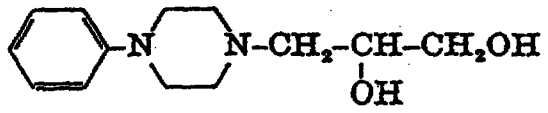
Description

The present invention relates to a process for optical resolution of dropropizine.

Dropropizine or 3-(4-phenyl-1-piperazinyl)-1,2-propanediol, has the following formula (I)



(I)

wherein the carbon atom marked with an asterisc is an asymmetrical carbon atom.

Dropropizine, in form of racemic mixture, is widely employed as antitussive agent (see belgian patent specification n. 601394).

Optical isomers of dropropizine, the levo- and dextrorotatory ones, were firstly described in Italian Patent specification n. 1 203 721, in the Applicant's name. Such Patent, inter alia, states that the levorotatory isomer shows an antitussive action markedly better than the one of dextrorotatory isomer, combined with an activity on central nervous system notably lower than that of the latter isomer, with accordingly decreased side-effects.

Hence, the levorotatory isomer, due to his higher action selectivity, is preferred to the dextrorotatory isomer.

Therefore, a process for the optical resolution of dropropizine, which process is simple, cheap and applicable on industrial scale, is required.

In accordance with the above cited Italian Patent specification n. 1 203 721 levodropropizine can be prepared starting from racemic dropropizine by "conventional means for optical resolution" or can be synthetized starting from optically active 1,2-isopropylidene-sn-glycerol. Nevertheless, whilst the ex novo synthesis method is widely described, no examples for optical resolution of racemic dropropizine are reported. Really, attempts for the optical resolution of the racemate with most of the usual agents for optical resolution failed to succeed.

Especially, trials were performed using the following optically active acids:

D(-) tartaric acid
D camphosulfonic acid
L camphosulfonic acid
Camphoric acid
D dibenzoyltartaric acid
L dibenzoyltartaric acid
D toluyltartaric acid
L toluyltartaric acid
D mandelic acid
L mandelic acid

Now it has been surprisingly found, and it is the object of the invention, that levodropropizine can be separated from racemic mixture in high yields and high purity, using L(+)tartaric acid as agent for optical resolution.

According to the invention, resolution of dropropizine is carried out by treating it with L(+)tartaric acid in aqueous medium: the precipitated salt is then crystallized, alkalinized and recrystallized to give levodropropizine.

Mother liquors containing the partially resolved R(+) isomer are alkalinized and then extracted with methylene cloride. Dropropizine enriched in partially resolved R(+) isomer thus obtained is racemized by mesylation and subsequent substitution of secondary mesyloxy group with an acetoxy or -OH group.

The optimum molar ratio of racemic dropropizine to L(+)tartaric acid is 1:1, nevertheless ratios ranging between 1:0.5 and 1:2 can also be used. The dropropizine/water ratio can range between 1:2 and 1:10.

The process according to the invention is further illustrated by the following examples.

EXAMPLE 1: Resolution of Dropropizine

a) Salification

A suspension of dropropizine (500 g) and L(+)tartaric acid (317 g) in water (2.5 l) is heated to dissolution. Any impurity is removed by hot filtering and the clear solution is left to cool to 25-28°C and

left to stand at this temperature for 24 hours. The precipitated salt is filtered and recrystallized 3 times from water. 150 g of an optically pure salt $[\alpha]_D$ = - 9.4° (c = 3% in H_2O) melting at 195-7°C is obtained.

b) Salt shifting

The salt obtained in a) is alkalinized to pH 11 with 10% sodium hydroxide and extracted many times with methylene chloride. The collected organic extracts are dried and evaporated to dryness. The residue, crystallized from acetone, yields 83 g of levodropropizine melting at 102-104°C. $[\alpha]_D$ = - 24.1° (c = 3 in CH_2Cl_2).

EXAMPLE 2 : Racemization of dropropizine rich in R(+) isomer

a) Recovery of partially resolved R(+) isomer. Mother liquor from salification is alkalinized to pH 11 with 10% sodium hydroxide and repeatedly extracted with methylene chloride. The oganic layers are dried and evaporated to dryness, yielding 280 g of dropropizine rich in R(+) isomer.

b) Racemization of partially resolved R(+) isomer. Mesylchloride (339 g) is slowly added to a solution of partially resolved R(+) isomer (280 g) and triethylamine (300 g) in methylene chloride (3 l). The reaction mixture is stirred for 1 hour, then washed with water. The organic layer is evaporated to dryness and the residue is dissolved in glacial acetic acid (5 l). Acetic anhydride (300 ml), potassium acetate (300 g) are added, and then heated to reflux for 3 hours. Most of the solvent is distilled off and the mixture is diluted with water, alkalinized to pH 10 with 10% sodium hydroxide and extracted 2 times with methylene chloride. The combined organic extracts are dried and evaporated to dryness. The residue is dissolved in 6N hydrochloric acid and the resulting solution is refluxed for 5 hours, then cooled to room temperature and alkalinized to pH 11 with 10% sodium hydroxide. Solution is repeatedly extracted with methylene chloride and the combined organic layers are dried and evaporated to dryness. 200 g of racemic dropropizine is yielded $[\alpha]_D$ = 0° (c = 3% in CH_2Cl_2).

Claims

1. A process for the optical resolution of racemic dropropizine, characterized in that it is carried out in aqueous medium using L(+)tartaric acid as the optical resolution agent, a racemic dropropizine/L(+)-tartaric acid molar ratio between 1:0,5 and 1:2 and a racemic dropropizine/water molar ratio between 1:2 and 1:10.

2. A process according to claim 1, characterized in that racemic dropropizine/L(+)tartaric acid molar ratio is 1:1.

3. A process according to claim 1 or 2, characterized in that R(+) isomer present in mother liquor is racemized by treatment with mesyl chloride and acetic anhydride, and in that, after suitable hydrolysis, the thus obtained racemic product is subjected to the treatment according to claim 1.

Patentansprüche

1. Verfahren zur optischen Trennung von racemischem Dropropizin, dadurch gekennzeichnet, daß es in wäßrigem Medium unter Verwendung von L(+)Weinsäure als optischem Trennmittel, bei einem Molverhältnis von racemischem Dropropizin zu L(+)Weinsäure zwischen 1:0,5 und 1:2 und einem Molverhältnis von racemischem Dropropizin zu Wasser zwischen 1:2 und 1:10 durchgeführt wird.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Molverhältnis von racemischem Dropropizin zu L(+)Weinsäure 1:1 ist.

3. Verfahren nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß das in der Mutterlauge vorhandene R-(+)Isomer durch Behandlung mit Mesylchlorid und Essigsäureanhydrid racemisiert wird und das nach geeigneter Hydrolyse erhaltene racemische Produkt der Behandlung gemäß Anspruch 1 unterworfen wird.

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Revendications

1. Procédé pour la résolution optique de la dropropizine racémique, caractérisé par le fait qu'il est effectué en milieu aqueux en utilisant de l'acide L(+)tartrique comme agent de résolution optique, un rapport molaire dropropizine racémique/acide L(+) tartrique situé entre 1:0,5 et 1:2 et un rapport molaire dropropizine racémique/eau situé entre 1:2 et 1:10.

2. Procédé selon la revendication 1, caractérisé par le fait que le raport molaire dropropizine racémique/acide L(+)tartrique est de 1:1.

3. Procédé selon la revendication 1 ou 2, caractérisé par le fait que l'isomère R(+) présent dans la liqueur-mère est racémisé par traitement par le chlorure de mésyle et l'anhydride acétique, et par le fait qu'après hydrolyse appropriée, le produit racémique ainsi obtenu est soumis au traitement tel que défini à la revendication 1.