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.

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.

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.

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, tetrahydrofurane, ethyltetrahydrofurane. Preferred solvents are selected from the group consisting of acetone, dioxane or tetrahydrofurane. A particularly preferred solvent is tetrahydrofurane.

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 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 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 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.

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)

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 CH_3CN and 6 ml of $CHCl_3$. 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-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide. The 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

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 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-ylacetoxy)-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 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	$CH_3CN/CHCl_3$	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

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 at an acceptable level of below 500 ppm.

CLAIMS

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 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 preceding claim 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 preceding claim wherein the solvent is selected from the group consisting of acetone, dioxane and tetrahydrofurane.

8. A process according to claim 7 wherein the solvent is tetrahydrofurane.

9. A process according to any preceding claim 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.