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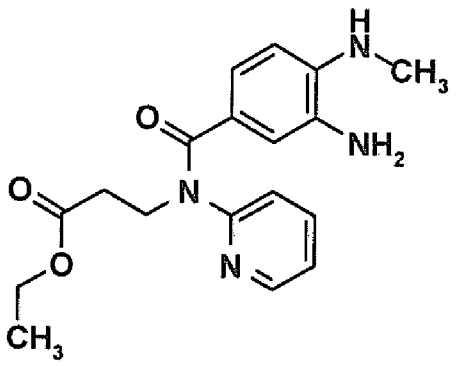
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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

(54) **Title**: PROCESS FOR THE MANUFACTURE OF AN INTERMEDIATE IN THE SYNTHESIS OF DABIGATRAN



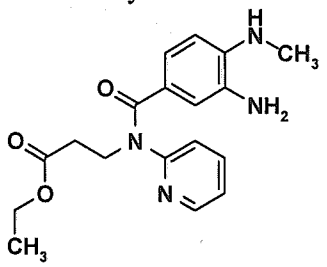
(1)

(57) **Abstract**: The invention relates to a process for the synthesis of the diamine of formula (1) an important intermediate in the synthesis of dabiagtran etexilate.

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PROCESS FOR THE MANUFACTURE OF AN INTERMEDIATE IN THE SYNTHESIS OF DABIGATRAN

The invention relates to a process for the synthesis of the diamine of formula 1



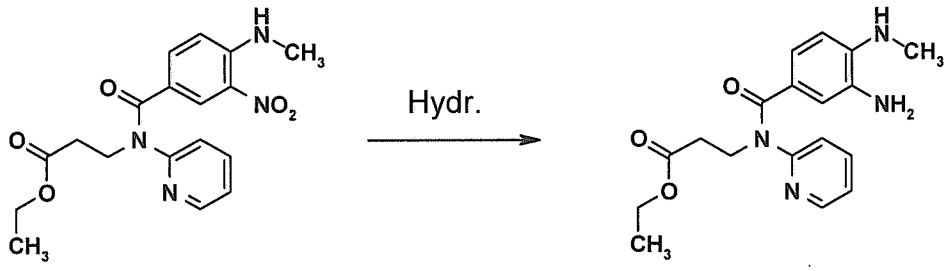
1

an important intermediate in the synthesis of dabiagtran etexilate.

Background of the invention

Dabigatrane etexilate is known in the art and was first disclosed in International patent application WO 98/37075. Processes for the manufacture of dabigatran etexilate are also known from WO 2006/000353 or Hauel et al. (J. Med. Chem, 2002, 45, 1757 ff).

According to Hauel et al 1 can be obtained from nitro-compound of formula 2 via hydrogenation on Pd/C.



2 1

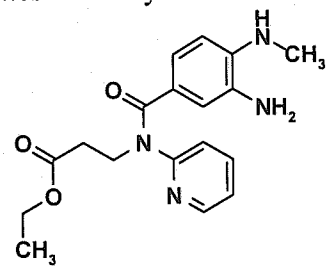
However, in particular in large-scale processes the reaction occasionally stops due to catalyst poisoning which leads to an incomplete turnover of the starting material. This can require further addition of catalyst during the course of the reaction. Moreover, reaction time is prolonged which has a negative influence on the quality of the reaction product 1. The process for manufacture of 2 is for instance disclosed in Hauel et al (J. Med. Chem, 2002, 45, 1757-1766). From the synthesis of 2 as disclosed in Hauel et al., it is apparent that process related sulfur impurities might be carried over into 2 with varying amounts. These impurities strongly influence the reaction time, quality and catalyst consumption in the manufacture of 1.

Therefore, it is the object of the invention to provide for an improved process for the manufacture of 1 which overcomes the foregoing deficiencies that are associated with catalyst poisoning.

Description of the invention

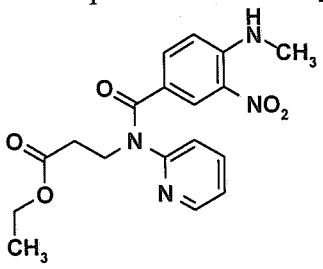
Surprisingly, it has been found that the problem underlying the invention can be solved by the addition of tertiary amine to the reaction mixture.

Consequently, the invention relates to the synthesis of compound of formula 1



1

through catalytic hydrogenation of compound of formula 2



2

characterized in that the reaction is conducted in the presence of a tertiary amine.

In a particularly preferred process, the hydrogenation is carried out in a temperature range from 0°C to 100°C, preferably from 10°C to 80°C, particularly from 20°C to 60°C. Also preferred is a process wherein the hydrogenation is carried out under a pressure of more than 0.5 bar to 25 bar, preferably under a pressure of 1 bar to 8 bar, particularly at about 2 - 6 bar.

The solvents preferably used within the process according to the invention may be both protic solvents - such as e.g. alcohols, carboxylic acids and/or water - or aprotic polar solvents such as e.g. ethers, esters, amides or lactams and/or mixtures thereof. Water may optionally be added to all the solvents. Preferred protic solvents used are branched or unbranched $C_1 - C_8$ alkanols, $C_1 - C_3$ carboxylic acids or mixtures thereof. Particularly

preferably, lower alcohols such as methanol, ethanol, n-propanol and isopropanol, carboxylic acids such as formic acid, acetic acid and propionic acid or mixtures thereof are used. Preferred aprotic solvents are polar ethers such as for example tetrahydrofuran or dimethoxyethylether, amides such as for example dimethylformamide, lactams such as for example N-methylpyrrolidone or esters like for instance ethyl acetate. Most preferred solvent according to the invention is ethyl acetate.

Suitable hydrogenation catalysts are generally transition metals such as for example nickel, platinum or palladium or the salts or oxides thereof. Raney nickel, platinum oxide and palladium on an inert carrier material, particularly palladium on activated charcoal (Pd/C), are preferred.

The tertiary amine is preferably selected from among trimethylamine, triethylamine, diisopropylethylamine and DBU (diazabicycloundecene). Most preferred amine is triethylamine.

The amount of tertiary amine used within the scope of the invention is based on the amount of starting material **2** in the range of 0,05 to 10 %, preferably 0,5 - 7 %, most preferred 2 - 6 %. The foregoing amount is indicated in weight percentage relative to starting material **2**.

In the following examples the same compound **2** batch was used as the starting material. Prior to the experiments it was determined that the batch contained about 380ppm of sulfur impurities.

Example according to the invention:

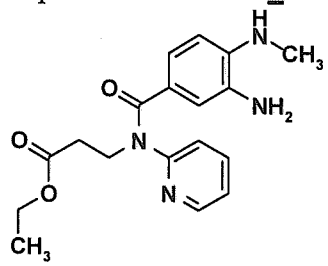
Under inert atmosphere (N_2) an autoclave is charged with 150g of compound **2**, 6g of a 10% Palladium on Charcoal catalyst, 7 ml of triethylamine and 630ml of ethyl acetate. The autoclave is heated to 30°C and hydrogen added until a pressure of 4 bars is observed. Then the temperature is adjusted to 50°C. The usual time for complete conversion of the starting material is 1 to 2h. The autoclave is then allowed to cool and the suspension filtered to remove the catalyst. The organic filtrate is concentrated on a rotary evaporator and diluted with 350ml of either isopropanol or toluene. Again the solution is concentrated using mild vacuum and 400ml of either isopropanol or toluene are added. The solution is cooled to 10°C to allow crystallisation of the product. The crude product is isolated by filtration and dried under vacuum to yield 123g (90% of theoretical yield) of compound **1**.

Reference Example (prior art):

Under inert atmosphere (N_2) an autoclave is charged with 150g of compound **2**, 6g of a 10% Palladium on Charcoal catalyst and 630ml of Ethyl acetate. The autoclave is heated to 30°C and Hydrogen added until a pressure of 4 bars is observed. Then the temperature is adjusted to 50°C. If hydrogen uptake ceases or is slow, the autoclave is flushed with nitrogen and additional catalyst is added (appr. 50% of the original amount), then new hydrogen is added and hydrogenation continued. The usual time for complete conversion of the starting material is approximately 4hours. The autoclave is then allowed to cool and the suspension filtered to remove the catalyst. The organic filtrate is concentrated on a rotary evaporator and diluted with 350ml of either isopropanol or toluene. Again the solution is concentrated using mild vacuum and 400ml of either isopropanol or toluene are added. The solution is cooled to 10°C to allow crystallisation of the product. The crude product is isolated by filtration and dried under vacuum to yield 116g (85% of theoretical yield) of **1**.

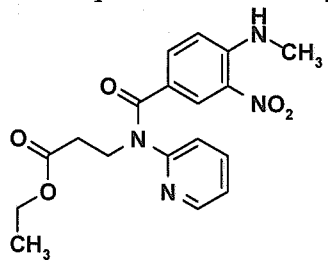
Claims

1) Process for the synthesis of compound of formula 1



1

through catalytic hydrogenation of compound of formula 2



2

characterized in that the reaction is conducted in the presence of a tertiary amine.

2) Process according to claim 1, wherein the tertiary amine is selected from from among trimethylamine, triethylamine, diisopropylethylamine and DBU (diazabicycloundecene).

3) Process according to claim 1 or 2, wherein the hydrogenation is carried out in a temperature range from 0°C to 100°C, preferably from 10°C to 80°C, particularly from 20°C to 60°C.

4) Process according to claims 1, 2 or 3, wherein the solvent is selected from among branched or unbranched $C_1 - C_8$ alkanols, $C_1 - C_3$ carboxylic acids, polar ethers, amides and esters.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/057265

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/75

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)
C07D

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 practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/071743 A (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; ZERBA) 28 June 2007 (2007-06-28) example 3	1-4
Y	HAUEL N H ET AL: "STRUCTURE-BASED DESIGN OF NOVEL POTENT NONPEPTIDE THROMBIN INHIBITORS" JOURNAL OF MEDICINAL CHEMISTRY, US AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 45, no. 9, 1 January 2002 (2002-01-01), pages 1757-1766, XP001098844 ISSN: 0022-2623 cited in the application page 1765, left-hand column, lines 14-19	1-4

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

☒ See patent family annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 July 2009	06/08/2009

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/057265

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007071743 A	28-06-2007	AR 058571 A1	13-02-2008
		AU 2006326980 A1	28-06-2007
		CA 2632310 A1	28-06-2007
		CN 101346355 A	14-01-2009
		DE 102005061624 A1	28-06-2007
		EP 1968949 A1	17-09-2008
		JP 2009520766 T	28-05-2009
		KR 20080081179 A	08-09-2008
		US 2007185173 A1	09-08-2007