

Patents Act 1977
OPINION UNDER SECTION 74A

Opinion Number 03/06

Patent	EP(UK) 1343750
Proprietor(s)	
Exclusive Licensee	
Requester	Mewburn Ellis LLP, on 16 March 2006
Observer(s)	Ciba Specialty Chemical Holdings Inc
Date Opinion issued	6 June 2006

The request

1. This opinion relates to a request seeking to establish whether the claims of the patent are obvious in view of a combination of disclosures contained in the following documents:

US 4535186 (HUSBANDS *et al*) (**D1**)

Yardley *et al*, *J Med Chem*, 1990, 33, 289-2905 (**D2**)

US 5266731 (AYERS *et al*) (**D3**)

Robinson *et al*, *Organic Syntheses*, Coll Vol 3, 720 (1955); Vol 23, 71 (1943) (**D4**)

US 3255248 (SUESSENGUTH *et al*) (**D5**)

March, *Advanced Organic Chemistry – Reactions, Mechanisms, and Structure*, Third Edition (1985) (**D6**)

Freidlin *et al*, *Russ Chem Rev*, 1964, 33, 319-330 (**D7**)

Observations; observations in reply

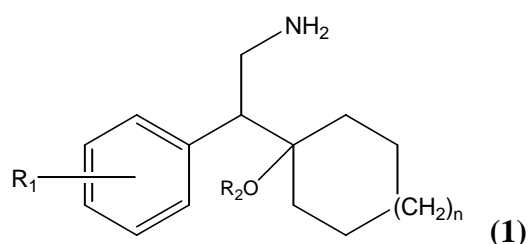
2. Observations were filed by the patent proprietor in which the allegations of obviousness were refuted.

3. Observations in reply have also been received from the requester in which a new citation, Michael *et al*, *Tetrahedron*, 1992, 48 (46), 10211-10220 (**D10**) was identified.

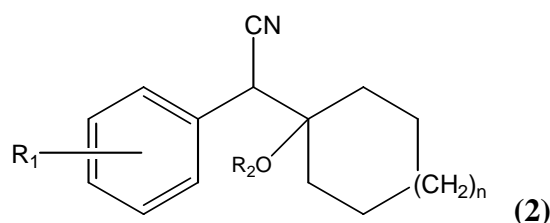
The patent

4. The invention disclosed in EP 1343750 relates to processes for preparing phenethylamine derivatives by hydrogenation in the presence of a nickel or cobalt catalyst. It also relates to particular phenethylamine derivatives *per se*. Accordingly, the patent contains three independent claims, which read as follows:

Claim 1 A process for the preparation of a compound of formula

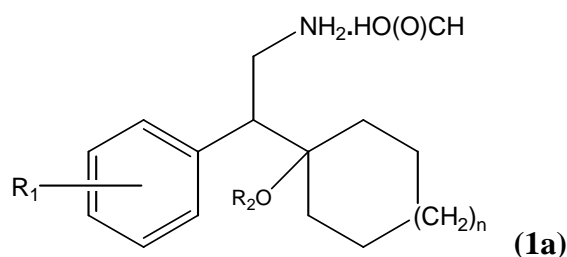


or salts thereof, wherein R_1 is hydrogen, hydroxyl, or unsubstituted or substituted alkyl or alkoxy, R_2 is hydrogen or a substituent which can be converted to hydrogen, and n is 0, 1 or 2 comprising hydrogenating a compound of formula



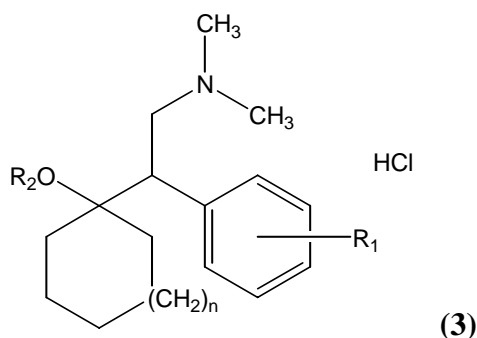
wherein R_1 , R_2 and n are as defined above, in the presence of a nickel or cobalt catalyst.

Claim 16 A compound of formula

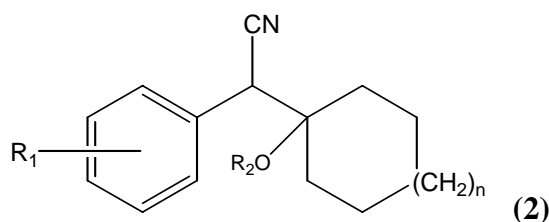


wherein R_1 , R_2 and n are as defined in claim 1.

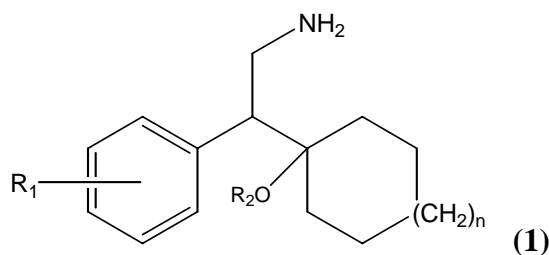
Claim 17 A process for the preparation of a compound of formula



wherein R_1 is hydrogen, hydroxyl, or unsubstituted or substituted alkyl or alkoxy, R_2 is hydrogen or a substituent which can be converted to hydrogen, and n is 0, 1 or 2 comprising hydrogenating a compound of formula



wherein R_1 , R_2 and n are as defined above, in the presence of a nickel or cobalt catalyst to give the compound of formula



wherein R_1 , R_2 and n are as defined above, and converting the compound of formula (1) to the compound of formula (3).

5. EP 1343750 is derived from a PCT application published as WO 02/50017. **D1** and **D2** were listed under category 'A' (background art) on the corresponding International Search report and no other documents were identified. **D2** shares many of the same authors as **D1** and discloses much of the same fundamental information, i.e. the use of rhodium to form a phenethylamine derivative through the catalytic hydrogenation of the corresponding nitrile. After a brief investigation, I established that at no stage were **D1** and **D2** elevated to novelty or inventive step citations prior to grant. As the possibility of obviousness was not formally raised during the pre-grant

process, no objection arises under rule 77D(1)(b) and it is entirely appropriate that the matter be considered here.

6. There are currently proceedings before the United States Patent and Trademark Office in connection with a corresponding US application, 10/130196. The US examiner has raised an inventive step objection in a report (submitted as **D8** by the requester) against claims 1-15 and 17-19 on the basis of **D1**. In writing this opinion, I have taken into account the content of **D8** as well as the proprietor's written rebuttal to US examiner's objection (submitted as **D9** by the requester), which contains similar arguments to those set out in the proprietor's observations. The version of US claims 1-19 accompanying **D9** would seem to be broadly equivalent to those in the EP patent.

7. The request refers only to the allegation of obviousness in respect of the claims as a whole rather than considering them on an individual basis. In general, a request for an opinion on validity or infringement should identify the specific claims that are alleged to be invalid or infringed. Nevertheless, the requester's comments are confined to the possibility that it would be obvious to use nickel or cobalt catalysts in the methods of **D1** and **D2**. I assume that the requester is therefore concerned only with those claims where these catalysts are used in a hydrogenation reaction. As claim 16 relates to *per se* compounds having a particular general formula, I deduce that the requester does not take issue with this claim and hence, I have not considered it in this opinion.

8. Independent claim 17 discloses the features of claim 1 but also includes the further step of converting the primary amine derivative to a tertiary amine, which is obtained in the form of a hydrogen chloride salt. Accordingly, if I conclude that claim 1 is inventive, it follows that claim 17 must also be non-obvious.

Discussion

9. There is no question that disclosures **D1** to **D7** and **D10** referred to by the requester were published before the priority date of the patent and therefore form part of the state of the art by virtue of section 2(2). The question I have to address is whether the combined teachings of these documents show that the claims of the patent lack an inventive step.

10. To determine whether the invention defined in the claims is inventive over the prior art, I will use the standard principles established in *Windsurfing International Inc v Tabur Marine (Great Britain) Ltd*, [1985] RPC 59. In particular, I shall follow the preliminary steps set out in that decision, namely to identify the difference between the cited prior art and the inventive concept and to ask whether the difference would have been obvious to a skilled person. In this case, I take such a person to be a competent but unimaginative chemist skilled in the field of organic synthesis. This person is held to be aware of what was common general knowledge in the art in question at the priority date of the invention.

11. The patent acknowledges that it was known at the priority date to form intermediates of formula (1) by hydrogenation in the presence of a rhodium catalyst and reference is made to **D1**. I note that the relevant disclosures of **D1** (e.g. Example 2) and **D2** (e.g. Method A for Compound 5) make clear that the product is obtained by hydrogenating the corresponding nitrile derivative, which coincides with formula (2) in the patent.

12. The requester remarks that **D1** envisages reduction using catalytic hydrogenation, borane reducing agents, LiAlH_4 , etc (see column 2, lines 49-56) and argues that this should be taken into account when considering the allegation of obviousness rather than concentrating on the use of rhodium. However, **D1** includes broad, generic formulae that envisage compounds falling both inside and outside the ambit of the patent. The proprietor is quite correct in my view that there is no explicit indication that an alternative to rhodium can be used to hydrogenate those nitrile compounds of **D1** specifically mentioned in the patent. Thus, I believe that it is only right for the focus to be on rhodium rather than the wider range suggested by the requester. I conclude that the distinction between the invention defined in claim 1 of the patent and the prior art is the use of a nickel or cobalt catalyst instead of rhodium. This is not to say that **D1** teaches against using other catalysts. However, I think the assertion that **D1** shows that hydrogenation catalysts *per se*, LiAlH_4 and borane reducing agents are definitely suitable for converting nitriles within the scope of formula (2) of the patent is perhaps a step too far.

13. In order to determine whether claim 1 of the patent involves an inventive step, I need to consider whether it would be obvious for the unimaginative person skilled in the art to use nickel or cobalt catalysts instead of the rhodium catalyst. Various approaches can be used to perform this substantive assessment although they should all lead to the same result. The requester argues on the basis of the so-called "obvious to try" test, which has been approved by the UK courts. Although page 7 of **D9** suggests that this approach has been discredited in the United States, US case law carries no weight in UK jurisprudence; indeed, I note that the proprietor makes no attempt to argue the point in the observations. I agree with the requester that this test is the most appropriate in the circumstances of the case.

14. In choosing this approach, one must imagine a skilled worker in a particular field who could be expected to know of a material to achieve a result in that area of technology. Thus, an invention concerned with the use of that material to achieve the result which had not been previously disclosed would be obvious if the likelihood of success would be sufficient to warrant a trial.

15. My first consideration, therefore, is whether a skilled addressee working in the field of organic synthesis would be aware of nickel or cobalt compounds as hydrogenation catalysts. Of this, there would seem to be no doubt: the patent admits as much in paragraph [0013] and there is additional support by way of **D3** to **D7**. I also note that the use of these catalysts in the hydrogenation of nitriles to amines is clearly reported in each piece of this prior art. For instance, column 1, lines 19-52 of

D3 states that “Raney nickel is one of the most widely used catalysts for secular hydrogenations to produce amines from nitriles” and that it “has become a hydrogenation catalyst of choice”. I disagree with the proprietor’s comment that **D6** does not directly discuss the use of suitable catalysts as there is explicit mention of NaBH_4 in the presence of CoCl_2 or Raney nickel (see first few lines of section 6-28 on page 815).

16. The proprietor argues that there is nothing that would encourage the skilled person to modify the hydrogenation reaction described in **D1** and **D2** so that there would be no reason to employ nickel, cobalt, or presumably any other catalyst. However, paragraph [0003] of the patent states that rhodium catalysts have economic drawbacks and implies that they are expensive. In order to reduce these costs, the patent states that the rhodium must be recycled, which introduces a further process step and potentially compromises the effectiveness of the catalyst. There is no suggestion in the patent that this is a new or previously unknown problem and I find it hard to believe that someone working in the field would not be aware of it. Faced with this situation, I am persuaded that there would be sufficient motivation for a skilled addressee to investigate other alternatives.

17. Thus, I am satisfied that the skilled person would understand that nickel and cobalt catalysts are suitable for hydrogenating nitrile compounds to amines and would be aware of the disadvantages of using rhodium in the process of **D1** and **D2**. I am now faced with the question of whether or not the person skilled in the art would find it obvious to combine the teachings and explore the use of nickel or cobalt catalysts in the particular hydrogenation reactions. The proprietor has put forward several arguments as to why the allegation of obviousness is not justified in the light of the documents identified by the requester and I shall deal with each of these in turn.

18. First of all, the proprietor states that where the prior art uses nickel or cobalt catalysts, the compounds to be converted are much simpler than those of **D1** and **D2**. However, **D3** to **D7** plainly illustrate the underlying principle that nickel and cobalt reagents can be used to hydrogenate nitriles to amines and I think there would be a reasonable expectation that the reaction could be applied to a vast range of compounds both simpler and indeed more complex than those referred to in **D3** to **D7**. I also believe the requester is quite right to draw attention to **D4**, which describes the conversion of benzyl cyanide to *phenylethylamine* as this molecule represents an important part of the compounds to be treated in **D1** and **D2**. Indeed, the patent itself refers to the same compound name in its title, ‘Process for the preparation of *phenethylamine* derivatives’. This would certainly appear to point to the fact that nickel and cobalt catalysts would be useful in the hydrogenation process of **D1** and **D2**.

19. The proprietor goes on to mention that the products of **D3** to **D7** are usually made for technical (i.e. industrial) rather than pharmaceutical purposes. I presume that this statement is intended to suggest that someone following the teachings of **D3** to **D7** would be unconcerned about product impurities and hence side reactions that

might arise from the utility of nickel or cobalt catalysts. In response, the requester has filed **D10** which is purported to show the use of a nickel-containing catalyst in the synthesis of an alkaloid. Whilst there is a question of whether this document should be considered since it was not referred to in the original request, the main issue here would appear to be in relation to the side reaction itself.

20. In essence, the proprietor's core argument against the requester's allegation of obviousness is that the use of a nickel or cobalt catalyst may promote an undesirable retro aldol side reaction during the conversion of the nitrile to the amine and in the production of a pharmaceutical, it is especially important that this should be avoided. There appears to be a difference of opinion between the parties as to whether this can be truly called a retro aldol side reaction but I do not think this issue is of major concern. Suffice it to say that there may be a possibility of some sort of unfavourable side reaction, which for the sake of argument I will refer to using the proprietor's chosen terminology.

21. The proprietor points out that **D3** (see column 1, lines 26-44) indicates that hydrogenations using Raney nickel tend to generate unwanted by-products which are difficult to remove. In actual fact, **D3** merely states that such products "*have been known*" to be formed, which implies that side reactions are by no means certain. I also agree with the requester that the disclosure identified by the proprietor in **D3** is specifically linked to the hydrogenation of adiponitrile (ADN) to hexamethylenediamine (HMD), where the by-product is 1,2-diaminocyclohexane (DAC). ADN and HMD are both non-aromatic, bifunctional molecules, which are quite different from the compounds envisaged in **D1** and **D2** and I am not convinced that they are subject to the same considerations. I also note that the remarks in **D3** only relate to a nickel catalyst and not necessarily to cobalt.

22. Thus, on the one hand, the proprietor reasons that **D3** is not important because it relates to hydrogenation of simpler compounds than those with which the patent is concerned. On the other hand, the proprietor implies that **D3** is relevant to its argument because it shows that hydrogenation of such compounds can lead to undesirable by-products. Clearly, there is some inconsistency between these two approaches. Nevertheless, the assertion of a retro aldol side reaction should still be borne in mind.

23. The requester is of the opinion that reference to the side reaction represents an unallowable attempt to reformulate the problem solved by the invention as it was not previously mentioned in the patent. To support this position, the requester draws attention to *Ranbaxy and Arrow Generic v Warner-Lambert* [2005] EWHC 2142. I note that paragraph 72 of the judgement states that "after-discovered advantages are highly unlikely to be capable of supporting inventiveness" and that "reformulation of the problem can only be allowed provided the skilled man could recognise the same as implied in or related to the problem initially suggested". I need to consider, therefore, whether the problem of the side reaction was disclosed, directly or indirectly, in the patent.

24. In my view, the only problems outlined in the patent in connection with the prior art were that rhodium was expensive and had shortcomings when recycled. Problems associated with low yields or side reactions were not mentioned. I do not place significant importance on the correlation alleged by the proprietor that nickel and cobalt catalysts result in high yields, which inevitably involve the avoidance of the side reaction. Yields can be dependent on various factors like process conditions and the nature of the starting material. At any rate, I am not convinced that a high yield automatically means that the side reaction, if it exists, has been averted entirely. Accordingly, I do not think that there is any indication that the side reaction represented a problem addressed by the patent.

25. Similarly, I am not persuaded by the proprietor's assertion that the skilled person would have been aware of the side reaction and would not have risked its occurrence by substituting the rhodium catalyst for nickel or cobalt. What was within the knowledge of a person skilled in the art is a matter for evidence and there is nothing to support the suggestion that the skilled addressee would have known about the side reaction at the date of priority. Accordingly, I concur with the requester that the reference to the retro aldol side reaction is an attempt to reformulate the problem and as such, cannot be relied upon to indicate inventiveness.

26. Even if there was no reformulation, the very existence of a side reaction is not supported by evidence and it seems to no more than a theoretical possibility. I also fail to see why the possibility of a side reaction would direct the skilled person to refrain from investigating the use of nickel or cobalt hydrogenation catalysts in the process of **D1** and **D2**. If a rhodium metal catalyst does not promote the side reaction, as intimated by the proprietor's observations, there is no clear reason why it should be automatically assumed by the skilled person that other metal catalysts like nickel or cobalt would. As I have already discussed, I do not consider the disclosure of **D3** to be particularly suggestive that there would be difficulties in this respect.

27. In contrast, I agree with the proprietor in rejecting the requester's assertion that the only advantage of using nickel and cobalt catalysts is in relation to their lower cost. Paragraph [0034] of the patent clearly states that nickel and cobalt catalysts have the surprising advantage of being recyclable without further treatment and with no change in activity. Moreover, by comparing the patent with **D2** (see Method A for Compound 5), it would appear that the yields for equivalent hydrogenation reactions are higher using nickel than with rhodium. In my opinion though, it is unclear as to how surprising these advantages are. For instance, page 319 (second paragraph of II. Reaction Conditions) of **D7** reports that both Raney nickel and cobalt catalysts retain activity for significant periods without regeneration.

28. If the nickel and cobalt catalysts do offer unforeseen benefits along the lines described, I must consider whether there would be any consequent impact on the matter of obviousness. In answering this, I refer to *Bristol-Myers Squibb Co v Baker Norton Pharmaceuticals Inc* [1999] RPC 253 discussed in section 3.25 of the Manual

of Patent Practice. This decision held that “an [unexpected] effect which was revealed by following an obvious course of action did not make the action non-obvious. It was wrong to ask whether you would have predicted the effect”. In other words, it is not legitimate to argue that the surprising effect, if it exists, resulting from the use of nickel or cobalt catalysts, demonstrates that the invention is non-obvious.

29. Having considered both the requester’s and proprietor’s arguments in depth, I conclude that it would be obvious for the skilled addressee to attempt the use of standard nickel or cobalt catalysts in the hydrogenation of the relevant nitrile compounds of **D1** and **D2** to the corresponding amine. As intimated by the patent, such catalysts are well known and are less expensive than rhodium. This advantage would, to my mind, be self-evident to the skilled addressee and provide sufficient motivation for at least a trial having a probability of success. In the absence of any supporting evidence, I am unable to accept the proprietor’s view that the retro aldol side reaction was a known problem or that there would be an expectation that the use of nickel or cobalt would promote this effect. I conclude that claim 1 is obvious.

30. Independent claim 17 discloses the features of claim 1 but also includes the further step of converting the primary amine derivative to a tertiary amine, which is obtained in the form of a hydrogen chloride salt. This additional reaction is plainly disclosed in **D1** (e.g. Example 3) and **D2** (e.g. preparation of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol on page 2903) and is performed using a mixture of formic acid and formaldehyde. Accordingly, since I am of the opinion that claim 1 lacks an inventive step, I conclude that claim 17 must also be obvious.

31. The requester has not submitted any arguments in respect of the dependent claims. Therefore, I do not intend to assess the subordinate claims in detail given the absence of any case being made one way or the other. However, it seems to me appropriate to identify those subsidiary claims which I believe to be clearly invalid but not those where the matter is less than straightforward. In this respect, I include claims 2-6, 11, and 12 (which are all dependent on claim 1) and claim 19 (dependent on claim 17). No conclusions are drawn in respect of the validity of the other subsidiary claims.

32. These claims read as follows:

Claim 2 *A process according to claim 1, wherein R_1 is hydroxyl or C_1 - C_4 alkoxy which is unsubstituted or substituted by phenyl, preferably methoxy.*

Claim 3 *A process according to claim 1 or 2, wherein R_1 is bonded in para position.*

Claim 4 *A process according to any of claims 1 to 3, wherein R_2 is hydrogen,*

silyl, benzyl, formyl or C₂-C₆ alkanoyl, preferably hydrogen.

- Claim 5 *A process according to any of claims 1 to 4, wherein n is 1.*
- Claim 6 *A process according to claim 1, wherein R₁ is methoxy, R₂ is hydrogen and n is 1.*
- Claim 11 *A process according to any of claims 1 to 10, wherein the catalyst is Raney nickel or Raney cobalt.*
- Claim 12 *A process according to any of claims 1 to 11, wherein a nickel catalyst, preferably Raney nickel, is used.*
- Claim 19 *A process according to claim 17 or 18, wherein R₁ is methoxy, R₂ is hydrogen and n is 1.*

33. The subject matter of each of claims 2-6 and 19 is to be found in **D1** (e.g. column 3, lines 6-60 and Example 2) and **D2** (e.g. preparation of 1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol on pages 2902-2903). The subject matter of claims 11 and 12 is to be found in **D3** (e.g. column 1, lines 19-25 & 48-51), **D4** (e.g. Procedure section on page 71), **D6** (e.g. first few lines of section 6-28 on page 815), and **D7** (e.g. section II. Reaction Conditions on pages 319-322).

34. I conclude that these claims are also obvious.

35. As mentioned at the beginning of this opinion, the requester has not filed any comments concerning the compounds *per se* envisaged in claim 16 and consequently, I have made no analysis of this independent claim.

Opinion

36. I conclude that claims 1-6, 11, 12, 17, and 19 do not involve an inventive step. For the reasons given above, I have not considered whether or not the other claims involve an inventive step.

Application for review

37. Under section 74B and rule 77H, the proprietor may within three months of the date of issue of this opinion, apply to the comptroller for a review of the opinion.

NOTE

This opinion is not based on the outcome of fully litigated proceedings. Rather, it is based on whatever material the persons requesting the opinion and filing observations have chosen to put before the Patent Office

Paul Minton
Examiner