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Oshima et al.

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[54] **DIBENZ[B,E]OXEPIN DERIVATIVE AND PHARMACEUTICAL COMPOSITIONS THEREOF**

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[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[5] **A61K 31/335;** C07D 313/12

[52] **U.S. Cl.** **514/450;** 548/215; 548/525; 549/354; 514/212; 514/228.2; 514/232.8; 514/253; 514/320; 514/374; 514/422; 540/596; 540/600; 544/62; 544/137; 544/147; 544/369; 544/375; 544/58.7; 546/196

[58] **Field of Search** 540/596, 602; 544/62, 544/137, 147, 369, 375, 98.7; 546/196; 548/215, 525; 549/354; 514/212, 222, 233, 234, 236, 237, 253, 320, 374, 422, 450, 228.2, 232.8

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[57] **ABSTRACT**

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.

3 Claims, No Drawings

DIBENZ[B,E]OXEPIN DERIVATIVE AND PHARMACEUTICAL COMPOSITIONS THEREOF

BACKGROUND OF THE INVENTION

Heretofore, it has been known that 11-unsubstituted, 11-hydroxy or 11-oxodibenz[b,e]oxepin derivative is used for antiinflammatory agents [J. Med. Chem., 21, 633–639 (1978)].

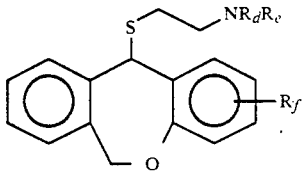
Further, it is known that dibenz[b,e]oxepin derivative wherein substitutents Ra and Rb at 11-position have the following definitions, is employed in the treatment and control of allergic conditions (U.S. Pat. No. 4,282,365).

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 =0, =CH—Rc wherein Rc is H or aryl.

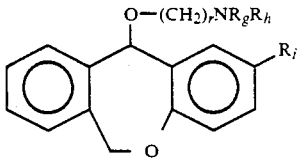
Furthermore, it is known that 11-(4-methylpiperazino) dibenz[b,e]oxepin derivative has an antiasthmatic activity (U.S. Pat. No. 4,396,550, U.S. Pat. No. 4,465,835, EP-A-38564).

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



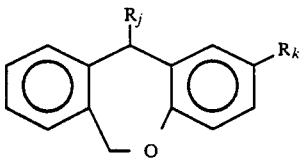
wherein Rd and Re are lower alkyl and Rf is lower alkyl or halogen, has an antiasthmatic activity (EP-A-85870).

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



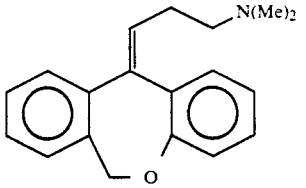
wherein Rg and Rh are alkyl, r is 2 or 3 and Ri is alkyl or halogen is known (JP-A-227879/84).

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

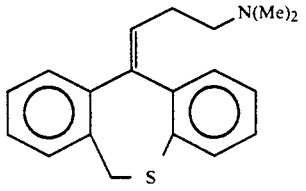


wherein Rj is 4-alkylpiperazino, 3-quinuclidylamino or —Xa—(CH_2)hd s—NR_lR_m wherein X_a is —NH—, —S— or —O—, s is 2 or 3 and R_l and R_m are alkyl, and R_k is CN, 5-tetrazolyl, $CONH_2$ or CO_2R_n wherein R_n is H, alkyl or 1-(ethoxycarbonyloxy)ethyl is known (EP-A-130555).

Doxepin having an antidepressant activity and having the following structural formula is known [Drugs, 13, 161 (1977)].



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

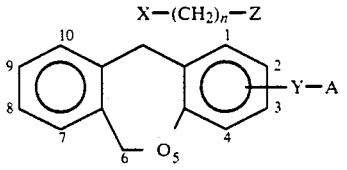


As the compound having both an antiallergic activity and an antiinflammatory activity, steroids are known.

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 triphenylmethyloxycarbonyl, —$CONR_1R_2$ (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)hd 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_6R_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 formula (I), the lower alkyl group includes straight or branched chain alkyl groups having 1 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.

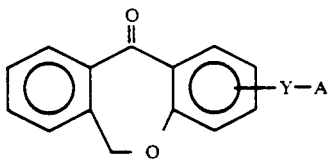
In the definition of the group A, the lower alkyl moiety of lower alkanoyl group and lower alkanoyloxymethyl group has the same meaning as previously defined.

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.

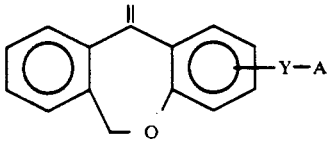
The pharmaceutically acceptable acid addition salt of Compound (I) includes inorganic acid salts such as hydrochloride, sulfate, phosphate, etc., and organic acid salts such as acetate, maleate, fumarate, tartrate, citrate, etc. The pharmaceutically acceptable metal salt includes alkalimetal salts such 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.

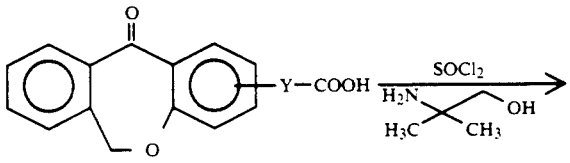
Compound (III) wherein —Y—A is —COOH is disclosed in JP-A-21679/83 and the other Compounds (III) can be prepared according to the method described in the publication though they do not occur in the publication.

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

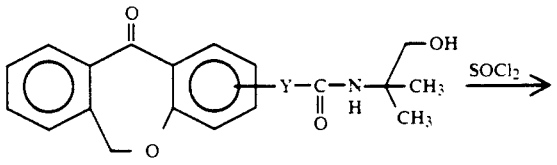
Process A

Synthesis of Compound (I) wherein X is =CH— (Part 1)

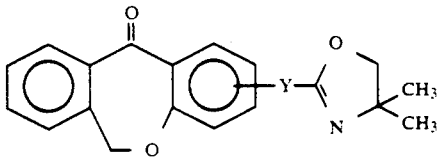
The carboxy group of Compound (IIa) is protected according to the following reaction scheme.



(IIa)



(IV)



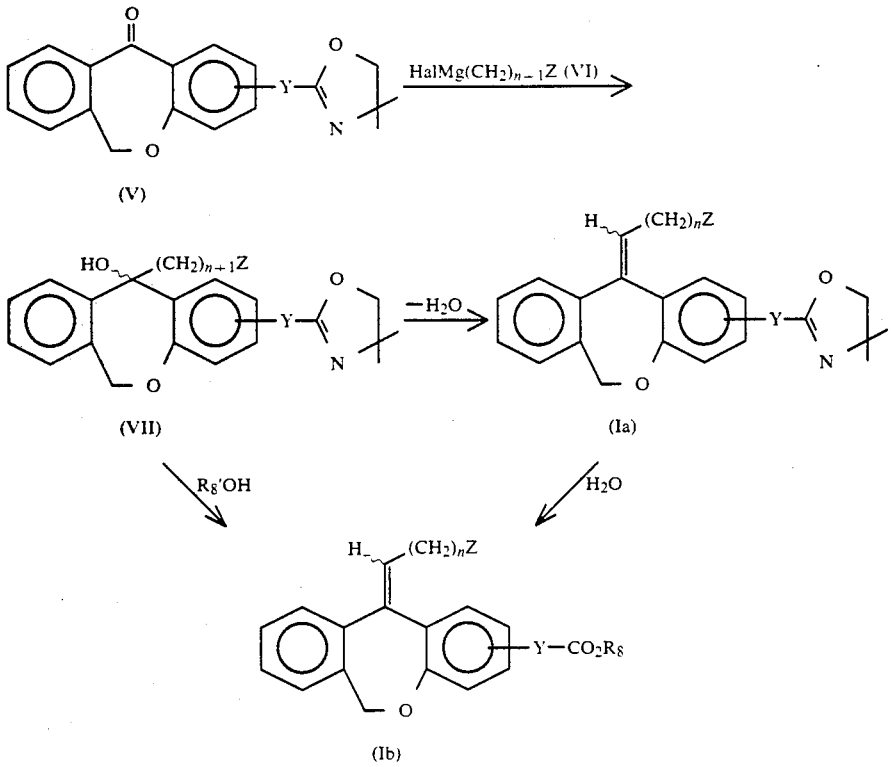
(V)

In the formulae, Y has the same meaning as previously defined, and Compound (IIa) is included in Compound (II) (compounds with an alphabet suffix following formula number are likewise included in compounds with common formula No.).

Compound (IIa) is reacted with 1 to 5 equivalents of thionyl chloride and 1 to 5 equivalents of 2-amino-2-methyl-1-propanol on the basis of Compound (IIa) in an inert solvent such as methylene chloride, if necessary in the presence of a base such as triethylamine at a temperature of from 0° C. to room temperature for 1–24 hours to form Compound (IV). Compound (IV) can also be obtained by reacting Compound (IIa) with thionyl chloride in advance and then with 2-amino-2-methyl-1-propanol.

Compound (IV) is reacted with 1–5 equivalents of thionyl chloride in an inert solvent such as methylene chloride, toluene and benzene at a temperature of from 0° C. to room temperature for 1–24 hours to form Compound (V).

Compounds (Ia) and (Ib) can be prepared from Compound (V) according to the following reaction scheme.



In the formulae, Y, Z, and n have the same meanings as previously defined. R_8 is hydrogen or a lower alkyl group, R'_8 is a lower alkyl group and Hal is halogen.

As used herein, the term lower alkyl has the same meaning as that of lower alkyl in each group of formula (I). Halogen includes chlorine, bromine and iodine. Compound (V) is reacted with 1–5 equivalents of Compound (VI) in an inert solvent such as tetrahydrofuran and diethyl ether under atmosphere of an inert gas such as nitrogen and argon to form Compound (VII). The reaction is carried out at a temperature of from 0° C. to room temperature and is usually completed in 1–24 hours.

Compound (VII) is reacted with 1–5 equivalents of thionyl chloride or phosphoryl chloride in an inert solvent such as methylene chloride in the presence of a base such as pyridine to form Compound (Ia). The reaction is carried out at a temperature of from 0° C. to room temperature and is completed in 1–24 hours.

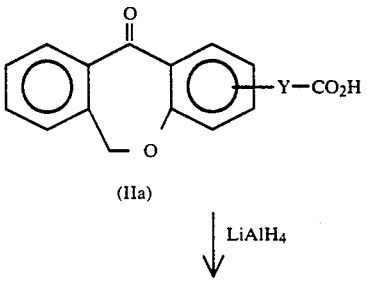
Compound (Ia) is incubated in an alcohol containing water, such as aqueous methanol solution, in the presence of an appropriate acidic catalyst such as p-toluenesulfonic acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (Ib) wherein R_8 is H. The reaction is completed in 1–24 hours.

Compound (VII) is incubated in a alcohol of $R_8'OH$ in the presence of an appropriate acidic catalyst such as p-toluenesulfonic acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (Ib) wherein R_8 is a lower alkyl. The reaction is completed in 1–24 hours.

Process B

Synthesis of Compound (I) wherein X is =CH— (Part 2)

The carboxy group of a compound represented by the formula (IIa) can be converted to a lower alkoxymethyl group or a trityloxymethyl group according to the following reaction scheme.



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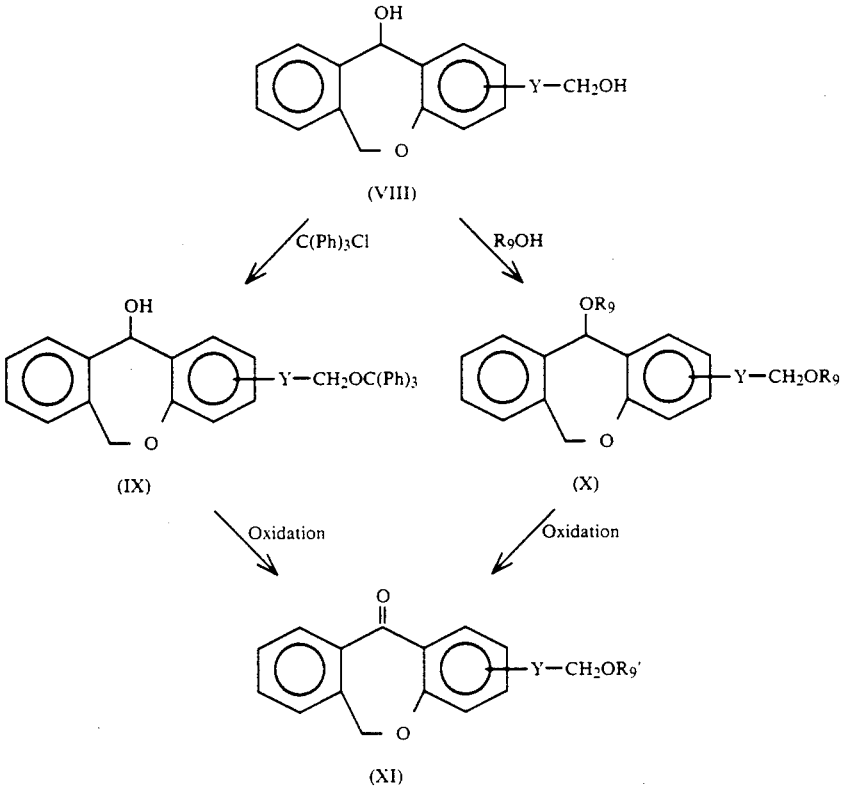


In the formulae, Y has the same meaning as previously defined, R_9 is a lower alkyl group and R_9' is a trityl group or a lower alkyl group. The term lower alkyl has the same meaning as that of lower alkyl in each group in formula (I).

Compound (IIa) is reduced with 1-5 equivalents of lithium aluminium hydride in tetrahydrofuran at a temperature of from 0° C. to room temperature for 1-24 hours to form Compound (VIII).

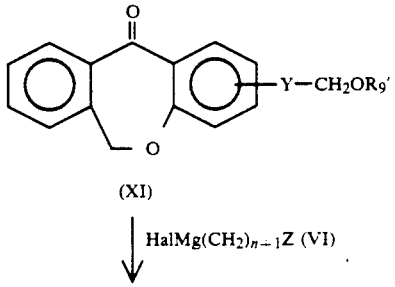
Compound (VIII) is reacted with 1-5 equivalents of trityl chloride in pyridine at a temperature of from room temperature to 100° C. for 1-24 hours to form Compound (IX).

Compound (IX) is oxidized with 1-5 equivalents of an appropriate oxidizing agent such as potassium permanganate and pyridinium chlorochromate in an inert solvent such as methylene chloride and acetone to form Compound (XI) wherein R_9' is trityl. The reaction is carried out at a temperature of from 0° C. to the boiling point of the solvent and is completed in 1-24 hours.

Compound (VIII) is incubated in an alcohol of R_9OH in the presence of an appropriate acidic catalyst such as sulfuric acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (X). The reaction is usually completed in 1-24 hours.

Compound (X) is oxidized with 1-5 equivalents of an appropriate oxidizing agent such as Jones reagent in an inert solvent such as acetone to form Compound (XI) wherein R_9' is a lower alkyl. The reaction is carried out at a temperature of from 0° C. to the boiling point of the solvent and is usually completed in 1-24 hours.

The compounds represented by the formulae (Ic) and (Id) and if desired, the compound represented by the formula (Ie) can be synthesized from Compound (XI) according to the following reaction scheme.



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