BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS | BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE | CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

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File Number: T 665/92 - 3.3.1

Application No.: 87 307 510.5

Publication No.: 0 266 033

Title of invention: Process for the preparation of indoline-2 derivatives

Classification: C07D 209/34

D E C I S I O N
of 11 January 1993

Applicant: Smith Kline & French Laboratories Limited

Headword: Indolines/SMITH KLINE

EPC Articles 54 and 56

Keyword: "Novelty (confirmed)"
"Inventive step (confirmed)"

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number : T 665/92 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 11 January 1993

Appellant : Smith Kline & French Laboratories Limited
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Representative : Giddings, Peter John, Dr. et al
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Decision under appeal : Decision of the Examining Division 005 of the European Patent Office dated 9 April 1992 refusing European patent application No. 87 307 510.5 pursuant to Article 97(1) EPC.

Composition of the Board :

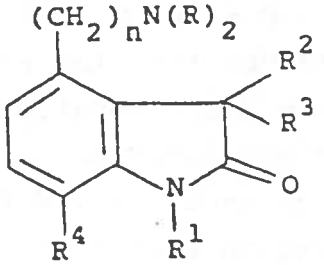
Chairman : K.J.A. Jahn
Members : R.W. Andrews
J-C. Saisset

Summary of Facts and Submissions

I. European patent application No. 87 307 510.5 (publication No. 0 266 033) was filed on 25 August 1987.

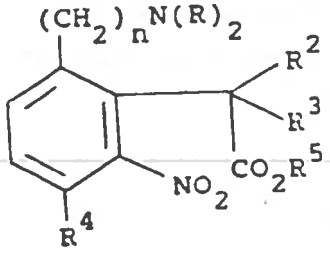
II. By a decision dated 9 April 1992 the Examining Division refused the application on the grounds that the subject-matter of the valid Claims 1 to 3 and 6 lacked novelty and that of Claims 4, 5 and 7 did not involve an inventive step. Claim 1, which represents part of Claim 1 as originally filed in combination with the part filed on 14 August 1991, reads as follows:

"1. A process for the preparation of a compound of structure (I)



(I)

in which,
each group R is hydrogen, C_{1-6}alkyl, C_{3-6}allyl, phenylC_{1-6}alkyl or 4-hydroxyphenylC_{1-6}alkyl;
R^1, R^2 and R^3 are hydrogen or C_{1-6}alkyl;
R^4 is hydrogen or hydroxy; and
n is 1 to 3
or a pharmaceutically acceptable salt thereof, which comprises reduction of a compound of structure (II)



(II)

in which R, R^2 to R^4 and n are as described above and R^5 is hydrogen or a cation, followed by cyclisation of the intermediate so formed, and, optionally, alkylating to form a compound of structure (I) in which R^1 is C_{1-6}alkyl and, optionally, forming a pharmaceutically acceptable salt thereof, characterised in that the reduction of the compound of structure (II) is carried out by catalytic transfer hydrogenation in the presence of a hydrogen donor in water as a solvent."

Claims 2 to 7 filed in 14 August 1991 correspond to original Claims 2 to 7.

The Examining Division held that the process of the present Claims 1 to 3 and 6 fully overlapped with the one disclosed in EP-A-0 113 964 (1). The Examining Division also considered that the subject-matter of Claims 4, 5 and 7, although novel, did not involve an inventive step since the solution to the problem of providing an improved process for the preparation of the indoline derivatives disclosed in document (1) was obvious in the light of the teaching of Methoden der Organischen Chemie, Houben-Wey1, Volume XI/I, pages 363 to 367 and 454 to 457, 1957 (document 2) and Synthesis, No. 8, pages 640 to 643, 1981 (document 4).

III. An appeal was lodged against this decision on 30 May 1992 with payment of the prescribed fee. In his statement of grounds of appeal filed on 20 July 1992, the Appellant contended that the claimed subject-matter was novel since document (1) does not make any reference to the use of catalytic transfer hydrogenation for the reduction of compounds of formula II.

In the Appellant's view, the problem underlying the application was to provide an alternative reduction method which overcame the disadvantages associated with the method disclosed in document (1) and which gave the desired products in high yields and purity. These disadvantages include the formation of undesirable by-products and the use of hydrogen under pressure.

The Appellant argued that the fact that the reaction under transfer hydrogenation conditions in water as a solvent gave exceptional yields of the desired indolones essentially free of by-products was unexpected in the view of the teaching in document (1), Journal of Medicinal Chemistry, Volume 28, pages 1533 to 1536, 1985 (document 7) and ibid, Volume 29, pages 939 to 947, 1986 (document 8).

The Appellant also submitted that, while certain advantages might possibly be expected from the use of water as solvent, the reduced yield of undesirable N-hydroxyindolinones, as shown by the experimental evidence filed on 14 August 1991, was totally surprising and unexpected.

IV. The Appellant requests that the decision under appeal be set aside and a patent granted on the basis of the documents underlying the Examining Division's decision.

Reasons for the Decision

1. The appeal is admissible.

2. There are no objections under Article 123(2) EPC to the present version of the claims. In particular, Claim 1 is

based on Claim 1 as originally filed and page 4, lines 5 and 6 of the published patent application, Claims 2 to 7 correspond to originally filed Claims 2 to 7.

3. The application in suit relates to a process for the preparation of a 2-indolinone derivative of the formula I or a pharmaceutically acceptable salt thereof which comprises the reduction of a corresponding 2-(2-nitrophenyl)acetic acid of the formula II or a salt thereof, cyclisation of the resulting intermediate and, optionally, alkylation to obtain a compound in which the symbol R_1 represents a C_{1-6}alkyl radical and/or formation of a pharmaceutically acceptable salt.

Document (1), which is considered to represent the closest state of the art, also describes a process for the preparation of compounds of formula I which comprises cyclising under reductive conditions the corresponding 2-(2-nitrophenyl)acetic acids and, optionally, alkylating and/or forming acid addition salts (cf. Claim 1). According to the paragraph bridging pages 5 and 6 of document (1) this reductive cyclisation is brought about by catalytic hydrogenation over a noble metal catalyst in a suitable solvent, such as a lower alcohol, dilute hydrochloric acid or glacial acetic acid, at low to moderate pressures of hydrogen and at a temperature in the range of room temperature to 60°C (cf. also Example 2 on page 13, lines 20 to 30 and Example 9 on page 21, lines 9 to 32).

However, this prior art process when considered with a view to conducting the process on a large scale for commercial purposes has the disadvantage that it is carried out under pressure with hydrogen gas.

Therefore, in the light of this closest prior art, the technical problem underlying the application is to provide an alternative reduction method which overcomes the above-mentioned disadvantage of the prior art process and which gives the desired product in high yield and purity (cf. published patent application, page 3, lines 3 to 10).

According to the disputed patent, this technical problem is solved by carrying out the reductive cyclisation of the compounds of formula II by transfer hydrogenation in the presence of a hydrogen donor in water as a solvent.

In view of the yields of 82.5% and 84% obtained in the example and in the experimental evidence submitted on 14 August 1991 and the extremely low amount (0.09%) of N-hydroxy by-product, the Board is satisfied that the above-defined technical problem has been solved.

4. As previously mentioned document (1) discloses the preparation of 2-indolinones falling within the scope of formula I by the reduction and cyclisation of the corresponding (2-nitrophenyl)acetic acids of formula II. However, this document makes no mention of bringing about this reduction and cyclisation by means of catalytic hydrogen transfer. Catalytic hydrogen transfer is a special kind of catalytic hydrogenation which is achieved by heating the compound to be hydrogenated in a solvent with a catalyst and a hydrogen donor, i.e. a compound which gives up its hydrogen (cf. Reductions in Organic Chemistry, Milos Hudlicky, page 13 (1984)). According to this document suitable hydrogen donors are hydrazine, formic acid, triethylammonium formate, cyclohexene, cyclohexadiene, tetralin, indoline, pyrrolidine, tetrahydroquinoline, triethylsilane and others. Catalysts such as platinum, palladium and Raney nickel may be used.

In the absence of any reference to this specific method of hydrogenation, the subject-matter of the present claims is novel.

4.1 The Examining Division considered that the reference to the use of dilute hydrochloric acid as a solvent in the paragraph bridging pages 5 and 6 of document (1) anticipated the claimed process. However, it is clear from this passage that hydrogen gas is the source of hydrogen for the reduction step of document (1). Clearly, the hydrochloric acid functions as a proton donor not as a hydrogen donor.

4.2 Since the disclosure of documents (7) and (8) with respect to the reduction and cyclisation reaction does not go beyond that of document (1), the claimed subject-matter is also novel having regard to these prior art documents.

5. It still remains to be decided whether the subject-matter of the present claims involves an inventive step.

The skilled person seeking a solution to the technical problem underlying the present application would be aware from, for example, documents (2) and (4), that catalytic transfer hydrogenation is one of the alternatives to catalytic hydrogenation with hydrogen gas for the reduction of nitro groups. In particular, document (2) discloses that chemically bound hydrogen, such as that of hydrazine, unsaturated hydroaromatics and formic acid, can be used in place of molecular hydrogen as the reducing agent (cf. first complete paragraph on page 366). The preferred solvents for the reaction are those which are capable of dissolving the water formed during the reaction since they ensure that a homogeneous liquid phase, which is favourable for the activity of the catalyst, is maintained. Suitable solvents are, therefore, lower

alcohols, monoethers of glycols, tetrahydrofuran, dioxane, dimethylformamide and pure pyridine (cf. fourth complete paragraph on page 366). Additionally, according to the first paragraph on page 367 of this document, water is recommended as a solvent, not only for the reduction of water-soluble nitro compounds, but also for the reduction of those nitro compounds which form water-soluble salts with alkalies.

The skilled person faced with the present technical problem would be equally aware from documents (1), (7) and (8) that the reductive cyclisation of compounds of formula II using catalytic hydrogenation in ethanol as solvent gives a yield of the desired compound of formula II of approximately 78% (cf. example 2 of document (1); right-hand column on page 1535 of document (7) under the heading "4-[2-(N,N-Di-n-propylamino)ethyl]-2(3H)-indolone Hydrochloride(Ic)" and Compound 28, Scheme III in Table 1 on page 942 of document (8)).

However, from documents (1) and (8) it would become immediately apparent to the skilled person that the reductive cyclisation of compounds of formula II involving the use of catalytic hydrogenation in ethanol and hydrochloric acid as solvent, i.e. using an aqueous rather than a non-aqueous solvent system, results in a mixture of products which must be separated by column chromatography and a poor yield of the desired compound of formula I (cf. Example 9, particularly lines 9 to 32 on page 21 of document (1); and Compounds 33 and 35 in Table 1 on page 942 and the paragraph headed "4-[2-[N-(4-Methoxyphenethyl)-N-n-propylamino]ethyl)-2-(3H)-indolone Hydrochloride (35)" in the left-hand column of page 946 of document (8)).

Therefore, if the skilled person were to contemplate using catalytic transfer hydrogenation in the reductive cyclisation reaction, he would, in the light of the teaching of documents (1) and (8) certainly avoid the use of water as a solvent despite the teaching of document (2) in this respect. In the light of his knowledge derived from documents (1), (7) and (8), the skilled person would initially use an organic solvent for the catalytic transfer hydrogenation reaction. If the skilled person were to follow this course of action he would find that, using n-propanol and tetrahydrofuran as solvent, the yield of the compound of formula I was 66% and 0% respectively and that of the corresponding undesirable 1-hydroxy compound 5.87 and 6.90% respectively (cf. experimental data submitted on 14 August 1991).

In the light of the above, the skilled person could have used catalytic transfer hydrogenation in water as a solvent, but he would not have done so in the expectation of solving the technical problem underlying the application.

Therefore, in the Board's judgment, the subject-matter of the present Claim 1 involves an inventive step. Thus, Claim 1 and Claims 2 to 7, which relate to preferred embodiments of the process according to Claim 1, are allowable.

6. It is pointed out that, before the grant of a patent, the term "C_{3-6}allyl" in the definition of the symbol R in the present Claim 1 and on page 3, line 24 should be clarified.

Order

For these reasons, it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Examining Division for further prosecution on the basis of Claim 1 (first part, page 5 of the application as filed; second part, page 6 filed on 14 August 1991) and Claims 2 to 7 filed on 14 August 1991.

The Registrar: The Chairman:

E. Görgmaier K.J.A. Jahn