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Datasheet for the decision of 1 June 2022

Case Number: T 1805/17 - 3.3.02

Application Number: 10011793.6

Publication Number: 2314589

IPC: C07D489/08, A61K31/485, A61P29/00

Language of the proceedings: EN

Title of invention:
Process for preparing oxycodone hydrochloride having less than 25ppm 14-hydroxycodeinone

Applicant:
EURO-CELTIQUE S.A.

Headword:

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step

Decisions cited:

Catchword:

Europäisches Patentamt
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Case Number: T 1805/17 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 1 June 2022

Appellant: (Applicant)	EURO-CELTIQUE S.A. 1, rue Jean Piret 2350 Luxembourg (LU)
Representative:	Maiwald Patent- und Rechtsanwaltsgesellschaft mbH Elisenhof Elisenstraße 3 80335 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 6 March 2017 refusing European patent application No. 10011793.6 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	P. O'Sullivan
	P. de Heij

Summary of Facts and Submissions

I. The appeal of the applicant (hereinafter appellant) lies from the decision of the examining division to refuse European patent application 10011793.6.

II. The following documents *inter alia* were cited in examination proceedings:

D1: WO 2004/016618 A1
D2: Kraβnig *et al.*, Arch. Pharm. Pharm. Med. Chem., 329, 325-326 (1996)
D3: US 7,906,647

In the contested decision, the main request, the only request relevant to the present decision, was rejected on the basis that its subject-matter lacked inventive step.

III. With the statement of grounds of appeal, the appellant contested this conclusion. The appellant also submitted the following documents:

D4: Experimental report from parallel proceedings in relation to European patent 2 305 683
D5: Declaration of Prof. Lamprecht dated 11 July 0216
D6: Summons to oral proceedings in EP 2 305 683
D7: Declaration of Prof. Diederichsen dated 16 July 2017
D8: US 6,008,355
D9: Coop *et al.*, Tetrahedron 55(1999) 11429-11436

IV. Requests relevant to the present decision

The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims of the main request, or alternatively of the first, second or third auxiliary request, all submitted with the statement of grounds of appeal. These requests are identical to those underlying the decision of the examining division.

V. The arguments of the appellant, insofar as relevant to the present decision, may be summarised as follows:

The subject-matter of claim 1 of the main request involved an inventive step. The objective technical problem solved by the claimed subject-matter was not just the provision of an alternative process for the preparation of oxycodone hydrochloride, but the provision of a process for the preparation of oxycodone hydrochloride with a lower content of 14-hydroxycodeinone, in particular with a 14-hydroxycodeinone content of less than 25 ppm. This problem was solved by the claimed subject-matter. The solution would not have been obvious to the skilled person.

Reasons for the Decision

Main request - Inventive step, Article 56 EPC

1. Background

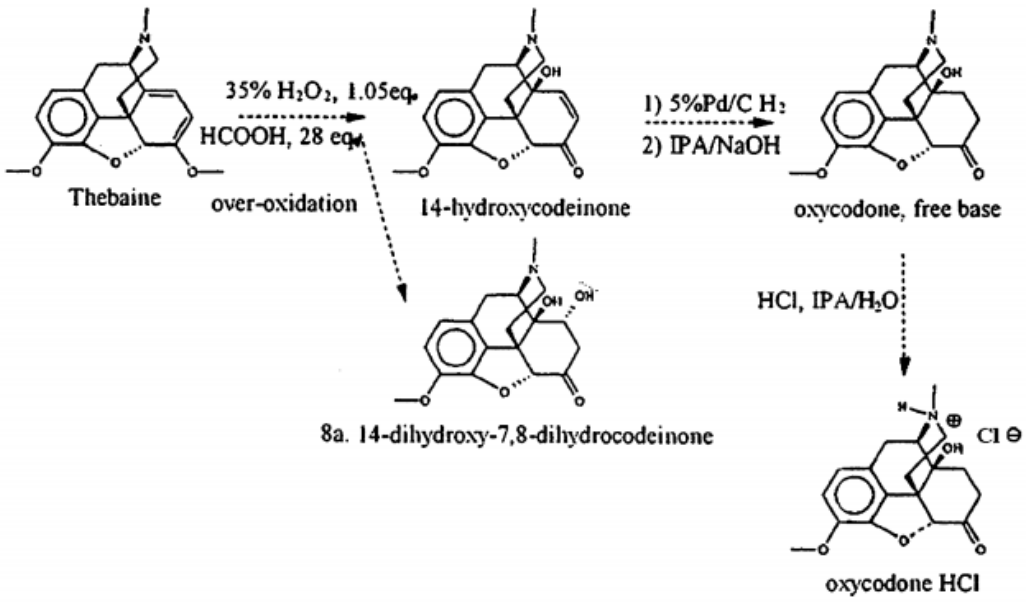
1.1 The application as filed concerns a process for reducing the amount of 14-hydroxycodeinone in an oxycodone hydrochloride (hereinafter oxycodone HCl) preparation (application, paragraph [0002]).

VI. The sole independent claim 1 of the main request reads as follows:

"*1. A process for preparing an oxycodone hydrochloride composition having less than* 25 ppm 14-hydroxycodeinone as determined by the HPLC method of Example 6, which process comprises the steps of:

(a) hydrogenating a 14-hydroxycodeinone composition to obtain an oxycodone free base composition;
(b) converting the oxycodone free base to oxycodone hydrochloride; and
(c) hydrogenating the oxycodone hydrochloride composition formed in step (b) to produce an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone."

1.2 The claimed process, and the reduction in the amount of 14-hydroxycodeinone achieved thereby can be understood by means of the reaction scheme depicted in figure 1 of the application, reproduced below:



1.3 This figure, in combination with paragraph [0013] of the application, explains how unwanted 14-hydroxycodeinone is obtained in oxycodone HCl compositions, as follows. The starting material of the process of claim 1 at issue is 14-hydroxycodeinone. According to the application (paragraph [0013]), this compound can be obtained through the oxidation of thebaine (not a feature of claim 1 at issue; depicted above). During this step (first reaction step in the above scheme), apart from 14-hydroxycodeinone, several overoxidised products are formed including 8,14-dihydroxy-7,8-dihydrocodeinone (depicted above). In the subsequent hydrogenation of 14-hydroxycodeinone to obtain oxycodone free base (step (a) of claim 1 at issue, second reaction step in the above scheme), 8,14-dihydroxy-7,8-dihydrocodeinone is carried through the process, and is thus present in the oxycodone free base product. In the conversion of oxycodone free base to oxycodone HCl (step (b) of claim 1 at issue, third reaction step in the above scheme), the 8,14-dihydroxy-7,8-dihydrocodeinone impurity undergoes an acid-catalysed dehydration to provide

14-hydroxycodeinone, which remains in the oxycodone HCl product.

1.4 According to the application (paragraph [0013]), commercially available oxycodone HCl API and oxycodone HCl prepared by known methods have 14-hydroxycodeinone levels of greater than 100 ppm. It was thus an object of the invention to provide a process for reducing the 14-hydroxycodeinone content to less than 25 ppm (paragraph [0016]). According to the application as filed, this is achieved by step (c) of claim 1 at issue.

2. Closest prior art

D1 was considered by the examining division to represent the closest prior art. D1 discloses the preparation of various polymorphs of oxycodone HCl (examples 1-9; "oxycodone" in D1 refers to oxycodone HCl; page 1, lines 7-9). Since oxycodone HCl is the product of contested claim 1, the board also agrees that D1 can represent the closest prior art.

3. Problem solved

3.1 According to the contested decision, the objective technical problem was the provision of an *alternative* process for the preparation of oxycodone HCl. However, this conclusion was reached without assessing the effect of the distinguishing feature of the claimed subject-matter over the closest prior art D1. At least in this regard, the contested decision did not correctly apply the problem-solution approach employed at the EPO for the assessment of inventive step.

3.2 D1 is silent on how oxycodone HCl used to prepare the polymorphs thereof is obtained (see D1, examples).

Even though not explicitly disclosed in D1, the appellant did not dispute that steps (a) and (b) as defined in claim 1 were known to the skilled person at the priority date of the application as filed. Indeed, the appellant stated that "*without step (c), the process of claim 1 is a conventional process for making oxycodone hydrochloride*" (statement of ground of appeal, page 3, fourth paragraph).

However, the subject-matter of claim 1 differs from D1 in at least step (c), namely the hydrogenation of oxycodone hydrochloride.

3.3 According to the appellant, the implementation of step (c) led to an improvement, namely a diminution of the 14-hydroxycodeinone level in the oxycodone HCl product to less than 25 ppm. This was demonstrated *inter alia* in the examples of the patent.

The board agrees. The examples of the patent convincingly demonstrate this improvement. In example 1, oxycodone HCl comprising 500 ppm 14-hydroxycodeinone was hydrogenated to provide a product comprising 8 ppm 14-hydroxycodeinone when analysed using the method of Example 6. Similar reductions in 14-hydroxycodeinone levels were obtained by hydrogenation in examples 2, 3 and 5, respectively.

3.4 The board notes in this regard that according to the contested decision (paragraph bridging pages 3 and 4, and page 4, second paragraph), no conclusion could be drawn from the examples of the patent on the basis that only step (c) was disclosed, or steps (b) and (c) in

combination, and therefore none of the examples disclosed the three step process (a) - (c) as claimed. In the view of the board, this approach is incorrect. There is no requirement in the EPC that to support inventive step, and more specifically the presence of a particular technical effect, the examples must disclose all of the features of the claim. Rather, as noted by the appellant, it is sufficient that the examples (or indeed, the description in general) allow the assessment of whether the claimed process leads to the alleged effect, namely a reduction in the amount of 14-hydroxycodeinone in the final oxycodone HCl product. As set out above, this has been demonstrated by the examples of the patent.

3.5 It can thus be accepted that the effect of the distinguishing feature of claim 1 is the reduction in the amount of 14-hydroxycodeinone present in oxycodone HCl.

3.6 The objective technical problem underlying the subject-matter of claim 1 is consequently the provision of a process for the preparation of oxycodone HCl with a lower 14-hydroxycodeinone content.

3.7 Obviousness

There is no pointer nor motivation in D1 nor in D2 which would lead the skilled person to the conclusion that the above-mentioned problem could be solved by the implementation of a step (c) as claimed. D1 does not address the issue at all. D2 on the other hand merely describes the catalytic hydrogenation of 14-hydroxycodeinone to oxycodone free base (page 325, "Experimental", second entry) and does not disclose the preparation of oxycodone HCl. Furthermore, as noted by

the appellant, it would be counter-intuitive for the skilled person to consider the purification of a compound using the same method by which it was produced, namely hydrogenation.

The examining division arrived at the conclusion that the claimed subject-matter lacked inventive step over D1 in combination with D2. However, this conclusion was reached starting from an objective technical problem formulated as the provision of a alternative process, and the view that step (c) was merely an arbitrary and thus obvious modification of an otherwise known process (contested decision, point 1.4). As set out above, this approach is incorrect.

4. Further arguments of the examining division

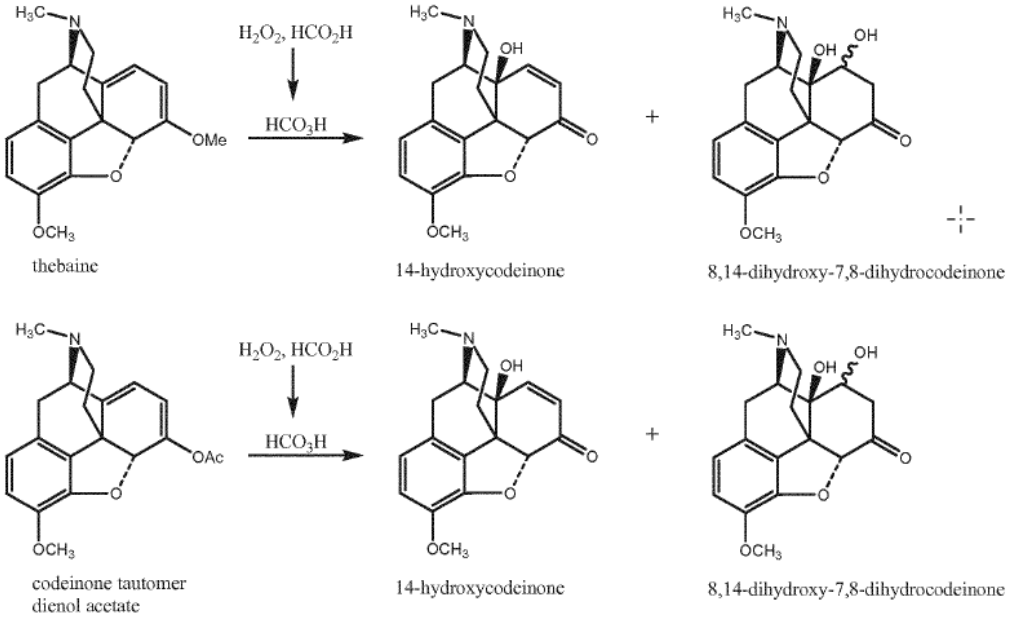
4.1 A further ground for denial of inventive step according to the contested decision was based on the fact that claim 1 at issue was exclusively directed to a process for preparing an oxycodone HCl composition starting from 14-hydroxycodeinone, and did not specify the manner in which the latter was prepared. The description on the other hand taught that unwanted 8,14-dihydroxy-7,8-dihydrocodeinone, and therefore 14-hydroxycodeinone in the product oxycodone HCl, was obtained exclusively in the oxidation of thebaine to prepare 14-hydroxycodeinone. However, other syntheses of oxycodone starting from codeine or codeinone were known (application, paragraphs [0006] and [0009]). Since these alternative routes may not have yielded 8,14-dihydroxy-7,8-dihydrocodeinone as an impurity in the preparation of 14-hydroxycodeinone at all, the examining division reasoned, claim 1 at issue did not address the problem associated with the formation of an impurity during the oxidation of thebaine.

4.2 The board understands the argument set out in the contested decision as follows: when 14-hydroxycodeinone is prepared from codeine or codeinone, i.e. a starting material other than thebaine, the problem associated with a 8,14-dihydroxy-7,8-dihydrocodeinone impurity does not arise. In such a process, step (c) would be futile, since unwanted 14-hydroxycodeinone would not be produced in the preparation of oxycodone HCl. For such a process therefore, the objective technical problem would be the provision of an alternative process to the conventional process (comprising steps (a) and (b) of claim 1 at issue) for preparing oxycodone HCl. The solution, the addition of a second hydrogenation in step (c), would be arbitrary and therefore lack inventive step.

The board does not agree with this approach. Firstly, it is set out in the application (paragraph [0014]) that oxycodone HCl prepared by known procedures has a 14-hydroxycodeinone level of greater than 100 ppm. This is further confirmed by post-published patent D3 (column 3, lines 39-44), as well as the fact that none of the cited prior art disclose oxycodone HCl having a lower level. If all known procedures lead to oxycodone HCl with such high levels of 14-hydroxycodeinone, it would appear reasonable to assume that similar issues with the generation of 8,14-dihydroxy-7,8-dihydrocodeinone would occur also in the processes to produce 14-hydroxycodeinone from codeine or codeinone mentioned in the application. Indeed, if this were not the case, one would have expected that the problem of unwanted 14-hydroxycodeinone could simply have been solved in the prior art by using a starting material different from thebaine. However, since D3 states that oxycodone

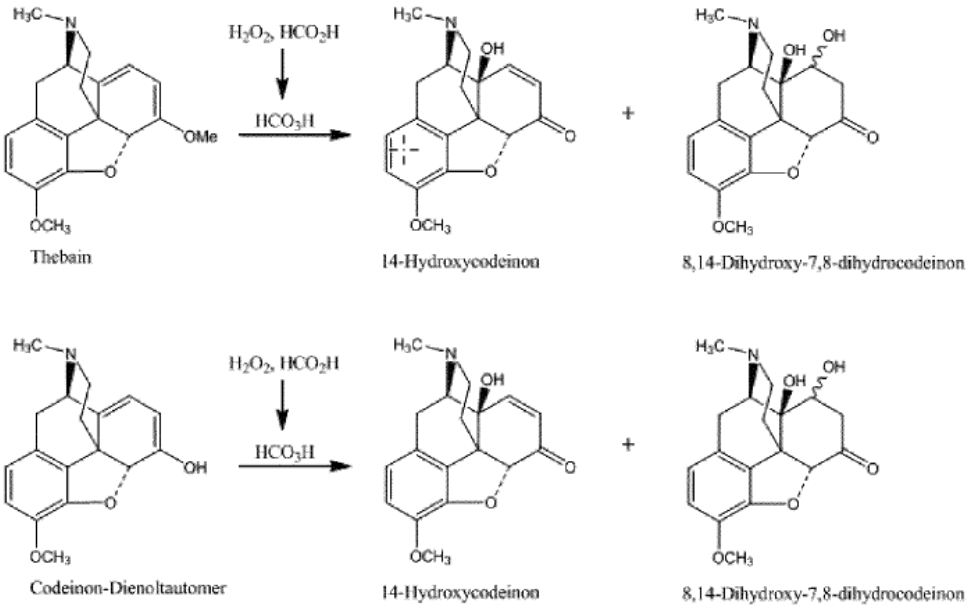
HCl prepared by all known procedures has 14-hydroxycodeinone levels above 100 ppm, this does not appear to have been possible.

4.3 Secondly, this conclusion is supported by the arguments of the appellant. The appellant analysed the prior art cited in paragraph [0009] of the application relating to the preparation of 14-hydroxycodeinone from codeinone, namely D8 and D9 in the present proceedings. As noted by the appellant and stated in expert declaration D7 (section H), 14-hydroxycodeinone prepared according to these documents will inevitably also contain 8,14-dihydroxy-7,8-dihydrocodeinone. Specifically, the method described in D8 starting from codeinone passes through a dienol acetate intermediate (D8, page 6, structure 1-3 in scheme). This dienol acetate is then converted to 14-hydroxycodeinone (structure 1-4). As noted by the appellant, the dienol acetate differs from thebaine only in the nature of the enol ether: acetate in the case of the compound of D8, and methoxy in the case of thebaine. The mechanistic similarity between the conversion of both of these compounds to 14-hydroxycodeinone was summarised schematically by the appellant (statement of grounds of appeal, page 16):



Given the structural similarity between thebaine and the codeinone tautomer dienol ether depicted above, it is reasonable to assume that the same overoxidation to 8,14-dihydroxy-7,8-dihydrocodeinone occurs in the reaction of the latter to prepare 14-hydroxycodeinone, as described in the application (paragraph [0013]) for the corresponding conversion of thebaine.

4.4 D8 also describes a direct oxidation of codeinone to 14-hydroxycodeinone without passing via the dienol acetate mentioned above (scheme on columns 7 and 8, structures 1-2 and 1-4). The mechanism for this transformation is described in D9 (e.g. scheme on page 11431). In declaration D7 (section page 7, final paragraph - page 9, first paragraph) it is stated that this transformation must also lead to the formation of 8,14-dihydroxy-7,8-dihydrocodeinone. Specifically, it is postulated, for example, that the reaction mechanism could proceed *inter alia* via a dienol tautomer which is a (non-isolatable) analogue of thebaine, according to the following scheme, in which the unwanted by-product is produced in the same manner:



It is also to be noted that D8 discloses that oxycodone can also be produced from codeine via codeinone, and thus describes the preparation of oxycodone from codeine described in paragraphs [0006] and [0008] of the application as filed (D8, scheme on page 6, structures 1-1 and 1-2). Therefore, that stated above for the process starting from codeinone is also valid for the corresponding process starting from codeine.

It is therefore reasonable to conclude that also in the preparation of 14-hydroxycodeinone starting from codeine or codeinone, 8,14-dihydroxy-7,8-dihydrocodeinone is produced as a by-product, and consequently that 14-hydroxycodeinone is co-prepared upon preparation of oxycodone HCl as discussed above, independently of the starting material used to prepare 14-hydroxycodeinone.

4.5 The objective technical problem underlying the subject-matter of claim 1 at issue therefore remains the provision of a process for the preparation of oxycodone

HCl with a lower 14-hydroxycodeinone content, independently of whether the starting material is thebaine, codeine or codeinone, and the conclusions under obviousness set out above apply.

It follows that the subject-matter of the claims of the main request involves an inventive step.

5. Further requirements of the EPC

The claims of the main request were refused by the examining division for lack of inventive step. The board does not see any reason to doubt that the further requirements of the EPC are met. Specifically:

- As noted in the contested decision, claims 1 and 2 find basis in the application in paragraphs [0029] and [0030] and in example 6 in relation to the HPLC method recited in claim 1. The requirements of Article 123(2) EPC are therefore met.
- The examples of the patent clearly set out how the claimed process is to be carried out. The requirements of Article 83 EPC are therefore met.

It follows that the main request is allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division with the order to grant a patent with the following claims and a description to be adapted thereto:

Claims 1-2 of the main request submitted with the statement of grounds of appeal.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated