/Z (1:3) of 3-(3-bromo-6, 11-dihydrodibenz[b,e]-11-ylidene)-N,N-dimethylpropylamine (3.0 g, 8.5 mmole) in 150 mL dry tetrahydrofuran at -70°C was reacted with 9.4 mmole n-butyl lithium in hexane followed by gaseous carbon dioxide by the procedure of Example 1, step c, to provide the corresponding carboxylic acids as an E/Z (1:3) stereoisomeric mixture. The mixture was chromatographed on a reverse phase PRP-1 semi-preparative column with water/acetonitrile (87:13) to provide 0.08 g of E-isomer (lyophilized powder) and 0.50 g of Z-isomer (lyophilized powder). pmr (E-isomer) ($CDCl_3$/TFA) δ: 7.85 (dd, J=8.0, 1.7 Hz, 1H, H_2) 7.50 (d, J=1.7 Hz, 1H, H_4), 7.32-7.43 (m, 4H, aromatic H), 7.16 (m, 1H, H_1), 5.99 (t, 1H, CH=), 5.50 (br s, 1H, ArCHO), 4.85 (br s, 1H, ArCHO), 3.25 (q, 2H, CH_2), 2,86 (s, 3H, NMe), 2.85 (s, 3H, NMe), 2.70 (q, 2H, NCH_2). pmr (Z-isomer) ($CDCl_3$/TFA) δ: 7.26 (m, 2H, H_2 and H_4), 7.24-7.36 (m, 4H, aromatic H), 7.16 (m, 1H, H_1), 5.71 (t, 1H, CH=), 5.20 (very br s, 2H, $ArCH_2O$), 3.32 (q, 2H, CH_2), 2.91 (s, 3H, NMe), 2.90 (s, 3H, NMe), 2.89 (m, 2H, NCH_2).

Analysis: Calcd. for $C_{20}H_{21}NO_3 \cdot 0.5$ HCl$\cdot 0.2$ H_2O: C, 69.58; H, 6.39; N, 4.06. Found (E-isomer): C, 69.64; H, 6.25; N, 4.03. Calcd. for $C_{20}H_{21}NO_3 \cdot 0.25$ H_2O: C, 73.26; H, 6.61; N, 4.27. Found (Z-isomer): C, 73.20; H, 6.60; N, 4.20.

Example 3: (E/(Z)-(11-(3-Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-8-carboxylic acid

a) 8-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-one

Phenol (8 g, 85 mmole) and potassium carbonate (11.7 g, 85 mmole) in 150 mL of N,N-dimethylformamide was reacted with methyl 4-bromo-α-bromo-2-toluate (20 g, 65 mmole) by the procedure of Example 2, step a and followed with alkaline hydrolysis by the procedure of Example 2, step b to give the crude 4-bromo-2-phenoxybenzoic acid (13 g) which was used without further purification.

The crude 4-bromo-(2-phenoxymethyl)benzoic acid (13 g, 42 mmole) was cyclized in 50 mL of trifluroacetic anhydride containing 1 mL of boron trifluorideether complex by the procedure of Example 2, step c. The solid was collected by filtration and washed with water to give 11.9 g of the tricyclic ketone, m.p. 125-126°C. pmr ($CDCl_3$) δ: 8.17-8.30 (m, 1H, H1), 6.99-7.86 (m, 6H, aromatic H), 5.14 (s, 2H, $ArCH_2O$).

Analysis: Calcd. for $C_{14}H_9BrO_2$: C, 58.16; H, 3.14; Br, 27.64. Found: C, 58.15; H, 3.17; Br, 27.73.

b) (E)/(Z)-3-(8-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-ylidene)-N,N-dimethylpropylamine

Anhydrous 3-(dimethylamino)propyltriphenylphosphonium bromide hydrobromide (24.5 g, 48 mmole), 96 mmole of n-butyl lithium in hexane, and 8-bromo-6, 11-dihydrodibenz[b,e]oxepin-11-one (10 g, 34.6 mmole) were reacted in 580 mL dry tetrahydrofuran by the procedure of Example I, step b. This provided an E/Z (1:3.5) isomeric mixture of bromoamines. Recrystallization of the mixture from diethyl ether gave 0.17 g of Z-isomer and 1.8 g of an E/Z (1:4) (assayed by HPLC on C18) isomeric mixture which was used in the next step without further purification. pmr (Z-isomer) ($CDCl_3$) δ: 7.38-7.44 (m, 2H, H_7 and H_9); 7.13-7.18 (m, 3H, aromatic H); 6.84-6.93 (m, 2H, H_2 and H_4); 5.70 (t, 1H, CH=); 5.15 (br s, 2H, $ArCH_2O$); 2.55 (q, 2H, CH_2); 2.43 (t, 2H, NCH_2); 2.22 (s, 6H, NMe_2).

Analysis: Calcd. for $C_{19}H_{20}BrNO$: C, 63.70; H, 5.63; N, 3.91. Found (Z-isomer): C, 63.85; H, 5.65; N, 3.92.

c) (E)/(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-8-carboxylic acid (Compounds 5/6).

An isomeric mixture E/Z (1:4) of 3-(8-bromo-6, 11-dihydrodibenz[b,e]-11-ylidene)-N,N-dimethylpropylamine (1.8 g, 5.0 mmole) in 100 mL dry tetrahydrofuran at -70°C was reacted with 5.5 mmole n-butyl lithium in hexane followed by gaseous carbon dioxide by the procedure of Example I, step c, to provide the corresponding carboxylic acid as an E/Z (1:5) stereoisomeric mixture. The mixture was chromatographed on a reverse phase PRP-1 semi-preparative column with water/acetonitrile (85:15) to provide 0.05 of E-isomers (lyophilized powder) and 0.28 g of Z-isomer (lyophilized powder). pmr (E-isomer) ($CDCl_3$) δ: 7.94 (br s, 1H, H_9), 7.70 (br s, 1H, CO_2H), 7.20-7.30 (m, 4H aromatic H), 7.14 (m, 1H, H_3), 6.87 (m, 1H, H_2), 6.76 (m, 1H, H_4), 5.88 (t, 1H, CH=), 5.54 (br s, 1H, ArCHO), 4.85 (br s, 1H, ArCHO), 3.00 (m, 2H. CH_2), 2.78 (m, 2H, NCH_2), 2.60 (s, 6H, NMe_2) pmr (Z-isomer) ($CDCl_3$) δ: 7.55 (d, J=7.0 Hz, 1H, H_9), 7.30 (br s, 1H, CO_2H), 7.00-7.25 (m, 4H, aromatic H), 6.84 (m, 2H, H_2 and H_4), 5.95 (t, 1H, CH=), 5.70 (br s, 1H, ArCHO), 4.80 (br s, H, ArCHO), 3.35 (br s, 1H CHC=), 2.50-3.00 (m, 3H, CHC= and NCH_2), 2.46 (s, 6H, NMe_2)

Analysis: Calcd. for $C_{20}H_{21}NO_3 \cdot HCl \cdot 0.4\ H_2O$: C, 65.44; H, 6.26; N, 3.82. Found (E-isomer): C, 65.55; H, 6.51; N, 3.91. Calcd. for $C_{20}H_{21}NO_3 \cdot 2.2\ H_2O$: C, 66.17; H, 7.05; N, 3.86. Found (Z-isomer): C, 66.25; H, 6.93; N, 3.83.

Example 4: (E)/(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]-oxepin-9-carboxylic acid

a) 9-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-one

9-Bromo-6, 11-dihydrodibenz[b,e]oxepin-11-one was prepared as described in US Patent 4,282,365, m.p. 104-106°C (Lit. m.p. 107.5-108.5°C). pmr ($CDCl_3$) δ: 8.02-8.27 (m, 2H, H_1 and H_{10}), 6.98-7.73 (m, 5H, aromatic), 5.14 (s, 2H, CH_2O).

Analysis: Calcd. for $C_{14}H_9BrO_2$: C, 58.16; H, 3.14; Br, 27.64. Found: C, 58.24; H, 3.18; Br, 27.51.

b) (E)/(Z)-3-(9-Bromo-6, 11-dihydrodibenz[b,e]oxepin-11-ylidene)-N,N-dimethylpropylamine.

Anhydrous 3-(dimethylamino)propyltriphenylphosphonium bromide hydrobromide (31 g., 60.9 mmole), 122 mmole of n-butyl lithium in hexane, and 9-bromo-6, 11-dihydrodibenz[b,e]oxepin-11-one (12.7 g., 43.8 mmole) were reacted in 750 mL dry tetrahydrofuran by the procedure of Example I, Step b. This provided an E/Z (1:6) isomeric mixture of bromoamines. Recrystallization of the mixture from ethyl acetate/methanol gave 1.2 g. of pure Z-isomer as its hydrochloride salt, melting range 91-100°C and 2.16 g. of an E/Z (1:4) isomeric mixture which was used in the next step without further purification. pmr (Z-isomer) ($CDCl_3$) δ: 6.94-7.46 (m, 7H, aromatic), 5.64 (t, J=8.0 Hz, 1H, CH=), 5.15 (br s, 2H, CH_2O), 3.07 (m, 4H, $NCH_2\ CH_2$), 2.75 (s, 6H, NMe_2).

Analysis: Calcd. for $C_{19}H_{20}BrNO \cdot HCl$: C, 57.80; H, 5.36; N, 3.54. Found (Z-isomer): C, 57.56; H, 5.41; N, 3.45.

c) (E)-11-3-(Dimethylamino)propylidene-6, 11-dihydrodibenz[b,e]oxepin-9-carboxylic acid (Compound 7).

An isomeric mixture E/Z (1:4) of 3-(9-bromo-6, 11-dihydrodibenz[b,e]-11-ylidene)-N,N-dimethylpropylamine (2.0 g., 5.6 mmole) in 100 mL dry tetrahydrofuran at -70°C was reacted with 6.2 mmole n-butyl lithium in hexane followed by gaseous carbon dioxide by the procedure of Example I, Step c, to provide the corresponding carboxylic acids as anE/Z (1:4) stereoisomeric mixture. The mixture was chromatographed on a reverse phase PRP-1 semi-preparative column with water/acetonitrile (85:15) to provide 0.06 g of E-isomer of ≥95% stereoisomeric purity (assayed by HPLC on C_{18}) as pale yellow glass. pmr (DMSO-d_6) δ: 7.83 (d, J≤ 1 Hz, 1H, H_{10}), 7.79 (dd, J=7.2, 1.5 Hz, 1H, H_8), 6.69-7.39 (m, 5H, aromatic), 5.85 (t, J=6.4 Hz, 1H, CH=), 5.22 (s, 2H, CH_2O), 2.81 (m, 4H, NCH_2CH_2), 2.61 (s, 6H, NMe_2).

Analysis: Calcd. for $C_{20}H_{21}NO_3 \cdot 2.8\ H_2O$: C, 64.26; H, 7.17; N, 3.75. Found: C, 64.23; H, 6.84; N, 3.76.

d) (Z)-11-3-(Dimethylamino)propylidene-6,11-dihydrodibenz[b,e]oxepin-9-carboxylic acid(Compound 8)

Pure (Z)-3-(9-bromo-6, 11-dihydrodibenz[b,e]oxepin-11-ylidene)-N,N-dimethylpropylamine (0.78 g., 2.2 mmole), in cold (-70°C) dry tetrahydrofuran (50 mL), was treated with 2.4 mmole n-butyl lithium in hexane followed by gaseous carbon dioxide by the procedure of Example I, Step c. This provided the desired carboxylic acid which was recrystallized from water to yield 0.15 g. pure Z-isomer, m.p. >205°C (decomp.) with melting at 210°C. pmr ($CDCl_3/D_2O$) δ: 7.84 (d, J=1.8 Hz, 1H, H_{10}), 7.81 (dd, J=6.4, 1.8 Hz, 1H, H_8), 6.94-7.35 (m, 5H, aromatic), 5.78 (t, J=6.9 Hz, 1H, CH=), 5.25 (s, 2H, CH_2O), 3.20 (m, 2H, NCH_2), 2.80 (s, 6H, NMe_2), 2.50-2.90 (m, 2H, CH_2).

Analysis: Calcd. for $C_{20}H_{21}NO_3 \cdot 0.33\ H_2O$: C, 73.06; H, 6.62; N, 4.26. Found: C, 72.92; H, 6.59; N, 4.13.

Example 5: (E)/(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-(E)-acrylic acid

a) Ethyl(E)-6,11-dihydro-11-oxodibenz[b,e]oxepin-acrylate

A mixture of palladium acetate (0.4 g, 1.73 mmole), triphenylphosphine (0.9 g, 3.46 mmole), 2-bromo-6, 11-dihydro-11-oxodibenz[b,e]oxepin (10 g, 34.6 mmole), ethyl acrylate (13 g, 130 mmole) and tri-n-butylamine (7.7 g, 57 mmole) was heated at 130-140°C under a nitrogen atmosphere for six hours. The reaction mixture was partitioned between diethyl ether (100 mL) and 0.1N hydrochloric acid (50 mL). Evaporation of the ether under reduced pressure gave a yellow solid residue. The crude material was chromatographed on a silica gel column (Waters Associates - Prep 500) with hexanes/ethyl acetate (8:2) to give 6.12 g of (E)-acrylate product. Recrystallization from ethyl acetate/hexanes gave an analytical sample, m.p. 113-114°C. pmr ($CDCl_3$) δ: 8.39 (d, J=2.4 Hz, 1H, H_1), 7.88 (dd, J=1.5, 7.5 H_z, 1H, H_{10}), 7.70 (d, J=16.4 Hz, 1H, ArCH=), 7.66 (dd, J=2.2, 8.6 H_2, 1H, H_3), 7.46-7.60 (m, 2H, H_8 and H_9), 7.38 (dd, J=1.0, 7.3 Hz, 1H, H_7), 7.07 (d, J=8.6 H_2, 1H, H_4), 6.42 (d, J=16.0 Hz, 1H, $=CHCO_2$), 5.23 (s, 2H, $ArCH_2O$), 4.26 (q, 2H, CH_2), 1.34 (t, 3H, CH_3).

Analysis: Calcd. for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 73.90; H, 5.28.

b) (E)/(Z)-11-(3-(Dimethylamino)propylidene)-6, 11-dihydrodibenz[b,e]oxepin-2(E)-acrylic acid (Compounds 9/10)

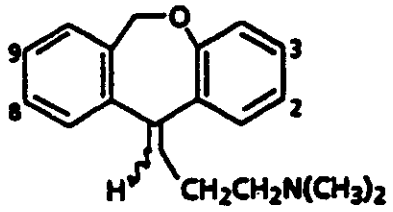
Anhydrous 3-(dimethylamino)propyltriphenylphosphonium bromide hydrobromide (0.8 g, 1.57 mmole) was suspended in 20 mL of dry tetrahydrofuran and 1.8 mL of a solution of n-butyl lithium in hexane (1.6M) was added dropwise at 0°C under a nitrogen atmosphere during a 10 minute period. After an additional 10 minutes, ethyl (E)-6, 11-dihydro-11-oxodibenz[b,e]oxepin-2-acrylate (0.34 g, 1.1 mmole) in 5 mL dry tetrahydrofuran was added slowly to the deep red solution and the reaction mixture was then refluxed for 18 hours. The reaction was worked up as described in Example I, step d. The crude material was dissolved in 1N sodium hydroxide (20 mL) and 20 mL of absolute ethanol, and then stirred at room temperature for 18 hours. After neutralization with 1N hydrochloric acid (20 mL) the solution was evaporated to dryness and the residue was chromatographed on a PRP-1 column with water/acetonitrile (78:22) to give 0.015 g of Z-isomer (lyophilized solid) and 0.009 g of E-isomer (lyophilized powder). pmr (Z-isomer) (CD_3OD) δ: 7.29-7.38 (m, 7H, aromatic H and ArCH=), 6.82 (d, J=8.5 Hz, 1H, H_4) 6.37 (d, J=16.0 H_z, 1H, $=CHCO_2$), 5.70 (t,1H CH=), 5.20 (very br s, 2H, $ArCH_2O$), 2.87 (m, 2H, CH_2), 2.77 (m, 2H, NCH_2), 2.50 (s, 6H, NMe_2). pmr (E-isomer) (CD_3OD) δ: 7.28-7.49 (m, 7H, aromatic H and ArCH=), 6.72 (d, J=8.5 H_z, 1H, H_4), 6.35 (d, J=16.0 H_z, 1H, = $CHCO_2$), 6.10 (t, 1H, CH=), 5.58 (very br s, 2H, $ArCH_2O$), 2.78 (m, 2H, CH_2), 2.50 (m, 2H, NCH_2), 2.40 (s, 6H, NMe_2).

Example 6: Antihistamine Activity

A. In vitro antihistamine activity: The longitudinal muscle was isolated from the intact ileum of guinea-pigs (Hartley, male 250–400 g) and placed in an organ bath under 300 mg tension. After one hour of equilibration, cumulative concentration-response curves (Van Rossum, J.M., Arch. Int. Pharmacodyn. Ther. 143, 299–330, 1963) to histamine were obtained. Following washing, the tissues were incubated for one hour with the test compound and then a second histamine concentration response curve was run. Shifts to the right of the agonist concentration-response curve produced by the antagonists were used to construct Schild plots (Arunlakshana, O. and Schild, H.O., Br. J. Pharmacol. 14, 48–58, 1959). Regression of Log (dr-1) on Log [B], where dr is an equiactive response in the presence and absence of antagonist and [B] is the molar concentration of antagonist, allowed an estimate of pA_2, i.e. the negative log of the concentration of antagonist which shifts the control histamine concentration response curve 2X to the right.

Table I

Antihistaminic Activity in *In Vitro* Assays



Compound No.	Compound	pA 2
-	Doxepin[a]	9.7
1	Z-2-CO_2H	8.3
2	E-2-CO_2H	8.3
6	Z-8-CO_2H	6.7
7	E-9-CO_2H	9.2
8	Z-9-CO_2H	7.8

[a]The Doxepin sample tested here had a Z:E ratio of 4:1

B. In vivo Antihistaminic Activity: Guinea pigs (Hartley, male, 300-350 g) were fasted for 20 hours and then dosed p.o. or i.p. with the test compound. One hour after dosing, on an individual basis, the guinea pigs were placed in a clear plastic chamber which was saturated and continually gassed with 0.25% histamine from an aerosol nebulizer. The guinea pigs were monitored for signs of histamine anaphylaxis (e.g. cough, sneeze, strong abdominal movements, cyanoses or loss of righting). Under the test conditions, control animals collapsed on average within 33 seconds. ED_{50}'s for protection against histamine were calculated by probit analysis. In this test the ED_{50} indicates that at that particular dose 50% of the animals were completely protected against histamine challenge at the time of testing (1 hour post-dosing). Complete protection was defined as no histamine symptoms for six minutes in the aerosol chamber (approximately 10X the collapse time of the control animals).

Table II

Results of *In Vivo* Antihistamine Assays

Compound[a]	ED_{50}[b] (mg/kg, p.o.) 4 hr post dosing
Doxepin (E:Z=4:1)	>>9
Z-2-CO_2H (1)	0.15

[a]The purity of these compounds was in excess of 96%

[b]The number of animals was at least 40

In addition to these results, it was found that Compound 1 could provide very long durations of antihistamic activity.

Example G: Anaphylactoid Activity

Non-fasted, Wister rats (180-300g) were dosed with the test compound (i.p. or p.o.) 2 hours before compound 48/80 challenge. One hour prior to challenge, 5 mg/kg i.p. of propranolol was administered. The anaphylactoid inducing agent, compound 48/80 which is well known in the art of pharmacology, was given intravenously at 2 mg/kg and the animals were monitored for symptoms of respiratory distress.

Data were analyzed by Probit determinations. The response was quantitated by determining the dose of test compound which protected 50% of the animals from death at a given time point.

The above experimental design does not give positive results for selective antihistamines. Also rats do not respond to histamine (i.v.) with symptoms of anaphylaxis. Agents which block the effects of compound 48/80 are commonly classified as inhibitors of anaphylactic mediators or inhibitors of the release of anaphylic mediators.

Table III

Inhibition of Compound 48/80 Induced Anaphylactoid Reaction

Compound	ED_{50}[a,b]
Triprolidine	>30
Doxepin	0.15
Z-2-CO_2H (1)	1.1

[a]Dose of compound (p.o.) providing 50% protection against death induced by compound 48/80.

[b]At least 50 animals were used in each assay.

Compound 1 (example 1) had an approximately LD_{50} in rats of 210 mg/kg (i.p.) and greater than 500 mg/kg (p.o.).

Example 7: Formulations

The active compound is (Z)-11-(3-(dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid, i.e., Compound 1.

(A)-Injection

Ingredient	Amount per ampoule
Active Compound	1.0 mg
Water for Injections, q.s.	1.0 mL

The finely ground active compound is dissolved in the water for injections. The solution is filtered and sterilized autoclaving.

(B)-Suppository

Ingredient	Amount per suppository
Active Compound	1.0 mg
Cocoa Butter	2.0 g
or Wecobee™ Base q.s.	

Wecobee is a trademark and is a hydrogenated fatty carboxylic acid.
The finely ground active compound is mixed with the melted suppository base (either Cocoa Butter or Wecobee™ base), poured into moulds and allowed to cool to afford the desired suppositories.

(C)-Syrup

Ingredient	Amount per mL
Active Compound	1.0 mg
Ethanol	0.3 mg
Sucrose	2.0 mg
Methylparaben	0.5 mg
Sodium Benzoate	0.5 mg
Cherry Flavour	q.s.
Colouring	q.s.
Water	Q.S. to 5.0 mL

Ethanol, sucrose, sodium benzoate, methylparaben, and flavouring are combined in 70% of the total batch quantity of water. Colouring and the active compound are dissolved in the remaining water, then the two solutions are mixed and clarified by filtration.

(D)-Tablet

Ingredient	Amount per Tablet
Active Compound	1.0 mg
Lactose	110.0 mg
Corn Starch, Pregelatinized	2.5 mg
Potato Starch	12.0 mg
Magnesium stearate	0.5 mg

The active compound is finely ground and intimately mixed with the powdered excipients lactose, corn starch, potato starch and magnesium stearate. The formulation is then compressed to afford a tablet weighing 126 mg.

(E)-Capsule

Ingredient	Amount per Capsule
Active Compound	1.0 mg
Lactose	440.0 mg
Magnesium Stearate	5.0 mg

The finely ground active compound was mixed with the powdered excipients lactose and magnesium stearate and packed into gelatin capsules.

(F)-Tablet

Ingredient	Amount per Tablet
Active Compound	1.0 mg
Pseudoephedrine HCl	60.0 mg
Lactose	62.5 mg
Potato Starch	14.0 mg
Magnesium Stearate	1.0 mg
Gelatin	2.8 mg

A tablet is prepared from the above formulation by the method previously described in example 7 (D)

(G)-Syrup

Ingredient		Amount per 5 mL
Active Compound		1.0 mg
Pseudoephedrine HCl		30.0 mg
Codeine Phosphate		10.0 mg
Guaifenesin		100 mg
Methylparaben		0.5 mg
Sodium benzoate		0.5 mg
Flavour		q.s.
Glycerol		500 mg
Sucrose		2000 mg
Purified Water	q.s. to	5.0 mL

A syrup containing other active ingredients in addition to a compound of formula (I) is prepared from the above ingredients by an analogous method to that described for Example 7 (C) above.

(H)-Nasal Spray

Ingredient		Amount per 100.0 mL
Active Compound		1 g
Sodium Chloride		0.8 g
Preservative		0.5 g
Purified Water	q.s.	100.0 mL

The preservative is dissolved in warm purified water and after cooling to 25-30°C the sodium chloride and the compound of formula (I) are added. The pH is then adjusted to 5.5-6.5 and purified water is added to bring the final volume to 100.0 mL.

(I)-Ophthalmic Solution

Ingredient		Amount per 100.0 mL
Active Compound		0.1 g
Sodium Chloride		0.8 g
Preservative		0.5 g
Water for Injection	q.s.	100.0 mL

This formulation is prepared in a similar way to the nasal spray.

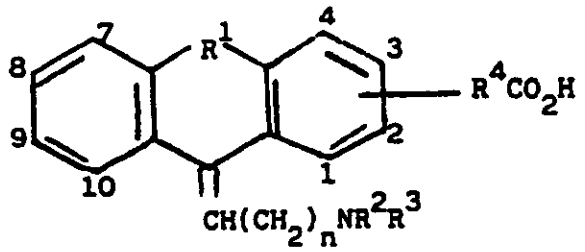
(J)-Topical Cream

Ingredient	Amount per 100.0 g
Active Compound	0.1 g
Emulsifying Wax, N.F.	15.0 g
Mineral Oil	5.0 g
White Petrolatum	5.0 g
Preservative	0.25 g
Purified Water q.s.	100.0 g

The preservative is dissolved in approximately 50 g of warm purified water and after cooling to about 25°-30°C the compound of formula (I) is added. In a separate container the emulsifying wax, mineral oil and white petrolatum are mixed well and heated to approximately 70°-80°C. The aqueous solution containing the compound of formula (I) is added to the warm mixture of emulsifying wax, mineral oil and petrolatum with vigorous mixing while cooling to 25°C. Additional purified water is added with mixing to bring the total weight of the cream to 100.0 g.

Claims for designated States: BE, CH, DE, FR, GB, IT, LI, NL, SE

1. A compound of formula (I)



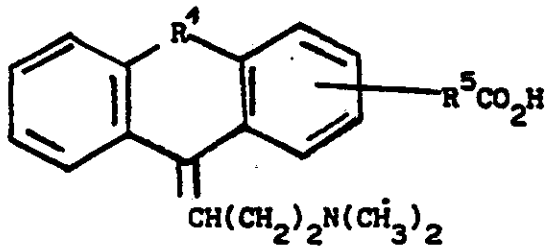
(I)

or a salt, ester or amide thereof; wherein R^1 is CH_2–O– or –OCH_2–; R^2 and R^3 are the same or different and are each hydrogen, C_{1-4} alkyl or taken together with the nitrogen comprise a nitrogen-containing heterocylic ring having four to six ring members; R^4 is a single bond or a C_{1-7} bivalent aliphatic hydrocarbon group and may be joined to the aromatic ring system at the 2, 3, 8 or 9 positions; n is 0 to 3.

2. A compound of formula (I) as defined in claim 1 wherein R^1 represents –CH_2O– or OCH_2–; R^2 and R^3 are the same or different and are each C_{1-4} alkyl, preferably methyl; R^4 is a single bond or a C_{1-7} bivalent aliphatic hydrocarbon group and may be joined to the aromatic ring at the 2, 3, 8 or 9 position, preferably at the 2-position and n is 0 to 3, and salts, amides and esters thereof.

3. A compound of formula (I) as defined in claim 1 wherein R^1 represents –CH_2O–; R^2 and R^3 are the same or different and are each C_{1-4} alkyl, preferably methyl; R^4 is a single bond or a C_{1-7} bivalent aliphatic hydrocarbon group and may be joined to the aromatic ring at the 2, 3, 8 or 9 position, preferably at the 2-position and n is 0 to 3, and salts, esters and amides thereof.

4. A compound of formula (II)



(II)

or a salt, ester or amide thereof; wherein R^1 is $-CH_2-O-$ or $-OCH_2$; and R^5 is a single bond or $-CH=CH$ joined to the aromatic ring system at the 2, 3, 8 or 9 positions.

5. A compound selected from:
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-2-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-2-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-3-carboxylic acid
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-3-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-8-carboxylic acid
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-8-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-9-carboxylic acid
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-9-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-2-acrylic acid
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b.e.]oxepin-2-acrylic acid.

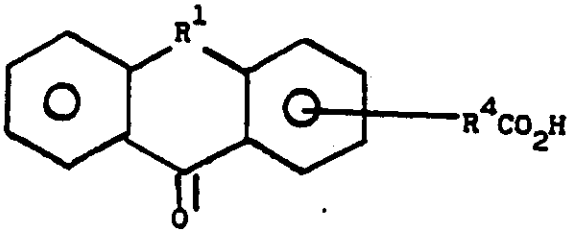
6. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 in admixture with a pharmaceutically acceptable carrier.

7. A compound of the formula (I) as defined in claim 1 for use in medicine.

8. A compound of the formula (I) as defined in claim 1 for the manufacture of a medicament for the control of allergy.

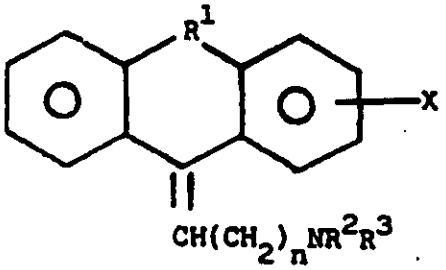
9. A compound of the formula (I) as defined in claim 1 for the manufacture of a medicament for relieving the detrimental effects of histamine, for the control or relief of the effects of an asthmatic condition, or for controlling bronchoconstriction or bronchospasm characteristic of allergic asthma.

10. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises
a) the reaction of a compound of the formula (III):



(III)

wherein R^1 and R^4 are as hereinbefore defined in Claim 1 with an appropriate Wittig reagent or with an appropriate Grignard reagent followed by dehydration or
b) the hydrolysis of a compound of the formula (V):



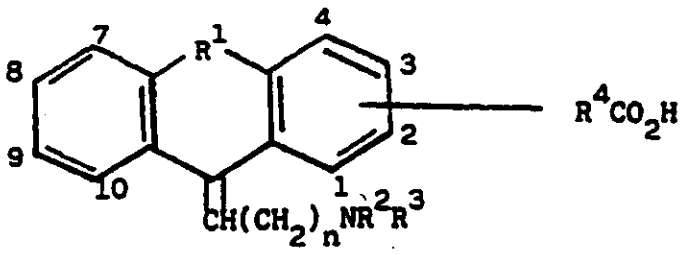
(V)

wherein X is R^4CN; and R^1, R^2, R^3, R^4 and n are as defined in Claim 1
c) when it is required to prepare a compound of the formula (I) wherein R^4 is a single bond, a carboxylation reaction on a compound of the formula (V) above wherein R^1 to R^3 and n are as hereinbefore defined in Claim 1 and X is a hydrogen or halogen atom, or
d) when it is required to prepare a compound of the formula (I) wherein R^4 is other than a single bond the reaction of a compound of the formula (V) above wherein X is a halogen atom and R^1 to R^3 and n

are as hereinbefore defined in Claim 1 with a compound: $CH_2=CHR^6COR^7$ in which R^6 is a C_{1-5} bivalent aliphatic hydrocarbon and R^7 is a protecting group and thereafter removing the protecting group when required, and
e) thereafter converting one compound of the formula (I) to another compound of the formula (I) if desired.

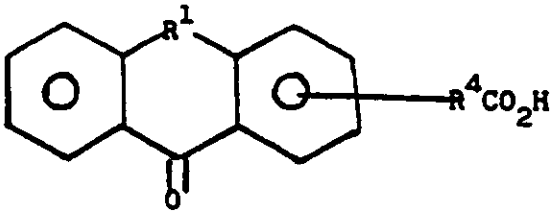
Claims for designated State: AT

1. A process for the preparation of a compound of formula (I)



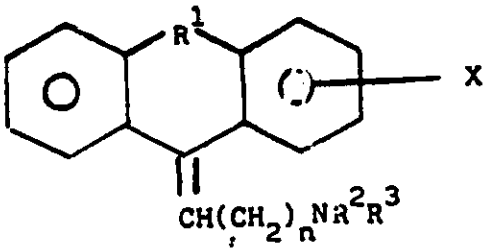
(I)

or a salt, ester or amide thereof; wherein R^1 is CH_2–O– or –OCH_2–; R^2 and R^3 are the same or different and are each hydrogen, C_{1-4} alkyl or taken together with the nitrogen comprise a nitrogen-containing heterocyclic ring having four to six ring members; R^4 is a single bond or a C_{1-7} bivalent aliphatic hydrocarbon group and may be joined to the aromatic ring system at the 2, 3, 8 or 9 positions; n is 0 to 3 which process comprises;
a) the reaction of a compound of the formula (III):



(III)

wherein R^1 and R^4 are as hereinbefore with an appropriate Wittig reagent or with an appropriate Grignard reagent followed by dehydration or
b) the hydrolysis of a compound of the formula (V):



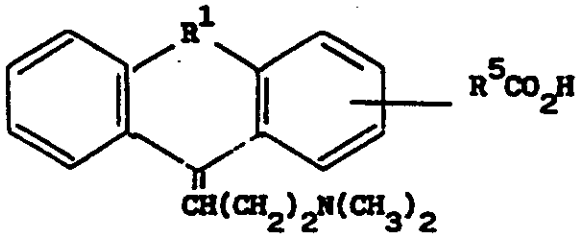
(V)

wherein X is R^4CN; and R^1, R^2, R^3, R^4 and n are as defined in Claim 1,
c) when it is required to prepare a compound of the formula (I) wherein R^4 is a single bond the carboxylation of a compound of the formula (V) above wherein R^1 to R^3 and n are as hereinbefore defined and X is a hydrogen or halogen atom, or
d) when it is required to prepare a compound of the formula (I) wherein R^4 is other than a single bond the reaction of a compound of the formula (V) wherein X is a halogen atom and R^1 to R^3 and n are as hereinbefore defined with a compound: $CH_2=CHR^6COR^7$ in which R^6 is a C_{1-5} bivalent aliphatic hydrocarbon and R^7 is a protecting group and thereafter removing the protecting group when required, and
e) thereafter converting one compound of the formula (I) to another compound of the formula (I) if desired.

2. A process according to Claim 1 for the preparation of a compound of formula (I) as defined in Claim 1 wherein R^1 represents –CH_2O– or –OCH_2–; R^2 and R^3 are the same or different and are each C_{1-4} alkyl, preferably methyl; R^4 is a single bond or a C_{1-7} bivalent aliphatic hydrocarbon group and may be joined to the aromatic ring at the 2, 3, 8 or 9 position, preferably at the 2-position and n is 0 to 3, and salts, amides and esters thereof.

3. A process according to Claim 1 for the preparation of a compound of formula (I) as defined in Claim 1 wherein R^1 represents $-CH_2O-$; R^2 and R^3 are the same or different and are each C_{1-4} alkyl, preferably methyl; R^4 is a single bond or a C_{1-7} bivalent aliphatic hydrocarbon group and may be joined to the aromatic ring at the 2, 3, 8 or 9 position, preferably at the 2-position and n is 0 to 3, and salts, esters and amides thereof.

4. A process according to claim 1C for the preparation of a compound of formula (II):



wherein R^1 is as defined above and R^5 is a single bond.

5. A process according to claim 1 for the preparation of a compound selected from:
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-3-carboxylic acid
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-3-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-8-carboxylic acid
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-8-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-9-carboxylic acid
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-9-carboxylic acid
(E)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acrylic acid
(Z)-11-(3-(Dimethylamino)propylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acrylic acid.

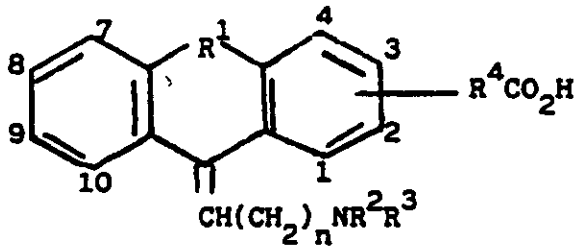
6. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 in admixture with a pharmaceutically acceptable carrier.

7. A process for the preparation of a pharmaceutical composition which comprises bringing a compound of the formula (I) as defined in claim 1 into association with a pharmaceutically acceptable carrier.

8. A compound of the formula (I) as defined in claim 1 for use in a method for the control of allergy.

Patentansprüche für die Vertragsstaaten: BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Verbindung der Formel (I)



(I)

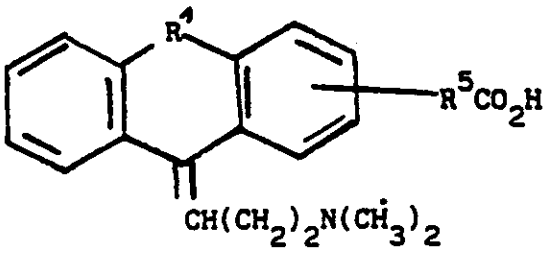
oder Salz, Ester oder Amid dieser Verbindung, worin
R^1 CH_2-O- oder $-O-CH_2-$ bedeutet,
R^2 und R^3 gleich oder verschieden sind und jeweils Wasserstoff oder eine C_{1-4}-Alkylgruppe bedeuten oder zusammengenommen mit dem Stickstoffatom einen Stickstoff enthaltenden heterocyclischen Ring mit 4 bis 6 Ringgliedern umfassen,
R^4 eine Einfachbindung oder eine zweiwertige, aliphatische C_{1-7}-Kohlenwasserstoff-Gruppe ist und mit dem aromatischen Ringsystem an den Positionen 2, 3, 8 oder 9 verbunden sein kann, und
n 0 bis 3 ist.

2. Verbindung der Formel (I) wie in Anspruch 1 definiert, worin
R^1 $-CH_2O-$ oder $-OCH_2-$ bedeutet,
R^2 und R^3 gleich oder verschieden sind und jeweils eine C_{1-4}-Alkylgruppe, vorzugsweise Methyl, bedeuten,
R^4 eine Einfachbindung oder eine zweiwertige, aliphatische C_{1-7}-Kohlenwasserstoff-Gruppe ist und mit dem aromatischen Ring an den Positionen 2, 3, 8 oder 9, vorzugsweise an der Position 2, verbunden sein kann, und

n 0 bis 3 ist,
sowie deren Salze, Amide und Ester.

3. Verbindung der Formel (I) wie in Anspruch 1 definiert, worin
R^1 $-CH_2O-$ bedeutet,
R^2 und R^3 gleich oder verschieden sind und jeweils für einen C_{1-4}-Alkylrest, vorzugsweise Methyl, stehen,
R^4 eine Einfachbindung oder eine zweiwertige, aliphatische C_{1-7}-Kohlenwasserstoff-Gruppe ist und mit dem aromatischen Ring an den Positionen 2, 3, 8 oder 9, vorzugsweise an der Position 2, verbunden sein kann, und
n 0 bis 3 ist,
und deren Salze, Ester und Amide.

4. Verbindung der Formel (II)



(II)

oder Salz, Ester oder Amid, worin
R^1 $-CH_2-O-$ oder $-O-CH_2$ bedeutet, und
R^5 eine Einfachbindung oder die Gruppe $-CH=CH$ bedeutet, die an das aromatische Ringsystem an den Positionen 2, 3, 8 oder 9 gebunden ist.

5. Verbindung, ausgewählt unter folgenden Verbindungen:
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-2-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-2-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-3-carbonsäure
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-3-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-8-carbonsäure
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-8-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-9-carbonsäure
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-9-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-2-acrylsäure
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-2-acrylsäure.

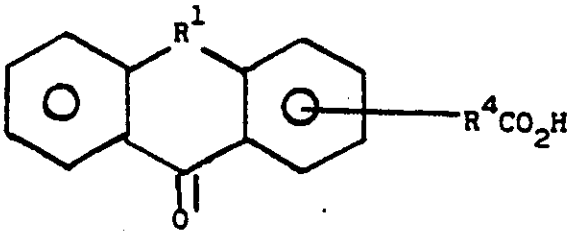
6. Pharmazeutische Zusammensetzung, umfassend eine Verbindung der Formel (I) wie in Anspruch 1 definiert in Abmischung mit einem pharmazeutisch annehmbaren Träger.

7. Verbindung der Formel (I) wie in Anspruch 1 definiert zur Verwendung in der Medizin.

8. Verbindung der Formel (I) wie in Anspruch 1 definiert zur Herstellung eines Arzneimittels für die Kontrolle von Allergie.

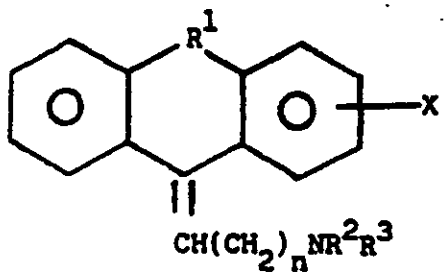
9. Verbindung der Formel (I) wie in Anspruch 1 definiert zur Herstellung eines Arzneimittels zur Verminderung der nachteiligen Wirkungen von Histamin, zur Kontrolle oder Linderung der Wirkungen eines asthmatischen Zustandes oder zur Kontrolle von Bronchokonstriktionen oder Bronchospasmen, wie sie für allergisches Asthma charakteristisch sind.

10. Verfahren zur Herstellung einer Verbindung der Formel (I) wie in Anspruch 1 definiert, wobei das Verfahren umfaßt:
(a) die Reaktion einer Verbindung der Formel (III)



(III)

worin R^1 und R^4 die in Anspruch 1 definierte Bedeutung haben, mit einem geeigneten Wittig-Reagenz oder mit einem geeigneten Grignard-Reagenz und nachfolgende Dehydratation, oder
(b) die Hydrolyse einer Verbindung der Formel (V)

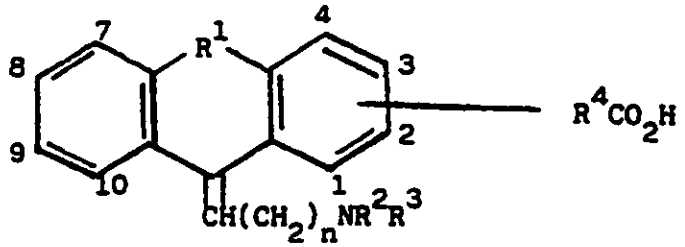


(V)

worin X R^4CN bedeutet und R^1, R^2, R^3, R^4 und n die in Anspruch 1 definierte Bedeutung haben,
(c) wenn es erforderlich ist, eine Verbindung der Formel (I) herzustellen, worin R^4 eine Einfachbindung ist, eine Carboxylierungsreaktion an einer Verbindung der Formel (V) wie oben angegeben, worin R^1 bis R^3 und n die in Patentanspruch 1 definierte Bedeutung haben und X ein Wasserstoff- oder ein Halogenatom ist, oder
(d) wenn es erforderlich ist, eine Verbindung der Formel (I) herzustellen, worin R^4 eine andere Bedeutung als die einer Einfachbindung hat, die Reaktion einer Verbindung der Formel (V) wie oben angegeben, worin X ein Halogenatom ist und R^1 bis R^3 und n die in Anspruch 1 definierte Bedeutung haben, mit einer Verbindung $CH_2=CHR^6COR^7$, worin R^6 für einen zweiwertigen aliphatischen C_{1-5}-Kohlenwasserstoff-Rest und R^7 für eine Schutzgruppe steht, und danach Entfernung der Schutzgruppe, wenn erforderlich, und
(e) danach Umwandeln einer Verbindung der Formel (I) in eine andere Verbindung der Formel (I), sofern gewünscht.

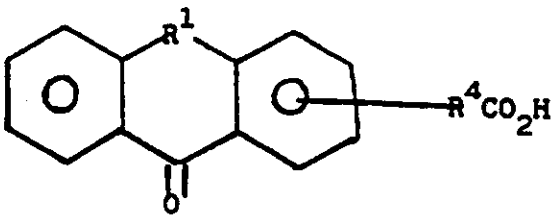
Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der Formel (I)



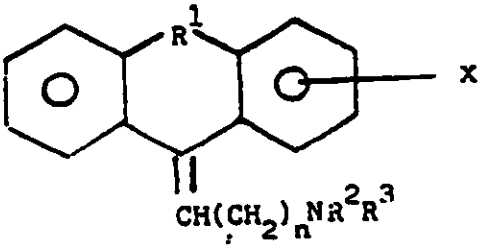
(I)

oder Salz, Ester oder Amid dieser Verbindung, worin
R^1 CH_2–O– oder –O–CH_2– bedeutet,
R^2 und R^3 gleich oder verschieden sind und jeweils Wasserstoff oder eine C_{1-4}-Alkylgruppe bedeuten oder zusammengenommen mit dem Stickstoffatom einen Stickstoff enthaltenden heterocyclischen Ring mit 4 bis 6 Ringgliedern umfassen,
R^4 eine Einfachbindung oder eine zweiwertige, aliphatische C_{1-7}-Kohlenwasserstoff-Gruppe ist und mit dem aromatischen Ringsystem an den Positionen 2, 3, 8 oder 9 verbunden sein kann, und
n 0 bis 3 ist,
wobei das Verfahren umfaßt:
(a) die Reaktion einer Verbindung der Formel (III)



(III)

worin R^1 und R^4 die in Anspruch 1 definierte Bedeutung haben, mit einem geeigneten Wittig-Reagenz oder mit einem geeigneten Grignard-Reagenz und nachfolgende Dehydratation, oder
(b) die Hydrolyse einer Verbindung der Formel (V)



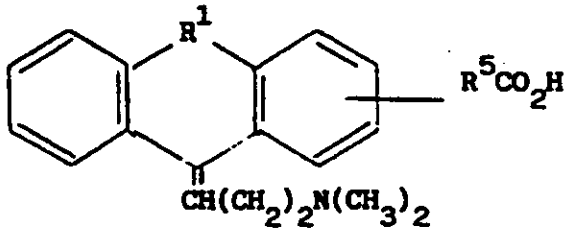
(V)

worin X R^4CN bedeutet und R^1, R^2, R^3, R^4 und n die oben definierte Bedeutung haben,
(c) wenn es erforderlich ist, eine Verbindung der Formel (I) herzustellen, worin R^4 eine Einfachbindung ist, eine Carboxylierungsreaktion an einer Verbindung der Formel (V) wie oben angegeben, worin R^1 bis R^3 und n die oben definierte Bedeutung haben und X ein Wasserstoff- oder ein Halogenatom ist, oder
(d) wenn es erforderlich ist, eine Verbindung der Formel (I) herzustellen, worin R^4 eine andere Bedeutung als die einer Einfachbindung hat, die Reaktion einer Verbindung der Formel (V), worin X ein Halogenatom ist und R^1 bis R^3 und n die oben definierte Bedeutung haben, mit einer Verbindung CH_2=CHR^6COR^7, worin R^6 für eine zweiwertige aliphatische C_{1-5}-Kohlenwasserstoff-Gruppe und R^7 für eine Schutzgruppe steht, und danach Entfernung der Schutzgruppe, wenn erforderlich, und
(e) danach Umwandeln einer Verbindung der Formel (I) in eine andere Verbindung der Formel (I), sofern gewünscht.

2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (I) wie in Anspruch 1 definiert, worin
R^1 $-CH_2O-$ oder $-OCH_2-$ bedeutet,
R^2 und R^3 gleich oder verschieden sind und jeweils eine C_{1-4}-Alkylgruppe, vorzugsweise Methyl, bedeuten,
R^4 eine Einfachbindung oder eine zweiwertige, aliphatische C_{1-7}-Kohlenwasserstoff-Gruppe ist und mit dem aromatischen Ringsystem an den Positionen 2, 3, 8 oder 9, vorzugsweise an der Position 2, verbunden sein kann, und
n 0 bis 3 ist,
sowie deren Salze, Amide und Ester.

3. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (I) wie in Anspruch 1 definiert, worin
R^1 $-CH_2O-$ bedeutet,
R^2 und R^3 gleich oder verschieden sind und jeweils für einen C_{1-4}-Alkylrest, vorzugsweise einen Methylrest, stehen,
R^4 eine Einfachbindung oder eine zweiwertige, aliphatische C_{1-7}-Kohlenwasserstoff-Gruppe ist und mit dem aromatischen Ring an den Positionen 2, 3, 8 oder 9, vorzugsweise an der Position 2, verbunden sein kann, und
n 0 bis 3 ist,
und deren Salze, Ester und Amide.

4. Verfahren nach Anspruch 1 (c) für die Herstellung einer Verbindung der Formel (II)



(II)

worin R^1 die oben definierte Bedeutung hat und R^5 eine Einfachbindung ist.

5. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung aus der Gruppe
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-2-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-2-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-3-carbonsäure
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-3-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-8-carbonsäure
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-8-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-9-carbonsäure
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-9-carbonsäure
(E)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-2-acrylsäure
(Z)-11-(3-(Dimethylamino)propyliden)-6,11-dihydrodibenz[b,e]oxepin-2-acrylsäure.

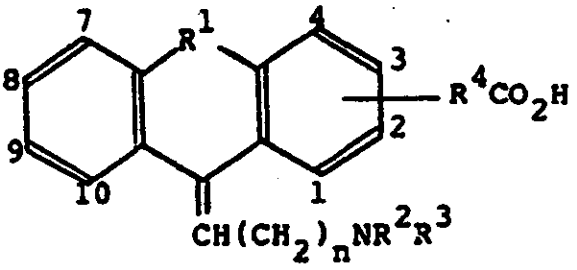
6. Pharmazeutische Zusammensetzung, umfassend eine Verbindung der Formel (I) wie in Anspruch 1 definiert in Abmischung mit einem pharmazeutisch annehmbaren Träger.

7. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, wobei das Verfahren den Schritt umfaßt, eine Verbindung der Formel (I) wie in Anspruch 1 definiert, in Verbindung mit einem pharmazeutisch annehmbaren Träger zu bringen.

8. Verbindung der Formel (I) wie in Anspruch 1 definiert zur Verwendung in einem Verfahren zur Kontrolle von Allergie.

Revendications pour les Etats contractants: BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Composé de formule (I)



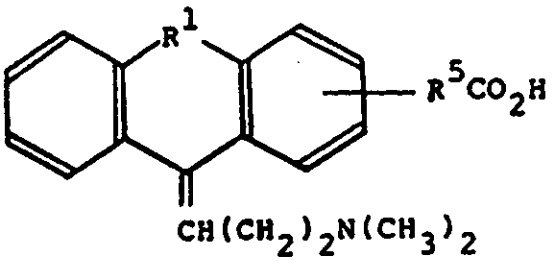
(I)

ou un sel, ester ou amide de celui-ci;
où R^1 est $-CH_2-O-$ ou $-O-CH_2-$;
R^2 et R^3 sont identiques ou différents et sont chacun hydrogène ou C_{1-4}-alcoyle ou bien pris ensemble avec l'atome d'azote forment un hétérocycle azoté comptant quatre à six chaînons de cycle;
R^4 est une liaison simple ou un radical hydrocarboné aliphatique bivalent en C_{1-7} et peut être uni au système cyclique aromatique aux positions 2, 3, 8 ou 9;
n est 0 à 3.

2. Composé de formule (I) tel que défini dans la revendication 1,
où R^1 représente $-CH_2O-$ ou $-OCH_2-$;
R^2 et R^3 sont identiques ou différents et sont chacun C_{1-4}-alcoyle, de préférence méthyle;
R^4 est une liaison simple ou un radical hydrocarboné aliphatique bivalent en C_{1-7} et peut être uni au cycle aromatique à la position 2, 3, 8 ou 9, de préférence à la position 2; et
n est 0 à 3,
et les sels, amides et esters de celui-ci.

3. Composé de formule (I) tel que défini dans la revendication 1,
où R^1 représente $-CH_2O-$;
R^2 et R^3 sont identiques ou différents et sont chacun C_{1-4}-alcoyle, de préférence méthyle;
R^4 est une liaison simple ou un radical hydrocarboné aliphatique bivalent en C_{1-7} et peut être uni au cycle aromatique à la position 2, 3, 8 ou 9, de préférence à la position 2, et
n est 0 à 3,
et les sels, esters et amides de celui-ci.

4. Composé de formule (II)



(II)

ou un sel, ester ou amide de celui-ci,
où R^1 est $-CH_2-O-$ ou $-O-CH_2-$; et
R^5 est une liaison simple ou $-CH=CH$ uni au cycle aromatique à la position 2, 3, 8 ou 9.

5. Composé choisi parmi:
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-2-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-2-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-3-carboxylique
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-3-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-8-carboxylique

l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-8-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-9-carboxylique
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-9-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acrylique
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acrylique.

6. Composition pharmaceutique comprenant un composé de formule (I) tel que défini dans la revendication 1 en mélange avec un excipient pharmaceutiquement acceptable.

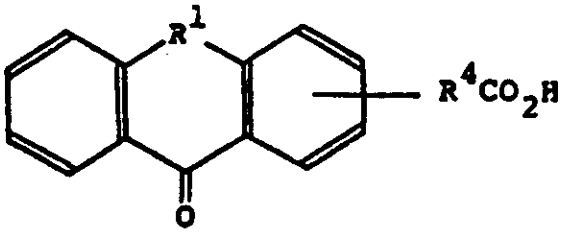
7. Composé de formule (I) tel que défini dans la revendication 1, à utiliser en médecine.

8. Composé de formule (I) tel que défini dans la revendication 1, pour la préparation d'un médicament pour lutter contre l'allergie.

9. Composé de formule (I) tel que défini dans la revendication 1, pour la préparation d'un médicament pour soulager les effets nuisibles de l'histamine, pour maîtriser ou soulager les effets d'un état asthmatique ou pour maîtriser la bronchoconstriction ou le bronchospasme caractéristique de l'asthme allergique.

10. Procédé de préparation d'un composé de formule (I) tel que défini dans la revendication 1, qui comprend

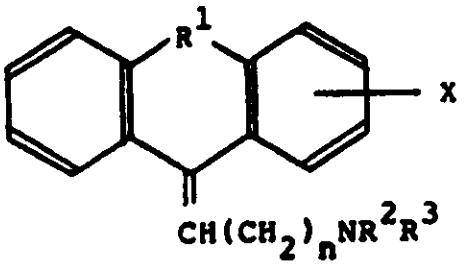
a) la réaction d'un composé de formule (III):



(III)

où R^1 et R^4 sont tels que définis dans la revendication 1, avec un réactif de Wittig approprié ou avec un réactif de Grignard approprié, suivie de la déshydratation, ou

b) l'hydrolyse d'un composé de formule (V):



(V)

où X est R^4CN et R^1, R^2, R^3, R^4 et n sont tels que définis dans la revendication 1,

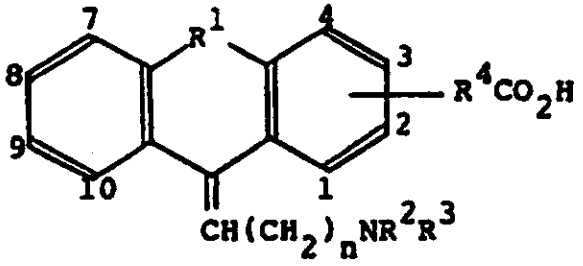
c) lorsqu'il est requis de préparer un composé de formule (I) où R^4 est une liaison simple, une réaction de carboxylation exécutée sur un composé de formule (V) ci-dessus où R^1 à R^3 et n sont tels que définis ci-dessus dans la revendication 1 et X est un atome d'hydrogène ou d'halogène, ou

d) lorsqu'il est requis de préparer un composé de formule (I) où R^4 est autre qu'une liaison simple, la réaction d'un composé de formule (V ci-dessus où X est un atome d'halogène et R^1 à R^3 et n sont tels que définis ci-dessus dans la revendication 1, avec un composé $CH_2=CHR^6COR^7$ où R^6 est un radical hydrocarboné aliphatique bivalent en C_{1-5} et R^7 est un radical protecteur, et ensuite l'élimination du radical protecteur lorsque la chose est nécessaire, et

e) ensuite, la conversion d'un composé de formule (I) en un autre composé de formule (I), si la chose est souhaitée.

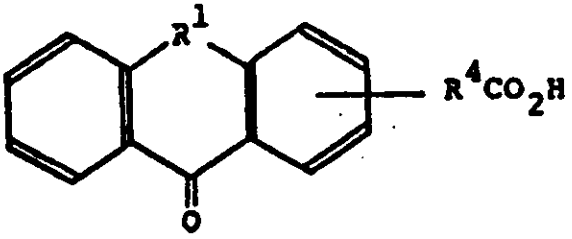
Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un composé de formule (I)



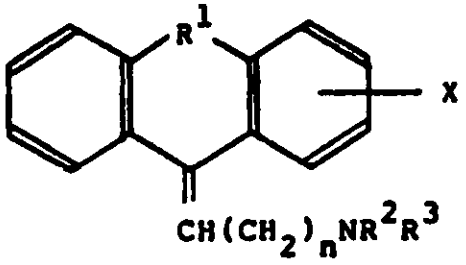
(I)

ou d'un sel, ester ou amide de celui-ci;
où R^1 est $-CH_2-O-$ ou $-O-CH_2-$;
R^2 et R^3 sont identiques ou différents et sont chacun hydrogène ou C_{1-4}-alcoyle ou bien pris ensemble avec l'atome d'azote forment un hétérocycle azoté comptant quatre à six chaînons de cycle;
R^4 est une liaison simple ou un radical hydrocarboné aliphatique bivalent en C_{1-7} et peut être uni au système cyclique aromatique aux positions 2, 3, 8 ou 9;
n est 0 à 3,
lequel procédé comprend:
a) la réaction d'un composé de formule (III):



(III)

où R^1 et R^4 sont tels que définis ci-dessus, avec un réactif de Wittig approprié ou avec un réactif de Grignard approprié, suivie de la déshydratation, ou
b) l'hydrolyse d'un composé de formule (V):



(V)

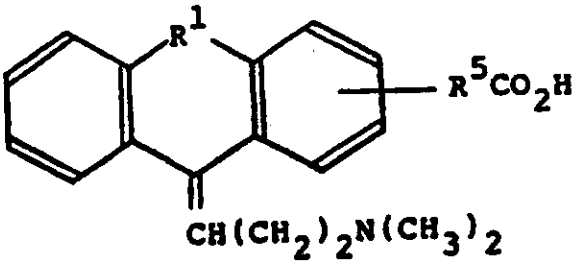
où X est R^4CN, et R^1, R^2, R^3, R^4 et n sont tels que définis dans la revendication 1,
c) lorsqu'il est requis de préparer un composé de formule (I) où R^4 est une liaison simple, la carboxylation d'un composé de formule (V) ci-dessus où R^1 à R^3 et n sont tels que définis ci-dessus et X est un atome d'hydrogène ou d'halogène, ou
d) lorsqu'il est requis de préparer un composé de formule (I) où R^4 est autre qu'une liaison simple, la réaction d'un composé de formule (V) où X est un atome d'halogène et R^1 à R^3 et n sont tels que définis ci-dessus, avec un composé $CH_2=CHR^6COR^7$ où R^6 est un radical hydrocarboné aliphatique bivalent en C_{1-6} et R^7 et un radical protecteur, et ensuite l'élimination du radical protecteur lorsque la chose est requise, et
e) ensuite la conversion d'un composé de formule (I) en un autre composé de formule (I), si la chose est souhaitée.

2. Procédé suivant la revendication 1, de préparation d'un composé de formule (I) tel que défini dans la revendication 1,
où R^1 représente $-CH_2O-$ ou $-OCH_2-$;
R^2 et R^3 sont identiques ou différents et sont chacun C_{1-4}-alcoyle, de préférence méthyle;
R^4 est une liaison simple ou un radical hydrocarboné aliphatique bivalent en C_{1-7} et peut être uni au cycle aromatique à la position 2, 3, 8 ou 9, de préférence à la position 2 et
n est 0 à 3,
et des sels, amides et esters de celui-ci.

3. Procédé suivant la revendication 1, de préparation d'un composé de formule (I) tel que défini dans la revendication 1,

où R^1 représente $-CH_2O$
R^2 et R^3 sont identiques ou différents et sont chacun C_{1-4}-alcoyle, de préférence méthyle;
R^4 est une liaison simple ou un radical hydrocarboné aliphatique bivalent en C_{1-7} et peut être uni au cycle aromatique à la position 2, 3, 8 ou 9, de préférence à la position 2, et
n est 0 à 3,
et des sels, esters et amides de celui-ci.

4. Procédé suivant la revendication 1c) de préparation d'un composé de formule (II):



(II)

où R^1 est tel que défini ci-dessus et R^5 est une liaison simple.

5. Procédé suivant la revendication 1, de préparation d'un composé choisi parmi:
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-2-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-2-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-3-carboxylique
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-3-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-8-carboxylique
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-8-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-9-carboxylique
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-9-carboxylique
l'acide (E)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acrylique
l'acide (Z)-11-(3-(diméthylamino)propylidène)-6,11-dihydrodibenz[b,e]oxépine-2-acrylique.

6. Composition pharmaceutique comprenant un composé de formule (I) tel que défini dans la revendication 1 en mélange avec un excipient pharmaceutiquement acceptable.

7. Procédé de préparation d'une composition pharmaceutique, qui comprend la mise en association d'un composé de formule (I) tel que défini dans la revendication 1 avec un excipient pharmaceutiquement acceptable.

8. Composé de formule (I) tel que défini dans la revendication 1, à utiliser dans un procédé pour lutter contre l'allergie.

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