

82884/87

COMMONWEALTH of AUSTRALIA
PATENTS ACT 1952

59 6481

APPLICATION FOR A STANDARD PATENT

XX
WeSYNTHELABO
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France

AFFIDAVIT ACCEPTED AND AMENDMENTS

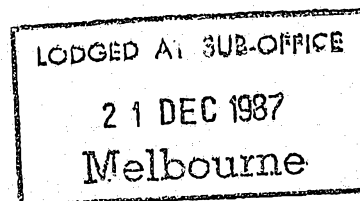
ALLOWED 22-2-90

hereby apply for the grant of a Standard Patent for an invention entitled:

"DIBENZO(be) OXEPINACETIC ACID DERIVATIVES, THEIR PREPARATION AND
PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"which is described in the accompanying ~~provisional~~ complete specification.

Details of basic application(s):—

<u>Number</u>	<u>Convention Country</u>	<u>Date</u>
86.17990	France	22nd December 1986

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little
Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

Dated this 21st

day of December

19 87

To: THE COMMISSIONER OF PATENTS

H. M. Rimmington.....
(a member of the firm of DAVIES &
COLLISON for and on behalf of the Applicant).

Davies & Collison, Melbourne and Canberra.

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

DECLARATION IN SUPPORT OF CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT

Insert title of invention.

In support of the Application made for a patent for an invention
entitled: " DIBENZO (be) OXEPINACETIC ACID DERIVATIVES,
THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS
CONTAINING THEM"

Insert full name(s) and address(es)
of declarant(s) being the appli-
cant(s) or person(s) authorized to
sign on behalf of an applicant
company.

~~W~~
~~xxx~~ Elizabeth Thouret-Lemaitre
of Synthelabo,
of 58, rue de la Glaciere, 75621,
Paris Cedex 13, France

Cross out whichever of paragraphs
1(a) or 1(b) does not apply

1(a) relates to application made
by individual(s)
1(b) relates to application made
by company; insert name of
applicant company.

do solemnly and sincerely declare as follows :-

1. (a) ~~xxx~~ the applicant ~~xxx~~ for the patent
~~we are~~

or (b) I am authorized by

Synthelabo

Cross out whichever of paragraphs
2(a) or 2(b) does not apply

2(a) relates to application made
by inventor(s)
2(b) relates to application made
by company(s) or person(s) who
are not inventor(s); insert full
name(s) and address(es) of inven-
tors.

the applicant..... for the patent to make this declaration on ^{its} behalf.
~~their~~ ~~xxx~~

2. (a) ~~xxx~~ the actual inventor ~~xxx~~ of the invention
~~we are~~

or (b)

Thomas Purcell of 47Bis, rue de la Milliere,
Les Mesnuls, 78490 Montfort L'Amaury;

Luc Rivron of 5, rue du Chateau, 92600 Asnieres
and

Lydia Zard of 6, Impasse des Quatre Vents,
La Croix Audierne, 91190 GIF S/YVETTE

all of France

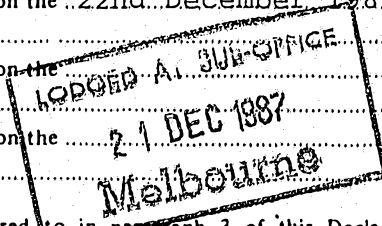
~~xxx~~ are the actual inventor(s)..... of the invention and the facts upon which the applicant.....
is entitled to make the application are as follows :-
~~xxx~~

The applicant would if a patent were granted or an
application made by the said inventors be entitled to
have the patent assigned to it.

State manner in which applicant(s)
derive title from inventor(s)

Cross out paragraphs 3 and 4
for non-convention applications.
For convention applications,
insert basic country(s) followed
by date(s) and basic applicant(s).

3. The basic application..... as defined by Section 141 of the Act ^{was} made
~~xxx~~ in France..... on the 22nd December 1986
by Synthelabo

in on the
by
in on the
by


4. The basic application..... referred to in paragraph 3 of this Declaration ^{was}
the first application..... made in a Convention country in respect of the invention the subject
of the application. ~~xxx~~

Insert place and date of signature.

Declared at Paris this 29th day of October 1987

SYNTHÉLABO

Signature of declarant(s) (no
attestation required)

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Note: Initial all alterations.

Elizabeth Thouret-Lemaitre

DAVIES & COLLISON, MELBOURNE and CANBERRA.

(12) PATENT ABRIDGMENT (11) Document No. AU-B-82884/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 596481

(54) Title
DIBENZO (BE) OXEPINACETIC ACID DERIVATIVES

International Patent Classification(s)
(51)⁴ **C07D 313/12 A61K 031/335**

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SYNTHELABO

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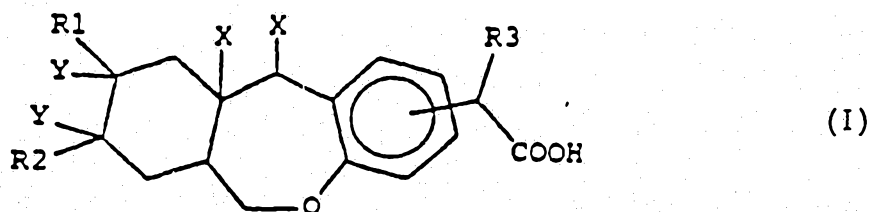
(74) Attorney or Agent
DAVIES & COLLISON, MELBOURNE

(56) Prior Art Documents
AU 577687 55916/86 C07D 313/12

(57) THE COMPOUNDS HAVE ANALGESIC AND ANTI-INFLAMMATORY ACTIVITIES.

CLAIM

1. A compound, in the form of a pure optical isomer or a racemate, which is a dibenzo[be]oxepinacetic acid of the general formula (I)



in which R1, R2 and R3, which may be the same or different, each represent hydrogen or methyl, each X represents a hydrogen atom or together they form a carbon-carbon bond, and each Y represents a hydrogen atom or together they form a carbon-carbon bond, or a pharmaceutically acceptable salt thereof.

596481

FORM 10

C O M M O N W E A L T H O F A U S T R A L I A

PATENTS ACT 1952-1973

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE:

CLASS

INT. CLASS

APPLICATION NUMBER:
LODGED:

COMPLETE SPECIFICATION LODGED:
ACCEPTED:
PUBLISHED:

PRIORITY:

RELATED ART:

This document contains the
amendments made under
Section 49 and is correct for
printing.

NAME OF APPLICANT:

Synthelabo

ADDRESS OF APPLICANT:

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ACTUAL INVENTOR(S):

THOMAS PURCELL, LUC
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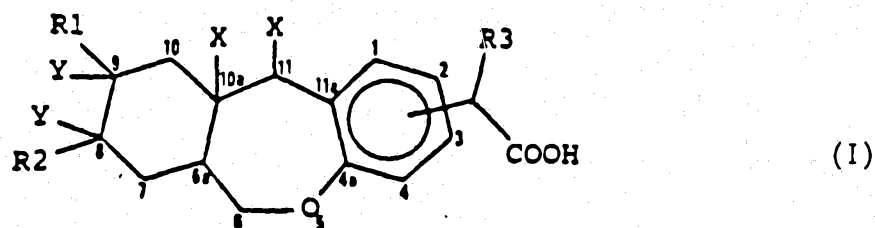
COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

"DIBENZO[be]OXEPINACETIC ACID DERIVATIVES, THEIR
PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"

The following statement is a full description of this invention,
including the best method of performing it known to us:-

The present invention relates to compounds which are
dibenzo[be]oxepinacetic acid derivatives or salts thereof, their
5 preparation and pharmaceutical compositions containing them.

The invention provides a compound which is a
dibenzo[be]oxepinacetic acid of formula (I)



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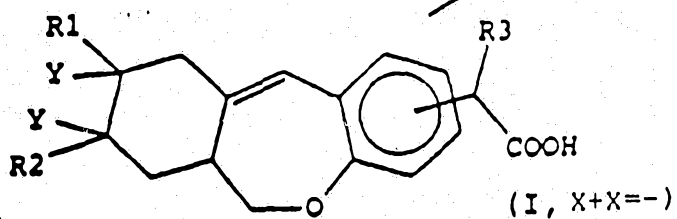
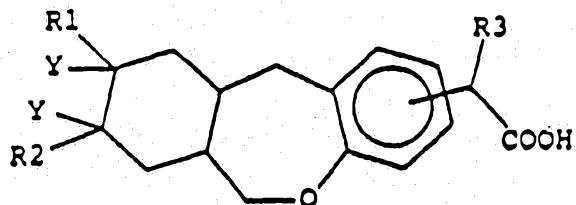
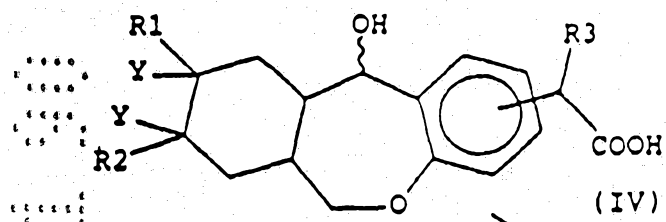
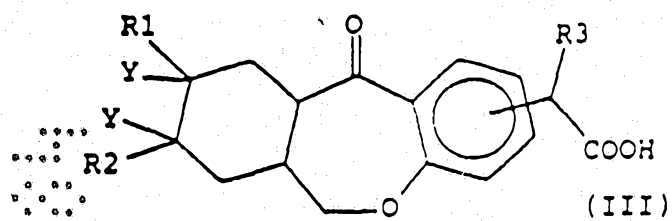
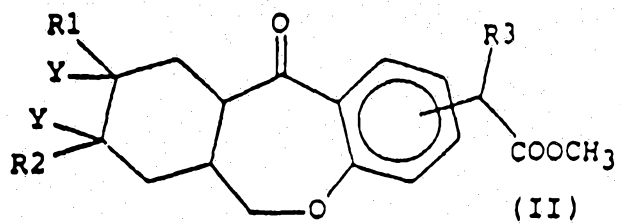
in which R1, R2 and R3, which may be the same or different, each
20 represent hydrogen or methyl, each X represents a hydrogen atom, or
together they form a carbon-carbon bond, and each Y represents a
hydrogen atom, or together they form a carbon-carbon bond, or a
pharmaceutically acceptable salt thereof.

The various stereoisomeric forms, i.e. pure optical isomers or
25 mixtures thereof, that can be taken by the compounds of formula (I)
also form part of the invention. In particular, when each X denotes
a hydrogen atom, there is cis or trans isomerism with respect to the
axis defined by the atoms 6a and 10a.

According to the invention, the compounds may be prepared
30 according to Scheme 1 on the following page.

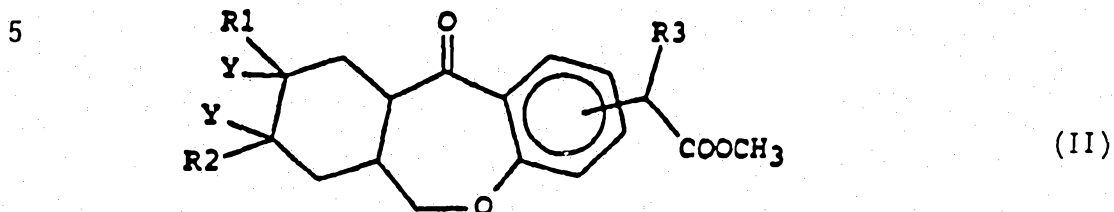


SCHEME 1



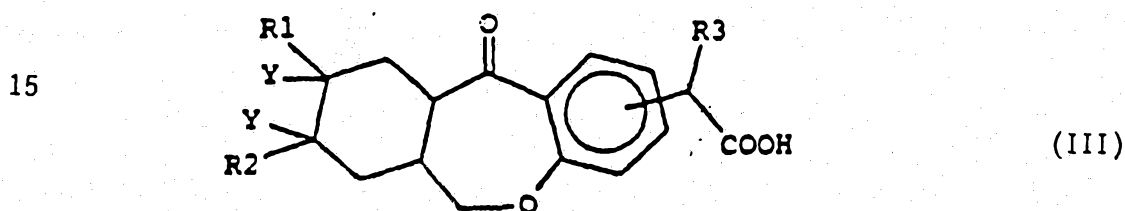
In accordance with this scheme, compounds of the invention are prepared by a process which comprises:-

(a) hydrolysing an ester of formula (II)

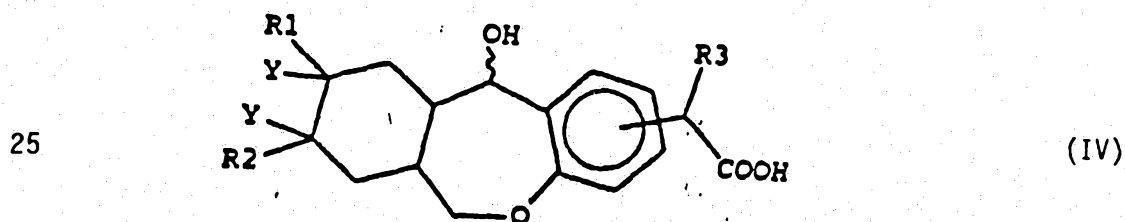


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(wherein the various symbols are as defined above) to form a free acid of formula (III)



20 (b) reducing the ketone group of free acid (III) to an alcohol group to form an alcohol of formula (IV)



(c) either (i) dehydrating the alcohol (IV) to provide an acid of formula (I) in which each X together forms a carbon-carbon bond and optionally catalytically hydrogenating said bond to provide a said acid in which each X represents a hydrogen atom, or (ii) reducing the

30



- alcohol (IV) to provide an acid of formula (I) in which each X
- 5 represents a hydrogen atom, (d) optionally if desired methylating a resulting compound of formula (I) in which R3 represents hydrogen so as to provide a compound of formula (I) in which R3 represents methyl, and
- (e) if desired converting a free acid of formula (I) into a
- 10 pharmaceutically acceptable salt thereof.

The starting esters of formula (II) in which each Y together forms a carbon-carbon bond are described in EP-A-0,198,762.

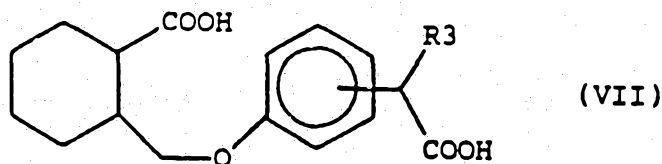
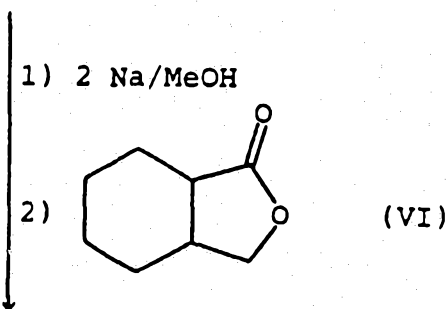
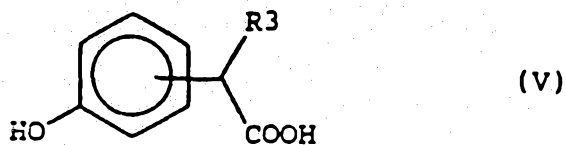
- If it is desired to prepare compounds (I) in the formula of which each Y represents a hydrogen atom, an ester (II, Y+Y=--) may
- 15 first be subjected to catalytic hydrogenation, for example under pressure in the presence of a catalyst such as platinum dioxide.

- The ester of formula (II) is hydrolysed, for example with sodium hydroxide in alcoholic medium, to obtain a free acid of formula (III). The acids (and their esters) of formula (III) in
- 20 which each Y denotes a hydrogen atom and R1 and R2 denote hydrogen atoms are also described in EP-A-0,037,254.

According to this document, they are obtained by a process illustrated by Scheme 2 on the following page.



SCHEME 2



(III)

A benzeneacetic acid of formula (V) is treated with sodium and the salt thereby obtained is reacted with 5 a lactone, octahydro-1-isobenzofuranone, of formula (VI), which gives the derivative of formula (VII) which is subjected to cyclization to provide the ^{acid}~~ester~~ (III).

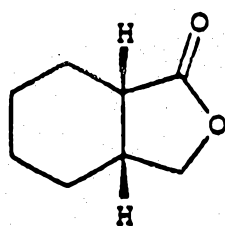
If the lactone of formula (VI) has a specified stereochemical structure, this leads to an intermediate of formula (III), and finally to a compound of formula (I),



which themselves have specified stereochemical structures.

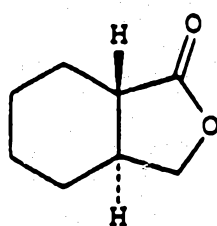
The lactone of formula (VIa) is described in Organic Syntheses
5 (1985), 63, 10 and that of formula (VIb) may be synthesized from the
diacid of formula (VIc) described in J. Org. Chem. (1963), 28, 48,
passing via the corresponding anhydride, according to methods similar
to those described in J. Org. Chem. (1964), 29, 3154 and J. Org.
Chem. (1970), 35, 3574.

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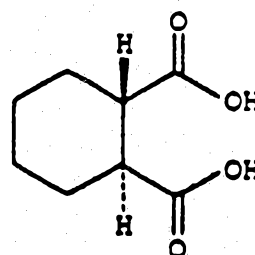


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(VIa)



(VIb)



(VIc)

20

The ketone group of the compound (III) may be reduced to a
secondary alcohol group by means of alkali metal borohydride. The
alcohol of formula (IV) thereby obtained can then be treated in two
different ways, depending on whether it is desired to prepare a
compound (I) in the formula of which each X denotes a hydrogen atom
or together they form a carbon-carbon bond.

25

Thus, on the one hand, the alcohol (IV) can be dehydrated, for
example in the presence of para-toluenesulphonic acid, in the heated
state and in a solvent such as benzene, thereby leading to a compound
of formula (I) in which each X together forms a carbon-carbon bond.



It is possible, on the other hand, to reduce the alcohol (IV), for example in the presence of sodium cyanoborohydride and zinc iodide, at room temperature and, for example, in a halogenated solvent, thereby providing a compound of formula (I) in which each X denotes a hydrogen atom. This reduction does not epimerize the 10a centre, the stereo-chemistry of the final compound being determined by that of the starting compound.

10 It is also possible to proceed from a compound of formula (I) in which each X together forms a carbon-carbon bond to a compound of formula (I) in which each X and each Y denote hydrogen atoms subjecting the former compound to a catalytic hydrogenation under pressure, for example in a solvent such as ethanol and in the
15 presence of palladinized charcoal. This hydrogenation is not stereoselective with respect to the sides of the bond 10a-11, and gives a 50:50 mixture of cis and trans isomers with respect to the bond 6a-10a.

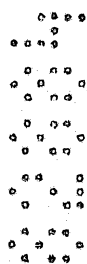
Finally, a compound of formula (I) in which R3 denotes a methyl
20 group may be prepared from a compound of formula (1) in which R3 denotes hydrogen by protecting the latter beforehand by esterification using a lower alcohol, for example methanol, at the refluxing temperature, then alkylating the ester thereby obtained, for example using a halide such as iodomethane in the presence of
25 lithium diisopropylamide (prepared in situ using diisopropylamine and n-butyllithium), in a solvent such as tetrahydrofuran, and then reconvertng to the acid by hydrolysing the

ester thereby obtained, for example with aqueous sodium hydroxide, in the heated state and in alcoholic medium.

The Examples which follow illustrate the preparation of a few compounds according to the invention.

5

The structures of the products obtained were confirmed by microanalyses and the IR and NMR spectra.



Example 1. 6,6a,7,8,9,10-Hexahydrodibenzo[be]oxepin-3-acetic acid.

a) Methyl 11-oxo-6,6a,7,8,9,10,10a,11-octahydrodibenzo[be]oxepin-3-acetate.

5 8.58 g (0.03 mole) of methyl 11-oxo-6,6a,7,10,10a,11-hexahydrodibenzo[be]oxepin-3-acetate, 1 g of platinum oxide and 200 ml of ethanol are introduced into a 500-ml hydrogenation vessel, and hydrogenation is performed at approximately 0.28 MPa for 45 minutes.

10 The catalyst is separated by filtration under argon and the filtrate is evaporated, and this leaves 8 g of an oil which is used in the following stage without further treatment.

b) 11-Oxo-6,6a,7,8,9,10,10a,11-octahydrodibenzo[be]oxepin-3-acetic acid.

15 8 g of the oil obtained according to 1a) is treated at 60°C for 1 h with a mixture of 100 ml of methanol, 100 ml of water and 4.5 ml of 30% strength sodium hydroxide solution. The alcohol is then evaporated off and the traces of residual ester are extracted with ethyl acetate. The aqueous phase is acidified with 1N hydrochloric acid and the organic acid extracted with ethyl acetate.

20 The organic phase is dried over magnesium sulphate, concentrated and distilled at between 185 and 190°C at approximately 25 Pa. After recrystallization of the distillate in isopropyl alcohol, 6.5 g of solid are

collected. m.p. 99-101°C.

c) 6,6a,7,8,9,10-Hexahydrodibenzo[be]oxepin-3-acetic acid.

5.48 g of the solid obtained according to 1b) are dissolved in 100 ml of ethanol and 1.2 g of sodium borohydride is added slowly. The mixture is stirred for 40 minutes and then concentrated.

The residue is taken up with 200 ml of water, hydrochloric acid is added slowly to pH 2, the mixture being cooled in ice, and the product is extracted with ethyl acetate.

The solvent is evaporated off at 25°C and the heat-sensitive product is rapidly taken up with 150 ml of benzene and 0.2 g of para-toluenesulphonic acid.

The water is driven off in a Dean and Stark apparatus in the space of approximately 30 minutes, the residue is concentrated at 40°C under vacuum to a residual volume of approximately 15 ml, and the product is then purified on a silica column, eluting with a 95:5 dichloromethane/methanol mixture.

After recrystallization of the pure fractions in the cold in an 8:2 cyclohexane/isopropyl ether mixture, 2.5 g of the pure product are collected. m.p. 145-147°C.

Example 2. 6,6a,7,10-Tetrahydrodibenzo[be]oxepin-3-acetic acid.

a) 11-Hydroxy-6,6a,7,10,10a,11-hexahydrodibenzo[be]oxepin-3-acetic acid.

2.72 g (0.01 mole) of 11-oxo-6,6a,7,10,10a,11-

hexahydrodibenzo[be]oxepin-3-acetic acid and 200 ml of ethanol are introduced into a 1-l Erlenmeyer, and the solution is treated with 3 g of sodium borohydride at 0°C.

5 After 30 min of reaction, the mixture is evaporated, the residue taken up with water, and the suspension cooled in an icebath and treated with hydrochloric acid to pH 3 in order to destroy the excess sodium borohydride.

10 The alcohol obtained is extracted with ethyl acetate. After the organic phase has been dried over magnesium sulphate and evaporated, the residue is recrystallized in an 8:2 ethyl acetate/cyclohexane mixture. 2 g of crystals are obtained. m.p. 138-140°C.

15 b) 6,6a,7,10-Tetrahydrodibenzo[be]oxepin-3-acetic acid.

2.7 g of alcohol obtained according to 2a) are subjected to dehydration in 300 ml of benzene under reflux, in the presence of 0.1 g of para-toluenesulphonic
20 acid.

After 30 min, the benzene is evaporated off and the residue purified by chromatography on a silica column, eluting with a 9:1 methanol/dichloromethane mixture and recrystallizing the product obtained in a 7:3 petroleum
25 ether/ethyl acetate mixture.

1.25 g of crystals are obtained. m.p. 120-122°C.

Example 3. 6,6a,7,8,9,10,10a,11-Octahydrodibenzo[be]-

oxepin-3-acetic acid (50:50 cis/trans mixture).

3 g of the compound of Example 1, 250 ml of ethanol and 0.3 g of activated palladinized charcoal (10% palladium) are introduced into a Parr vessel, and hydrogenation is performed at approximately 0.28 MPa for 8 hours.

The catalyst is separated by filtration under argon, the solvent evaporated off and the residue recrystallized in a 6:4 cyclohexane/pentane mixture. 1.5 g of pure product is obtained. m.p. 102-105°C.

10 Example 4. 6,6a,7,,8,9,10,10a,11-Octahydrodibenzo[be]-oxepin-3-acetic acid (trans isomer).

a) 11-Hydroxy-6,6a,7,8,9,10,10a,11-octahydrodibenzo[be]-oxepin-3-acetic acid.

15 14 g of sodium borohydride are added to a solution, cooled to -10°C and placed under argon, of 34 g of 11-oxo-6,6a,7,8,9,10,10a,11-octahydrodibenzo[be]-oxepin-3-acetic acid in 340 ml of absolute ethanol, and the mixture is allowed to return to room temperature while being stirred.

20 The mixture is poured into ice-cold water and evaporated, and the residue is taken up with water, which is washed with ether, acidified and extracted with ether.

After evaporation of the solvent, there remain 31 g of crystalline residue which is used in the stage
25 b) without further treatment.

b) 6,6a,7,8,9,10,10a,11-Octahydrodibenzo[be]oxepin-3-acetic acid.

8.62 g of zinc iodide and 8.5 g of sodium cyanoborohydride are added at room temperature to a solution of 5 g of crude alcohol obtained according to 4a) in 90 ml of 1,2-dichloroethane, and the mixture is left stirred for 2 h.

5 The mixture is poured into ice-cold water, acidified with 10% strength hydrochloric acid, dichloromethane is added and the mixture is left to outgas overnight. The organic phase is separated, dried and evaporated under vacuum, and this leaves 4.3 g of crystalline residue.

10 1.5 g of this is recrystallized in toluene, and 1.1 g of pure crystals is obtained. m.p. 175°C (decomposition).

Example 5. Laevorotatory enantiomer of 6,6a,7,8,9,10-hexahydrodibenzo[be]loxepin-3-acetic acid.

a) 3-[(2-Carboxycyclohexyl)methoxy]benzeneacetic acid.

15 1.97 g (0.0856 mole) of sodium is dissolved in 50 ml of anhydrous methanol, and 6.52 g (0.0428 mole) of 3-hydroxybenzeneacetic acid are added under an argon atmosphere. The solvent is evaporated off and 7.2 g (0.0514 mole) of lactone of formula (VIa) are added to
20 the salt thereby obtained. The mixture is heated to 195°C for 45 min and allowed to cool, ice-cold water and 10% strength hydrochloric acid are added and the mixture is extracted with ether. After drying over magnesium sulphate, decolorization with vegetable charcoal
25 and evaporation of the solvent, 13.64 g of oily residue are obtained, and this is used in the following stage without further treatment.

b) 11-Oxo-6,6a,7,8,9,10,10a,11-octahydrodibenzo[be]oxepin-3-acetic acid.

120 g of polyphosphoric acid are added to 13.5 g of the oil obtained above, and the mixture is heated on an oil bath to 70°C while being stirred. As soon as this temperature is reached, the heating is removed, since the temperature is maintained by itself.

When the reaction is complete, the mixture is poured into ice-cold water, extracted with ether and then with dichloromethane, the two organic phases are dried over magnesium sulphate and evaporated, and the residues are purified by chromatography on a silica column and the pure fractions are combined and distilled under vacuum. 1.15 g of a yellow oil is finally collected, and this is used in the following stage without further treatment.

c) 11-Hydroxy-6,6a,7,8,9,10,10a,11-octahydrodibenzo[be]oxepin-3-acetic acid.

1.15 g of the oil obtained above is dissolved in 15 ml of absolute ethanol, the solution is cooled to -10°C and 0.47 g (0.0125 mole) of sodium borohydride is added under an argon atmosphere. The mixture is allowed to return to room temperature and, after 1 h, is poured into ice-cold water. The ethanol is evaporated off, the aqueous phase washed with ether, 2N hydrochloric acid is added and the product is extracted with ether. After drying over magnesium sulphate and evaporation under vacuum, 1 g of a colourless oil is obtained, and this is

used in the following stage without further treatment.

d) 6,6a,7,8,9,10-Hexahydrodibenzo[be]oxepin-3-acetic acid.

1 g of the oil obtained above is dissolved in 50 ml of anhydrous benzene, a few crystals of para-toluenesulphonic acid are added and the mixture is heated to reflux while the water is removed with a Dean and Stark apparatus.

When all the water has been removed, the solvent is evaporated off and the mixture is left to cool, and crystallizes.

0.6 g of crystals are separated by filtration, and these are recrystallized in benzene after being treated with vegetable charcoal. 0.27 g of pure enantiomer is finally obtained.

m.p. 137-138°C $[\alpha]^{20} = -28.27^\circ$ (c = 0.29; CHCl₃).

D

Example 6. Dextrarotatory enantiomer of 6,6a,7,8,9,10-hexahydrodibenzo[be]oxepin-3-acetic acid.

a) 3-[(2-Carboxycyclohexyl)methoxy]benzeneacetic acid.

8.2 g (0.355 mole) of sodium are dissolved in 100 ml of anhydrous methanol, and 27 g (0.18 mole) of 3-hydroxybenzeneacetic acid are added under an argon atmosphere.

The solvent is evaporated off and 30 g (0.214 mole) of lactone of formula (VIb) are added to the salt thereby obtained. The mixture is heated to 195°C for 2 h, allowed to cool and poured into ice-cold water, the mixture is

washed with ether, 10% strength hydrochloric acid is added to the aqueous phase and the product is extracted with ether.

After drying over magnesium sulphate and decolorization with vegetable charcoal, the solvent is evaporated off and 48 g of residue are obtained, and this is recrystallized in toluene. 22 g of crystals are finally collected, and these are used in the following stage without further treatment.

b) 11-Oxo-6,6a,7,8,9,10,10a,11-octahydrodibenzo[be]oxepin-3-acetic acid.

220 g of polyphosphoric acid are added to 22 g of the crystals obtained above, and the mixture is heated in an oil bath at 75°C for 30 min.

It is allowed to cool and poured into ice-cold water, the product is extracted with ether, the organic phase is dried over magnesium sulphate and the solvent evaporated off under vacuum. 15 g of orange-coloured foamy residue are obtained, and this is used in the following stage without further treatment.

c) 11-Hydroxy-6,6a,7,8,9,10,10a,11-octahydrodibenzo[be]oxepin-3-acetic acid.

15 g (0.0546 mole) of the product obtained above are dissolved in 300 ml of absolute ethanol, the solution is cooled to -10°C and 6.2 g (0.163 mole) of sodium borohydride are added under an argon atmosphere.

The mixture is allowed to return to room temperature

and, after 2 h, is poured into ice-cold water. The ethanol is evaporated off, the aqueous phase is washed with ether, 10% strength hydrochloric acid is added and the product is extracted with ether.

5 After drying over magnesium sulphate and evaporation under vacuum, 13 g of yellow foamy residue are obtained. This is ground in dichloromethane, giving 4.21 g of crystals which are used in the following stage without further treatment.

10 d) 6,6a,7,8,9,10-Hexahydrodibenzo[be]oxepin-3-acetic acid.

15 4 g (0.0144 mole) of the crystals obtained above are dissolved in 200 ml of anhydrous benzene, 50 mg of para-toluenesulphonic acid are added and the mixture is heated under reflux while the water is removed with a Dean and Stark apparatus.

20 After 2 h, the clear solution obtained is concentrated to approximately 20 ml and purified without further treatment on a silica column, eluting with a 95:5 dichloromethane/methanol mixture. 3.17 g of beige crystals are recovered, and these are recrystallized in benzene, finally giving 2.36 g of shiny white crystals of pure enantiomer.

m.p. 136-138°C $[\alpha]_D^{20} = + 29.21$ (c = 0.38 ; CHCl₃).

25 Example 7. α-Methyl-6,6a,7,8,9,10-hexahydrodibenzo[be]oxepin-3-acetic acid.

a) Methyl 6,6a,7,8,9,10-hexahydrodibenzo[be]oxepin-3-

acetate.

A mixture of 5 g (0.0194 mole) of 6,6a,7,8,9,10-hexahydrodibenzo[be]oxepin-3-acetic acid and 50 ml of methanol, treated with a few drops of concentrated sulphuric acid, is heated under reflux for 1 h.

The mixture is evaporated to dryness, the residue taken up with water and neutralized with sodium carbonate, and the product extracted with ether.

After drying over magnesium sulphate and evaporation of the ether, 4.8 g of an oil are obtained, and this is purified by chromatography on a silica column, eluting with dichloromethane. 4.4 g of ester are collected, and this is used in the following stage without further treatment.

b) Methyl α -methyl-6,6a,7,8,9,10-hexahydrodibenzo[be]oxepin-3-acetate.

4.44 ml of diisopropylamine are dissolved in 62 ml of tetrahydrofuran, the solution is cooled to -70°C and 20.5 ml of 1.6M solution of n-butyllithium are introduced dropwise.

The mixture is stirred for 15 min and 4.3 g (0.0158 mole) of the ester obtained above, dissolved in 50 ml of tetrahydrofuran, are added dropwise. The mixture is stirred for 20 min and, still at -70°C , 2.64 g (0.0186 mole) of iodomethane are added.

Stirring is maintained for 1 h 30 min at -70°C , the mixture is then allowed to return to room temperature

and poured into ice-cold water, the product is extracted with ethyl acetate and the organic phase is separated, dried over magnesium sulphate and evaporated. 4 g of an oil are obtained, and this is used in the following stage without further treatment.

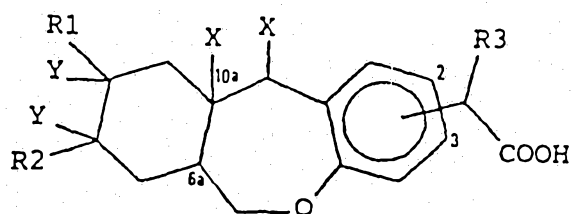
c) α -Methyl-6,6a,7,8,9,10-hexahydrodibenzo[be]oxepin-3-acetic acid.

4 g of the oil obtained above are dissolved in 25 ml of methanol, water and 6 ml of sodium hydroxide are added and the mixture is heated for 1 hour while evaporating off the methanol, and then for 2 hours under reflux.

The mixture is allowed to cool and is washed with ether, the aqueous phase is acidified and the precipitate extracted with ether. The ether phase is treated with vegetable charcoal, dried over magnesium sulphate, filtered and evaporated. The residue is recrystallized in cyclohexane and 3 g of pure product are finally collected. m.p. 143-145°C.

The table on the following page illustrates the structures and physical properties of a few compounds according to the invention.

Table



(I)

Compound (Example)	Position -CHR ₃ COOH	X+X ~~XX~~	Y+Y ~~YY~~	R1	R2	R3	Config. 6a-10a	m.p. (°C)
1 (1)	3	—	HH	H	H	H	-	145-147
(5)		enantiomer		(-)			-	137-138
(6)		enantiomer		(+)			-	136-138
2 (2)	3	—	—	H	H	H	-	120-122
3	3	—	—	CH ₃	CH ₃	H	-	170-171
4 (3)	3	HH	HH	H	H	H	cis/trans (50/50)	102-105
5 (4)	3	HH	HH	H	H	H	trans	175(dec.)
6	3	HH	HH	H	H	H	cis/trans (80/20)	100-103
7	2	—	HH	H	H	H	-	125-126
8	3	HH	—	H	H	H	trans	145-146
9	3	HH	—	CH ₃	CH ₃	H	trans	140-141
10	2	HH	HH	H	H	H	cis/trans (50/50)	88(dec.)
11 (7)	3	—	HH	H	H	CH ₃	-	143-145



The compounds of the invention were subjected to various trials which demonstrated their value as substances having therapeutic, especially anti-inflammatory, applications.

5 Their acute toxicity is low, the oral lethal dose LD₅₀ in mice most frequently being more than 1,000 mg/kg.

For studying the anti-inflammatory activity, trials were performed using the test of carrageenin-induced
10 oedema in rats according to the method of Winter et al ("Carrageenin-induced oedema in hind paw of the rat as an assay for anti-inflammatory drugs". Proc. Soc. Exp. Biol. Med. 1962, 111, 544-547). The animals used are Charles River (France) male CD rats having an average
15 weight of 120 to 130 g, distributed in batches at random using a distribution table.

The compounds are administered orally at doses of between 20 and 200 mg/kg, 1 hour before the injection of 0.1 ml of carrageenin, in a 1% strength suspension in
20 sterile physiological saline, under the plantar aponeurosis of one of the hind paws. The control animals receive only placebo, a 1% strength solution of Tween 80[®]. The increase in volume of the paw is measured 3 hours after the injection of carrageenin by means of an Ugo Basile plethysmometer.
25 The AD₄₀ dose, the dose of substance which decreases the volume of the oedema by 40% compared with the control animals, is determined graphically.

The oral AD₄₀ values of the compounds of the invention are between 1 and 50 mg/kg.

The analgesic activity of the compounds of the invention was demonstrated in the test of Koster et al
5 (acetic acid "writhing test" in mice, Fed. Proc., 18, 412, 1959). Male CD₁ mice, fasted for 18 hours, are given the test compound, dissolved in Tween 80[®] at a concentration of 1%, orally in the proportion of 0.2 ml per 20 g of
10 bodyweight; after 30 min, acetic acid (dissolved at a concentration of 0.6% in a mixture of carboxymethylcellulose and Tween 80[®], in the proportion of 10 ml per kg of bodyweight) is administered intraperitoneally. In the control animals, this injection initiates, in the space of a few minutes, a syndrome of stretching movements and
15 contortions (writhing) which may be regarded as the expression of a diffuse abdominal pain.

The total number of contortions are noted during 15 min, the percentage protection compared with the control batch is determined and the AD₅₀ (the dose which
20 protects 50% of the animals) is calculated by a graphic method.

The oral AD₅₀ values of the compounds of the invention are between 75 and 170 mg/kg.

The results of the trials show that the compounds
25 of the invention may be used as active substances of medicinal products and pharmaceutical compositions that are usable for the treatment of inflammation and pain of

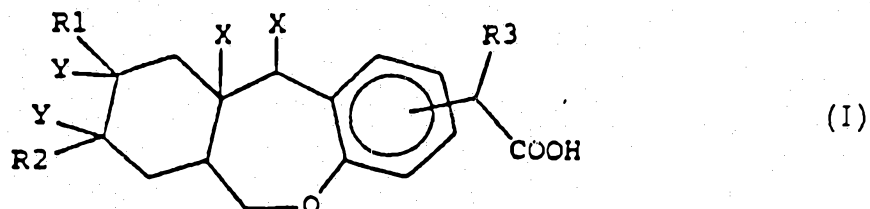
various origins.

For this purpose, they may be presented in all forms suitable for enteral or parenteral administration, for example the form of tablets, gelatin capsules, dragees, 5 syrups, suppositories, suspensions to be taken orally or injectable suspensions, in combination with suitable excipients.

The daily dosage can range from 50 to 1000 mg of active substance.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound, in the form of a pure optical isomer or a racemate, which is a dibenzo[be]oxepinacetic acid of the general formula (I)



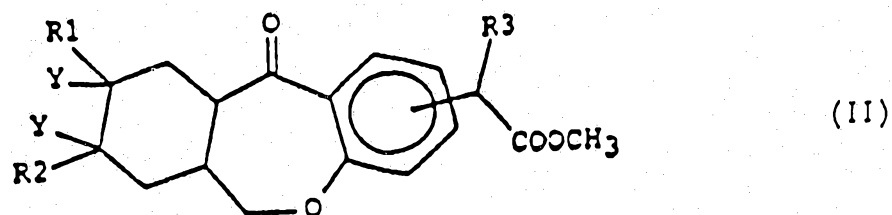
in which R1, R2 and R3, which may be the same or different, each represent hydrogen or methyl, each X represents a hydrogen atom or together they form a carbon-carbon bond, and each Y represents a
15 hydrogen atom or together they form a carbon-carbon bond, or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, wherein R1, R2 and R3 each represent hydrogen, each X together forms a carbon-carbon bond, each Y represents a hydrogen atom and the group-CH(R3)COOH is at the 3-
20 position.

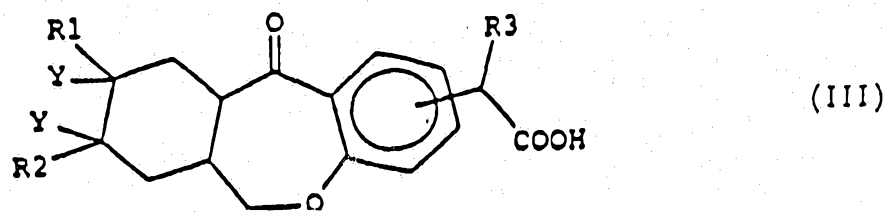
3. A compound according to Claim 1 which is a dibenzo [b,e]oxepinacetic acid identified as any one of Compounds 1 to 11 in the Table, or is a pharmaceutically acceptable salt of such a compound.

- 25 4. A process for preparing a compound as claimed in Claim 1, which comprises:-

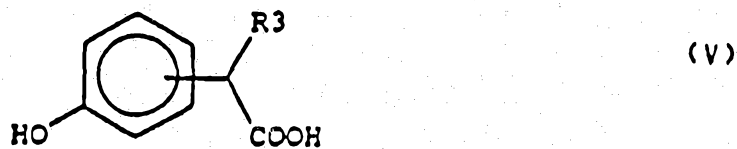
(a) (i) hydrolysing an ester of formula (II)



10 (wherein the various symbols are as defined in Claim 1) to form a free acid of formula (III)



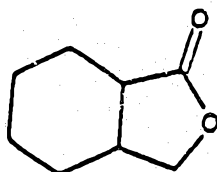
20 or (ii) treating a benzeneacetic acid of formula (V)



30 (in which R3 is as defined in Claim 1) with sodium, reacting the salt thereby obtained with a lactone of formula (VI)

35

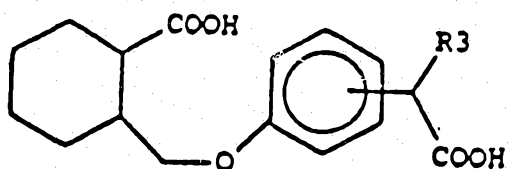
5



(VI)

to obtain a compound of formula (VII)

10

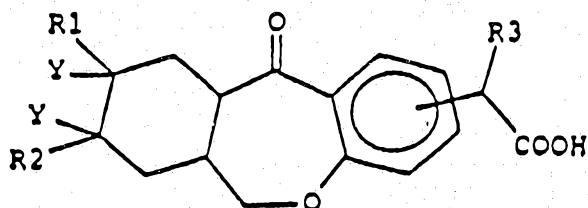


(VII)

15

and cyclising the compound of formula (VII) to form a
20 free acid of formula (III)

25



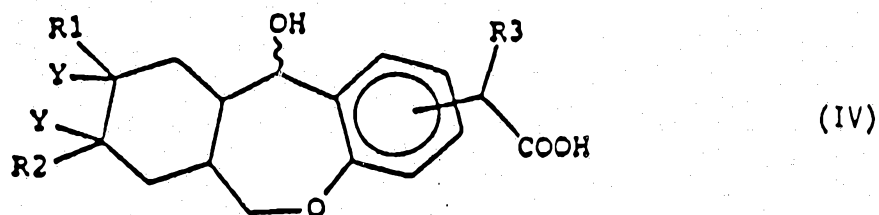
(III)

30 in which each Y represents a hydrogen atom, R1 and R2
each represent hydrogen and R3 is as defined in Claim 1



(b) reducing the ketone group of free acid (III) to an alcohol group to form an alcohol of formula (IV)

5



- 10 (c) either (i) dehydrating the alcohol (IV) to provide an acid of formula (I) in which each X together forms a carbon-carbon bond and optionally catalytically hydrogenating said bond to provide a said acid in which each X represents a hydrogen atom, or (II) in which each
- 15 X represents a hydrogen atom.
- (d) optionally if desired methylating a resulting compound of formula (I) in which R3 represents hydrogen so as to provide a compound of formula (I) in which R3 represents methyl, and
- 20 (e) if desired converting a free acid of formula (I) into a pharmaceutically acceptable salt thereof.

54. A process according to Claim 4 wherein in step (a) the ester of formula (II) is one in which each Y represents a hydrogen atom and has been obtained by the catalytic hydrogenation of an ester of formula (II) in which each Y together forms a carbon-carbon bond.
- 5 65. A process according to Claim 4 or 5 ~~or 6~~ wherein in step (b) the ketone group is reduced by means of an alkali metal borohydride.
76. A process according to any one of Claims 4 to 6 wherein para-toluene sulfonic acid is employed in the dehydrating step (c)(i).
86. A process according to any one of Claims 4 to 6 wherein sodium
10 cyanoborohydride and zinc iodide are employed in the reducing step (c)(ii).
96. A process according to Claim 4 substantially as described with reference to any one of Examples 1 to 7.
106. A pharmaceutical composition, which comprises, as active
15 ingredient, a compound as claimed in Claim 1, 2 or 3 in association with a pharmaceutically acceptable excipient.
116. Compounds of the general formula (I) and methods for their manufacture substantially as hereinbefore described with reference to any one of the Examples.

20

12 December, 1989

SYNTHELABO

By Its Patent Attorneys

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