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Datasheet for the decision of 20 November 2022

Case Number: T 1426/19 - 3.3.02

Application Number: 14704633.8

Publication Number: 3027621

IPC: C07D489/08

Language of the proceedings: EN

Title of invention:
PROCESS FOR THE PREPARATION OF MORPHINAN-6-ONE COMPOUNDS

Applicant:
MacFarlan Smith Ltd

Headword:

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

Keyword:
Procedural Violation (no)
Inventive step - (no)
Amendments - auxiliary requests - added subject-matter (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 1426/19 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 20 November 2022

Appellant: (Applicant)	MacFarlan Smith Ltd Wheatfield Road Edinburgh EH11 2QA (GB)
Representative:	Lawrie IP Limited 310 St. Vincent Street Glasgow G2 5RG (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 6 December 2018 refusing European patent application No. 14704633.8 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	M. Maremonti
	P. de Heij

Summary of Facts and Submissions

I. The appeal lodged by the applicant ("appellant") lies from the decision of the examining division to refuse European patent application No. 14704633.8.

II. Documents D3 and D5 were referred to, *inter alia*, during examination proceedings:

D3: WO 2008/072018 A1

D5: WO 2008/118654 A1

III. In the course of the proceedings the appellant filed two sets of claims, according to its main request and an auxiliary request. The examining division came *inter alia* to the following conclusion.

- The subject-matter of claim 1 of the main and auxiliary request did not involve an inventive step in view of document D5 taken as the closest prior art.

IV. With its statement of grounds of appeal, the appellant filed sets of claims according to a main request and auxiliary requests 1 to 6. It criticised the examining division's conduct at the oral proceedings. Moreover, it submitted that the claimed subject-matter involved an inventive step. It corroborated its arguments by relying on the following new items of evidence:

Annex 1: Comparative experimental data relating to the hydrogenation of nor-14-hydroxymorphinone

Annex 2: The Safety Data Sheet for peracetic acid from Supelco

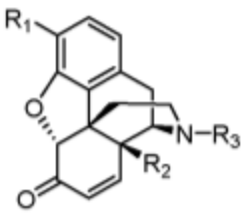
V. The main request filed with the statement of grounds of appeal corresponds to the main request underlying the

appealed decision. It contains twelve claims, independent claims 1 and 7 reading as follows (text in square brackets inserted by the board):

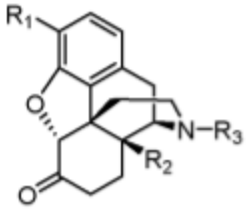
"*1. A process for preparing an aqueous acid solution of a compound of formula (3), the process comprising the steps of:*

(a) *providing an aqueous acidic solution comprising a starting material which is a compound of formula (1) and, as an impurity, a compound of formula (2); and*

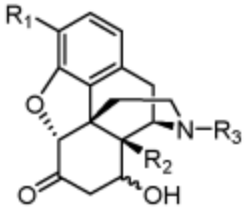
(b) *treating the aqueous acidic solution of step (a) such that the compound of formula (2) dehydrates to form a compound of formula (1) and the compound of formula (1) is reduced to form an aqueous acidic solution of the compound of formula (3),*



(1)



(3)



(2)

wherein:

the treating of step (b) is carried out at one or more temperatures in the range of ≥ 75°C to ≤ 100°C in the presence of a hydrogenation catalyst and hydrogen gas; and

the aqueous acidic solution of step (a) is heated to one or more temperatures in the range of ≥ 75°C to ≤ 100°C before it is exposed to the hydrogen gas; and

wherein for the compounds of formulae (1), (2) and (3):

i) R_1 is -OH, R_2 is -OH and R_3 -H; or

iv) R_1 is $-OCH_3$, R_2 is -H and R_3 -H; or

v) R_1 is-OH, R_2 is-H and R_3-H; or

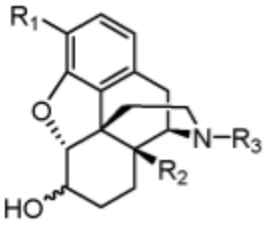
vi) R_1 is $-OCH_3$, R_2 is -OH and R_3 -H."

"*7. A process for preparing an aqueous acidic solution of a compound of formula (3), the process comprising the steps of:*

(I) hydrogenating an aqueous acidic solution comprising a starting material which is a compound of formula (1) and, as an impurity, a compound of formula (2), wherein the hydrogenation is carried out at a temperature of 30°C or less in the presence of a hydrogenation catalyst and hydrogen gas; and

(II) hydrogenating the aqueous acidic product of step (I) at one or more temperatures in the range of ≥ 75°C to ≤ 100°C in the presence of a hydrogenation catalyst and hydrogen gas to form an aqueous acidic solution of the compound of formula (3) comprising ≤ 0.05 area % of the compound of formula (1) as determined by HPLC and ≤ 2.00 area % of a compound of formula (4) as determined by HPLC,

[formulae (1), (2) and (3) as in claim 1]



(4)

wherein the hydrogen gas present in step (I) is substantially removed before the aqueous acidic product of step (I) is heated to one or more temperatures in the range of ≥ 75°C to ≤ 100°C; and

wherein for the compounds of formulae (1), (2), (3) and 4 [sic]*:*

i) R_1 *is -OH,* R_2 *is -OH and* R_3 *-H; or*

iv) R_1 *is* $-OCH_3$*,* R_2 *is -H and* R_3 *-H; or*

v) R_1 *is-OH,* R_2 *is-H and* R_3*-H; or*

vi) R_1 *is* $-OCH_3$*,* R_2 *is -OH and* R_3 *-H.*"

VI. The appellant was summoned to oral proceedings as per its request. In preparation for oral proceedings, the board issued a communication under Article 15(1) RPBA 2020, in which, *inter alia*, it expressed the preliminary opinion that it did not find anything unreasonable in the way the examining division had proceeded. Moreover, the subject-matter of claim 1 of the main request and auxiliary request 2 did not appear to involve an inventive step in view of document D5, taken as the closest prior art. Additionally, the subject-matter claimed in auxiliary requests 1 and 3 to 6 appeared to infringe Article 123(2) EPC.

VII. By its letter dated 4 November 2022, the appellant withdrew its request for oral proceedings and confirmed that it would not attend the scheduled oral

proceedings. No arguments contesting the board's provisional opinion were submitted.

VIII. By a subsequent communication, the board cancelled the oral proceedings.

IX. Requests

The appellant requested in writing that the appealed decision be set aside and that the application be remitted to the examining division with the order to grant a patent on the basis of the claims of the main request or, alternatively, the claims of one of auxiliary requests 1 to 6, all requests filed with the statement of grounds of appeal.

X. The appellant's submissions, where relevant to the present decision, are summarised as follows. For further details, reference is made to the reasons for the decision below.

Conduct of the examining division:

- It was unreasonable for the examining division to raise the topic of the absence of comparative data in view of D5 only at the oral proceedings.

Inventive step:

- Document D5 might be regarded as representing the closest prior art.
- The objective technical problem in view of D5 had to be seen as the provision of a process for preparing the claimed compounds of formula (3) having improved impurity profiles and exhibiting a greater resistance to α,β-unsaturated ketone regrowth.

- Nothing in D5 or the other available prior-art documents prompted the skilled person to arrive at the claimed process.
- It had to be concluded that the claimed subject-matter involved an inventive step.

Auxiliary requests:

- The amendments in the claims of the auxiliary requests were based on the application as filed.
- As regards inventive step, the same arguments as for the main request applied *mutatis mutandis*.

Reasons for the Decision

Conduct of the proceedings before the examining division

1. The appellant argued (statement of grounds of appeal, pages 9 and 10) that, until the oral proceedings, in assessing inventive step the examining division had never raised the issue of the absence of comparative data in view of document D5, taken as the closest prior art. The appellant submitted that it was unreasonable for the examining division to raise the topic of comparative data at such a late stage in the proceedings, especially as it had issued only a single examination report before the summons to oral proceedings. Had the appellant had the opportunity to respond to more than one examination report, and had the subject of comparative data been raised appropriately during that time, the data would have been submitted. This might have allowed the appellant to avoid the time and expense involved in the appeal.

2. These arguments are not convincing.

2.1 In the communication issued by the examining division on 23 February 2017, i.e. more than a year and a half before the oral proceedings (date of oral proceedings: 13 November 2018), objections of lack of inventive step were raised, and D1, D4 and D5 were indicated as possible documents representing the closest prior art. In the summons to oral proceedings dated 13 April 2018, the inventive step objection in view of D1 as the closest prior art was reiterated by the examining division. The relevance of D5 was also reiterated (points 12 and 12.1).

2.2 One month before the oral proceedings, the appellant filed a new main request and an auxiliary request. Substantial amendments were made to independent claims 1 and 7 of both requests. In particular, alternatives ii) and iii) for the substituents R_1, R_2 and R_3 were deleted and the temperature range of 75°C to 100°C was inserted.

2.3 In view of these substantial amendments filed only one month before the oral proceedings, the examining division considered document D5 to better represent the closest prior art. In correctly applying the problem-solution approach, the examining division observed that no technical effect could be established over D5 because no comparative data were available.

2.4 The board does not see anything unreasonable in the way the examining division proceeded. An applicant filing substantial amendments only shortly before oral proceedings should be prepared to argue the case for inventive step in view of a different closest prior-art document, especially if such a document had already been identified as very relevant in the course of the proceedings, as D5 was in the present case. Part of the arguments made must necessarily include the technical

effect, if any, achieved by the features distinguishing the claimed invention from the closest prior art.

2.5 Finally, the board observes that, according to the minutes of the oral proceedings before the examining division, the appellant did not request any adjournment of the oral proceedings on the basis that D5 had been selected by the examining division as the closest prior art.

2.6 If the appellant's submission is to be understood as an allegation of a procedural violation, this allegation is rejected. The board concludes that no procedural violation, let alone a substantial one, was committed by the examining division.

2.7 It is noted that the board's disagreement with the appellant's submissions had already been communicated to the appellant in the communication under Article 15(1) RPBA 2020, issued in preparation for the (later cancelled) oral proceedings. No arguments contesting this opinion were submitted by the appellant.

Main request - claim 1 - inventive step under Article 56 EPC

3. Closest prior art

3.1 The appellant argued inventive step in view of document D5 taken as the closest prior art.

3.2 Document D5 (pages 2 to 4, page 7, page 9, second paragraph, page 10 and the examples on pages 12 to 19) discloses a process for producing an aqueous acidic solution of oxymorphone (formula III in D5) from an aqueous acidic solution of 14-hydroxymorphinone (formula II in D5), by exposing the latter to hydrogen gas in the presence of a hydrogenation catalyst at high temperature. In particular, examples 3 to 7 disclose such a process, in which a two-step hydrogenation is carried out first at ambient temperature and then at

80°C. In examples 8 to 12, the hydrogenation is carried out directly at a temperature of 85 to 90°C. D5 also discloses the formation of a solid salt of the obtained oxymorphone.

4. Distinguishing features

4.1 The appellant argued that the subject-matter of claim 1 differed from the process of D5 in the preparation of the four individualised nor-morphinan-6-ones listed under alternatives i), iv), v) and vi) in claim 1. Moreover, unlike the process in D5, the solution of step (a) was heated to a temperature of from 75°C to 100°C before exposure to hydrogen gas.

4.2 However, the board notes that claim 1 does not require the preparation of all four individualised compounds listed under alternatives i), iv), v) and vi), but only one of them. In view of the conversion of 14-hydroxymorphinone into oxymorphone disclosed in D5 (*loc. cit.*), alternative i) of claim 1 only differs from the process of D5 in that substituent R_3 is -H. In 14-hydroxymorphinone and oxymorphone as disclosed in D5, this substituent is methyl. As regards the temperature, the board concurs with the appellant that, according to the examples of D5, the mixture is heated to the disclosed temperature (80°C in examples 2 to 7, 85°C to 90°C in examples 8 to 12) while being exposed to hydrogen gas, and not before as required by claim 1. Hence, the distinguishing features of alternative i) of claim 1 over D5 are:

(a) the substituent R_3 in the compound involved in the claimed process, this substituent being hydrogen according to claim 1 but methyl in D5, and

(b) the fact that the mixture is heated before being exposed to hydrogen gas, whereas in D5 it is heated while being exposed to hydrogen.

5. Objective technical problem

5.1 The appellant referred to the examples of the application (pages 19 to 21) and argued that the distinguishing features had the technical effects of improving the impurity profile of the product (reduced 6β isomer of compound (4)), this product exhibiting a greater resistance to α,β-unsaturated ketone (ABUK) regrowth. In view of this, it submitted that the objective technical problem was the provision of a process for preparing the claimed compounds of formula (3) having improved impurity profiles and exhibiting a greater resistance to ABUK regrowth.

5.2 The board disagrees.

5.2.1 According to the problem-solution approach, technical effects, if any, have to be associated with the features distinguishing the claimed subject-matter from the closest prior art. The results reported in the application on pages 19 to 21, invoked by the appellant, show a reduction especially of nor-14-hydroxymorphone after hydrogenation at 80°C as compared with hydrogenation carried out at ambient temperature. However, the latter does not reflect the teaching of D5 (see above), which discloses a hydrogenation carried out at temperatures of 80°C and 85°C to 90°C.

5.2.2 As a consequence, the results reported in the application are not suitable for establishing the presence of a technical effect of the claimed process over the disclosure in D5. Also the remaining part of the application does not disclose any technical effect deriving from heating the solution of step (a) to the required temperature before exposure to hydrogen gas.

5.2.3 Nor has a technical effect deriving from the selected substituent R_3 been put forward (distinguishing feature (a) above).

5.2.4 In the absence of any technical effect, the objective technical problem has to be seen as the provision of an alternative process for preparing an aqueous solution of compounds of formula (3).

5.3 The appellant also submitted (statement of grounds of appeal, page 7) that it did not attempt to reproduce the examples of D5, as this was considered unsafe in view of the use of excess peroxyacetic acid in the presence of Pd/C hydrogenation catalyst. It referred to Annex 2 (point IV above), especially Sections 2 and 10.3, reporting the hazardousness of using peroxyacetic acid.

5.4 The board notes that, in the examples of D5 (see above), peroxyacetic acid is only used in the conversion of oripavine into 14-hydroxymorphinone and not in the reaction of the latter to give oxymorphone, i.e. in the process at issue. Moreover, according to several examples in D5 (see e.g. examples 7 to 10 and 12), excess peroxyacetic acid is neutralised before the hydrogenation reaction in the presence of the hydrogenation catalyst is carried out. According to examples 8 to 10 and 12, a separate vessel is used for the hydrogenation. Therefore, this assertion by the appellant is not convincing.

6. Obviousness of the claimed solution

6.1 The appellant argued that at least a two-fold selection was needed within scheme 2 of D5 (page 2) to arrive at substituents R_1, R_2 and R_3 according to items i), iv), v) and vi) of claim 1. Moreover, nothing in D5 or in the other prior-art documents prompted the skilled person to heat the solution before adding hydrogen. Thus, an inventive step should be acknowledged.

6.2 This argument is not convincing.

6.2.1 When starting from the conversion of 14-hydroxymorphinone into oxymorphone as disclosed in D5 (see above), only a single selection is needed to arrive at alternative i) of claim 1, namely the replacement of the methyl substituent connected to the N atom by hydrogen. This possibility is clearly suggested in D5 itself, see e.g. Scheme 2 on page 4, where R^1 (corresponding to R_3 in claim 1) can be -H for a compound of formula III.

6.2.2 Moreover, since no technical significance is associated with the feature of heating the mixture before adding hydrogen, this feature is regarded as an arbitrary option, on which no inventive step can be based. In this context the board notes that the appellant did not argue that the claimed subject-matter was not obvious if the objective technical problem was the provision of an alternative process.

6.2.3 Furthermore, document D3 also discloses (examples 1.1B-1.1C, 1.2B-1.2C, 2.2B-2.2C, 3.1B-3.2C on pages 27 to 33) the hydrogenation of acidic mixtures of 14-hydroxymorphinone to oxymorphone hydrochloride at temperatures higher than ambient, especially at 65°C. According to D3, the acidic mixture is heated to 50°C to 60°C before hydrogen is added. Then hydrogenation is performed at 65°C. Therefore, the claimed possibility of heating the solution before adding hydrogen is known to the skilled person from D3.

6.2.4 For these reasons, the board concludes that the subject-matter of claim 1 does not involve an inventive step in view of D5 taken as the closest prior art, either alone or in combination with document D3 (Article 56 EPC).

6.3 It is noted that this opinion of the board had already been communicated to the appellant in the communication

under Article 15(1) RPBA 2020, issued in preparation for the (later cancelled) oral proceedings. No arguments contesting this opinion were submitted by the appellant.

For these reasons, the main request is not allowable (Articles 52(1) and 56 EPC).

Auxiliary request 2 - claim 1 - inventive step under Article 56 EPC

7. Auxiliary request 2 corresponds to the auxiliary request underlying the appealed decision.

7.1 As compared with claim 1 of the main request (point V above), claim 1 of auxiliary request 2 has been restricted by deleting alternatives iv), v) and vi) for the substituents R_1, R_2 and R_3. These have been restricted to alternative i) only.

7.2 As set out above, the inventive step of the subject-matter of claim 1 of the main request has been assessed with respect to alternative i). Therefore, all the board's observations on lack of inventive step of claim 1 of the main request apply *mutatis mutandis* to claim 1 of auxiliary request 2.

7.3 It follows that the subject-matter of claim 1 of auxiliary request 2 does not involve an inventive step within the meaning of Article 56 EPC, for the same reasons as the main request.

7.4 Therefore, auxiliary request 2 is not allowable.

Auxiliary requests 1 and 3 to 6 - claim 1 - added subject-matter under Article 123(2) EPC

8. In claim 1 of all auxiliary requests 1 and 3 to 6, the expression "*the process* ***comprising*** *the steps of*" as present in claims 1 and 7 of the main request was

amended to "*the process **consisting** the steps of*" [sic] (emphasis added by the board).

8.1 No basis for this amendment in the application as filed has been indicated by the appellant. Nor does the board see any direct and unambiguous disclosure in the application as filed of a process consisting only of the two steps mentioned in claim 1 of auxiliary requests 1 and 3 to 6. In particular, the examples of the application clearly disclose that the claimed process comprises several steps in addition to the two steps defined in claim 1. The same is confirmed by several dependent claims, defining additional steps of the claimed process.

8.2 It follows that the amendment of "*comprising*" to "*consisting*" results in subject-matter extending beyond the content of the application as filed, contrary to the requirements of Article 123(2) EPC.

8.3 Moreover, in claim 1 of auxiliary requests 1 and 3, the feature of claim 1 of the main request reading "*the aqueous acidic solution of step (a) is heated to one or more temperatures in the range of ≥ 75°C to ≤ 100°C before it is exposed to the hydrogen gas*" (point V above) was amended to "*the aqueous acidic solution of step (a) is heated to one or more temperatures in the range of ≥ 75°C to ≤ 100°C and beginning the hydrogenation by exposing the aqueous acidic solution to the hydrogen gas*". The appellant indicated that page 5, lines 29 to 31 of the application as filed was the basis for this amendment.

The board disagrees. The passage on page 5 of the application as filed invoked by the appellant recites "***Once the reaction mixture reaches the desired temperature,*** *the hydrogenation reaction may begin by exposing the reaction mixture to hydrogen*

gas" (emphasis added by the board). The feature that the solution of step (a) is first heated to the required temperature and only then does the exposure to hydrogen gas begin, as expressed in this passage on page 5, is not included in claim 1. Therefore, the amendment made results in subject-matter that extends beyond the content of the application as filed, contrary to the requirements of Article 123(2) EPC.

8.4 Claim 1 of auxiliary requests 5 and 6 corresponds to claim 7 of the main request (point V above), with the feature reading "*the compound of formula (3) comprising ≤ 0.05 area % of the compound of formula (1) as determined by HPLC and ≤ 2.00 area % of a compound of formula (4) as determined by HPLC*" amended to "*the compound of formula (3) comprising ≤ 0.05 area % of the compound of formula (1) as determined by HPLC and ≤ 1.00 area % of the 6β-isomer of the compound of formula (4)*". The appellant indicated that page 11, lines 33 to 39 of the application as filed was the basis for this amendment.

The board disagrees. The passage on page 11 of the application as filed invoked by the appellant discloses an embodiment in which **the solid salt** of compound (3) comprises ≤ 1.00 area % of the 6β-isomer of the compound of formula (4). By contrast, claim 1 of auxiliary requests 5 and 6 does not mention the solid salt of compound (3). Moreover, in contrast to claim 1, the indicated passage does not specify an amount of the compound of formula (1) that is included in the disclosed embodiment of the solid salt of compound (3). Therefore, the amendment made to claim 1 of auxiliary requests 5 and 6 results in subject-matter extending beyond the application as filed, contrary to the requirements of Article 123(2) EPC.

8.5 For the reasons set out above, none of auxiliary requests 1 and 3 to 6 complies with Article 123(2) EPC. It follows that auxiliary requests 1 and 3 to 6 are not allowable.

Conclusions

9. None of the appellant's claim requests is allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated