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**Datasheet for the decision
of 29 October 2015**

Case Number: T 0719/12 - 3.3.10

Application Number: 03762669.4

Publication Number: 1539673

IPC: C07C213/08, C07D307/46,
C07D333/22, C07C225/12,
C07C221/00

Language of the proceedings: EN

Title of invention:
PROCESS FOR THE PREPARATION OF N -MONOSUBSTITUTED BETA-AMINO
ALCOHOLS

Patent Proprietor:
Lonza AG

Opponent:
Merck Patent GmbH

Headword:

Relevant legal provisions:
EPC Art. 54

Keyword:
Novelty -
(yes) compound disclosed by name in prior art, but not
available to public as no method for its preparation available
at publication date of prior art

Decisions cited:
T 0206/83

Catchword:



**Beschwerdekammern
Boards of Appeal
Chambres de recours**

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Case Number: T 0719/12 - 3.3.10

D E C I S I O N
of Technical Board of Appeal 3.3.10
of 29 October 2015

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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 25 January 2012
revoking European patent No. 1539673 pursuant to
Article 101(3)(b) EPC.**

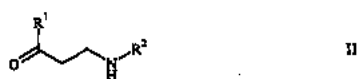
Composition of the Board:

Chairman P. Gryczka
Members: J. Mercey
F. Blumer

Summary of Facts and Submissions

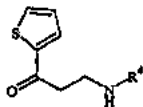
- I. The Appellant (Proprietor of the Patent) lodged an appeal against the decision of the Opposition Division revoking European patent No. 1 539 673. Claims 9 and 10 of the patent as granted read as follows:

"9. A compound of formula



and its addition salts of proton acids, wherein R¹ represents furanyl, benzofuranyl, isobenzofuranyl, thienyl or benzo[b]thienyl, each being optionally substituted with halogen, linear or branched C₁₋₄alkyl, linear or branched C₁₋₄alkoxy, C₃₋₆cycloalkyl, CF₃, C₂F₅, OCF₃ or OC₂F₅; and wherein R² is selected from the group consisting of linear or branched C₁₋₈alkyl, C₃₋₈cycloalkyl, furanyl, benzofuranyl, thienyl, benzo[b]thienyl and aralkyl, wherein the alkyl moiety of the aralkyl residue is linear C₁₋₄alkyl, and the aryl moiety is selected from the group consisting of naphthyl, furanyl, benzofuranyl, thienyl and benzo[b]thienyl, each aryl or aralkyl being optionally substituted with halogen, linear or branched C₁₋₄alkyl, linear or branched C₁₋₄alkoxy, C₃₋₆cycloalkyl, CF₃, C₂F₅, OCF₃ or OC₂F₅ with the exception of compounds wherein R¹ represents 3,4,5-trichlorothien-2-yl.

10. A compound of formula



VI

and its addition salts of proton acids, wherein R⁴ represents methyl, ethyl, isobutyl or tert-butyl."

II. Notice of Opposition had been filed by the Respondent (Opponent) requesting revocation of the patent in its entirety on the grounds of lack of novelty and inventive step (Article 100(a) EPC) and lack of sufficiency of disclosure (Article 100(b) EPC), *inter alia* the following documents being cited:

- (1) F.F. Blicke *et al.*, J. Am. Chem. Soc., 1942, 64, 451 to 454,
- (7) C. Mannich *et al.*, Chem. Ber., 1922, 55, 356 to 365, and
- (10) F.F. Blicke, "The Mannich Reaction", Organic Reactions, Vol. 1, 1941, pages 303 to 341,

the Respondent also filing an experimental report V1.

III. In the decision under appeal, the Opposition Division found that the process of claims 1 to 8 of the patent as granted was sufficiently disclosed, but that the compounds of claims 9 and 10 lacked novelty over the disclosure of document (1).

IV. The Appellant submitted that although document (1) identified the compound methyl-2-(α -thenoyl)-ethylamine by its chemical name, said compound falling under claims 9 and 10 of the granted patent, said compound had not been made available to the public because the information in document (1) did not enable its

preparation and separation. Indeed to the contrary, the authors of document (1) explicitly indicated that after performing the Mannich reaction they were able to isolate only the tertiary amine, and on subjecting said amine to steam distillation, no evidence could be obtained that the secondary amine was formed. Documents (1) and (7) taught that only phenyl, and not thienyl, ketones gave a secondary amine in the Mannich reaction with primary amines, document (10) being published after the publication date of document (1). Thus, although it was the aim of the authors of document (1) to investigate the usefulness of the Mannich reaction for preparing secondary amines, they were unable to prepare such a secondary amine starting from α -acetylthiophene. The experimental report V1 filed by the Respondent could not cure this lack of availability to the public, as said report was based on *ex post facto* knowledge, since it involved a treatment of the filtrate obtained in document (1) not described in this document. In addition, analysis methods (HPLC, HPLC-MS) were used in V1 which were not available at the publication date of document (1), nor had the β -ketoamine obtained in V1 been unambiguously identified as a compound according to claims 9 and 10. In any case, said report did not repeat the method of preparation of document (1) exactly, since in document (1) the reactants were heated on a steam-bath, whereas according to V1, they were heated under reflux. The documents (13) to (17) filed by the Respondent (see point V below) to show that the compound methyl-2-(α -thenoyl)-ethylamine could have been prepared by other conventional methods available to the skilled person at the date of publication of document (1), were irrelevant, as they did not relate to the compound methyl-2-(α -thenoyl)-ethylamine, nor did they represent common general knowledge at the publication date of

document (1). In any case, to arrive at the proposed synthetic route, a complex combination of these documents was required, there being no pointer whatsoever in document (1) towards said documents. With letter dated dated 7 March 2013, the Appellant filed auxiliary requests 1 to 3.

- V. The Respondent submitted that it had been known since the publication of document (7) that the Mannich reaction with primary amines resulted in the production of both secondary and tertiary amines, as confirmed by document (1) itself, and by document (10). The experimental report V1 showed that the compound methyl-2-(α -thenoyl)-ethylamine had indeed been produced according to the method described in document (1). Thus, experimental report V1 repeated the preparation of the tertiary amine methyl[di-2-(α -thenoyl)-ethyl]amine **5** and separation thereof by precipitation, filtration, concentration of the filtrate, and recrystallisation from alcohol, described in document (1) and showed that this recrystallisation led to methyl-2-(α -thenoyl)-ethylamine being concentrated to a level of 90% purity in the mother liquor, such that said compound had been made available to the public by document (1) alone. The separation of the secondary amine from this mother liquor by recrystallisation was a method well known to the skilled person at the publication date of document (1). In any case, the skilled person would have known that methyl-2-(α -thenoyl)-ethylamine could be prepared by other conventional synthetic methods, for example, by the Friedel-Crafts reaction of thiophene with a 3-halopropionyl chloride, followed by reaction of the resulting 3-halo-propio-2-thienone with methylamine. With letter dated 23 October 2012, the Respondent filed the following documents:

- (13) F.F. Blicke *et al.*, J. Am. Chem. Soc., 1942, 64, 477 to 480,
- (14) DE 612496,
- (15) H. Scheibler *et al.*, Chem. Ber., 1921, 54, 139 to 154,
- (16) F.F. Blicke *et al.*, J. Am. Chem. Soc., 1930, 52, 235 to 240, and
- (17) D. Steinkopf *et al.*, Justus Liebigs Annalen der Chemie, 1917, 413, 3, 343 to 349.

to show that said synthetic methods were available to the public at the publication date of document (1).

- VI. The Appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request, namely the granted claims, or, alternatively on the basis of any of auxiliary requests 1 to 3 filed with letter dated 7 March 2013.

The Respondent requested that the appeal be dismissed.

- VII. Oral proceedings were held on 29 October 2015 in the absence of the Respondent who, after having been duly summoned, did not attend. At the end of the oral proceedings, the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

Novelty

Main request

2. Neither party contests that the document (1) (see page 452, right hand column, lines 12 to 13) discloses the compound methyl-2-(α -thenoyl)-ethylamine by name, said compound being a compound of formula (II) wherein R¹ is thienyl and R² is methyl according to claim 9, and of formula (VI) wherein R⁴ is methyl according to claim 10, of the contested patent. The parties were, however, divided as to whether said compound had been made available to the public.
 - 2.1 It is the established jurisprudence of the Boards of Appeal that the subject-matter described in a document can only be regarded as having been made available to the public, and therefore as comprised in the state of the art pursuant to Article 54(1) EPC, if the information given therein is sufficient to enable the skilled person, at the relevant date of the the document, to practise the technical teaching which is the subject of the document, taking into account also the general knowledge at the time in the field to be expected of him (see T 206/83, OJ EPO 1987, 5).
 - 2.2 Document (1) investigates the extent to which the Mannich reaction might be serviceable for the preparation of secondary amines. It discloses that when equimolar quantities of α -acetyl-thiophene, paraformaldehyde and methylamine hydrochloride, amounts described as **favouring the formation of the secondary amine**, namely methyl-2-(α -thenoyl)-ethylamine, were allowed to react, **only the tertiary amine could be**

isolated. This was then subjected to steam distillation, but **no evidence** could be obtained that the secondary amine was formed (emphasis added). Thus, document (1) merely postulates the compound methyl-2-(α -thenoyl)-ethylamine as a potential theoretical product of a Mannich reaction or the steam distillation of the corresponding tertiary amine, but categorically states that said compound could neither be isolated nor obtained when said reactions were actually carried out, in spite of the use of conditions which were considered favourable for its formation. Thus, the Board holds that document (1) alone does not make the compound methyl-2-(α -thenoyl)-ethylamine available to the public, since the specific attempts to prepare it which are described in said document, failed.

- 2.3 The Respondent argued that document (1) did nonetheless make the compound methyl-2-(α -thenoyl)-ethylamine available to the public, since on repeating the preparation of the tertiary amine methyl[di-2-(α -thenoyl)-ethyl]amine **5** of document (1), the compound methyl-2-(α -thenoyl)-ethylamine was indeed produced. Thus, document (1) (see page 453, Experimental and Table) described the preparation of compound **5** by heating a mixture of 0.10 mole of the ketone, 0.10 mole of the amine hydrochloride, 0.12 mole of paraformaldehyde and about 20 cc of absolute alcohol on a steam bath for two to three hours, followed by cooling, filtering the precipitated material, concentrating the filtrate to recover more of the desired compound, and recrystallisation of the precipitate from alcohol. The Respondent alleged that its experimental report V1 showed that preparation and separation of the tertiary amine by recrystallisation in this manner led to methyl-2-(α -thenoyl)-ethylamine being concentrated to a level of 90% purity in the

mother liquor, such that said compound had been made available to the public by document (1). The separation of the secondary amine from this mother liquor by recrystallisation was a method well known to the skilled person at the publication date of document (1). In any case, according to the decision under appeal, isolation of a compound was not a requirement for making it available to the public.

However, the Board holds that in view of the categorical statement in document (1) that despite attempts to synthesise it, the secondary amine could be neither isolated nor obtained, the skilled person, at the date of publication of document (1), would not have seriously contemplated repeating its teaching in order to undertake further investigations as to whether the secondary amine was formed after all. Thus, regardless of whether the report V1 repeats the method of document (1) exactly, the Appellant contesting this fact (see point IV above), the skilled person had no motivation to perform the steps in the experimental report V1 which are not disclosed in document (1), namely of analysing the product mixture obtained or of recrystallising from the mother liquor. Thus the Board holds that the additional steps carried out in the experimental report V1 result from *ex post facto* considerations. It has not been shown that on repeating the preparation of compound **5** exactly according to the method of document (1), i.e. without any additional analysis and/or work up steps, that the skilled person **could not have overseen** the formation of methyl-2-(α -thenoyl)-ethylamine. Thus, even if said compound had been present in the mother liquor resulting from the recrystallisation of the tertiary amine **5**, this fact cannot be deduced from reading document (1) alone, nor on repeating its teaching, such that its presence would

not have been recognised by the skilled person at the date of publication of document (1). Hence, even if methyl-2-(α -thenoyl)-ethylamine were inevitably produced by a method described in document (1), since its presence remained undetected by the skilled person, it had not been made available to the public.

- 2.4 The Respondent also argued that the skilled person did indeed have the motivation to question the teaching of document (1) at its date of publication, since it had been known since the publication of document (7) that the Mannich reaction with primary amines resulted in the production of both secondary and tertiary amines, and that steam distillation of the tertiary amine results in its decomposition to the secondary amine, document (10) confirming this knowledge.

However, document (7) (see page 358, lines 18 to 31) teaches that the Mannich reaction of formaldehyde and methylamine with **acetophenone** leads *inter alia* to a secondary amine. Even in the light of this teaching, the skilled person would not have considered that the teaching of document (1) was incorrect, or that the authors thereof had not worked assiduously, since document (1) itself (see page 452, left hand column, lines 1 to 27) and footnote 4) acknowledges that the **only** case of a secondary amine being produced in the Mannich reaction with a primary amine, is when **acetophenone** is used as a reactant. Thus, the teaching of document (1), even in combination with document (7), is that the Mannich reaction of formaldehyde and methylamine with acetophenone, **but not α -acetyl-thiophene**, leads to a secondary amine. This is in keeping with the initial hypothesis of document (1) (see page 451), that the usefulness of the Mannich reaction for preparing secondary amines would be a

"very limited one". Document (10) was published after document (1), since document (1) is cited therein (see footnote 10 on page 307), such that the skilled person would not have considered its teaching at the date of publication of document (1).

- 2.5 The Respondent also argued that at the publication date of document (1), the skilled person would have been able to prepare methyl-2-(α -thenoyl)-ethylamine by conventional methods, for example, by the Friedel-Crafts reaction of thiophene with a 3-halopropionyl chloride, followed by reaction of the resulting 3-halopropio-2-thienone with methylamine, citing documents (13) to (17) in this respect.

However, the Board holds the Respondent has not shown that such a synthetic method belonged to the common general knowledge of the skilled person at the publication date of document (1), none of documents (13) to (17) being general textbooks. Furthermore, the necessity to combine five documents in order to arrive at the synthetic route further implies that said method involved more than common general knowledge. In addition, as has been shown by virtue of document (1), the replacement of a phenyl group by a thienyl group in the ketone reactant in the Mannich reaction, for example, results in different types of products, such that the skilled person could not necessarily have expected that the reactions described in documents (13) to (17) to be transferable to analogous compounds, the Respondent not actually having carried out the postulated method and shown that the compound methyl-2-(α -thenoyl)-ethylamine can indeed be produced thereby. Hence, it has not been shown that the proposed synthesis of methyl-2-(α -thenoyl)-ethylamine actually

works, let alone that it belonged to the general knowledge at the time in the field.

- 2.6 Therefore, the Board concludes that the subject-matter of claims 9 and 10 is novel within the meaning of Articles 52(1) and 54 EPC over the disclosure of document (1).

3. *Remittal*

Having so decided, the Board has not taken a decision on the whole matter, since the decision under appeal dealt exclusively with novelty and sufficiency of disclosure. As the Opposition Division has not yet ruled on the other grounds for opposition, namely inventive step, the Respondent no longer contesting sufficiency of disclosure of the process of claims 1 to 8 on appeal, the Board considers it appropriate to exercise its power conferred on it by Article 111(1) EPC to remit the case to the Opposition Division for further prosecution on the basis of the claims according to the granted patent in order to enable the first instance to decide on the outstanding issues.

Auxiliary requests 1 to 3

4. Since the main request, namely the claims as granted, is remitted to the first instance for the reasons set out above, there is no need for the Board to decide on the auxiliary requests.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance for further prosecution on the basis of the claims as granted.

The Registrar:

The Chairman:



K. Boelicke

P. Gryczka

Decision electronically authenticated