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Aktenzeichen / Case Number / N° du recours : T 65/83

Anmeldenummer / Filing No / N° de la demande : 80 301 854.8

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Bezeichnung der Erfindung:
Title of invention:
Titre de l'invention : A salt of 3-thienylmalonic acid and a process for the preparation of 3-thienylmalonic acid

ENTSCHEIDUNG / DECISION
vom / of / du 4 June 1984

Anmelder/Patentinhaber:
Applicant/Proprietor of the patent:
Demandeur/Titulaire du brevet : BEECHAM GROUP LIMITED

Stichwort / Headword / Référence :

EPÜ / EPC / CBE Art 52(1), 56

"Inventive Step" "problem-solution approach"

Leitsatz / Headnote / Sommaire

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Case Number: T 65 / 83

DECISION

of the Technical Board of Appeal 3.3.1

of 4 June 1984

Appellant: BEECHAM GROUP LIMITED
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Representative: Hesketh, Alan, Dr.
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Decision under appeal: Decision of Examining Division 008 of the European Patent Office dated 8 November 1982 refusing European patent application No 80301854.8 pursuant to Article 97(1) EPC

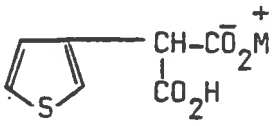
Composition of the Board:

Chairman: D. Cadman
Member: K. Jahn
Member: O. Bossung

SUMMARY OF FACTS AND SUBMISSIONS

I. European patent application No. 80 301 854.8 filed on 4 June 1980 and published on 7 January 1981, claiming the priority from a prior US application of 19 June 1979, was rejected by a decision of the European Patent Office dated 8 November 1982 on the basis of 5 claims submitted on 17 November 1981 reading as follows:

1. A salt of 3-thienylmalonic acid of formula (II):

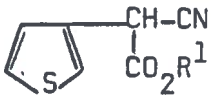


(II)

wherein ^{+}M represents an alkali metal ion or an ammonium ion.

2. The monosodium salt of 3-thienylmalonic acid.

3. A process for the preparaton of 3-thienylmalonic acid which process comprises hydrolysing a 3-thienyl-cyanoacetate of formula (IV):



(IV)

wherein R^1 represents an alkyl or aryl group, with an alkali metal hydroxide, isolating a salt according to claim 1 and converting it to 3-thienylmalonic acid.

4. A process according to claim 3 wherein the monosodium salt of 3-thienylmalonic acid is isolated by precipitation.

5. A process according to claim 3 wherein R^1 is C_{1-6} alkyl."

II. The stated ground for the rejection was that the subject matter of the application did not involve an inventive step having regard to GB-A-1 139 164 (1) and US-A-2 513 140 (2).

This closely related prior art teaches that the 3-thienylacetonitriles and also similar heterocyclic acetonitriles can be easily subjected to a normal hydrolysis reaction. The man skilled in the art seeking a method for the production of 3-thienylmalonic acid useful as intermediate in the preparation of penicillins would have his attention, in view of the above art, inevitably drawn to the known hydrolysis methods. His knowledge that malonic acid derivatives having a second carboxylic group in the ß-position would more readily undergo decarboxylation than monocarboxylic acid derivatives would not prevent him from exploring the used hydrolysis in accordance to the known reaction in which the corresponding acetic acid derivatives are used, in order to produce the corresponding desired malonic acid. Since the applicants use the starting material 3-thienylcyanoacetate in 70% or less purity, it is absolutely obvious for a skilled man to precipitate and isolate the claimed intermediate in order to get a sufficiently pure 3-thienylmalonic acid.

Consequently, the claimed process does not exhibit any surprising or unexpected advantages over the prior art.

Further the claimed intermediates do not show any properties pe se with respect to the antibiotic activities of the final products which have a completely different structure and have antibiotic activities which were known before the filing date of the present application.

III. On 10 January 1983 the appellant lodged an appeal against the above-mentioned decision of rejection with payment of the appeal fee followed on 22 February 1983 by a Statement of Grounds, the essence of which was that since malonic acid derivatives are known to undergo decarboxylation readily, this fact is in itself prejudice againt use of a hydrolysis reaction for preparing 3-thienylmalonic acid given the requirement of highly pure compounds as intermediates for phamaceuticals.

However, it has surprisingly and unexpectedly been found that if the hydrolysis is carried out in such a way that a mono-salt of 3-thienylmalonic acid can be precipitated, this salt can be produced in high yield and then be converted to the pure acid in high yield too.

The invention relies on the isolaion of a monosalt of 3-thienylmalonic acid which is a well-formed crystalline entity and which selectively precipitates at a lower pH where all other impurities remain soluble. It is certainly not obvious that such a selective purification from a very impure substrate could have been predicted.

From this it can be concluded that the applicants wish the impugned decision to be reversed.

REASONS FOR THE DECISION

1. The appeal is in accordance with Articles 106-108 and Rule 64 EPC; it is therefore admissible.

2. No formal objection to the current version of the claims including Claims 3 and 4 was raised by the first instance. It would appear doubtful, however whether these claims comply with the requirement according to Rule 29(1) EPC in the absence of features requiring the precipitation of the intermediates as an essential feature of the process. However, in view of the Board's finding, this question can be left in abeyance.

3. In denying inventive step for the claimed method the Examining Division considered solely the fact that hydrolysis of 3-thienyl-cyanoacetate represents merely an analogous method with a foreseeable result. In view of (1) and (2) that assessment may be justified, but it does not fully cover the claimed method leading to the salts of formula II; rather it is necessary to take the further step of their isolation, in the knowledge that all undesired impurities thereby remain in solution.

   The first instance did indeed establish that the step of isolation, too, was obvious in view of the use of impure starting materials and the intended further use of the intermediates formed for production of the appropriate penicillins. No reasons of substance were given, however, precisely why the monoalkali salts of

3-thienyl malonic acid should present themselves for such a separation and purification operation by precipitation with an alkali metal or ammonium salt of an alkanoic acid. It has neither been alleged to be, nor is the Board aware that this is, a matter of common general knowledge.

4. In particular the first instance failed to examine the question of the technical problem forming the basis of the present application in its two embodiments, and then to judge the obviousness of the claimed solution from that point of view in the light of the state of the art. The Board considers this to be in contravention of the established practice of the Technical Boards of Appeal
(cf. "Metal refining" T 24/81, OJ EPO 1983, 133;
"Carbonless copying paper" T 01/80, OJ EPO 1981, 206
"Shell-Aryloxybenzaldehyd" T 20/81, OJ EPO 192, 217;
"Light-reflecting slates" T 39/82, OJ EPO 1982, 419;
"Containers" T 26/81, OJ EPO 1982, 211;
"Cleaning apparatus for conveyor belt" T 32/81, OJ EPO 1982, 225;
"Electromagnetically operated switch" T 21/81 OJ EPO 1983, 15,18).

Disregard for the "problem-solution approach", well established in European patent practice when assessing inventive step, can no longer go uncriticised by the Board, and may result in remittance of cases to Examining Divisions for completion of examination.

5. Points of departure for ascertaining the technical problem according to the application are contained therein (page 4, paragraphs 1 and 4) and in the grounds

for appeal (point 6). However, as pointed out in the decision "Metal refining", determination of the technical problem must be based on objective, not subjective, criteria. This requires checking what is claimed by the applicant to have been achieved. Only what has actually been achieved vis-à-vis the closest state of the art qualifies for determination of the technical problem. If the applicant claims, for example, advantages in yield or purity, evidence in support ought to be produced.

6. For assessment of inventive step in the application's subject matter particular attention should be given to the Decision on "Bis-epoxy ethers" (OJ EPO 1982, pp. 341, 346, 348). There, a new intermediate was held inventive where it was made available with the view of producing known and desired end products in a surprisingly advantageous new complete chemical process which was not conceivable without the said intermediate.

It was suggested that the surprising properties which derive from a chemical substance and manifest themselves in the form of a particular effectiveness in a technical field of application are to be rated no higher when assessing that substance's inventive step, than those revealed when it undergoes further chemical processing.

This effect-centred concept made no distinction between end-products and intermediates, but recognised an inventive step for both types of chemical compounds in consequence of the unpredictability of the attainment of the effect in the light of the prior art. This reference appears worthwhile, since the Examining Divi-

sion in the present case deviated from this principle in assessing the inventive step of the intermediates as claimed (cf. page 5 paragraph 3 last sentence of the impugned decision).

7. As regards the effect to be ascertained, a further question to be examined is whether that effect is attributable mainly to the salt itself as claimed and thus, to the extent that it is surprising, supports its patentability. This is at present not clear, in that the further processing of the salts of formula II to prepare e.g. ticarcillin requires three further reaction steps, namely: conversion into the free acid (Example 2 purity?), then into a reactive derivative of malonic acid (monochloride, mixed anhydride) and finally the reaction of that with 6-aminopenicillanic acid, in the course of which decarboxylation and/or loss in yield and purity may occur. In this context attention is drawn to GB-A-1 004 670 Example 6, which appears to show that the two last-mentioned reaction steps result in only 60% pure pencillin being obtained, despite the fact that the decarboxylated by-products have already been separated by column chromatography (cf. page 2, lines 21-40).

8. Clarification of all these questions is an essential element in any properly conducted examination and therefore falls within the competence of the first instance. Under these circumstances the Board deems it not timely to decide on the issue of inventive step, but makes use of its power given by Article 111(1) EPC to remit the case to the first instance for further prosecution.

ORDER

For these reasons,

it is decided that:

1. The decision of the Examining Division of the European Patent Office is set aside.

2. The case is remitted to the Examining Division for further prosecution.

1/6.84 J. [illegible]

4.6.84 D C Cadman