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D E C I S I O N
of 7 January 2004

Case Number: T 1239/01 - 3.3.1

Application Number: 96304797.2

Publication Number: 0751128

IPC: C07D 217/26

Language of the proceedings: EN

Title of invention:
Process for producing optically active amides

Patentee:
Ajinomoto Co., Inc.

Opponent:
-

Headword:
NCA/AJINOMOTO

Relevant legal provisions:
EPC Art. 54(3)(4), 56, 87(4), 89

Keyword:
"Priority validly claimed (yes)"
"Inventive step: claimed process (yes) - claimed intermediate (yes) - non obvious solution"

Decisions cited:
T 0022/82, T 0163/84, T 0648/88

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1239/01 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 7 January 2004

Appellant: (Proprietor of the patent)
Ajinomoto Co., Inc.
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 30 October 2001 concerning maintenance of European patent No. 0751128 in amended form.

Composition of the Board:

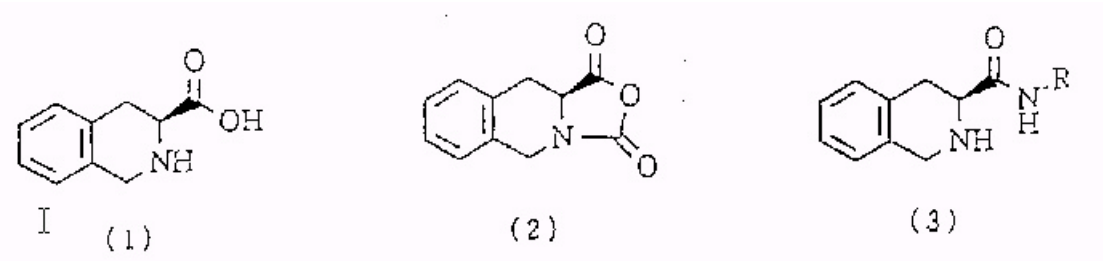
Chairman: A. J. Nuss
Members: P. P. Bracke
S. C. Perrymann

Summary of Facts and Submissions

I. The Proprietor of the patent and the Opponent lodged an appeal against the Opposition Division's interlocutory decision, maintaining the European patent No. 0 751 128, filed on 28 June 1996 and claiming the priority of JP 166536/95 (filing date: 30 June 1995), according to the then pending second auxiliary request.

The set of claims according to the main request underlying the decision consisted of 4 claims reading:

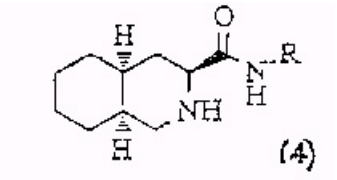
"1. A process for producing a tetrahydroisoquinoline-3(S)carboxamide derivative represented by formula (3), which comprises reacting tetrahydroisoquinoline-3(S)-carboxylic acid represented by formula (1) with phosgene, phosgene dimer or triphosgene to form N-carboxy anhydride (NCA) represented by formula (2), and then reacting this NCA (without its being isolated or purified) with tert-butylamine:



I (1) (2) (3)

wherein R represents a tert-butyl group; thereby to produce the optically active amide."

"2. A process for producing a decahydro(4aS,8aS)isoquinoline-3(S)-carboxamide derivative represented by formula 4:

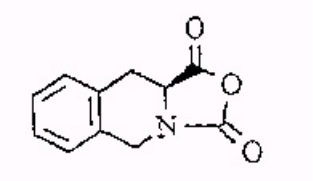


(4)

(wherein R represents a tert-butyl group), which comprises producing a tetrahydroisoquinoline-3(S)-carboxamide derivative of formula (3) by the process of claim 1, and reducing this derivative in the presence of a metal catalyst."

"3. The process of claim 2, wherein the metal catalyst is Ru."

"4. Tetrahydroisoquinoline-3(S)-carboxylic acid N-carboxy anhydride represented by formula (2)



(2)

"

The set of claims according to the second auxiliary request underlying the decision differed from the one according to the main request by the deletion of phosgene as possible reactant with the carboxylic acid in Claim 1 and by the deletion of Claim 4.

II. The Opposition Division considered that the priority in the present case was not validly claimed, that therefore document

(21) WO-A-97/30976), filed on 18 October 1996 and published on 28 August 1997 and, claiming the priority of US 08/603 744 (filing date: 20 February 1996),

represented state of the art according to Article 54(3) and (4) EPC and that all features of Claim 1 according to the then pending main request were disclosed in document (21).

Moreover, the Opposition Division found that Claim 4 of the main request was not inventive over the disclosure of *inter alia* document

(1) Chimika Chronika, New Series, 1989, 18, pages 3 to 17,

and that the processes according to Claims 1 to 3 of the second auxiliary request were not obviously derivable from the state of the art, starting from the closest prior art, represented by document

(2) US-A-5 256 783.

III. With letter dated 4 June 2002 the Opponent withdrew its opposition and its appeal against the decision of the Opposition Division.

IV. The Proprietor of the patent, further designated as the Appellant, filed with letter dated 6 March 2002, as "Main Request", Claims 1 to 4, which were identical with Claims 1 to 4 of the main request underlying the contested decision, and four auxiliary requests.

The Appellant essentially argued that Claim 1 according to the main request was entitled to the claimed priority date, since the feature of "reacting NCA (without its being isolated or purified) with the

amine" was implicitly disclosed in the Japanese application of which priority was claimed, as illustrated by the passage on page 9 of document

(30) the English translation of JP 166536/95,

citing that "NCA (2) can ordinarily be subjected to the subsequent amidation step as it is". Furthermore, the Appellant submitted that the optically active NCA claimed in Claim 4 of the main request meets the requirement of inventive step as it is an intermediate in an inventive process.

V. The Appellant requested maintenance of the patent on the basis of the main request filed with the grounds of appeal on 6 March 2002. Oral proceedings were requested if the Board did not intend to grant that request.

Reasons for the Decision

1. The appeal is admissible.

2. *Article 123(2) and (3) EPC*

Present Claim 1 differs from Claim 1 of the application as filed only by the specification that NCA is reacted with an amine **without its being isolated or purified**, by the restrictions of R to **tert-butyl** and of the amine reagents to **tert-butyl amine** and by the additional feature "**thereby to produce the optically active amide**".

Since it was stated in the application as filed that

- NCA may be used for the subsequent amidation step without being isolated or purified (page 6, lines 9 to 11);

- tert-butyl amine was the preferred amine (page 6, lines 23 and 24); and

- the invention relates to a process for producing optically active amides (page 1, lines 3 and 4)

and since processes wherein R is tert-butyl were disclosed in original Claim 4, all features of present Claim 1 were directly and unambiguously derivable from the application as filed.

Present Claim 2 is supported by original Claim 2 in combination with original Claim 4; present Claim 3 corresponds with original Claim 3; and present Claim 4 is identical with original Claim 4.

Moreover, all amendments resulted in the restriction of the scope in comparison with the granted claims.

Thus, present Claims 1 to 4 fulfil the requirements of Article 123(2) and (3) EPC, which has never been contested.

3. Novelty

As the content of document (21) is identical with the content of the document of which it claims its priority, it has never been contested that the priority in document (21) was validly claimed.

Since the priority date claimed in document (21) lies between the priority date and the filing date of the patent in suit, in determining whether document (21) is to be considered as state of the art according to Article 54(3) EPC, the question arises whether the priority has been validly claimed in the patent in suit.

3.1 Right of Priority

It was not contested that the content of document (30) corresponds with the content of JP 166536/95 and that document (30) describes a process for producing an optically active amide of formula (3) by reacting a carboxylic acid of formula (1) with phosgene, phosgene dimer or triphosgene to form NCA of formula (2) and then reacting NCA with tert-butyl amine. The only contested point in the discussion whether the priority was validly claimed was the fact that according to present Claim 1 the NCA is reacted **without its being isolated or purified** with tert-butyl amine whereas in document (30) it is only stated that NCA can be subjected to the subsequent amidation step **as it is** (see the second paragraph on page 9).

The Opposition Division was of the opinion that from the teaching "reacting NCA as it is" it could not be directly and unambiguously derived that NCA is reacted

"without its being isolated or purified". In particular, the Opposition Division referred to synthesis Example 1 of document (30), wherein after the completion of the reaction of the carboxylic acid of formula (1) with triphosgene in tetrahydrofuran (THF), THF is distilled off and the residue is dissolved in THF again before a solution of tert-butyl amine in THF is added. This illustrated, according to the Opposition Division, that NCA was effectively isolated before being used in the further amidation reaction.

However, as the skilled person to whom document (30) is addressed is necessarily a chemist with organic synthesis background, in assessing whether or not synthesis Example 1 of document (30) teaches reacting NCA without its being isolated or purified with tert-butyl amine, the question arises whether such chemist would have understood the distilling off of the THF as an isolation or purification step.

Such chemist certainly realises that hydrogen chloride (HCl) is formed in converting the carboxylic acid of formula (1) into the NCA with triphosgene and that such HCl forms a salt with tert-butyl amine used in the subsequent amidation step, thus deactivating an amount of tert-butyl amine equivalent to the amount of HCl present in the starting mixture of the amidation reaction. In order to prevent or to minimise such deactivation, a skilled chemist would thus look for methods of eliminating or minimising the amount of HCl before adding the tert-butyl amine. As distillation is a well-known tool to eliminate, at least partially, HCl and as it is also well-known that, due to its boiling point, THF may be distilled off together with HCl, the

removal of THF in synthesis Example 1 is not to be understand as a method of isolating or purifying the NCA but rather as a method of eliminating, at least partially, HCl before reacting the NCA with tert-butyl amine.

Moreover, in synthesis Example 1 of document (30) it is stated that after the solvent is distilled off, the **residue** was re-dissolved. As for a chemist with organic synthesis background "isolating" or "purifying" a chemical compound refers to the separation of a particular chemical compound or compounds from all other substances, distilling off the solvent and re-dissolving the residue does not mean isolating or purifying the NCA before the amidation reaction.

This is not contradicted by synthesis Examples 2 and 5, wherein the isolation of the NCA is described, since those examples only concern the preparation of the purified NCA and not the preparation of the optically active amide of formula (3).

In the absence of any evidence that in document (30) the statement that NCA can be subjected to the subsequent amidation step "as it is" could mean anything else as that the NCA is reacted without its being isolated or purified, the Board comes to the conclusion that all the features of Claim 1 are directly and unambiguously derivable from the priority document and, consequently, that the priority has been validly claimed in that both relate to the same subject-matter (Article 87(4) EPC).

3.2 As thus, according to Article 89 EPC, the date of priority counts as the filing date of the European patent application for the purpose of Article 54(2) and (3) EPC, document (21) does not belong to the state of the art and, consequently, is not to be considered in assessing the novelty of the claimed subject-matter.

After examination of the remaining cited prior art documents, the Board has reached the conclusion that the claimed process and the claimed NCA were not described in any of those documents. As novelty over a the cited prior art other than document (21) was never disputed, it is not necessary to give detailed reasons for this finding.

4. *Inventive step of Claim 1*

Since the Opposition Division recognised an inventive step for the claimed process as long as phosgene dimer or triphosgene is used as reactant with the carboxylic acid of formula (1), due to the principle of prohibition of reformatio in peius, it remains only to be decided whether an inventive step can be accepted for the claimed process wherein phosgene is used as such reactant.

4.1 In accordance with the "problem-solution approach" applied by the Boards of Appeal to assess inventive step on an objective basis, it is in particular necessary to establish the closest state of the art forming the starting point, to determine in the light thereof the technical problem which the invention addresses and solves, and to examine the obviousness of

the claimed solution to this problem in view of the state of the art.

4.2 The "closest state of the art" is normally a prior art document disclosing subject-matter aiming at the same objective as the claimed invention. Since Claim 1 relates to a process for producing N-tert-butyl tetrahydroisoquinoline-3(S)-carboxamide, and since document (2), cited in the patent in suit, describes a process for producing the S-enantiomer of that carboxamide, whereas document(1) is silent about whether the prepared carboxamides are obtained as racemate or in a specific enantiomeric form, not document (1) but rather document (2) can serve, as the closest prior art, as a suitable starting point for evaluating the inventive merit of the invention.

Document (2) discloses a process of producing N-tert-butyl tetrahydroisoquinoline-3(S)-carboxamide by converting N-benzyloxycarbonyl-L-phenylalanine into its tert-butylamide, cyclizing the amide with formaldehyde to benzyl 3(S)-(tert-butylcarbamoyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate and splitting off the benzyl group by hydrogenolysis (see Examples 1 and 2).

4.3 On page 4, lines 9 to 12, of the patent in suit it is stated that with the process disclosed in document (2) N-tert-butyl tetrahydroisoquinoline-3(S)-carboxamide is obtained from phenylalanine in an overall yield of 44%, whereas such overall yield with the claimed process is more than 40% higher.

Therefore, starting from the disclosure in document (2), the problem underlying the invention can be seen in providing a process enabling conversion of phenylalanine into N-tert-butyl tetrahydroisoquinoline-3(S)-carboxamide in higher yield.

4.4 The patent in suit claims to solve this problem by the method defined in Claim 1.

4.5 It has never been contested that it has been convincingly shown that by the process according to Claim 1 the problem underlying the patent in suit has effectively been solved. Considering Example 4 of the patent in suit, the Board has no reason to doubt this.

4.6 Therefore, it remains to be decided, whether in the light of the teachings of the cited documents a skilled person seeking to solve the above-mentioned problem would have arrived at the process of Claim 1 in an obvious way or not.

4.7 It was not contested that both reaction steps of present Claim 1, namely a process for preparing NCA's by reacting á-amino-acids with phosgene and the amidation of those NCA's with an amine, were known in the art. However, from none of the cited prior art documents could it be derived that with both reaction steps of present Claim 1 it would be possible to convert phenylalanine into N-tert-butyl tetrahydroisoquinoline-3(S)-carboxamide in higher yield than with the reaction steps described in document (2). Since the Opposition Division already came to this same conclusion, it is not necessary to give detailed reasons for this finding.

5. Claim 2, which comprises the process steps of Claim 1, and dependent Claim 3 derive their patentability from the same inventive concept as Claim 1.

6. *Inventive step of Claim 4*

The claimed product is an intermediate product in a two-step process for the preparation of a known end product.

The Opposition Division was of the opinion, that a skilled person would have been aware that optically active amides of formula (3) could successfully be prepared by reacting a carboxylic acid with phosgene or one of its analogues and subsequently amidating the intermediately formed NCA. Therefore, the provision of the optically active form of the intermediate of formula 8 disclosed in document (1) as a useful intermediate for the preparation of the optically active amide was not considered to be inventive.

However, according to the jurisprudence of the Boards of Appeal, an intermediate intended for the preparation of a known end product is deemed to be inventive if its preparation took place in the course of an inventive complete process (see T 22/82 OJ EPO 1982, 341, point 7 of the Reasons, and T 648/88 OJ EPO 1991, 292, point 8 of the Reasons).

In assessing inventive step of the intermediate of formula (2) the relevant question is not, whether it was obvious to prepare the optically active form of the intermediate of formula 8 disclosed in document (1).

According to the generally applied principle, as described, for example, in T 163/84 OJ EPO 301, point 5 of the Reasons, the only relevant question is whether it was obvious to a skilled person to expect an improved conversion of phenylalanine into N-tert-butyl tetrahydroisoquinoline-3(S)-carboxamide by using a process sequence wherein the claimed NCA is formed as intermediate. As the Board came to the conclusion that this could not be expected from the cited prior art (see point 4.7), also Claim 4 meets the requirement of inventive step.

7. In the light of the above findings, there is no need for the Appellant to be heard in oral proceedings nor to consider the auxiliary requests.

8. The description is not yet adapted to the allowable claims. The Board deems it appropriate to make use of its power under Art. 111(1) EPC and to remit the case for the purpose of this adaptation to the Opposition Division.

Order

For these reasons it is decided that:

1. The contested decision is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the main request filed with letter of 6 March 2002 and a description to be adapted.

The Registrar: The Chairman:

N. Maslin A. Nuss