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Anmeldenummer / Filing No / N° de la demande : 79 102 058.9
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Bezeichnung der Erfindung: Method for stabilizing hydrolysis-prone labile
Title of invention: organic reagents in liquid media and so stabilized
Titre de l'invention: product

ENTSCHEIDUNG / DECISION

vom / of / du 23 July 1984

Anmelder / Applicant / Demandeur : Modrovich, Ivan Endre

Stichwort / Headword / Référence :

EPO / EPC / CBE	Article 123(2)	Article 111 (1)
	Amendments to claims	Remittal of the case

Leitsatz / Headnote / Sommaire



Case Number : T 18/83

DECISION
of the Technical Board of Appeal 3.4.1
of 23 July 1984

Appellant: Modrovich, Ivan Endre
628 Calle Plano
Camarillo California 93010
USA

Representative: Patentanwälte
Dipl.-Ing. A. Grünecker, Dr.-Ing. H. Kinkeldey,
Dr.-Ing. W. Stockmair, Dr.rer.nat. K. Schumann,
Dipl.-Ing. P.H. Jakob, Dr.rer.nat. G. Bezold
Maximilianstr. 43
D-8000 München 22
Bundesrepublik Deutschland

Decision under appeal: Decision of Examining Division 061 of the
European Patent Office dated 2 August 1982
refusing European patent application
No 79 102 058.9 pursuant to Article 97 (1) EPC

Composition of the Board:

Chairman: R. Kaiser
Member: O. Huber
Member: P. Ford

Summary of Facts and Submissions

- I. European patent application No. 79 102 058.9 entitled "Method for stabilizing hydrolysis-prone labile organic reagents in liquid media and so stabilized product", filed on 21 June 1979 and published on 9 January 1980 (publication No. 0 006 582) and claiming priority of 26 June 1978 from a previous application in the USA, was refused by decision of Examining Division 061 of the European Patent Office dated 2 August 1982 on the basis of Claims 1-28 received on 1 March 1982. The ground for refusal was that it would be obvious to a man skilled in the art to stabilize the unstable organic reagents enumerated in Claim 1 in the same way as disclosed in FR-A-2 344 570 and FR-A-2 308 639 for the stabilization of labile coenzymes. Therefore, no inventive step was seen in the subject matter of Claim 1 (Articles 56 and 52(1)).
- II. On 1 October 1982 the appellant lodged an appeal against the decision and paid the appeal fee. The appellant submitted a Statement of Grounds on 2 December 1982. On 24 February 1984 two sets of Claims (main request and auxiliary request) were submitted. In response to a communication of the rapporteur dated 26 March 1984 the appellant submitted two new sets of Claims (main request and auxiliary request) on 4 June 1984. Claim 1 of the main request is practically identical with Claim 1 of the auxiliary request received on 24 February 1984. The presently effective main Claims read as follows:

a) main request:

A method for stabilizing a labile organic reagent which is unstable in an aqueous medium and stable in a non-aqueous medium which comprises the steps of dissolving at least one reagent which is gamma-glutamyl-p-nitroanilide or bilirubin in a water-miscible organic solvent which is liquid at room temperature and which is nondegradably reactive with respect to such organic reagent to form a solution of the organic reagent in the organic solvent, said organic solvent comprising dimethylsulfoxide, acetone, and mixtures thereof; adding at least one percent by weight of inert, high-surface-area, particulate desiccant in the solvent, either before or after dissolving the reagent in the solvent, for entrapping water with the desiccant so that the residual water content in solution is below 0.5 percent; and sealing the solution.

b) auxiliary request:

A method for stabilizing a labile organic reagent which is unstable in an aqueous medium and stable in a non-aqueous medium which comprises the steps of dissolving gammaglutamyl-p-nitroanilide in a water-miscible organic solvent which is liquid at room temperature and which is nondegradably reactive with respect to such organic reagent to form a solution of the organic reagent in the organic solvent, said organic solvent comprising dimethylsulfoxide or a mixture of dimethylsulfoxide and acetone; adding at least one percent by weight of inert, high-surface-area, particulate desiccant in the solvent, either before or after dissolving the reagent in the solvent, for entrapping water with

the desiccant so that the residual water content in solution is below 0.5 percent; and sealing the solution.

In the above-mentioned communication, the rapporteur pointed out that the combination bilirubin - acetone or mixture of acetone and dimethylsulfoxide (DMSO) included in the present Claim 1 according to the main request was not sufficiently disclosed in the original documents and that such a claim would not be allowable pursuant to Article 123(2) EPC. In response to the communication dated 26 March 1984, the applicant's representative argued that the combination in question has not been spelled out in the original documents but it nevertheless has been disclosed by a combined reading of originally filed Claims 1, 7 and 10 which have the following wording:

1. A method for stabilizing a labile organic reagent which is unstable in aqueous media and stable in a non-aqueous media comprising the steps of:

A. dissolving at least one such organic reagent in a water-miscible, organic solvent which is liquid at room temperature and which is nondegradatively reactive with such organic reagent to form a solution of such organic reagent in the organic solvent;

B. adding at least 1 percent by weight of an inert, high surface area, particulate dessicant, to the solvent either before or after dissolving the reagent in the solvent for entrapping water with the dessicant so that the residual water content of the solution is below about 0.5 percent; and sealing the solution.

7. A method of claim 1 in which the step of dissolving an organic reagent selected from the group consisting of:

.....
 bilirubin

10. The method of claim 1 in which the step of adding gamma glutamyl-p-nitroanilide (to) a solvent selected from the group consisting of dimethylsulfoxide, acetone, and combinations thereof.

Since original claims 7 and 10 has been referred back to Claim 1 the latter giving the overall concept, in view of the appellant, the combination bilirubin - acetone or mixture of acetone and DMSO is also disclosed. Furthermore, regarding the basic idea of the original application the original disclosure is not restricted to the compounds that are explicitly mentioned.

III. The appellant has requested the cancellation of the decision refusing the European patent application and according to the main request the grant of a patent - clearly on the basis of Claims 1 and 2 filed on 4 June 1984 and according to the alternative request the remittal of the case to Examining Division for further prosecution on the basis of Claims 1 and 2 as an auxiliary request filed on 4 June 1984.

Reasons for the Decision

1. The appeal complies with Articles 106 - 108 and Rule 64 EPC and is therefore admissible.

2. Concerning the main request:

It has to be examined whether Claim 1 extends beyond the content of the application as filed (Article 123(2) EPC). Claim 1 also comprises the combination bilirubin as labile organic reagent - acetone or a mixture of acetone and DMSO as solvent. The original Claim 7 listed a number of organic reagents, including bilirubin, for stabilizing according to the overall concept of Claim 1. Indeed, in the original Claim 10, as dependent upon Claim 1, the use of acetone or a mixture of acetone and DMSO as solvents is mentioned but only in combination with gamma-glutamyl-p-nitroanilide as reagent. Claim 10 does not disclose the feature that acetone or mixtures of acetone and DMSO are appropriate solvents for all the reagents listed in Claim 7 and therefore also for bilirubin. In the original documents only DMSO (see Claim 15 and Example 8) or a mixture of phenol and methanol (see Claim 16 and Example 9) are specified as solvents for bilirubin. There is therefore nothing in any of the original documents to indicate that the method for stabilizing bilirubin now claimed in Claim 1 can be considered to be adequately disclosed. This lack of disclosure is not compensated for by the fact that original Claim 1 is not restricted to specified reagents and solvents but offers a general teaching. Such a general claim may be limited to particular combinations of reagents and solvents but they must be indicated in the original documents.

The patent application has consequently been amended in such a way that it now contains subject-matter which extends beyond the content of the application as filed. This constitutes an infringement of Article 123(2) EPC.

Claim 1 is therefore not allowable.

Claim 2 is formulated as a dependent claim. It is not allowable since its existence is conditional on the allowability of Claim 1.

3. Concerning the auxiliary request :

3.1 There can be no objection to the present Claim 1 on formal grounds. It is adequately supported by the original documents, see Claims 1 and 10.

3.2 The method according to Claim 1 as far as it concerns the different steps, namely dissolving the organic reagent in water-miscible organic solvent, adding at least 1% by weight of a desiccant so that the residual water content in solution is below 0,5% and sealing the solution in a container, is known from FR-A-2 344 570 for stabilizing coenzymes, e.g. NADH_2 . The solution may additionally contain other unstable organic compounds, see page 9, line 11-31. Stabilizing of gammaglutamyl-p-nitroanilide and the use of DMSO or a mixture of DMSO and acetone as solvent is not mentioned in this document.

In FR-A-2 308 639 only the stabilization of NADH_2 by dissolving it in a dry, water-miscible solvent is described. The cited solvents are neither DMSO nor acetone.

According to US-A-3 776 900 stabilization of reduced coenzymes such as reduced diphosphopyridine nucleotide and reduced triphosphopyridine nucleotide is achieved

by dissolving the reduced coenzyme in a solvent mixture consisting of a water-soluble alkanol and a water-soluble polyhydroxyalcohol.

Page 1403 in "Clinical Chemistry" by R.J. Henry, D.C. Cannon and J.W. Winkelman, second edition 1974, relates to the extraction of cholesterol, and page 1054 provides the teaching to dissolve bilirubin in DMSO and to add albumin in order to prolong the utility in the deep freeze.

A Text-Book of Practical Organic Chemistry by A.I. Vogel, third edition, 1957, page 965, recommends storing the unstable reagent xanthidrol in the form of an alcoholic solution.

None of the cited documents refers to the stabilizaion of gammaglutamyl-p-nitroanilide.

Thus the subject matter of the application, as set out in Claim 1, is new.

- 3.3 The Examining Division has not examined whether the method according to the new Claim 1, filed on 4 June 1984, has an inventive step. Therefore the case must be remitted to the Examining Division (Article 111(1) EPC) as the appellant has already suggested in the letter dated 4 June 194, page 4, last paragraph.

Order

For these reasons, it is decided that:

- (1) The decision of the Examining Division of the European Patent Office dated 2 August 1982 is set aside.
- (2) The appeal, insofar as it relates to the set of Claims according to the main request is rejected.
- (3) The case is remitted to Examining Division for further prosecution on the basis of Claims 1 and 2 as an auxiliary request, filed on 4 June 1984.

The Registrar:

J. Ruckerl

The Chairman:

R. Kaiser