BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen
(D) [ ] No distribution

Datasheet for the decision of 11 October 2010

Case Number: T 1728/07 - 3.3.01

Application Number: 97938263.7

Publication Number: 0922040

IPC: C07D 263/28

Language of the proceedings: EN

Title of invention:
Process for preparing intermediates to florfenicol

Patentee:
Schering Corporation

Opponents:
KRKA
VIRBAC S.A.

Headword:
Florfenicol synthesis/SCHERING

Relevant legal provisions:
EPC Art. 123(2), 83, 54, 56
EPC R. 139

Relevant legal provisions (EPC 1973):
-

Keyword:
"Correction of error in formula (allowable)"
"Sufficiency of disclosure (yes)"
"Novelty (yes), one-pot reaction"
"Inventive step (yes), non-obvious combination of features in satisfactory yields"
"Remittal for adaptation of the description"

Decisions cited:
–

Catchword:
–

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1728/07 **-** 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 11 October 2010

Appellant: (Patent Proprietor)
Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033 (US)

Representative:
Klusmann, Peter
HOFFMANN EITLE
Patent- und Rechtsanwälte
Arabellastrasse 4
D-81925 München (DE)

Party as of right: (Opponent 1)
KRKA
Smarjeska cesta 6
SI-8501 Novo Mesto (SI)

Representative:
Straus, Alexander
Patentanwälte
Becker, Kurig, Straus
Bavariastrasse 7
D-80336 München (DE)

Respondent: (Opponent 2)
VIRBAC S.A.
1ère Avenue, 2065M LID
F-06516 Carros (FR)

Representative:
Macquet, Christophe
Macquet & Associés
Arche des Dolines
7, rue Soutrane
F-06560 Sophia Antipolis (FR)

Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 6 August 2007 revoking European patent No. 0922040 pursuant to Article 102(1),(3) EPC 1973.

Composition of the Board:

Chairman: P. Ranguis
Members: L. Seymour
L. Bühler

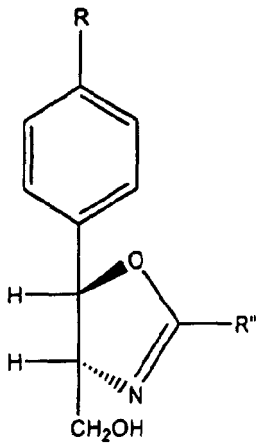
Summary of Facts and Submissions

I. European patent No. 0 922 040, which was filed as application number 97 938 263.7, based on international application WO 98/07709, was granted on the basis of eight claims.

Independent claim 5, including a minor correction to the chemical name of florfenicol introduced by decision of the examining division dated 23 February 2005 under Rule 89 EPC 1973, read as follows:

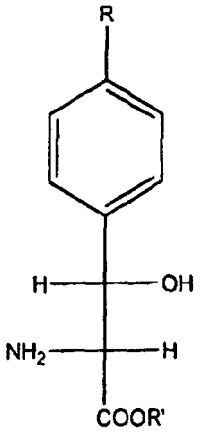
"5. A process for producing florfenicol ([R-(R*, S*)]-2,2,-dichloro-N-[1-(fluoromethyl)-2-hydroxy-2-[4-methylsulfonyl)phenyl]ethyl]acetamide), which comprises:

(a) preparing a compound of formula (I):



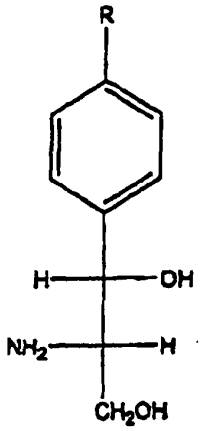
(I)

wherein R is H, NO_2, CH_3S, CH_3SO_2, or C_4 to C_6 alkyl; and R" is aryl, halo aryl, benzyl, substituted benzyl, C_1 to C_6 alkyl, C_3 to C_7 cycloalkyl, and haloalkyl, and the configuration of the oxazoline ring is 4R trans by contacting a compound of formula II:



(II)

wherein R is as described above, and R' is H, C_1 to C_6 alkyl, C_3 to C_7 cycloalkyl, benzyl, substituted benzyl, or aryl;
with a reducing agent in a protic solvent, in a suitable reaction vessel, to obtain a compound of formula III:



(III)

wherein R is as described above, and

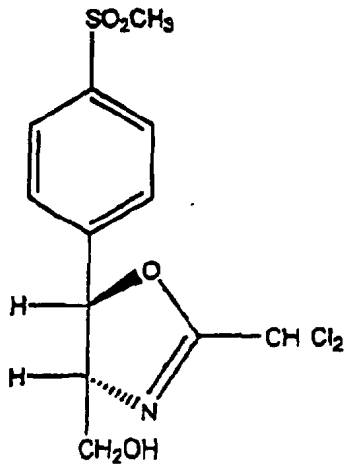
(b) then in the same reaction vessel reacting a compound of formula III, with a compound of the formula IV:

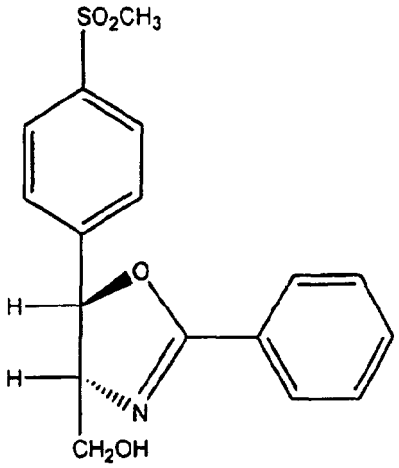
R"—C≡N (IV)

to obtain a compound of the formula I, and

(c) converting said compound of formula (I) to florlenicol."

Dependent claims 6 and 7 each related to a process according to claim 5 wherein the following compounds of formula I were formed, respectively:





II. Notices of opposition were filed by opponents I and II (now party as of right and respondent, respectively) requesting revocation of the patent in its entirety pursuant to Articles 100(c), 100(b) and 100(a) EPC (lack of novelty and inventive step).

III. The following documents were cited *inter alia* during the opposition/appeal proceedings:

(1) J E Clark et al., Synthesis, 1991, 891—894

(2) D P Schumacher et al., J. Org. Chem., 1990, 55, 5291—5294

(8) US 2 759 001

(9) US 4 876 352

(15) WO 90/14434

(21) US 5 382 673

Annex A Experimental report annexed to appellant's letter of 15 December 2006

Annex B Experimental report annexed to appellant's letter of 15 December 2006

Annex C Experimental report annexed to appellant's letter of 19 February 2007

Annex D Experimental report annexed to statement of grounds of appeal

Annex E Experimental report annexed to statement of grounds of appeal

IV. The appeal lies from the decision of the opposition division revoking the patent under Article 102(1),(3) EPC 1973, based on the patent as granted and as amended according to a first auxiliary request filed at oral proceedings before the opposition division.

The opposition division considered that the claims as granted contained subject-matter extending beyond the content of the application as filed, since the amendment of formula (I) could not be seen as an obvious correction in the sense of Rule 88 EPC 1973 (now Rule 139 EPC 2000).

Concerning the first auxiliary request, the opposition division considered that the subject-matter claimed complied with the requirements of Articles 123(2)(3), 83 and 54(1)(2) EPC.

With respect to the issue of inventive step, document (1) was considered by the opposition division to represent the closest prior art. The opposition division was of the opinion that the evidence presented by the patentee did not convincingly demonstrate that

the problem of providing an advantageous process for the preparation of florfenicol had actually been solved. The opposition division therefore reformulated the definition of the problem to be solved as lying in the provision of an alternative process for the preparation of florfenicol. The solution proposed was considered to be obvious in view of the teaching of document (15).

Concerning the request for apportionment of costs, the opposition division found that opponent II (respondent) was entitled to the refund of the costs incurred by the holding of the second oral proceedings before the opposition division (Article 104(1) EPC).

V. The appellant (patentee) lodged an appeal against this decision and filed grounds of appeal, in so far as the decision related to the revocation of the patent. Two auxiliary requests and additional comparative data (Annexes D and E) were also filed. In addition, the appellant requested a reimbursement of the appeal fee on the ground of a substantial procedural violation in first instance proceedings.

VI. With letter of 9 April 2008, a third party filed observations under Article 115 EPC, following on from the observations it had filed in the first instance proceedings dated 28 February 2007, received on 8 March 2007.

VII. With letter of 6 May 2008, the respondent filed counterarguments to the grounds of appeal.

VIII. With letter of 21 October 2008, the appellant reiterated its previous arguments.

IX. Oral proceedings were held before the board on 11 October 2010.

X. During oral proceedings the appellant stated that the previously filed first auxiliary request was to be considered as the new main and sole request. In addition, the appellant withdrew its request for reimbursement of the appeal fee.

The **main and sole request** consists of three claims corresponding to claims 5 to 7 of the claim set as granted, wherein the meaning of R has been restricted to "CH_3SO_2" (cf. point I above).

XI. The appellant's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

In connection with the ground of opposition raised under Article 100(c) EPC, the appellant emphasised that compounds of formula (I) were in themselves well known from the prior art as intermediates for the synthesis of florfenicol, as was their synthesis starting from compounds of formula (II) via compounds of formula (III). In addition, in view of basic mechanistic considerations concerning oxidation state and stability, the person skilled in the art would have immediately recognised that the application as originally filed contained obvious errors in the depiction of the compounds of formula (I). Moreover, it was clear how this error should be corrected. In this context, the appellant referred to document (9) cited in the application as originally filed (see page 1, lines 17 to 20).

The appellant further submitted that the objection under Article 100(b) EPC was unfounded since clear and complete instruction was provide in the patent in suit to enable the skilled person to carry out the process as claimed. Moreover, the suitable reaction conditions to be used in the reduction of esters to alcohols belonged to the common general knowledge of the skilled, as confirmed by a number of textbook citations that had been introduced during the opposition proceedings.

On the question of novelty, the appellant submitted that the subject-matter claimed was novel over document (15) since there was no direct and unambiguous disclosure therein of all the features of present claim 1 in combination. For example, one of the key features of present claim 1, namely, that steps (a) and (b) were conducted in the same reaction vessel, was not disclosed in document (15).

Turning to the issue of inventive step, the appellant started from document (1) as representing the closest prior art, and defined the problem to be solved as lying in the provision of an improved, industrially useful procedure for producing florfenicol. The solution proposed consisted of two measures for synthesising the key intermediate of formula (I) as defined in claim 1, namely, the use of (i) a sulfone rather than a sulfide starting material and (ii) a one-pot rather than a two-pot procedure. This process clearly provided a major improvement, since it allowed good yields to be obtained whilst reducing the number of reaction steps and eliminating the need for a complex work-up procedure involving large amounts of

dichloromethane solvent. The first of the above-mentioned measures alone would not have solved the problem posed, since the two-pot procedure using a sulfone starting material of formula (II) had been found to give very poor yields, as demonstrated in Annex A, and confirmed by the data provided in Annex C as well as by the third party during the first instance proceedings. There was no suggestion in the prior art that this initial failure could be overcome by means of the second measure of moving to a one-pot procedure.

XII. The respondent's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

The respondent disputed the appellant's submissions with respect to Article 100(c) EPC, and maintained that the skilled person, on reading the application as originally filed, would not have immediately detected that an error had occurred with respect to the structural formula (I). This was all the more true in view of the fact that the application as originally related not only to the preparation of oxazoline intermediates for the synthesis of florfenicol but also of analogues thereof. Moreover, the amino group at position 4 of the oxazoline ring appeared repeatedly in the application as originally filed, in general formula (I) itself, as well as in the corresponding formulae relating to specific embodiments. The skilled person would therefore have no reason to believe that these were not the intended structures. Concerning the higher oxidation state of the carbon atom at position 4 of the oxazoline ring in formula (I) compared to that of the corresponding atom in formula (III), the

respondent argued that the use of the term "comprising" in the definition of the claimed process meant that additional oxidation steps could not be ruled out.

Moreover, the respondent submitted that, even had the skilled person established that an error had occurred, it would not have been obvious how this should be corrected, since it was known from the prior art, such as documents (2), (8) and (21), that two regioisomers could be obtained in the present cyclisation step.

The respondent was therefore of the opinion that the requirements of Rule 139 EPC were not met with respect to the correction of formula (I).

The respondent supported its objection under Article 100(b) EPC with several lines of arguments.

The respondent firstly criticised that the stereochemistry defined in the structural formula (I) according to claim 1 was not adequately defined, since the carbon atoms at positions 4 and 5 of the oxazoline ring were drawn as bearing three substituents in a single plane. Owing to this ambiguity, the skilled person would be unable to work the invention.

Moreover, it was not apparent from the patent in suit how the skilled person could obtain an oxazoline of formula (I) with "4R trans" configuration starting from serine esters of formula (II) having stereo-configurations other than that specifically exemplified, or how the oxazolines of formula (I) were to be further processed to yield florfenicol. In particular, with reference to the definition of R" in claim 1, the

respondent argued that the patent in suit failed to provide sufficient information in order to allow the skilled person to synthesise florfenicol for the full scope claimed.

Finally, the respondent submitted that the reagents and solvents were very broadly defined in claim 1. The patent in suit failed to provide sufficient guidance with regard to the choice of suitable combinations of reducing agents and protic solvent for step (a), which would also be compatible with step (b). For example, certain combinations protic solvents and reducing agents might produce explosive mixtures. Therefore, the process as defined in claim 1 could not be performed by a skilled person within the entire scope claimed.

The respondent maintained its objection of lack of novelty of the subject-matter of claim 1 with respect to document (15). The respondent argued that the combination of specific features as now claimed could be derived from the following passages of document (15): page 1, lines 15 to 16, and the scheme on page 9, in combination with the definition of the substituent Y on page 3, lines 7 to 8. The respondent further submitted that the feature "in the same reaction vessel" was, at the very least, implicitly disclosed, for example, in claim 11.

In its assessment of inventive step, the respondent was also of the opinion that document (1) could be viewed as constituting the closest prior art, but also suggested that document (15) could serve as an equally suitable starting point.

The respondent argued that the experimental data provided by the appellant in Annexes A to C was full of inconsistencies and could not be reconciled with the yields obtained in prior art documents (1) and (2). In this context, the respondent referred to the submissions provided by a third party dated 9 April 2008 and also to the analysis of the opposition division in the decision under appeal. In the respondent's view, the data provided by the appellant was therefore to be regarded as being unreliable and should be disregarded.

The problem to be solved could therefore only be viewed as lying in the provision of a process for the synthesis of florfenicol which would be economical on an industrial scale.

The respondent submitted that use of a sulfone starting material was rendered obvious by document (15). Moreover, the skilled person would be aware of the fact that document (1) was a scientific publication. In developing the process for industrial purposes, the skilled person would inevitably consider reducing the number of reaction vessels used and cutting out unnecessary steps such as the isolation of intermediates. This was all the more true in view of the fact that the purity for the intermediate aminodiol as a crude product was quite acceptable, as confirmed by Annex A. The skilled person would therefore inevitably avoid purification steps, which were known to result in the loss of product yield. Moreover, it was known from the prior art that present steps (a) and (b) could both be conducted in protic solvents. This provided further incentive to combine these two steps

in a one-pot procedure. Certainly, no evidence of any prejudice against such a combination had been provided by the appellant.

XIII. The appellant (patent proprietor) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request corresponding to the former first auxiliary request submitted with the statement of grounds of appeal dated 17 December 2007, all previous requests having been withdrawn.

The respondent (opponent 02) requested that the appeal be dismissed.

XIV. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.

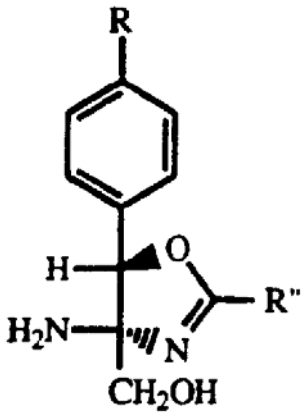
2. *Amendments (Articles 100(c), 123(3), 123(2) EPC)*

2.1 *Amendments of the structural formulae*

2.1.1 The sole objection raised under Article 100(c) EPC concerned the question of whether or not the amendments of the structural formulae representing oxazoline derivatives, found to be allowable under Rule 88 EPC 1973 (now Rule 139 EPC 2000) during examination proceedings, introduced subject-matter extending beyond the content of the application as filed. Since these

formulae are still present in the main request (cf. points I and X above), it must be decided whether these amendments represent corrections of an obvious error within the meaning of Rule 139 EPC.

2.1.2 Throughout the patent application as originally filed, the compounds of formula (I) are depicted as bearing an amino substituent at position 4 of the oxazoline ring, as illustrated by the following formula appearing in claim 1 as originally filed (see also claims 3, 4; page 2, line 1; page 6, lines 1, 2; page 8, lines 12 to 14, page 9, lines 10 to 12):



In the corresponding formulae disclosed in the main request, and in the specification of patent in suit, the amino substituent at position 4 of the oxazoline ring (H_2N-) has been replaced by hydrogen (H-) (cf. points I and X above, and also patent in suit, paragraphs [0003], [0013], [0022], [0024]).

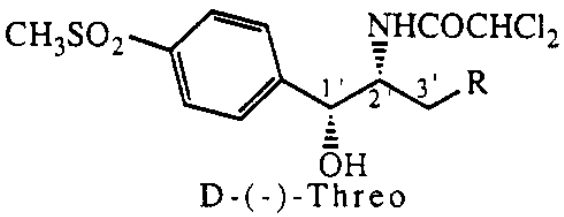
According to Rule 139 EPC, second sentence, "the correction must be obvious in the sense that it is immediately evident that nothing else would have been intended than what is offered as the correction". This means that it must be immediately apparent to the

skilled person that (i) an error had occurred and (ii) how it should be corrected.

2.1.3 Concerning requirement (i), it is noted that the application as originally filed discloses the oxazoline compounds of formula (I) as being obtained by reaction of an aminodiol of formula (III) with a nitrile of formula (IV) (see claim 1, step (b); page 3, lines 1 to 7; page 6, lines 1 to 3 in combination with page 7, lines 7 to 20). In examples 1 and 2, the aminodiol sulfone, referred to as ADS (see page 5, lines 11 to 13), is reacted with benzonitrile and dichloro-acetonitrile, respectively.

Mapping atoms from the starting material to product, the skilled person would immediately recognise that there was an inconsistency in the substitution pattern of the carbon atom bearing an amino substituent in formula (III) and the corresponding carbon atom in formula (I), that is, between the H_2N┼H fragment in the former and the H_2N┼N fragment in the latter.

Furthermore, in the application as originally filed, it is stated that "the present invention relates to intermediates to florfenicol" (see page 1, lines 7, 16), which is a known compound having the following structure (reproduced from document (2)):



D-(-)-Threo

1 R = F Florfenicol

On examining the structure of florfenicol (see 2'-position) and comparing it to that of formula (III), the skilled person would have immediately recognised that the H_2N-H fragment was intended to be conserved in the desired end product, and would therefore have identified the H_2N-N fragment in formula (I) as being erroneous.

This would have further been confirmed by the fact that the configuration at the oxazoline ring is specified to be "4R trans" in the application as originally filed (page 2, lines 4, 5 and page 11, lines 7, 8). The term "trans" in this context can only be intended to denote the relative arrangement on opposite sides of the ring of a substituent at position 4 and a substituent at position 5. The skilled person would therefore note a further contradiction, since the designation "trans" does not make any chemical sense for the structure depicted for formula (I) as originally filed, owing to the presence of two substituents at position 4.

The respondent's argument that it could not be excluded that formula (I) as originally filed was in fact the intended structure owing to the use of the terms "analogs" and "comprising" is not convincing:
There is no mention whatsoever in the originally filed application of the presence of an oxidising agent or of the possibility of an additional oxidising step. It is noted that the error in the oxazoline formula is also present in the examples, where an oxidising agent is certainly not present. Moreover, the wording used in claim 1, step (b), namely, "reacting a compound of formula III, with a compound of the formula IV ... **to**

obtain a compound of the formula I" (emphasis added) makes it clear that the compound of formula (I) is the direct product of the reaction between the compounds of formulae (III) and (IV) (see also page 3, lines 3 to 7). The skilled person would therefore recognise that an oxidation of the carbon atom at position 4 of the oxazoline ring was not intended and disregard this as being a chemical nonsense, particularly in view of the stated aim of providing "an efficient and economical process for preparing florfenicol" (application as originally filed, page 3, lines 8 to 10). As explained above, an oxazoline intermediate containing an H_2N–N fragment would not be suited to this aim.

Therefore, the board concludes that the skilled person would have no doubt that an error had occurred in the structure depicted for formula (I) as originally filed (cf. requirement (i)).

2.1.4 With respect to requirement (ii), it must be decided whether the corrected feature is directly and unambiguously derivable from the content of the application as originally filed taken as a whole.

The application as originally filed contains the following cross-reference to document (9) (see page 1, lines 17 to 20): "The intermediates described in the present specification can be used to prepare florfenicol as can be seen, for example, in U.S. Pat. No. 4,876,352, which is hereby incorporated by reference". The only intermediates disclosed in document (9) that match those disclosed in the present application as originally filed are the oxazolines of formula (II) (cf. claim 1 and column 2). Specific

embodiments thereof are disclosed in document (9) in Table I, claims 10 to 13, and as starting materials in the examples, for example, in examples 7 and 8 for the synthesis of florfenicol. In all these intermediates, the oxazoline ring bears a hydrogen atom and not an amino substituent at the position 4. Based on this information, the person skilled in the art would have no doubt that the H_2N- substituent present in the pictorial representations of formula (I) was a misprint that should be replaced by H-, thus removing all the contradictions outlined above.

The respondent's argument that the skilled person would not know how to correct the error once detected, is not considered to be convincing. It is true that the formation of a second regioisomer is possible in the reaction of an aminodiol of formula (IV) with a nitrile of formula (III) (cf. e.g. document (2), page 5292, scheme, compounds **6** and **8**; document (8), column 1, lines 25 to 30; document (21), formula (I)). However, it is evident from the cross-reference to document (9) that this is not the intended product, since said second regioisomer is not disclose therein. Moreover, the skilled person would ***a priori*** not consider the structure of the second regioisomer as a possible correction since it is structurally remote from the erroneous structure and does not include a stereocentre at position 4 of the oxazoline ring; the required "4R trans" configuration is therefore not possible for this structure.

Thus, the second requirement for allowing a correction in the sense of Rule 139 EPC is also fulfilled in the present case.

2.1.5 Accordingly, the amendment to formula (I) is allowable under Rule 139 EPC and does not introduce subject-matter that extends beyond the content of the application as originally filed. The ground for opposition according to Article 100(c) EPC does not therefore prejudice the maintenance of the patent on the basis of the main request.

2.2 The respondent did not raise any further objections under Articles 123(2) and 123(3) EPC resulting from the amendments made to the main request (cf. point X above), and the board sees no reason to differ. The amended set of claims of the main request is therefore also considered to meet the requirements of Articles 123(2) and 123(3) EPC.

3. *Sufficiency of disclosure (Articles 100(b), 83 EPC)*

3.1 In order to assess whether the requirement of sufficiency of disclosure is fulfilled in the present case, it must be assessed whether the patent in suit as a whole, that is, the claims and the description (including the examples), disclose the claimed synthesis of florfenicol in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, in the light of the general common knowledge of the technical field involved.

Present claim 1 relates to a process for producing florfenicol, which is an antibacterial agent of known structure (cf. patent in suit, paragraph [0002]; see also formula on page 14 above). The first step of the synthesis (step (a)) involves the reduction of a

phenylserine derivative of formula (II) in a protic solvent to obtain the aminodiol sulfone of formula (III), also known as ADS (cf. patent in suit, paragraph [0012], last line). Then, in the same reaction vessel, ADS is reacted with a nitrile of formula (IV) to obtain an oxazoline of formula (I) (step (b)), which is converted to florlenicol (step (c)).

The patent in suit provides two preparative examples illustrating the conversion of the D-*threo* stereoisomer of a phenylserine derivative of formula (II) into an oxazoline intermediate of formula (I) (examples 1 and 2). Further, details of suitable reaction conditions for steps (a) and (b) are given in paragraphs [0014] to [0017]. With respect to the further processing to florfenicol, the patent in suit refers to document (9) (see page 2, lines 12 to 14), and this cross-referenced document discloses present step (c) in examples 7 and 8.

3.2 The respondent's arguments are not considered to be persuasive for the following reasons:

As outlined under point 3.1, the stereoisomer to be used as starting material of formula (II) is defined in examples 1 and 2. Moreover, the configuration of the intermediate oxazoline of formula (I) is defined without ambiguity as being "4R trans". There appears to be no reason to doubt that, based on this information, the skilled person would be able to obtain the final product florfenicol having the correct absolute stereochemistry.

The objections of the respondent with respect to discrepancies or ambiguities in the pictorial representation of the stereochemistry in the formulae appearing in claim 1 relate to the issue of lack of clarity (Article 84 EPC) rather than to that of insufficient disclosure (Article 83 EPC). Since the features objected to were already present in the claims as granted, they are not open to objection under Article 84 EPC, which does not constitute a ground of opposition under Article 100 EPC.

The argument of the respondent with respect to the breadth of R" is also not convincing. According to document (9), the oxazoline of formula (I) wherein R" is phenyl is converted into florfenicol by fluorination of the free hydroxyl group, hydrolysis of the oxazoline group to give the corresponding 2-amino-3-fluoro-1-propanol, followed by a dichloroacetylation reaction (see example 7 for first step, and example 8 for second and third steps). Thus, in the second of these steps, the R" group is removed by hydrolysis. There is therefore no reason to suppose that the exact nature of this group is critical in the context of the present reaction.

Finally, the respondent did not provide any evidence to support its attack with respect to the reaction conditions used in present steps (a) and (b). This objection is to be rejected as being unsubstantiated in the absence of evidence to the contrary.

3.3 In view of the above considerations, the board sees no reason to doubt that the skilled person would be in a position to select appropriate starting materials of

formula (II) and convert these into florfenicol according to the method defined in claim 1.

Consequently, the requirement of sufficiency of disclosure is considered to be met by the main request and the objection under Article 100(b) EPC is to be rejected.

4. *Novelty (Articles 52(1) and 54 EPC)*

The respondent maintained its novelty objection with respect to document (15), mainly based on the scheme on page 9. This scheme depicts the enzymatic resolution of phenylserine esters of formulae (I) and (II) and their further processing by various alternative routes to a dichloroacetylated aminodiol derivative of formula IV. When Y is $-SO_2CH_3$, the compound of formula (IV) is known as thiamphenicol (page 10, lines 24 to 27), which serves as a starting material for preparing florfenicol (page 1, lines 15, 16). One of the routes disclosed in this scheme involves a reduction to produce an aminodiol of formula (III) followed by formation of an oxazoline of formula (V). However, there is no direct and unambiguous disclosure in document (15) that this specific reaction sequence is to be performed with compounds wherein Y is $-SO_2CH_3$. The only specific disclosure in this respect can be found on page 10, lines 21 to 27, wherein thiamphenicol is prepared by direct dichloroacetylation of the aminodiol of formula (III), and not via the oxazoline of formula (V). For this reason alone, said scheme cannot provide the basis for a successful novelty attack.

Furthermore, as pointed out by the appellant, several additional features of present claim 1 are not to be found in document (15), such as the requirement that the reduction and oxazoline formation are to be performed "in the same reaction vessel". Contrary to the assertions of the respondent, there is no disclosure of this feature, implicit or otherwise, in document (15). Indeed, separate paragraphs in document (15) deal with the reduction and oxazoline-formation steps (see page 10, lines 7 to 20 and page 11, lines 18 to 24, respectively).

Thus, the subject-matter of claim 1, and that of dependent claims 2 and 3, are novel over document (15).

None of the remaining cited prior art documents disclose a process according to present claim 1.

Accordingly, the subject-matter of the main request meets the requirements of novelty.

5. *Inventive step (Articles 52(1) and 56 EPC)*

5.1 The subject-matter of claim 1 relates to a process for producing florfenicol comprising two key steps, namely, reduction to obtain the aminodiol sulfone ADS, followed by oxazoline formation, in the same reaction vessel.

The board understands the feature "in the same reaction vessel" to mean that the intermediate ADS is formed and undergoes further reaction in a single reaction vessel without being isolated, in other words, in a so-called "one-pot" process. These two terms were used

interchangeably by the parties during the appeal proceedings.

The board considers, in agreement with the appellant and respondent, that document (1) represents the closest state of the art. Document (15), suggested as a possible alternative by the respondent, relates to similar subject-matter to that dealt with in document (1), but is a less suitable starting point since it only provides a general disclosure of the relevant reaction steps.

Document (1) relates to a process for the synthesis of florfenicol (see title and introduction). In the first step of the second reaction sequence disclosed on page 892, methyl D-*threo*-3-(4-methylthiophenyl)serinate hydrochloride ((2*S*,3*R*)-**5**.HCl) is reduced to give the corresponding (methylthiophenyl)aminodiol **6**. The detailed experimental procedure for this step is given on page 894, left-hand column. The reaction is performed on a milligram scale (377 mg of (2*S*,3*R*)-**5**.HCl), and the work-up procedure involves a filtration step, an extraction of the aqueous phase with dichloromethane, drying of the combined organic layers, and evaporation to give a white solid in 92% yield. A portion of this is recrystallised from methanol to provide white crystals in 75% yield.

In the second step of the reaction sequence, the aminodiol **6** is then subjected to condensation with benzonitrile followed by oxidation with peracetic acid, according to the method described in reference [8] to give a methylsulfonyl oxazoline derivative **7**, which corresponds to present formula (I) wherein R" is phenyl.

The corresponding experimental procedure in reference [8] (document (2) in present proceedings) can be found on page 5293, right-hand column, "Method B". In Scheme I of document (2), this reaction sequence corresponds to the conversion **3** → **5** → **7**. According to "Method B" this sequence is performed starting with 50.0 g of **3**, without isolation of **5**, to yield **7** in 93% yield. In document (2) the further conversion of **7** to florfenicol (**1**) is also disclosed (cf. Scheme I).

Thus, document (1), in combination with document (2) referenced therein, discloses a complete synthesis of florfenicol starting from the serinate sulfide (2*S*,3*R*)-**5**.HCl. The reduction thereof to the aminodiol is performed in a first step (document (1)), and the cyclisation and oxidation to the oxazoline sulfone of present formula (I) in a second step (document (2)). No precise yield is available for this two-pot procedure, since the two steps according to documents (1) and (2) are performed on very different scales (cf. previous two paragraphs). However, a rough estimate can be obtained by simple multiplication of yields, namely, 85% (92% × 93%) or 64% (92% × 75% × 93%), depending on whether the intermediate compound taken over to the second step is recrystallised or not.

5.2 The problem to be solved in the light of the closest prior art can be seen, as submitted by the appellant, as lying in the provision of an improved, industrially useful procedure for producing florfenicol.

The solution as defined in claim 1 relates to a combination of measures wherein the amino acid employed as starting material is a sulfone rather than a sulfide,

and wherein the two key steps of reduction and cyclisation are performed in the same reaction vessel, that is, in a one-pot synthesis.

5.3 As a next step, it has to be decided whether it has been rendered plausible that the problem defined under point 5.2 has been successfully solved with respect to the closest prior art.

The two distinguishing features listed under point 5.2 may be seen as providing advantages of relevance in developing an industrially useful procedure: as a result of the first measure, an oxidising agent is no longer required, given that the phenyl substituent is already in the correct oxidation state for producing florfenicol (CH_3SO_2-); as a result of the second measure, less solvent and equipment is required, since the work-up procedure disclosed in document (1) is avoided. However, that these features can actually be seen as providing an improvement presupposes that the resulting procedure is efficient in the sense of providing satisfactory yields, since it would otherwise not be of industrial relevance.

According to the examples of the patent in suit, the one-pot synthesis starting with 5 g of D-*threo*-(*p*-methylsulfonylphenyl)serine ethyl ester provides a yield of 81% for the compound of formula (I) wherein R" is phenyl (example 1), and 65% when R" is $-CHCl_2$ (example 2) (cf. specific compounds reproduced on page 3 above). In Annex B, the appellant repeated the one-pot synthesis on the smaller scale and with the reagents used in document (1) (368.5 mg), and obtained a yield of 53.3%. This reaction was repeated by

Professor Dötz of the University of Bonn, commissioned by the appellant: yields of ca. 85% and 94% were obtained (Annex C, experiment (b), entries 1 and 2). During the first instance proceedings, a third party submitted results according to which it had obtained yields of 55, 59 and 63% on repeating the process disclosed in example 1 of the patent in suit (cf. point VI above, and observations under Article 115 EPC dated 28 February 2007, received on 8 March 2007, page 6, last paragraph and page 7, first paragraph).

Summarising these results it may be concluded that yields varying between 53 and 94% have been obtained for the process according to the patent in suit, depending on scale, operator and reaction conditions. These yields can be considered to be satisfactory in the context of the present reaction, in the sense that they are comparable to those estimated for the prior art (cf. point 5.1, last paragraph).

Having regard to the considerations outlined above, the board is therefore satisfied that the problem posed has been credibly solved by the reaction defined in claim 1.

5.4 It remains to be investigated whether the proposed solution would have been obvious to the skilled person in the light of the prior art.

As already outlined under point 4 above, one of the routes generally disclosed in the scheme on page 9 of document (15) involves a reduction to produce an aminodiol of formula (III) followed by formation of an oxazoline of formula (V). The substituent Y, corresponding to present substituent R, is ***inter alia***

defined as being -S-R^2 or -SO_2R^2 wherein R^2 is alkyl (page 3, lines 7, 8). Thus, based on the teaching of document (15), the skilled person would have expected the methylsulfide (CH_3S-) and methylsulfonyl (CH_3SO_2-) derivatives to behave in a similar manner in the context of the disclosed reactions.

However, the appellant has demonstrated by means of comparative tests that this is not the case:

Thus, as outlined above under point 5.1 above, document (1) discloses the reduction of the serine ester bearing a CH_3S- substituent to give the corresponding crude aminodiol **6** in a yield of 92%, following filtration, extraction and drying. The yield for the subsequent crystallisation step is 75%. The overall yield is therefore 69% (92% × 75%). A similar overall yield of 68% was obtained by the appellant in Annex D.

In contrast, in Annex A, the corresponding results obtained for ADS starting from the serine ester bearing a CH_3SO_2- substituent were 61.6% for crude ADS, and 28.22% for the recrystallisation step, which amounts to an overall yield of 17.4%. According to Annex C, method (a), the corresponding results as repeated by Professor Dötz were (see entries 1 and 2, respectively): 64.3 and 52.7% for crude ADS, and an overall yield of 19.3% and 12.4%. Similarly, in Annex E, an overall yield of 10.3% was obtained for this process.

Therefore, the comparative data outlined in the previous two paragraphs convincingly demonstrate that, by simply substituting the starting methylsulfide amino

acid according to document (1) by the methylsulfonyl amino acid, according to the teaching of document (15), much worse yields would in fact be obtained.

Concerning the second distinguishing feature according to present claim 1, namely, that the steps (a) and (b) are performed "in the same reaction vessel", no information can be found in the cited prior art as to whether this type of reaction sequence would be amenable to a one-pot procedure, in the sense of producing satisfactory yields. The skilled person would therefore have no reason to expect that, by implementing this further modification, the problems of the poor yields obtained for ADS, as outlined above, could be overcome.

Consequently, no teaching can be found in the prior art that would have led the skilled person to the present modifications of the closest prior art reaction as a solution to the problem posed.

5.5 The respondent's arguments with respect to inventive step do not hold for the following reasons:

It cannot be accepted that the variability in the yields obtained is such that the data submitted by the appellant should be disregarded. A certain amount of variation in yield depending on scale, reaction conditions and skill of operator is to be expected. As explained above under points 5.3 and 5.4, the data in question cannot be regarded as being irrelevant, since consistent trends and meaningful conclusions can be derived therefrom.

Moreover, it is true that a one-pot synthesis may, in principle, be a desirable strategy that would be considered by the skilled person involved in process development. However, this does not mean that the skilled person would expect that this could be successfully implemented regardless of the multistep process under consideration. In the present case, document (1) teaches that the insolubles generated after hydrolysis of the reducing agent should be removed by filtration, before the aminodiol is taken through to the subsequent step (see page 894, left-hand column). There is no suggestion in the prior art that comparable yields would be obtained if the filtration step were to be omitted. In other words, although there may be no prejudice against combining present steps (a) and (b), there was also no expectation that satisfactory yields would be obtained on doing so.

5.6 Hence, the subject-matter of claim 1 of the main request involves an inventive step. The same is true of dependent claims 2 and 3.

Accordingly, it is concluded that the subject-matter of the claim set according to the main request meets the requirements of Articles 52(1) and 56 EPC.

6. *Remittal (Article 111(1) EPC)*

The description has yet to be adapted to the allowable claims according to the main request. For this purpose, the board exercises its discretion under Article 111(1) EPC and remits the case to the department of first instance.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside but for the order on the apportionment of costs.

2. The case is remitted to the department of first instance with the order to maintain the patent as amended in the following version:

   – claims 1—3 of the main request filed as 1st auxiliary request with the statement of grounds of appeal dated 17 December 2007

   – and a description to be adapted accordingly.

The Registrar: The Chairman:

M. Schalow P. Ranguis