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(54) **Dibenz [b,e] oxepin derivative and antiallergic and antiinflammatory agent.**

(57) Novel dibenz[b,e]oxepin derivatives are employed in the treatment and control of allergic conditions such as allergic asthma and also employed in the treatment of inflammation.

DIBENZ[b,e]OXEPIN DERIVATIVE AND ANTIALLERGIC AND ANTIINFLAMMATORY AGENT

Background of the Invention

Heretofore, it has been known that ll-unsubstituted, ll-hydroxy or ll-oxodibenz[b,e]oxepin derivative is used for antiinflammatory agents [J. Med. Chem., 2l, 633 -639 (l978)].

Further, it is known that dibenz[b,e]oxepin derivative wherein substitutents Ra and Rb at ll-position have the following definitions, is employed in the treatment and control of allergic conditions (USP 4,282,365).

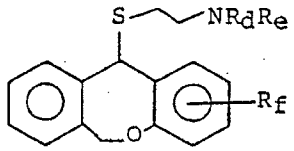
Ra : H, OH, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, arylthio, NH_2, NHCHO or imidazolyl;

Rb : H or lower alkyl;

or Ra and Rb taken together are = O, = CH-Rc wherein Rc is H or aryl.

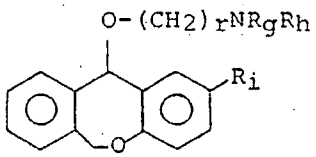
Furthermore, it is known that ll-(4-methylpiperazino) dibenz[b,e]oxepin derivative has an antiasthmatic activity (USP 4,396,550, USP 4,465,835, EP-A-3856).

It is also known that dibenz[b,e]oxepin derivative having the following formula:



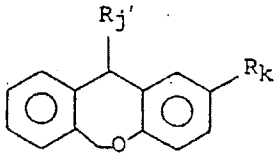
wherein Rd and Re are lower alkyl and Rf is lower alkyl or halogen, has an antiasthmatic activity (EP-A-85870).

Dibenz[b,e]oxepin derivative having an antiallergic activity and having the following structural formula:



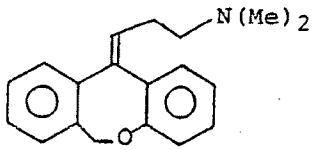
wherein Rg and Rh are alkyl, r is 2 or 3 and Ri is alkyl or halogen is known (JP-A-227879/84).

Dibenz[b,e]oxepin derivative having an antiallergic activity and having the following structural formula:

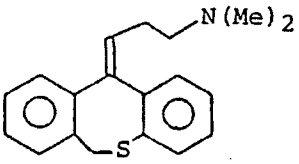


wherein R_j is 4-alkylpiperazino, 3-quinuclidylamino or $-Xa-(CH_2)_s-NR_lR_m$ wherein X_a is -NH-, -S-or -O-, s is 2 or 3 and R_l and R_m are alkyl, and R_k is CN, 5-tetrazolyl, $CONH_2$ or CO_2R_n wherein R_n is H, alkyl or l-(ethoxycarbonyloxy)ethyl is known (EP-A-l30555).

Doxepin having an antidepressant activity and having the following structural formula is known [Drugs, l3, l6l (l977)].



Dothiepin having an antidepressant activity and having the following structural formula is known [Arz.-Forsch., 13 1039 (1963); ibid., 14 100 (1964)].

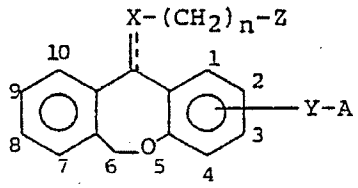


As the compound having both an antiallergic activity and an antiinflammatory activity, steroids are known.

It is always desired that a novel compound having an antiallergic activity or an antiinflammatory activity be developed.

Summary of the Invention

The present invention relates to a dibenz[b,e] oxepin derivative represented by the formula (I):



(I)

wherein A represents a hydroxymethyl, a lower alkoxymethyl, a triphenylmethyloxymethyl, a lower alkanoyloxymethyl, a lower alkanoyl, a carboxy, a lower alkoxy carbonyl, a triphenylmethyioxycarbonyl, -CONR$_1$R$_2$ (wherein R$_1$ and R$_2$ are the same or different and represent hydrogen atom or lower alkyl) 4,4-dimethyl-2-oxazoline-2-yl group or -CONHOH; Y represents -(CH$_2$)$_m$-, -CHR$_3$-(CH$_2$)$_m$-or -CR$_4$ =CR$_5$-(CH$_2$)$_m$- which is substituent at 2-or 3-position of the mother nucleus (wherein R$_3$ represents a lower alkyl, R$_4$ and R$_5$ are the same or different and represent a hydrogen atom or a lower alkyl, m is 0, 1, 2, 3 or 4, and the left side of the group of Y mentioned above is bound to benzen nucleus); X represents = N-, = CH-or -CH$_2$-; n is 0, 1, 2, 3 or 4; Z represents 4-methylpiperazino, 4-methylhomopiperazino, piperidino, pyrrolidino, thiomorpholino, morpholino, or -NR$_6$R$_7$ (wherein R$_6$ and R$_7$ are the same or different and represent a hydrogen atom or a lower alkyl); and ——— means a single bond or double bond [hereinafter referred to as Compound (I) and Compounds with other formula numbers are hereinafter likewise referred to], and a pharmaceutically acceptable salt thereof. The present invention further pertains to a pharmaceutical composition containing an effective amount of Compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient, and a carrier or an excipient.

The present Compound (I) is useful for treatment of allergic conditions and inflammation.

Detailed Description of the Invention

In the definition of each group of fomrula (I), the lower alkyl group includes straight or branched chain alkyl groups having I to 6 carbon atoms, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, etc. In the definition of the group A, lower alkyl moiety of lower alkoxymethyl group and lower alkoxycarbonyl group has the same meaning as previously defined.

The lower alkoxymethyl group includes methoxymethyl, ethoxymethyl, n-propoxymethyl, isopropoxy, etc. and the lower alkoxycarbonyl group includes methoxycarbonyl, ethoxycarbonyl, etc.

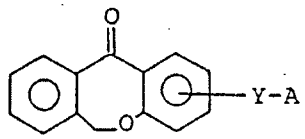
In the definition of the group A, the lower alkyl moiety of lower alkanoyl group and lower alkanoyloxymethyl group has the same meaning as previously defined.

The lower alkanoyl group includes formyl, acetyl, etc. and the lower alkanoyloxymethyl group includes formyloxymethyl, acetyloxymethyl, etc.

The pharmaceutically acceptable salt of Compound (I) includes pharmaceutically acceptable acid addition salt, metal salt, ammonium salt, organic amine addition salt, amino acid addition salt, etc.

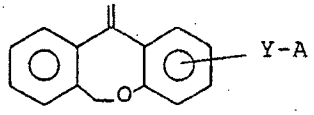
The pharmaceutically acceptable acid addition salt of Compound (I) includes inorganic acid salts such as hydrochloride, sulfate, phosphate, etc., and organic acid salts such as acetate, maleate, fumarate, tartrate, citrate, etc. The pharmaceutically acceptable metal salt includes alkalimetal salts such as sodium salt, potassium salt, etc., alkaline earch metal salts such as magnesium salt, calcium salt, etc., and alminium salt, zinc salt, etc. The pharmaceutically acceptable organic amine addition salt includes addition salt of morpholine and piperidine and the pharmaceutically acceptable amino acid addition salt includes addition salt of lysine, glysine, phenylalanine, etc.

Compound (I) is prepared by using a compound represented by the formula (II):



(II)

wherein Y and A have the same meanings as previously defined or a compound represented by the formula (III):



(III)

wherein Y and A have the same meanings as previously defined as the starting compound. Compound (II) is disclosed in J. Med. Chem., 19, 941 (1976), ibid., 20 , 1499 (1977) and JP-A-21679/83.

Compound (III) wherein -Y-A is -COOH is disclosed in JP-A-21679/83 and the other Compounds (III) can be prepared according to the method described in the publication though they do not occur in the publication.

The process for preparing Compound (I) is explained, depending on the kind of the group X.

Process A

[Synthesis of Compound (I) wherein X is =CH-(Part I)]

The carboxy group of Compound (IIa) is protected according to the following reaction scheme.

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