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Datasheet for the decision of 6 September 2019

Case Number: T 1899/14 - 3.3.02

Application Number: 07840163.5

Publication Number: 2073636

IPC: A01N43/42, A61K31/44, C07D489/08

Language of the proceedings: EN

Title of invention:
PROCESS FOR PREPARING OXYMORPHONE

Patent Proprietor:
Penick Corporation

Opponent:
Garberg, Morten

Headword:

Relevant legal provisions:
EPC Art. 123(2), 83, 56

Keyword:
Inventive step - closest prior art

Decisions cited:

Catchword:

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Boards of Appeal

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Case Number: T 1899/14 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 6 September 2019

Appellant: (Patent Proprietor)	Penick Corporation 33 Industrial Park Road Pennsville NJ 08070 (US)
Representative:	Weickmann & Weickmann PartmbB Postfach 860 820 81635 München (DE)
Appellant: (Opponent)	Garberg, Morten c/o Hofmann Eitle Arabellastrasse 4 81925 München (DE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 17 July 2014 concerning maintenance of the European Patent No. 2073636 in amended form.**

Composition of the Board:

Chairman	M. O. Müller
Members:	P. O'Sullivan
	L. Bühler

Summary of Facts and Submissions

I. The appeals of the proprietor and the opponent lie from the interlocutory decision of the opposition division according to which European patent EP 2 073 636 in amended form and the invention to which it relates were found to meet the requirements of the EPC.

II. The patent was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claims thereof did not involve an inventive step, the invention defined therein was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and its subject-matter extended beyond the content of the application as filed.

III. The contested decision was based on the patent as granted (main request) and first, second and third auxiliary requests.

According to the decision under appeal:

(a) The subject-matter of the claims of the main request met the requirements of Article 123(2) EPC, and the invention defined therein was sufficiently disclosed. D2 was the closest prior art for the purpose of assessing inventive step. Claim 1 differed from D2 in the method of preparing the intermediate 14-hydroxymorphinone. The technical problem was the provision of an alternative process for preparing oxymorphone, and the solution was obvious in view of D2 in combination with the disclosure in D1.

(b) The set of claims of auxiliary request 1 failed to meet the requirements of Article 56 EPC, and the

set of claims of auxiliary request 2 failed to meet the requirements of Article 123(3) EPC.

(c) The set of claims of auxiliary request 3 fulfilled the requirement of the EPC and in particular involved an inventive step starting from D2 as closest prior art.

IV. The following evidence *inter alia* was cited during opposition proceedings:

D1 : Coop *et al.*, J. Org. Chem., 1996, 61, 6774
D2 : Weiss, J. Org. Chem., 1957, 22, pp 1505-1508
D14: WO 2005/028483

For ease of reference in the following the board refers to the parties as proprietor and opponent, since both are appellant in appeal proceedings.

V. Final requests

The proprietor requested that the contested decision be set aside and the patent be maintained as granted, or, alternatively, that the patent be maintained in amended form on the basis of one of the claim sets of auxiliary requests 1 or 2 filed with the statement of grounds of appeal.

Furthermore, the proprietor requested that the objections of the opponent under Article 123(2) EPC in respect of claim 1 of auxiliary request 2 not be admitted into the appeal proceedings, or, alternatively, to remit the case to the opposition division for further prosecution.

The opponent requested in writing that the decision under appeal be set aside and that the patent be revoked.

VI. A communication of the board was sent in preparation for oral proceedings. Therein the board *inter alia* expressed the preliminary opinion that neither D1 nor D14 appeared to represent suitable starting disclosures for the skilled person in the assessment of whether the subject-matter of claim 1 of the main request involved an inventive step.

VII. Independent claim 1 of the main request (claims as granted) reads as follows:

"*A method of preparing oxymorphone or a salt thereof comprising:*

- *a single oxidizing step of oripavine to obtain 14-hydroxymorphinone, said oxidizing step comprising oxidizing oripavine with an oxidising agent selected from performic acid, peracetic acid or m-chloroperoxybenzoic acid, the reaction being carried out in a solvent comprising:*

  - *formic acid, when the agent comprises performic acid; and*
  - *acetic acid when the agent comprises peracetic acid or m-chloroperoxbenzoic acid; and*

- *reducing the 14-hydroxymorphinone to obtain oxymorphone*."

VIII. Oral proceedings before the board were held on 6 September 2019 in the absence of the opponent as announced by letter dated 29 July 2019.

IX. The opponent's arguments, insofar as relevant to the present decision, may be summarised as follows:

Main request (claims as granted)

Amendments - Article 100(c) EPC

The subject-matter of granted claim 1 was not derivable from the application as filed. Firstly, the term "single oxidising step" found no generally applicable basis in the application and represented an intermediate generalisation of the schemes and examples disclosed therein. Secondly, this feature in combination with the oxidising agent of claim 1 as filed, the identity of the oxidising agents from claims 3-5 as filed, and the identity of the solvent from paragraph [0012] as filed led to a combination of features not derivable from the application.

Sufficiency of disclosure - Article 100(b) EPC

Example 1 of D14 was concerned with the oxidation of oripavine, and despite employing the same oxidation method and reagents as those of granted claim 1, resulted in a different product, namely 14-hydroxymorphinone-N-oxide. This served as proof that some embodiments falling within the scope of claim 1 did not work, with the result that the invention defined therein was insufficiently disclosed.

Inventive step - Article 100(a) EPC

The subject-matter of claim 1 lacked inventive step in view of D2 as closest prior art, in combination with D1. D2 disclosed the reduction of 14-hydroxymorphinone

to obtain oxymorphone, corresponding to the final step of the method of claim 1 at issue. The subject-matter of claim 1 was distinguished from the disclosure in D2 in the definition of a method to prepare 14-hydroxymorphinone by oxidation of oripavine. The resulting technical problem was the provision of an alternative process for the formation of oxymorphone, and the solution was obvious in view of D1, which disclosed that said oxidation may be carried out with m-chloroperbenzoic acid. Although a solvent was not specified in D1, the oxidant/solvent combinations recited in claim 1 were obvious to the skilled person.

Although D14 did not disclose the synthesis of oxymorphone from oripavine, and was consequently a less appropriate starting point than D2 in the assessment of inventive step, starting therefrom nevertheless led to the conclusion that the subject-matter of claim 1 lacked inventive step. Thus the skilled person starting from D14 and wishing to provide a method to prepare oxymorphone would use retrosynthesis to develop an appropriate synthesis, thereby identifying D2, which disclosed that oxymorphone may be prepared from 14-hydroxymorphinone; the final reduction step of claim 1 at issue. Continuing the retrosynthesis, the skilled person would have then searched for how to prepare 14-hydroxymorphinone, thereby finding D1, which disclosed that oripavine was a useful starting material for preparing 14-hydroxymorphinone. Thus, starting at D14 as closest prior art, the solution proposed in claim 1 at issue was obvious in view of D2 and D1.

X. The proprietor's arguments, insofar as relevant to the present decision, may be summarised as follows:

Main request (claims as granted)

Amendments - Article 100(c) EPC

It was clear from the application documents as filed that the process of claim 1 comprised two steps, and that the first step was a single oxidising step whereby oripavine was converted to 14-hydroxymorphinone with a single specific oxidising agent, e.g. performic acid. This was derivable from *inter alia* paragraphs [0009] and [0013] of the application, and all of the examples according to which said oxidation was performed as a single step.

Sufficiency of Disclosure - Article 100(b) EPC

The description provided the skilled person with sufficient information as to the means and techniques to be employed in order to carry out the invention, as well as examples describing specific procedures for oxidising oripavine to obtain the desired intermediate 14-hydroxymorphinone. Furthermore, the patent taught that during the reaction, the remaining amount of oripavine may be determined by any method, in particular TLC and HPLC (paragraph [0017] and example 2b), such that the skilled person was able to monitor the conversion to the desired product. The reaction conditions underlying Example 1 of D14, disclosing the preparation of the corresponding 14-hydroxymorphinone-N-oxide, were not comparable to those employed according to the examples of the patent. In the former, a neutralisation step was performed subsequent to which the mixture was reacted further, whereas according to

the examples of the patent, the reaction was carried out in an acidic medium. The target product was not the same in D14, and thus the preparation of 14-hydroxymorphinone-N-oxide therein did not serve as proof that the invention defined in claim 1 was insufficiently disclosed.

Inventive step - Article 100(a) EPC

D14 was the most appropriate starting point for the assessment of inventive step, as it disclosed the preparation of intermediates useful in the preparation of 14-hydroxy opiates. Although oxymorphone was not a preferred product of the process of D14, the method taught therein required at least four process synthetic steps to obtain oxymorphone from oripavine. D14 furthermore failed to disclose either of the synthetic steps recited in claim 1 at issue. The effect of this difference was *inter alia* reduced reaction complexity and increased yield, and the technical problem to be solved was the provision of this effect. The solution involved an inventive step in view of the prior art.

Reasons for the Decision

Main request (claims as granted)

1. Amendments - Article 100(c) EPC

1.1 The expression "single oxidizing step" recited in claim 1 as granted is not explicitly disclosed in the application as filed. Claim 1 as filed refers merely to "oxidizing oripavine to obtain 14-hydroxymorphinone". This wording covers both oxidation in a single oxidizing step, as required by claim 1 as granted, and

oxidation in multiple oxidising steps. Claim 1 as granted thus represents a selection from the subject-matter falling within the scope of claim 1 as filed. According to examples 1-3 of the application as filed, representing all examples in which an oxidising step is described, a single oxidising step is implemented. Furthermore, the scheme in paragraph [0013] of the application as filed specifies "step 1" for the oxidation and "step 2" for the subsequent reduction, which confirms that only a single oxidising step is intended. Lastly, a single oxidation step is also disclosed in paragraph [0009] of the application as filed, according to which "oripavine is oxidized with **an** oxidizing agent...".

1.2 The application as filed thus provides a clear pointer to an oxidation which is carried out in a single oxidizing step as required by claim 1. The "single oxidizing step" of granted claim 1 is thus implicitly, but nevertheless directly and unambiguously disclosed in the application as filed.

1.3 Additionally, the oxidising agents disclosed in paragraph [0010] of the application as filed as well as the oxidising agent / solvent pairs disclosed in paragraph [0012] thereof correspond to those recited in claim 1 as granted, such that in the latter, no multiple selection of sub-groups of oxidising agents and pairs of oxidizing agents / solvents has been made.

1.4 It follows that the combination of features contained in claim 1 is directly and unambiguously derivable from the application as filed. Consequently, the ground for opposition under Article 100(c) EPC does not prejudice the maintenance of the patent as granted.

2. Sufficiency of disclosure - Article 100(b) EPC

2.1 Claim 1 refers to a method of preparing oxymorphone or a salt thereof comprising the two steps of (i) oxidizing, under specific conditions, oripavine to 14-hydroxymorphinone, and (ii) reducing the 14-hydroxymorphinone to oxymorphone. Claim 1 requires the first step to be carried out in formic or acetic acid as the solvent.

2.2 The opponent submitted that example 1 of D14 concerned the reaction of oripavine under oxidation conditions corresponding to those recited in claim 1, but resulted in a different product (14-hydroxymorphinone-N-oxide). This was proof that some embodiments falling within the scope of claim 1 would not work, rendering it insufficiently disclosed.

2.3 Example 1 of D14 discloses the reaction of oripavine to provide 14-hydroxymorphinone-N-oxide. This product is indeed different from that obtained in the first step of claim 1, i.e. 14-hydroxymorphinone. The reaction is carried out under acidic conditions followed by neutralisation by addition of NaOH. The board can follow the opponent's argument that the reaction conditions employed in example 1 of D14 are as required by granted claim 1.

2.4 The patent discloses several examples (1, 2 and 2b) detailing the preparation by oxidation of the desired product of the first step, 14-hydroxymorphinone. Furthermore, detailed information on the specific reagents and conditions which may be employed are provided in the description (paragraphs [0010] to [0017]). Both claim 1 and said passages of the patent

require that the first step is carried out in formic or acetic acid.

2.5 D14 on the other hand, in example 1 thereof, is concerned with the preparation of 14-hydroxymorphinone-N-oxide. This is the desired product according to D14, and as such the appropriate reaction conditions underlying said example would have been devised with a view to preparing that product. As set out above, those conditions involve initial reaction under acidic conditions followed by neutralisation over 2 hours by addition of NaOH and further reaction thereafter, while the patent solely teaches reaction in an acid. Consequently, even if the skilled person were to attempt to carry out the oxidation step of claim 1 at issue by including a neutralisation step such as that disclosed in example 1 of the D14, and were to fail to obtain 14-hydroxymorphinone, it would not represent an undue burden to return to the teaching of the patent, e.g. as reflected in the examples thereof, in order to successfully prepare the desired product.

2.6 Consequently, there is no evidence that the skilled person is faced with undue burden in order to reproduce the oxidation step of claim 1 at issue and obtain the intermediate 14-hydroxymorphinone.

2.7 It follows that the invention as defined in the claims is sufficiently disclosed, and the ground for opposition under Article 100(b) EPC does not prejudice the maintenance of the patent as granted.

3. Inventive step - Article 100(a) EPC

The choice of closest prior art

3.1 According to the opponent, D2 was the closest prior art, while the proprietor was of the view that D2 was unsuitable, and that D14 was more appropriate.

3.2 According to established jurisprudence, in selecting the closest prior art, a central consideration is that it must be directed to the same purpose or effect as the invention, otherwise it cannot lead the skilled person in an obvious way to the claimed invention. In particular, when the claims are directed to a process for the preparation of a known compound, the closest prior art is normally confined to disclosures describing that compound and its manufacture.

3.3 D2 is directed to the preparation of derivatives of morphine, one of which is 14-hydroxymorphinone, corresponding to the intermediate product of the first step of the process recited in claim 1 at issue. 14-hydroxymorphinone is obtained in D2 by demethylation of 14-hydroxycodeinone (first paragraph of the article, and the scheme on page 1507, top right hand structure, conversion of III into IV). For the purposes of "*... final proof of structure*" (page 1505, right hand column, second full paragraph), 14-hydroxycodeinone (IV) was converted to oxymorphone (structure II, scheme page 1507, top left hand structure), corresponding to the product of claim 1 at issue. This conversion was performed by catalytic hydrogenation (page 1505, right hand column, second full paragraph) and is described in the experimental section of D2 (page 1507, left hand column, "*Catalytic hydrogenation of 14-hydroxymorphinone*").

3.4 Thus D2 discloses the second step of claim 1 at issue, namely the reduction of 14-hydroxymorphinone to obtain the desired product, oxymorphone.

3.5 Nevertheless, the board does not consider D2 as an appropriate starting point for the skilled person, for the following reasons. The authors of D2 did not set out to prepare oxymorphone, and as noted above, its preparation was merely performed for the purpose of characterisation (i.e. identification) of 14-hydroxycodeinone. As stated in D2 (page 1505, right hand column, first full paragraph), the characterisation of structure IV (14-hydroxymorphinone)

"*follows from its composition and physical and chemical properties: solubility in aqueous alkali with bright yellow color, typical of phenolic α,β-unsaturated ketones of the morphine series; blue color with $FeCl_3$ in aqueous medium, no color in ethanolic medium, a behavior characteristic of morphine derivatives with intact oxygen bridge. The location of the carbonyl band in the infrared spectra is additional evidence for the presence of an α,β-unsaturated ketone*"

The subsequent paragraph details that for the purposes of "*... final proof of structure*" (page 1505, right hand column, second full paragraph), 14-hydroxycodeinone (IV) was converted to oxymorphone (structure II, scheme page 1507, top left hand structure); corresponding to the product of claim 1 at issue.

3.6 It is clear therefore that the preparation of oxymorphone in D2 was not performed with a view to obtaining the compound itself, nor was it intended as a

useful preparative method, but merely as a final step in the characterisation of compound IV. In 1957, the publication year of D2, powerful modern techniques for precise characterisation of organic compounds (for example nuclear magnetic resonance (NMR) spectroscopy and high resolution mass spectroscopy (HRMS)) had not yet been developed. Then, as is demonstrated in D2, the structural elucidation of compounds was a skillful process of inference, deduction and confirmation, deriving information and hints from different source, for example, shifts in IR spectra, solubility, colour in solution, crystallinity, the colour and shape of the resultant crystals, as well as the chemical reactivity of the compound, i.e. its facility to convert to other compounds, from which deductions could be made with regard to the structure of the starting material. This is evident on reading D2 as a whole, the majority of which is concerned with such characterisation.

3.7 Consequently, since the preparation of oxymorphone in D2 was not performed with a view to establishing a route to or a synthesis of oxymorphone, the board considers it unsuitable and unrealistic as a starting point for the skilled person in the assessment of inventive step of the subject-matter of claim 1 at issue.

3.8 For the purpose of argument, and in the opponent's favour, if it were assumed that the skilled person would nevertheless start from D2 as the closest prior art, the following applies.

In order to arrive at the subject-matter of claim 1 starting at D2, the skilled person would have to select the disclosure in D2 that oxymorphone could be obtained by hydrogenation of 14-hydroxymorphinone, merely for

the purposes of analytical characterisation of the latter and would have to combine this step with the synthetic step of preparing 14-hydroxymorphinone by oxidation of oripavine known from D1 (page 6774, right hand column, linew 23-26). However, in the absence of evidence or convincing argumentation as to why the person carrying out the characterising step of D2 would have been motivated to tackle the issue of providing an alternative preparative synthesis of oxymorphone, and based on this motivation would have combined this characterising step of D2 with the oxidising step disclosed in D1, this approach must also fail.

3.9 On the other hand, D14, considered to represent the closest prior art by the proprietor, does not explicitly nor implicitly disclose a process for the synthesis of oxymorphone. This was acknowledged by the opponent (reply to the grounds of appeal, section 2.1.1.1). The proprietor submitted that oxymorphone is represented in D14 by the final structure of scheme 1 on page 13, wherein R=H and the nitrogen substituent (R') is CH_3. However, in describing the methylation reaction, although not excluded, R'=CH_3 is not included in the exemplary groups mentioned, which are defined to be C_{2-6} alkyl, alkenyl or alkynyl (D14, page 14, lines 6-10). Additionally, compounds having the structure on page 3 to which the invention in D14 is directed (D14, page 3, lines 20-22) also do not include the option where the nitrogen substituent (R) is methyl (D14, page 4, lines 1-3). On the contrary, D14 is concerned with the synthesis of compounds which at least include the replacement of the N-methyl group of morphine with alternatives (page 3, lines 1-7), consistent with the only explicit mention of oxymorphone in D14 as a starting material subjected to demethylation (example 4).

3.10 Consequently, since D14 does not disclose a process for the synthesis of oxymorphone, it also does not represent an appropriate starting point for the skilled person in the assessment of inventive step of the subject-matter of claim 1 at issue.

4. It follows from the foregoing that without exercising inventive step, neither D2 nor D14 as closest prior art would lead the skilled person to the subject-matter of claim 1 at issue. The claims as granted consequently involve an inventive step, and the ground for opposition under Article 100(a) EPC does not prejudice the maintenance of the patent as granted.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is maintained as granted.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated