



Office de la Propriété
Intellectuelle
du Canada

Un organisme
d'Industrie Canada

Canadian
Intellectual Property
Office

An agency of
Industry Canada

CA 2657679 C 2014/10/21

(11)(21) **2 657 679**

(12) **BREVET CANADIEN
CANADIAN PATENT**

(13) **C**

(86) **Date de dépôt PCT/PCT Filing Date:** 2007/07/16
(87) **Date publication PCT/PCT Publication Date:** 2008/01/24
(45) **Date de délivrance/Issue Date:** 2014/10/21
(85) **Entrée phase nationale/National Entry:** 2009/01/13
(86) **N° demande PCT/PCT Application No.:** EP 2007/006278
(87) **N° publication PCT/PCT Publication No.:** 2008/009397
(30) **Priorité/Priority:** 2006/07/21 (ES P200601951)

(51) **Cl.Int./Int.Cl. C07D 453/02** (2006.01)
(72) **Inventeurs/Inventors:**
BUSQUETS BAQUE, NURIA, ES;
PAJUELO LORENZO, FRANCESCA, ES
(73) **Propriétaire/Owner:**
ALMIRALL, S.A., ES
(74) **Agent:** BLAKE, CASSELS & GRAYDON LLP

(54) **Titre : PROCEDE DE PREPARATION DE BROMURE DE 3(R)-(2-HYDROXY-2,2-DITHIEN-2-YLACETOXY)-1-(3-PHENOXYPROPYL)-1-AZONIABICYCLO[2.2.2]OCTANE**
(54) **Title: PROCESS FOR MANUFACTURING 3(R)-(2-HYDROXY-2,2-DITHIEN-2-YLACETOXY)-1-(3-PHENOXYPROPYL)-1-AZONIABICYCLO[2.2.2]OCTANE BROMIDE**

(57) **Abrégé/Abstract:**

This invention is directed to a process for manufacturing 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide by reacting 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester and 3-phenoxypropyl bromide, wherein the reaction takes place in a solvent or mixtures of solvents having a boiling point between 50 and 210°C and selected from the group consisting of ketones and cyclic ethers.



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
24 January 2008 (24.01.2008)

PCT

(10) International Publication Number
WO 2008/009397 A8

(51) International Patent Classification:
C07D 453/02 (2006.01)

(21) International Application Number:
PCT/EP2007/006278

(22) International Filing Date: 16 July 2007 (16.07.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P200601951 21 July 2006 (21.07.2006) ES

(71) Applicant (for all designated States except US): **LABORATORIOS ALMIRALL, S.A.** [ES/ES]; Ronda del General Mitre, 151, E-08022 Barcelona (ES).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BUSQUETS BAQUE, Nuria** [ES/ES]; C/Camelias 22, 3° 2a, E-08024 Barcelona (ES). **PAJUELO LORENZO, Francesca** [ES/ES]; Avda. 11 de Septiembre 263, 3°2a, E-08820 El Prat de Llobregat (ES).

(74) Agent: **SRINIVASAN, Ravi, Chandran**; J.A. Kemp & CO, 14 South Square, Gray's Inn, London WC1R 5JJ (GB).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

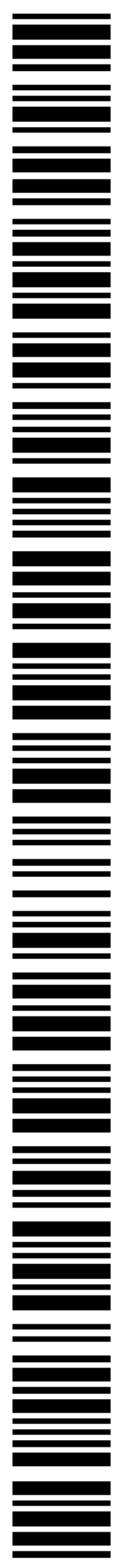
(48) Date of publication of this corrected version:

22 January 2009

(15) Information about Correction:
see Notice of 22 January 2009

(54) Title: PROCESS FOR MANUFACTURING 3(R)-(2-HYDROXY-2,2-DITHIEN-2-YLACETOXY)-1-(3-PHENOXYPROPYL)-1-AZONIABICYCLO[2.2.2]OCTANE BROMIDE

(57) Abstract: This invention is directed to a process for manufacturing 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide by reacting 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester and 3-phenoxypropyl bromide, wherein the reaction takes place in a solvent or mixtures of solvents having a boiling point between 50 and 210°C and selected from the group consisting of ketones and cyclic ethers.



WO 2008/009397 A8

Process for manufacturing 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide

The present invention relates to a process for the manufacture of 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane.

This compound as well as a process for its manufacture are described in WO 01/04118 A2.

10

The inventors have now unexpectedly found that by proper selection of the reaction conditions the process described in WO 01/04118 A2 can be optimized enabling to decrease the reaction time and the quantity of solvents and alkylating reactant used while increasing the yield and maintaining the level of impurities.

15

These objectives can be achieved by carrying out the quaternization reaction between 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester and 3-phenoxypropyl bromide in a solvent or mixture of solvents having a boiling point of between 50 and 210 °C and selected from the group consisting of ketones and cyclic ethers. In an advantageous embodiment of the present invention a single solvent is used.

20

The following are some examples of ketones or cyclic ethers that can be used as solvents for carrying out the invention: acetone, methyl ethyl ketone, methyl isobutyl ketone, phenyl methyl ketone, cyclopentanone, dioxane, tetrahydrofuran, ethyltetrahydrofuran. Preferred solvents are selected from the group consisting of acetone, dioxane or tetrahydrofuran. A particularly preferred solvent is tetrahydrofuran.

25

30

In particular, it has been advantageous to use an equivalent ratio of 3-phenoxypropyl bromide to 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester in the range of 1.0 to 3.0, more preferably between 1.1 and 1.5, most preferably between 1.2 and 1.3.

In a further preferred embodiment the 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester is suspended (or dissolved) in a volume of solvent or solvent mixture comprised between 1,7 and 7 liters of solvent(s) per
5 mol of 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester. More preferably the ester is suspended (or dissolved) in a volume of solvent comprised between 1 and 7, preferably between 2 and 4 liters per mol of ester.

Under these conditions it has proven adequate to allow the mixture to react for
10 a time period not exceeding 24 hours, preferably not longer than 12 hours more preferably not longer than 9 hours and most preferably up to 6 hours.

Particularly good results are obtained when 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester is suspended in 2 to 4 l of
15 tetrahydrofurane per mole of 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester, from 1.2 to 1.3 equivalents of 3-phenoxypropyl bromide are added to the resulting suspension and the mixture is stirred for not more than 9 hours, preferably not more than 6 h at reflux in an inert atmosphere.

20 The following examples show illustrative methods for preparing compounds according to the present invention, and are not intended to limit the scope of the invention.

Experimental section**COMPARATIVE EXAMPLE 1 (according to WO 01/04118)**

5 0.6 mmol of 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester are suspended in 4 ml of CH₃CN and 6 ml of CHCl₃. 0.48 ml of 3-phenoxypropyl bromide were added to the resulting suspension and the mixture was stirred for 72 h at room temperature in an inert atmosphere. The solvents were subsequently evaporated to yield (90%) of 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxo)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide. The
10 product is isolated by filtration at room temperature and the level of 3-phenoxypropyl bromide is determined to be 117 ppm.

EXAMPLES 2 to 8

15

The moles of 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester indicated in column **B** were suspended in the amount (column **E**) of the solvent indicated in column **D**. Then, the amount of 3-phenoxypropyl bromide resulting from multiplying column **B** by column **C** was added to the resulting
20 suspension and the mixture was stirred for 6 h at reflux in an inert atmosphere. The solvents were subsequently evaporated to yield 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxo)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide. The product was isolated by filtration at room temperature and both the yield and the level of 3-phenoxypropyl bromide were determined and indicated in
25 columns **F** and **G**, respectively.

The following table summarizes the results of comparative example 1 and examples 2 to 8 of the present invention.

TABLE I

A	B	C	D	E	F	G
Ex	Amount of 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester (mmoles)	Ratio (Eq) of 3-phenoxypropyl bromide to 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester	Solvent	Amount of solvent (l/mol)	Yield (%)	Amount of 3-phenoxypropyl bromide (ppm)
1*	0,6	5.0	CH ₃ CN/CHCl ₃	16.7	90	117
2	71.53	1.25	THF	2.1	95.0	148
3	71.53	1.10	THF	2.1	92.4	60
4	71.53	1.10	Acetone	2.1	95.3	152
5	71.53	1.25	Acetone	2.1	98.7	173
6	71.53	1.25	Acetone	7.0	93.7	60
7	14.31	1.50	Methyl ethyl ketone	2.1	96.9	304
8	14.31	1.50	Methyl isobutyl ketone	3.5	94.7	410
9	42.92	1.25	Dioxane	2.1	98.2	31
10	71.53	1.25	Methyl THF	2.1	96.7	212
11	42.92	1.25	Acetophenone	2.1	98.5	53
12	42.92	1.25	Cyclopentanone	2.1	94.4	167

* The reaction of comparative example 1 was carried out by stirring at room temperature during 72 hours

5 As can be seen from the results of table I show that the method of the present invention allows shortening the reaction time and reducing the quantity of 3-phenoxypropyl bromide employed while simultaneously increasing the yield and yet maintaining the amount of the genotoxic 3-phenoxypropyl bromide impurity

10 at an acceptable level of below 500 ppm.

We Claim:

1. A process for manufacturing 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide by reacting 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester and 3-phenoxypropyl bromide, wherein the reaction takes place in a solvent or mixtures of solvents having a boiling point between 50 and 210°C and selected from the group consisting of ketones and cyclic ethers.
2. A process according to claim 1 wherein the equivalent ratio of 3-phenoxypropyl bromide to 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester is in the range of 1.0 to 3.0.
3. A process according to claim 2 wherein the equivalent ratio is in the range of 1.1 to 1.5.
4. A process according to claim 2 wherein the equivalent ratio is in the range of 1.2 to 1.3.
5. A process according to any one of claims 1 to 4, wherein 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester is suspended or dissolved in a volume of solvent or solvent mixture comprised between 1.7 and 7 liters of solvent(s) per mol of 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester.
6. A process according to claim 5 wherein the volume of solvent is comprised between 2 and 4 liters per mol of 2-hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)yl ester.
7. A process according to any one of claims 1 to 6, wherein the solvent is selected from the group consisting of acetone, dioxane and tetrahydrofuran.
8. A process according to claim 7 wherein the solvent is tetrahydrofuran.
9. A process according to any one of claims 1 to 8, wherein the mixture is allowed to react for a time period not exceeding 24 hours.
10. A process according to claim 9 wherein the time period is not more than 12 hours.

11. A process according to claim 10 wherein the time period is not more than 9 hours.
12. A process according to claim 11 wherein the time period is not more than 6 hours.