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Datasheet for the decision of 6 August 2009

Case Number: T 1194/06 - 3.3.01

Application Number: 01943553.6

Publication Number: 1300407

IPC: C07D 453/02

Language of the proceedings: EN

Title of invention:
Carbamates derived from arylalkylamines

Patentee:
LABORATORIOS S.A.L.V.A.T., S.A.

Opponent:
Almirall Prodesfarma S.A.

Headword:
Arylalkylamine carbamates/LABOARATORIOS S.A.L.V.A.T.

Relevant legal provisions:
EPC Art. 114, 54(3), 56

Keyword:
"Main and first auxiliary request: not allowable (reformatio in peius)"
"Admission of a late filed unsubstantiated objection (no)"
"Second auxiliary request: Novelty (yes) - individual compounds novel over generic disclosure; iventive step (yes) - improved selectivity not obvious"

Decisions cited:
G 0001/99, G 0001/03, G 0007/93, G 0009/91, T 0012/90, T 0012/81, T 0007/86, T 0939/92, T 0270/90

Catchword:
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Case Number: T 1194/06 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 6 August 2009

Appellant: (Opponent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 16 May 2006 concerning maintenance of European patent No. 1300407 in amended form.

Composition of the Board:

Chairman: P. Ranguis
Members: G. Seufert
C. Rennie-Smith

Summary of Facts and Submissions

I. The Appellant (Opponent) lodged an appeal against the interlocutory decision of the Opposition Division of 16 May 2006 maintaining the European patent No. 1 300 407 in amended form, and on 18 September 2006 filed a written statement setting out the grounds of appeal.

II. In this decision the following numbering will be used to refer to the documents:

(2) WO-A-02/51841
(3) Acta Pharm. Suecica 5, (1968), p. 71-76
(4) US-A-3 287 471

III. Opposition was filed requesting revocation of the patent in suit in its entirety on the grounds of lack of novelty and inventive step (Article 100(a) EPC in combination with Article 54 and 56 EPC) and insufficiency of disclosure with respect to the subject-matter of claims 7-12 (Article 100(b) EPC in combination with Article 83 EPC).

IV. The decision under appeal was based on a main request consisting of the claims as granted and a second and third auxiliary request filed during opposition proceedings. The first auxiliary request had been abandoned by the Respondent (Patent Proprietor).

The Opposition Division held that the then pending third auxiliary request fulfilled the requirement of Article 123(2) EPC, that its subject-matter was novel over document (2) and involved an inventive step over

the documents (3) and (4), and that the subject-matter of claims 7-12 was sufficiently disclosed. The objection of insufficiency of disclosure against the subject-matter of claims 1-6 raised for the first time during oral proceedings before the Opposition Division was considered late filed, speculative and unsubstantiated and its admission was refused.

V. In reply to the statement of grounds of appeal the Respondent maintained as its main request the set of claims upheld by the Opposition Division and filed auxiliary requests I-V. Furthermore, the Respondent resubmitted experimental data already provided during the opposition procedure.

VI. With the summons to oral proceedings, the Board sent a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), indicating its preliminary opinion. In particular, the Board raised concerns whether claim 1 as maintained by the Opposition Division in view of the disclaimer, which had been introduced during the opposition procedure, fulfilled the requirement of Article 123(2) EPC. Furthermore, the Board informed the parties that it considered the problem to be solved as providing compounds which are selective for the M_3 receptor and that it would be discussed whether the proposed solution would have been obvious in view of the fact that neither document (3) nor document (4) addressed the question of selectivity.

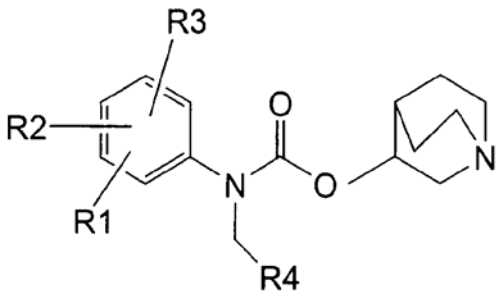
VII. In reply to the Board's communication the Respondent filed auxiliary requests VI-VIII.

VIII. At the beginning of the oral proceedings before the Board, held on 6 August 2009, the parties were informed that the disclaimer present in claim 1 of the main request might not have been properly worded insofar as it excluded N-oxides and solvates which were not part of the disclosure of document (2). Their exclusion was, therefore, not necessary for restoring novelty over that document. However, excluding N-oxides and solvates from the disclaimer would broaden the scope of the claims as maintained by the Opposition Division, which is prohibited since the Patent Proprietor is not Appellant. Furthermore, it would seem that claim 7 relates to compounds which are excluded by the disclaimer. This might render the set of claims inconsistent and objectionable under Article 84 EPC.

In reply the Respondent filed a new main request as well as a new auxiliary request I. The former auxiliary request I was resubmitted as auxiliary request II. All lower ranking requests were withdrawn.

The main request consists of 13 claims, independent claims 1 and 7 reading as follows:

1. A compound of formula (I)



(I)

wherein R1, R2 and R3 are the same or different radicals, attached to the benzenic ring at any of their possible positions, and they are selected from the group consisting of H, OH, SH. CN, F, Cl, Br, I, (C_1-C_4)-alkylthio, (C_1-C_4)-alkoxyl, (C_1-C_4)-alkoxyl substituted with one or several F, carbamoylamine, (C_1-C_4)-alkyl and (C_1-C_4)-alkyl substituted with one or several F or OH; alternatively, either R1 and R2, or R2 and R3 may be forming a biradical selected from the group consisting of -CH_2-CH_2-CH_2- and -CH_2-CH_2-CH_2-CH_2-; and R4 is a radical selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, norbornenyl, bicyclo[2.2.1]heptanyl, 2-, 3-thienyl, 2-, 3-furyl, 2-, 3-, 4-pyridyl, 1-, 2-naphthyl, 1-, 2-benzodioxolanyl, 1-, 2-benzodioxanyl, phenyl, and phenyl substituted with one or several substituents selected from the group consisting of OH, SH, CN, F, Cl, Br, I, carbamoylamine, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylthio, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxyl, (C_1-C_4)-alkyl substituted with one or several F or OH, and (C_1-C_4)-alkoxyl substituted with one or several F;
and their pharmaceutically acceptable (C_1-C_4)-alkylammonium salts over the quinuclidyl nitrogen, and their N-oxides over the quinuclidyl nitrogen; as well as stereoisomers, stereoisomers mixtures, pharmaceutically acceptable salts, and pharmaceutically acceptable solvates thereof, provided that for compounds that are not N-oxides or solvates, if each of Rl, R2, and R3 represent hydrogen, or if one member of R1, R2, and R3 represents a halogen atom, a (C1-C4)-alkyl group or a cyano group, the remaining two members

representing hydrogen, R4 may not be unsubstituted phenyl, 2-, 3-thienyl, or 2-, 3-furyl.

7. 3-Quinuclidyl N-benzyl-N-phenylcarbamate hydrochloride; (R)-3-Quinuclidyl N-benzyl-N-phenylcarbamate hydrochloride; (R)-3-(N—benzyl-N-phenylcarbamoyloxy)-1-methylquinuclidinium iodide; N—Phenyl-N-benzyl-3-quinuclidyl carbamate N-oxide; (R)-3-Quinuclidyl N-benzyl-N-(2-fluorophenyl)carbamate; (R)-3-Quinuclidyl N-benzyl-N-(3-chlorophenyl) carbamate; (R)-3-Quinuclidyl N-benzyl-N-(3-bromophenyl)carbamate; (R)-3-Quinuclidyl N-benzyl-N-(m-tolyl)carbamate; (R)-3-Quinuclidyl N-benzyl-N-(4-cyanophenyl)carbamate; (R)-3-[N-benzyl-N-(o-tolyl)carbamoyloxy]-1-methylquinuclidinium iodide; (R)-3-[N-benzyl-N-(2-fluorophenyl)carbamoyloxy]-1-methylquinuclidinium iodide.

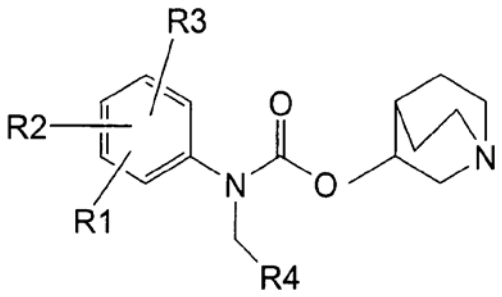
Independent claims 8, 10, 11 and 13 of the main request refer to the use of a compound as defined in any one of claims 1 to 7, in the manufacture of a medicament for the treatment of urinary incontinence, irritable bowel syndrome and respiratory disease, and for ophthalmic interventions.

In the first auxiliary request independent claim 7 has been modified and reads as follows:

7. N—Phenyl-N-benzyl-3-quinuclidyl carbamate N-oxide.

The second auxiliary request is distinguished from the main request in that independent claims 1 and 7 have been modified to read as follows:

1. A compound of formula (I)



(I)

wherein R1, R2 and R3 are the same or different radicals, attached to the benzenic ring at any of their possible positions, and they are selected from the group consisting of H, OH, SH, CN, F, Cl, Br, I, (C_1-C_4)-alkylthio, (C_1-C_4)-alkoxyl, (C_1-C_4)-alkoxyl substituted with one or several F, carbamoylamine, (C_1-C_4)-alkyl and (C_1-C_4)-alkyl substituted with one or several F or OH; alternatively, either R1 and R2, or R2 and R3 may be forming a biradical selected from the group consisting of -CH_2-CH_2-CH_2- and -CH_2-CH_2-CH_2-CH_2-; and R4 is a radical selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, norbornenyl, bicyclo[2.2.1] heptanyl, 2-, 3-, 4-pyridyl, 1-, 2-naphthyl, 1-, 2-benzodioxolanyl, 1-, 2-benzodioxanyl, and phenyl substituted with one or several substituents selected from the group consisting of OH, SH, CN, F, Cl, Br, I, carbamoylamine, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylthio, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxyl, (C_1-C_4)-alkyl substituted with one or several F or OH, and (C_1-C_4)-alkoxyl substituted with one or several F;

and their pharmaceutically acceptable (C_1-C_4)-alkylammonium salts over the quinuclidyl nitrogen, and their N-oxides over the quinuclidyl nitrogen; as well as stereoisomers, stereoisomers mixtures, pharmaceutically acceptable salts, and pharmaceutically acceptable solvates thereof.

7. 3-Quinuclidyl N-benzyl-N-phenylcarbamate hydrochloride;(R)-3-Quinuclidyl N-benzyl-N-phenyl-carbamate hydrochloride; (R)-3-(N-benzyl-N-phenyl-carbamoyloxy)-1-methylquinuclidinium iodide; N-Phenyl-N-benzyl-3-quinuclidyl carbamate N-oxide; (R)-3-Quinuclidyl N-benzyl-N-(2-fluorophenyl)carbamate; (R)-3-Quinuclidyl N-benzyl-N-(3-chlorophenyl)carbamate; (R)-3-Quinuclidyl N-benzyl-N-(3-bromophenyl)carbamate; (R)-3-Quinuclidyl N-benzyl-N-(2, 6-difluorophenyl) carbamate; (R)-3-Quinuclidyl N-benzyl-N-(3, 4-difluoro-phenyl)carbamate; (R)-3-Quinuclidyl N-benzyl-N-(m-tolyl)carbamate; (R)-3-Quinuclidyl N-benzyl-N-(2, 6-dimethylphenyl)carbamate; (R)-3-Quinuclidyl N-benzyl-N-(5-indanyl) carbamate; (R)-3-Quinuclidyl N-benzyl-N-(4-cyanophenyl) carbamate; (R)-3-Quinuclidyl N-benzyl-N-(2-hydroxyphenyl)carbamate; (R)-3-[N-benzyl-N-(o-tolyl)carbamoyloxy]-1-methyiquinuclidinium iodide; (R)-3-[N-benzyl-N-(2-fluorophenyl)carbamoyloxy]-1-methylquinuclidinium iodide.

IX. The arguments submitted by the Appellant in the written procedure and during the oral proceedings to the extent that they are relevant for this decision can be summarised as follows:

By removing the N-oxides and solvates from the disclaimer in claim 1 of the main request and the first

auxiliary request, the Respondent had broadened the scope of claim 1 of the request on which the Opposition Division intended to maintain the patent in suit, which puts the Appellant in a worse position than if he had not appealed. Since, in accordance with the decision G 1/99 of the Enlarged Board of Appeal, further limitation was possible taking into account the Respondent's requests filed on 30 January 2007, the main and first auxiliary requests are inadmissible and unallowable as they violate the principle of *reformatio in peius*.

The subject-matter of claim 7 is not novel over the disclosure of document (2), in particular in view of examples 52, 2, 25 and 22 of that document. In addition, the compounds of claim 7 do not represent a new selection. They are encompassed by the general formulae of document (2) and, although they represent a narrow selection, they are not far removed from the examples of that document and represent no new technical teaching. Thus, the criteria of a selection invention developed by the Boards of Appeal are not fulfilled.

In view of document (3), which should be considered to represent the closest state of the art, the technical problem to be solved was the provision of further anti-cholinergic compounds. The proposed solution, namely the replacement of the phenyl ring on the carbamate nitrogen atom of the compound of document (3) by a benzyl ring, was obvious for the skilled person in the light of document (4), which discloses N-phenyl N-benzyl carbamate with similar biological activity. Furthermore, the scope of the claims is such that it

encompasses compounds which cannot be manufactured into drugs and will have no biological activity. However, the mere provision of further compounds without any activity cannot be considered as involving an inventive step.

X. The arguments of the Respondent in the written procedure and during the oral proceedings to the extent that they are relevant for this decision can be summarised as follows:

Although it is possible to amend the claims in such a way that the principle of *reformatio in peius* is respected, the main and first auxiliary request should be allowed considering the exceptional circumstances of the present case. The further limitation would severely reduce the scope of the claims. Additionally, the present situation, which occurred as a consequence of the decision G 1/03 of the Enlarged Board of Appeal on the allowability of a disclaimer, could not have been envisaged in the decision G 1/99 concerning a possible exception to the principle of *reformatio in peius*.

The objection under Article 100(b) with respect to the subject-matter of claims 1-6 represented a late attack in view of the fact that only the use claims were objected to in the notice of opposition. Accordingly, the Opposition Division refused to admit this objection into the procedure and no consent is given to introduce this new ground of opposition into the appeal procedure. Furthermore, being based on a compound which does not even form part of the claims, the Appellant's objection is a priori without merit.

None of the individual compounds of claim 7 is anticipated by document (2): example 52 of that document does not refer to a hydrochloride, there is no clear and unambiguous disclosure for the combination of example 2 of document (2) with the general disclosure on its page 5, and examples 22 and 25 of document (2) differ from those presently claimed in the substitution pattern on the phenyl ring. Furthermore, the Appellant's approach with regard to a selection invention is not applicable. The criteria relied on by the Appellant were developed by the Boards of Appeal to examine the novelty of a selection of parameter ranges from a broader range. However, claim 7 refers to individual compounds. Novelty of individual compounds is not taken away by a generic formula.

The objective problem to be solved by the patent in suit was the provision of compounds with a higher selectivity for the M_3 receptor. This problem has been solved by all the compounds of the patent in suit. Furthermore, experimental data, resubmitted with the reply to the statement of the grounds of appeal, also show that the compound (I) of document (3) has a low selectivity for the M_3 receptor. The proposed solution is not obvious from the combination of documents (3) and (4) in view of the fact that compound (I) of document (3) is the less active of the two compounds (I) and (II) and that document (4) referring generally to the activity on cholinergic receptors, including ganglion (nicotinic) and atropinoic (muscarinic) receptors, does not suggest a particular selectivity for the M_3 receptor, which is only one of several atropinic receptors. With regard to the Appellant's allegation that part of the claimed compounds are not

active or cannot be formulated into drugs, reference is made to the broad structural variations in the examples of the patent is suit, for all of which the desired M_3 receptor antagonistic activity has been demonstrated. Furthermore, it is the Appellant which has the burden of proving its own allegations.

XI. The Appellant requested that the decision under appeal be set aside and that the patent be revoked.

XII. The Respondent requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or, alternatively, of the auxiliary requests I or II filed during the oral proceedings.

XIII. At the end of the oral proceedings, the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. *Admissibility of the Respondent's main and first auxiliary requests*

2.1 A new main request as well as a new first auxiliary request were filed by the Respondent during oral proceedings immediately after having been informed by the Board that in its opinion the disclaimer in the request upheld by the Opposition Division, insofar as it concerned the N-oxides and the solvates, is

objectionable under Article 123(2) EPC (see point VIII above).

2.2 Since these new requests were filed as a direct response to objections raised by the Board in this form for the first time during the oral proceedings and as an attempt to address these objections, the Board in exercising its discretion to accept amended claims even at a late stage of the proceedings admitted the new main and first auxiliary request into the proceedings. Auxiliary request II had already been submitted as auxiliary request I in reply to the statement of grounds of appeal

3. *Allowability of the Respondent's main and first auxiliary request - reformatio in peius*

3.1 Claim 1 of the request on the basis of which the Opposition Division intended to maintain the patent contained a disclaimer introduced during the opposition proceedings in order to remove the area of overlap between the claimed subject-matter and document (2), a document in the sense of Article 54(3) EPC for those parts of the claims for which the priority was not considered to be valid. The disclaimer has been added at the end of the claim following the definition of the compounds, their pharmaceutically acceptable (C_1-C_4)-alkylammonium salts over the quinuclidyl nitrogen, their **N-oxides** over the quinuclidyl nitrogen, as well as their stereoisomers, stereoisomers mixtures, pharmaceutically acceptable salts, and pharmaceutically acceptable **solvates** thereof, and reads as follows:

"*provided that if each of Rl, R2, and R3 represent hydrogen, or if one member of R1, R2, and R3 represents a halogen atom, a (C_1-C_4)-alkyl group or a cyano group, the remaining two members representing hydrogen, R4 may not be unsubstituted phenyl, 2-, 3-thienyl, or 2-, 3-furyl*".

Thus, the disclaimer also excludes the N-oxides and solvates for the defined area, said derivatives not being disclosed in document (2) (see point VIII above).

3.2 Claim 1 of the main request as well as the first auxiliary request differs from claim 1 as upheld by the Opposition Division insofar as the disclaimer, which was not considered allowable by the Board, has been modified in such a way that N-oxides and solvates are no longer excluded within the disclaimed area (see point VIII above), which modification extends the scope of protection afforded by the claim. Allowing such a claim would put the Opponent and sole Appellant in a worse situation than if it had not filed an appeal. In such a case, where an inadmissible amendment was held allowable by the Opposition Division, the non appealing Patent Proprietor/Respondent, according to the principles developed in the decision G 1/99 of the Enlarged Board of Appeal (OJ EPO 2001, 381, point 15 of the reasons), has three possibilities for amendments:

a) In the first place, it is allowed to amend by introducing one or more originally disclosed features which limit the scope of the patent as maintained.

b) If such a limitation proves impossible the Patent Proprietor may file amendments introducing one or

more originally disclosed features which extend the scope of the patent as maintained, but within the limits of Article 123(3) EPC.

c) If such an amendment proves impossible the Patent Proprietor may delete the inadmissible amendment maintained by the Opposition Division, but within the limits of Article 123(3) EPC.

3.3 The Board observes that the Respondent had filed with its reply to the statement of grounds of appeal several auxiliary requests, including the present auxiliary request II, which due to further limitations in the definition of the substituent R4 (deletion of the connotation 2-, 3-thienyl, 2-,3-furyl and unsubstituted phenyl) did not contain the unallowable disclaimer and restricted the scope of the patent as maintained. Thus, the Board agrees with the Appellant that the Respondent could, by making use of the possibility a) referred to above, further restrict the scope of the claims as upheld by the Opposition Division and overcome the objection raised with regard to the prohibition of *reformatio in peius*.

3.4 The Respondent admitted that a limitation according to the first route mentioned in the decision G 1/99 was possible, but argued that this would result in a substantial restriction of the scope of the claims. It further argued that in the present case exceptional circumstances existed insofar as the present situation concerning an unallowable disclaimer occurred as a result of the decision G 1/03 of the Enlarged Board of Appeal which result could not have been envisaged by the decision G 1/99.

3.5 The Board is aware of the fact that the Respondent, by restricting itself to one of the auxiliary requests not containing the disclaimer, for example auxiliary request II, would lose part of the protection afforded by the patent as maintained by the Opposition Division. It is, however, clear from the decision G 1/99 (see point 15 of the reasons) that the principle of *reformatio in peius* has to be respected by the Boards of Appeal and that an exception to this principle should be construed narrowly. It is also clear that the conditions for such an exception should be considered in the cited sequence. Thus, the possibility b), such as now under consideration, should be considered if, and only if, possibility a) is not possible.

There is also no reason for the Board to assume that the Enlarged Board of Appeal considered even a substantial limitation of the scope of protection unacceptable, taking into account that the first possibility a) referred to above mentions limitations without indicating any further conditions to be fulfilled. The decision G 1/99 also does not distinguish between different "types" of unallowable amendment. Thus, the Board can see no reason to assume that an amendment concerning an unallowable disclaimer should be treated in any way differently than other unallowable amendments, even if the question of what is considered to be an unallowable disclaimer has been clarified after the decision G 1/99.

3.6 Since the Respondent had at least one possibility of limiting the claimed subject-matter according to condition a) referred to above, which would not put the Appellant in a worse position than if he had not

appealed, the Respondent's main and first auxiliary request must be refused for violating the principle of prohibition of *reformatio in peius*.

Auxiliary Request II

4. *Admissibility of the ground of lack of sufficiency with respect to claim 1*

4.1 In its notice of opposition the Appellant raised an objection with respect to the subject-matter of claims 7 to 12 referring to the use of a compound defined in any one of the claims 1-6 in the manufacture of a medicament for certain specific diseases on the grounds that "*there was no general disclosure of pharmaceutical compositions or specific disclosure of individual compositions, nor is there any disclosure of routes of administration and dosages ranges appropriate to those routes*".

4.2 At oral proceedings before the Opposition Division the Opponent raised an objection under Article 100(b) EPC with respect to the subject-matter of claims 1-6 related to compounds of the formula (I) on the grounds that some of the claimed compounds cannot be prepared. The Opposition Division rejected this "new ground of opposition" for the reasons that the Patent Proprietor did not have sufficient time to prepare its response or to produce experimental evidence. Furthermore, the Opponent's allegation has been considered as unsubstantiated and mere speculation and therefore did not prima facie prejudice the maintenance of the patent.

4.3 In accordance with Article 114(2) EPC it was within the discretion of the Opposition Division to refuse such a late filed submission. In the Board's opinion a Board of Appeal should only overrule the way in which a first instance department has exercised its discretion if it comes to the conclusion that the first instance department has exercised its discretion according to the wrong principles, or without taking into account the right principles, or in an unreasonable way considering that, if a first instance department is required under the EPC to exercise its discretion in certain circumstances, such a department should have a certain degree of freedom when exercising that discretion, without interference from the Boards of Appeal (G 7/93, point 2.6 of the reasons).

4.4 In the present case, the Board finds that the department of the first instance has exercised its discretion correctly and in a reasonable way. In this context it is to be remarked that the question whether or not the claimed compounds could be prepared is an entirely different issue compared to the question whether or not there was a general disclosure of pharmaceutical compositions, specific disclosure of individual compositions, or any disclosure of routes of administration and appropriate dosage rates. Admitting such a new attack brought forward by the Opponent for the first time during oral proceedings must certainly be considered as unexpected for the Patent Proprietor and contains the risk of depriving it of the possibility to respond adequately to the new objection. Thus, the risk of violating Article 113(1) would have been very high. In addition, the Opponent/Appellant has apparently not provided any factual evidence for its

allegation. The Board, therefore, is of the opinion that the Opposition Division was within its right to consider the objection as unsubstantiated and prima facie not relevant for the maintenance of the disputed patent and to refuse to admit it into the proceedings.

4.5 The Appellant has not challenged the way in which the first instance department has exercised its discretion. In its statement of the grounds of appeal, the Appellant merely raised again the same objection of insufficiency with respect to claim 1. During oral proceedings before the Board the Appellant presented no further arguments and referred to its written statement.

4.6 The Board notes that according to the decision G 9/91 (see point 18 of the reasons) the purpose of the appeal procedure inter partes is mainly to give the losing party the possibility of challenging the decision of the Opposition Division on its merits. The objection against claims 1-6 does not form part of this decision and, as set out in point 4.4. above, the Board is of the opinion that the Opposition Division correctly exercised its discretion not to admit this objection into the procedure. Furthermore, in view of the fact that the Appellant did not provide any factual evidence and based its allegation on a compound which does not even fall within the scope of claims of the disputed patent, the Board considers this objection as *prima facie* not relevant. Accordingly, the Board sees no reason to admit it *ex officio* (Article 114(1) EPC) into the appeal proceedings.

5. *Amendments*

5.1 Independent claim 1 of the auxiliary request II is based on claim 1 as originally filed and is distinguished from this claim as well as from the claims as granted in that a small number of residues has been removed from the definition of the variable R4. The specific compounds of claim 7 are based on examples 1-14, 65 and 68 of the application as filed and as granted.

5.2 The removal of these few residues from the definition of the variable R4 does not generate subject-matter extending beyond the content of the application as filed (no singling out) and restricts the scope of the claims as granted. Thus, the requirements of Article 123(2) and (3) EPC are satisfied.

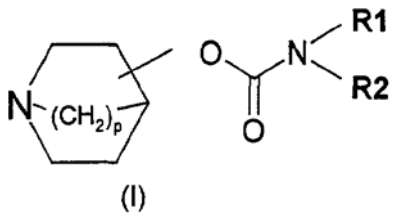
6. *Novelty*

6.1 The Appellant contested the novelty of claim 7 of the auxiliary request II in view of the disclosure of document (2), especially with regard to examples 52, 2, 25 and 22 of that document.

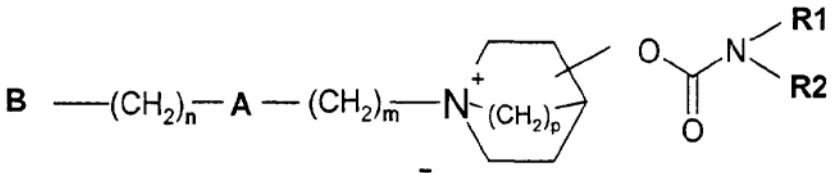
Claim 7 of the auxiliary request II is directed to a list of **individual** quinuclidyl carbamates or salts, each of them characterised by a specific selection of substituents on the phenyl, benzyl or quinuclidyl group and/or a specific stereochemistry (see point VIII above).

6.2 Document (2), which is comprised in the state of the art in the sense of Article 54(3) EPC for those

compounds of claim 7 for which the priority date of the patent in suit cannot be validly claimed, discloses quinuclidine compounds of **general** formula (I) and (II).



(I)



(II)

wherein the variable R1 includes residues like un- or mono-substituted phenyl, thienyl and furanyl, and the variable R2 benzyl, phenethyl and furanmethyl, the variable A includes groups like $-CH_2-$, -CH=CR4-, -CR4=CH-, -C(O)- and -O-, the variable B includes hydrogen, alkoxy, cycloalkyl, and COOR4, m is an integer from 0-8 and n is an integer from 0-4. Examples 52, 2, 25 and 22 refer to the following individual compounds (the nomenclature has been adapted to the nomenclature used in the patent in suit in order to facilitate the comparison):

ex.52: (S)-3-quinuclidyl N-benzyl-N-phenylcarbamate

ex 2: (R)-3-(N-benzyl-N-phenylcarbamoyloxy)-1-methylquinuclidinium acetate

ex.25: (R)-3-quinuclidyl N-benzyl-N-(p-tolyl) carbamate

ex22: (R)-3-[N-benzyl-N-(4-fluorophenyl)carbamate.

6.3 None of these compounds as well as none of the individual compounds of any of the other examples of document (2) shows the specific selection of substituents and/or stereochemistry of one of the individual carbamates and salts of claim 7.

6.4 The Appellant argued in support of its objection of lack of novelty that the compound "3-quinuclidyl N-benzyl-N-phenylcarbamate hydrochloride" of claim 7 must, in view of the clear reference to stereoisomers on page 3, line 27 of the patent in suit, be understood as covering all stereoisomers of this particular compound. Claim 7 therefore lacked novelty over example 52 of document (2) directed to the (S)-isomer.

6.5 However, the compound according to example 52 of document (2) is not a hydrochloride. For this reason alone it cannot anticipate the 3-quinuclidyl N-benzyl-N-phenylcarbamate hydrochloride of claim 7.

6.6 Furthermore, the Appellant based its novelty objection on the combination of example 2 of document (2) with the general disclosure on page 5, line 30 of document (2), which refers to a list of preferable anions for compound (II) of document (2), among them iodide. The replacement of the acetate in example 2 by iodide mentioned as a possible anion would lead to the compound (R)-3-(N-benzyl-N-phenylcarbamoyloxy)-1-methylquinuclidinium iodide of claim 7.

6.7 In this context, it is to be remarked that according to the jurisprudence of the Boards of Appeal regarding the examination of novelty, the teaching of a document is

not limited to the detailed information given in the examples, but embraces the disclosure of that document as a whole. Nevertheless, it is a general and consistently applied principle of the Boards of Appeal that for deciding lack of novelty there must be a direct and unambiguous disclosure in the state of the art which inevitably leads the skilled person to subject-matter falling within the scope of the claims. Applying this principle, the Board is of the opinion that for the examination of novelty different passages in a document can only be combined if there is a clear disclosure leading the skilled reader to combine them.

In the present case, there is no such disclosure. Example 2 of document (2) describes the preparation of a **particular** acetate salt and page 5, lines 24-32 of the description refers to a **generic** disclosure of possible anions in formula (II) of document (2). There is no clear and unambiguous disclosure for the skilled reader of document (2) to select a particular anion (i.e. iodide) from the generic disclosure of the description which also indicates other anions to be equally suitable and to combine it particularly with the quinuclidine carbamate compound of example 2. This modification of the example 2 by the Appellant can only be seen as the result of an ex post facto interpretation of document (2) made with the knowledge of the invention and with the purpose of reconstructing a compound of claim 7.

6.8 For the reasons set out in points 6.5 and 6.7 above the Board concludes that the compounds "3-quinuclidyl N-benzyl-N-phenylcarbamate hydrochloride" and "(R)-3-(N-benzyl-N-phenylcarbamoyloxy)-1-methylquinuclidinium

iodide" of claim 7 of the second auxiliary request are not disclosed in document (2).

6.9 With regard to the other compounds of claim 7 referred to by the Appellant, namely "(R)-3-Quinuclidyl N-benzyl-N-(**m-tolyl**) carbamate", "(R)-3-[N-benzyl-N-(**o-tolyl**)carbamoyloxy]-1-methylquinuclidinium iodide" and "(R)-3-[N-benzyl-N-(**2-fluorophenyl**)carbamoyloxy]-1-methylquinuclidinium iodide", the Appellant itself already admitted that they are **not identical** with the compounds of examples 25 and 22 of document (2), but merely "*structurally very similar*". In view of the fact that the compounds of document (2) disclose carbamate derivatives having a **p-tolyl** or a **4-fluorophenyl** residue, respectively, the Board can only agree with the Appellant's assessment. The aforementioned compounds of claim 7 are, therefore, not anticipated by examples 25 and 22 of document (2).

6.10 The Appellant also based its arguments concerning lack of novelty of claim 7 on the fact that this claim does not represent a novel selection over document (2), arguing in particular that the selection criteria established by the Boards of Appeal are not complied with, namely:

a) the selected sub-range is narrow
b) the selected sub-range should be sufficiently far removed from the known range illustrated by means of examples
c) the selected area should not provide an arbitrary specimen from the prior art, i.e. not a mere embodiment of the prior description, but another

invention (purposive selection, new technical teaching)

The Appellant considered the first criteria to be fulfilled, but argued that for example the compounds of claim 7, in particular the compound (R)-3-(N-benzyl-N-phenylcarbamoyloxy)-1-methylquinuclidinium iodide, or the compounds mentioned in point 6.9 are not far removed from the examples in document (2) and that no new technical teaching is present. In support of its arguments the Appellant referred to the decision T 12/90.

Finally, the Appellant also argued in support of its novelty objection that in view of example 2 and the disclosure on page 5, lines 31-32 of document (2) the skilled person would only have to make a selection from a very short list of compounds.

6.11 The Board observes that the compounds of claim 7 do not form a sub-range out of the broader range of compounds disclosed in document (2). Instead, claim 7 refers to a list of individualised compounds, i.e. single points within the generically disclosed area of document (2), resulting from a selection of specific substituents from several lists. The selection criteria, on which the Appellant relied and which have been applied by the Boards of Appeal to establish whether or not a selection of a **sub-range** out of a broader range is novel, are not applicable in the present case.

It is, however, established jurisprudence of the Boards of Appeal that subject-matter resulting from a specific combination requiring the selection of elements from at

least two lists is normally regarded as novel (see e.g. T 12/81, point 13 of the reasons, OJ EPO 1982, 296 or T 7/86, OJ EPO 1988, 381, point 5.1 of the reasons). Applying this principle in the present case, to arrive at each of those individual compounds of claim 7 encompassed by the general disclosure of document (2), several selections are necessary, namely a) R1 is a phenyl group substituted with a substituent selected from R3, b) R2 is a benzyl group, c) p is 2 and d) the quinuclidine ring is substituted in position 3. Even considering the preferred definition for the group NR1R2 on page 7, lines 9-31 and page 8, line 22-23 of document (2), at least two further selections are required to arrive at compounds of claim 7, namely p is equal to 2 and the substitution on the quinuclidine ring is in position 3.

The decision T 12/90 can also not support the Appellant's case. This decision is concerned with the examination of novelty of the area of overlap between two generally disclosed groups of compounds, each group defined by a Markush formula. Novelty was recognised, if in the area of overlap a novel element is added to the state of the art. The situation in the present case differs from that in T 12/90 insofar as the subject-matter of claim 7 does not refer to a group of compounds defined by a Markush formula, which overlaps with the Markush formula of document (2), but to individualised compounds. This difference in concept has also been acknowledged in the decision T 12/90 (see point 2.8 of the reasons).

The Board is also not convinced by the Appellant's arguments concerning the length of the list from which

the skilled person could allegedly choose. As set out above (see point 6.7) the combination of an example with part of the description in a prior art document cannot be used to argue lack of novelty unless there is a clear disclosure for this combination in the prior art, which is not the case in document (2). Accordingly, the length of such an arbitrarily selected list of compounds is irrelevant for the assessment of novelty.

6.12 For the reasons set out above the Board concludes that the subject-matter of claim 7 is novel within the meaning of Article 52(1) and 54(3) EPC.

7. *Inventive Step*

7.1 According to established jurisprudence of the Boards of Appeal, it is necessary, in order to assess inventive step, to establish the closest state of the art, to determine in the light thereof the technical problem which the invention addresses and successfully solves and to examine the obviousness of the claimed solution to this problem in view of the state of the art.

The patent in suit is directed to quinuclidine carbamate derivatives of the general formula (I). These compounds act as muscarinic receptor antagonists, particularly as selective M_3 receptor antagonists, and are therefore useful in the treatment of urinary incontinence, irritable bowel syndrome and respiratory disease, and for ophthalmic interventions.

7.2 Document (3) describes, amongst other quinuclidine derivatives, a structurally very similar carbamate

compound (see compound I on page 72 of document (3)), which is distinguished from the compounds of claim 1 of the auxiliary request II in that a phenyl residue instead of the residue -CH_2-R4 is attached to the nitrogen atom of the carbamate group. The compounds of document (3) have been tested for antagonistic activity to acetylcholine on isolated guinea-pig ileal preparations, and compared to atropine, which is a known muscarinic antagonist. Compound I has been found to be one of the two most active compounds (see document (3), table 2). Document (3) does not mention a particular activity on any of the muscarinic sub-receptors.

According to the Opposition Division as well as both parties, document (3) represents the closest state of the art. The Board sees no reason to depart from this finding and hence takes it as the starting point for assessment of an inventive step.

7.3 In the light of this closest prior art, the Board sees the problem to be solved by the present invention as the provision of compounds which are selective M_3 receptor antagonists, thereby avoiding undesirable effects caused by the "blockade (*sic*) of other muscarinic receptors" (see patent in suit page 2, lines 22-24, page 3, lines 4-6, page 4, lines 39-43).

As the solution to this underlying technical problem the patent in suit proposes the quinuclidine carbamate compounds according to formula (I).

In order to prove that these compounds achieve the solution, the Respondent relied on the data present in

the table on pages 8-17 of the patent in suit. This table shows in the fourth column the M_2/M_3 ratio resulting from binding tests to human M_2 and M_3 muscarinic receptors (see page 6, lines 1-18 of the disputed patent). A value of greater than 1 indicates selectivity for the M_3 receptor. For all but one compound, for which no data has been given, the value is above 1. The Board is thus satisfied that the underlying problem has been solved.

7.4 The Appellant has argued that the problem to be solved by the patent in suit is simply the provision of further anti-cholinergic compounds in view of the fact that the compound I of the document (3) has the same biological activity as those of the patent in suit and shows activity on guinea pig ileum.

7.5 The Board does not share the Appellant's point of view. Although document (3) describes compounds with muscarinic antagonistic activity, it mentions nowhere, either directly or indirectly, a particular selectivity for one of the muscarinic sub-receptors, let alone an even more particular selectivity for the M_3 receptor. The reference to the activity on the ileum cannot support a particular M_3 selectivity in view of the fact that in the smooth muscle of the intestinal tract, to which the ileum belongs, M_3 and M_2 receptor coexist (see also the page 2, lines 20-21). In addition, the Respondent has provided data, which has not been contested by the Appellant, that compound (I) of document (3) has a low selectivity for the M_3 receptor. The Board sees, therefore, no reason why the technical problem the invention set out to solve, namely the

provision of selective M_3 receptor antagonists, should be reformulated.

7.6 It remains to be decided whether or not the proposed solution is obvious in view of the prior art.

7.6.1 The Appellant argued that the solution proposed by the patent in suit is obvious in view of the combination of document (3) with document (4), the latter disclosing N-benzyl-N-phenyl carbamates as atropinoid and ganglion blocking agents. Trying to replace the phenyl group of compound (I) of document (3) by a benzyl group with reasonable expectation to obtain further active compounds would therefore have been obvious for the skilled person.

7.6.2 The Board observes that document (3), although concerned with the muscarinic activity of a compound, which is structurally similar to those of the patent in suit, does not indicate a particular selectivity for certain muscarinic sub-receptors. Hence the skilled person could not find in this document the suggestion to modify the compound in such a way as to arrive at the compounds proposed in the disputed patents. The same conclusion applies to document (4), which no more addresses the question of selectivity than does document (3). Document (4) generally describes carbamate derivatives whereby the nitrogen atom of the carbamate is substituted by an optionally substituted phenyl and an optionally substituted benzyl group. The compounds differ from those of the patent in suit in that the oxygen atom of the carbamic group is not attached to a quinuclidine residue, but linked to a pyrrolidinyl ring, either directly or through a

methylene group. The compounds are described as atropinoid and ganglion blocking agents. Document (4) is completely silent on the question of selectivity for different muscarinic sub-receptors.

7.6.3 Thus, in view of the prior art the skilled person had no incentive to combine the teaching of documents (3) and (4) to arrive at the presently claimed compound in order to solve the problem of providing selective M_3 receptor antagonists. To come to a different conclusion would require hindsight based on a knowledge of the invention.

7.6.4 The Appellant further alleged that claim 1 of the auxiliary request II also embraces compounds which do not solve a technical problem, arguing that it would be self evident to any person skilled in the art that not all compounds falling within the scope of the claims are biologically active or could be manufactured into drugs. Further proof, according to the Appellant, was, therefore, not required. A mere provision of further compounds without any activity, however, could not be considered as involving an inventive step. Moreover, example 4 on page 9 of the patent in suit could be considered as evidence that not all compounds are active.

In support of its arguments the Appellant referred to the decision T 939/92 (OJ EPO, 1996, 309), especially to point 2.5.3 of the reasons. Furthermore, the Appellant pointed out that in this decision, despite the number of tested compounds, the Board considered it inherently unlikely that all the claimed compounds, or at least substantially all of them will have the

desired activity. In the Appellant's opinion the same applies in the present case.

7.6.5 However, decision T 939/92 legally as well as factually is not applicable to the present case.

On a legal point of view decision T 939/92 relates to an *ex parte* case whereas the present case is *inter partes*. Such a procedure is by its very nature less of an investigative than an administrative procedure (see G 9/91, OJ EPO 1993, 408, point 18 of the reasons). This is of particular importance as far as the evidence is concerned. In *ex parte* proceedings the applicant bears the burden of proof of the facts he relies on (see Case law, 5th edition, VI.K.5.1).

By contrast, as a fundamental principle of *inter partes* proceedings, each of the parties to the proceedings carries the burden of proof of the facts it alleges (see T 270/90, OJ EPO 1993, 725, point 2.1). Therefore, the burden of proof lies upon the Opponent/Appellant to support its contention that the technical problem is not solved over the whole claimed area.

7.6.6 The Board observes that the Appellant did not provide any verifiable data or facts demonstrating that part of the claimed compounds lacked the desired activity or could not be converted into drugs. Accordingly, in the absence of any substantiating facts and corroborating evidence, the Board considers the Appellant's allegations as mere speculation. The reference to example 4 of the patent in suit cannot support the Appellant's allegation as this compound is not described as inactive in the patent in suit. The table

on page 9, where the compound is mentioned, merely shows the symbol "-" in those columns referring to the binding affinity constant M_3 and the ratio of M_2 to M_3, which can equally well be interpreted as an indication that these parameters have not been measured for this compound. Moreover, the Board considers this as the more likely interpretation, taking into account that the same symbol has been used in the column referring to IR signals for other compounds, where it cannot be reasonably interpreted as the absence of IR signals.

7.6.7 Even if the Board had considered that T 939/92 was applicable from the legal point of view, the facts of that case differ considerably from the present case. In the decision T 939/92 the Board came to its conclusion that it was inherently unlikely that all compounds had the desired activity on the basis of several facts. Firstly, an unlimited number of compounds was claimed due to the use of the expression "optionally substituted", without mentioning any particular substituent. Secondly, the substitution pattern in the tested compounds had been very limited and thirdly, in view of the general common knowledge relied upon by the Patent Applicant/Appellant itself, namely that the influence of structural modification on the desired activity is unpredictable, these tested compounds did not support the alleged activity for compound which could be substituted by absolutely anything. The Board in T 939/92 also offered the Patent Applicant/Appellant the possibility to restrict its claims to compounds for which the Board was prepared to accept the alleged effect.

7.6.8 In the present case the expression "optionally substituted" has not been used. Thus, the scope of the claims is not unlimited. Furthermore, the examples of the disputed patent include compounds

- where the phenyl ring is mono-substituted by different substituents, poly-substituted by the same or different substituent, or forms a condensed ring system;
- where the variable R4 represents different residues like substituted phenyl, various cycloalkyl groups or a benzodioxolanyl or benzodioxanyl group;
- where the quinuclidyl nitrogen forms an ammonium salt

According to the tables on pages 8-17 of the description all these compounds show the desired activity. The Board is, therefore, satisfied that in the present case, unlike the situation in T 939/92, the examples reasonably reflect the breadth of the claimed subject-matter and that it has been made credible that a problem, namely the provision of selective M_3 receptor antagonists, is solved and that it is solved over the whole breadth.

7.7 For the reasons set out above the Board concludes that the subject-matter of the claims of auxiliary request II involves an inventive step within the meaning of Article 56 EPC.

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 maintain the patent on the basis of auxiliary request II filed during oral proceedings and a description to be adapted thereto.

The Registrar: The Chairman:

M. Schalow P. Ranguis