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**D E C I S I O N**  
of 18 February 1998

**Case Number:** T 0713/97 - 3.3.1

**Application Number:** 92107537.0

**Publication Number:** 0516982

**IPC:** C07D 231/12

**Language of the proceedings:** EN

**Title of invention:**  
Process for producing a heterocyclic tertiary amine

**Applicant:**  
Nissan Chemical Industries Ltd.

**Opponent:**  
-

**Headword:**  
N-alkylation/NISSAN

**Relevant legal provisions:**  
EPC Art. 56

**Keyword:**  
"Inventive step (yes) - non-obvious process"  
"Manufacture of known compounds"  
"Problem-solution approach"

**Decisions cited:**  
T 0641/89.

**Catchword:**  
-



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Boards of Appeal

Chambres de recours

Case Number: T 0313/97 - 3.3.1

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.1  
of 18 February 1998

**Appellant:**

Nissan Chemical Industries Ltd.  
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Chiyoda-ku  
Tokyo (JP)

**Representative:**

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**Decision under appeal:**

Decision of the Examining Division of the  
European Patent Office posted 14 February 1997  
refusing European patent application  
No. 92 107 537.0 pursuant to Article 97(1) EPC.

**Composition of the Board:**

**Chairman:** A. J. Nuss  
**Members:** P. Krasa  
R. E. Teschemacher

## Summary of Facts and Submissions

I. This appeal lies from the Examining Division's decision refusing the European patent application No. 92 107 537.0, relating to a process for producing a heterocyclic tertiary amine, for not complying with the requirements of Articles 52(1) and 56 EPC.

II. The stated ground of refusal in the decision under appeal was that the then pending Claims 1 to 7 of the application in suit did not meet the requirements of Article 123(2) EPC and that the process claimed did not involve an inventive step in view of documents

- (1) EP-A-O 034 480 and
- (3) Bulletin of the Chemical Society of Japan, vol. 50 (6), 1510-1512 (1977).

The Examining Division considered document (1) to represent the closest state of the art, since it disclosed not only processes employing the same alkylating agents, metal catalysts and ligands as the process of the application in suit, but also their applicability to the alkylation of heterocyclic aromatic amines. The technical problem to be solved in relation to this citation was seen by the Examining Division in the provision of a process for alkylating heteroaromatic secondary amines. The solution, i.e. the application of the process of document (1) to the compounds of the application in suit, was said to be within the skills and abilities of those skilled in the art.

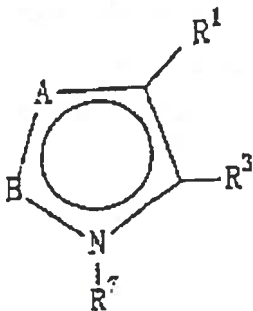
The Examining Division further noted that the higher yields obtained according to the process of the application in suit as compared with that of citation (3) were not surprising, since the process according to the latter document did not employ a metal catalyst, the beneficial effect of which had been known from document (1).

The Board, on its own motion, will also consider document

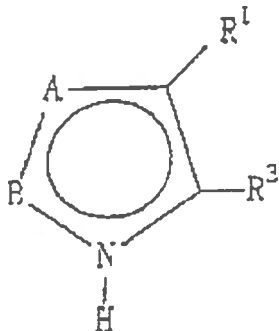
(4) FR-A-2 342 728.

III. The Appellant (applicant), with the statement of grounds for appeal, submitted a new set of six claims, which he further amended in response to a communication from the Board commenting thereupon. Claim 1 thereof reads (after amendment of two obvious clerical errors as requested by the Appellant in the course of a phone conversation with the Rapporteur on 13 February 1998, i.e. after changing "a trialkylphosphine, a triarylphosphine" to "a trialkylphosphine, a triarylphosphine"):

"A process for producing an aromatic heterocyclic tertiary amine of the formula (III):



wherein A is a nitrogen atom or C-R<sup>5</sup>, B is a nitrogen atom or C-R<sup>6</sup>, and each of R<sup>1</sup>, R<sup>3</sup>, R<sup>5</sup> and R<sup>6</sup> which may be the same or different, is a hydrogen atom, a C<sub>1-6</sub>alkyl group, and R<sup>7</sup> is a C<sub>1-6</sub>alkyl group, which process comprises reacting an aromatic heterocyclic secondary amine of the formula (I):



wherein A, B, R<sup>1</sup> and R<sup>3</sup> are as defined above, with an alkylating agent of the formula (II):



wherein R<sup>7</sup> is as defined above, and X is a hydroxyl group, in the presence of a catalyst selected from a rhodium catalyst and a ruthenium catalyst, and a ligand selected from a trialkylphosphine, a triarylphosphine, a trialkyl phosphite and a triaryl phosphite at a temperature of from 50 to 250°C and a pressure of from 1 to 150 kg/cm<sup>2</sup>."

- IV. The Appellant, submitted in essence that the technical problem to be solved, i.e. to produce in excellent yields the particular alkylated heteroaromatic compounds mentioned in the claims of the application in

suit, was not disclosed in document (1) and that citation (3) did not contain any incentive leading a person skilled in the art to the claimed solution of this problem.

- V. The Appellant requested that the decision under appeal be set aside and a patent be granted with the set of six claims dated 26 January 1998 and with the following description: pages 2, 4 to 26, and 28 to 36 filed 26 January 1998; 1 and 27 filed 6 February 1998; and 3 to 3a filed 13 February 1998.

As an auxiliary request, the Appellant also requested oral proceedings.

### Reasons for the Decision

1. The appeal is admissible.
2. *Amendments*
  - 2.1 The amendments of Claim 1 consist in essence in a confinement of the claimed process to the alkylation of aromatic compounds and in a restriction of the meanings of the various substituents in the formulae of the claim to particular alternatives. All these alternatives were explicitly disclosed in the application as filed (see, e.g. Claim 1, page 37, lines 13 to 14, page 39, line 25, page 41, line 5). The aromatic compounds employed as the starting materials in the claimed process and the products resulting therefrom are the sub-groups of the original group of compounds of formulae (I) and (III), respectively, wherein the heterocyclic ring contains a second double bond (see, e.g. the application as filed, Claim 1, page 37, lines 5 to 12, and page 42, lines 10 to 18).

The ruthenium and the rhodium catalysts now specified find their basis on page 16, lines 24 to 26 of the application as filed as being particularly preferred. The newly incorporated ranges of the process temperature and of the process pressure were disclosed on page 27, lines 1 to 6 of the application as filed. New dependent Claims 2 and 3 are supported by the application as filed (see page 17, line 7, and page 19, line 15) and original Claims 3 and 4, respectively. New dependent Claims 4, 5, and 6 are directed to the manufacture of three specific compounds and are supported, e.g. by the examples 1, 5, and 13 of the application as filed.

- 2.2 The amended claims are also clear. Thus, no objections arise against Claims 1 to 6 under Articles 84 and 123(2) EPC.

3. *Novelty*

The Board is satisfied that the subject-matter of the claims is not disclosed in any of the citations on file. This not being in dispute, the Examining Division having already acknowledged novelty for claims having a broader scope than the present ones, it is not necessary to give detailed arguments in this respect.

4. *Inventive step*

- 4.1 The application in suit relates to a one-step process for the production of particular aromatic heterocyclic tertiary amines as defined in Claim 1 by alkylating an -NH-group which is a ring member of an appropriate

aromatic heterocyclic starting compound (I). It is not in dispute that the resulting aromatic heterocyclic tertiary amines are known compounds (see also below nos. 4.4.1 and 4.4.2).

4.2 In a situation as the present one, where the background of the invention lies in difficulties encountered in conventional processes for the manufacture of known chemical compounds (see page 2, line 22 to page 3, line 10 of the application as filed), the documents to be considered when determining the closest prior art are those which describe these compounds and their manufacture. The reason is that only such documents allow to compare validly the technical effects and results of the respective processes, e.g. the yields achieved for the desired compounds according to the state of the art and according to the application in suit (see T 0641/89 of 24 September 1991, not published in the OJ EPO, cited in Case Law of the Boards of Appeal of the EPO, 1996, I.D.3.1, point 3.1 of the reasons for the decision). This has to be borne in mind when it comes to the selection of the appropriate starting point for evaluating inventive step.

4.3 In document (1) a generic process is disclosed for the alkylation of amines which may be heterocyclic, aliphatic or aromatic (page 3, lines 12 to 13). According to a passing remark, the heterocyclic amines also may be aromatic (page 3, lines 16 to 18). However, contrary to documents (3) and (4), no concrete disclosure of the alkylation of heteroaromatic compounds can be found in citation (1). Thus, document (1) is not an appropriate starting point for the evaluation of inventive step. This was indicated



already in the decision under appeal when stating that the yields given in this document are not directly comparable with those of the application in suit, since different amines were alkylated (last but one complete sentence on page 5 of the decision under appeal).

4.4 Only documents (3) and (4) actually disclose products resulting from the process of present Claim 1.

4.4.1 Document (4) discloses the two step alkylation of aromatic heterocyclic compounds such as imidazole, pyrazole, 1,2,3-triazole, etc. whereby a stannyl derivative of the aromatic heterocyclic compound is formed in a first step and the resulting tin organic compound is then reacted in a second step with a primary or a secondary halogen compound (see page 3, line 40 to page 4, line 6, and lines 25 to 31, in combination with page 2, lines 10 to 12). The use of tin organic compounds has nothing in common with the process of present Claim 1.

4.4.2 By way of contrast, document (3) discloses the one-step alkylation of, e.g. imidazole and pyrazole, by means of a dialkyl phosphite as the alkylating agent (the first complete sentence of the right hand column on page 1510 and the first and the third entry of table 1 on the same page). Therefore, this latter state of the art is closer to the process of the application in suit (which is also a one-step process involving phosphorous compounds) than that of citation (4).

4.5 Consequently, the state of the art disclosed in document (3) qualifies as the appropriate starting point for investigating inventive step.

With respect to this state of the art, the technical problem underlying the claimed invention can be defined as providing a process for the manufacture of the respective aromatic heterocyclic tertiary amines as defined by formula III of present Claim 1 by applying simple and readily available alkylation agents and in comparable or even improved product yields.

4.6 According to the examples of the application in suit, the compounds of formula (II) are used as alkylation agents. Regarding the product yields, the manufacture of 1-methyl pyrazole and of 1-methyl imidazole from the respective non-methylated heteroaromatic compounds allows a direct comparison. The respective figures calculated from the Appellant's letter of 3 May 1996 (on the basis of the respective conversion rates and selectivities given) and those taken from document (3) are as follows:

	1-methyl-pyrazole (yield %)	1-methyl-imidazole (yield %)
letter of 03.05. 96	~68	~98
document (3)	69	58

4.7 The comparison shows that the yields achieved by the claimed process are about equal or even better than those obtained according to document (3). Thus, on the basis of the available information, it is credible that the above defined technical problem is solved by the process of Claim 1 of the application in suit.

4.8 Neither document (3) nor document (4) contain any hint to the claimed solution of the existing technical problem. The use of an alcohol of formula (II) as the alkylating agent was not foreshadowed in these citations (see also above points 4.4.1 and 4.4.2).

- 4.9.1 Document (1) broadly discloses a generic method for preparing N-alkyl- or N,N-dialkyl-amines by reacting primary or secondary amines with a primary or secondary alcohol in the presence of a salt or of a complex of, inter alia, rhodium or ruthenium (page 2, lines 8 to 14).
- 4.9.2 Morpholine, piperidine, pyrrolidine, and piperazine, which all are heterocycloaliphatic compounds, are mentioned as examples of suitable heterocyclic amines (document (1), page 3, lines 21 to 23). Further, aliphatic amines, cyclic or linear, are designated as a group of suitable amines (document (1), the paragraph bridging the pages 3 and 4). The Board accepts that it is common general knowledge of those skilled in the art that all these amines are strongly basic compounds (pKa values in the range of 8.5 [morpholine] to 11.3 [piperidine]) whereas the aromatic heterocyclic amines to be alkylated according to the application in suit are weakly basic compounds (pKa values in the range of 2.5 [pyrazole] to 7.0 [imidazole]).
- 4.9.3 A closer inspection of the examples of document (1) confirms that the basicity of the starting compound has a pronounced effect on the yields of the alkylation reaction. According to the examples 3, 7, 8, and 9, the reaction of pyrrolidine, butylamine, cyclohexylamine, and N-methyl-butylamine with methanol in the presence of  $\text{RhH}[\text{P}(\text{C}_6\text{H}_5)_3]_4$  resulted in yields of 97.2%, 98.5%, 98.9%, and 45% of the respective methylated product at reaction times of not more than 10 hours. In contrast, example 11 shows that with the same catalyst, the reaction of methanol with aniline, which is generally known as a weak base (pKa about 4.7), yields only 16.2% of N-methyl aniline after **one day** reaction time and not more than 38.7% of N-methyl aniline after a reaction

time of three days (see the paragraph bridging pages 9 and 10). It is to be noted that the basicity of aniline is in the range of that of the aromatic heterocyclic amines to be alkylated according to the application in suit.

4.9.4 Moreover, when comparing the yields of around 98% disclosed in document (1) for the alkylation of a primary amino group with that of 45% for the alkylation of a secondary amino group (i.e. that of N-methyl-butylamine; see no. 4.9.3), a person skilled in the art would have noted a significantly reduced reactivity of the latter amino groups in this reaction.

4.9.5 Therefore, in the Board's judgement, the results disclosed in document (1) for the alkylation of various amino compounds, in particular the poor results obtained with the alkylation of aniline, would have deterred the notional skilled person from applying the technical teaching of document (1) for solving the existing technical problem, i.e. for the manufacture of the desired compounds by the claimed alkylation of the secondary amino groups in weakly basic starting compounds.

5. For these reasons, the Board concludes that none of the documents (1), (3), and (4), taken alone or in combination, renders obvious the subject-matter of Claim 1 of the application in suit, which therefore complies with the requirements of Articles 52(1) and 56 EPC. Claims 2 to 6 relate to particular embodiments of the subject-matter of Claim 1 and involve, therefore also an inventive step.

6. Under these circumstances, it was not necessary to summon the Appellant to attend oral proceedings.

**Order**


**For these reasons it is decided that:**

1. The decision under appeal is set aside.
2. The case is remitted to the first instance with the order to grant a patent in the following version:
  - Claims 1 to 6 submitted 26 January 1998 with the amendments as set forth in point III of the Facts and Submissions,
  - pages 2, 4 to 26, and 28 to 36 filed 26 January 1998;  
pages 1 and 27 filed 6 February 1998; and  
pages 3 to 3a filed 13 February 1998.

The Registrar:

  
E. Gorgmaier

The Chairman:

  
A. Nuss

Order

You have received the enclosed check

for the amount of \$100.00

This check is payable to the order of the

Account of the order of the

of the order of the