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D E C I S I O N
of 13 November 2002

Case Number: T 0211/02 - 3.3.1

Application Number: 93907437.3

Publication Number: 0631581

IPC: C07D 475/04

Language of the proceedings: EN

Title of invention:
Intermediates and a process for synthesis of tetrahydropteridine C6-stereoisomers, including (6S)-tetrahydrofolate and N5-formyl-(6S)-tetrahydrofolate

Applicant:
BAILEY, StevenW., et al

Opponent:
-

Headword:
Tetrahydropteridines/BAILY, et al

Relevant legal provisions:
EPC Art. 56, 84, 111(1), 113(2)
EPC R. 67

Keyword:
"Remittal (no) - claim submitted at appeal stage consistutes a fresh case but contains subject-matter objected by the first instance"
"Clarity (yes) - allowable functional feature"
"Inventive step (yes) - non-obvious solution of the technical problem"
"Reimbursement of appeal fee (yes) - substantial procedureal violation"

Decisions cited:
T 0068/85, T 0694/92

Catchword:
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Case Number: T 0211/02 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 13 November 2002

Appellant: BAILEY, StevenW.
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Decision under appeal: Decision of the Examining Division of the European Patent Office posted 18 September 2001 refusing European patent application No. 93 907 437.3 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: A. J. Nuss
Members: J. M. Jonk
S. C. Perryman

Summary of Facts and Submissions

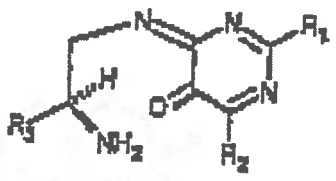
I. This appeal lies from the decision of the Examining Division refusing the European patent application No. 93 907 437.3, published under the International Publication Number WO 93/19069, on the grounds that the subject-matter of Claim 3 as submitted by letter dated 22 June 1998 lacked clarity within the meaning of Article 84 EPC, and inventive step within the meaning of Article 56 EPC in view of documents

(1) EP-B-0 138 995, and

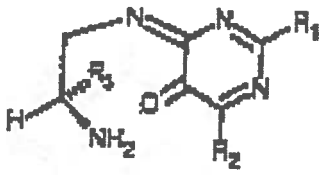
(2) EP-A-0 108 890.

II. Said Claim 3 related to a process for preparing 6-monosubstituted tetrahydropteridine C6-enantiomers comprising

(a) subjecting a ketopyrimidine 2'-enantiomer of the formula II or II':



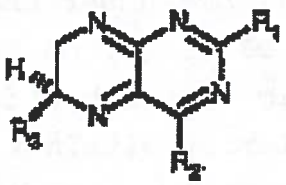
II



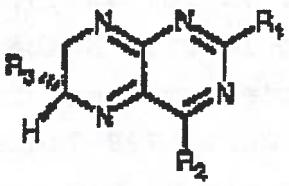
II'

said 5-ketopyrimidine 2'-enantiomer being in an acidic solution, to a chirality maintaining cyclisation, wherein said chirality maintaining cyclisation comprises adjustment of the pH of said acidic solution to a pH of between about 8 and 12 (the term pH as used herein, when said solution is primarily non-aqueous, referring to the pH of the solution after 10-fold dilution with water) to

give a solution of a 6-monosubstituted quinoid dihydropteridine enantiomer of formula VIII or VIII', respectively:



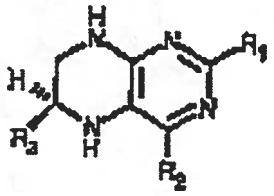
VIII



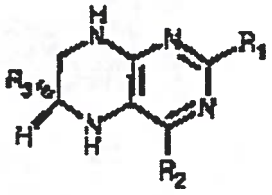
VIII'

and

(b) subjecting said solution of a 6-monosubstituted quinoid dihydropteridine enantiomer to a chirality maintaining reduction comprising addition of a reductant, said reductant being capable of reducing quinoid dihydropteridines, but not 7,8-dihydropteridines, to tetrahydropteridines to give a 6-monosubstituted tetrahydropteridine enantiomer of the formula IX or IX', respectively:



IX



IX'

possessing substantial C6 enantiomeric purity,

wherein R^1, R^2 and R^3 of the formulae have the specified meanings.

III. The Examining Division held in particular that said Claim 3, having regard to the functionally defined reductant as applied in the chirality maintaining reduction step (b), was not acceptable under Article 84 EPC, since in view of the relevant state of the art it merely claimed the underlying technical problem instead of seeking protection in terms of clear technical features, such that the skilled person, after reading the description, would be able to readily perform the invention over the whole area claimed without undue burden and without needing inventive skill. In this context, it referred to the "Headnote of Decision T 694/92".

Furthermore, it held with respect to inventive step that the skilled person, who was interested in the synthesis of a 6-monosubstituted tetrahydropteridine C6-enantiomer would have tried to adapt the process known from documents (1) and (2) by using a chiral starting material and selecting a reductant suitable to retain the chirality at the 6-position. Accordingly he would have tested the reductants known from documents (1) and (2) and in doing so automatically arrive at particular reductants, such as mercaptoethanol, falling under the scope of Claim 3. Such a routine testing of said known reductants did not involve an inventive step.

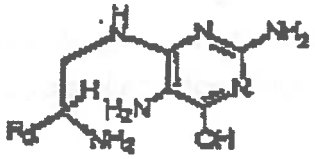
IV. Oral proceedings before the Board were held on 13 November 2002.

V. The Appellant firstly observed that the Examining Division based its decision to refuse the present application on a wrong Claim 3, ie a claim which did not correspond to Claim 3 of the main request then on file, and that already for this reason the decision under appeal had to be set aside.

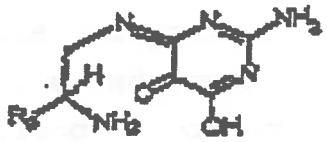
VI. Furthermore, he defended the patentability of the subject-matter of the present application on the basis of a set of claims filed during the oral proceedings before the Board on 13 November 2002 comprising independent Claims 1 and 3, which both essentially corresponded to those of the main request actually on file before the Examining Division.

Independent **Claim 3** of this set of claims related to the process set out under point II above, except that, **according to step (a)**, the starting compound of formula II or II' being in an acidic solution **in a concentration of less than 0.1 M** was subjected to a **C6**-chirality maintaining cyclisation, wherein said chirality maintaining cyclisation comprised adjustment of the pH of said acidic solution, **at a temperature of less than 5°C**, to a pH of between 8 and 12 to give a solution of a 6-monosubstituted quinoid dihydropteridine enantiomer of formula VIII or VIII', respectively, and **according to step (b)**, the solution obtained in step (a) was subjected to a **C6**-chirality maintaining reduction.

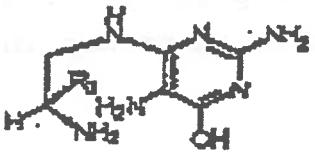
Independent **Claim 1** concerned intermediates of the formulae I, II, I' and II'



I



II



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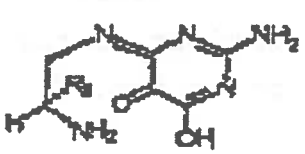

II'

for the synthesis of 6-monosubstituted tetrahydropteridine C6-enantiomers, wherein R_3 has the specified meanings.

VII. The Appellant argued that the functionally defined reductant as applied in step (b) of the process of present Claim 3 met the requirements of Article 84 EPC, since otherwise a proper scope of protection would not be possible, and because a skilled person would have no difficulty in verifying whether or not a given reducing agent would meet the functional requirements of the claim. In support, he referred to a statement from Dr June Ayling and a test-report both submitted on 13 October 2002.

Furthermore, concerning inventive step, he essentially argued:

- that document (2) represented the closest prior art;

- that in the light of this document the technical problem underlying the present patent application, and successfully solved, was the provision of a

process for preparing 6-monosubstituted tetrahydropteridines having a desired stereochemistry and optical activity with regard to the C6 position; and

- that the solution of this technical problem in accordance with Claim 3, in particular by using the cyclisation step indicated under (a), was not obvious to the skilled person in view of the cited prior art.

VIII. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of Claims 1 to 8 of the request filed at oral proceedings on 13 November 2002, and that the appeal fee be reimbursed.

IX. At the conclusion of the oral proceedings the Board's decision was pronounced.

Reasons for the Decision

1. The appeal is admissible.

2. *Procedural matters*

2.1 The Board concurs with the Appellant's submission that the Examining Division based its decision on a wrong Claim 3, ie on a claim which did not correspond to Claim 3 of the main request then on file. Therefore, already for this reason the decision under appeal has to be set aside (Article 113(2) EPC), and the case not yet having been considered by the Examining Division could be remitted for further prosecution on the basis of the present set of Claims (Article 111(1) EPC). However, since present Claim 3 comprises a functional

feature, which was already present in Claim 3 considered by the Examining Division and found to be not allowable in its decision, the Board in the exercise of its discretion under Article 111(1) EPC deems it appropriate to deal with the case itself.

3. *Amendments under Article 123(2) EPC*

3.1 Present Claim 3 is supported by:

- Claim 3 as originally filed;

- page 8, lines 1 to 3, and the paragraph bridging pages 8 and 9 of the application as filed with respect to the acidic solution of the 5-ketopyrimidine 2'-enantiomer;

- Claim 8 as originally filed concerning the concentration of the 5-ketopyrimidine 2'-enantiomer in the acidic solution of less than 0.1 M;

- page 9 of the application as filed under "Cyclization", lines 5 and 6, and 10 to 13, with respect to the performance of the cyclisation at a temperature of less than 5°C;

- page 9 of the application as filed under "Cyclization", lines 1 to 7, concerning the adjustment of the pH;

- page 11 of the application as filed, last paragraph, lines 1 and 2, concerning the measuring of the pH values; and

- page 8 of the application as filed, first paragraph, lines 6 and 7, concerning the functional definition of the reductant.

Present Claim 7, which is dependent from present Claim 3, is supported by:

- Claim 8 as originally filed;

- page 8, lines 1 to 3, and the paragraph bridging pages 8 and 9 of the application as filed concerning the acidic solution of the 5-ketopyrimidine 2'-enantiomer;

- page 9, second paragraph, line 9, of the application as filed in relation to the use of an alkali or alkaline earth hydroxide; and

- page 9 of the application as filed, last paragraph, with respect to the timing of the addition of the reductant.

Present Claim 8 is supported by page 10 of the application as filed, first paragraph, lines 4 to 9.

Present Claims 1, 2, 4, 5 and 6 are supported by Claims 1, 2, 4, 5, and 6, respectively, of the application as filed.

3.2 Therefore, the subject-matter of present Claim 1 does not contravene Article 123(2) EPC, which requires that no subject-matter extending beyond the application as filed is added by an amendment to a European patent or patent application.

4. *Clarity under Article 84 EPC*

4.1 Having regard to the clarity objection of the Examining Division concerning the functionally defined reductant as applied in the chirality maintaining reduction step (b) as indicated under point III above, the Board firstly observes that according to the established

jurisprudence of the boards of appeal (see, for instance, T 68/85, OJ EPO 1987, 228, under points 8.2 to 8.4.3) functional features defining a technical result are permissible in a claim

(i) if such features cannot otherwise be defined more precisely without restricting the scope of the invention, and thus without rendering it possible to secure an adequate and reasonable protection, and

(ii) if these features provide instructions which are sufficiently clear for a person skilled in the art in the light of the disclosure of the patent application and on the basis of common general knowledge to reduce them to practice without undue burden, if necessary with reasonable experiments.

4.2 In this respect, the Examining Division held essentially that the functional feature as defined in the C6 chirality maintaining reduction step (b) was the sole technical feature differentiating the claimed process from the closest prior art, and consequently represented the main technical contribution over this prior art. Moreover, it considered that the skilled person would have to determine by trial and error whether a particular reducing agent had the required selectivity and that it was evident that the finding of suitable reducing agents would not be possible without undue burden. It concluded, that under these circumstances, and in accordance with the decision T 694/92, Claim 3 did not comply with the clarity requirement of Article 84 EPC.

4.3 However, these findings were based on a wrong claim version, which - as indicated above (points V and VI) - did not comprise the C6-chirality maintaining cyclisation step (a) of present Claim 3 involving the

presence of the starting compound of formula II or II' in an acidic solution **in a concentration of less than 0.1 M**, and the adjustment of the pH of said acidic solution **at a temperature of less than 5°C**.

Moreover, as submitted by the Respondent and also follows from the specification of the present application (see page 9, second paragraph), said concentration of the starting compound and said temperature condition as claimed are necessary in order to achieve a substantial C6-chirality maintaining cyclisation and, therefore, represent essential technical features of the claimed invention.

Therefore, the Board cannot accept the conclusion of the Examining Division that the functional feature as defined in the C6-chirality maintaining reduction step (b) was the sole technical feature differentiating the claimed process from the closest prior art.

4.4 Furthermore, the Board concurs with the Appellant's submission, that in the circumstances of the present case, in which the cyclisation step as claimed under (a) represents a critical step of the claimed process (see also point 4.3, second paragraph, above), a restriction of the reduction step (b) to the use of merely a thiol reagent, a dithionite salt and ascorbic acid exemplified in the specification of the application in suit as suitable reducing agents (see page 10, first paragraph), so as to render the claimed subject-matter more precise, would mean limiting the scope of the invention unjustifiable to particular embodiments and thus restricting the scope of protection to only part of the invention as disclosed.

In this context, it is the Board's position that, because of the structural diversity of said suitable reducing agents, the skilled person would rather expect that also other reducing agents would be applicable, and that it would be difficult to define classes of reducing agents which would meet the selectivity criteria without unduly limiting the scope of the invention. This point of view is supported by the test-report filed by the Appellant on 13 October 2002 showing that dihydroxyfumaric acid and tris-(2-carboxyethyl)-phosphine hydrochloride also represent suitable reducing agents.

4.5 The Board also concurs with the Appellant's submissions that in the light of the common general knowledge in the art the functional feature as defined under (b) of present Claim 3 provides indeed instructions which are sufficiently clear for the skilled person to reduce them to practice without undue burden and without undue experimentation. Lists of reducing agents can be derived from standard reference sources and a large number of them are commercially available. Moreover, as the Appellant plausibly submitted, the selection of a suitable reducing agent at the time of the filing date of the application in suit was not a random exercise to the skilled person, since the electrochemical half potential of quinoid dihydropteridines was known and hence provided an indication of the minimum strength of the reducing agent needed, and because it was generally known that hydride reducing agents, such as lithium aluminium hydride and sodium borohydride would reduce imine bonds such as present in the 7,8-dihydropteridines. Furthermore, the Board observes that it could be directly and positively verified by standard chemical test methods whether or not a

particular reducing agent will reduce the quinoid dihydropteridine of formula VII or VIII', but not 7,8-dihydropteridines, to give the desired compound of formula IX or IX'.

4.6 Finally, the Board observes that according to the decision T 694/92 referred to by the Examining Division in situations, in which an invention consists in the achievement of a certain technical effect by a functionally defined process feature, a proper balance must be found between, on the one hand, the actual technical contribution to the state of the art by said invention, and, on the other hand, the terms in which it is claimed, so that, if patent protection is granted, its scope is fair and adequate, and that in such situations, in which the skilled person would not be able to readily perform the claimed invention over the whole area claimed without undue burden, ample technical details restricting the scope of the claim would be necessary (see points 3,4 and 5 of the Reasons for the Decision).

These considerations are in fact in line with the established jurisprudence of the boards of appeal as summarised under point 4.1 above. Moreover, as for the amount of technical detail providing instructions which are sufficiently clear for the skilled person to reduce them to practice without undue burden, ie with no more than a reasonable amount of experimentation, and without applying inventive skill, this is a matter which depends on the correlation of the facts of each particular case.

4.7 Thus, in the circumstances of the present case and in view of the above considerations, the Board concludes that present Claim 3 meets the clarity requirement within the meaning of Article 84 EPC.

5. *Novelty*

5.1 After examination of the cited prior art, the Board has reached the conclusion that the subject-matter of the present claims is novel. Since novelty was not in dispute, it is not necessary to give reasons for this findings.

6. *Inventive step*

6.1 Article 56 EPC states that an invention is held to involve an inventive step if, having regard to the state of the art (in the sense of Article 54(2) EPC), it is not obvious to a person skilled in the art.

6.2 For deciding whether or not a claimed invention meets this criterion, the Boards of Appeal consistently apply the problem and solution approach, which involves essentially identifying the closest prior art, determining in the light thereof the technical problem which the claimed invention addresses and successfully solves, and examining whether or not the claimed solution to this problem is obvious for the skilled person in view of the state of the art.

6.3 The Board considers, in agreement with both the Appellant and the Examining Division, that the closest state of the art with respect to the claimed subject-matter of the application in suit is the disclosure of document (2).

This document is concerned with 6-monosubstituted and 6,6-disubstituted tetrahydropteridines, and their preparation comprising a cyclisation step and a reduction step (see page 1, last paragraph, to page 3, fourth paragraph; and page 7, last line, to page 9, last paragraph, line 6). Furthermore, it discloses that said compounds contain asymmetric carbon atoms and

therefore may be obtained in different isomeric forms and as mixtures of isomeric forms (see page 4, second paragraph). However, it provides no teachings as how to obtain optically active forms.

6.4 Thus, in the light of the closest state of the art, the technical problem underlying the application in suit can be seen in the provision of a process for preparing 6-monosubstituted tetrahydropteridines C6-enantiomers (see page 3, lines 4 and 5, of the application in suit).

6.5 According to present Claim 3 this technical problem is essentially solved by a C6-chirality maintaining cyclisation of a 5-ketopyrimidine 2'-enantiomer of formula II or II' using specific reaction conditions as defined under (a) to give a 6-monosubstituted quinoid dihydropteridine enantiomer of formula VIII or VIII', and, subsequently, a C6-chirality maintaining reduction of said 6-monosubstituted quinoid dihydropteridine enantiomer using an appropriate reduction agent as functionally defined under (b) to give the desired enantiomer of formula IX or IX', whilst substantially avoiding the forming of 7,8-dihydropteridines.

The fact, that the examples of the application in suit give rise to the formation of C6 enantiomers having a high chiralic purity amply illustrates that this technical problem has been solved. Further examples illustrating the effectiveness of the claimed process in this respect were submitted with letter of 8 April 1999.

6.6 The question now is whether the claimed solution of said technical problem would have been obvious to the skilled person in view of the cited prior art.

6.7 As indicated above, document (2) does not provide any teaching as to how to obtain optically active forms of the compounds disclosed therein. In fact, the preferred compounds are the (+/-) compounds, ie **mixtures of + and - enantiomers** (see page 4, first paragraph, last sentence). Furthermore, this document is of no help when trying to solve the above defined technical problem as it does not disclose or suggest the process parameters defined under (a) of present Claim 3, ie the concentration of the starting compound of formula II or II' of less than 0.1 M and the adjustment of the pH to a value between 8 and 12 at a temperature of less than 5°C. Therefore, already in view of these essential process parameters, this document does not provide the skilled person with a useful pointer to the solution of the above defined technical problem as claimed.

6.8 Document (1) is less relevant than document (2), since it is only concerned with **racemic 6,6-disubstituted tetrahydropteridines** (see page 7, line 29, to page 10, line 31; and page 13, lines 27 to 34) and not with 6-**monosubstituted** tetrahydropteridine **C6-enantiomers**. It is true, that it discloses a process for preparing said racemic 6.6-disubstituted compounds comprising a cyclisation step and a reduction step (see page 28, Scheme I; page 34, lines 9 to 30), but - as in case of document (2) - it does not disclose or suggest a cyclisation step comprising the process parameters defined under (a) of present Claim 3, ie the concentration of the starting compound of formula II or II' of less than 0.1 M and the adjustment of the pH to a value between 8 and 12 at a temperature of less than 5°C in order to achieve 6-monosubstituted C6-enantiomers.

6.9 Thus, in view of these considerations, the Board concludes that the solution of the above defined technical problem as claimed in Claim 3 of the patent in suit is not obvious to the skilled person in the light of the cited documents, and consequently involves an inventive step in the sense of Article 56 EPC.

Independent present Claim 1 relates to intermediate compounds, which - in accordance with the established jurisprudence of the boards of appeal - are deemed inventive, since their preparation took place in connection with an inventive preparation method.

Claim 2 and Claims 4 to 8 relate to particular embodiments of the subject-matter of Claim 1 and Claim 3, respectively. They are therefore also allowable.

7. *Reimbursement of the appeal fee*

7.1 According to Rule 67 EPC, 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.

7.2 In the present case, the Appellant has been successful on appeal to the extent requested. The fact that the decision to refuse the present application was based on a claim not agreed upon by the Applicant constitutes a substantial procedural violation (Article 113(2) EPC). Having regard to the fact that the Examining Division mistakenly emphasised in its decision that the functionally defined process step (b) of Claim 3 was the sole technical feature differentiating the claimed process from the closest prior art, and consequently represented the main technical contribution over this prior art, so that an appeal would probably have been

unnecessary if the Examining Division had considered the right Claim 3 comprising the cyclisation step (a) as the most critical technical feature of the claimed invention, in the Board's judgment, it is therefore equitable to reimburse the appeal fee pursuant to Rule 67 EPC.

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 grant a patent on the basis of Claims 1 to 8 of the request filed at oral proceedings on 13 November 2002 and a description to be adapted.

3. The appeal fee is to be reimbursed.

The Registrar: The Chairman:

N. Maslin A. Nuss