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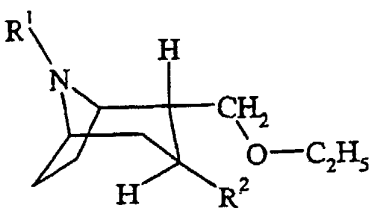
Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) Title: METHOD FOR PRODUCING A 2-(ETHOXYMETHYL)TROPANE DERIVATIVE

(54) Bezeichnung: VERFAHREN ZUR HERSTELLUNG EINES 2-(ETHOXYMETHYL)-TROPANDERIVATES



(I)

(57) Abstract: The invention relates to a method for producing a 2-(ethoxymethyl)tropane derivative or a pharmaceutically acceptable salt thereof. The inventive is method is characterized by treating the corresponding 2-(hydroxymethyl)tropane derivative with ethyl bromide in the presence of a base, a phase transfer catalyst, and optionally a diluent and then optionally with an acid.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft ein Verfahren zur Herstellung eines 2-(Ethoxymethyl)-tropanderivates der Formel (I) oder einem pharmazeutisch akzeptablen Salz davon, wobei man das entsprechende 2-(Hydroxymethyl)-tropanderivat mit Ethylbromid in Gegenwart einer Base, eines Phasentransferkatalysators, und gegebenenfalls einem Verdünnungsmittel umsetzt, und anschliessend gegebenenfalls mit einer Säure behandelt.

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METHOD FOR PRODUCING A 2-(ETHOXYMETHYL)-TROPANE DERIVATIVE

The present invention relates to an improved process for preparing a 2-(ethoxymethyl)-tropane derivative by reacting a 2-(hydroxymethyl)-tropane derivative with ethyl bromide in the presence of a base and a phase transfer catalyst.

Background to the invention

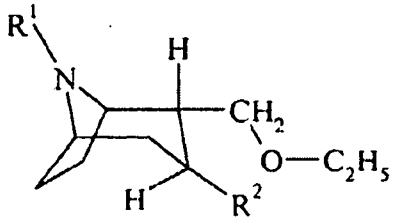
2-(Ethoxymethyl)-tropane derivatives are valuable pharmaceutical active substances for the treatment of various central nervous disorders, such as e.g. Parkinson's or Alzheimer's disease.

According to the teaching of International Patent Application WO 97/30997 they are prepared either from a 2-(tosylmethyl)-tropane derivative by reacting with ethoxide or by reacting a 2-(hydroxymethyl)-tropane derivative with sodium hydride as base and diethylsulphate. For safety reasons production on an industrial scale using sodium hydride is virtually impossible. Moreover, this ethoxylation is not really reproducible, the reaction times are long and the active substance is produced in unsatisfactory yields as a solid which is difficult to isolate.

The problem underlying the present invention is thus to provide a process which enables 2-(ethoxymethyl)-tropane derivatives to be produced in good yields on a large industrial scale while avoiding the disadvantages that occur with the processes known from the prior art.

Detailed description of the invention

Surprisingly it has now been found that 2-(ethoxymethyl)-tropane derivatives of formula (I) or a pharmaceutically acceptable salt thereof,

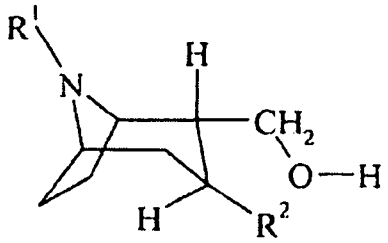


(I)

wherein

R^1 denotes hydrogen or C_{1-6} alkyl, particularly methyl; and

R^2 denotes phenyl optionally mono- or polysubstituted by halogen, trifluoromethyl or cyano, particularly 3,4-dichlorophenyl; may be prepared in good yields and on an industrial scale by reacting a 2-(hydroxymethyl)-tropane derivative of formula (II),



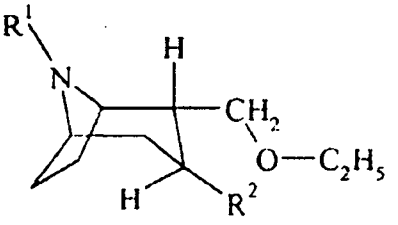
(II)

wherein R^1 and R^2 are defined as for formula (I),

with ethyl bromide in the presence of a base, a phase transfer catalyst, and optionally a diluent.

The invention thus relates to an improved process for preparing a 2-(ethoxymethyl)-tropane derivative of formula (I) or a pharmaceutically acceptable salt thereof, in which a 2-(hydroxymethyl)-tropane derivative of formula (II) is reacted with ethyl bromide in the presence of a base, a phase transfer catalyst and optionally a diluent, and then optionally treated with an acid.

In one aspect, the present invention provides a process for the preparation of a 2-(ethoxymethyl)-tropane derivative of formula (I) or a pharmaceutically acceptable salt thereof,



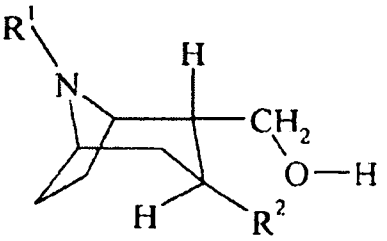
(I)

wherein

R^1 represents hydrogen or C_{1-6} alkyl; and

R^2 represents phenyl, optionally substituted one or more times with halogen, trifluoromethyl or cyano;

characterised in that a 2-(hydroxymethyl)-tropane derivative of formula (II)



(II)

wherein R^1 and R^2 have the meaning specified for formula (I)

is reacted with ethyl bromide in the presence of a base, a phase transfer catalyst, and optionally a diluent, and subsequently optionally treated with an acid; and

wherein lithium hydroxide, sodium hydroxide or potassium hydroxide is used as a base.

Preferred embodiments of the process according to the invention are processes wherein:

(A) an alkali metal hydroxide, such as for example lithium hydroxide, sodium hydroxide or potassium hydroxide, particularly powdered potassium hydroxide, is used as base;

(B) the phase transfer catalyst (PTC) used is a tetraalkylammonium or tetraalkylphosphonium salt, while the alkyl groups may be identical or different, such as for example salts of tetraoctylammonium, methyltrioctyl ammonium, tetramethylammonium, tetraethylammonium, tetrahexylammonium, Aliquat 175 (tributylmethylammonium) or Aliquat 336 (methyltrioctylammonium). Preferably the PTC is a tetraalkylammonium halide, a tetraalkylammonium sulphate, a tetraalkylammonium hydrogen sulphate, a tetraalkylammonium nitrate or a tetraalkylammonium phosphate, particularly a tetraalkylammonium hydrogen sulphate, most particularly preferably tetra-*n*-butylammonium hydrogen sulphate.

The term "alkyl" as used above and hereinafter in relation to the phase transfer catalyst includes straight-chain and branched alkyl groups with 1 to 8, preferably 2 to 6, particularly 4 carbon atoms. Preferred alkyl groups which may be mentioned are thus ethyl, *n*-propyl, *i*-propyl, *n*-butyl, 2-butyl, *tert*-butyl, *n*-pentyl, 2-pentyl, *neo*-pentyl, *n*-hexyl- and 2-hexyl group. The *n*-butyl group is most particularly preferred.

Other preferred embodiments of the process according to the invention are processes wherein:

(C) the diluent used is an aromatic hydrocarbon, preferably benzene, toluene or xylene, particularly toluene, or an optionally halogenated aliphatic hydrocarbon, preferably cyclohexane, methylcyclohexane, dichloromethane, chloroform, carbon tetrachloride or dichloroethane, particularly dichloromethane or an ether, preferably tetrahydrofuran (THF), diethyl ether, diisopropylether, *tert*-butylmethylether (TBME) or 1,2-dimethoxyethane (DME), particularly 1,2-dimethoxyethane;

(D) the reaction is carried out at temperatures in the range from –10 °C to +90 °C, preferably from 0 °C to 80°C, particularly from 20 to 65°C;

(E) 0.75 to 100 equivalents, preferably 1.5 to 5.5 equivalents, particularly about 4 equivalents of ethyl bromide are used to 1 equivalent of a compound of formula (II);

(F) 2.5 to 100 equivalents, preferably 3.8 to 10.5 equivalents, particularly 7.5 to 8.5 equivalents of base are used to 1 equivalent of a compound of formula (II);

(G) 0.01 to 0.5 equivalents, preferably 0.02 to 0.2 equivalents, particularly 0.05 to 0.15 equivalents of phase transfer catalyst are used to 1 equivalent of a compound of formula (II);

(H) after the end of the reaction, water is added to the reaction mixture, the phases are separated, the organic phase is washed with water, evaporated down under reduced pressure and the residue is treated with an acid and the acid addition salt obtained is isolated;

(I) the active substance of formula (I) obtained is treated with an inorganic or organic acid treated. The resulting acid addition salts are, for example, hydrochlorides, hydrobromides, phosphates, nitrates, perchlorates, sulphates, citrates, lactates, tartrates, maleates, fumarates, mandelates, benzoates, ascorbates, cinnamates, benzenesulphonates, methanesulphonates, stearates, succinates, glutamates, glycollates, toluene-p-sulphonates, formates, malonates, naphthalene-2-sulphonates, salicylates and acetates. The citrates are particularly preferred. These salts are prepared using correspondingly well-known production methods.

In a particularly preferred embodiment 4 equivalents of ethyl bromide, optionally dissolved in 1,2-dimethoxyethane, are metered into a mixture of 1 equivalent of a compound of formula (II), about 20 times as much, by weight, of 1,2-dimethoxyethane based on (II), about 8 equivalents of KOH, and about 0.1 equivalents of tetra-*n*-butylammonium hydrogen sulphate within 5 to 60 minutes at a temperature between 20 and 35 °C, with stirring. After the addition has ended the mixture is stirred for 30 to 300, preferably about 45 to 180 minutes at a temperature between 40 and 80 °C. Then water is added, and at the temperature specified the mixture is stirred for a further 30 to 300, preferably about 45 to 180 minutes, then the organic phase is separated off. The organic phase is evaporated down and the residue is treated with an acid, preferably citric acid.

The acid salt of the compound of formula (I) is isolated and dried

Other advantageous aspects of the procedure according to the invention are the high space-time yield of the present process and the high yield and purity of the compound of formula (I) or its salt obtained without any further purification processes.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

The Examples that follow serve to illustrate processes carried out by way of example for preparing a compound of formula (I). They should be understood as being possible procedures illustrate by way of example without restricting the invention to their content.

Example 1 (1R,2R,3S)-2-ethoxymethyl-3-(3,4-dichlorophenyl)-tropane citrate

14.6 g (0.134 mol) of ethyl bromide is metered into a mixture of 10 g (0.0333 mol) (1R,2R,3S)-2-hydroxymethyl-3-(3,4-dichlorophenyl)-tropane (prepared according to WO 97/30997), 14.92 g powdered (0.266 Mol KOH) caustic potash, 1.16 g (0.00334 mol) of tetra-*n*-butylammonium hydrogen sulphate and 200 ml DME within 15 minutes at a temperature of between 20 and 31°C, with stirring.

After the addition has ended the mixture is stirred for 1.5 hours at a temperature between 58 and 62 °C. Then 76 ml of water are added, the mixture is stirred for another hour at this temperature and the organic phase is separated off. The organic phase is evaporated down using the rotary evaporator under reduced pressure. The residue is dissolved with 90 ml acetone at 55 °C, filtered and rinsed with 10 ml acetone. The solution obtained is treated with a mixture of 6.4 g (0.0333 mol) of citric acid and 20 ml of methanol at 40 °C. The crystal suspension is cooled to 20 °C and stirred for one hour at 15 to 20°C. The obtained crystals are isolated and washed with 33 ml acetone. After drying in the vacuum drying cupboard at 40 °C 14.55 g (83.6 % of theory) of the title compound are obtained as yellowish crystals with a purity of more than 99.4 %.

Example 2 (1R,2R,3S)-2-ethoxymethyl-3-(3,4-dichlorophenyl)-tropane citrate

17.5 g (0.161 mol) of ethyl bromide dissolved in 20 ml of 1,2-dimethoxyethane are metered within 15 minutes into a mixture of 12 g (0.0400 mol) of (1R,2R,3S)-2-hydroxymethyl-3-(3,4-dichlorophenyl)-tropane (prepared according to WO 97/30997), 17.9 g of powdered (0.320 mol KOH) caustic potash, 1.39 g (0.00409 mol) of tetra-*n*-butylammonium hydrogen sulphate and 220 ml DME, at a temperature between 20 and 31°C ,with stirring.

After the addition has ended the mixture is stirred for 1.5 hours at a temperature between 58 and 62 °C. Then 76 ml of water are added, the mixture is stirred for another hour at this temperature and the organic phase is separated off. The organic phase is evaporated down under reduced pressure using the rotary evaporator. The

residue is dissolved with 108 ml acetone at 55 °C, filtered and rinsed with 40 ml acetone. The solution obtained is treated with a mixture of 7.68 g (0.0400 mol) of citric acid and 24 ml of methanol at 40 °C. The crystal suspension is cooled to 20 °C and stirred for one hour at 15 to 20 °C. The crystals obtained are isolated and washed with at least 80 ml acetone. After drying in the vacuum drying cupboard at 40 °C, 17.44 g (83.85 % of theory) of the title compound are obtained as yellowish crystals with a purity of more than 99.5 %.

Comparative Example 1

(1R,2R,3S)-2-ethoxymethyl-3-(3,4-dichlorophenyl)-tropane citrate

(according to WO 97/30997)

Sodium hydride (60% in oil) (4.6 g, 0.12 mol) and ethylsulphate (15.7 ml, 0.12 mol) are added to a mixture of (1R,2R,3S)-2-hydroxymethyl-3-(3,4-dichlorophenyl)tropane (26.9 g, 0.09 mol) and THF (200 ml) and heated to 30-40°C for half an hour. The reaction mixture is stirred overnight at ambient temperature, then heated to 30-40°C for half an hour and poured into 500 ml of water. The mixture is extracted twice with TBDME, the organic phases are washed with water and dried over $MgSO_4$. 32.82 g of the base are obtained.

Citric acid (19.2 g, 0.1 mol) is added to a solution of the resulting (1R,2R,3S)-2-ethoxymethyl-3(3,4-dichlorophenyl)tropane in 96% ethanol (275 ml). The solution is refluxed and left to stand for 3 hours at ambient temperature in order to crystallise. The mixture is placed over an ice bath for half an hour, the crystalline product is filtered off and washed with 96% ethanol (50 ml and 25 ml). After drying 32.85 g (70% of theory) of the title compound is obtained with a melting point of 153-155.5 °C.

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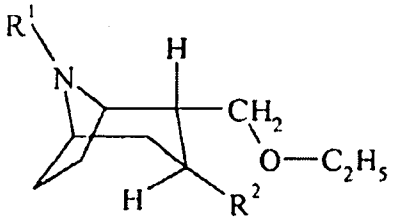
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Process for the preparation of a 2-(ethoxymethyl)-tropane derivative of formula (I) or a pharmaceutically acceptable salt thereof,



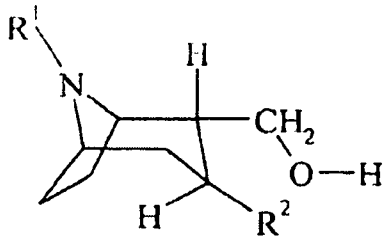
(I)

wherein

R^1 represents hydrogen or C_{1-6} alkyl; and

R^2 represents phenyl, optionally substituted one or more times with halogen, trifluoromethyl or cyano;

characterised in that a 2-(hydroxymethyl)-tropane derivative of formula (II)



(II)

wherein R^1 and R^2 have the meaning specified for formula (I)

is reacted with ethyl bromide in the presence of a base, a phase transfer catalyst, and optionally a diluent, and subsequently optionally treated with an acid; and

wherein lithium hydroxide, sodium hydroxide or potassium hydroxide is used as a base.

2. Process according to claim 1, wherein

R^1 represents methyl, and

R^2 represents 3,4-dichlorophenyl.

3. Process according to claim 1 or 2, wherein powdered potassium hydroxide is used as a base.

4. Process according to any one of claims 1 to 3, wherein a tetraalkylammonium salt or tetraalkylphosphonium salt is used as the phase transfer catalyst.

5. Process according to claim 4, wherein a tetraalkylammonium hydrogen sulphate is used as the phase transfer catalyst.

6. Process according to any one of claims 1 to 5, wherein an aromatic hydrocarbon, an optionally halogenated aliphatic hydrocarbon or an ether is used as a diluent.

7. Process according to claim 6, wherein toluene, dichloromethane or 1,2-dimethoxyethane is used as a diluent.

8. Process according to any one of claims 1 to 7, wherein the reaction is carried out in a temperature range from -10 °C to +90 °C.

9. Process according to any one of claims 1 to 8, wherein the ethyl bromide is metered within 5 to 180 minutes and the reaction mixture obtained is subsequently stirred for a further 30 to 180 minutes.

10. Process according to any one of claims 1 to 9, wherein 0.75 to 100 equivalents of ethyl bromide are used based on 1 equivalent of formula (II).

11. Process according to any one of claims 1 to 10, wherein 2.5 to 100 equivalents of base are used based on 1 equivalent of formula (II).

12. Process according to any one of claims 1 to 11, wherein 0.01 to 0.5 equivalents of phase transfer catalyst are used based on 1 equivalent of formula (II).

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13. Process for the preparation of a salt of a 2-(ethoxymethyl)-tropane derivative of formula (I) according to any one of claims 1 to 12, wherein after the reaction of the compound of formula (II) with ethyl bromide is complete, water is added to the reaction mixture, the phases are separated, the organic phase is washed with water and concentrated under reduced pressure, and the residue is treated with the corresponding acid without further purification.

14. A 2-(ethoxymethyl)-tropane derivative as defined in claim 1, prepared by the process according to any one of claims 1 to 13.

15. A process according to claim 1 substantially as hereinbefore described with reference to any one of the Examples.