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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(in))*

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(54) Title: PROCESS FOR THE PREPARATION OF GLYCEROL PHENYLBUTYRATE

(57) Abstract: The present invention relates to the process for the preparation of glycerol phenylbutyrate (I) by reacting phenylbutyryl chloride (II) with glycerol (III) in presence of organic base in C_1-C_5 chlorinated solvent. Glycerol phenylbutyrate (I) prepared according the process of the present invention is having HPLC purity >99%.

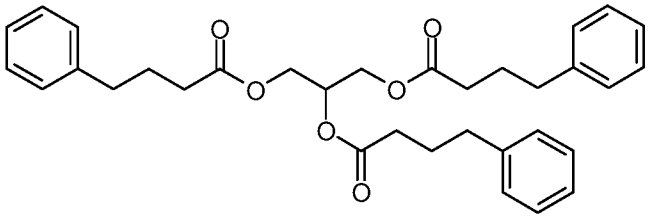
PROCESS FOR THE PREPARATION OF GLYCEROL PHENYLBUTYRATE

Field of the invention:

The present invention relates to the process for the preparation of glycerol phenylbutyrate.

Background of the invention:

Glycerol phenylbutyrate is a triglyceride containing three molecules of 4-phenylbutyric acid linked to a glycerol backbone, the chemical name of which is benzenebutanoic acid, 1,1',1''-(1,2,3-propanetriyl) ester and the structural formula is:



I

It is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients ≥2 years of age with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.

US patent 5968979 covers glycerol phenylbutyrate generically. This patent merely states that the compounds of the invention can be produced by standard esterification procedures. There is no specific process disclosed for the preparation of glycerol phenylbutyrate in this patent.

IT 1317073 B1 describes preparation of glycerol phenylbutyrate in 75% yield by treatment of 4-phenylbutyric acid with 5-fold excess thionyl chloride to give 4-phenylbutyryl chloride, followed by removal of excess thionyl chloride and treatment of the 4-phenylbutyryl chloride with a stoichiometric amount of glycerol.

Kasumov et al (Drug Metabolism and Disposition, Volume: 32, Issue: 1, Pages: 10-19, 2004) describes preparation of glycerol phenylbutyrate by reacting glycerol with excess 4-

phenylbutyryl chloride in the presence of pyridine and catalytic amounts of ***N,N***-dimethylaminopyridine. The product was purified by flash column chromatography on silica.

Chang et al, (Journal of Biotechnology, Volume: 127, Issue: 4, Pages: 694-702, 2007; Journal of Molecular Catalysis B: Enzymatic Volume 61, Issues 3-4, December 2009, Pages 117-122) describes preparation of glycerol phenylbutyrate from glycerol and 4-phenylbutyric acid by lipase-catalyzed esterification in a solvent-free system.

EP 2607366 A1 describes preparation of 4-phenyl-butyric acid 2-hydroxy-3-(4-phenyl-butyryloxy)-propyl ester by reacting glycerol with 4-phenylbutyryl chloride. In this preparation glycerol phenylbutyrate is obtained as side product in 1.7 % yield.

The prior art processes suffers serious disadvantages such as use of 5-fold excess of thionyl chloride. Due to hazardous and toxic nature of thionyl chloride it is very difficult to handle on large quantity. Another drawback of the prior art process is that it uses pyridine as solvent which is also toxic in nature and moreover it is used in large excess. Pyridine is Class 2 solvent with ICH limit of 200 ppm in final API. Thus the process of prior art are non-economical and hazardous.

Summary of the Invention:

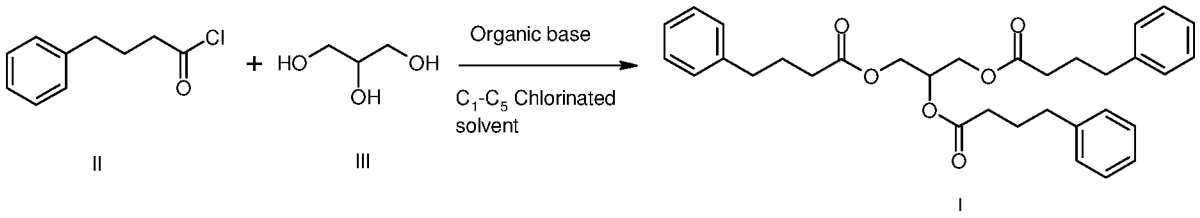
The present invention relates to the process for the preparation of glycerol phenylbutyrate (I) by reacting 4-phenylbutyryl chloride (II) with glycerol (III) in presence of organic base in C_1-C_5 chlorinated hydrocarbon solvent. Glycerol phenylbutyrate (I) prepared according the process of the present invention is having HPLC purity >99%.

Detailed description of the invention:

The present invention relates to a process for the preparation of glycerol phenylbutyrate (I) comprising

a) reacting 4-phenylbutyryl chloride (II) with glycerol (III) in presence of organic base in C_1-C_5 chlorinated hydrocarbon solvent and

b) isolating the glycerol phenylbutyrate (I) by chromatographic technique.



II III I

The step (a) is carried out at temperature in a range of -10 °C to 20 °C, preferably -5 °C to 5 °C.

The quantity of 4-phenylbutyryl chloride (II) is 3 to 4 molar equivalent of glycerol (III).

The organic base is selected from imidazole or 1-alkylimidazole such as 1-methylimidazole, 1-ethylimidazole.

The quantity of organic base is 4 to 5 molar equivalent of glycerol (III).

The C_1-C_5 chlorinated hydrocarbon solvent in step (a) is selected from chloroform, dichloromethane, carbontetrachloride, ethylenedichloride.

The quantity of C_1-C_5 chlorinated hydrocarbon solvent in step (a) is 15 to 25 volumes per weight of glycerol.

Glycerol phenylbutyrate (I) prepared according the process of the present invention is having HPLC purity >99%.

We have studied this reaction using 1-methylimidazole in ethyl acetate as solvent, and found that reaction was very slow, the product glycerol phenylbutyrate (I) formed only upto 62 % in 11 hours. This shows that chlorinated hydrocarbons are better solvent for this reaction compared to ester solvents.

In another embodiment there is provided process for the preparation of 4-phenylbutyryl chloride (II) which comprises i) reacting 4-phenylbutyric acid with thionyl chloride in $\mathbf{C_1}$-$\mathbf{C_5}$ chlorinated hydrocarbon solvent and ii) isolating the 4-phenylbutyryl chloride (II) by removing the solvent using vacuum distillation.

The $\mathbf{C_1}$-$\mathbf{C_5}$ chlorinated hydrocarbon solvent in step (i) is selected from chloroform, dichloromethane, carbontetrachloride, ethylenedichloride.

The quantity of $\mathbf{C_1}$-$\mathbf{C_5}$ chlorinated hydrocarbon solvent in step (i) is 1.2 to 2 volumes per weight of 4-phenylbutyric acid.

The quantity of thionyl chloride is 1.1 to 1.5 molar equivalent of 4-phenylbutyric acid.

The glycerol phenylbutyrate is isolated by chromatographic technique selected from column chromatography, flash column chromatography, preparative HPLC.

The process of the present invention has following advantages

1. suitable for the large scale production.
2. provides glycerol phenylbutyrate having HPLC purity >99%.
3. economical.

Experimental:

Method for reaction monitoring: Monitored by HPLC

Reaction mixture was treated with dry methanol and unreacted 4-phenylbutyryl chloride was checked as corresponding methyl ester.

Example 1

Preparation of 4-phenyl butyryl chloride (II)

4-phenylbutyric acid (300 g, 1.827 mol) was dissolved in dichloromethane (450 ml). Dimethylformamide (3 ml) was added and the reaction mixture was stirred to get a clear solution. Thionyl chloride (172 ml, 2.375 mol) was added drop wise at temperature 20-30 °C and stirred for one hour. 4-phenyl butyryl chloride (II) was isolated as oil by removing the solvent and thionyl chloride by distillation under reduced pressure.

Example 2

Preparation of glycerol phenylbutyrate (I)

4-phenyl butyryl chloride (II) (118.2 g, 0.6467 mol) was mixed with dichloromethane (237 ml). The reaction mass was cooled to -5 °C. A solution of glycerol (III) (17 g, 0.1847 mol) and 1-methylimidazole (67 ml, 0.8403 mol) in dichloromethane (118 ml) was added while maintaining temperature -5 to 5 °C. The reaction mixture was stirred for 90 minutes at -5 to 5 °C. Water (354 ml) was added to the reaction mixture. The organic layer was separated and washed with 5 % aqueous sodium bicarbonate solution (354 ml X 3) followed by water (354 ml). The organic layer was concentrated under reduced pressure to get crude glycerol phenylbutyrate (I) (92 g).

HPLC purity- 96.87 %

4-phenylbutyric acid - 0.15 %

4-phenylbutyric acid methyl ester - 0.05 %

The crude glycerol phenylbutyrate (I) (10 g) was purified by Gravity column chromatographic technique using silica gel (100-200 mesh) as stationary phase and 0.5% - 3% ethyl acetate in cyclohexane as mobile phase. Ethyl acetate was gradually increased and fractions (500 ml each) were collected. Fractions containing any individual impurity less than

0.05 % were collected and solvent was distilled off under reduced pressure. Yield: 5.48 g, HPLC Purity - 99.81%.

Example 3

Glycerol (1 g, 0.0108 mol) and 1-methylimidazole (3.1 g, 0.0378 mol) were mixed with ethyl acetate (15 ml) at 25-30 °C. 4-phenyl butyryl chloride (II) (7 g, 0.038 mol) in ethyl acetate (20 ml) was added drop wise to the reaction mixture at 25-30 °C under stirring. The stirring was continued for 11 hours.

HPLC purity- 61.59 %

4-phenylbutyric acid - 9.60 %

4-phenylbutyric acid methyl ester - 14.62 %.

CLAIMS

Claim 1. A process for the preparation of glycerol phenylbutyrate (I) comprising

a) reacting 4-phenylbutyryl chloride (II) with glycerol (III) in presence of organic base in C_1-C_5 chlorinated hydrocarbon solvent and

b) isolating the glycerol phenylbutyrate (I) by chromatographic technique.

Claim 2. The process of claim 1, wherein the organic base is imidazole, 1-methyhmidazole or 1-ethylimidazole.

Claim 3. The process of claim 2, wherein the organic base is 1-methyhmidazole.

Claim 4. The process of claim 1, wherein the **C_1-C5** chlorinated hydrocarbon solvent is selected from chloroform, dichloromethane, carbontetrachloride, ethylenedichloride.

Claim 5. The process of claim 4, wherein the **C_1-C5** chlorinated hydrocarbon solvent is dichloromethane.

Claim 6. The process of claim 1, wherein the step (a) is carried out at temperature in a range of

-10 °C to 20 °C.

Claim 7. The process of claim 6, wherein the temperature in a range of -5 °C to 5 °C.

Claim 8. The process of claim 1, wherein the 4-phenylbutyryl chloride (II) is 3 to 4 molar equivalent of glycerol (III).

Claim 9. The process of claim 1 wherein the glycerol phenylbutyrate (I) is isolated by chromatographic technique selected from column chromatography, flash column chromatography, preparative HPLC.

Claim 10. Glycerol phenylbutyrate (I) obtained according the process of claim 1 having HPLC purity >99%.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/065578

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C67/14 C07C67/48 C07C67/56
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IT 1 317 073 B1 (MINI RICERCA SCIENT TECNOLOG [IT]) 26 May 2003 (2003-05-26) cited in the appl ication	10
A	examples 2,3	1-9

X	KASUM0V ET AL. : DRUG METABOLISM AND DISPOSITION , vol . 32, no. 1, 2004, pages 10-19, XP002736935, cited in the appl ication	10
A	Esters of phenyl butyrate; page 12	1-9

X	EP 2 607 366 A1 (LUNAMED AG [CH]) 26 June 2013 (2013-06-26) cited in the appl ication	10
A	page 47; example 7	1-9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
9 March 2015	27/03/2015

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2014/065578

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
IT 1317073 B1	26-05-2003	NONE	
EP 2607366 A1	26-06-2013	NONE	