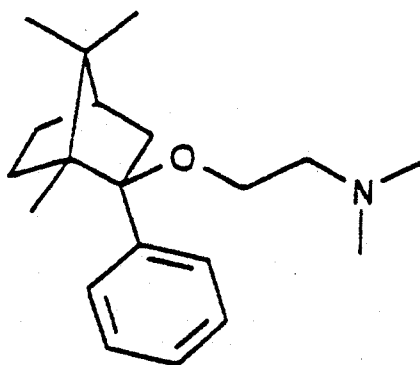


Process for preparing (1R,2S,4R)-(-)-2-[(2'-
-{N,N-dimethylamino}-ethoxy)]-2-[phenyl]-1,7,7
-tri-[methyl]-bicyclo[2.2.1]heptane and
pharmaceutically acceptable acid addition
salts thereof

The invention relates to a process for preparing
 (1R,2S,4R)-(-)-2-[(2'-{N,N-dimethylamino}-ethoxy)]-2-
 -[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane and
 pharmaceutically acceptable acid addition salts thereof.

The 2-(E)-butenedioate (1 : 1) salt (fumarate) of
 (1R,2S,4R)-(-)-2-[(2'-{N,N-dimethylamino}-ethoxy)]-2-
 -[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane of
 Formula



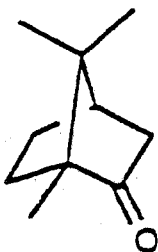
I

is a known anxiolytic active principle having the INN
 "deramciclanc fumarate".

The compound of Formula I falls under the general
 Formula I of Hungarian patent No. 179,164 but has not been
 actually and explicitly disclosed in this patent
 specification, nor the preparation thereof has been
 exemplified. According to Hungarian patent No. 179,164 the
 alkanol amine cycloalkyl ethers of its general Formula I
 are prepared by reacting (+)-1,7,7-tri-[methyl]-

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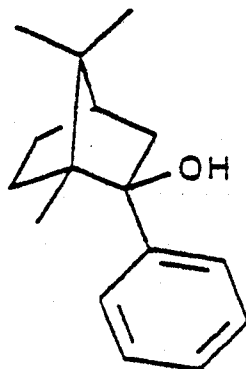
-bicyclo[2.2.1]heptane-2-one, i. e. (+)-camphor of Formula



II

with the corresponding organic metal compound, subjecting the adduct obtained to hydrolysis and introducing onto the hydroxy group of the product obtained the basic side chain by etherification. As organic metal compound a Grignard compound or an organic alkali metal compound, preferably lithium or sodium compound, is used.

The preparation of the compound of Formula I has been actually disclosed in Hungarian patent No. 212,574. The essence of this process is that purification of the product is carried out at a later stage of the synthesis. According to the process (+)-camphor of Formula II is subjected to Grignard reaction with phenyl magnesium bromide in diethyl ether to give (1R,2S,4R)-(-)-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane-2-ol of Formula



III

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with a yield of 28% (according to GC). The compound (1R,2S,4R)-(-)-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane-2-ol of Formula III is in the reaction mixture and is not isolated. The complex is decomposed, the reaction mixture is converted without purification into the sodium salt by reaction with sodium amide or sodium hydride and the sodium salt obtained is reacted with anhydrous (2-{chloro}-ethyl)-dimethylamine in toluene as medium. The reaction mixture contains beside the base (1R,2S,4R)-(-)-2-[(2'-{N,N-dimethylamino}-ethoxy)]-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane of Formula I (being present in an amount of 20 to 30% a considerable amount of impurities and starting materials, e.g. unreacted (+)-camphor of Formula II, (1R,2S,4R)-(-)-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane-2-ol, 1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane-2-ol and biphenyl, triphenyl impurities etc. The base (1R,2S,4R)-(-)-2-[(2'-{N,N-dimethylamino}-ethoxy)]-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane of Formula I is separated from said contaminations by extraction with aqueous tartaric acid, whereupon the base is set free and the fumarate salt is formed. The total amount of unreacted (+)-camphor of Formula II and (1R,2S,4R)-(-)-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane-2-ol of Formula III remains in the organic phase of the tartaric acid extraction step, which can be re-used in the Grignard reaction after removing the solvent and water (i.e. it can be re-circulated into the process). Thus the (+)-camphor used can be more efficiently utilized; without re-circulation only about 16% by weight of the (+)-camphor used can be utilized, while in case of a one-fold and three-fold re-circulation this value is increased to 22% by weight and 25% by weight, respectively. Thus the yields are too low, particularly in the view of the commercial feasibility.

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It is very important and is to be emphasized that a considerable part of (+)-camphor of Formula II used in the Grignard reaction does not react and this starting material cannot be technically removed from the desired product because of the physical properties of (+)-camphor and the lability of the compound (1R,2S,4R)-(-)-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane-2-ol of Formula III formed since compound (1R,2S,4R)-(-)-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane-2-ol of Formula III is susceptible to decomposition. For this reason according to the process disclosed in Hungarian patent No. 212,574 the alkylation step always takes place in the presence of (+)-camphor of Formula II.

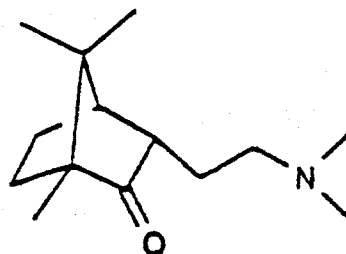
The aforesaid gives rise to the drawbacks of the process disclosed in Hungarian patent No. 212,574. The alkali hydrides and amides used in the first step of the alkylation reaction form salts not only with the alcohol (1R,2S,4R)-(-)-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane-2-ol of Formula III but also with (+)-camphor of Formula II and other compounds containing an active hydrogen atom being present in the reaction mixture. For this reason beside the desired compound (1R,2S,4R)-(-)-2-[(2'-{N,N-dimethylamino}-ethoxy)]-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane of Formula I further alkylated derivatives formed, e.g. from unreacted (+)-camphor, are obtained and the desired compound (1R,2S,4R)-(-)-2-[(2'-{N,N-dimethylamino}-ethoxy)]-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane of Formula I is to be recovered from a mixture containing such impurities and also unreacted compounds (+)-camphor and (1R,2S,4R)-(-)-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane-2-ol of Formulae II and III. The crude compound (1R,2S,4R)-(-)-2-[(2'-{N,N-dimethylamino}-ethoxy)]-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane of Formula I can only be purified, though incompletely, by means of recrystallization from

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dimethyl formamide. However, with the aid of said recrystallization only non-basic contaminations can be completely removed, which do not form salts.

5 A further disadvantage of recrystallization from dimethyl formamide is that the traces of the solvent cannot be removed from the desired pharmaceutical active principle to the required extent.

10 It has been found that in case of the alkylation reaction of (1R,2S,4R)-(-)-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane-2-ol of formula III carried out with (2-{chloro}-ethyl)-dimethylamine (+)-camphor of Formula II being always present gives rise to the formation of
15 considerable amounts of by-products, e. g. (1R,3S,4R)-3-[(2'-{N,N-dimethylamino}-ethyl)]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane-2-one of Formula



20
25 The by-product (1R,3S,4R)-3-[(2'-{N,N-dimethylamino}-ethyl)]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane-2-one of Formula V is formed as follows: under the conditions used
30 in the etherification reaction (+)-camphor of Formula II forms an alkali salt in position 3 which in turn reacts with the (2-{chloro}-ethyl)-dimethylamine used as alkylating agent to yield the compound of Formula V. The amount of the by-product of Formula V may be as high as 1
35 to 10%.

The solubility of the fumarate 2-(E)-butenedioate (1 : 1) of the compound of (1R,3S,4R)-3-[(2'-{N,N-dimethylamino}-ethyl)]-1,7,7-tri-[methyl]-

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-bicyclo[2.2.1]heptane-2-one of Formula V is approximately identical with that of the fumarate of the desired compound (1R,2S,4R) - (-)-2-[(2'-{N,N-dimethylamino}-ethoxy)]-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane of Formula I and therefore crystallizes together with the fumarate of the compound (1R,2S,4R) - (-)-2-[(2'-{N,N-dimethylamino}-ethoxy)]-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane of Formula I and contaminates the desired end product. If the etherification is carried out in toluene, as described in Hungarian patent No. 212,574, the product obtained after salt formation in ethanol contains considerable amounts of the impurity (1R,3S,4R) - 3-[(2'-{N,N-dimethylamino}-ethyl)]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane-2-one of Formula V.

The salt is a highly unsoluble compound and can be recrystallized only from dimethyl formamide. However, recrystallization from dimethyl formamide fails to provide a compound (1R,2S,4R) - (-)-2-[(2'-{N,N-dimethylamino}-ethoxy)]-2-[phenyl]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane of Formula I in a purity required by the Pharmacopoeias for the following reasons:

- a) The product obtained after recrystallization from dimethyl formamide still contains the compound (1R,3S,4R) - 3-[(2'-{N,N-dimethylamino}-ethyl)]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane-2-one of Formula V in an amount above the threshold value permitted by Pharmacopoeia (about 0.5%);
- b) Dimethyl formamide has a high boiling point and cannot be removed from the product in the required degree because at the high temperature decomposition of the product takes place.

A purification to yield products with a purity sufficient for medicaments according to the Pharmacopoeias could