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D E C I S I O N
of 21 February 2001

Case Number: T 0164/97 - 3.3.1

Application Number: 90313782.6

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IPC: C07C 51/10

Language of the proceedings: EN

Title of invention:

Process for preparing ibuprofen and its alkyl esters

Patentee:

ALBEMARLE CORPORATION

Opponent:

Hoechst Celanese Corporation

Headword:

-

Relevant legal provisions:

EPC Art. 54(1)(2), 56, 123(2)(3)

Keyword:

"Main request - support in the application as filed (yes) -
novelty (yes)"

"Inventive step (yes) - non obvious alternative"

Decisions cited:

T 0002/81, T 0198/84, T 0666/89

Catchword:

-



Case Number: T 0164/97 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 21 February 2001

Appellant: ALBEMARLE CORPORATION
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 13 December 1996
revoking European patent No. 0 434 343 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: P. P. Bracke
Members: P. F. Ranguis
S. C. Perryman

Summary of Facts and Submissions

- I. The Appellant (Proprietor of the patent) lodged an appeal against the decision of the Opposition Division posted on 13 December 1996 revoking under Article 102(1) EPC the European patent No. 0 434 343 (European patent application No. 90 313 782.6).
- II. The decision was based on a set of claims consisting of Claims 1 to 9 filed on 24 January 1996 and Claim 10 as granted, the only independent Claim 1 reading as follows:
- "A process for preparing ibuprofen or an ester thereof which comprises carbonylating a 1-halo-1-(4-isobutylphenyl)ethane with carbon monoxide in a neutral or acidic medium containing at least 1 mol of water or a C₁ to C₆ linear or branched aliphatic alcohol per mol of 1-halo-1-(4-isobutylphenyl)ethane at a temperature between 10°C and 200°C and a carbon monoxide pressure of at least 101 kPa (one atmosphere) in the presence of (a) a palladium compound in which the palladium compound has a valence of 0 to 2 and characterised by the presence of (b) at least one trihydrocarbylphosphine ligand which is employed in an amount such that 8 to 20 moles of ligand are present per mole of palladium."
- III. The following documents were considered *inter alia* in the contested decision:

- (1) EP-A-0 338 852.
- (2) EP-A-0 284 310,

(7) EP-A-0 222 460.

(10) Tests submitted by the Appellant with letter of 5 November 1996 in order to illustrate the significance of the P:Pd mole ratio.

IV. The Opposition Division acknowledged novelty of the then pending request in view of document (1) as there was in that document no clear and unambiguous teaching that would have led the person skilled in the art to seriously contemplate using P:Pd mole ratios of 8 or higher.

The Opposition Division held that the then pending request did not involve an inventive step in the light of the disclosure of document (1) on the ground that the claimed subject-matter could only be seen as an arbitrary selection of a sub-range within the scope of the teaching of document (1). The requirement that a selection had to be purposive to comply with the provision of Article 56 EPC was not met.

V. In the course of the appeal proceedings, the Appellant submitted on 18 April 1997 sets of claims according to the first and second auxiliary requests, on 25 January 2001 a set of claims according to the third auxiliary request and on 5 November 1998 sets of claims according to the fourth to seventh auxiliary requests.

VI. Regarding the main request (see point II above), the Appellant's submissions both in the written proceedings and at the oral proceedings can be summarised as follows:

- The disclosure of document (1) related to a

process for the preparation of ibuprofen by carbonylating 1-(4'-isobutylphenyl) ethyl halide (or 1-halo-1-(4-isobutylphenyl)ethane according to the nomenclature of the patent in suit) with carbon monoxide in an acidic aqueous medium in the presence of a palladium catalyst. Preferred catalysts were complexes of palladium with phosphine ligands. The amount of ligands was preferably sufficient to complex with the palladium present such as the P:Pd mole ratio was equal to at least about 1:1 when the Pd:arylethyl halide mole ratio was at least about 1:5000 and at least about 2:1 when the Pd:arylethyl halide mole ratio was below 1:10.000. However, in the context of the description, the expression "preferably sufficient to complex with the palladium present" referred to the amount of ligands that palladium could accept, the maximum mole ratio being, therefore, 4:1. It followed that the disclosure of document (1) could not be interpreted as teaching a P:Pd mole ratio ranging from 1 to infinity and the feature related to a P:Pd mole ratio from 8 to 20 according to the patent in suit could not be seen as a selection within a broad range from 1 to infinity but as a range outside the disclosure of document (1).

- Regarding inventive step, the problem to be solved in view of document (1) as the closest state of the art might be seen as a further process for preparing ibuprofen or an ester thereof from 1-halo-1-(4-isobutylphenyl) ethane. In that context, the claimed subject matter was *prima facie* unobvious for the disclosure of document (1) did not teach a P:Pd mole ratio greater than 4.

VII. The Respondent (Opponent) submitted in essence the following arguments against the novelty and inventive step of the main request (see point II above):

- The subject matter of Claim 1 fell squarely within the teaching of document (1), which disclosed that the preferred catalysts were complexes of palladium with phosphine ligands. Those complexes were allowed to be formed in situ by separate addition of phosphine ligands and palladium salts. As this document furthermore disclosed that the P:Pd mole ratio could be at least about 1:1 and that an excess of phosphine ligand could be used such that the P:Pd mole ratio was at least about 2:1, there was nothing which precluded the use of up to, or even more than, 20 moles of ligand per mole of palladium. It was, therefore, clear that the claimed subject matter could, at best, only be seen as a selection from the teaching of document (1).

Moreover, given that an excess of phosphine ligand such that the P:Pd mole ratio was at least about 2:1 could be used and given that tetrakis(triphenyl phosphine) palladium was explicitly disclosed, there was no doubt that the person skilled in the art would have seriously contemplated applying the technical teaching of document (1) with a slightly greater excess of ligand such that between 8 and 20 moles of ligand were present per mole of palladium. In accordance with the precepts established in the decisions T 666/89 (OJ EPO 1993, 495) and T 198/84 (OJ EPO 1985, 209), it was, therefore, submitted that the subject matter of Claim 1 lacked novelty over

document (1).

- Alternatively, the subject matter of Claim 1 lacked inventive step in the light of the disclosure of document (1) or in the light of the disclosure of document (1) in combination with the disclosure of document (2). Furthermore, no significant unexpected advantage could rebut this finding.

- First, there could be no inventive step in optimizing the process disclosed in document (1) by mere routine experiments. As document (1) taught that the P:Pd mole ratio was at least about 2:1, there would have been sufficient motivation for the person skilled in the art to use a higher P:Pd mole ratio to get a comfortable margin, especially because the amount of phosphine was taught to be a significant parameter.

- Furthermore, document (2), which was closely related prior art, disclosed a process for preparing ibuprofen by carbonylating 1-(4'-isobutylphenyl) ethanol (IBPE) with carbon monoxide in acidic aqueous medium in the presence of a catalyst consisting essentially of a palladium compound in which the palladium had a valence of 0 to 2 and was complexed with at least one acid stable, monodentate phosphine ligand, the phosphorus:palladium mole ratio being at least about 2:1 when the mole ratio of palladium to IBPE was below about 1:10000. Suitable palladium catalysts included bis(triphenylphosphine)-dichloro complex, tetrakis(triphenylphosphine) complex, for instance. On page 4, lines 34 to 38,

it was indicated that: "the palladium salts and phosphine ligands making up the foregoing catalyst complexes may also be added separately to the reaction zone. In this case, the amount of ligand added is preferably sufficient to complex with the palladium present such that the P:Pd mole ratio is equal to at least about 1:1 when the Pd:IBPE mole ratio is at least about 1:5000. However, when the latter is below about 1:10000, it is necessary to use an excess of phosphine ligand such that the P:Pd ratio is at least about 2:1". Examples 89 to 93 employed a P:Pd mole ratio of 10:1 and examples 97 and 98 used a P:Pd mole ratio of 27:1. It would have been, therefore, obvious, for the person skilled in the art seeking to investigate embodiments according to document (1) to employ a P:Pd mole ratio of 10:1 in view of document (2).

VIII. The Appellant requested that the decision under appeal be set aside and that the patent be maintained as main request on the basis of the amended description and Claims 1 to 9 filed on 24 January 1996 and Claim 10 as granted, or on the basis of the claims of the first or second auxiliary requests filed 18 April 1997 or of the third auxiliary request filed on 25 January 2001 or of the fourth, fifth, sixth or seventh auxiliary requests filed on 5 November 1998.

The Respondent requested that the appeal be dismissed.

IX. Oral proceedings were held on 21 February 2001. At the end of the oral proceedings the decision of the Board was given orally.

Reasons for the Decision

1. The appeal is admissible.

Main request

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

- 2.1 The sole amendment made with respects to the set of claims as granted concerns the modification in Claim 1 of the P:Pd mole ratio, namely "8 to 20 moles of ligand are present per mole of palladium" (present main request) instead of "4 to 20 moles of ligand are present per mole of palladium" (Claim 1 as granted).

- 2.2 The P:Pd mole ratio 8 to 20:1 derives from the combination of the two mole ratios disclosed in the application as filed i.e. 4 to 20:1 and 8 to 12:1 (see page 8, lines 2 to 6). As the end-points of the now defined ratio are specifically named in the ratios previously disclosed, the amendment is supported by the application as filed (see T 2/81, OJ EPO 1982, 394, point 3 of the reasons).

Further, Claim 1 is a combination of features as disclosed in the application as filed and Claims 2 to 10 correspond with Claims 2 to 10 as filed, which was never contested.

- 2.3 The Board is, therefore, satisfied that Claims 1 to 10 are not amended in such a way that they contain subject-matter which extends beyond the content of the application as filed. Those claims are not amended as to extend the protection conferred, either. Those findings were not contested by the Respondent.

3. *Novelty - Article 54(1) and (2) EPC*

3.1 The sole issue to be dealt with concerning novelty is whether the subject matter of the present claims is novel in view of document (1). The disclosure of document (1) relates to a process for preparing ibuprofen involving the same starting compound, the same palladium catalyst complexes and the same reaction parameters as the process according to Claim 1 of the present request. The sole question to decide is whether the P:Pd mole ratio between 8 and 20 as defined in Claim 1 is explicitly disclosed in document (1).

3.2 As pointed out by both the Appellant and the Respondent, the relevant part of document (1) relating to the P:Pd mole ratio mentions that the amount of ligand is preferably sufficient to complex with the palladium present and equal to at least about 1:1 when the Pd:arylethyl halide mole ratio is at least about 1:5000 and at least about 2:1 when the Pd:arylethyl halide mole ratio is below 1:10 000.

3.3 In the Board's judgment, the fact that no upper limit is mentioned for the P:Pd mole ratios does not imply that the only upper limit is infinity. It is therefore necessary to decide what upper limit has been made available in the relevant part of the description.

3.4 Paragraph, page 4, lines 20 to 32, mentions that the palladium catalyst may or may not be complexed with at least one ligand chosen among carbonyl or phosphine ligands. Tetrakis (triphenyl phosphine) palladium complex is cited at lines 26 to 27. The valence of palladium being four, it is not possible to obtain a complex of palladium having more than four ligands. The

next paragraph, page 4, lines 34 to 39 indicates:

"The preferred catalysts are complexes of palladium with phosphine ligands. The palladium salts and phosphine ligands making up the catalyst complexes may also be added separately to the reaction zone. In such a case, the amount of ligand added is preferably sufficient to complex with palladium present such that the P:Pd mole ratio is equal to at least about 1:1 when the Pd:arylethyl halide mole ratio is at least about 1:5000. However, when the latter ratio is below 1:10 000, it is necessary to use an excess of phosphine ligand such that the P:Pd mole ratio is at least about 2:1".

This paragraph can only be understood in the light of the previous one from which it can be deduced that the number of phosphine ligand per palladium is between 1 and 4. The Board concludes that the ratio P:Pd of at least 2:1 extends to 4:1 only.

3.5 In the Board's opinion, the Respondent's submissions according to which the P:Pd mole ratios of at least 1:1 or 2:1 did not preclude the person skilled in the art using up to, or even more than, 20 moles of ligand per mole of palladium is not in line with the disclosure of document (1) for those P:Pd mole ratios are directly related to the preceding expression "the amount of ligand is preferably sufficient to complex with the palladium present", i.e. a mole ratio of 1 to 4. The term "excess" used in relation with the P:Pd mole ratio 2:1 can only be understood in that context.

3.6 Nor can the Board deviate from this conclusion in the light of the examples which all disclose experiments

involving $\text{PdCl}_2(\text{Ph}_3)_2$ as catalyst (P: Pd mole ratio equal to 2).

- 3.7 Having determined that document (1) disclosed a process for preparing ibuprofen by carbonylating 1-(4'-isobutylphenyl) ethyl halide (or 1-halo-1-(4-isobutylphenyl)ethane according to the patent in suit) with carbon monoxide in an acidic aqueous medium in the presence of a complex of palladium with phosphine ligands, the P: Pd mole ratio being between 1 and 4, it is the Board's conclusion that Claims 1 to 10 meet the novelty requirement according to Article 54 (1) and (2) EPC. The present claimed subject matter not being a selection with respect to the disclosure of document (1), decisions T 666/89 and T 198/84, which deal with the novelty issue of a claimed subject-matter in relation to the prior art where there is an overlap of numerical ranges or where there is a selection out of a broad numerical range, are not relevant.

4. *Inventive step - Article 56 EPC*

4.1 The Board considers, in agreement with the parties, that the closest state of the art is represented by the disclosure of document (1). Indeed, this document aims at the same objective and has the most relevant technical features in common with the claimed subject matter.

4.2 In the course of the opposition proceedings, the Appellant filed comparative tests aimed at showing the improvements provided by using a P:Pd mole ratio comprised between 8 and 20 (document (10)). However, the Board is not convinced that those experiments are relevant for demonstrating the alleged improvement. Indeed, according to well established jurisprudence of the Boards of Appeal, in the case where comparative tests are chosen to demonstrate an inventive step with an improved effect over a claimed area, the nature of the comparison with the closest state of the art must be such that the effect is convincingly shown to have its origin in the distinguishing feature of the invention. This is not the case here given that depending on the experiments, not only the P:Pd mole ratio varies but also the 1-chloro-1-(4-isobutylphenyl) ethane (CEBB):Pd ratio. The Board cannot, therefore, conclude that the obtained improved yields of ibuprofen are only due to the P:Pd mole ratio.

4.3 In view of document (1) as the closest state of the art, and in the absence of any evidence showing an improvement in respect thereof, the technical problem to be solved cannot be seen in providing a more economical process, as said in column 1, lines 6 to 8, of the patent in suit, but in the provision of a

further process for preparing ibuprofen from 1-chloro-1-(4-isobutyphenyl) ethane.

- 4.4 The description of the patent in suit, in particular Examples Nos. 1 to 5, demonstrates that the claimed subject matter represents indeed a solution to the technical problem as defined in point 4.3 above.
- 4.5 It remains to be decided whether or not the proposed solution to the problem underlying the claimed subject matter is obvious in view of the cited prior art.
- 4.6 The Board has already concluded that document (1) disclosed a process for preparing ibuprofen by carbonylating 1-(4'-isobutylphenyl) ethyl halide (or 1-halo-1-(4-isobutylphenyl)ethane according to the patent in suit) with carbon monoxide in an acidic aqueous medium in the presence of a complex of palladium with phosphine ligands, the P:Pd mole ratio being between 1 and 4 (see points 3.4 and 3.7 above).
- 4.7 The Respondent argued that, since document (1) had an explicit teaching of the use of a P:Pd mole ratio of 4:1, it would have been a matter of routine experimental work to optimise the reaction conditions, including the relative proportions of the active species. In particular, there would have been sufficient motivation for using higher P:Pd mole ratios for two reasons: First, the person skilled in the art would naturally wish to consider using an amount of ligand that would have given him a comfortable margin over the stated Figure and, second, as the amount of phosphine is taught to be a significant parameter, he would have sought to optimise the amount of ligand.

4.8 The Board concurs with the Respondent that mere routine experiments do not go beyond the common general activity of the person skilled in the art. However, said skilled person can only envisage routine experiments within the general teaching of a document. As soon as an embodiment goes beyond the general teaching of a document, it is not allowed to consider it as a routine experiment. Furthermore, the Respondent has not substantiated that the person skilled in the art would have considered using an amount of ligand that would have given him a comfortable margin over the stated figure. This finding is, in fact, in contradiction with the second submission according to which the amount of phosphine is taught to be a significant parameter. Indeed, where a parameter is stated to be significant, the person skilled in the art will tend to keep its use within the teaching of the disclosure and therefore within the P:Pd mole ratio specifically mentioned.

4.9 Contrary to the Respondent's submissions, the person skilled in the art would not have considered document (2) to solve the technical problem because this document does not relate to the same kind of reaction. The Respondent did not file any evidence showing that the mechanism of carbonylation of 1-(4'-isobutylphenyl) ethanol (IBPE) was so close to that of 1-chloro-1-(4-isobutylphenyl) ethane (CEBB), that the person skilled in the art could have used the information drawn from document (2) to solve the above defined technical problem. For the same reasons document (7) is not relevant, either, as it relates to carbonylation of halo-hydrocarbons in basic medium. While inventive step issue is assessed in the light of the prior art as a whole, the person skilled in the art must nevertheless

have reason to combine the different pieces of prior art. In the Board's judgment, this requirement is met neither by document (2), nor by document (7).

- 4.10 To summarize, from document (1), the sole document that the person skilled in the art would have considered to solve the technical problem, there is no hint that would have directed him towards the present claimed subject matter. In particular, the Board cannot see any hint which would have led him to increase the P:Pd mole ratio disclosed in document (1). The requirement of Article 56 EPC is met.

Auxiliary request

5. The Board is satisfied that the claims of the main request meet the requirements of the EPC. No need arises to consider the auxiliary requests.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the first instance with the order to maintain the patent on the basis of the amended description and Claims 1 to 9 filed on 24 January 1996 and Claim 10 as granted.

The Registrar:

The Chairman

N. Maslin

P. P. Bracke