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EXAMINER

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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*Ex parte* JOERG BRANDENBURG and WERNER BELZER<sup>1</sup>

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Appeal 2015-005320  
Application 12/524,630  
Technology Center 1600

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Before JEFFREY N. FREDMAN, JOHN G. NEW, and  
DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

NEWMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to a process for preparing a scopinium salt compound. The Examiner entered final rejections for obviousness.

We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

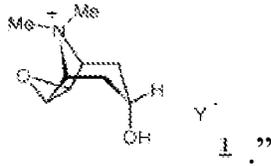
STATEMENT OF THE CASE

*Background*

“The invention relates to a new method of preparing scopinium salts of general formula 1

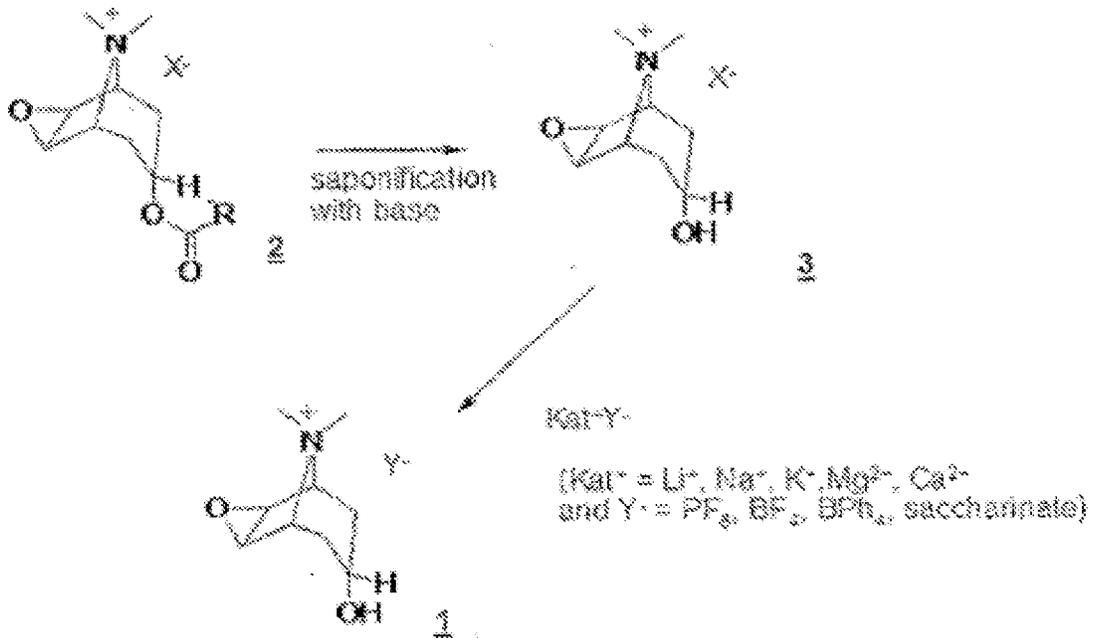
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<sup>1</sup> Appellants identify the Real Party in Interest as Boehringer Ingelheim International GmbH. App. Br. 1.



Spec. 1:1–4.

The Specification discloses “[t]he process according to the invention is characterised *inter alia* in that it allows direct access to salts of formula 1 from compounds of formula 2 in a single step without the need to isolate the intermediate compound of formula 3.” Spec. 3:5–8. The synthesis occurs as shown below:

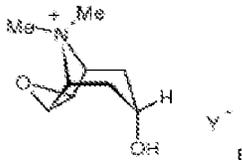


App. Br. 6.

*The Claims*

Claims 1, 2, and 9–13 are on appeal. Sole independent claim 1 is illustrative and reads as follows:

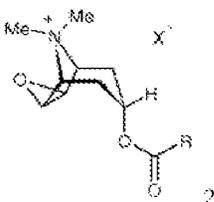
1. A process for preparing a scopinium salt of formula 1



wherein

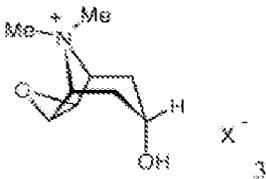
- Y<sup>-</sup> denotes an anion with a single negative charge, wherein the anion is selected from among hexafluorophosphate, tetrafluoroborate, tetraphenylboronate and saccharinate, comprising:

saponifying a compound of formula 2



wherein

- X<sup>-</sup> denotes an anion with a single negative charge selected from among chloride, bromide, iodide, methanesulphonate, p-toluenesulphonate, nitrate and trifluoromethanesulphonate; and
- R denotes a group selected from C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl and C<sub>1</sub>-C<sub>4</sub>-alkylene-phenyl, which may be substituted in each case by hydroxy, hydroxymethyl or C<sub>1</sub>-C<sub>4</sub>-alkoxy, optionally in the form of the solvates or hydrates thereof, in a solvent with the addition of a base to form initially a compound of formula 3



wherein X<sup>-</sup> has the meanings given above, and

converting the compound of formula 3, without being isolated, into the compound of formula 1 by reacting with a salt Kat<sup>+</sup>Y<sup>-</sup>, wherein Kat<sup>+</sup> denotes a cation selected from among Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, Ca<sup>2+</sup>, and Y<sup>-</sup> has the meanings given above.

### *The Issues*

The Examiner rejected claims 1, 2, and 9–13 under 35 U.S.C. § 103(a) as obvious over Moffett,<sup>2</sup> Honma,<sup>3</sup> Brandenburg,<sup>4</sup> and Qureshi<sup>5</sup> (Ans. 2).

The Examiner finds that the claimed process “involves the formation of a particular hexafluorophosphate salt of scopolamine through the process of ester hydrolysis followed by anion exchange.” Ans. 4. The Examiner finds “Moffett [] teaches the hydrolysis of quaternary scopolamine salt esters and subsequent isolation as the methylbromide.” *Id.* at 2. The Examiner finds

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<sup>2</sup> Robert B. Moffett and Edward R. Garrett, *Alkaline Hydrolysis of Scopolamine Methyl Bromide and Other Esters of Quaternary Amino Alcohols*, 77 JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 1245–1248 (1955) (“Moffett”).

<sup>3</sup> US 2006/0166103 A1, published July 27, 2006 (“Honma”).

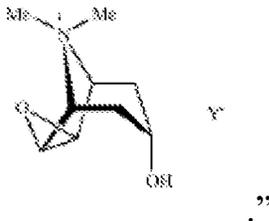
<sup>4</sup> US 6,747,154, issued June 8, 2004 (“Brandenburg”).

<sup>5</sup> Altaf Qureshi and Novis Smith, *Industrial hexafluorophosphate chemistry*, Abstracts of Papers, 228th American Chemical Society National Meeting, Philadelphia, PA, United States, August 22–26, 2004, FLU0-013 (“Qureshi”).

Honma “describes the standard ion exchange reactions of quaternary ammonium halides to various other inorganic counterions, including hexafluorophosphate of the elected species as well as tetrafluoroborate.” *Id.* at 3. The Examiner finds that “the hexafluorophosphate salt of this particular compound would be selected” because “[t]he compounds of the instant claims are commercially important in the art due to their intermediacy in the synthesis of pharmaceuticals” and that Qureshi describes interest in the “hexafluorophosphate anion” “due to the stability of its organic quaternary salts and the relative low reactivity of the anion.” *Id.* at 4–5.

*Findings of Fact (FF)*

1. Brandenburg discloses “the present invention relates to the use of compounds of formula 2



Brandenburg, 7:50–60.

2. Qureshi teaches that “[a]lthough the hexafluorophosphate anion has been available for over 50 y[ears] com[mercially], it is only now beginning to gain com[mercial]. interest due to the stability of its organic quaternary salts and the relative low reactivity of the anion.” Abstract.

3. Moffett discloses:

When scopolamine methyl bromide (I) was hydrolyzed with sodium hydroxide difficulties were encountered in the

separation of the quaternary salt from the sodium salts and therefore barium hydroxide was used which could be removed as a sulfate prior to isolation of the quaternary salt. In this way I-tropic acid (III) and a nicely crystalline quaternary bromide were obtained in good yield which gave the same analysis and melting point as scopoline methyl bromide (III), prepared from authentic scopoline. Moreover a mixed melting point gave no depression. However, the crystal shape of this salt (needles) was different from that of scopoline methyl bromide (III) (cubes) even when the two salts were recrystallized from the same solvent and seeded with the same sample of scopoline methyl bromide. Furthermore, the infrared spectra showed that the two salts were definitely different even though the same functional groups were indicated. Although both salts are quite stable at room temperature it was found that the hydrolysis product could be converted to scopoline methyl bromide (III) by heating the solid above 200°. All this evidence seemed to indicate that scopolamine methyl bromide (I) is hydrolyzed to the unarranged scopine methyl bromide (IV). That this is indeed the case was confirmed by converting authentic scopine prepared as described by Willstätter and Berner, to its methyl bromide quaternary salt, which was found to be identical in all respects with the hydrolysis product of scopolamine methyl bromide.

Moffett 1246:col. 2–1247:col 1.

4. Honma discloses:

The quaternary ammonium salt of the formula (5) of the present invention can be produced by various methods. Mentioned as preferable production methods are a production method in which a quaternary ammonium halide of the formula (13)



(wherein,  $R^4$ ,  $R^5$ ,  $R^{10}$ ,  $R^{11}$ ,  $k$ ,  $l$ ,  $m$  and  $n$  have the same meanings as described above, and  $X$  represents a halogen atom.) is reacted with a compound of the formula (7):



(wherein,  $M$  and  $A$  have the same meanings as described above.) to allow a halogen ion of the quaternary ammonium halide (13) to be ion-exchanged with a bis(trifluoromethylsulfonyl) imidate ion  $[\text{N}(\text{SO}_2\text{CF}_3)_2^-]$ , tetrafluoroborate ion ( $\text{BF}_4^-$ ) or hexafluorophosphate ion ( $\text{PF}_6^-$ ); and other methods.

As the halogen ion of the quaternary ammonium halide (13), for example, a chlorine ion, bromine ion, iodine ion and the like are mentioned.

Examples of the compound (7) include bis(trifluoromethylsulfonyl) imidic acid  $[\text{HN}(\text{SO}_2\text{CF}_3)_2]$ , tetrafluoroboric acid ( $\text{HBF}_4$ ), hexafluorophosphoric acid ( $\text{HPF}_6$ ), alkali metal salts thereof (for example, lithium salt, sodium salt, potassium salt and the like), and the like.

Ion exchange is carried out usually according to the following method.

The quaternary ammonium halide (13) and the compound (7) are mixed in water, an organic solvent showing low solubility in water (for example, ethyl acetate, methylene chloride and the like) is mixed with the resulted aqueous solution, then, an aqueous layer and an organic layer are separated, thus, a solution of a quaternary ammonium salt of the present invention can be obtained as the organic layer. The quaternary ammonium salt of the present invention can be obtained as a residue by washing the resulted organic layer with water if necessary, then, removing the organic solvent by distillation.

*Principles of Law*

“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

*Analysis*

We adopt the Examiner’s findings regarding the scope and content of the prior art as they pertain to the claims at issue (Final Act. 5–7; FF 1–4) and agree that the claimed process would have been obvious over the teachings of Moffett, Honma, Brandenburg, and Qureshi. We address Appellants’ arguments below.

Appellants acknowledge “[t]he first step of the two-step process is taught by Moffett” and that they “are not relying on unexpected advantages to show nonobviousness.” Reply Br. 1–2. Accordingly, the sole issue disputed by Appellants is whether there was “‘some articulated reasoning with some rational underpinning’ for one of ordinary skill in the art to perform the reaction step disclosed in Moffett followed by [] a second step of converting the salt of compound 2 to a salt with the distinct hexafluorophosphate, tetrafluoroborate, tetraphenylboronate and saccharinate anion of compound 1.” App Br. 7.

Appellants argue Moffett does not suggest performing the additional step of “converting the salt of compound 2 to a salt with the distinct hexafluorophosphate, tetrafluoroborate, tetraphenylboronate and saccharinate anion of compound 1.” *Id.*

Appellants argue Honma “does not describe [] an anion-exchange reaction for any and all quaternary ammonium halides and does not describe

a ‘general process’ for converting anions in any and all quaternary ammonium compounds” but instead “teaches performing such an anion conversion reaction for its specific quaternary ammonium halides of formula (1) containing the multiple ethyleneoxy groups (-CH<sub>2</sub>CH<sub>2</sub>O-).” *Id.* at 8. Appellants further argue the compound used in Moffett is “totally different structurally and functionally” from those disclosed in Honma, that “[t]here is no reasonable expectation that the reaction step conducted by Honma for its compounds would be successful on the Moffett compound,” and that “Honma fails to provide one of ordinary skill in the art a reason to conduct the anion conversion step on the Moffett compound.” *Id.*

Appellants further argue “Brandenburg discloses compounds that are similar to appellants’ formula 1 (i.e., tiotropium salts and intermediates for preparing them) **but with different anions.**” *Id.* Appellants argue “Brandenburg does not disclose compounds according to compound 1 of the instant claims” or teach any compounds “with a hexafluorophosphate, tetrafluoroborate, tetraphenylborate or saccharinate anion.” *Id.* at 8–9. According to Appellants, Brandenburg uses “formula 2 compound . . . as a starting material [and] thus provides no teachings for preparing compounds analogous to the compound 1 of the claimed invention or any step for converting anions of such a compound,” meaning there is no reason for the skilled artisan “to modify the process of Moffett to perform the second step of the claimed invention.” *Id.* at 9.

Appellants argue Qureshi “is merely an abstract showing that the hexafluorophosphate anion was known [and] teaches nothing about the use of the hexafluorophosphate anion with any particular compounds.” *Id.*

Appellants argue “Qureshi teaches nothing about processes for making hexafluorophosphate compounds or any process step analogous to the second step of the claimed process” and is “much too general to reasonably suggest applying a hexafluorophosphate anion to any specific compound.” *Id.*

Appellants further argue that none of the references, individually, or in combination, provide a “hint to combine the Moffett and Honma methods” or give “one of ordinary skill in the art a motivation to prepare compounds of appellants’ formula 1.” *Id.* at 10. Instead, “[a]ll of the references lack the essential feature of suggesting the second step of the claimed invention for making the scopine intermediates of the claimed invention with the specific anion as claimed.” *Id.*

Appellants’ arguments do not persuade us that the Examiner erred in rejecting claim 1 for obviousness over Moffett, Honma, Brandenburg, and Qureshi. As stated by the Examiner, “[b]oth steps of the process are known in the art and the alternative salt form has been shown to offer some advantages.” Ans. 6. Brandenburg teaches the compound of formula 3, the end compound of Appellants’ disclosed process. FF 1. Qureshi provides motivation for one of skill in the art to make the compound of formula 3, due to its use as a pharmaceutical intermediate that is also stable in salt form. FF 2. Moffett teaches hydrolysis of quaternary scopine salt esters and subsequent isolation as the methylbromide. FF 3. Appellants do not dispute any of these facts.

Honma provides evidence that an ion exchange reaction may be used to substitute inorganic counterions for quaternary ammonium halides, and

specifically suggests tetrafluoroborate or hexafluorophosphate ion as the exchange ion. FF 4. One of skill in the art, having read Moffett, Honma, Brandenburg, and Qureshi, would recognize compound 1 as a starting compound for the anion exchange and the conversion of compound 2 to a hexafluorophosphate salt, and would have had a reasonable expectation of success in doing so. FF 1–4. “Obviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success.” *In re O’Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988).

Appellants do not provide any evidence for their argument that the reaction disclosed in Honma is not a “general process” for converting anions in any and all quaternary ammonium compounds (App Br. 8) or explain why the process would not work as predicted by the Examiner. Without evidence, this attorney argument is not persuasive. *See In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974) (“Attorney’s argument in a brief cannot take the place of evidence.”). Absent evidence to the contrary, we agree with the Examiner that Honma’s disclosure provides guidance for one of skill in the art regarding the process of ion exchange as applied to the instant compounds. FF 4.

We are likewise not persuaded by Appellants’ arguments that the individual references, alone or in combination, fail to teach or suggest the second step of the claimed invention (e.g., Reply Br. 2–3). It is well established that prior art references need not disclose an express motivation to combine the teachings that is identical to that stated by a patent applicant in order to motivate the combination. *See In re Kemps*, 97 F.3d 1427, 1430

(Fed. Cir. 1996) (“[T]he motivation in the prior art to combine the references does not have to be identical to that of the applicant to establish obviousness.”). Brandenburg and Qureshi provide motivation to make the compound of formula 3. FF 1–2. In addition, our reviewing court has held that improvement-related factors may motivate a combination:

[A]n implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art **as a whole**, but when the “improvement” is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal—and even common-sensical— . . . there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him *capable* of combining the prior art references.

*DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1368 (Fed. Cir. 2006) (bold emphasis added). Accordingly, we affirm the Examiner’s rejection of obviousness of claim 1 over the cited references.

#### *Conclusion of Law*

The evidence of record supports the Examiner’s conclusion that claim 1 is obvious over the cited prior art.

Claims 2, and 9–13 have not been argued separately and therefore fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

Appeal 2015-005320  
Application 12/524,630

SUMMARY

We affirm the rejection of claims 1, 2, and 9–13 under 35 U.S.C. § 103(a) as obvious over Moffett, Honma, Brandenburg, and Qureshi.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED