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D E C I S I O N
of 2 August 2005

Case Number: T 0573/03 - 3.3.1

Application Number: 99941923.7

Publication Number: 1098876

IPC: C07D 205/08

Language of the proceedings: EN

Title of invention:
Cyclisation Process

Applicant:
AstraZeneca AB

Opponent:
-

Headword:
Azetidine-2-carboxylic acid/ASTRAZENECA

Relevant legal provisions:
EPC Art. 54, 56, 84, 123(2), 111(1)
EPC R. 29(1)

Keyword:
"Main request, first to third auxiliary request: requirements of Article 84 EPC and Rule 29(1) EPC not met"
"Process claim containing only the result to be achieved - absence of technical features"
"Fourth auxiliary request: inventive step (yes) - non obvious solution"

Decisions cited:
G 0002/88

Catchword:
-

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Case Number: T 0573/03 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 2 August 2005

Appellant: AstraZeneca AB
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Representative: McNeeney, Stephen, PhD
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 13 December 2002 refusing European application No. 99941923.7 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: P. P. Bracke
Members: R. Menapace
P. Ranguis

Summary of Facts and Submissions

I. This appeal lies from the decision of the Examining Division to refuse the European application No. 99 941 923.7 (publication No. 1 098 876) on the ground that the claims according to the then pending request did not comply with the requirements of Articles 84 and 56 EPC.

II. The request refused by the Examining Division was the set of ten claims as originally filed. Independent Claim 1 and dependent Claims 6, 8 and 9 read as follows:

"1. A process for the cyclisation of 4-amino-2-halobutyric acid to azetidine-2-carboxylic acid wherein more than 20 g of 4-amino-2-halobutyric acid is cyclised per litre of reaction mixture."

"6. A process as claimed in any of claims 1 to 5, characterized in that the 4-amino-2-halobutyric acid is added as its hydrohalide salt to hot aqueous base."

"8. A process as claimed in claim 6 or claim 7, characterised in that the base is at a temperature of more than 80°C."

"9. A process as claimed in any one of claims 6 to 8, characterised in that haloamino acid hydrochloride salt, dissolved in water, is added dropwise to a solution of base".

III. In its decision, the Examining Division held that Claim 1 did not contain the features essential to

define the invention and, as a result, did not meet the requirements of Article 84 and Rule 29(1) and (3) EPC.

Since Claim 1 did not contain any technical features, the additional reasons related to the lack of inventive step were based on particular embodiments set out in Claims 6, 8 and 9 (see point II above).

The Examining Division held in that context that, starting from document

(1) Bull. Soc. Chim. France, 1968, No. 10, 4079-4081,

as the closest state of the art, the technical problem to be solved was to be seen in the provision of an improved process in terms of yield and concentration for the cyclisation of 4-amino-2-halobutyric acid to azetidine-2-carboxylic acid. The features of Claims 6, 8 and 9 represented an optimization of the process which was within the ambit of the person skilled in the art and lacked inventive step.

IV. Oral proceedings before the Board took place on 2 August 2005. The requests on which the present decision is based are the following:

As "New main request", a set of eight claims submitted at the oral proceedings before the Board, Claim 1, the sole independent claim reading as follows:

"1. A process for the cyclisation of 4-amino-2-halobutyric acid to azetidine-2-carboxylic acid wherein more than 50 g of 4-amino-2-halobutyric acid is cyclised per litre of reaction mixture."

As first, second and third auxiliary requests, sets of claims submitted with the letter received on 29 June 2005 wherein Claim 1 respectively read as follows:

"1. A process for the cyclisation of 4-amino-2-halobutyric acid to azetidine-2-carboxylic acid wherein more than 100 g of 4-amino-2-halobutyric acid is cyclised per litre of reaction mixture."

"1. A process for the cyclisation of 4-amino-2-halobutyric acid to azetidine-2-carboxylic acid wherein the final concentration of azetidine-2-carboxylic acid in the reaction mixture corresponds to more than 20 g of 4-amino-2-halobutyric acid having been cyclised per litre of reaction mixture."

"1. A process for the cyclisation of 4-amino-2-halobutyric acid to azetidine-2-carboxylic acid wherein the final concentration of azetidine-2-carboxylic acid in the reaction mixture corresponds to more than 100 g of 4-amino-2-halobutyric acid having been cyclised per litre of reaction mixture."

As fourth auxiliary request, a set of eight claims submitted at the oral proceedings before the Board, Claim 1, the sole independent claim, reading as follows:

"1. A process for the cyclisation of 4-amino-2-halobutyric acid to azetidine-2-carboxylic acid wherein more than 20 g of 4-amino-2-halobutyric acid is cyclised per litre of reaction mixture, characterized in that the 4-amino-2-halobutyric acid is added as its

hydrohalide salt to aqueous base, which base is at a temperature of more than 80°C."

The Appellant also filed a fifth, a sixth and a seventh auxiliary request.

V. The Appellant's arguments in the course of the written proceedings and during the oral proceedings before the Board may be summarized as follows:

The claimed subject-matter of Claim 1 of the main request is defined in terms of a functional feature achieving a technical result. This functional language is not objectionable according to the EPO guidelines for examination and the numerous examples in the Case Law of the Boards of Appeal if:

- the invention can either only be defined in such terms, or cannot otherwise be defined more precisely without unduly restricting the scope of the claims; and

- the result is one which can be directly and positively verified by tests or procedures adequately specified in the description or known to the person skilled in the art and which do not require undue experimentation.

In the present case, the truly surprising result that had been achieved by way of the process specifically described did not necessarily limit it to the specific reagents and reaction conditions disclosed in the examples. Such limitation would be unfair and would be unduly restricting of the scope of the claims. There

was no reason to suspect that different reagent and reaction conditions to those specified would not work.

In terms of the means for testing the result to be achieved, any skilled person could easily characterise whether they had more than a certain amount per litre of starting material in the mixture prior to carrying out the reaction as well as whether more than such amount per litre of this starting material is cyclised to azetidine-2-carboxylic acid. There was in that context no problem for the public to determine the scope of protection.

The same argumentation applied to the subject-matter of Claim 1 of the first to third auxiliary requests.

Regarding the inventive step of Claim 1 of the fourth auxiliary request, the technical problem to be solved in view of the closest state of the art, for instance document

(8) Agr. Biol. Chem., 37, pp 649-652, 1973,

was to be seen in the provision of a process of cyclisation of 4-amino-2-halobutyric acid to azetidine-2-carboxylic acid at high concentrations rendering said process viable on an industrial scale.

Documents (1), (2), i.e. FEBS letters, Vol. 308, No. 3, August 1992 cited by the Examining Division and documents

(3) Nature, Lond., **1955**, Vol. 176, pp. 347-348,
(4) Tetrahedron, **1992**, Vol. 48, No. 35, pp. 7165-7172,

(5) Biochem J., **1956**, Vol. 64, pp. 323-332,
(6) J. Heterocyclic Chem., **1969**, 6, pp. 435-437 and
(7) J. Biol. Chem., **1952**, 198, pp. 587-597

submitted by the Appellant showed in that context that there had been many attempts to develop an efficient large-scale synthesis of this compound, hitherto without any success.

It was surprisingly discovered that the cyclisation reaction might be conducted cleanly and efficiently at higher concentrations than used in document (8) by performing the claimed process. The claimed invention was, therefore, inventive in view of the prior art.

VI. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the following requests:

- Claims 1-8 submitted as "New main request" during the oral proceedings before the Board

- First to third and sixth and seventh auxiliary request filed with letter of 29 June 2005

- Claims 1-8 or 1-5 submitted as fourth, respectively fifth auxiliary request during the oral proceedings before the Board.

VII. At the end of the oral proceedings the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. Article 84 EPC - Rule 29(1) EPC

2.1 By a communication attached to the summons to oral proceedings, the Board taking up the objection of the first instance had informed the Appellant that the question arose whether or not Claim 1 as refused (see point II above) met the requirements of Article 84 and Rule 29(1) EPC. Claim 1 of the present main request differs only therefrom in that the figure "20 g" was replaced by "50 g" (see point IV above).

However, this amendment does not change the issue. Indeed, the sole wording qualifying the claimed subject-matter is the result of a process of cyclisation, i.e. " wherein more than 50 g of 4-amino-2-halobutyric acid is cyclised per litre of reaction mixture", the cyclisation as such of 4-amino-2-halobutyric acids to form azetidine-2-carboxylic acid being well-known in the art (see page 1, fourth paragraph of the application as originally filed).

2.2 Article 84 EPC provides that the claims shall define the matter for which the protection is sought. Rule 29(1) EPC states furthermore that the claims shall define the matter for which protection is sought in terms of the technical features of the invention. The present Claim 1 is a process of producing a compound and relates therefore to a physical activity. The

technical features of a claim to an activity are the physical steps which define such activity (see G 2/88, OJ EPO 1990, 93, point 2.5). It derives therefrom that at least one physical step must be present to define a process claim. The final result of a process is not a physical step but the consequence of this step and is therefore not to be considered as a technical feature of a process claim.

2.3 Therefore, the wording "wherein more than 50 g of 4-amino-2-halobutyric acid is cyclised per litre of reaction mixture" is not a technical feature in the sense of Rule 29(1) EPC. Since the present Claim 1 does not contain anything more than this wording, it does not contain any technical feature and does not define the matter for which the protection is sought contrary to the requirement of Article 84 EPC.

2.4 It follows that the question debated at length by the Appellant regarding the allowability of a functional feature misses the point. The Board does not deny that a physical step may be defined in terms of a functional technical feature. However, a technical feature, here a physical step, must be present. It is not so in the present case.

2.5 In conclusion, the subject-matter of Claim 1 of the main request contravenes the requirements of Article 84 EPC and Rule 29(1) EPC. Since the Board can only decide on a request as a whole, this request is rejected.

First, second and third auxiliary requests

3. Article 84 EPC - Rule 29(1) EPC

3.1 Claim 1 of the first auxiliary request differs from Claim 1 of the main request in that the figure "20 g" has been replaced by "100 g". That amendment does not change the issue raised by Claim 1 of the main request and for this reason the first auxiliary request is also rejected.

3.2 Claim 1 of the second and third auxiliary requests differs from Claim 1 of the main respectively first auxiliary request in that the wording "the final concentration of azetidine-2-carboxylic acid in the reaction mixture corresponds to" was inserted. This does not change the fact that Claim 1 thus amended contains nothing else than a final result. The second and third auxiliary requests are, therefore, rejected for the same reasons which have led the Board to reject the main request.

Fourth auxiliary request

4. Article 123(2) EPC

4.1 Compared to Claim 1 as originally filed, Claim 1 of the present request was amended to add that:
"the 4-amino-2-halobutyric acid is added as its hydrohalide salt to aqueous base, which base is at a temperature of more than 80°C."

Such an amendment finds support in the application as originally filed (see Claims 6 and 8).

4.2 The subject-matter of Claims 2 to 8 of the present request corresponds to the subject-matter of Claims 2 to 5, 7, 9 and 10 as originally filed respectively with the proper renumbering.

4.3 There is, therefore, no objection under Article 123(2) EPC.

5. *Article 84 EPC - Rule 29(1) EPC*

5.1 Claim 1 is defined by a physical step, i.e. "the 4-amino-2-halobutyric acid is added as its hydrohalide salt to aqueous base, which base is at a temperature of more than 80°C." and thus does not give rise to any objection under Article 84 EPC and Rule 29(1) EPC.

6. *Article 54(1)(2) EPC*

6.1 Since none of the prior art cited discloses the cyclisation of 4-amino-2-halobutyric acid to azetidine-2-carboxylic acid through the addition of the 4-amino-2-halobutyric acid as its hydrohalide salt, the subject-matter of Claim 1 meets the requirements of Article 54(1)(2) EPC.

6.2 That finding applies to dependent Claims 2 to 8.

7. *Article 56 EPC*

7.1 The present invention as reflected by Claim 1 of this request relates basically to a process for the cyclisation of 4-amino-2-halobutyric acid to azetidine-2-carboxylic acid under basic conditions according to

the method of Fowden, the author who for the first time devised a process for preparing azetidine-2-carboxylic acid, by cyclisation of 4-amino-2-bromobutyric acid.

7.2 In accordance with the "problem-solution" approach consistently applied by the Boards of Appeal, it is necessary, as a first step, to establish the closest state of the art which is normally a prior art document disclosing subject-matter aiming at the same objective as the claimed invention and having the most relevant technical features in common.

7.2.1 Since the objective of the claimed invention is to provide a process for preparing azetidine-2-carboxylic acid by cyclisation of 4-amino-2-halobutyric acid, the closest state of the art is to be sought among the documents aiming at this objective.

7.2.2 Document (8) was cited and discussed by the Appellant in the examining-appeal proceedings and in a declaration signed by Doctor J. Alvhäll submitted before the US-PTO relating to the corresponding US application and introduced by the Appellant in the present appeal procedure with fax of 29 June 2005.

Document (8) discloses a process for preparing azetidine-2-carboxylic acid by performing the following steps:

3-Bromo-2-methoxy-1-pyrroline (5 g) was refluxed in 3N HCl solution (70 ml). Water and hydrogen chloride was removed and the residue dissolved in 50 ml of water. Although not mentioned explicitly, that residue is without doubt made solely or substantially of 4-amino-

2-bromobutyric acid. The residue in solution was added dropwise to the refluxing solution of $Ba(OH)_2$-$8H_2O$ (14.7 g in 500 ml of water). After purification, azetidine-2-carboxylic acid was obtained. Yield 1.50 g (53%).

7.2.3 Document (1) also relates to the preparation of azetidine-2-carboxylic acid by cyclisation of 4-amino-2-bromobutyric acid under basic conditions. It aims, therefore, at the same objective as the claimed subject-matter. However, it has fewer technical features in common with the claimed process than document (8) given that the soda is added as a solid pellet and the mixture is heated thereafter.

7.2.4 Documents (3) and (5) also relate to the Fowden method. Although those documents disclose substantially the same reaction as that of document (8), the reaction is conducted on a smaller scale (in the order of 20 ml). Since the present application seeks to propose a process to be used on an industrial scale, the Board finds it more realistic to select document (8) as the closest prior art since the amounts of reactants involved therein are of the order of 500 ml.

Therefore, in the Board's judgment, document (8) is the closest state of the art.

7.3 In view of this prior art, the technical problem to be solved is to be determined.

7.3.1 The Appellant argued that the process according to document (8) required using high dilutions (low concentrations) and that the advantages of the claimed

process over the process described in that document were that the cyclisation reaction could be conducted at higher concentrations.

7.3.2 The Board observes that in document (8) the concentration of 4-amino-1-bromobutyric acid obtained by hydrolysis of 3-bromo-2-methoxy-1-pyrroline is at most 9.2 g per litre in the reaction mixture, provided that the conversion is complete (see page 650, right-hand column, bottom paragraph). By contrast, the concentration of 4-amino-2-chlorobutyric acid according to the example of the application as originally filed is of the order of 105 g per litre of reaction mixture.

7.3.3 The Board can, therefore, accept the formulation of the technical problem to be solved proposed in the application as originally filed and submitted in the appeal proceedings, in particular, in the declaration of Doctor J. Alvhäll, namely to provide a process to achieve the cyclisation of 4-amino-2-halobutyric acid for preparing azetidine-2-carboxylic at concentrations higher than that used in document (8) and high enough to be of practical utility on an industrial scale (see page 2, third paragraph of the application as originally filed).

The present application proposes to solve this problem by the claimed process, which essentially differs from the one described in document (8) in that a **hydrohalide** salt of 4-amino-2-halobutyric acid is used as starting product instead of 4-amino-2-halobutyric acid.

7.4 In view of the example described and the general description, the Board has no reason to doubt that this improved result can be obtained within the whole claimed area.

7.5 It remains to be decided whether or not the proposed claimed solution was obvious in view of the cited prior art. In particular, the question arises whether or not the person skilled in the art would have been led to replace the 4-amino-2-halobutyric acid by the hydohalide salt thereof to solve the above technical problem.

7.5.1 Apart from document (8), three other documents, i.e. documents (3), (5) and (1) disclose a method of preparing azetidine-2-carboxylic acid by cyclisation of 4-amino-2-halobutyric acid under basic conditions.

Although Fowden briefly mentioned the cyclisation of 4-amino-2-bromobutyric acid (see document (3), page 347, right-hand column, bottom paragraph), the first description of that cyclisation was given some months later by the same author in document (5). 4-amino-2-bromobutyric acid was dissolved in 10 ml of water and 10 ml of hot N-$Ba(OH)_2$ was added (see page 330, bridging paragraph, left- and right-hand columns). From the amount of 4-aminobutyric acid involved, it turns out that at most 17.67 g of 4-amino-2-bromobutyric acid is used per litre of reaction mixture. Those documents do not give any hint to the person skilled in the art to use higher concentrations, let alone to use as starting product a hydro halide salt.

Nor can document (1) be of any assistance in that respect, given that the concentration of 4-amino-2-bromobutyric involved is also low (50 g per litre or less) and that, in addition, soda is added in pellet form.

In view of the above, none of the four documents, i.e. (8), (3), (5) and (1), gives any hint to the person skilled in the art that by using the hydrohalide salt form of 4-amino-2-bromobutyric acid the cyclisation may be performed at higher concentrations.

7.5.2 The same is true as far as document (2) is concerned. Although it is not clear, in the Board's judgment, whether the starting product is carboxylic acid bromide or carboxylic acid, since the reaction conditions appear similar to those disclosed in document (5), the cyclisation is performed, in any case, at low concentration (less than 13 g per litre or so).

7.5.3 Document (4) supports the finding that the claimed process was not merely a matter of optimization within the ambit of the skilled person but involved an inventive step (see point 7.5.1 above).

Indeed, document (4) points out that the ring closure to azetidines is a rather unfavourable process, due to strain and entropic factors (see page 7166, third paragraph). This document leads the person skilled in the art to assume that he will encounter some difficulties in performing such a reaction at higher concentration as it is well known that, if an intramolecular cyclisation is unfavourable, intermolecular side reactions become a problem unless

high dilutions are used (see, for example, Introduction to Organic Chemistry, second edition, 1981, A. Streitwieser and C.H. Heathcock, pages 179-180). Although not establishing a prejudice against the claimed solution in the sense of the Case Law of the Boards of appeal, that document nevertheless teaches away from the proposed solution.

7.5.4 Even more, document (6) teaches simply that the Fowden method as reported in document (5) is tedious and that this method is not readily applicable to the production of large quantities of azetidine-2-carboxylic acid (see page 435, left-hand column, second paragraph). In view of that, the person skilled in the art would not have been encouraged to pursue a solution in the direction offered by the Fowden method to solve the above technical problem.

7.5.5 Finally, document (7) does not relate to the production of azetidine-2-carboxylic acid.

7.6 It is, therefore, the Board's conclusion that the prior art cited, taken as a whole, would not have led the person skilled in the art to solve the technical problem defined above by implementing a process involving an hydrohalide salt of 4-amino-2-halobutyric acid according to the claimed solution. For this reason Claim 1 of this request meets the requirement of Article 56 EPC.

This finding applies to the dependent Claims 2 to 8 which relate to specific embodiments of Claim 1.

Fifth, sixth, seventh auxiliary requests

8. In view of the above, there is no need to consider these requests.

9. *Remittal to the first instance - Article 111(1) EPC*

Although the Board has come to the conclusion that the fourth auxiliary request was to be allowed, it was noted that the description has still to be brought into conformity with the claims of the present fourth auxiliary request. Therefore, having regard to the fact that the function of the Boards of Appeal is primarily to give a judicial decision upon the correctness of the earlier decision taken by the first instance, the Board exercises its discretion under Article 111(1) EPC to remit the case to the first instance in order for the description to be adapted to the allowable claimed subject-matter according to the fourth auxiliary request.

In particular, the Examining Division should make sure that a reference to document (8) as the closest state of the art is inserted in the description to be adapted.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to grant a patent on the basis of Claims 1-8 submitted as fourth auxiliary request during the oral proceedings before the Board, description yet to be adapted.

The Registrar: The Chairman:

N. Maslin P. P. Bracke