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D E C I S I O N
of 10 January 2001

Case Number: T 0018/97 - 3.3.1

Application Number: 90123978.0

Publication Number: 0440930

IPC: C07C 45/65

Language of the proceedings: EN

Title of invention:

Process for the debromination of 2-substituted-5-bromo-6-methoxynaphthalenes

Patentee:

Alfa Chemicals Italiana S.r.l.

Opponent:

ZAMBON GROUP S.p.A.

Headword:

methoxynaphthalenes/ZAMBON

Relevant legal provisions:

EPC Art. 56, 113(1)

Keyword:

"Substantial procedural violation (no)"
"Reimbursement of the appeal fee (no)"
"Inventive step (yes) - non-obvious alternative"

Decisions cited:

G 0004/92, T 0028/87, T 0536/88

Catchword:

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Case Number: T 0018/97 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 10 January 2001

Appellant: ZAMBON GROUP S.p.A.
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Representative: -

Respondent: Alfa Chemicals Italiana S.r.l.
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Representative: Hucker, Charlotte Jane
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 5 November 1996
rejecting the opposition filed against European
patent No. 0 440 930 pursuant to Article 102(2)
EPC.

Composition of the Board:

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

Summary of Facts and Submissions

I. The Appellant (Opponent) lodged an appeal against the decision of the Opposition Division, posted on 5 November 1996, to reject the opposition filed against the European patent No. 0 440 930 (patent application No. 90 123 978.0) under Article 100(a) on the ground that the patent in suit lacked inventive step.

II. The opposition was supported by four documents:

(1) EP-A-0 203 557,

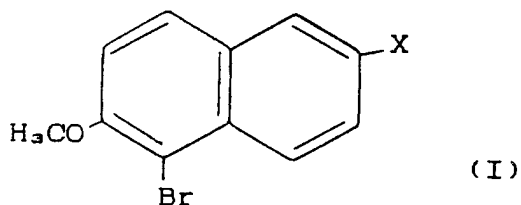
(2) A.R. Pinder, *Synthesis*, 1980, 425-452,

(3) J. March, "Advanced Organic Chemistry", John Wiley and Sons, 3rd Ed., 1985, 510-511,

(4) DE-A-3 212 170.

III. The decision was based on the Claims 1 to 8 as granted, independent claim one reading as follows:

"Process for the debromination of 2-substituted-5-bromo-6-methoxynaphthalenes of formula



wherein X is a substituent selected from the group consisting of acetyl, propionyl, 1-carboxyethyl, 1-

alkoxycarbonylethyl, 1-cyanoethyl and 1-aminocarbonylethyl, the nitrogen atom of this latter group being optionally substituted by alkyl or hydroxyalkyl groups, characterized in that these compounds are treated with acceptors of bromine in the presence of Lewis acids, wherein compounds selected from alkylarenes and alkoxyarenes are used as acceptors of bromine.

IV. The Opposition Division held in particular that, starting from document (4) as the closest state of the art, the claimed invention was not obvious in view of the teaching of document (1) since the structural difference between the starting materials of both processes, namely, compounds being bromo-substituted in á of the keto group in document (1) and compounds without a bromine atom in á of the keto group as in the claimed invention was of considerable significance when one considered the susceptibility of the group COCH_2CH_3 (and the other groups X) to bromination. This finding was confirmed by the fact that the bromine acceptor in document (1) i.e. 2-propionyl-6-methoxynaphthalene was one of the final products according to the disputed patent.

It was the conclusion of the Opposition Division, in that respect, that in applying the process of document (1) to the debromination of a starting compound according to the claimed invention, it would have been expected that the final product would interfere in the reaction in accepting as a side reaction the bromo atom taken out from position 5 of the naphthyl moiety of the said starting compound. To the Appellant's argument that this side reaction could not have occurred due to the use of a stronger bromine acceptor, such as

alkylarenes or alkoxyarenes, the Opposition Division held that there was no teaching in document (1) that, first, alkylarenes were bromine acceptors and, secondly, that alkoxyarenes were stronger bromine acceptors than (6-methoxy 2-naphthyl)-ethyl-ketone, or indeed than alkyl-aryl ketones in general.

The Opposition Division also held that the use of a Lewis acid alone was not obvious in view of documents (1), (2) or (3), especially in combination with the particular bromine acceptors mentioned in the claimed invention. It was observed, in particular, that although document (3) taught that aryl halides could be dehalogenated by Friedel and Crafts catalysts, the reaction, except for deiodination, was seldom used for preparative purposes. Migration of halogen was also found, both intramolecular and intermolecular.

It was the conclusion of the Opposition Division that the claimed invention might not be derived in an obvious manner from document (1) without ex post-facto analysis and that the claimed invention met the requirements of Articles 52(1) and 56 EPC.

V. In the statement of grounds of appeal, the Appellant submitted in essence that the teaching of document (1) in combination with document (2) would have directed the person skilled in the art to solve the technical problem as defined above towards the claimed solution.

First, the alleged risk of a simultaneous bromination at the carbon atom in α of the carbonyl group was not founded for the following reasons: The fact that alkylarenes and alkoxyarenes were stronger bromine acceptors than an alkyl-aryl-ketone did not need to be

demonstrated. It was furthermore well known from document:

- (5) K. Peter C. VOLLHARDT "Organic Chemistry", 1987, W.H. FREEMAN and Co., New York, page 913,

that electron donating substituents such as hydroxy, alkoxy and alkyl activated the electrophilic aromatic substitution, while alkylcarbonyl substituents deactivated the said substitution. It could thus be deduced that at least an alkoxyarene would be a better bromine acceptor than an alkyl-aryl ketone. In view of document (1), it was therefore obvious to use an alkoxyarene as bromine acceptor to debrominate the starting products in the claimed invention, without the person skilled in the art fearing a side reaction.

Contrary to the opinion of the Opposition Division, the use of a Lewis acid for debrominating arylbromides was well known from document (2), in particular from the second paragraph in the right-hand column page 443, where it was reported that tin(II) chloride, a commonly known Lewis acid according to document:

- (6) J. MARCH "Advanced Organic Chemistry" 3rd edition, 1985, John Wiley and Sons, page 229,

was useful for the dehalogenation of aryl halides. The combination of documents (1) and (2), therefore, rendered the claimed invention obvious.

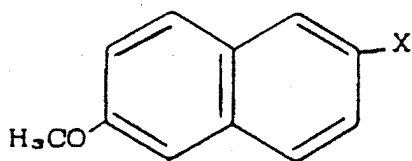
It was furthermore pointed out that document (2), page 435, Table 2 cited specifically tin(II) chloride for debrominating α -bromo-ketones. Consequently, the person skilled in the art would have been strongly

motivated to use a Lewis acid for debrominating compounds of formula (I) while avoiding α -bromination.

The combination of documents (1) and (4) made by the Opposition Division to reject the opposition, while the statement of grounds of opposition was based on the lack of inventive step in view of documents (1), (2) and (3), document (4) being only cited as a proof of the fact that it was known to carry out the debromination reaction of this kind of substrates, was a new line of argumentation. No opportunity was given to the Appellant to comment. This amounted to a substantial procedural violation.

VI. In a communication, the Board of Appeal informed the parties that

- document (4) might be considered as the closest state of the art and that, in the light thereof, the problem underlying the patent in suit seemed to consist of providing a further process for the production of compounds of formula (II):



wherein X is a substituent selected from the group consisting of acetyl, propionyl, 1-carboxyethyl, 1-alkoxycarbonylethyl, 1-cyanoethyl and 1-aminocarbonylethyl, the nitrogen atom of this latter group being optionally substituted by alkyl

or hydroxyalkyl groups,

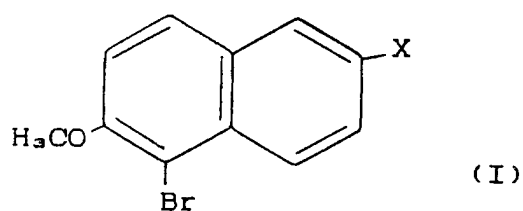
- the decision of the Opposition Division did not seem to amount to a substantial procedural violation.

VII. In response, the Appellant declared that he was ready to accept document (4) as the starting point and maintained that the Opposition Division in rejecting the opposition on the base of a new line of argumentation without giving the opportunity to the Opponent to comment on this new argument had committed a substantial procedural violation.

VIII. Oral proceedings before the Board were held on 10 January 2001. The Appellant, having been duly summoned, informed the Board that he would not be represented at these oral proceedings. They thus took place in the absence of the Appellant (Rule 71(2) EPC).

IX. At the said oral proceedings, the Respondent (Proprietor of the patent) abandoned its request related to the dismissal of the appeal and submitted two sets of claims as main request and auxiliary request I. Claim 1 of the main request was the sole independent claim and read as follows:

"Process for the debromination of 2-substituted-5-bromo-6-methoxynaphthalenes of formula



wherein X is a substituent selected from the group consisting of acetyl, propionyl, 1-carboxyethyl, 1-alkoxycarbonylethyl, 1-cyanoethyl and 1-aminocarbonylethyl, the nitrogen atom of this latter group being optionally substituted by alkyl or hydroxyalkyl groups, characterized in that these compounds are treated with acceptors of bromine in the presence of Lewis acids selected from the group formed by aluminium chloride, ferric chloride, zinc chloride and titanium tetrachloride, wherein compounds selected from alkylarenes and alkoxyarenes are used as acceptors of bromine."

Moreover, he submitted amended pages 4, 6, 7 and 8 of the description of the patent in suit.

X. The Respondent's arguments in support of the inventive step submitted in writing and during the oral proceedings may be summarised as follows:

- in view of document (4) as the closest state of the art, the technical problem was to be seen in the provision of a further process as set out in point VI above. Regarding the disclosure of document (1) the person skilled in the art would have noted that the presence of a bromine atom on the carbon atom in á of the carbonyl group

provided a critical difference compared with the starting compounds according to the patent in suit. Furthermore, a preferred embodiment, as illustrated in the Example No. 1, consisted in transferring the bromine atom of the 5-position of the aromatic ring to the carbon in á to the ketone function of 6-methoxy-2-naphthyl-ethyl-ketone, acting as bromine acceptor. This compound was identical to the desired final product according to the patent in suit. The person skilled in the art would have had, therefore, serious reasons to doubt the applicability of the disclosed process for solving the above cited technical problem, due to a possible side-reaction. Nor could the person skilled in the art have learnt anything concrete from the other examples which related to the debromination, in the presence of phenols, of ketal type compounds and not ketone compounds. It was also pointed out that the debromination according to document (1) involved the use of an hydrogen halide acid as an essential feature, while the claimed process required the use of Lewis acids selected from the group formed by aluminium chloride, ferric chloride, zinc chloride and titanium tetrachloride. Those selected Lewis acids were not suggested by the other cited documents.

XI. The Appellant requested that the decision under appeal be set aside and the patent in suit be revoked. He furthermore requested the reimbursement of the appeal fee.

The Respondent requested that the decision under appeal be set aside and that the patent be maintained as main

request on the basis of Claims 1 to 7 of the main request filed at oral proceedings on 10 January 2001 and amended pages 4, 6, 7 and 8 of the description filed at oral proceedings on 10 January 2001 and pages 2, 3, 5 and 9 of the description as granted, or as auxiliary request on the basis of Claims 1 to 7 of the auxiliary request filed at oral proceedings on 10 January 2001.

XIII. 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 Board is satisfied that Claims 1 to 7 are not amended in such a way that they contain subject-matter which extends beyond the content of the application as filed, and that they are not amended so as to extend the protection conferred. In particular, Claim 1 is a combination of the features of Claims 1, 3 and 4 as originally filed (i.e. Claims 1 and 2 as granted) and the additional features of dependent Claims 2 to 7 are supported by Claims 5 to 10 respectively as originally filed.

2.2 The modifications made to pages 4, 6 to 8 of the description at the request of the Board put its content in conformity with amended Claim 1 and, moreover,

cancel the Examples Nos. 6 and 8 which related respectively to $\hat{\alpha}$ -naphthol and naphthalene as bromine acceptors, those bromine acceptors being outside the scope of the amended patent in suit. Those amendments meet the requirements of Article 123(2) and (3) EPC.

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

After examination of the cited prior art documents, the Board has reached the conclusion that the process as defined in Claims 1 to 7 is novel, since a method for the debromination of compounds of formula (I) as defined in Claim 1, in the presence of alkylarene or alkoxyarene as bromine acceptors and Lewis acids selected from the group formed by aluminium chloride, ferric chloride, zinc chloride and titanium tetrachloride, was not disclosed in any of the cited prior art documents.

Since this was not disputed, it is not necessary to give detailed reasons for this finding.

4. *Inventive step - Article 56 EPC*

- 4.1 Of the six citations, document (4) is the sole one which aims at the same objective as the claimed invention, namely the preparation of the 2-(6-methoxy-2-naphthyl)-propionic acid which is one of the final compounds obtained by the claimed process and therefore document (4) represents the closest state of the art.

Document (4) discloses a process for the preparation of 2-(6-methoxy-2-naphthyl)-propionic acid by debromination of 2-(5-bromo-6-methoxy-2-naphthyl) propionic acid by means of reduction with various

hydrogenation systems, in a basic medium at a temperature between room temperature and 100°C (see page 10, lines 20 to 36).

- 4.2 In view of document (4), the problem underlying the application in suit is to be seen in providing a **further** process for producing compounds of formula (II) (see point VI above).
- 4.3 In view of the Examples Nos. 1 to 5, 7, 9 to 17 and the general description of the application as filed, the Board is satisfied that the claimed invention represents a solution to the problem above defined.
- 4.4 It remains to be decided whether a skilled person in the art starting from document (4) and by following the suggestions made in the cited prior art, when trying to solve the indicated technical problem, would arrive at the claimed solution.
- 4.5 Document (1) relates to a process for the preparation of (6-methoxy-2-naphthyl)-(1-bromo-ethyl)-ketone and ketals thereof, wherein (5-bromo-6-methoxy-2-naphthyl)-(1-bromo-ethyl)-ketone or ketals thereof are selectively debrominated in the 5-position by means of a bromine acceptor and an acid, in an inert organic solvent (see Claim 1). As bromine acceptors may be used:
- (6-methoxy-2-naphthyl)-ethyl-ketone or its ketal (see page 2, lines 18 to 25 and page 4, lines 6 to 9) or
 - aromatic compounds active to electrophilic substitution such as phenols, phenol ethers, aryl

ketones, aryl-alkyl ketones and more specifically phenol, anisole, naphthols, cresols, acetophenone, benzophenone, tetrahydronaphthalene and the like (see page 6, lines 11 to 14).

As suitable acids may be used halogenohydric acids, HSO_3F , $\text{CF}_3\text{SO}_3\text{H}$ or systems comprising halogenohydric acids and Lewis acids such as $\text{HBr}+\text{ZnBr}_2$ and $\text{HCl}+\text{AlCl}_3$ (see page 4, lines 1 to 3).

- 4.6 First, the fact that reference is made in the introduction of the description of the patent in suit (and also in the application as originally filed) to document (1) cannot be rated to the Respondent's disadvantage as a neighbouring field merely on account of this reference (see T 28/87, OJ EPO 1989, 383, in particular reasons 5.4). This does not, indeed, spare the Board the need of examining the content of this document. The Respondent argued that the products referred to in this document having a bromine atom on the carbon atom in α of the carbonyl group rendered difficult or even impossible any substitution on this carbon, while the products involved in the claimed process possessed a methylene group in α of the carbonyl group, one of the hydrogen atom of this group being labile and liable to be substituted. There was, therefore a critical difference between the technical field to which document (1) belonged and that of the patent in suit. The Appellant submitted, by contrast, that the patent in suit related to the debromination in position 5 of the naphthalene nucleus, namely the same reaction as document (1). In the Board's judgment, it is not permitted to define the technical field in such general terms. It is however the opinion of the Board that the technical field to which document (1) belongs

is sufficiently close to the technical field of the patent in suit because they both relate to the chemistry of Naproxen, a drug possessing anti-inflammatory and analgesic activity. It is reasonable to assume that the person skilled in the art working on the chemistry of this drug considers the prior art related to it.

- 4.7 Document (1) actually teaches two kinds of bromine acceptors for debrominating (5-bromo-6-methoxy-2-naphthyl)-(1-bromo-ethyl)-ketone or ketals thereof, namely phenol ethers or phenols on one hand and (6-methoxy-2-naphthyl)-ethyl-ketone or its ketal on the other hand.
- 4.8 In line with the established case law of the boards of appeal, when investigating inventive step it should be borne in mind that the technical disclosure in a prior art document should be considered in its entirety, as it would be done by a person skilled in the art and that it is not justified arbitrarily to isolate parts of such document from their context in order to derive from them technical information which would be distinct from the integral teaching of the document (see decisions referred in the compendium "Case Law of the Boards of Appeal" (3rd edition 1998) at page 126, point 6.3).
- 4.9 While it is true that document (1) teaches a debromination route using phenols or phenol ethers as bromine acceptors in the presence of halogen halide acids, possibly in mixture with a Lewis acid such as $AlCl_3$, the person skilled in the art would have recognised that applying this method to the 2-acetyl-5-bromo-6-methoxynaphthalene would have yielded the 2-

acetyl-6-methoxynaphthalene, which is precisely the bromine acceptor of one of the debromination routes according to document (1). Therefore, in the Board's judgment, there exists *a priori* a clear risk that the bromine atom taken out of the aromatic ring attacks the carbon in α of the carbonyl in order to give the corresponding α bromoketone as a side reaction.

4.10 The Appellant argued that this alleged risk of side reaction did not actually exist given that alkylarenes and alkoxyarenes were stronger bromine acceptors than alkyl-arylketone. This fact was well known on the basis of the general knowledge of the person skilled in the art represented by document (5). Regarding document (5), the Board notes that it relates in its Table 20-2 to the reactivity and orientation induced by substituents in electrophilic aromatic substitution. This document teaches at a theoretical level that the substituents -OH and -OR are strong activators to the ortho and para direction and the substituents -C(=O)-R are strong deactivators to the meta direction. The Board seeks in vain any information regarding the compounds carrying simultaneously an alkoxy or alkyl group and an acyl group. Furthermore, the Board notes that the Appellant's contention is in contradiction with the teaching of document (1) insofar as acetophenone is deemed to be as efficient as phenol or anisole as a bromine acceptor (see page 6, lines 13 to 14). It is, therefore, the Board's conclusion that the Appellant failed to show that the clear risk of a side reaction would be disregarded.

4.11 The Appellant also argued that it was obvious to use a Lewis acid in view of document (2), related to dehalogenation of organic halides, for preventing any

bromination on the carbon in α of the carbonyl group (see page 435, Table 2). However, the Board cannot share the conclusion of the Appellant at least in view of the fact that none of the Lewis acids mentioned in the present claims are cited among the compounds for conducting hydrogenolysis of α -bromoketones according to this document.

4.12 The Appellant also argued that the use of Lewis acids, in particular tin (II) chloride, for debrominating aryl bromides was well-known from document (2) (see paragraph 4.4, in particular the second paragraph in the left-hand column on page 443). It is true that tin (II) chloride is cited as a dehalogenation agent (the type of halide being unspecified). However, contrary to the Appellant's contention, this cited paragraph does not provide any information either regarding the specific arylbromides at issue in the present case, or the Lewis acids involved in the present Claim 1, or the specific halide i.e. a bromine atom. In the Board's judgment, such a generalisation can all the less be made, given that document (3), another textbook, teaches on page 510 that, although aryl halides can be dehalogenated by Friedel-Crafts catalysts, this reaction is seldom used for preparative purposes except for deiodination and migration of halogen is also found, both intramolecular and intermolecular. This last information might, moreover, reinforce the fears of the person skilled in the art of a side reaction in debrominating the starting product of Claim 1.

4.13 From the above and as correctly recognised by the Opposition Division, it is seen that the trend of thought in document (1) teaches away from the solution proposed in the claims at issue. The Appellant

submitted no convincing argument to rebut this opinion *a priori*, neither as concerns the bromine acceptors, nor the now selected Lewis acids.

4.14 It is therefore the Board's conclusion that the person skilled in the art faced with the problem to provide a **further** process for obtaining the desired products (see point 2 above) would not have been directed towards the solution defined in Claim 1 in view of the prior art cited.

4.15 Thus, it follows from the above considerations, that the subject-matter of present Claim 1 involves an inventive step within the meanings of Articles 52(1) and 56 EPC.

Furthermore, for the same reasons, the Board also concludes that the subject-matter of dependent Claims 2 to 7 involves an inventive step too.

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 request.

6. *Request for reimbursement of the appeal fee*

6.1 According to Rule 67 EPC the reimbursement of the appeal fee shall be ordered where the Board of Appeal deems an appeal to be allowable and if such reimbursement is **equitable** by reason of a **substantial procedural violation**.

6.2 The Appellant argued, in particular, that the

combination of documents (1) and (4) by the Opposition Division to reject the opposition was a new line of argumentation upon which no opportunity to comment had been given to the Appellant.

6.3 The Board observes, first, that the opposition was based on the alleged lack of inventive step of the patent in suit and that the decision of the Opposition Division rejects the opposition on the ground that the said patent meets the requirements of Article 52(1) and 56 EPC. Therefore, the decision was not based on a new ground.

6.4 Secondly, document (4), mentioned in the Statement of Grounds of Opposition, was considered as closest prior art in the patent in suit, and used as the prior art document in relation to which Claim 1 defined the claimed invention. According to established case law (see decision T 536/88 (OJ EPO 1992, 638) and other cases referred to in the compendium "Case Law of the Boards of Appeal" (3rd edition 1998) at page 312), this document forms part of the opposition proceedings even if not cited by a party, still more if this document was cited as in the present case.

6.5 That the Opposition Division would start from document (4) from which the disputed patent started, could reasonably be expected and does not amount to a substantial procedural violation.

6.6 The reimbursement of the appeal fee is refused.

7. *Article 113(1) EPC*

The Board holds that the present decision to maintain

the patent on the basis of a set of claims amended during oral proceedings in the absence of the Appellant does not conflict with the principles laid down in the decision of the Enlarged Board of Appeal G 4/92 (OJ EPO 1994, 149), whereby a decision may not be based on new facts put forward for the first time during the oral proceedings. The submission of restricted claims is neither a fact nor can it be evidence within the meanings of the above decision. The Appellant had reasonably to expect that the Respondent would try to overcome the objections based on the lack of inventive step in restricting the scope of the claims by combining the features of Claims 1 and 2 as granted (see point 2.1 above). Consequently, the absence of the Appellant at the oral proceedings did not prevent the Board from taking a decision.

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 maintain the patent on the basis of:

Claims: Claims 1 to 7 of main request as filed at oral proceedings on 10 January 2001.

Description: pages 4, 6, 7 and 8 as filed at oral proceedings on 10 January 2001.
pages 2, 3, 5 and 9 as granted.

3. The request for the reimbursement of the appeal fee is refused.

The Registrar:

The Chairman:

N. Maslin

P. P. Bracke