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**Datasheet for the decision
of 12 January 2018**

Case Number: T 0278/14 - 3.3.01

Application Number: 05819134.7

Publication Number: 1828222

IPC: C07J53/00, A61K31/585,
A61P15/18

Language of the proceedings: EN

Title of invention:

PROCESS FOR THE PREPARATION OF DROSPIRENONE

Patent Proprietor:

INDUSTRIALE CHIMICA S.r.l.

Opponent:

BAYER PHARMA AG

Headword:

Drospirenone/INDUSTRIALE CHIMICA

Relevant legal provisions:

EPC Art. 56
RPBA Art. 12(4), 13(1)

Keyword:

Inventive step, main request (no) - obvious alternative
Admission, auxiliary request (no)

Decisions cited:

Catchword:



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Case Number: T 0278/14 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 12 January 2018

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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on
10 December 2013 rejecting the opposition filed
against European patent No. 1828222 pursuant to
Article 101(2) EPC**

Composition of the Board:

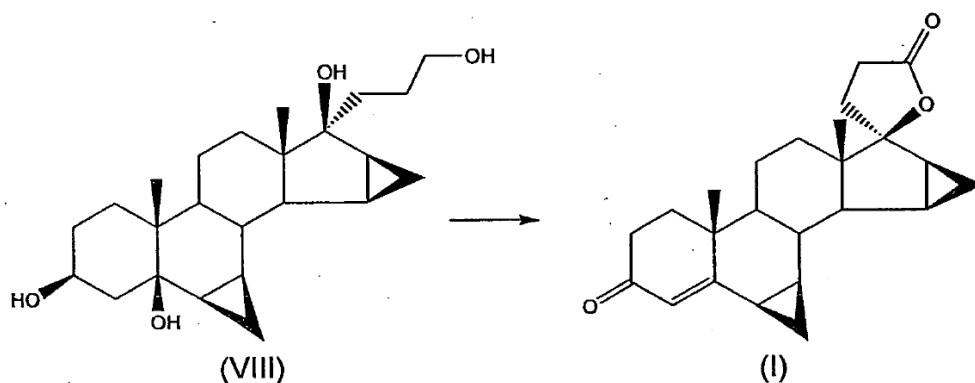
Chairman A. Lindner
Members: J. Molina de Alba
M. Blasi

Summary of Facts and Submissions

- I. The present appeal lies from the decision of the opposition division to reject the opposition filed against European patent No. 1 828 222.

Claim 1 of the patent as granted (main request) reads as follows:

1. Process for the preparation of drospirenone, comprising the oxidation of 17α -(3-hydroxypropyl)- 6β , 7β , 15β , 16β -dimethylene- 5β -androstane- 3β , 5 , 17β -triol of formula (VIII) with a suitable oxidising agent in an organic solvent in the presence of a catalytic amount of the 2,2,6,6-tetramethylpiperidine-1-oxyl radical or a derivative thereof, said oxidation being followed by the addition of a protic acid directly into the same container in which the oxidation took place, to obtain the drospirenone of formula (I)



- II. In the following, the 2,2,6,6-tetramethylpiperidine-1-oxyl radical will be referred to as "TEMPO".
- III. The evidence invoked by the parties during the present appeal proceedings included *inter alia* the following documents cited in the opposition proceedings, in which

document (14) had not been admitted by the opposition division:

(1) A.E.J. de Nooy et al., Synthesis, 1996, 1153-1174

(3) US 6,121,465

(14) EP-B-1 746 101

IV. In the appealed decision, the opposition division held that the invention underlying the granted claims was sufficiently disclosed and that the process in granted claim 1 involved an inventive step starting from document (3) as the closest prior art.

V. In its statement of grounds of appeal, the appellant (opponent) contested the decision under appeal and argued that the invention was not sufficiently disclosed and that the process in granted claim 1 lacked an inventive step over the combination of documents (3) and (1).

VI. With its reply dated 19 August 2014, the respondent (patent proprietor) filed document (14).

Later, with a letter dated 24 October 2017 in response to a communication by the board annexed to the summons to oral proceedings, the respondent filed two claim sets as auxiliary requests 1 and 2.

VII. Oral proceedings were held before the board on 12 January 2018.

In the course of the oral proceedings, the respondent withdrew its then pending auxiliary requests 1 and 2

and filed a new auxiliary request which contained one single claim.

The claim of the new auxiliary request corresponds to granted claim 1, with the specification that the protic acid is added at the end of the oxidation reaction.

VIII. The appellant's arguments where relevant to the present decision may be summarised as follows:

Document (14) had been filed late, namely at the oral proceedings before the opposition division. The division had not admitted it because it did not belong to the prior art. Hence, the board should not admit it either.

For the assessment of inventive step in respect of the process claimed in the patent as granted (main request), the disclosure in document (3) was the closest prior art. The process in granted claim 1 differed therefrom in the oxidising system used.

Granted claim 1 solved the technical problem of providing an alternative process for the preparation of drospirenone starting from the compound of formula (VIII) defined therein. Contrary to the respondent's opinion, the problem could not be formulated as the provision of a process for the preparation of drospirenone which did not require a final chromatographic purification for removing metal impurities, because granted claim 1 did not exclude the use of metal oxidants, co-oxidants or catalysts.

The solution proposed in the patent was obvious in view of document (1), which in points 4.3.1 and 4.3.2 taught the oxidising systems defined in granted claim 1.

Furthermore, even admitting the respondent's contention that carrying out the oxidation and dehydration steps in the same container constituted an additional difference from the closest prior art, the process of granted claim 1 would still be obvious because this additional difference was not associated with any unexpected effect, and document (3) explicitly disclosed it in column 2.

The auxiliary request presented by the respondent after the board had concluded at oral proceedings that the process of granted claim 1 lacked an inventive step was late-filed. It was not a reaction to a new situation arising at oral proceedings, because the objection of lack of inventive step had been in the proceedings from the beginning. In addition, the amendment proposed in the request was not suitable for overcoming the objection.

IX. The respondent's arguments where relevant to the present decision may be summarised as follows:

The opposition division had not exercised its discretion properly when it decided not to admit document (14), because the document had been filed in reaction to the appellant's submissions in preparation for oral proceedings, where inventive step was discussed in relation to the prior art for the first time. In addition, the document had not been filed as prior art but as evidence of the appellant's own opinion that the oxidation of steroids closely related to those of granted claim 1 using TEMPO-based catalysts was inventive. In any case, document (14) should be admitted into the appeal proceedings on the basis of the board's own discretion.

In the context of the assessment of inventive step starting from document (3), a distinction had to be made between the prior art discussed in columns 1 and 2 therein and the invention with which the document was concerned. The latter represented the closest prior art, and involved the preparation of drospirenone by subsequent oxidation and dehydration of the compound (VIII) in granted claim 1, with isolation of the intermediate product (see column 4, lines 1 to 52, and the example in column 6). The process in granted claim 1 differed from that invention in two features: its oxidation system and the fact that the intermediate product was not isolated.

The problem to be solved was the provision of a process for the production of drospirenone which did not require the use of heavy or toxic metals, such that there was no need for chromatographic purification at the end of the process.

The solution proposed in granted claim 1 was a two-step process that had to be analysed as a whole, not as isolated steps. This process was not obvious because, starting from document (3), the skilled person would not have chosen the particular oxidation systems disclosed in document (1), nor would he have found a hint in the prior art that acidification of the intermediate product without previous isolation could successfully yield drospirenone. Moreover, in order to arrive at the process of granted claim 1, a combination of three pieces of prior art would have been required (invention of document (3), document (1) and prior art of document (3)), which confirmed that the process of granted claim 1 was not obvious.

Regarding the choice of oxidation system, the prior art contained many alternative oxidants, and there was no particular reason for the skilled person to select those in document (1). Thus, although document (3) related to replacing chromium oxidants with less toxic oxidants, and although the oxidising systems according to granted claim 1 were known long before the filing date of document (3), the applicant of document (3) chose oxidising systems based on ruthenium salts rather than the nitroxyl radicals of document (1). In addition, in the 30 years of research with TEMPO-based oxidants reviewed by document (1), only one example had been carried out on a steroid (see table 2, entry 11), and that particular example involved acidic catalysis, which was incompatible with drospirenone due to its lability in acidic media.

With respect to the dehydration step, document (3) taught the isolation of the intermediate product as part of its contribution over the prior art. So its teaching was contrary to a one-pot process.

Moreover, in document (14), which is a patent from the appellant with a filing date later than that of the patent in suit, it was stated that the successful oxidation of the steroids therein with TEMPO-based oxidants was surprising (see paragraph [0008]). Accordingly, document (14) indirectly acknowledged that the process in granted claim 1 was inventive.

The auxiliary request should be admitted into the proceedings because it had been filed in reaction to the unexpected situation arising during oral proceedings that the board considered the process of granted claim 1 not to be inventive. Furthermore, the filing of auxiliary requests in a reaction to an actual

situation that had occurred should be allowable. Otherwise, the board would be flooded with auxiliary requests.

- X. The final requests of the parties were as follows:
- The appellant requested that the decision under appeal be set aside and that the patent be revoked.
 - The respondent requested that the appeal be dismissed.
- XI. At the end of the oral proceedings, the board's decision was announced.

Reasons for the Decision

1. The appeal is admissible.
2. *Admission of document (14) - Article 12(4) RPBA*

The appellant objected to the admission of document (14), maintaining that it had not been admitted by the opposition division because it had been filed late and because it lacked relevance, as it did not belong to the prior art.

The board, however, concurs with the respondent that the filing of document (14) can be seen as a legitimate reaction to the appellant's arguments regarding lack of inventive step in relation to the prior art, which had been submitted for the first time after the opposition division had summoned to oral proceedings. In view of

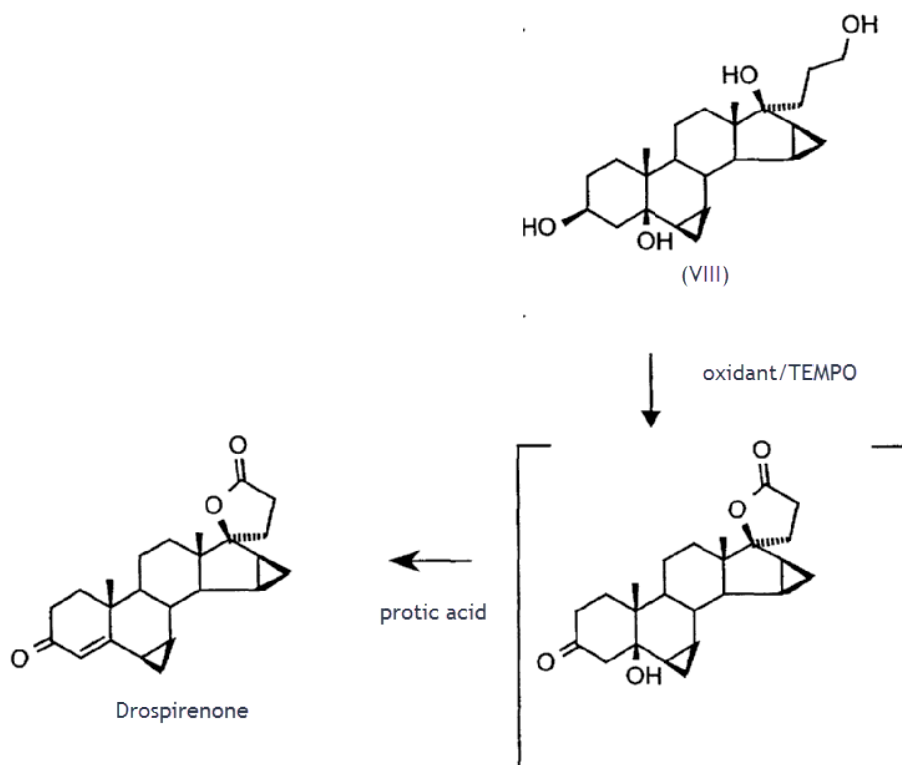
the fact that these arguments were further pursued by the appellant in its statement of grounds of appeal, the presentation of document (14) and of the alleged facts and arguments based upon it by the respondent in its reply to the appeal can also be accepted as a legitimate reaction to the appeal. Accordingly, the board does not hold document (14) inadmissible under Article 12(4) RPBA.

In this context, the board notes that the non-admission of document (14) by the opposition division was not an obstacle to the board considering it. Article 12(4) RPBA does not prohibit the board from taking into account facts, evidence or requests which were not admitted in the first-instance proceedings. Rather, in such cases, the board has discretion over whether or not to take them into account, even if they were presented at the beginning of the appeal proceedings and related to the case under appeal, thus forming part of a party's case. It was therefore not necessary for the board to further assess, by applying the established principles for reviewing first-instance decisions taken in the exercise of discretion, whether or not the opposition division's decision not to admit document (14) was to be set aside.

3. *Inventive step of the process in claim 1 of the main request (patent as granted) - Articles 100(a) and 56 EPC*

3.1 The patent is directed to a one-pot process for the preparation of drospirenone starting from the compound of formula (VIII) defined in granted claim 1. This process involves an oxidation reaction in an organic solvent using TEMPO or a TEMPO derivative as a

catalyst, followed by dehydration in the same container with a protic acid. It may be represented as follows:



3.2 *Closest prior art*

The parties and the opposition division concurred that the disclosure of document (3) was the closest prior art.

Like the patent, document (3) was concerned with the provision of a process for the preparation of drospirenone by oxidation/dehydration of the compound of formula (VIII). In the section discussing the prior art, it was acknowledged that the preparation of drospirenone by oxidation/dehydration of compound (VIII) was already known as a one-pot process which used chromium-based oxidising agents (see columns 1 and 2). Thus, having regard to the toxicity of chromium

compounds, there was a need to provide a process which did not require the use of such oxidising agents (see column 3, lines 21 to 25). The solution proposed in document (3) was the use of a ruthenium-based oxidising system which allowed both dispensing with the use of chromium compounds and isolating the intermediate product before the dehydration step (see column 4, lines 48 to 52; and column 4, line 59, to column 5, line 5).

The board accepts the view of the opposition division and the respondent that the closest prior art may be represented by the invention disclosed in document (3) and that the process in granted claim 1 differs therefrom in two features: the oxidation system and the fact that the two steps of the process are carried out in the same container without isolation of the intermediate product.

3.3 *Objective technical problem*

The respondent considered that the objective technical problem to be solved lay in the provision of a process for the production of drospirenone which did not require the use of heavy or toxic metals, such that there was no need for chromatographic purification at the end of the process.

Given that claim 1 does not exclude the use of heavy or toxic metals as suitable oxidants, co-oxidants or catalysts, and that the patent even cites a heavy metal salt within one of its preferred oxidising systems (see CuCl in paragraph [0017]), claim 1 encompasses processes that would require subsequent chromatographic purification. Hence, the technical problem as formulated by the respondent is not solved by claim 1

across its whole scope and needs to be reformulated in a less ambitious manner.

Considering that there is no evidence on file that the process in claim 1 provides any advantage over the process of the closest prior art, the board concludes, in agreement with the opposition division and the appellant, that the problem to be solved is the provision of an alternative process for the preparation of drospirenone by oxidation/dehydration of the compound of formula (VIII) defined in claim 1.

3.4 *Solution*

The solution proposed in claim 1 consists of a process wherein the oxidising system contains TEMPO or a TEMPO derivative as a catalyst and wherein the oxidation and dehydration reactions are carried out subsequently without isolation of the intermediate product.

3.5 *Obviousness*

3.5.1 *Oxidising system*

Document (1) is a review of the oxidation of primary and secondary alcohols using organic nitroxyl radicals (see introduction; page 1155, left column, paragraph 2; and point 4.3). As examples of such oxidations, document (1) in points 4.3.1 and 4.3.2 discloses reactions that involve the use of the oxidising systems defined in granted claim 1, i.e. comprising a primary oxidant, catalytic amounts of TEMPO or a TEMPO derivative, and an organic solvent.

Particularly relevant to the present case is the general knowledge depicted in the introduction of

document (1) (see first paragraph) that the regioselective oxidation of one alcohol group in the presence of others is generally not feasible and that, in particular, the selective oxidation of primary alcohols in the presence of secondary ones is still a difficult conversion in organic synthesis. Furthermore, it is concluded in the last paragraph of document (1) that although organic nitroxyl radicals (e.g. the TEMPO-based systems in granted claim 1) can oxidise primary alcohols with high selectivity, secondary alcohols too are oxidised in good yields under mild conditions.

Consequently, the skilled person knew from document (1), especially from its first and last paragraphs and from its points 4.3.1 and 4.3.2, that the TEMPO-based oxidising systems proposed in granted claim 1 were a suitable alternative to the ruthenium-based systems used in document (3), since they easily oxidised both primary and secondary alcohol groups.

3.5.2 *Non-isolation of the intermediate product*

Regarding the requirement in granted claim 1 for the oxidation/dehydration process to be carried out without isolation of the intermediate product, this difference from the closest prior art does not contribute to an inventive step of the claimed subject-matter because, as taught in document (3) (see column 2, lines 7 to 24), the dehydration of the intermediate product in the presence *inter alia* of acids is thermodynamically favourable and occurs so easily that in certain circumstances it cannot even be suppressed (e.g. when using chromium oxidants). Thus, the skilled person knew from document (3) that isolation of the intermediate product was challenging and that the easiest way to

proceed was by carrying out the dehydration without previously isolating the intermediate product, as was done in the prior art discussed in document (3).

3.5.3 In conclusion, the use of TEMPO-based oxidising systems and the choice of carrying out the process without isolation of the intermediate product were obvious modifications to the process of document (3) in the light of document (1) and the skilled person's knowledge depicted in column 2 of document (3). Therefore, the board holds that the skilled person would have arrived at the process of granted claim 1 without the involvement of an inventive step.

3.5.4 The respondent argued that the skilled person would not have replaced the ruthenium-based oxidising systems in document (3) with those disclosed in document (1), because there were many oxidants available in the prior art and there were no particular reasons to specifically select those in document (1). Furthermore, in the 30 years reviewed by document (1), only one example had been carried out on a steroid (see table 2, entry 11), and this had been done under conditions that were incompatible with the invention.

The board disagrees with that view, because the skilled person's intention was to provide an alternative to the process of the closest prior art. Therefore, any oxidising system that the skilled person would have considered to be suitable for the oxidation of the primary and secondary hydroxyl groups in compound (VIII) was obvious. This is the case with the TEMPO-based oxidising systems disclosed in points 4.3.1 and 4.3.2 of document (1), known to oxidise both primary and secondary alcohols. This teaching cannot be countered by the absence of specific examples with

steroids in document (1), since there is no reason to believe that the hydroxyl groups present on a steroid have a different reactivity to other hydroxyl groups, merely because they are on a steroid.

Another of the respondent's arguments was that the need to combine three pieces of prior art, namely the invention of document (3), the teaching of document (1) and the previous knowledge depicted in document (3), in order to arrive at the claimed process confirmed the presence an inventive step.

This argument is not convincing either, because there is no general principle which determines that in order for a lack of inventive step to be established only two documents may be combined. Thus if, as in the present case, none of the modifications proposed in granted claim 1, whether independently or in combination, are linked to an unexpected effect, the fact that each modification was suggested in a different piece of prior art does not render the claimed subject-matter inventive. This is even more true of granted claim 1, where the non-isolation of the intermediate product was in the best case an option if not an unavoidable circumstance.

Lastly, the respondent argued that the appellant had indirectly recognised the inventiveness of the process in granted claim 1 because it stated in paragraph [0008] of document (14) that the successful oxidation of the steroids therein with TEMPO derivatives was surprising; this statement would apply *mutatis mutandis* to the process of granted claim 1.

In that respect, the board holds that the statement in paragraph [0008] of document (14) merely constitutes

the appellant's personal opinion given in one of its patents. Such a statement can neither replace the assessment of inventive step before the board nor overturn the outcome of the problem-solution approach as applied above. Therefore, the respondent's argument based on document (14) has to be rejected.

- 3.6 For these reasons, the board concludes that the process in granted claim 1 is not inventive, and so Article 100(a) in combination with Article 56 EPC prejudices the maintenance of the patent as granted.

4. *Admission of the auxiliary request - Article 13(1) RPBA*

The auxiliary request was filed by the respondent in the course of the oral proceedings before the board, after the board had announced its opinion on the main request, i.e. at a very late stage of the appeal proceedings. The request contains a sole claim which is based on granted claim 1, with the specification that the protic acid is added at the end of the oxidation reaction.

According to the respondent, the request was a reaction to the unexpected situation arising during oral proceedings that the board considered the process of granted claim 1 not to be inventive.

This argument is not convincing because the reasons that led the board to the conclusion that the process of granted claim 1 was not inventive had already been raised by the appellant in its statement of grounds of appeal (see point 4.1.2). Hence, the board's conclusion cannot have taken the respondent by surprise.

The respondent further argued that a reaction to a particular situation that had arisen should be permissible because, if it was not, a large number of auxiliary requests would need to be filed at an earlier stage and the boards would be flooded with auxiliary requests.

The board cannot see that, in the circumstances of the present case, it would have been faced with an exceptionally high number of auxiliary requests if the respondent had wished to react earlier to the objections presented by the appellant in the written submissions filed at the appeal stage. Moreover, the respondent's approach disregards the fact that the parties to the proceedings have to present their case as completely as possible at the beginning of the appeal proceedings, as clearly indicated by the requirements laid down in Article 12 RPBA. This includes the presentation of foreseeable fall-back positions.

In addition, the board agrees with the appellant that the auxiliary request does not change the situation with regard to inventive step as to the main request, because the addition of the protic acid at the end of the oxidation reaction was already implicit in the discussion of the main request. So the amendment proposed in the auxiliary request *prima facie* does not overcome the outstanding objection of lack of inventive step and, at the same time, goes against the principle of procedural economy since its admission would have resulted in a repetition of the discussion on inventive step already held in relation to the main request.

Accordingly, the auxiliary request was not admitted into the proceedings (Article 13(1) RPBA).

5. In view of the outcome of the present decision in relation to the issue of inventive step, there was no need to decide on the ground of sufficiency of disclosure.

Order

For these reasons it is decided that:

1. **The decision under appeal is set aside.**
2. **The patent is revoked.**

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated