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

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| EP-A- 0 069 810 | EP-A- 0 130 555 |
| EP-A- 0 188 802 | GB-A- 1 003 950 |
| GB-A- 1 018 995 | US-A- 3 509 176 |

JOURNAL OF MEDICINAL CHEMISTRY, vol. 21, no. 7, July 1978, pages 633-639, American Chemical Society; "Novel arabinofuranosyl derivatives of cytosine resistant to enzymatic deamination and possessing potent antitumor activity"

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**EP 0 235 796 B1**

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## Description

## Background of the Invention

5 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 substituents Ra and Rb at 11-position have the following definitions, is employed in the treatment and control of allergic conditions (USP 4,282,365).

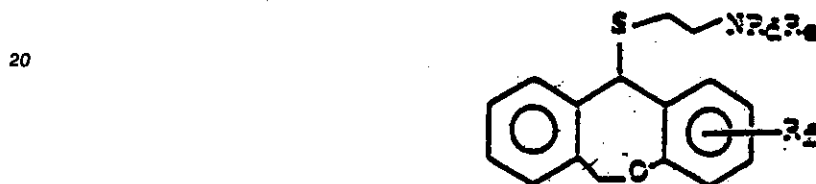
10 Ra : H, CH, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, arylthio, NH<sub>2</sub>, NHCHO or imidazolyl;

Rb : H or lower alkyl;

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

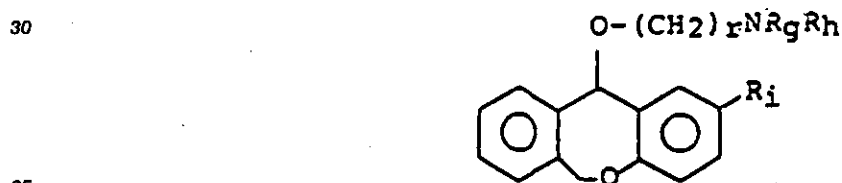
Furthermore, it is known that 11-(4-methylpiperazino) dibenz[b,e]oxepin derivative has an antiasthmatic activity (USP 4,396,550 USP 4,465,835, EP-A-38564).

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



25 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:



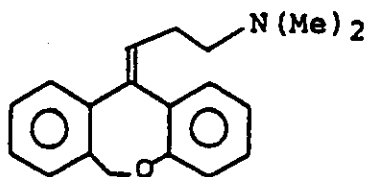
wherein Rg and Rh are alkyl, r is 2 or 3 and Ri is alkyl or halogen is known (JP-A-227879/84).

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

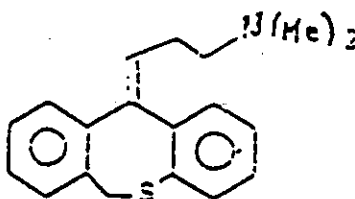


wherein Rj is 4-alkylpiperazino, 3-quinuclidylamino or -Xa-(CH<sub>2</sub>)s-NR<sub>l</sub>R<sub>m</sub> wherein Xa is -NH-, -S- or -O-, s is 2 or 3 and R<sub>l</sub> and R<sub>m</sub> are alkyl, and R<sub>k</sub> is CN, 5-tetrazolyl, CONH<sub>2</sub> or CO<sub>2</sub>R<sub>n</sub> wherein R<sub>n</sub> is H, alkyl or 1-(ethoxycarbonyloxy)ethyl is known (EP-A-130555).

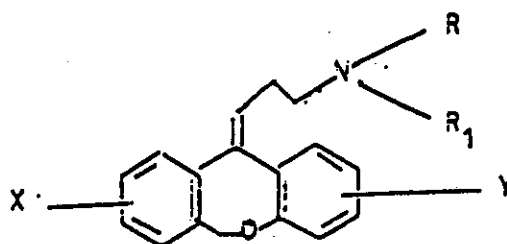
Doxepin having an antidepressant activity and having the following structural formula is known [Drugs, 13, 161 (1977)].



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



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



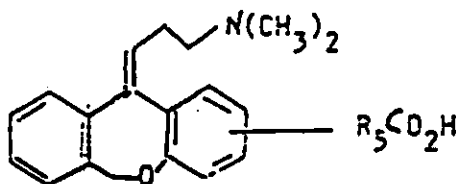
wherein :

R is hydrogen or methyl ;

R<sub>1</sub> is a lower alkyl, lower alkenyl or lower cycloalkyl ;

X and Y are each hydrogen, lower alkyl, lower alkoxy, lower alkylthio, chloro, fluoro, trifluoromethyl, lower acyl or dialkylsulfonamido, have an antidepressant activity (GB 1,018,955).

It is known that dibenz [b,e] oxepin derivatives of formula :



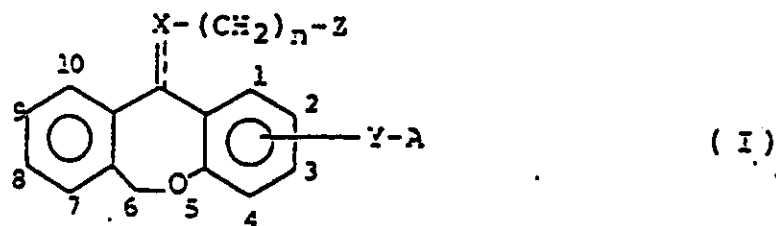
wherein R<sub>5</sub> is a single bond or -CH=CH-, have an anti-asthmatic activity (EP 214779).

As the compound having both an anti-allergic activity and an anti-inflammatory activity, steroids are known.

It is always desired that a novel compound having an antiallergic activity and 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):



wherein A represents a hydroxymethyl, a lower alkoxyethyl, a triphenylmethyloxymethyl, a lower alkanoyloxymethyl, a lower alkanoyl, a carboxy, a lower alkoxy carbonyl, a triphenylmethyloxycarbonyl, -CONR<sub>1</sub>R<sub>2</sub> (wherein R<sub>1</sub> and R<sub>2</sub> 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<sub>2</sub>)<sub>m</sub>-, -CHR<sub>3</sub>-(CH<sub>2</sub>)<sub>m</sub>- or -CR<sub>4</sub>=CR<sub>5</sub>-(CH<sub>2</sub>)<sub>m</sub>- which is substituent at 2- or 3-position of the mother nucleus (wherein R<sub>3</sub> represents a lower alkyl, R<sub>4</sub> and R<sub>5</sub> 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 benzene nucleus); X represents = N-, = CH- or -CH<sub>2</sub>-; n is 0, 1, 2, 3, or 4;

Z represents 4-methylpiperazino, 4-methylhomopiperazino, piperidino, pyrrolidino, thiomorpholino, morpholino, or -NR<sub>6</sub>R<sub>7</sub> (wherein R<sub>6</sub> and R<sub>7</sub> are the same or different and represent a hydrogen atom or a lower alkyl); and --- means a 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 and inflammation diseases.

## Detailed Description of the Invention

In the definition of each group of formula (I), the lower alkyl 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 alkoxyethyl group and lower alkoxy carbonyl group has the same meaning as previously defined.

The lower alkoxyethyl group includes methoxyethyl, ethoxyethyl, n-propoxyethyl, isopropoxyethyl, etc. and the lower alkoxy carbonyl group includes methoxycarbonyl, ethoxycarbonyl.

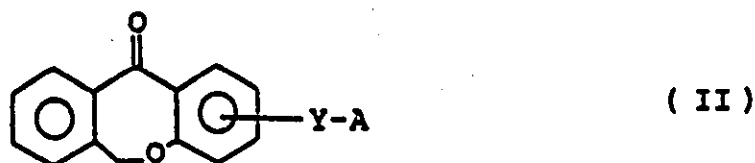
In the definition of the group A, the lower alkyl moiety of lower alkanoyl group lower alkanoyloxymethyl group has the same meaning as previously defined.

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

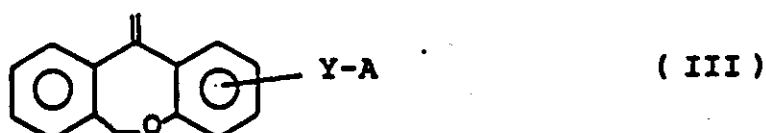
The pharmaceutically acceptable salt of Compound (I) includes pharmaceutically acceptable acid addition salt, metal salt, ammonium salt, organic amine addition salt, amino acid addition salt.

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 alkali metal salts such as sodium salt, potassium salt, etc., alkaline earth metal salts such as magnesium salt, calcium salt, etc., and aluminium 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, glycine, phenylalanine, etc.

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



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



20 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.

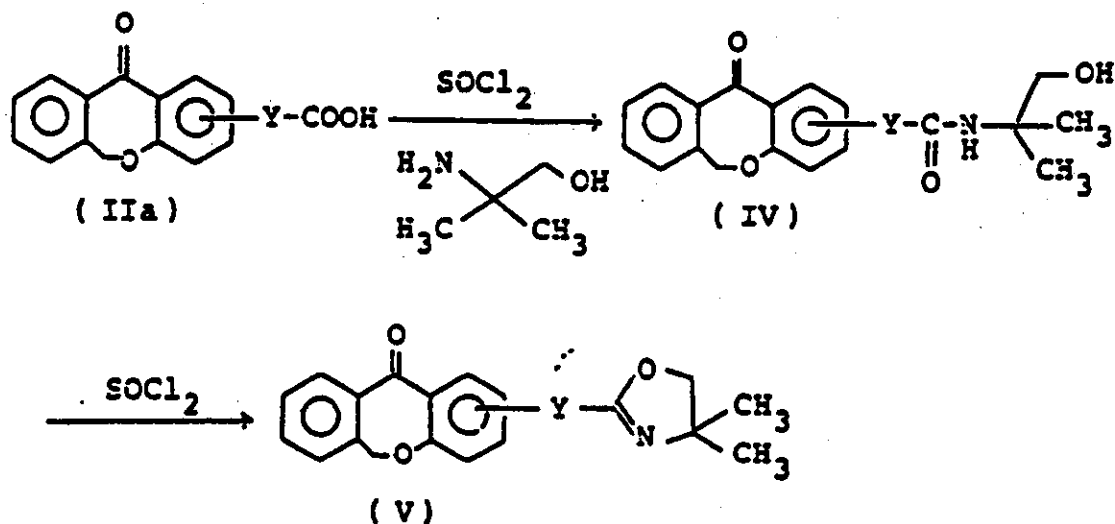
Compound (III) wherein -Y-A is -COOH is disclosed in JP-A-21679/83 and the other Compounds (III) can be prepared according to the method described in the publication though they do not occur in the publication.

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

#### 25 Process A

[Synthesis of Compound (I) wherein X is =CH- (Part 1)]

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

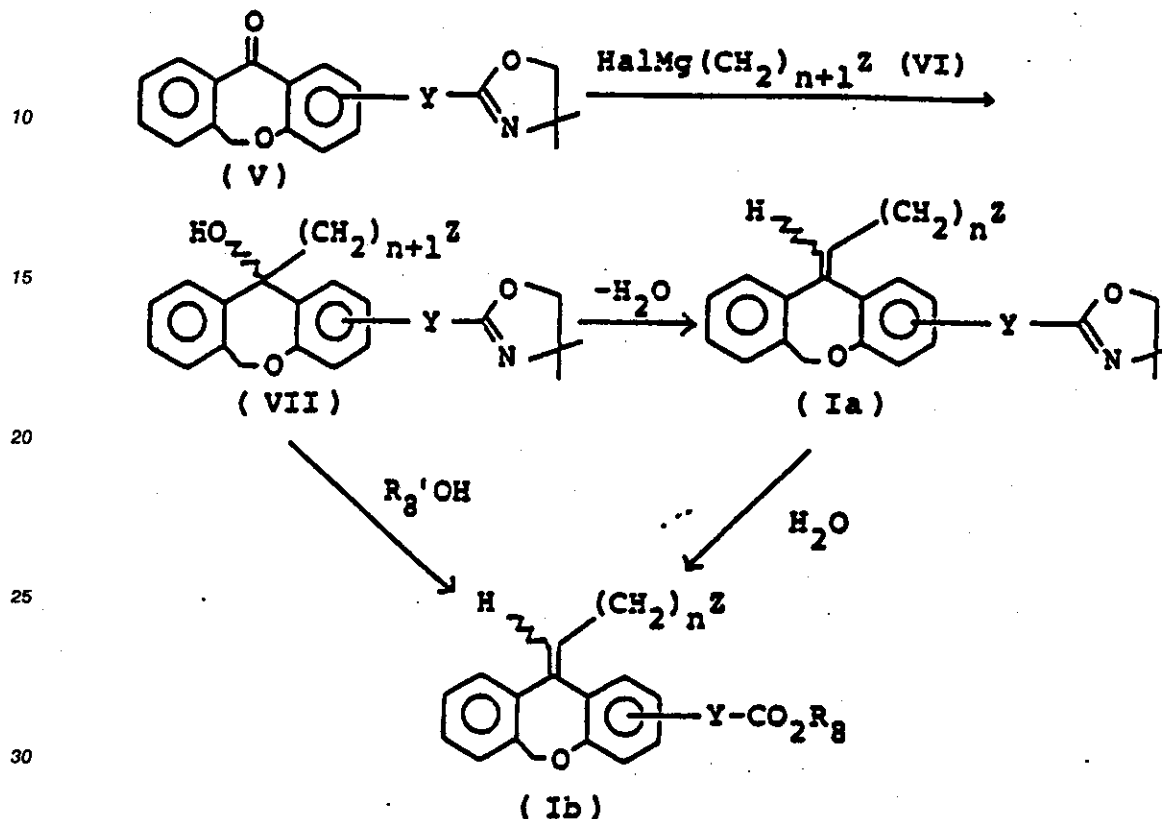


50 In the formula, Y has the same meaning as previously defined, and Compound (IIa) is included in Compound (II) (compounds with an alphabet suffix following formula number are likewise included in compounds with common formula no.)

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  
55 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,  $\text{R}_8$  is hydrogen or a lower alkyl group,  $\text{R}_8'$  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.

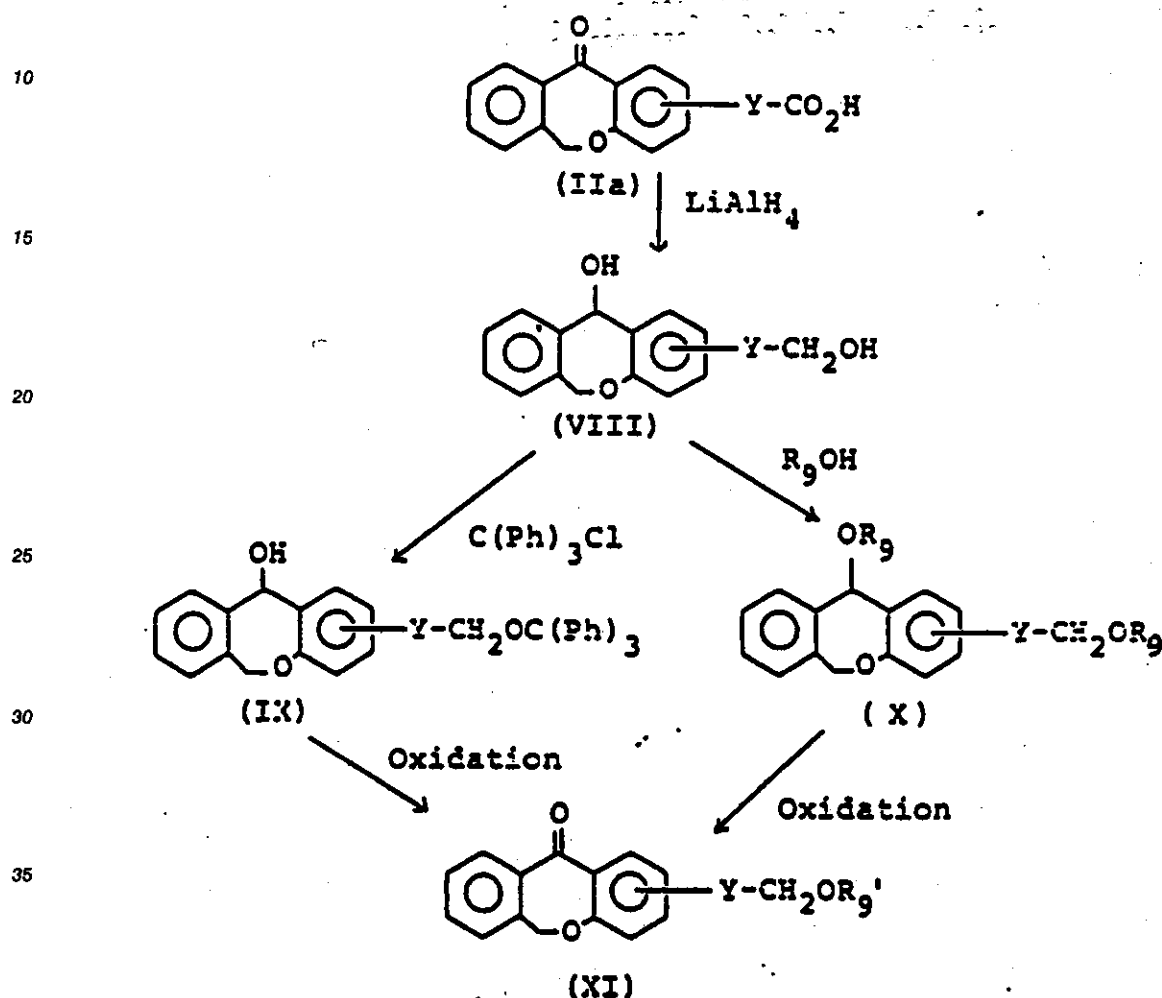
Compound (Ia) is incubated in an alcohol containing water, such as aqueous methanol solution, in the presence of an appropriate acidic catalyst such as p-toluenesulfonic acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (Ib) wherein  $\text{R}_8$  is H. The reaction is completed in 1 - 24 hours.

Compound (VII) is incubated in an alcohol  $\text{R}_8'\text{OH}$  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  $\text{R}_8$  is a lower alkyl. The reaction is completed in 1 - 24 hours.

## Process B

[Synthesis of Compound (I) wherein X is =CH- (Part 2)]

- 5 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.



40 In the formulae, Y has the same meaning as previously defined, R<sub>9</sub> is a lower alkyl group and R<sub>9</sub>' 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).

45 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).

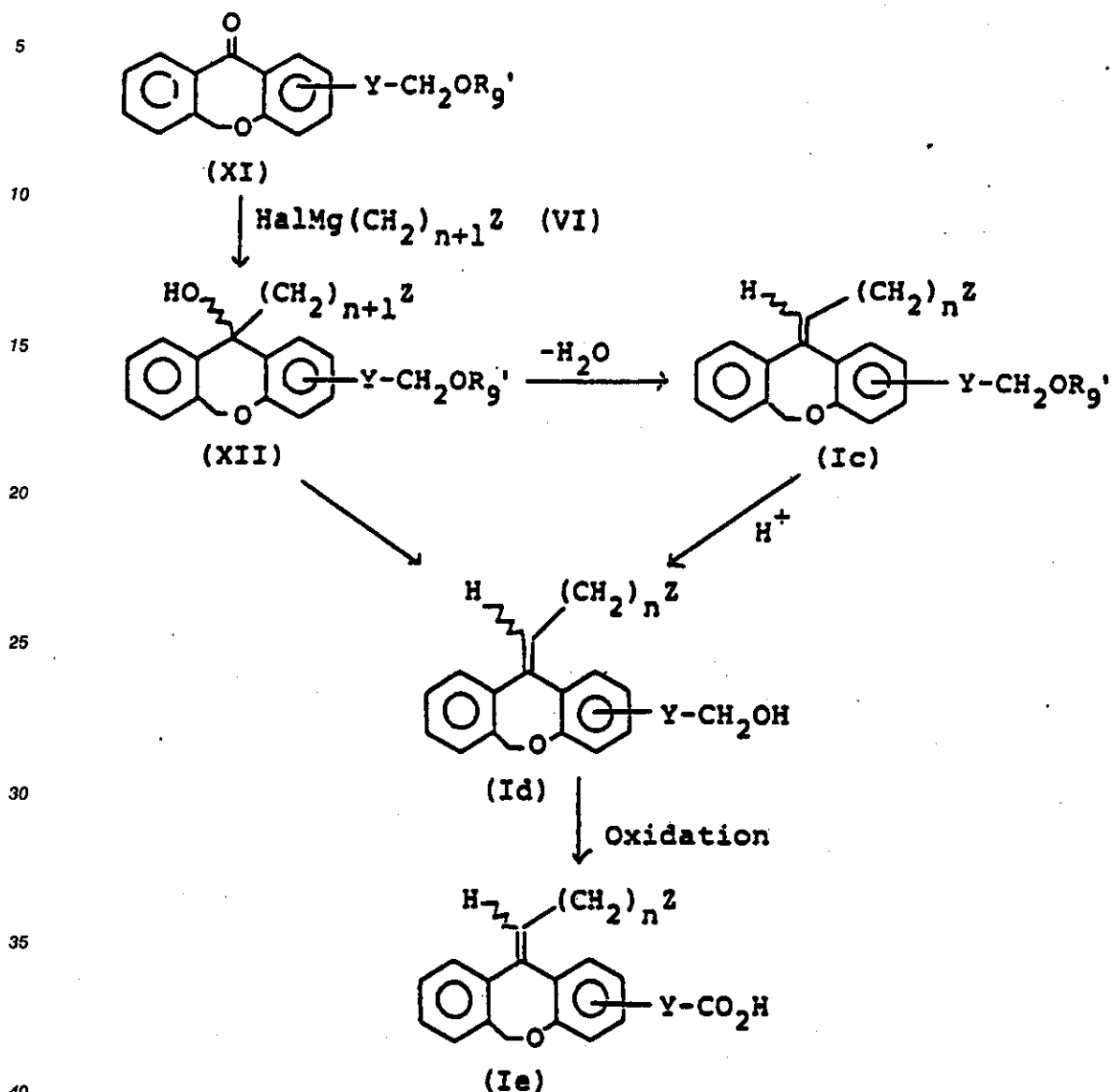
Compound (VIII) is reacted with 1 - 5 equivalents of trityl chloride in pyridine at a temperature of from room temperature to 100 °C for 1 - 24 hours to form Compound (IX).

50 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<sub>9</sub> 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<sub>9</sub>OH 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.

55 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<sub>9</sub>' 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.



In the formulae, Y, Z,  $R_{9'}$ , n and Hal have the same meanings as previously defined.

Compound (XI) is reacted with Compound (VI) which is Grignard reagent according to the same manner as in the reaction step from Compound (V) to Compound (VII) in Process A to form Compound (XII).

Compound (XII) is subjected to reaction according to the same manner as in the reaction step from Compound (VII) to Compound (Ia) in Process A to form Compound (Ic).

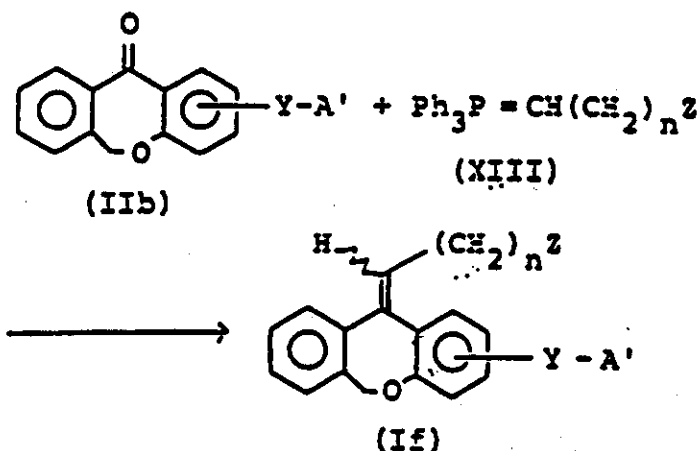
Compound (Ic) is incubated in a solvent containing water such as aqueous dioxane in the presence of an appropriate acidic catalyst such as p-toluenesulfonic acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (Id). The reaction is usually completed in 1 - 24 hours.

Compound (Id) can also be obtained in one step by incubating Compound (XII) in a solvent containing water such as aqueous dioxane in the presence of an appropriate acidic catalyst such as sulfonic acid at a temperature of from room temperature to the boiling point of the solvent. The reaction is usually completed in 1 - 24 hours.

If desired, Compound (Id) 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 (Ie). 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.

## Process C

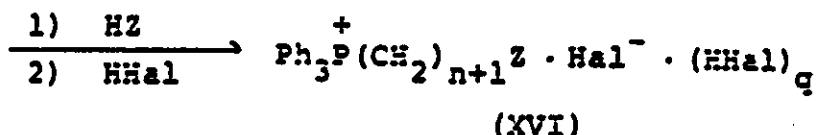
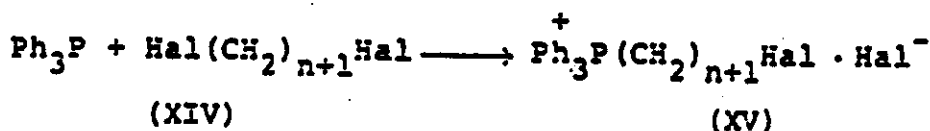
[Synthesis of Compound (I) wherein X is =CH- (Part 3)].



In the formulae, Y, Z, and n have the same meanings as previously defined. A' represents the groups falling within the definition of A but lower alkanoyl group.

Compound (IIb) is reacted with 1 - 5 equivalents of Compound (XIII) in an inert solvent such as tetrahydrofuran under atmosphere of an inert gas such as nitrogen and argon at a temperature of from 0°C to room temperature for 1 - 24 hours to form Compound (If).

Compound (XIII) which is ylide, can be prepared according to the method described in C.A. 63 16366a (1965).



In the formulae, Hal, n and Z have the same meanings as previously defined and q is 1 or 2.

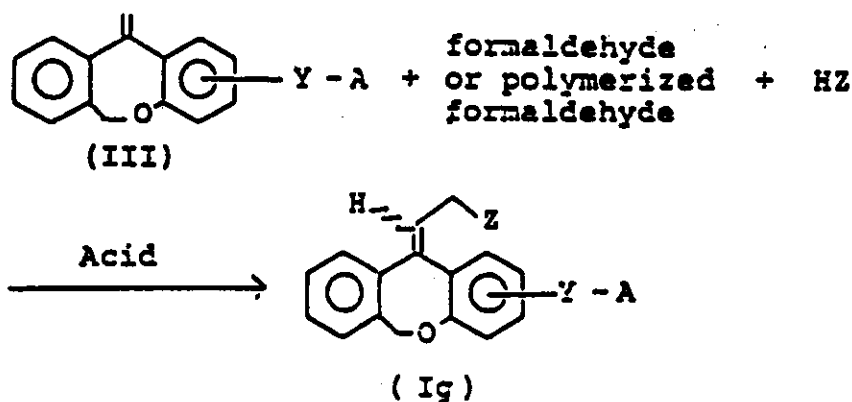
Compound (XIV) is reacted with an equivalent of triphenylphosphine in toluene at reflux of the solvent for 1 - 24 hours to form Compound (XV).

Compound (XV) is reacted with 1 - 5 equivalents of HZ in ethanol at reflux of the solvent for 1 - 24 hours and excess HZ is distilled away under reduced pressure. After the addition of 1 - 5 equivalents of HHal on the basis of Compound (XV), the mixture is incubated at a temperature of from 0°C to the boiling point of the solvent for 1 - 24 hours to form Compound (XVI) which is Wittig reagent.

Compound (XVI) is treated with 1 - 2 equivalents of an appropriate base such as n-butyl lithium in an inert solvent such as tetrahydrofuran under atmosphere of an inert gas such as nitrogen and argon to form ylide (XIII). The reaction is carried out at -78°C ~ room temperature and is usually completed in 1 - 24 hours.

## Process D

[Synthesis of Compound (I) wherein X is =CH- (Part 4)]



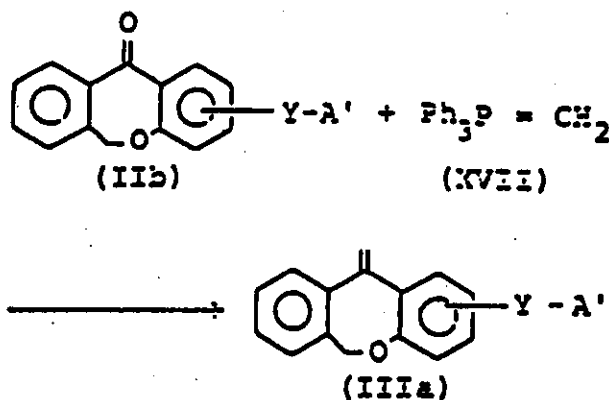
20 In the formulae, Y, Z and A have the same meanings as previously defined.

The process is known as Prince reaction [New Experimental Chemical Course (Maruzen), Vol. 14, Synthesis and Reaction of Organic Compound III, page 1375 (1977)].

Compound (III), 1 to 5 equivalents of formaldehyde and 1 to 5 equivalents of HZ are subjected to reaction in an inert solvent such as tetrachloroethane in the presence of an acid or reaction in an acid as such serving as a solvent under atmosphere of an inert gas such as nitrogen and argon to yield Compound (Ig).

25 The formaldehyde or polymerized formaldehyde includes p-formaldehyde, trioxane, etc. The acid includes acetic acid, trichloroacetic acid, trifluoroacetic acid, etc. The reaction is carried out at a temperature of from room temperature to the boiling point of the solvent and is completed in 1 - 24 hours.

Compound (III) which is the starting material can be prepared according to the process described in JP-A-21679/83, as shown below.



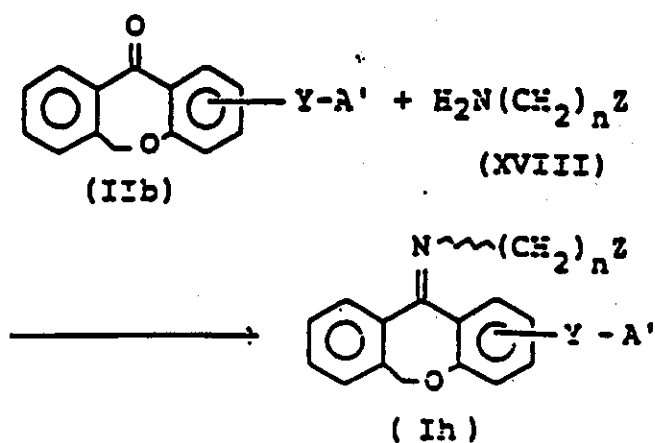
That is, Compound (IIb), 1 to 5 equivalents of methyltriphenylphosphonium bromide and 1 to 5 equivalents of n-butyl lithium on the basis of Compound (IIb) are subjected to reaction in an inert solvent at from -78°C to room temperature for 1 to 5 hours to yield ylide (XVII) which is reacted with an equivalents of Compound (IIb) in an inert solvent at from -78°C to room temperature under atmosphere of an inert gas for 1 to 24 hours to yield Compound (IIIa).

The inert gas includes nitrogen, argon, etc. and the inert solvent includes tetrahydrofuran, etc.

The group A' in Compound (IIIa) can easily be converted to a lower alkanoyl group and therefore, Compound (III) can easily be prepared.

Process E

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



Compound (IIb) and 1 to 10 equivalents of Compound (XVIII) are subjected to reaction in an inert solvent such as benzene in the presence of 1 to 10 equivalents of titanium tetrachloride at from 0°C to the boiling point of the solvent under atmosphere of an inert gas such as nitrogen and argon for 1 to 48 hours to yield Compound (Ih).

Table 1 shows examples of Compound (I) or pharmaceutically acceptable salts thereof and Table 2 shows the structural formula thereof.

Table 3 shows characteristic signals in NMR and Table 4 shows retention time in HPLC.

|    |   |                                                                                                                                                                            |
|----|---|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5  | 1 | Methyl cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate<br>Methyl trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate |
| 10 | 2 | Ethyl cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate<br>Ethyl trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate   |
| 15 | 3 | Cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid<br>Trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid       |
| 20 | 4 | Methyl cis-11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate<br>Methyl trans-11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate   |
| 25 | 5 | Cis-11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid<br>Trans-11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid         |
| 30 | 6 | Methyl cis-11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate<br>Methyl trans-11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate     |
| 35 |   |                                                                                                                                                                            |
| 40 |   |                                                                                                                                                                            |
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| 50 |   |                                                                                                                                                                            |
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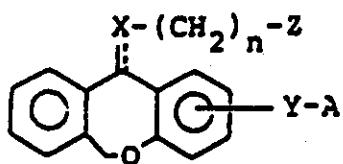
|    |                                                                                                                                                                                                |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 7  | Cis-11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid<br>Trans-11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid                               |
| 8  | Methyl cis-11-[2-(4-methylpiperazino)-ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetate<br>Methyl trans-11-[2-(4-methylpiperazino)-ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetate       |
| 9  | Cis-11-[2-(4-methylpiperazino)-ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid<br>Trans-11-[2-(4-methylpiperazino)-ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid             |
| 10 | Methyl cis-3-[11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate<br>Methyl trans-3-[11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate |
| 11 | Cis-3-[11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid<br>Trans-3-[11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid       |
| 12 | Methyl cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-3-acetate<br>Methyl trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-3-acetate                     |
| 13 | Cis-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid<br>Trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid                           |
| 14 | Cis-11-(3-dimethylaminopropylidene)-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin<br>Trans-11-(3-dimethylaminopropylidene)-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin                 |

|    |    |                                                                                                                                                                                                      |
|----|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5  | 15 | Cis-11-(3-dimethylaminopropylidene)-2-(2-triphenylmethoxy, ethyl)-6,11-dihydrodibenz[b,e]oxepin<br>Trans-11-(3-dimethylaminopropylidene)-2-(2-triphenylmethoxy, ethyl)-6,11-dihydrodibenz[b,e]oxepin |
| 10 | 16 | Cis-11-(3-dimethylaminopropylidene)-2-(3-hydroxypropyl)-6,11-dihydrodibenz[b,e]oxepin<br>Trans-11-(3-dimethylaminopropylidene)-2-(3-hydroxypropyl)-6,11-dihydrodibenz[b,e]oxepin                     |
| 15 | 17 | Methyl <sup>Syn</sup> -11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate<br>Methyl anti-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate                  |
| 20 | 18 | <sup>Syn</sup> -11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid<br>Anti-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid                        |
| 25 | 19 | Methyl <sup>Syn</sup> -11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate<br>Methyl anti-11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate                    |
| 30 | 20 | <sup>Syn</sup> -11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid<br>Anti-11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid                          |
| 35 |    |                                                                                                                                                                                                      |
| 40 |    |                                                                                                                                                                                                      |
| 45 |    |                                                                                                                                                                                                      |
| 50 |    |                                                                                                                                                                                                      |
| 55 |    |                                                                                                                                                                                                      |

|    |                                                                                                                                                                                                                   |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 21 | <p><i>Syn</i><br/>Methyl 1-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate</p> <p>Methyl anti-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate</p>                 |
| 22 | <p><i>Syn</i><br/>1-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid</p> <p>Anti-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid</p>                       |
| 23 | <p><i>Syn</i><br/>Methyl 1-3-[11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate</p> <p>Methyl anti-3-[11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate</p> |
| 24 | <p><i>Syn</i><br/>1-3-[11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid</p> <p>Anti-3-[11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid</p>       |
| 25 | <p>Methyl cin-2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate</p> <p>Methyl anti-2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate</p>            |
| 26 | <p><i>Syn</i><br/>2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid</p> <p>Anti-2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid</p>       |
| 27 | <p><i>Syn</i><br/>Methyl 1-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate</p> <p>Methyl anti-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate</p>                   |
| 28 | <p><i>Syn</i><br/>1-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid</p> <p>Anti-11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid</p>                         |

|    |                                                                                                                                                                                          |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 29 | <sup>Syn</sup><br>Methyl -11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate<br>Methyl anti-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate |
| 30 | <sup>Syn</sup><br>-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid<br>Anti-11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid       |
| 31 | 11-(3-Dimethylaminopropylidene)-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin                                                                                          |
| 32 | Methyl cis-11-(3-methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate<br>Methyl trans-11-(3-methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate                   |
| 33 | Cis-11-(3-methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid<br>Trans-11-(3-methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid                         |
| 34 | Methyl cis-11-(3-aminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate<br>Methyl trans-11-(3-aminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate                               |
| 35 | Cis-11-(3-aminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid<br>Trans-11-(3-aminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid                                     |

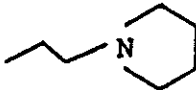
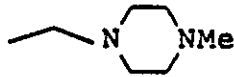
|        |                                                                        |
|--------|------------------------------------------------------------------------|
| 3'     | Fumarate . 3/2 hydrate of Compound <sup>3</sup><br>(trans form 95%)    |
| 5 9'   | Fumarate . 2/3 hydrate of Compound <sup>9</sup><br>(trans form 88%)    |
| 10 11' | Fumarate . 1/2 hydrate of Compound <sup>11</sup><br>(trans form 63%)   |
| 14'    | 1/2 Fumarate . 1 hydrate of Compound <sup>14</sup><br>(trans form 95%) |
| 16'    | <sup>16</sup><br>Fumarate of Compound (cis form 100%)                  |
| 15 24' | Sodium salt of Compound (anti form 98%)                                |
| 20 26' | Sodium salt . 1 hydrate of Compound <sup>26</sup><br>(anti form 99%)   |

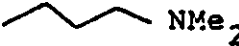
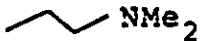
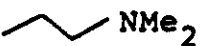
Table 2

Me : methyl group

Ph : phenyl group

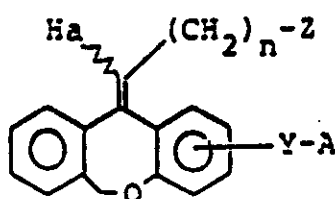
Et : ethyl group

| Compound No. | X  | -Y-A                                                  | -(CH <sub>2</sub> ) <sub>n</sub> -Z                                                  |
|--------------|----|-------------------------------------------------------|--------------------------------------------------------------------------------------|
| 1            | CH | 2-CH <sub>2</sub> COOMe                               |    |
| 2            | "  | 2-CH <sub>2</sub> COOEt                               | "                                                                                    |
| 3            | "  | 2-CH <sub>2</sub> COOH                                | "                                                                                    |
| 4            | "  | 2-CH <sub>2</sub> COOMe                               |    |
| 5            | "  | 2-CH <sub>2</sub> COOH                                | "                                                                                    |
| 6            | "  | 2-CH <sub>2</sub> COOMe                               |    |
| 7            | "  | 2-CH <sub>2</sub> COOH                                | "                                                                                    |
| 8            | "  | 2-CH <sub>2</sub> COOMe                               |   |
| 9            | "  | 2-CH <sub>2</sub> COOH                                | "                                                                                    |
| 10           | "  | 2-CH <sub>2</sub> CH <sub>2</sub> COOMe               |  |
| 11           | "  | 2-CH <sub>2</sub> CH <sub>2</sub> COOH                | "                                                                                    |
| 12           | "  | 3-CH <sub>2</sub> COOMe                               | "                                                                                    |
| 13           | "  | 3-CH <sub>2</sub> COOH                                | "                                                                                    |
| 14           | "  | 2-CH <sub>2</sub> CH <sub>2</sub> OH                  | "                                                                                    |
| 15           | "  | 2-CH <sub>2</sub> CH <sub>2</sub> OC(Ph) <sub>3</sub> | "                                                                                    |
| 16           | "  | 2-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH  | "                                                                                    |
| 17           | "  | 2-CH <sub>2</sub> COOMe                               |  |
| 18           | "  | 2-CH <sub>2</sub> COOH                                | "                                                                                    |

| Compound No. | X  | -Y-A                                                                                | -(CH <sub>2</sub> ) <sub>n</sub> -Z                                                                   |
|--------------|----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| 19           | N  | 2-CH <sub>2</sub> COOMe                                                             |  NEt <sub>2</sub>   |
| 20           | "  | 2-CH <sub>2</sub> COOH                                                              | "                                                                                                     |
| 21           | "  | 2-CH <sub>2</sub> COOMe                                                             |  NMe <sub>2</sub>   |
| 22           | "  | 2-CH <sub>2</sub> COOH                                                              | "                                                                                                     |
| 23           | "  | 2-CH <sub>2</sub> CH <sub>2</sub> COOMe                                             |  NEt <sub>2</sub>   |
| 24           | "  | 2-CH <sub>2</sub> CH <sub>2</sub> COOH                                              | "                                                                                                     |
| 25           | "  | 2-CH(CH <sub>3</sub> )COOMe                                                         |  NMe <sub>2</sub>   |
| 26           | "  | 2-CH(CH <sub>3</sub> )COOH                                                          | "                                                                                                     |
| 27           | "  | 3-CH <sub>2</sub> COOMe                                                             | "                                                                                                     |
| 28           | "  | 3-CH <sub>2</sub> COOH                                                              | "                                                                                                     |
| 29           | "  | 3-CH <sub>2</sub> COOMe                                                             |  NMe <sub>2</sub> |
| 30           | "  | 3-CH <sub>2</sub> COOH                                                              | "                                                                                                     |
| 31           | CH |  |  NMe <sub>2</sub> |

| Compound No. | X | -Y-A                    | -(CH <sub>2</sub> ) <sub>n</sub> -Z                                                                               |
|--------------|---|-------------------------|-------------------------------------------------------------------------------------------------------------------|
| 32           | " | 2-CH <sub>2</sub> COOMe |  NMe <sub>3</sub> <sup>+</sup> |
| 33           | " | 2-CH <sub>2</sub> COOH  | "                                                                                                                 |
| 34           | " | 2-CH <sub>2</sub> COOMe |  NH <sub>2</sub>               |
| 35           | " | 2-CH <sub>2</sub> COOH  | "                                                                                                                 |

Table 3



| Compound | Chemical shift of Ha proton (ppm) |       | Measure solvent |
|----------|-----------------------------------|-------|-----------------|
|          | Cis                               | Trans |                 |
| 1        | 5.69                              | 6.06  | A               |
| 2        | 5.70                              | 6.07  | A               |
| 3        | 5.66                              | 6.00  | B               |
| 4        | 5.66                              | 6.02  | A               |
| 5        | 5.67                              | 6.02  | B               |
| 6        | 5.69                              | 5.99  | A               |
| 7        | 5.60                              | 5.92  | A               |
| 8        | 5.84                              | 6.17  | A               |
| 9        | 5.72                              | 6.05  | B               |
| 10       | 5.69                              | 6.57  | A               |
| 11       | 5.50                              | 5.99  | B               |
| 14       | 5.66                              | 5.99  | A               |

| Compound | Chemical shift of Ha proton (ppm) |       | Measure solvent |
|----------|-----------------------------------|-------|-----------------|
|          | Cis                               | Trans |                 |
| 15       | 5.69                              | 6.97  | A               |
| 16       | 5.65                              |       | A               |
| 32       | 5.63                              | -     | A               |
| 33       | 5.65                              | -     | B               |
| 34       | 5.68                              | -     | A               |
| 35       | 5.67                              | -     | B               |

A = CDCl<sub>3</sub>B = DMSO-d<sub>6</sub>

Table 4

| Compound | Retention time in HPLC<br>(Minutes) |       | Eluent |
|----------|-------------------------------------|-------|--------|
|          | Cis                                 | Trans |        |
| 3        | 9.93                                | 7.46  | B      |
| 5        | 11.10                               | 8.40  | B      |
| 7        | 10.50                               | 8.00  | B      |
| 9        | 11.20                               | 8.93  | B      |
| 11       | 11.60                               | 9.10  | B      |
| 16       | 11.06                               | -     | B      |
| 32       | 10.77                               | -     | B      |
| 35       | 10.65                               | -     | B      |

Instrument: SHIMAZU LC-3A

Column Yamamurakagaku YMC A-312

A 0.01M PIC B-8

in 54.3% MeOH

B 0.01M PIC B-8

in 61.3% MeOH

C 0.01M PIC B-8

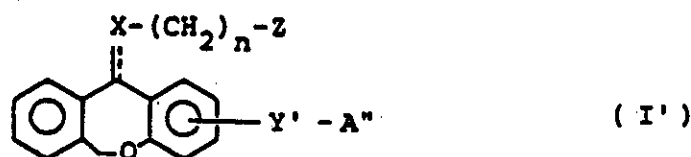
in 66.0% MeOH

\* PIC : PIC reagent (Produced by Water  
Associates)

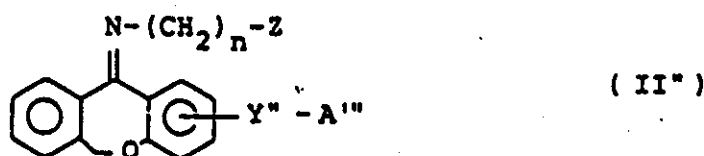
Pressure : 85 - 95 kg/cm<sup>2</sup>

Temperature: room temperature

Compound (I) has both an antiallergic activity and antiinflammatory activity. Among Compound (I), the compound represented by the formula (I') has strong antiallergic activity and the compound represented by the formula (II') has strong antiinflammatory activity.



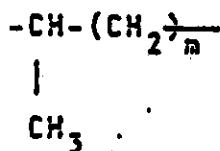
In the formula, X, n and Z are as previously defined, -Y'-A'' is -Y-A when X is = CH - and is -Y-A which is bound at 2 position of the mother nucleus when X is = N-, and Y and A are as previously defined.



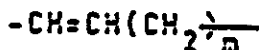
In the formula, n and Z are as previously defined; Y'' is -CH<sub>2</sub>- or -CHR<sub>3</sub>- substituted at 2 or 3 position of the mother nucleus wherein R<sub>3</sub> is a lower alkyl; A''' is a hydroxymethyl, a loweralkoxymethyl, a triphenylmethyloxymethyl, a lower alkanoyloxymethyl, a formyl, a carboxyl, a lower alkoxy carbonyl, a triphenylmethyloxycarbonyl, -CONR<sub>1</sub>R<sub>2</sub> wherein R<sub>1</sub> and R<sub>2</sub> are the same or different and are hydrogen atom or a lower alkyl, 4,4-dimethyl-2-oxazoline-2-yl or -CONHOH.

the preferred compounds according to the invention are the compounds of formula (I) as above defined wherein A is a member selected from the group consisting of lower alkoxy carbonyl, (-CONR<sub>1</sub>R<sub>2</sub>), carboxyl; Y is bound at 2-position of the mother nucleus; X is member selected from the group consisting of =N- and =CH-; n is 1 or 2; and Z is a member selected from the group consisting of dimethylamino, diethylamino, methylamino, amino, morpholino and thiomorpholino.

Of those particular compounds, those of formula (I) wherein Y is a member selected from the group



and



and m is 1 or 2, are preferred and more particularly those of formula (I) wherein X is =CH- and A is a carboxyl.

The most preferred compounds are those of formula (I) wherein -Y-A is a member selected from the group consisting of carboxymethyl, 2-carboxyethyl, X is =CH-, n is 2 and Z is a member selected from the group consisting of dimethylamino, diethylamino methylamino, amino, morpholino and thiomorpholino.

The antiallergic activity and antiinflammatory activity of Compound (I) are described below:

Test for antiallergic activity:

Antiallergic activity was investigated by a homologous PCA (passive cutaneous anaphylaxis) of rats for 48 hours, where Wistar male rats having body weights of 180 to 220 g were used for sampling of antiserum and Wistar male rats having body weights of 120 to 140 g were used for the PCA test.

## A) Preparation of anti EWA rat serum

Anti-egg white albumin (EWA) rat serum was prepared according to Stotland and Share's method [Canad. J. Physiol. Pharmacol. 52, 1114 (1974)]. That is, 1 mg of EWA was mixed with 20 mg of aluminum hydroxide gel and 0.5 ml of mixed vaccine of pertussis, diphtheria and tetanus, and the mixture was subcutaneously administered in four portions into rat's footpad. After 14 days, blood was sampled from the carotid artery, and the serum was separated from the sampled blood, and preserved under freezing at -80°C. The potency of the antiserum in the homologous PCA for 48 hours was 1 : 32.

## B) Homologous PCA test of rats for 48 hours

Groups each consisting of 3 rats were used, and 0.05 ml of anti-EWA rat serum diluted with a physiological saline solution to 8 times as much was incutaneously injected each at two positions of depilated back to make the animals passively sensitised. After 47 hours, the compound of the present invention, or its solution (physiological saline solution or CMC solution) was orally administered. One hour thereafter, 0.5 ml/100 g of 1% Evan's blue physiological saline solution containing 2 mg of the antigen EWA was administered into the tail vein, and 30 minutes thereafter, the animals were sacrificed by exsanguination. Then, the skins were stripped and the amount of leaked pigment at the blue-dyed parts was measured according to the Katayama et al method [Microbiol. Immunol. 22, 89 (1978)]. That is, the blue-dyed parts were cut out by scissors, and placed in test tubes containing 1 ml of 1N KOH and incubated at 37°C for 24 hours. Then, 9 ml of a mixture of 0.6N phosphoric acid and acetone (5 :13) was added thereto, and the mixture was shaken and centrifuged at 2,500 rpm for 10 minutes. Absorbancy of the supernatant at 620 µm was measured, and the amount of leaked pigment was quantitatively determined by the calibration curve prepared in advance. An average of measurements at the two position was made a value for one zooid, and inhibition rate for the individual zooid was calculated by the following formula:

**Inhibition rate (%) =**

$$\frac{\text{Average leaked amount of solvent-administered group} - \text{Leaked amount of test compound-administered group}}{\text{Average leaked amount of solvent-administered group}} \times 100$$

Cases where, the inhibition rate is 50% or higher, were regarded as positive PCA inhibition activity, and the minimum administered dosage, where a positive case was observed in at least one of three zooids was regarded as minimum effective dosage (MED). The results are shown in Table 5.

## Acute toxicity test:

Groups each consisting of 3 dd, male mice having body weights of 20 ± 1 g were used, and the compound of the present invention was administered orally (po: 300 mg/kg) or intraperitoneally (ip: 100 mg/kg). Mortality 7 days after the administration was observed to obtain MLD (minimum lethal dosage). The results are shown in Table 5.

## Antiinflammatory activity test:

Antiinflammatory activity was examined according to Rat carrageenin paw edema [J. Pathol. 104, 15-29 (1971)]. Groups each consisting of three Wistar male rats weighing 150 g were used. The test compound was suspended in 0.3% aqueous CMC solution and the suspension was given orally. Sixty minutes later, 0.1 ml of 0.1% carrageenin solution was subcutaneously injected in a hind paw to form carrageenin paw edema.

The volume of paw was measured before the administration and 3 hours after the administration of carrageenin with plethysmometer.

The ratio of the volume 3 hours after the administration to that before the administration of carageenin was calculated and each ratio is compared with the ratio of control group (0.3% CMC solution was administered) to give the edema inhibiting percentage. The results are shown in Table 6.

Table 5

| Compound                                   | Acute toxicity (MLD) mg/kg |      | Antiallergic Activity<br>Number of positive zooids<br>in one group of 3 zooids<br>Dosage mg/kg |     |     |     |      |       | M E D<br>mg/kg |
|--------------------------------------------|----------------------------|------|------------------------------------------------------------------------------------------------|-----|-----|-----|------|-------|----------------|
|                                            | po                         | ip   | 100                                                                                            | 10  | 1   | 0.1 | 0.01 | 0.001 |                |
| 3 <sup>r</sup><br>(trans)                  | >300                       | >100 | 3/3                                                                                            | 3/3 | 3/3 | 1/3 | 0/3  | -     | 0.1            |
| 3<br>(trans)                               | >300                       | >100 | 2/3                                                                                            | 2/3 | 3/3 | 3/3 | 0/3  | 0/3   | 0.1            |
| 3<br>(cis)                                 | >300                       | >100 | 3/3                                                                                            | 3/3 | 3/3 | 3/3 | 1/3  | 0/3   | 0.01           |
| 5<br>(cis:trans<br>= 92 : 8)               | >300                       | >100 | 3/3                                                                                            | 3/3 | 2/3 | 1/3 | 0/3  | -     | 0.1            |
| 9 <sup>r</sup><br>(cis:trans<br>= 12 : 88) | >300                       | >100 | 3/3                                                                                            | 3/3 | 2/3 | 0/3 | -    | -     | 1              |

5

10

15

20

25

30

35

40

45

50

55

|                                 |      |      |     |     |     |     |     |     |      |
|---------------------------------|------|------|-----|-----|-----|-----|-----|-----|------|
| 11'<br>(cis:trans<br>= 37 : 63) | >300 | >100 | 3/3 | 3/3 | 3/3 | 2/3 | 2/3 | 0/3 | 0.01 |
| 11<br>(cis)                     | >300 | >100 | 3/3 | 2/3 | 3/3 | 1/3 | 0/3 | -   | 0.1  |
| 11<br>(trans)                   | >300 | >100 | 3/3 | 3/3 | 2/3 | 2/3 | 1/3 | 0/3 | 0.01 |
| 14'<br>(trans)                  | >300 | >100 | 3/3 | 3/3 | 3/3 | 1/3 | 0/3 | -   | 0.1  |
| 17<br>(trans)                   | >300 | >100 | 3/3 | 3/3 | 2/3 | 3/3 | 0/3 | -   | 0.1  |
| 14<br>(cis)                     | 200  | >100 | -   | 3/3 | 3/3 | 2/3 | 0/3 | 0/3 | 0.1  |
| 16'<br>(cis)                    | NT   | NT   | 3/3 | 3/3 | 1/3 | 0/3 | -   | -   | 1    |
| 18<br>( :anti<br>= 8 : 92)      | 300> | 100> | 3/3 | 3/3 | 0/3 | -   | -   | -   | 10   |
| 20<br>( :anti<br>= 2 : 98)      | 300> | 100> | 3/3 | 2/3 | 3/3 | 0/3 | -   | -   | 1    |
| 22<br>( :anti<br>= 3 : 97)      | 300> | 100> | 3/3 | 2/3 | 1/3 | 0/3 | -   | -   | 1    |
| 24<br>( :anti<br>mixture)       | 300> | 100> | 3/3 | 2/3 | 0/3 | 0/3 | -   | -   | 10   |
| 26'<br>(anti)                   | 300> | 100> | 3/3 | 3/3 | 2/3 | 0/3 | -   | -   | 1    |

Table 6

| Compound No. | Carrageenin paw edema inhibiting percentage (%)<br>(Average value in one group of 3 rats, 100 mg/kg oral administration) |
|--------------|--------------------------------------------------------------------------------------------------------------------------|
| 18           | 51.6                                                                                                                     |
| 20           | 50.2                                                                                                                     |
| 22           | 38.7                                                                                                                     |
| 26'          | 63.1                                                                                                                     |
| 28           | 46.0                                                                                                                     |
| 30           | 24.1                                                                                                                     |

As is evidenced in Tables 5 and 6, Compound (I) and pharmaceutically acceptable salt thereof have PCA inhibiting activity and/or carrageenin paw edema inhibiting activity.

PCA inhibiting activity is believed to be on the basis of an activity inhibiting liberation of chemical mediator such as histamine from fat skin cell. Therefore, Compound (I) and pharmaceutically acceptable salts thereof are believed to be useful for treating an allergic disease such as bronchus asthma which is caused by trachea contracting activity of chemical mediator such as histamine.

On the other hand, carrageenin paw edema inhibiting activity is believed to be on the basis of prostaglandin biosynthesis inhibiting activity. Thus, Compound (I) and pharmaceutically acceptable salts thereof are believed to be useful for treating an acute inflammation and rheumatism which are ascribed to excessive prostaglandin.

Compound (I) includes a compound having both antiallergic and antiinflammatory activities described above which is useful for the treatment of allergic diseases accompanied by inflammation.

In view of the pharmacological activity of Compound (I), Compound (I) can be used in various medicament forms for the administration purposes.

The present medicament composition can be prepared by uniformly mixing an effective amount of a free Compound (I) or a pharmaceutically acceptable salt thereof as an active component with a pharmaceutically acceptable carrier or excipient. The carrier can take a wide range of forms in accordance with a desirable medicament form for the administration. These medicament compositions are desirably in a unit dosage form suitable for the oral administration or injection administration. In the preparation of a composition in the oral dosage form, any useful, pharmaceutically acceptable carrier can be used. For example, an oral liquid preparation such as a suspended medicament or syrup medicament can be prepared using water; sugars such as sucrose, sorbitol, fructose, etc.; glycols such as polyethylene glycol, propylene glycol, etc.; oils such as sesame oil, olive oil, soybean oil, etc.; antiseptics such as alkyl parahydroxybenzoate, etc.; and flavors such as strawberry flavor, peppermint, etc. Powder, pills, capsules and tablets can be prepared using an excipient such as lactose, glucose, sucrose, mannitol, etc.; a disintegrator such as starch, sodium alginate, etc.; a lubricant such as magnesium stearate, talc, etc.; a binder such as polyvinyl alcohol, hydroxypropylcellulose, gelatin, etc.; a surfactant such as fatty acid esters; and a plasticizer such as glycerine, etc. Tablets and capsules are the most useful, oral unit dosage forms because of easy administration. To prepare tablets and capsules, solid carriers for medicament are used. Injection solution can be prepared using a carrier consisting of a salt solution, a glucose solution or a mixture of the salt solution and the glucose solution. The effective dosage of Compound (I) is 1 to 20 mg/kg/day for a human being, and number of administration is 3 to 4 per day.

Examples and Reference Examples are given below:

#### Reference example I

(Raw material I) Methyl 11-oxo-6,11-dihydrodibenz[b,e] oxepin-2-carboxylate

In this example, 348.9 g of sodium salt of methyl p-hydroxybenzoate, 402.4 g of phthalide and 200 g of sodium chloride are mixed with one another and stirred at 150°C for 6 hours. After completion of the reaction, the mixture is cooled until the temperature is brought back to room temperature, 4 l of aqueous 10 % acetic acid solution is added thereto and the mixture is allowed to stand at room temperature overnight. After stirring the mixture at room temperature for 3 hours, deposited crystals are separated by filtration, and 6 l of water is added thereto. After stirring the mixture at room temperature for 30 minutes, the deposited crystals are separated by filtration. After the addition of 3 l of toluene to the crystals, the mixture is stirred at room temperature for one hour. The crystals are separated by filtration and dried over heating under reduced pressure to yield 393.9 g of 2-(4-methoxycarbonylphenoxy) methyl benzoic acid.

IR (KBr disk): 3400, 1700, 1610, 1260, 1235  $\text{cm}^{-1}$

The thus obtained 2-(4-methoxycarbonylphenoxy) methyl benzoic acid (392.7 g) is suspended in 5.0 l of methylene chloride and 266.0 g of trifluoroacetic anhydride is added thereto. After stirring the mixture at room temperature for one hour, 19.4 g of boron trifluoride-ethylether complex is added thereto and the mixture is stirred at room temperature for two hours. The reaction solution is poured into ice water. After an organic solvent layer is separated from the mixture, the organic layer is washed with diluted aqueous sodium hydroxide solution and water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain 335.3 g of methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate as a white crystal.

Melting point and elementary analysis are shown in Table 7.

IR (KBr disk): 1710, 1650, 1610, 1250, 1010  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 3.84(s, 3H), 5.14(s, 2H), 6.87-8.93(m, 7H)

#### Reference examples 2 - 5

(Raw material 2) 11-Oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid

(Raw material 3) 11-Oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid

(Raw material 4) 2-(11-Oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionic acid

(Raw material 5) 3-(11-Oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionic acid

Raw materials 2 - 5 are produced by respectively substituting p-hydroxyphenyl acetic acid, m-hydroxyphenyl acetic acid, 2-(p-hydroxyphenyl)-propionic acid and 3-(p-hydroxyphenyl)-propionic acid for methyl p-hydroxybenzoate in Reference example 1.

Melting points and elementary analyses thereof are shown in Table 7.

#### Reference example 6

(Raw material 6) Methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate

In 100 ml of tetrahydrofuran is suspended 25 g of methyltriphenylphosphonium bromide and 40 ml of 1.6 N-n-butyl lithium hexane solution is dropwise added thereto under a nitrogen atmosphere and ice-cooling. After stirring the mixture under ice-cooling for 30 minutes, a solution obtained by dissolving 15 g of methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in 250 ml of tetrahydrofuran is dropwise added thereto and the mixture is stirred at room temperature for two hours. The solvent is distilled away under reduced pressure and the residue is purified by column chromatography on silica gel (eluent: hexane :ethyl acetate = 3 : 1) to obtain 3.7 g of the desired product as a colorless oily matter.

NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 3.83(s, 3H), 5.15(s, 2H), 5.29 (s, 1H), 5.74(s, 1H), 6.69-8.22(m, 7H)

Melting point and elementary analysis are shown in Table 7.

#### Reference example 7

(Raw material 7) Methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-acetate

The desired product is obtained by substituting 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in Reference example 6.

Colorless oily matter

NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 3.48(s, 2H), 3.61(s, 3H), 5.05 (s, 2H), 5.20(s, 1H), 5.62(s, 1H), 6.59-7.43 (m, 7H)

IR (neat,  $\text{cm}^{-1}$ ): 2950, 1740, 1615, 1490, 1010

Melting point and elementary analysis are shown in Table 7.

#### Reference example 8

(Raw material 8) 11-Methylene-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid

To a mixed solvent of 200 ml of methanol and 50 ml of 2N-aqueous sodium hydroxide solution is added 2.9 g of methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-acetate (raw material 7, Reference example 7) and the mixture is heated at reflux for two hours. After allowing the mixture to stand for cooling, the mixture is concentrated under reduced pressure, and the pH of the mixture is adjusted to 1.0 with aqueous 4N-hydrochloric acid solution. The mixture is extracted with 500 ml of ethyl acetate, then the organic layer is washed with aqueous 1N-hydrochloric acid solution and saturated aqueous sodium chloride solution in order

and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure and the resultant crude product is crystallized from hexane to obtain 2.7 g of the desired product as a white solid.

NMR (DMSO- $d_6$  + D<sub>2</sub>O,  $\delta$ , ppm): 3.45(s, 2H), 5.02(s, 2H), 5.16(s, 1H), 5.60(s, 1H), 6.45-7.44(m, 7H)

Melting point and elementary analysis are shown in Table 7.

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Reference example 9

(Raw material 9) Methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-3-acetate

The desired product is obtained by substituting 11-oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in Reference example 6.

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## Reference example 10

(Raw material 10) II-Methylene-6,II-dihydrodibenz[b,e]oxepin-3-acetic acid

The desired product is obtained by substituting methyl II-methylene-6,II-dihydrodibenz[b,e]oxepin-3-acetate for methyl II-methylene-6,II-dihydrodibenz[b,e]oxepin-2-acetate in Reference example 8.

Table 7

| Raw material | Melting point (°C)                 | Elementary analysis (%) or mass spectrum |       |      |
|--------------|------------------------------------|------------------------------------------|-------|------|
| 1            | 128 - 129<br><br>(Isopropyl ether) | as $C_{16}H_{12}O_4$                     |       |      |
|              |                                    |                                          | C     | H    |
|              |                                    | Calculated                               | 71.63 | 4.51 |
|              |                                    | Found                                    | 71.55 | 4.48 |
| 2            | 130 - 132<br><br>(Ethyl acetate)   | as $C_{16}H_{12}O_4$                     |       |      |
|              |                                    |                                          | C     | H    |
|              |                                    | Calculated                               | 71.63 | 4.51 |
|              |                                    | Found                                    | 71.86 | 4.55 |

| Raw material | Melting point (°C)           | Elementary analysis (%) or mass spectrum                                                            |
|--------------|------------------------------|-----------------------------------------------------------------------------------------------------|
| 3            | 111 - 114<br>(Ethyl acetate) | as $C_{16}H_{12}O_4$<br><br>C      H<br>Calculated    71.63    4.51<br>Found          71.53    4.66 |
| 4            | Syrup                        | as $C_{17}H_{14}O_4$<br>(M + 282)                                                                   |
| 5            | 144 - 145<br>( Water )       | as $C_{17}H_{14}O_4$<br><br>C      H<br>Calculated    72.33    5.00<br>Found          72.45    5.20 |
| 6            | Syrup                        | as $C_{17}H_{14}O_3$<br>(M + 266)                                                                   |
| 7            | Syrup                        | as $C_{18}H_{16}O_3$<br>(M + 280)                                                                   |
| 8            | 162 - 163<br>( Water )       | as $C_{17}H_{14}O_3$<br><br>C      H<br>Calculated    76.68    5.30<br>Found          76.29    5.16 |

#### Reference example II

(Reagent I) (3-Dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide

In this example, 350.0 g of triphenylphosphine and 270.0 g of dibromopropane are suspended in 700 ml of toluene and the suspension is heated at reflux for 25 hours. After allowing the suspension to stand for cooling, the formed product is separated by filtration and washed with 2 l of toluene to obtain 550.0 g of (3-bromopropyl)-triphenylphosphonium bromide hydrobromide having m.p. 233 - 234 °C.

Then, 100.0 g of (3-bromopropyl)-triphenylphosphonium bromide hydrobromide is suspended in 500 ml of ethanol and 300 ml of 50 % aqueous dimethylamine solution is added thereto. After heating the mixture at reflux for 10 minutes, the mixture is allowed to stand for cooling. The solvent is distilled away under reduced pressure and the resultant crude product is recrystallized from ethanol to obtain 64.0 g of the desired product having the physicochemical properties as identified in Table 8.

## Reference examples 12 - 14

(Reagent 2) (3-Diethylaminopropyl)-triphenylphosphonium bromide hydrobromide • 1/3 hydrate

(Reagent 3) (4-Dimethylaminobutyl)-triphenylphosphonium bromide hydrobromide

5 (Reagent 4) (3-Pyrrolidinopropyl)-triphenylphosphonium bromide hydrobromide • 1/2 hydrate

The above-captioned compounds are prepared according to the same manner as in Reference example 11 and the physicochemical properties are shown in Table 8.

Table 8

| Reagent | Melting point<br>(°C)      | Elementary analysis (%)                                                                               |
|---------|----------------------------|-------------------------------------------------------------------------------------------------------|
| 1       | 287 - 289<br>(Ethanol)     | as $C_{23}H_{28}NPBr_2$<br>C H N<br>Calculated 54.24 5.54 2.75<br>Found 54.12 5.63 2.93               |
| 2       | 228 - 230<br>(Isopropanol) | as $C_{25}H_{32}NPBr_2 \cdot 1/3H_2O$<br>C H N<br>Calculated 55.33 6.05 2.58<br>Found 55.31 6.19 2.68 |
| 3       | 255 - 257<br>(Isopropanol) | as $C_{24}H_{30}NPBr_2$<br>C H N<br>Calculated 55.09 5.78 2.68<br>Found 55.04 5.91 2.62               |
| 4       | 291 - 293<br>(Ethanol)     | as $C_{25}H_{30}NPBr_2 \cdot 1/2H_2O$<br>C H N<br>Calculated 55.17 5.74 2.57<br>Found 55.18 5.95 2.66 |

## Example 1

11-(3-Dimethylaminopropylidene)-2-(2-triphenylmethoxyethyl)-6,11-dihydrodibenz[b,e]oxepin (Compound 15)

## 50 Process A:

11-Hydroxy-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 20 g of methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate is dissolved in 500 ml of tetrahydrofuran. To the solution is added 6.0 g of lithium aluminium hydride and the mixture is stirred at room temperature for one hour. After decomposing an excess of the reagent by the addition of water to the solution, the mixture is filtered to remove an inorganic salts and the filtrate is concentrated to dryness under reduced pressure to obtain 17.7 g of the desired product as a white solid.

Melting point:

132 - 136 °C

NMR (CDCl<sub>3</sub> + DMSO-d<sub>6</sub> + D<sub>2</sub>O, δ, ppm):2.59(t, 2H, J=6.8Hz), 3.55(t, 2H, J=6.8Hz), 4.89 and 5.71-  
(ABq, 2H, J=12.6Hz), 5.60(s, 1H), 6.46-7.49(m, 7H)

## 5 Process B

## 11-Hydroxy-2-(2-triphenylmethoxyethyl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 17.2 g of 11-hydroxy-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in 50 ml of pyridine. To the solution is added 30 g of triphenylchloromethane and the mixture is stirred at 50 °C for 5 hours. After adding water and stirring the mixture for 2 hours, the solvent is distilled away under reduced pressure. The mixture is extracted with 1000 ml of ethyl acetate, then the organic layer is washed with saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure and the resultant residue is purified by column chromatography on silica gel (eluent: hexane : ethyl acetate = 3 : 1) to obtain 21.7 g of the desired product as a colorless amorphous matter.

NMR (CDCl<sub>3</sub> + D<sub>2</sub>O, δ, ppm): 2.47-2.95(m, 2H), 2.96-3.45(m, 2H), 4.87 and 5.71(ABq, 2H, J=13.2Hz), 5.43(s, 1H), 6.33-7.51(m, 22H)

## 20 Process C:

## 11-Oxo-2-(2-triphenylmethoxyethyl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 10 g of 11-hydroxy-2-(2-triphenylmethoxyethyl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in a solution comprising 800 ml of acetone, 1000 ml of water, 20 ml of saturated aqueous magnesium sulfate solution and 0.2 g of disodium phosphate. To the solution is dropwise added 2.6 g of aqueous sodium permanganate solution and the mixture is stirred at room temperature for 4.5 hours. Then, 100 ml of methanol is added thereto and the mixture is heated at reflux for 3 hours. After allowing the mixture to stand for cooling, the mixture is filtered and the filtrate is extracted with 1000 ml of ethyl acetate, the organic layer is washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure and the resultant crude product is recrystallized from isopropanol to obtain 8.0 g of the desired product having melting point of 132 -134 °C as a white crystal.

35

| Elementary analysis (%): as C <sub>35</sub> H <sub>28</sub> O <sub>3</sub> |         |        |
|----------------------------------------------------------------------------|---------|--------|
| Calculated:                                                                | C 84.65 | H 5.68 |
| Found:                                                                     | C 84.56 | H 5.67 |

40

NMR (CDCl<sub>3</sub>, δ, ppm): 2.61-3.04(m, 2H), 3.05-3.46 (m, 2H), 5.01(s, 2H), 6.63-8.07(m, 22H)

## Process D:

## 11-(3-Dimethylaminopropyl)-11-hydroxy-2-(2-triphenylmethoxyethyl)-6,11-dihydrodibenz[b,e]oxepin

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To a solution of 3-dimethylaminopropyl magnesium chloride obtained by reacting 0.2 g of magnesium with 1.0 g of 3-dimethylaminopropyl chloride in 10 ml of tetrahydrofuran under a nitrogen atmosphere using dibromoethane as a catalyst, is dropwise added a solution obtained by dissolving 2.0 g of 11-oxo-2-(2-triphenylmethoxyethyl)-6,11-dihydrodibenz[b,e]oxepin in 10 ml of tetrahydrofuran under ice cooling and the mixture is stirred at room temperature for one day. Aqueous ammonium chloride solution is added thereto and the pH of the mixture is adjusted to 7.0 with aqueous 4N-hydrochloric acid solution. The solvent is distilled away under reduced pressure. The mixture is extracted with 200 ml of methylene chloride and the organic layer is washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order. After drying the extract over anhydrous sodium sulfate, the solvent is distilled away under reduced pressure. The resultant residue is purified by column chromatography on silica gel (eluent: hexane : ethyl acetate : triethylamine = 10 : 10 : 1) to obtain 1.2 g of the desired product as a colorless amorphous matter.

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NMR (CDCl<sub>3</sub>,  $\delta$ , ppm): 0.85-1.83(m, 4H), 2.08(s, 6H), 2.67-3.44(m, 6H), 4.94 and 5.36(ABq, 2H, J=15.8Hz), 6.63-8.13(m, 22H)  
 Mass spectrum (m/z): 583 (M<sup>+</sup>)

#### 5 Process E:

##### II-(3-Dimethylaminopropylidene)-2-(2-triphenylmethoxyethyl)-6,II-dihydrodibenz[b,e]oxepin

In this process, 1.2 g of II-(3-dimethylaminopropyl)-II-hydroxy-2-(2-triphenylmethoxyethyl)-6,II-dihydrodibenz[b,e]oxepin is dissolved in 50 ml of pyridine. To the solution is dropwise added 0.8 g of phosphorus oxychloride under a nitrogen atmosphere and ice-cooling. After stirring the mixture at room temperature for one hour, the solvent is distilled away under reduced pressure. The residue is extracted with 100 ml of methylene chloride, and the organic layer is washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order. After drying the mixture over anhydrous sodium sulfate, the solvent is distilled away under reduced pressure. The resultant residue is purified by column chromatography on silica gel (eluent: hexane : ethylacetate : triethylamine = 10 : 10 : 1) to obtain 0.82 g of the desired product as a colorless oily matter.

NMR (CDCl<sub>3</sub>,  $\delta$ , ppm): 2.16(s, 6H), 2.30-2.40(m, 4H), 2.79(t, 2H, J=6Hz), 3.24(t, 2H, J=6Hz), 5.97 (t, 1H, J=7Hz), 6.60-7.40(m, 22H), (trans form)  
 Mass spectrum (m/z): 565 (M<sup>+</sup>)

#### Example 2

##### II-(3-Dimethylaminopropylidene)-2-(2-hydroxyethyl)-6,II-dihydrodibenz[b,e]oxepin (Compound 14)

In this example, 0.92 g of II-(3-dimethylaminopropylidene)-2-(2-triphenylmethoxyethyl)-6,II-dihydrodibenz[b,e]oxepin is dissolved in a mixed solvent of 20 ml of water and 20 ml of dioxane. To the solution is added 60 mg of p-toluene sulfonic acid and the mixture is heated at reflux for two hours. The solvent is distilled away under reduced pressure and the residue is extracted with 200 ml of ethylacetate, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure. The resultant residue is purified by column chromatography on silica gel (eluent: ethylacetate : triethylamine = 10 : 1) to obtain 0.4 g of the desired product.

#### 35 Cis form white solid,

Melting point: 100 -102 ° C (diethylether)  
 NMR (CDCl<sub>3</sub>,  $\delta$ , ppm): 2.32(s, 6H), 2.30-2.70(m, 4H), 2.76(t, 2H, J=6Hz), 3.78(t, 2H, J=6Hz), 5.66(t, 1H, J=7Hz), 6.80-7.40(m, 7H)  
 Mass spectrum: 323 (M<sup>+</sup>)

#### Trans form white solid,

Melting point: 96 - 97 ° C (diethylether)  
 NMR (CDCl<sub>3</sub>,  $\delta$ , ppm): 2.21(s, 6H), 2.30-2.70(m, 4H), 2.76(t, 2H, J=6Hz), 3.78(t, 2H, J=6Hz), 6.01(t, 1H, J=7Hz), 6.68-7.40(m, 7H)  
 Mass spectrum (m/z): 323 (M<sup>+</sup>)

#### Example 3

##### II-(3-Dimethylaminopropylidene)-6,II-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 3)

In this Example, 2.2 g of II-(3-dimethylaminopropylidene)-2-(2-hydroxyethyl)-6,II-dihydrodibenz[b,e]oxepin is dissolved in 100 ml of acetone. The Jones reagent is added to the solution until the reaction solution shows an orange color and the mixture is stirred at room temperature for one hour. Sodium bicarbonate is added thereto and an inorganic substance is removed by filtration. The solvent of the filtrate is distilled away under reduced pressure to obtain the desired product. The physicochemical properties of the product coincide with those of the product obtained in Example 17.

Example 4

Methyl 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 1)

5 In this example, 48 g of (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide is suspended in 200 ml of tetrahydrofuran under a nitrogen atmosphere and 80 ml of 1.6N-n-butyl lithium hexane solution is added thereto under ice-cooling. The mixture is stirred under ice-cooling for one hour. A solution obtained by dissolving 5.0 g of 11-oxo-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid in 120 ml of tetrahydrofuran is dropwise added under ice-cooling. After stirring the mixture at room temperature for two  
10 hours, the solvent is distilled away under reduced pressure. Then, 200 ml of water is added to the residue and the mixture is washed with 200 ml of diethyl ether. The pH of the mixture is adjusted to 1 with aqueous 4N-hydrochloric acid solution and the mixture is washed with diethyl ether.

Then, aqueous 10N-sodium hydroxide solution is added thereto to adjust the pH of the mixture to 7 and the solvent is distilled away under reduced pressure. The resultant residue is dissolved in 400 ml of  
15 methanol and 5 g of p-toluene sulfonic acid is added thereto. After heating the mixture at reflux for two hours, the solvent is distilled away under reduced pressure. The residue is extracted with 300 ml of ethyl acetate, and the organic layer is washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order and dried over anhydrous sodium sulfate.

The solvent is distilled away under reduced pressure and the resultant residue is purified by column  
20 chromatography on silica gel (eluent: hexane : ethyl acetate : triethylamine = 10 : 10 : 1) to obtain 4.0 g of the desired product as a colorless oily matter.

Cis form

25 NMR (CDCl<sub>3</sub>, δ, ppm): 2.06-2.67(m, 4H), 2.16(s, 6H), 3.46(s, 2H), 3.58(s, 3H), 5.08(bs, 2H), 5.69 (t, 1H, J = 7Hz), 6.53-7.30(m, 7H)

Trans form

30 NMR (CDCl<sub>3</sub>, δ, ppm): 2.06-2.67(m, 4H), 2.16(s, 6H), 3.46(s, 2H), 3.58(s, 3H), 5.08(bs, 2H), 6.06 (t, 1H, J = 7Hz), 6.53-7.30(m, 7H)

Example 5

35 Methyl 11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 4)

The desired product is obtained by substituting (4-dimethylaminobutyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 4.

Example 6

Methyl 11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 6)

The desired product is obtained by substituting (3-pyrrolidinopropyl)-triphenylphosphonium bromide hydrobromide•1/2 hydrate for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Ex-  
45 ample 4.

Example 7

50 Methyl 3-[11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate (Compound 10)

The desired product is obtained by substituting 3-(11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionic acid for 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid in Example 4.

Example 8

Methyl 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-3-acetate (Compound 12)

- 5 The desired product is obtained by substituting 11-oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid for 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid in Example 9.

Example 9

- 10 Methyl 11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 17)

In this example, 22.0 g of methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate and 68.7 g of N,N-dimethylethylenediamine are dissolved in 700 ml of dried benzene. To the solution is dropwise added a solution of 17.2 ml of titanium tetrachloride in 40 ml of dried benzene and the mixture is stirred at room temperature overnight. A saturated aqueous sodium bicarbonate solution is added thereto. After removing an insoluble solid by filtration, the filtrate is extracted with 500 ml of ethylacetate, and the organic layer is washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order, and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure and the residue is purified by column chromatography on silica gel with ethylacetate /triethylamine (10 /1) as an eluent to obtain 13.8 g of the desired product as a colorless oily matter.

NMR (CDCl<sub>3</sub>,  $\delta$ , ppm): 2.14(s, 6H), 2.63(t, 2H, J=6.9Hz), 3.51(s, 2H), 3.58(s, 3H), 3.38-3.80 (m, 2H), 5.04(bs, 2H), 6.56-7.60(m, 7H)

IR (neat, cm<sup>-1</sup>): 2950, 1740, 1630, 1305, 1015

Mass spectrum (m/z): 352 (M<sup>+</sup>)

25

Example 10

Methyl 11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 19)

- 30 The desired product is obtained by substituting N,N-diethylethylenediamine for N,N-dimethylethylenediamine in Example 9 as a colorless oily matter.

Mass spectrum (m/z): 380 (M<sup>+</sup>) for C<sub>23</sub>H<sub>28</sub>O<sub>3</sub>N<sub>2</sub>

Example 11

35

Methyl 11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 21)

The desired product is obtained by substituting N,N-dimethylpropylenediamine for N,N-dimethylethylenediamine in Example 9 as a colorless oily matter.

- 40 Mass spectrum (m/z): 366 (M<sup>+</sup>) for C<sub>22</sub>H<sub>26</sub>O<sub>3</sub>N<sub>2</sub>

Example 12

Methyl 3-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate (Compound 23)

45

The desired product is obtained by substituting methyl 3-(11-oxo-6,11-dihydrodibenz[b,e]oxepin 2-yl)-propionate for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate in Example 10 as a colorless oily matter.

Mass spectrum (m/z): 394 (M<sup>+</sup>) for C<sub>24</sub>H<sub>30</sub>O<sub>3</sub>N<sub>2</sub>

Example 13

Methyl 2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate (Compound 25)

- 55 The desired product is obtained by substituting methyl 2-(11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionate acid for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate in Example 9 as a colorless oily matter.

Mass spectrum (m/z): 366 (M<sup>+</sup>) for C<sub>22</sub>H<sub>26</sub>O<sub>3</sub>N<sub>2</sub>

Example 14

Methyl II-(2-dimethylaminoethyl)imino-6,II-dihydrodibenz[b,e]oxepin-3-acetate (Compound 27)

5 The desired product is obtained by substituting methyl II-oxo-6,II-dihydrodibenz[b,e]oxepin-3-acetate for methyl II-oxo-6,II-dihydrodibenz[b,e]oxepin-2-acetate in Example 9 as a colorless oily matter.

Mass spectrum (m/z): 352 ( $M^+$ ) for  $C_{21}H_{24}O_3N_2$

Example 15

10

Methyl II-(3-dimethylaminopropyl)imino-6,II-dihydrodibenz[b,e]oxepin-3-acetate (Compound 29)

The desired product is obtained by substituting methyl II-oxo-6,II-dihydrodibenz[b,e]oxepin-3-acetate for methyl II-oxo-6,II-dihydrodibenz[b,e]oxepin-2-acetate in Example 11 as a colorless oily matter.

15 Mass spectrum (m/z): 366 ( $M^+$ ) for  $C_{22}H_{26}O_3N_2$

Reference Example 15

Methyl II-[2-(4-methylpiperazino)ethylidene]-6,II-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 10)

20

In this example, 1.5 ml of 4-methylpiperazine and 0.37 g of p-formaldehyde are dissolved in 100 ml of tetrachloroethane. To the solution is dropwise added 5 ml of trifluoroacetic acid. After stirring the mixture at 60°C for 2 hours, a solution obtained by dissolving 1.8 g of methyl II-methylene-6,II-dihydrodibenz[b,e]oxepin-2-carboxylate in 30 ml of tetrachloroethane is dropwise added thereto and the mixture is stirred at

25 90°C for 3 hours.

The mixture is concentrated to dryness under reduced pressure and aqueous 4N-hydrochloric acid solution is added to the residue to adjust the pH to 1. After washing the solution with diethylether, aqueous 10N-sodium hydroxide solution is added thereto to adjust the pH to 13. The mixture is extracted with 200 ml of methylene chloride, washed with saturated aqueous sodium chloride solution and dried over anhydrous

30

sodium sulfate. The solvent is distilled away under reduced pressure. The residue is purified by column chromatography on silica gel (eluent: hexane : ethyl acetate : triethylamine = 5 : 5 : 1) to obtain 2.2 g of the desired product as a colorless oily matter.

Cis form NMR ( $CDCl_3$ ,  $\delta$ , ppm): 2.24(s, 3H), 2.45(s, 8H), 2.94-3.32(m, 2H), 3.84(s, 3H), 5.22(bs, 2H), 5.85(t, 1H, J = 6.8Hz), 6.66-8.07(m, 7H)

35 Mass spectrum (m/z): 378 ( $M^+$ )

Trans form NMR ( $CDCl_3$ ,  $\delta$ , ppm): 2.24(s, 3H), 2.45(s, 8H), 2.94-3.32(m, 2H), 3.84(s, 3H), 5.22(bs, 2H), 6.22(t, 1H, J = 6.8Hz)

Mass spectrum (m/z): 378 ( $M^+$ )

40 Example 16

Methyl II-[2-(4-methylpiperazino)ethylidene]-6,II-dihydrodibenz[b,e]oxepin-2-acetate (Compound 8)

The desired product is obtained by substituting methyl II-methylene-6,II-dihydrodibenz[b,e]oxepin-2-acetate for methyl II-methylene-6,II-dihydrodibenz[b,e]oxepin-2-carboxylate in Reference example 15.

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Example 17

II-(3-Dimethylaminopropylidene)-6,II-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 3)

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The product is obtained by hydrolysis of methyl II-(3-dimethylaminopropylidene)-6,II-dihydrodibenz[b,e]oxepin acetate in presence of sodium hydroxide.

Cis form white crystal

55

Melting point: 118 - 120°C (Isopropanol)

NMR ( $DMSO-d_6$ ,  $\delta$ , ppm): 2.16(s, 6H), 2.30-2.60(m, 4H), 4.04(s, 2H), 5.15(bs, 2H), 5.69(t, 1H, J = 7Hz),

EP 0 235 796 B1

IR (KBr disk,  $\text{cm}^{-1}$ ): 6.73-7.40(m, 7H)  
3400, 1580, 1225, 1005  
Mass spectrum (m/z): 337 ( $\text{M}^+$ )

5

| Elementary analysis (%): as $\text{C}_{21}\text{H}_{23}\text{O}_3\text{N} \cdot \text{monohydrate}$ |       |      |      |
|-----------------------------------------------------------------------------------------------------|-------|------|------|
|                                                                                                     | C     | H    | N    |
| Found                                                                                               | 70.77 | 7.36 | 3.74 |
| Calculated                                                                                          | 70.96 | 7.09 | 3.94 |

10

Trans form white crystal

15 Melting point: 158 - 160 ° C (Acetonitrile)  
NMR ( $\text{DMSO-d}_6$ ,  $\delta$ , ppm): 2.05(s, 6H), 2.30-2.60(m, 4H), 4.04(s, 2H), 5.15(bs, 2H), 6.06(t, 1H,  $J=7\text{Hz}$ ),  
6.73-7.40(m, 7H)  
IR (neat,  $\text{cm}^{-1}$ ): 3380, 1575, 1220, 1005  
Mass spectrum (m/z): 337 ( $\text{M}^+$ )

20

| Elementary analysis (%): as $\text{C}_{21}\text{H}_{23}\text{O}_3\text{N} \cdot \text{monohydrate}$ |       |      |      |
|-----------------------------------------------------------------------------------------------------|-------|------|------|
|                                                                                                     | C     | H    | N    |
| Found                                                                                               | 71.06 | 6.66 | 3.92 |
| Calculated                                                                                          | 70.96 | 7.09 | 3.94 |

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## Examples 18 -21

11-(4-Dimethylaminobutylidene)-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid (Compound 5)

5 11-(3-Pyrrolidinopropylidene)-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid (Compound 7)

11-[2-(4-Methylpiperazino)ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 9)

3-[11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz [b,e]oxepin-2-yl]-propionic acid (Compound 11)

10 These products are obtained by hydrolysis in the same manner as in Example 17. The physicochemical properties are shown in Table 9.

Table 9

| Compound   | Melting point<br>(°C)                         | Elementary analysis (%)                                                                                                                                                                                                                                                           |      |   |   |   |       |       |      |      |            |       |      |      |
|------------|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|---|---|---|-------|-------|------|------|------------|-------|------|------|
| 5          | White solid<br>206 - 209<br><br>(Isopropanol) | Cis : Trans = 92 : 8<br>as C <sub>22</sub> H <sub>25</sub> O <sub>3</sub> N<br><table><tr><td></td><td>C</td><td>H</td><td>N</td></tr><tr><td>Found</td><td>75.20</td><td>7.28</td><td>4.02</td></tr><tr><td>Calculated</td><td>75.19</td><td>7.17</td><td>3.99</td></tr></table> |      | C | H | N | Found | 75.20 | 7.28 | 4.02 | Calculated | 75.19 | 7.17 | 3.99 |
|            | C                                             | H                                                                                                                                                                                                                                                                                 | N    |   |   |   |       |       |      |      |            |       |      |      |
| Found      | 75.20                                         | 7.28                                                                                                                                                                                                                                                                              | 4.02 |   |   |   |       |       |      |      |            |       |      |      |
| Calculated | 75.19                                         | 7.17                                                                                                                                                                                                                                                                              | 3.99 |   |   |   |       |       |      |      |            |       |      |      |
| 5          | White solid<br>206 - 209<br><br>(Isopropanol) | Cis : Trans = 1 : 9<br>as C <sub>22</sub> H <sub>25</sub> O <sub>3</sub> N<br><table><tr><td></td><td>C</td><td>H</td><td>N</td></tr><tr><td>Found</td><td>75.19</td><td>7.17</td><td>3.99</td></tr><tr><td>Calculated</td><td>75.15</td><td>7.28</td><td>3.96</td></tr></table>  |      | C | H | N | Found | 75.19 | 7.17 | 3.99 | Calculated | 75.15 | 7.28 | 3.96 |
|            | C                                             | H                                                                                                                                                                                                                                                                                 | N    |   |   |   |       |       |      |      |            |       |      |      |
| Found      | 75.19                                         | 7.17                                                                                                                                                                                                                                                                              | 3.99 |   |   |   |       |       |      |      |            |       |      |      |
| Calculated | 75.15                                         | 7.28                                                                                                                                                                                                                                                                              | 3.96 |   |   |   |       |       |      |      |            |       |      |      |

## 40 Compound 11

Cis form white crystal

Melting point: 136 -138° C (Isopropylether)

45 NMR (DMSO-d<sub>6</sub>, δ, ppm): 2.32(m, 2H), 2.38(s, 6H), 2.44-2.56(m, 2H), 2.73(m, 4H), 5.15(bs, 2H), 5.50-(m, 1H), 6.7-7.4(m, 7H)

IR (KBr disk, cm<sup>-1</sup>): 3380, 1645Mass spectrum (m/z): 351 (M<sup>+</sup>)

| Elementary analysis (%): as C <sub>22</sub> H <sub>25</sub> NO <sub>3</sub> |       |      |      |
|-----------------------------------------------------------------------------|-------|------|------|
|                                                                             | C     | H    | N    |
| Found                                                                       | 74.83 | 7.31 | 3.97 |
| Calculated                                                                  | 75.19 | 7.17 | 3.99 |

Trans form white crystal

Melting point: 148 - 149 °C (Acetonitrile)  
 NMR (DMSO-d<sub>6</sub>, δ, ppm): 2.05(s, 6H), 2.24(m, 2H), 2.35(m, 2H), 2.47(t, 2H, J = 7.5Hz), 2.72(t, 2H, J = 7.5Hz), 4.80-5.50(broad, 2H), 5.99(t, 1H, J = 7.1Hz), 6.6-7.5(m, 7H)  
 IR (KBr disk, cm<sup>-1</sup>): 3380, 1700  
 Mass spectrum: 351 (M<sup>+</sup>)

| Elementary analysis (%) : as C <sub>22</sub> H <sub>25</sub> NO <sub>3</sub> • 1/5 hydrate |       |      |      |
|--------------------------------------------------------------------------------------------|-------|------|------|
|                                                                                            | C     | H    | N    |
| Found                                                                                      | 74.53 | 7.20 | 4.32 |
| Calculated                                                                                 | 74.42 | 7.21 | 3.95 |

Example 22

11-(2-Dimethylaminoethyl)imino-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid (Compound 18)

The desired product is obtained as a 8 : 92 mixture of syn-form and anti-form by hydrolysis in the same manner as in Example 16.

White crystal

Melting point: 174 -176 °C (as 1/2 hydrate)  
 NMR (DMSO-d<sub>6</sub>, δ, ppm): 2.07(s, 6H), 2.30-2.80(m, 4H), 3.47(s, 2H), 4.90-5.30(broad, 2H), 6.74-7.62(m, 7H)  
 IR (KBr disk, cm<sup>-1</sup>): 3330, 1573, 1370, 1010

| Elementary analysis (%) : as C <sub>20</sub> H <sub>22</sub> N <sub>2</sub> O <sub>3</sub> • 1/2 hydrate |       |      |      |
|----------------------------------------------------------------------------------------------------------|-------|------|------|
|                                                                                                          | C     | H    | N    |
| Found                                                                                                    | 69.47 | 5.77 | 8.06 |
| Calculated                                                                                               | 69.14 | 6.67 | 8.06 |

Examples 23-28

11-(3-Dimethylaminopropyl)imino-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid (Compound 20)

11-[3-(2-Dimethylaminopropyl)imino-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid (Compound 22)

3-[11-(2-Diethylaminoethyl)imino-6,11-dihydrodibenz [b,e]oxepin-2-yl] propionic acid (Compound 24)

2-11-(2-Dimethylaminoethyl)imino-6,11-dihydrodibenz [b,e]oxepin-2-yl]-propionic acid (Compound 26)

11-(2-Dimethylaminoethyl)imino-6,11-dihydrodibenz [b,e]oxepin-3-acetic acid (Compound 28)

11-(3-Dimethylaminopropyl)imino-6,11-dihydrodibenz [b,e]oxepin-3-acetic acid (Compound 30)

The desired compounds are obtained by hydrolysis in the same manner as in Example 22. The physicochemical properties are shown in Table 10.

Table 10

| Compound | Melting point (°C)                                          | Elementary analysis (%) or Mass spectrum                                                              |
|----------|-------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| 20       | White solid<br>161 - 162<br>(Ethyl acetate)                 | Anti : 98%<br>as $C_{22}H_{26}O_3N_2$<br>C H N<br>Found 72.25 7.24 7.58<br>Calculated 72.11 7.15 7.64 |
| 22       | White solid<br>171 - 173<br>(Isopropanol)                   | Anti : 97%<br>as $C_{21}H_{24}O_3N_2$<br>C H N<br>Found 71.35 6.92 7.69<br>Calculated 71.57 6.86 7.95 |
| 24       | Colorless Oily                                              | as $C_{23}H_{28}O_3N_2$<br>380 ( $M^+$ )                                                              |
| 26       | White solid<br>132 - 135<br>( Water )                       | Anti > 95%<br>as $C_{21}H_{24}O_3N_2$<br>C H N<br>Found 71.39 6.99 7.91<br>Calculated 71.57 6.86 7.95 |
| 28       | White solid<br>194 - 195<br>(Decomposition)<br>( Methanol ) | Anti > 95%<br>as $C_{20}H_{22}O_3N_2$<br>C H N<br>Found 70.87 6.80 7.93<br>Calculated 70.96 6.55 8.28 |

| Compound   | Melting point<br>(°C)                                        | Elementary analysis (%)<br>or Mass spectrum                                                                                                                                                                                                                                       |      |   |   |   |       |       |      |      |            |       |      |      |
|------------|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|---|---|---|-------|-------|------|------|------------|-------|------|------|
| 30         | White solid<br>174 - 175<br>(Decomposition)<br>(Isopropanol) | Anti > 95%<br>as C <sub>21</sub> H <sub>24</sub> O <sub>3</sub> N <sub>2</sub> <table><tr><td></td><td>C</td><td>H</td><td>N</td></tr><tr><td>Found</td><td>71.42</td><td>7.03</td><td>8.06</td></tr><tr><td>Calculated</td><td>71.57</td><td>6.86</td><td>7.95</td></tr></table> |      | C | H | N | Found | 71.42 | 7.03 | 8.06 | Calculated | 71.57 | 6.86 | 7.95 |
|            | C                                                            | H                                                                                                                                                                                                                                                                                 | N    |   |   |   |       |       |      |      |            |       |      |      |
| Found      | 71.42                                                        | 7.03                                                                                                                                                                                                                                                                              | 8.06 |   |   |   |       |       |      |      |            |       |      |      |
| Calculated | 71.57                                                        | 6.86                                                                                                                                                                                                                                                                              | 7.95 |   |   |   |       |       |      |      |            |       |      |      |

## reference example 29

1/2 Furamarate \* 1/5 hydrate of Compound C (Compound C')

In this example, 3.95 g of 11-(3-dimethylaminopropylidene)-6,11-dihydrobenz[b,e]oxepin-2-carboxylic acid (Compound 3) is dissolved in 100 ml of acetone and 1.42 g of fumaric acid is added thereto. The mixture is stirred at room temperature. The deposited crystals are recovered by filtration and recrystallized from isopropanol to obtain 4.15 g of the 1/2 furamarate 1/5 hydrate of the starting compound as a white solid.

Melting point: 253 - 254° c

Isomer purity: Trans form 99% (measured by HPLC)

| Elementary analysis (%): as $C_{20}H_{21}NO_3 \cdot 1/2C_4H_4O_4 \cdot 1/5H_2O$ |       |      |      |
|---------------------------------------------------------------------------------|-------|------|------|
|                                                                                 | C     | H    | N    |
| Found                                                                           | 68.74 | 6.35 | 3.61 |
| Calculated                                                                      | 68.63 | 6.13 | 3.64 |

Examples 30-34

The products are identified in Table 11, and then physico-chemical properties are shown in Table 12.

Table 11

| Compound No. |                                           |                  |
|--------------|-------------------------------------------|------------------|
| 3'           | Monofumarate · 3/2 hydrate of Compound 3  | (Trans form 95%) |
| 9'           | Monofumarate · 2/3 hydrate of Compound 9  | (Trans form 88%) |
| 11'          | Monofumarate · 1/2 hydrate of Compound 11 | (Trans form 63%) |

| Compound No. |                                           |                  |
|--------------|-------------------------------------------|------------------|
| 14'          | 1/2 Fumarate · monohydrate of Compound 14 | (Trans form 95%) |
| 16'          | Monofumarate of Compound 16               | (Cis form 100%)  |

| Compound | Melting point<br>(°C)                                                           | Elementary analysis (%)                                                                                     |
|----------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| 3'       | White solid<br>135 - 138<br>(Isopropyl ether)                                   | as $C_{25}H_{27}O_7N \cdot 3/2H_2O$<br>C H N<br>Found 62.58 6.12 2.77<br>Calculated 62.49 6.29 2.91         |
| 9'       | White solid<br>108 - 110<br>(Isopropanol)                                       | as $C_{27}H_{30}O_7N_2 \cdot 2/3H_2O$<br>C H N<br>Found 64.15 6.47 5.24<br>Calculated 64.02 6.24 5.53       |
| 11'      | White amorphous<br>vague owing to<br>absorption of<br>moisture                  | as $C_{26}H_{29}NO_7 \cdot \frac{1}{2}H_2O$<br>C H N<br>Found 66.58 6.61 2.82<br>Calculated 66.80 6.25 3.00 |
| 14'      | White solid<br>vague owing to<br>absorption of<br>moisture<br>(Petroleum ether) | as $C_{23}H_{27}O_4N \cdot H_2O$<br>C H N<br>Found 65.53 6.81 2.96<br>Calculated 65.39 6.92 3.32            |
| 16'      | White solid<br>146<br>(Acetone)                                                 | as $C_{26}H_{31}O_6N$<br>C H N<br>Found 68.81 7.16 3.22<br>Calculated 68.86 6.89 3.09                       |

## 45 Reference Example 17

Monosodium salt \* monohydrate of Compound 35 (Compound 35')

In this example, 1.00 g of 11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 35) is dissolved in 100 ml of methanol and 5.5 ml of 28% sodium methoxide methanol solution is added thereto. After stirring the mixture for one hour, the solvent is distilled away under reduced pressure. The residue is triturated by adding isopropylether and is recovered by filtration to obtain 0.98 g of the monosodium salt monohydrate of the starting compound as a white solid.

Melting point: vague owing to absorption of moisture

55 Ratio to isomer: Syn : Anti = 1 : 1

| Elementary analysis: as $C_{21}H_{25}O_4N_2Na \cdot H_2O$ |       |      |      |
|-----------------------------------------------------------|-------|------|------|
|                                                           | C     | H    | N    |
| Found                                                     | 64.23 | 6.62 | 7.01 |
| Calculated                                                | 64.27 | 6.68 | 7.14 |

## Examples 35 to 36'

The products are identified in Table 13, and their physicochemical properties are shown in Table 14.

Table 13

| Compound No. |                                          |                 |
|--------------|------------------------------------------|-----------------|
| 24'          | Sodium salt of Compound 24               | (Anti form 98%) |
| 26'          | Sodium salt * monohydrate of Compound 26 | (Anti form 99%) |

Table 14

| Compound No. | Melting point (°C)                                         | Elementary analysis (%)   |       |      |
|--------------|------------------------------------------------------------|---------------------------|-------|------|
| 24'          | White solid<br>vague owing to<br>absorption of<br>moisture | as $C_{23}H_{27}O_3N_2Na$ |       |      |
|              |                                                            | C                         | H     | N    |
|              |                                                            | Found                     | 68.46 | 7.00 |
| 26'          | White solid<br>140 - 145<br>(Isopropyl<br>ether)           | Calculated                | 68.64 | 6.76 |
|              |                                                            | Found                     | 64.11 | 6.57 |
|              |                                                            | Calculated                | 64.27 | 6.42 |

## Example 37 Powder

A powder comprising the following components is prepared in conventional manner.

|                                                                                                                               |        |
|-------------------------------------------------------------------------------------------------------------------------------|--------|
| Trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid * monofumarate * 3/2 hydrate (Compound 3'): | 30 mg  |
| Lactose:                                                                                                                      | 270 mg |

Example 33 Syrup

A syrup comprising the following components is prepared in a conventional manner.

|    |                                                                                           |        |
|----|-------------------------------------------------------------------------------------------|--------|
| 5  | 11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 18): | 300 mg |
|    | Purified sucrose:                                                                         | 40 g   |
|    | Methyl p-oxybenzoate:                                                                     | 40 mg  |
|    | Propyl p-oxybenzoate                                                                      | 10 mg  |
| 10 | Strawberry flavor:                                                                        | 0.1 cc |
|    | Water is added to the above components until the total volume becomes 100 cc              |        |

Example 39

Methyl 11-(3-methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 32)

The desired product is obtained by substituting (3-methylaminopropyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 4 as a colorless oily matter.

Mass spectrum (m/z): 337 (M<sup>+</sup>) for C<sub>21</sub>H<sub>23</sub>O<sub>3</sub>N

Example 40

Methyl 11-(3-aminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 34)

The desired product is obtained by substituting (3-aminopropyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 4 as a colorless oily matter.

Mass spectrum (m/z): 323 (M<sup>+</sup>) for C<sub>20</sub>H<sub>21</sub>O<sub>3</sub>N

## Examples 41 - 42

II-(3-Methylaminopropylidene)-6,II-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 33)

II-(3-Aminopropylidene)-6,II-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 35)

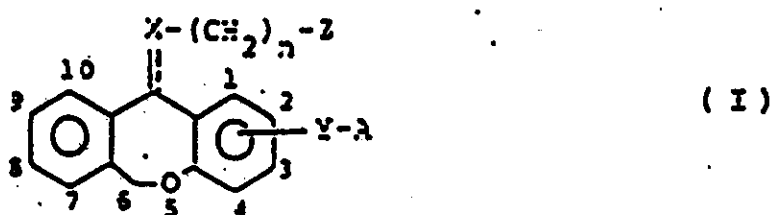
The physicochemical properties of these compounds are shown in Table 15.

Table 15

| Compound | Melting point (°C)                                 | Elementary analysis (%) or Mass spectrum                                                                                                                                                                                                                                           |
|----------|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 33       | White solid<br>236 - 238<br><br>( Water )          | Cis form 100%<br>as $C_{20}H_{21}O_3N$<br><br>C                      H                      N<br>Found                      74.01                      6.60                      4.01<br>Calculated                      74.28                      6.55                      4.33 |
| 35       | White solid<br>250<br>(Decomposition)<br>( Water ) | Cis form 100%<br>as $C_{19}H_{19}O_3N$<br><br>C                      H                      N<br>Found                      73.57                      6.38                      4.44<br>Calculated                      73.77                      6.19                      4.53 |

## Claims

1. A dibenz[b,e]oxepin compound represented by the formula (I)



wherein

A represents a carboxyl, a straight or branched  $(C_1-C_6)$  alkoxy carbonyl group,  $-CONHOH$  or  $-CONR_1R_2$  wherein  $R_1$  and  $R_2$  are the same or different and represent hydrogen atom or straight or branched  $(C_1-C_6)$  alkyl;

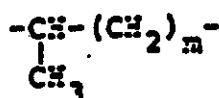
Y represents  $-(CH_2)_m-$ ,  $-CHR_3-(CH_2)_m-$  or  $-CR_4=CR_5-(CH_2)_m-$  wherein  $R_3$  represents a straight or branched  $(C_1-C_6)$  alkyl, a lower alkyl,  $R_4$  and  $R_5$  are the same or different and represent a hydrogen atom or a straight or branched  $(C_1-C_6)$  alkyl, and  $m$  is 1, 2, 3 or 4, which is the substituent at 2- or 3-position of the mother nucleus and the left side of the group Y is bound to benzen nucleus ;

X represents  $=N-$ ,  $=CH-$  ;

$n$  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 hydrogen atom or a straight or branched  $(C_1-C_6)$  alkyl and  $==$  means double bond; and the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein said salt is selected from acid addition salt, metal salt, ammonium salt, organic amine addition salt, and amino acid addition salt.
3. A compound according to claim 1, wherein A is a member selected from the group consisting of a straight or branched (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, -CONR<sub>1</sub>R<sub>2</sub> and carboxyl; Y is bound at 2-position of the mother nucleus; X is a member selected from the group consisting of =N- and =CH-; n is 1 or 2; and Z is a member selected from the group consisting of dimethylamino, diethylamino, methylamino, amino, morpholino and thiomorpholino.
4. A compound according to claim 3, wherein Y is a member selected from the group consisting of -(CH<sub>2</sub>)<sub>m</sub>-.

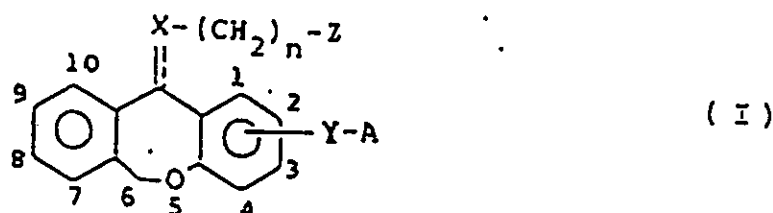


and CH = CH-(CH<sub>2</sub>)<sub>m</sub>-; and m is 1 or 2.

5. A compound according to claim 4, wherein A is a carboxyl; and X is =CH-.
6. A compound according to claim 1, wherein -Y-A is a member selected from the group consisting of carboxymethyl, 2-carboxyethyl, X is =CH-, n is 2 and Z is a member selected from the group consisting of dimethylamino, diethylamino, methylamino, amino, morpholino and thiomorpholino.
7. A compound according to claim 1, wherein -Y-A is 2-CH<sub>2</sub>COOH, X is =CH-, n is 2 and Z is dimethylamino.
8. A compound according to claim 1, wherein -Y-A is 2-CH<sub>2</sub>CH<sub>2</sub>COOH, X is =CH-, n is 2 and Z is dimethylamino.
9. Use of a compound as defined in anyone of claims 1 to 8 for the preparation of medicaments for the therapeutic treatment of allergic and inflammatory diseases.

## Revendications

1. Composé dibenzo[b,e] oxépine, représenté par la formule (I) :



dans laquelle :

- A représente un groupe carboxyl, un groupe (alcoxy en C<sub>1</sub>-C<sub>6</sub>)-carbonyle à chaîne droite ou ramifiée, un groupe -CONHOH ou un groupe -CONR<sub>1</sub>R<sub>2</sub>, R<sub>1</sub> et R<sub>2</sub> étant identiques ou différents et représentant chacun un atome d'hydrogène ou un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> à chaîne droite ou ramifiée;
- Y représente -(CH<sub>2</sub>)<sub>m</sub>-, -CHR<sub>3</sub>-(CH<sub>2</sub>)<sub>m</sub>- ou -CR<sub>4</sub>=CR<sub>5</sub>-(CH<sub>2</sub>)<sub>m</sub>-,
- R<sub>3</sub> représentant un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> à chaîne droite ou ramifiée, un groupe alkyle inférieur, R<sub>4</sub> et R<sub>5</sub> étant identiques ou différents et représentant chacun un atome d'hydrogène ou un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> à chaîne droite ou ramifiée, et m valant 1, 2, 3 ou 4, ce substituant étant placé en position 2- ou 3- du noyau parent et le côté gauche du groupe Y étant lié au noyau benzénique;
- X représente =N-, =CH-;

n vaut 0,1,2,3 ou 4;

Z représente un groupe 4-méthylpipérazino, 4-méthylhomopipérazino, pipéridino, pyrrolidino, thiomorpholino, morpholino ou  $-NR_6R_7$ ,  $R_6$  et  $R_7$  étant identiques ou différents et représentant chacun un atome d'hydrogène ou un groupe alkyle en  $C_1-C_6$  à chaîne droite ou ramifiée, et  $\text{---}$  représente une

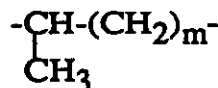
double liaison;

ainsi que les sels pharmaceutiquement acceptables de ce composé.

2. Composé conforme à la revendication 1, ledit sel étant choisi parmi les sels d'addition d'acide, les sels de métaux, les sels d'ammonium, les sels d'addition d'amine organique, et les sels d'addition d'acide aminé.

3. Composé conforme à la revendication 1, dans lequel A est un élément choisi parmi le groupe constitué par (alcoxy en  $C_1-C_6$ )-carbonyle à chaîne droite ou ramifiée,  $-\text{CONR}_1R_2$  et carboxyle; Y est lié en position 2 du noyau parent; X est un élément choisi dans le groupe constitué par  $=N-$  et  $=CH-$ ; n vaut 1 ou 2; et Z est un élément choisi dans le groupe constitué par diméthylamino, diéthylamino, méthylamino, amino, morpholino et thiomorpholino.

4. Composé conforme à la revendication 3, dans lequel Y est un élément choisi dans le groupe constitué par  $-(CH_2)_m-$ ,



et  $CH=CH-(CH_2)_m-$ ; et m vaut 1 ou 2.

5. Composé conforme à la revendication 4, dans laquelle A représente un groupe carboxy; et X représente  $=CH-$ .

6. Composé conforme à la revendication 1, dans lequel  $-Y-A$  est un élément choisi dans le groupe constitué par carboxyméthyle, 2-carboxyéthyle, X représente  $=CH-$ , n vaut 2 et Z représente un élément choisi dans le groupe constitué par diméthylamino, diéthylamino, méthylamino, amino, morpholino et thiomorpholino.

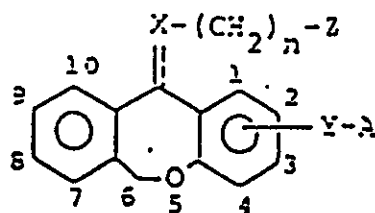
7. Composé conforme à la revendication 1, dans lequel  $-Y-A$  représente  $2-CH_2COOH$ , X représente  $=CH-$ , n vaut 2 et Z représente diméthylamino.

8. Composé conforme à la revendication 1, dans lequel  $-Y-A$  représente  $2-CH_2CH_2COOH$ , X représente  $=CH-$ , n vaut 2 et Z représente diméthylamino.

9. Utilisation d'un composé tel que défini dans l'une quelconque des revendications 1 à 8, pour la préparation de médicaments destinés au traitement thérapeutique de maladies allergiques et de maladies inflammatoires.

## Patentansprüche

1. Dibenz[b,e]oxepin-Verbindung der Formel (I)



( I )

in der

der Rest A eine Carboxylgruppe, einen gerad- oder verzweigt-kettigen C<sub>1</sub>-C<sub>6</sub>-Alkoxycarbonylrest, einen Rest der Formel -CONHOH oder -CONR<sub>1</sub>R<sub>2</sub> bedeutet, in der R<sub>1</sub> und R<sub>2</sub> gleich oder verschieden sind und ein Wasserstoffatom oder einen gerad- oder verzweigt-kettigen C<sub>1</sub>-C<sub>6</sub>-Alkylrest darstellen;

Y die Bedeutung -(CH<sub>2</sub>)<sub>m</sub>-, -CHR<sub>3</sub>-(CH<sub>2</sub>)<sub>m</sub>- oder -CR<sub>4</sub>=CR<sub>5</sub>-(CH<sub>2</sub>)<sub>m</sub>- hat, wobei R<sub>3</sub> einen gerad- oder verzweigt-kettigen C<sub>1</sub>-C<sub>6</sub>-Alkylrest, oder einen Niederalkylrest bedeutet, R<sub>4</sub> und R<sub>5</sub> gleich oder verschieden sind und ein Wasserstoffatom oder einen gerad- oder verzweigt-kettigen C<sub>1</sub>-C<sub>6</sub>-Alkylrest darstellen und m den Wert 1, 2, 3 oder 4 hat, der den Substituenten in 2- oder 3-Stellung am Hauptkern darstellt, wobei die linke Seite des Restes Y an den Benzolring gebunden ist,

X die Gruppen =N- oder =CH- bedeutet,

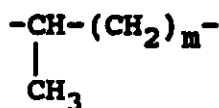
n den Wert 0, 1, 2, 3 oder 4 hat,

Z eine 4-Methylpiperazino-, 4-Methylhomopiperazino-, Piperidino-, Pyrrolidino-, Thiomorpholino-, Morpholinogruppe oder den Rest mit der Formel -NR<sub>6</sub>R<sub>7</sub> bedeutet, in der R<sub>6</sub> und R<sub>7</sub> gleich oder verschieden sind und ein Wasserstoffatom oder einen gerad- oder verzweigt-kettigen C<sub>1</sub>-C<sub>6</sub>-Alkylrest bedeuten und das Symbol  $\text{---}$  eine Doppelbindung bedeutet, und pharmazeutisch verträgliche Salze davon.

2. Verbindung nach Anspruch 1, wobei das Salz ausgewählt ist aus einem Säureadditionssalz, Metallsalz, Ammoniumsalz, organischen Aminadditionssalz und Aminosäureadditionssalz.

3. Verbindung nach Anspruch 1, wobei der Rest A ausgewählt ist aus gerad- oder verzweigt-kettigen C<sub>1</sub>-C<sub>6</sub>-Alkoxycarbonylresten, dem Rest der Formel -CONR<sub>1</sub>R<sub>2</sub> und der Carboxylgruppe, Y in der 2-Stellung des Hauptkerns gebunden ist, X ausgewählt ist aus den Gruppen =N- und =CH-, n den Wert 1 oder 2 hat und Z ausgewählt ist aus der Dimethylamino-, Diethylamino-, Methylamino-, Amino-, Morpholino- und Thiomorpholinogruppe.

4. Verbindung nach Anspruch 3, wobei der Rest Y ausgewählt ist aus -(CH<sub>2</sub>)<sub>m</sub>-,



und -CH=CH-(CH<sub>2</sub>)<sub>m</sub>- und m den Wert 1 oder 2 hat.

5. Verbindung nach Anspruch 4, wobei der Rest A eine Carboxylgruppe bedeutet und X die Gruppe =CH- darstellt.

6. Verbindung nach Anspruch 1, wobei der Rest der Formel -Y-A die Carboxymethyl- oder 2-Carboxyethylgruppe bedeutet, X die Gruppe =CH- bedeutet und n den Wert 2 hat und Z ausgewählt ist aus der Dimethylamino-, Diethylamino-, Methylamino-, Amino-, Morpholino- und Thiomorpholinogruppe.

7. Verbindung nach Anspruch 1, wobei der Rest der Formel -Y-A die Gruppe 2-CH<sub>2</sub>COOH bedeutet, X die Gruppe =CH- bedeutet, n den Wert 2 hat und Z eine Dimethylaminogruppe darstellt.

8. Verbindung nach Anspruch 1, wobei der Rest der Formel -Y-A die Gruppe 2-CH<sub>2</sub>CH<sub>2</sub>COOH bedeutet, X die Gruppe =CH- bedeutet, n den Wert 2 hat und Z eine Dimethylaminogruppe darstellt.

9. Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 8 zur Herstellung von Arzneimitteln zur therapeutischen Behandlung von allergischen und entzündlichen Erkrankungen.

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