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(54) **1-Phenyl-3-dimethylaminopropane compounds having pharmacological effect**

(57) l-phenyl-3-dimethylaminopropane compounds are disclosed, also a preparation method thereof, and the use of these substances as pharmaceutical active ingredients.

EP 0 693 475 A1

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Description

The present invention relates to l-phenyl-3-dimethylaminopropane compounds, to a method of preparing them, and to the use of these substances as pharmaceutical active ingredients.

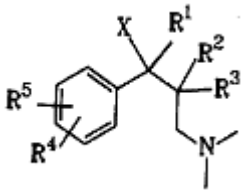
The treatment of chronic and non-chronic pain situations is of great importance in medicine. This is reflected in the large number of publications. Thus, for example, 1-naphthyl-3-aminopropane-1-ols with an analgesic-narcotic effect are known from EP 176 049. Secondary and tertiary alcohols with γ-amino groups are described in J. Pharm. Sci. 59, 1038 (1970) and in J. Prakt. Chem. 323, 793 (1981). Phenyl-dimethylaminopropanols containing a para-substituted phenyl radical are described in Chem. Abstr. 54, 20963c (1960) and in Chem. Abstr. 63, 6912e (1965). These compounds also possess analgesic properties. In contrast, the 3-dimethylaminopropan-1-ols containing 2-phenyl radicals described in DE 32 42 922 have an antidepressant effect. The 1-phenyl-propan-1-ols described in J. Pharm. Sci. 57, 1487 (1968) have different pharmacological effects depending on the γ-aza ring.

Opioids have been used for many years as analgesics for the treatment of pain, although they give rise to a series of side effects, for example addiction and dependency, respiratory depression, gastrointestinal inhibition and obstipation. They can therefore only be given over an extended period of time or in higher doses subject to special precautionary measures such as special prescription regulations (Goodman, Gilman in "The Pharmacological Basis of Therapeutics", Pergamon Press, New York (1990)).

Tramadol hydrochloride - (1RS,2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride - assumes a special position amongst centrally-acting analgesics, since this active ingredient gives rise to a pronounced inhibition of pain without the side effects which are known for opioids (J. Pharmacol. Exptl. Ther. 267, 331 (1993)). Tramadol is a racemate and consists of identical amounts of (+) and (-) enantiomer. In vivo the active ingredient forms the metabolite O-desmethyl-tramadol, which is likewise present as a mixture of enantiomers. Investigations have shown that both the enantiomers of tramadol and the enantiomers of tramadol metabolites contribute to the analgesic effect (J. Pharmacol. Exp. Ther. 260, 275 (1992)).

The underlying object of the present invention was to provide substances with an analgesic effect, which are suitable for the treatment of severe pain without giving rise to the side effects which are typical of opioids. A further object was to provide analgesic substances which do not exhibit the side effects, for example nausea and vomiting, which occur during treatment with tramadol in some cases.

It has been found that these stringent requirements are met by certain 1-phenyl-dimethylaminopropane compounds. These substances are characterized by a pronounced analgesic effect which is significantly enhanced compared with that of tramadol. The present invention accordingly relates to l-phenyl-3- dimethylaminopropane compounds of formula I

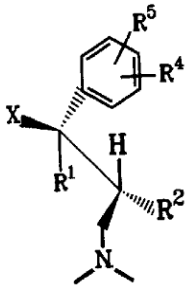


in which

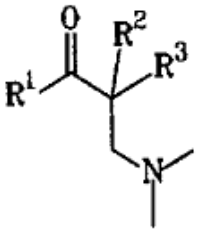
X denotes OH, F, Cl, H or an $OCOR^6$ group in which R^6 is a C_{1-3} -alkyl group;
R^1 is a C_{1-4} -alkyl group, R^2 denotes H or a C_{1-4}-alkyl group and R^3 denotes H or a straight chain C_{1-4} -alkyl group, or R^2 and R^3 together constitute a C_{4-7}-cycloalkyl radical, and if R^5 is H, R^4 denotes meta-O-Z, where Z is H, C_{1-3}-alkyl, $PO(OC_{1-4}\text{-alkyl})_2$, $CO(OC_{1-5}\text{-alkyl})$, $CONH\text{-}C_6H_4\text{-}(C_{1-3}\text{-alkyl})$ or $CO\text{-}C_6H_4\text{-}R^7$, wherein R^7 is ortho-$OCOC_{1-3}$-alkyl or meta- or para-$CH_2N(R^6)_2$, where R^6 is C_{1-4}-alkyl or 4-morpholino, or R^4 denotes meta-S-C_{1-3}-alkyl, meta-Cl, meta-F or meta-$CR^9R^{10}R^{11}$, where R^9, R^{10}, R^{11} are H or F, ortho-OH, ortho-O-C_{2-3}-alkyl, para-F or para-$CR^9R^{10}R^{11}$, or
or
if R^5denotes Cl, F, OH or O-C_{1-3}-alkyl in the para-position, R^4 denotes Cl, F, OH or O-C_{1-3}-alkyl in the meta-position, or R^4 and R^5 together represent 3,4-OCH=CH- or 3,4-OCH=CHO--, as diastereoisomers or enantiomers in the form of free bases or salts of physiologically acceptable acids.

1-phenyl-3-dimethylaminopropane compounds of formula I are preferred in which X constitutes OH, F, Cl or H; R^1 is an C_{1-4}-alkyl group; R^2 is H or CH_3, and R^3 is H or CH_3, and if R^5 is H, R^4 denotes -OC_{1-3}-alkyl, -OH, -S-C_{1-3}-alkyl, F, Cl, CH_3, -CF_2H or –CF_3 in the meta-position, or para-CF_3, or if R5 is a para-Cl or para-F, R_4 represents meta-Cl or meta-F, or R_4 and R_5 together represent 3,4-OCH=CH-.

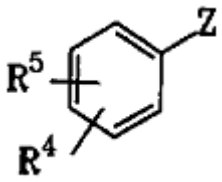
1-phenyl-3-dimethylaminopropane compounds of formula I are particularly preferred in which the R^2 and R^3 radicals are different, in the form of their diastereoisomers of configuration Ia



The present invention also relates to a method of preparing 1-phenyl-3-dimethylaminopropane compounds of formula I, in which the variable X represents OH, which is characterized in that a β-dimethylaminoketone of formula II



is reacted with an organometallic compound of formula III



in which Z denotes MgCl, MgBr, MgI or Li, to form a compound of formula I with X = OH.

The reaction of a β-dimethylaminoketone with a Grignard reagent of formula III, in which Z denotes MgCl, MgBr or MgI, or with an organolithium compound of formula III, can be carried out in an a aliphatic ether, for example diethyl ether and/or tetrahydrofuran, at temperatures between -70° C and +60° C. Organolithium compounds of formula III can be obtained by the replacement of halogen by

lithium, for example, by reacting a compound of formula III, in which Z represents Cl, Br or I, with for example a solution of n-butyllithium in n-hexane.

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