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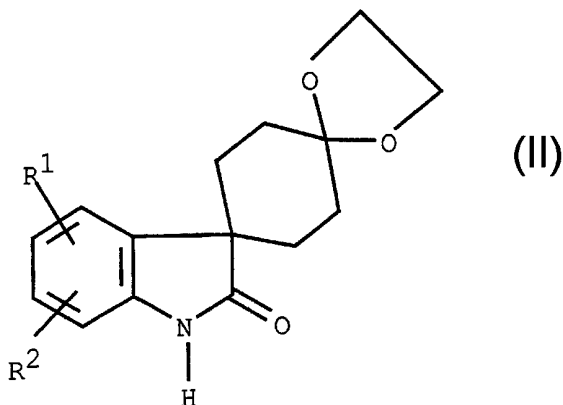
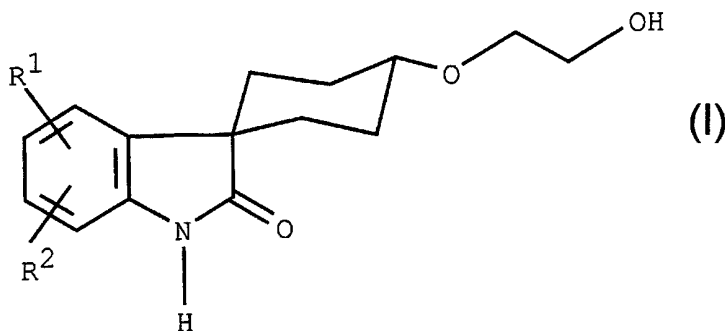
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(54) Title: PROCESS FOR THE PREPARATION OF SPIRO-[cis-4-(β-HYDROXYETHYLOXY)CYCLOHEX-
ANE-[3H]INDOL]-2'-[1'H]ONE DERIVATIVES



(57) Abstract: The invention relates to a process for the preparation of spiro[cis-4-(β-hydroxyethyloxy)cyclohexane-[3H]-2'-[1'H]-one derivatives of the formula (I) wherein R¹ and R² stand independently from each other for hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, C₁₋₄polyfluoroalkyl, C₁₋₄polyfluoroalkoxy, C₃₋₇cycloalkyloxy, C₃₋₇cycloalkylthio, phenoxy, benzyloxy or nitro group by reduction of a dispiro [(1,3-dioxolane)-2,4'-cyclohexane-1',3''-[3H]indol]-2''[1'H]-one derivative of general formula (II), wherein R¹ and R² are as defined above, which comprises carrying out the reduction (a) with sodium cyanoborohydride in the presence of a Lewis acid, or (b) with sodium borohydride in the presence of a strong acid.



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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

**Process for the preparation of spiro[*cis*-4-(β -hydroxyethyloxy)cyclohexane-
[3*H*]indol]-2'[1'*H*]one derivatives**

The subject of the present invention is a process for the preparation of spiro[*cis*-4-
5 (β -hydroxyethyloxy)cyclohexane-[3*H*]indol]-2'[1'*H*]-one derivatives of general
formula I.

The spiro[*cis*-4-(β -hydroxyethyloxy)cyclohexane-1,3'-(5'-ethoxy)-[3*H*]indol]-
2'[1'*H*]-one is an important intermediate to the vasopressin V₂ antagonistic agent,
10 SR 121463. Preparation of the latter compound and its intermediate of formula I are
described in patent application of WO 9715556.

According to the process described in the above patent application, the compounds
of general formula I are prepared from the compounds of general formula II using
15 zinc borohydride reducing agent in the presence of chlorotrimethylsilane in the
mixture of dichloromethane and diethyl ether. By this method the desired *cis*-isomer
is obtained in 50-54% yield. The reaction time is long, approximately 20 hours, the
zinc borohydride reagent has to be prepared in situ (it also takes approximately 20
hours) and the diethyl ether can not be substituted by an other solvent.

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Surprisingly, we have found that the reaction can be accomplished under more
simple conditions.

The subject of our invention is a process for the preparation of spiro[*cis*-4-(β -
25 hydroxyethyloxy)cyclohexane-[3*H*]indol]-2'[1'*H*]-one derivatives of the formula I ,
- wherein

R¹ and R² stand independently from each other for hydrogen, C₁₋₄alkyl, C₁₋₄
alkoxy, C₁₋₄alkylthio, C₁₋₄polyfluoroalkyl, C₁₋₄polyfluoroalkoxy, C₃₋₇
cycloalkyloxy, C₃₋₇ cycloalkylthio, phenoxy, benzyloxy or nitro group -

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by reduction of a dispiro[(1,3-dioxolane)-2,4'-cyclohexane-1',3''-[3*H*]-2''[1''*H*]-one derivative of the general formula II, wherein R¹ and R² are as defined above, which comprises carrying out the reduction

- 5 a) with sodium cyanoborohydride in the presence of a Lewis acid, or
 b) with sodium borohydride in the presence of a strong acid (see Figure 1).

Reducing agents sodium cyanoborohydride and sodium borohydride are available from the market.

- 10 In the process according to the present invention as for Lewis acid aluminum chloride, zinc chloride, iron/III/ chloride, preferably boron trifluoride etherate; as for strong organic acid trifluoroacetic acid, dichloro acetic acid, methanesulfonic acid, trifluoromethanesulfonic acid, preferably trichloroacetic acid can be used.
- 15 A further advantage of the process of the present invention is that the use of diethyl ether as solvent can be eliminated, as for solvents, halogenated hydrocarbons, preferably dichloromethane can be applied.

20 By the method according to the present invention the pure cis-isomer can be obtained by 67-75% yield.

Further details of the invention are demonstrated by the following examples, without limiting the claims to the examples.

Examples

1.) Into the solution made of 121,3 g of dispiro[(1,3-dioxolane)-2,4'-cyclohexane-1',3''-(5''-ethoxy)-[3*H*]indol]-2''[1''*H*]-one in 1000 ml of dichloromethane, under
5 inert atmosphere 37,2 g of sodium cyanoborohydride is added, then dropwise, at -5 °C 170,3 g of borontrifluoride etherate. The reaction mixture is then allowed to warm up to room temperature (approx. 45 minutes) and stirred at that temperature for 1,5 hours. To the diluted suspension 500 ml of 10% sodium hydroxide solution is dropped and after 30 minutes of stirring dichloromethane is distilled off. After
10 cooling back to room temperature, to the aqueous mixture, slowly, 500 ml of ethanol is added, and the mixture is then stirred and heated at reflux temperature for 1 hour. Ethanol is distilled off in vacuum, the residue is diluted with 300 ml of water, extracted with 4 x 100 ml of dichloromethane, washed with 2 x 250 ml of water, dried with sodium sulfate and evaporated. The residual brown oil is
15 dissolved under reflux in 350 ml of toluene, clarified with active carbon and filtered. The precipitating crystals are filtered off. The resulting 100,6 g (82 %) product is recrystallized from 300 ml of toluene.

Thus, 91 g product of appropriate purity is obtained. Yield: 74,5 %.

Ratio of the isomers (HPLC): cis: 95,5%; trans 1,8%.

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2.) 9.1g of dispiro[(1,3-dioxolane)-2,4'-cyclohexane-1',3''-(5''-ethoxy)-[3*H*]indol]-2''[1''*H*]-one is dissolved in 100 ml of dichloromethane, to the solution 3,4 g of sodium borohydride and 0,6 g of benzyltriethylammonium chloride is added. To the mixture at room temperature, in a period of 1 hour, the solution of 29,4 g of
25 trichloroacetic acid in 50 ml of dichloromethane is added. The mixture is stirred for an additional hour, then 130 ml of 1 N sodium hydroxide solution is added to it. After 30 minutes of stirring the ethanol is distilled off in vacuum, the residue is diluted with 100 ml of water and extracted with dichloromethane. The organic phase is evaporated, the oily residue is crystallized from 50 ml of toluene. Thus,
30 6,25 g of product is obtained, mp.: 123-124 °C. Yield: 68 %.

Ratio of the isomers (HPLC): cis 98,7%, trans 1%.

Claims

1.) Process for the preparation of spiro[*cis*-4-(β -hydroxyethyloxy)cyclohexane-[3*H*]indol]-2'[1'*H*]-one derivatives of the formula I ,

5 - wherein

R¹ and R² stand independently from each other for hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, C₁₋₄polyfluoroalkyl, C₁₋₄polyfluoroalkoxy, C₃₋₇cycloalkyloxy, C₃₋₇ cycloalkylthio, phenoxy, benzyloxy or nitro group -
by reduction of a dispiro[(1,3-dioxolane)-2,4'-cyclohexane-1',3''-[3*H*]indol]-
10 2''[1''*H*]-one derivative of the general formula II, wherein R¹ and R² are as defined
above, which comprises carrying out the reduction

- a.) with sodium cyanoborohydride in the presence of a Lewis acid, or
- b) with sodium borohydride in the presence of a strong acid.

15 2.) Process according to claim 1., which comprises using as Lewis acid aluminum chloride, zinc chloride, iron/III/ chloride, preferably boron trifluoride etherate.

3.) Process according to claim 1., which comprises using as strong organic acid trifluoroacetic acid, dichloro acetic acid, methanesulfonic acid,
20 trifluoromethanesulfonic acid, preferably trichloroacetic acid.

4.) Process according to claim 1., which comprises using as solvent halogenated hydrocarbons, preferably dichloromethane.

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Figure 1

