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DECISION
of 8 August 1996

Case Number: T 0407/94 - 3.3.4

Application Number: 88110404.6

Publication Number: 0297560

IPC: C07K 5/06

Language of the proceedings: EN

Title of invention:
Imides; a process for their production and a process for the production of dipeptides using them

Patentee:
AJINOMOTO CO., INC.

Opponent:
-

Headword:
Imides/AJINOMOTO

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step - yes"

Decisions cited:
-

Catchword:
-

Case Number: T 0407/94 - 3.3.4

DECISION
of the Technical Board of Appeal 3.3.4
of 8 August 1996

Appellant:

AJINOMOTO CO., INC.
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Chuo-ku
Tokyo 104 (JP)

Representative:

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Decision under appeal: Decision of the Examining Division of the European Patent Office posted 20 December 1993 refusing European patent application No. 88 110 404.6 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: R. E. Gramaglia
S. C. Perryman

Summary of Facts and Submissions

I. European patent application No. 88 110 404.6 relating to imides, a process for their production and a process for the production of dipeptides using them, was published with number 0 297 560 with 18 claims.

II. The application was refused by the Examining Division on the grounds that the subject-matter of claims 1 to 18 did not meet the requirements of Article 56 EPC in view of documents:

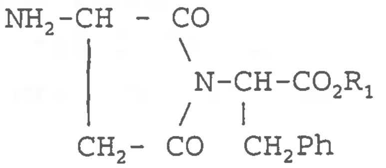
(1) WO-A-83/01619

(2) A. Darbre, "Practical Protein Chemistry-A Handbook", Wiley and Sons, pages 81-83 (1986)

(3) Römpp Chemie Lexikon, 9th Edition, Georg Thieme Verlag, Stuttgart, New York, pages 3270-3272.

III. Rejected independent claims 1, 3 and 9 were worded as follows:

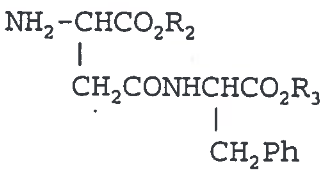
"1. An imide of the formula:



wherein R_1 is hydrogen or C_{1-4} alkyl."

"3. A process for the production of an imide of formula (1) where R_1 is hydrogen or C_{1-4} alkyl which comprises:

converting a β-aspartylphenylalanine derivative of the formula:



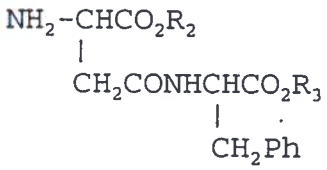
$$\begin{array}{l} NH_2\text{-}CHCO_2R_2 \\ \qquad | \\ \qquad CH_2CONHCHCO_2R_3 \\ \qquad\qquad\qquad | \\ \qquad\qquad\qquad CH_2Ph \end{array}$$

(2)

wherein R_2 is C_{1-4} alkyl and R_3 represents hydrogen or C_{1-4} alkyl, into said imide in a non-alcoholic solvent."

"9. A process for the production of an α-aspartylphenylalanine derivative which comprises:

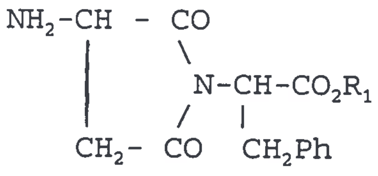
converting a β-aspartylphenylalanine derivative of the formula:



$$\begin{array}{l} NH_2\text{-}CHCO_2R_2 \\ \qquad | \\ \qquad CH_2CONHCHCO_2R_3 \\ \qquad\qquad\qquad | \\ \qquad\qquad\qquad CH_2Ph \end{array}$$

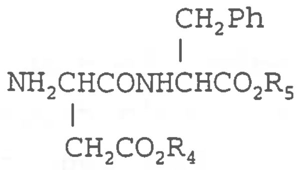
(2)

wherein R_2 is C_{1-4} alkyl and R_3 is hydrogen or C_{1-4} alkyl in a non-alcoholic solvent into an imide intermediate of the formula:



(1)

wherein R_1 is hydrogen or C_{1-4} alkyl; and thereafter converting said imide into an α-aspartylphenylalanine derivative of the following formula in the presence of a base:



$$NH_2\underset{\substack{|\\ CH_2CO_2R_4}}{C}HCONH\overset{\substack{CH_2Ph\\ |}}{C}HCO_2R_5 \qquad (3)$$

wherein R_4 and R_5 are each hydrogen or C_{1-4} alkyl."

IV. The Examining Division came to the conclusion that the skilled person would have learned from document (1) the possibility of converting a β-aspartylphenylalanine derivative into the desired α-aspartylphenylalanine derivative by first preparing a cyclic aspartimide from the β-aspartylphenylalanine derivative (first step) and then subjecting this cyclic intermediate product to hydrolysis to obtain the corresponding α-aspartylphenylalanine derivative (second step). Consequently the claimed subject-matter lacked inventive step and did not fulfil the requirement of Article 56 EPC.

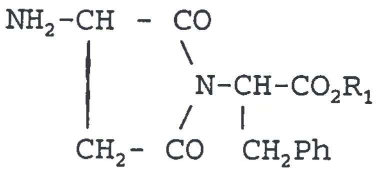
V. An Appeal was filed on the basis of a main request and three auxiliary requests. The written grounds of appeal referred to a new document

(5) US-A-4,673,744.

VI. In a communication accompanying the summons to oral proceedings the Board expressed doubts about the patentability of claim 14 and its dependent claims of the main and first auxiliary requests and claim 12 and its dependent claims of the second and third auxiliary requests. These claims were directed to the second step by itself of the two stage process of claim 9 (main and first auxiliary requests) or of claim 8 (second and third auxiliary requests). The Appellant filed new sets of claims, from which the dubious claims to the second step by itself were omitted.

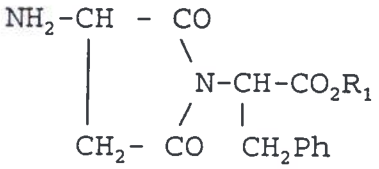
VII. At the oral proceedings held on 8 August 1996 the Appellant submitted a main request and a first auxiliary request. Independent claims 1, 3 and 7 of the main request were worded as follows:

"1. An imide of the formula:



wherein R_1 is hydrogen or C_{1-4} alkyl.

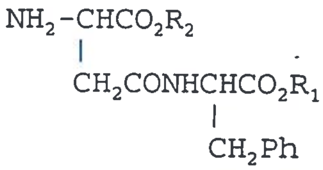
"3. A process for the production of an imide of the formula:



(1)

where R_1 is hydrogen or C_{1-4} alkyl, which comprises:

converting a β-aspartylphenylalanine derivative of the formula:

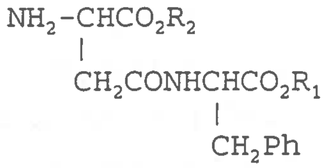


$NH_2\text{-}CH(CO_2R_2)CH_2CONHCH(CH_2Ph)CO_2R_1$ (2)

wherein R_2 is C_{1-4} alkyl and R_1 represents hydrogen or C_{1-4} alkyl, into said imide in a solvent selected from aromatic hydrocarbons, halogenated hydrocarbons, hydrocarbons such as pentane, hexane, ketones, fatty acid esters, fatty acids, water, and mixtures thereof, and in the presence of an acid.

"7. A process for the production of an α-aspartylphenylalanine derivative which comprises:

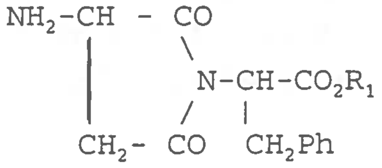
converting a β-aspartylphenylalanine derivative of the formula:



$$\begin{array}{l} NH_2\text{-}CHCO_2R_2 \\ \quad\;\; | \\ \quad\;\; CH_2CONHCHCO_2R_1 \\ \qquad\qquad\quad | \\ \qquad\qquad\quad CH_2Ph \end{array}$$

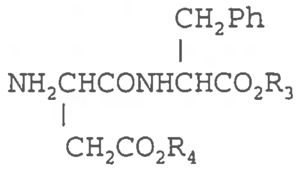
(2)

wherein R_2 is C_{1-4} alkyl and R_1 is hydrogen or C_{1-4} alkyl in a solvent selected from aromatic hydrocarbons, halogenated hydrocarbons, hydrocarbons such as pentane, hexane, ketones, fatty acid esters, fatty acids, water, and mixtures thereof, and in the presence of an acid, into an imide intermediate of the formula:



(1)

where R_1 is hydrogen or C_{1-4} alkyl; and thereafter converting said imide into an α-aspartylphenylalanine derivative of the following formula in the presence of a base:



$$\begin{array}{l} \qquad\qquad\quad CH_2Ph \\ \qquad\qquad\quad | \\ NH_2CHCONHCHCO_2R_3 \\ \quad | \\ \quad CH_2CO_2R_4 \end{array}$$

(3)

wherein R_3 and R_4 are each hydrogen or C_{1-4} alkyl."

VIII. The Appellant argued essentially as follows:

- There were essential differences between the first step of the claimed process and the first step reaction disclosed by document (1). In the present invention cyclization occurred by removal of an alcohol R_2OH in a non alcoholic solvent without taking measures in order to shift the equilibrium of the reaction to the side of the aspartimide intermediate. In the first step of the reaction disclosed by document (1), cyclization was effected by a strong dehydrating agent (acetic anhydride) between the free carboxyl group and the

-NH- of the amidic linkage. Since document (1) taught the skilled person that a dehydrating agent was required for cyclization to occur, it was not obvious how to obtain the aspartimide intermediate with a different process involving no dehydrating agent and in a solvent system having no dehydrating activity.

- It was also surprising that, despite no measures being taken for shifting the equilibrium toward the final product, the reaction yields were almost 100% with the formation of no or very little undesired diketopiperazine (DKP) side product.

- The skilled person would have been dissuaded from using as the starting material an N-unprotected β-aspartylphenylalanine derivative as in the application in suit because document (5) showed that the cyclization of an N-unprotected β-aspartylphenylalanine derivative yielded the undesired DKP as by-product.

IX. 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 filed as main request or first auxiliary request respectively at the oral proceedings on 8 August 1996.

Reasons for the Decision

Main Request
Article 123(2) EPC

1. Claims 1, 2, 5, 6, 9 and 10 of the main request correspond to original claims 1, 2, 7, 8, 12 and 13, respectively. Claims 4 and 8 are restricted versions of original claims 5 and 10 in which the option that R_2 is hydrogen has been deleted. Claims 3 and 7 comprise the wording "in the presence of an acid" based on that used in original claim 4 and on page 8, lines 19 to 21 of the original description, and also the wording "selected from aromatic hydrocarbons, halogenated hydrocarbons, hydrocarbons such as pentane, hexane, ketones, fatty acid esters, fatty acids, water, and mixtures thereof" based on the passage on page 7, lines 24-26 of the original description. These claims thus contain only limitations having a basis in the originally filed text, and thus fulfil the requirements of Article 123(2) EPC.

Novelty (Article 54 EPC)

2. In relation to the process claims 3 to 10, the Board sees no prior art that would require it to reconsider the Examining Division's finding that these are novel.

In connection with the imide intermediates of claims 1 and 2, the Board raised the question that they could possibly lack novelty over document (1) (see page 4, lines 19 to 25) if during the reaction disclosed therein of N-(1-carbomethoxy-2-phenylethyl)-2-N-formylamino-succinimide (i.e., the N-formylated form of the imide intermediate of claim 1) with hydrochloric acid at a pH of 2.5 to 3.5 for one hour, the deformylation reaction took place before the imidic ring opening. Yet the submission by the Appellant that this does not actually occur, is convincing. In addition, it appears neither from document (1), wherein reference is made (*loc. cit.*) to the "**simultaneous** isomerisation of the β-isomer of N-formyl aspartame and the deformylation thereof" (emphasis added), nor from any other evidence presently available to the Board. In the absence of such evidence the Board can accept the assurance made on behalf of the appellants that this imide intermediate is not formed in the reaction according to document (1), and can accept that claims 1 and 2 are directed to something novel.

The Board thus concludes that on the evidence no objections to the novelty of the claims of the main request exist.

Inventive step (Article 56 EPC)
Closest prior art

3. In relation to the intermediate compound of independent claim 1 and the processes of independent claims 3 and 7, in each case document (1) is regarded by the Appellant as the closest prior art and the Board agrees. It relates to the conversion of a β-aspartylphenylalanine derivative into an α-aspartylphenylalanine derivative by cyclization under the action of acetic anhydride, which conversion involves the intermediate compound N-(1-carbomethoxy-2-phenylethyl)-2-N-formylamino-succin imide, i.e., the N-formylated form of the imide intermediate of claim 1 of the patent in suit.

Problem to be solved and its solution

4. In the light of document (1), the technical problem to be solved can be seen as the provision of a new way of converting a β-aspartylphenylalanine derivative into an α-aspartylphenylalanine derivative with very high yields and in the absence of DKP as undesired by-product. This problem is solved by the process of claim 7, and essential contributions to this solution are made by providing the imide intermediate of claim 1 and the process of claim 3 for making this imide intermediate. In view of the Examples, the Board is satisfied that this problem has been solved.

The process of claim 3

5. This process is the cyclization of a β-aspartylphenylalanine derivative in which at least the α-carboxyl group of the β-aspartyl has been esterified, to an aspartimidylphenylalanine derivative.

6. The Board first observes that the claimed process differs in substance from the one disclosed by document (1). The latter process is a cyclization by condensation, namely by substraction of water (H_2O) by a strong dehydrating agent (acetic anhydride), which elimination takes place between the free carboxyl group and the -NH- of the amidic linkage. In the process of claim 3 of the patent application, however, ring closure occurs by nucleophilic attack by the imide to the ester carbonyl and the subsequent elimination of an alcohol (R_2OH). This is rendered possible by the presence of the ester group in the β-aspartyl moiety. This feature is to be found in claim 3 and in all the Examples of the patent in suit. In conclusion it is thus a cyclization by elimination of an alcohol, while the process of document (1) is a cyclization by dehydration. The two processes are neither comparable

nor interchangeable. A fundamental feature in the process of document (1) is that the α-carboxyl group of the aspartyl moiety of the starting compound should be free, while its amino group should be protected, for avoiding autocondensation, since removal of water can also occur between a free amino group and a free carboxyl group. In the claimed process, no dehydrating agent is used, so that there is no need to protect the amino group of the starting compound. However, a leaving group should be present on the α-carboxyl group of the aspartyl moiety of this molecule. In view of this, the Appellant's line of argument that the claimed process hinges on a different reaction than the process of document (1) to which different reaction document (1) provides no pointer, is convincing. The Board thus sees no reason why a skilled person should even contemplate departing from the process of document (1) in the direction of the claimed process.

7. Secondly, the process of document (1) is carried out under conditions that shift the reaction equilibrium to the right, namely towards the ring closure. This is shown by the 10 kg of the dehydrating agent acetic anhydride added to only 2 kg of starting product (see page 4, line 15). Acetic anhydride is used in great excess over the starting product and it is thus not surprising that all the starting product undergoes ring closure. Therefore, even assuming that the skilled person would have tried to modify the process of document (1), he would not have opted, in the Board's view, for a process such as the claimed one, devoid of any measure for shifting the reaction equilibrium to the side of the imide. That the claimed process turns out to proceed with almost quantitative yields towards the ring closure despite no such above mentioned measures are taken, is indeed found by the Board to be unexpected and not something that could reasonably have been predicted by the skilled person.

8. As to document (2), it is true, as stated by the Examining Division, that it mentions the α,β-transpeptidation in acid solution of peptides comprising an α-aspartyl moiety (see page 82, Scheme 2.14). However, the Board observes that Scheme 2.14 relates to the conversion $\alpha\rightarrow\beta$ rather than $\beta\rightarrow\alpha$, as in the process of claim 3. Scheme 2.14 cannot be seen as an equilibrium reaction since the author makes use of single arrows ($\rightarrow$). Yet double arrows ($\rightleftarrows$) are used for the equilibrium reaction of Scheme 2.13 on the same page. Therefore Scheme 2.14 relates to an irreversible reaction occurring in the direction $\alpha\rightarrow\beta$ opposite to the claimed reaction. The Scheme thus at best leaves the skilled person uncertain as to whether the reaction $\beta\rightarrow\alpha$ also occurs in acid solution.

It is, therefore, the Board's view that document (2) does not render the process of claim 3 obvious.

9. The Examining Division held, in order to deny the inventive step of the process of claim 3, that the skilled person would expect that no DKP would form under the reaction conditions of claim 3. However this is contradicted by newly filed document (5) showing the contrary. In fact, there is a high risk of attack of the $-CO_2R_2$ (claim 3) or $-CO_2R'$(document (5), see the scheme of column 1) by the free $-NH_2$ group and this is exactly what happens in an alcoholic solution as shown in the Examples of document (5). This phenomenon is discussed on page 2, lines 4 to 21 of the present application. The selection according to claim 3 of conditions (solvent) that render possible the quasi total conversion to the desired compound without DKP as a by-product is thus not suggested by any prior art, be it alone or in combination, and it is thus found to involve an inventive step.

The process of claim 7

10. The two step process of claim 7 also fulfils the requirements of Article 56 EPC since it comprises as a first step the process of claim 3, held by the Board to involve an inventive step (see points 5 to 9 *supra*).

The cyclic imide of claim 1

11. The cyclic imide of claim 1 is novel (see point 2 supra). The process of making this intermediate according to claim 3 has already been considered inventive. The only use suggested in the patent in suit is as an intermediate in the process of claim 7. The intermediate compound N-(1-carbomethoxy-2-phenylethyl) -2-N-formylaminosuccinimide of document (1) represents the closest prior art in respect of the imide of claim 1. This differs from the imide intermediate of claim 1 by the presence of a formyl residue linked to the amino group. The remaining question on inventive step to be decided is thus whether document (1) makes the manufacture of the imide of claim 1 obvious, by some process other than that of claim 3, for use in the process of document (1) instead of the different intermediate there suggested. While structurally close to the imide of document (1) it appears to the Board that the skilled person would not contemplate using the imide of claim 1 in the process of document (1), because, if he thought about it at all, he would expect the process of manufacturing it to yield far more unwanted by-product than the imide suggested by document (1) because of the absence of the N-formyl protecting group. In the Board's opinion, N-formyl group plays a fundamental role in the process disclosed by document (1). In fact, in the process of document (1), ring closure takes place by the action of an excess of the dehydrating agent acetic anhydride which subtracts water between the free carboxyl group

and the -NH- of the amidic linkage. Should a free (and thus unprotected) amino group also be present in the starting product, water substraction would also occur between the free carboxyl group and said free amino group, thus yielding to intermolecular peptidic bond formation (polymerization). So the skilled person would not consider the imide of claim 1 as a possible substitute, and inventive step must be acknowledged for claim 1.

Claims 2, 4 to 6 and 8 to 10

12. These claims are dependent on claims 1, 3 and 7 respectively, and so the finding of an inventive step for these claims also makes these dependent claims allowable under Article 56 EPC.

13. Since the claims of the main request are found to fulfil the requirements of the EPC, there is no need to decide on the claims of the auxiliary request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The matter is remitted to the First Instance with the order to grant a patent on the basis of the set of claims filed as main request on 8 August 1996, and a description to be adapted.

The Registrar:	The Chairperson:
A. Townend	U. Kinkeldey