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54 **Tricyclic compounds.**

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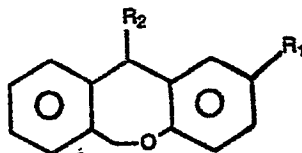
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Description

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 herein-after referred to by its generic name, doxepin. Doxepin has been accepted as an antidepressant in human clinical chemotherapy and an antipruritic for veterinary use.

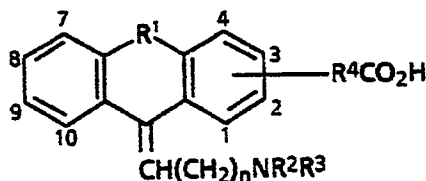
Published European Patent Application No 130 555 discloses compounds of formula:



wherein R_1 represents a cyano group, a 5-tetrazolyl group, a carbamoyl group or $-\text{CO}_2R_3$ [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 $-\text{X}-(\text{CH}_2)_n-\text{NR}_4R_5$ (wherein X represents $-\text{NH}-$, $-\text{S}-$ or $-\text{O}-$, 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*.

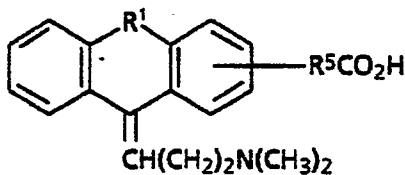
Accordingly this invention provides a compound of the formula (I),



(I)

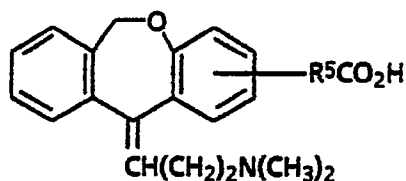
or a salt, ester or amide thereof; wherein R^1 is $-\text{CH}_2-\text{O}-$ or $-\text{O}-\text{CH}_2-$; R^2 and R^3 are the same or different and are each hydrogen, C_{1-4} alkyl or taken together with the nitrogen comprise a nitrogen-containing heterocyclic ring having four to six ring members; R^4 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 9.

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 $-\text{CH}=\text{CH}-$, 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

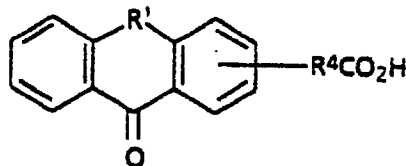
The compounds of the present invention exist in either the cis (Z) or trans (E) isomers (in relation to the bridge oxygen in the case of formula (IIA)). If the compounds of formula (I) or (II) contain a double bond in the acid bearing side chain, i.e. R⁴ or R⁵, there exists a second possibility of Z 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 C₁₋₆ alkyl esters wherein the alkyl group is straight or branched chain and is optionally substituted by halogen. Alkyl esters (C₁₋₄) 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 C₁₋₄ 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.

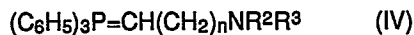
The present invention also provides analogous methods for preparing compounds of formula (I), for example:

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)

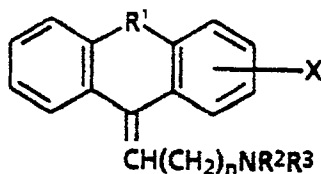
The Wittig reagent, $\text{Ph}_3\text{P}=\text{CH}(\text{CH}_2)_n\text{NR}_2\text{R}_3$; i.e., formula (IV), is conveniently



5 prepared by reacting a compound of the formula $\text{Ph}_3\text{PCH}_2(\text{CH}_2)_n\text{NR}_2\text{R}_3\text{Br}$, 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.

10 (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. $\text{R}^2\text{R}^3\text{NCH}_2\text{CH}_2\text{CH}_2\text{Mg X}$ where X is a halogen atom, is reacted with a compound of formula (III), followed by dehydration with a strong acid.

15 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)

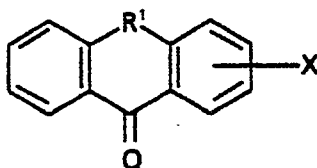
25 wherein R^1 , R^2 , R^3 and n are as defined, *vide supra* and X is a hydrogen or halogen atom (suitably a bromine or chlorine atom attached directly to the ring system in the 2, 3, 8 or 9 positions. For example, a compound of formula (V) can be treated with a metalating agent such as butyl lithium 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).

30 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),



35 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.

45 d) When the preparation of a compound of the formula (I) wherein R^4 is $\text{CH}=\text{CH}$ is required, a compound of the formula (VII)

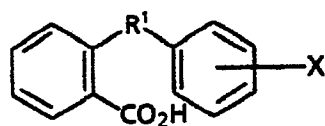


(VII)

50 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.

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

65



5

(VIII)

wherein R¹ and X are as defined, vide supra with a dehydrating agent such as (CF₃CO)₂O/BF₃·OEt₂.

10 (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 Ph₃P=CH₂(CH₂)_nNR₂R₃ as described, vide supra.

15 (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 CO₂H 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).

20 (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.

25 (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.

30 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 bronchospasm 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.

35 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).
45 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.

50 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.

55 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
65 formulation and not deleterious to the recipient thereof.

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