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(54) Title: PURIFICATION OF TRAMADOL

(57) Abstract

A process for the preparation of Tramadol according to a Grignard reaction of 2–(dimethylaminomethyl)cyclo–hexanone with the reagent 3–methoxyphenylMgX, where X is a halogen, to obtain the crude base which is then introduced to a solvent, *characterised by* contacting the crude base with water to form a hydrate of Tramadol.

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Purification of Tramadol

Technical Field

This invention relates to the production of a pharmaceutical product obtained through a process which initially produces a crude base as a mixture of isomers together with side products from which a selected isomer is to be separated. In particular the invention is concerned with the separation and purification of the selected isomer to achieve a substantially increased yield of same.

Background Art

The desired product (±)-trans-2-dimethylaminomethyl-1-(3-methoxyphenyl)cyclohexanol, (Tramadol) is difficult to isolate by distillation because the mixed geometric *cis* and *trans* isomers boil around 138°C - 140°C. However the target compound can be obtained through subsequent recrystallisation steps by converting the crude base to the hydrochloride salt as described in US-A-3,652,589 and GB-A-997,399.

The production of Tramadol hydrochloride as described in GB-A-997,399 involves a Grignard reaction to produce mixed *cis*-and *trans*-isomers of 2-dimethylaminomethyl-1-(3-methoxy-phenyl)cyclohexanol and side products. The crude mixed isomer base is obtainable by distilling the complex mixture obtained from the Grignard reaction under a high vacuum. The distilled isomer mixture is dissolved in diethyl ether and treated with gaseous hydrogen chloride. The resulting crude mixture of *cis*- and *trans*-isomer hydrochlorides is precipitated and filtered. This procedure yields an isomer mixture with a relatively high content of *cis*-isomer. The isomer mixture is then refluxed with a five-fold volume of moist dioxane, and the resulting suspension is filtered while still hot. The filter cake is boiled once more with dry dioxane and filtered; the residue obtained consists of the target trans hydrochloride.

The commercial production of Tramadol is believed to have always followed the process described in GB-A-997,399 but certain disadvantages of the process described have caused the acceptability of such a process to be questioned. One such disadvantage lies in that the solvent used in that process is dioxane which is now considered as an unacceptable toxic compound for which the tolerance set for its residual content in the product is extremely low, of the order of several parts per billion. Furthermore dioxane is considered to be a health risk which is toxic by inhalation or through skin absorption as a carcinogen, central nervous system depressant and an agent causing necrosis of the liver and kidney. It is also considered to be a hazardous material by its flammability, and ability to form explosive peroxides.

There is also the need to improve the original method because the high vacuum distillation of the isomers prior to their isolation is undesirable.

A further method for purification and separation of Tramadol hydrochloride is proposed in US-A-5,414,129 wherein it is suggested that Tramadol hydrochloride is obtainable from the Grignard reaction mixture containing the isomers and side products by combining the mixture with a solution of hydrochloric acid in a low molecular weight alcohol or with gaseous hydrogen chloride in the presence of an organic solvent selected from medium molecular weight alcohols, ketones, esters, and ethers or aromatic ethers, to effect the selective precipitation of Tramadol hydrochloride.

Although suggesting that alternative solvents to dioxane are very hard to find, a large number of solvents, including alcohols, ketones, esters, ethers and aromatic ethers are suggested as being found suitable. Repetition of the work as described therein suggests that it is unlikely that the actual isomer separation of the hydrochlorides is achievable under the conditions described. Separation may be achievable during

the subsequent two re-crystallisation steps mentioned therein, the conditions for which are not described in the patent, but the unwanted isomer still remains at 2.2%. Even so it is considered that results might be achievable on a laboratory scale but the process, at least as described in the patent, would create processing problems if the method were to be attempted for full scale production.

More recently published EP-A-0 778 262 proposes an improved method of purification of Tramadol base reliant again on the use of the hydrochloride for this purpose which is based on treating mixtures otherwise difficult to resolve by simple hydrochloride salt formation in a solvent with acid to selectively dehydrate the unwanted isomer. Subsequently the hydrochloride salt formation allows for better resolution and re-crystallisation. Therefore, this dehydration stage allows resolution of mixtures by hydrochloride formation and re-crystallisation more efficiently than previously. Published EP-A-0-778 262 also comments on and confirms that the hydrochloride salt of Tramadol is not an efficient method for resolving the isomers and indicates that this additional dehydration step is necessary in order to achieve a resolution which is workable.

Therefore currently, it remains the position that as for approximately the last 20 years or so, the commercial production of Tramadol relies essentially on the process of GB-997,399 whereby the purification of the Tramadol base is by re-crystallisation of the hydrochloride with an improvement made by the dehydration stage above.

An object of the present invention is to provide a method which obviates or mitigates the aforesaid disadvantages of the prior art methods and does not require the dehydration stage.

Disclosure of Invention

It has now been surprisingly found that crude Tramadol base can be converted to a hydrate form which preferentially leads

to the target trans isomer being recoverable. The hydrate of Tramadol base has not been described in the literature and is regarded as a hitherto unrecognised and novel compound useful in this field.

Thus according to one aspect of the invention there is provided a process for the preparation of Tramadol according to a Grignard reaction of 2-(dimethylaminomethyl)cyclohexanone with the reagent 3-methoxyphenylMgX, where X is a halogen such as the bromide, to obtain the crude base which is then introduced to a solvent, *characterised by* contacting the crude base with water to form a hydrate of Tramadol.

A number of solvents may be used, including ethers such as diethylether, and di-isopropyl ether, aromatic solvents such as toluene, paraffinic or aliphatic solvents such as hexane, and ketones such as methyl isobutyl ketone. Preferred solvents include toluene, methyl isobutyl ketone, and di-isopropyl ether which have been observed to provide good enantiomeric purity.

Modes for Carrying Out the Invention

The invention will now be further described by way of the following illustrative examples.

Examples:

Tramadol base

In the present invention firstly a preparation of a crude Tramadol base is necessary. This follows traditional Grignard conditions which are well understood in the art. Here the Grignard reaction is between 2-(dimethylaminomethyl) cyclohexanone and 3-methoxyphenylmagnesium bromide to achieve the target base. The quality of the crude base is typically 74.8%(RR,SS) : 15.6%(RS,SR).

Secondly resolution of the base is achieved by forming a hydrate by conducting the following steps.

Tramadol hydrate

Charge Tramadol base (crude, 40g) to vessel with di-isopropyl ether (300ml) and stir at 20°C to 25°C.

Charge water (10ml) and stir with cooling to 0°C to -5°C.

Observe precipitation occurring after approximately 5 to 10 minutes.

Filter off the solid and air dry to obtain 30g of solid hydrate of Tramadol base which is predominantly the desired (RR,SS) isomer. Typical yield is 30g of hydrate [98% (RR,SS) : 1.4% (RS,SR)].

Optional processing steps

The thus highly purified Tramadol base hydrate can then be readily converted to a preferred pharmaceutically acceptable form for example Tramadol hydrochloride. The product may be a bulk product or formed into suitable pharmaceutical dosage forms for therapeutic usage in a similar way to the current formulation of Tramadol.

The procedure was repeated using a number of other solvents as outlined below.

Tramadol base preparation

A stock quantity of Tramadol base was prepared following a an established procedure.

The first stage was preparation of 2-(dimethylaminomethyl) cyclohexanone. This was made by reaction of cyclohexanone with formalin and monodimethylamine sulphate solution. The next stage was formation of the base. This was prepared by a Grignard reaction on 2-(dimethylaminomethyl) cyclohexanone using 3-bromoanisole in THF with magnesium.

Resolution of amide base

Aliquots of Tramadol base were dissolved in various solvents and heated if necessary for dissolution.

Traces of water were added as a co-solvent and any solid precipitating out was filtered off, washed and dried. HPLC analysis for purity was run.

RESULTS

Table 1 - HPLC analysis of resolved Tramadol base

Example	*Base (g)*[1]	*Solvent*	*Co-solvent*	*HPLC %area*		*Yield % w/w*
				RSSR	*RRSS*	
No. 2	19.6	Diethylether	H_2O	2.9	96.4	38.1
No. 3	11.7	Toluene	H_2O	2.5	97.4	3.6
No. 4	22.1	Diisopropyl ether (IPE)	H_2O	2.7	97.1	50.9
No. 5	10.5	Hexane	H_2O	2.8	96.9	46.5
No. 6	10.3	Methylisobutyl ketone (MIBK)	H_2O	1.2	98.6	20.3
No. 7	10.0	Dichloro-methane[2]	H_2O	-	-	-
No. 8	20.0	IPE	H_2O	2.9	96.4	69.6
No. 9	40.1	IPE	H_2O	0.7	98.5	74.8

[1] HPLC analysis of Tramadol base was: 15.6%, RSSR, 82.8% RRSS by area normalisation

[2] No crystallisation/precipitation

Results have shown that a crude Tramadol base can be successfully resolved using the procedure described above. The crude Tramadol base used as the input was 15.6% RSSR and 82.8% RRSS by HPLC area normalisation.

The solvents which gave the best results in terms of enantiomeric purity were MIBK and toluene giving 98.6% and 97.4% respectively of the desired isomer. IPE, hexane and diethylether also gave encouraging results of 97.1%, 96.9% and 96.4% respectively. In some instances crystallisation was slow but once it began product formation occurred quickly.

Therefore, whereas for many years the method of choice for purifying (±)-*cis,trans*-2-dimethylaminomethyl-1-(3-methoxyphenyl)cyclohexanol free base to selectively obtain the target Tramadol *trans* isomer has been via formation of the hydrochloride, the resolution has not been particularly good

and several re-crystallisation steps were necessary to obtain any useful product at all, the present invention represents a significant development.

Therefore, some advantages of this invention are apparent in that it provides a quick and easy method of producing the desired isomer whilst also obtaining a high resolution of same.

Furthermore, the hydrate can also be readily converted to a pharmaceutically acceptable form for example the hydrochloride. For producing the hydrochloride the hydrate can simply be dissolved in absolute alcohol and di-isopropyl ether and treated with gaseous hydrogen chloride.

Therefore the advantages offered by this invention include the absolute simplicity offered by the few steps required for forming a hydrate of the Tramadol base and the high purity of product obtainable thereby.

Industrial Applicability

This invention is applicable in the production of Tramadol which is useful therapeutically as a non-additive analgesic.

Claims

1. A process for the preparation of Tramadol according to a Grignard reaction of 2-(dimethylaminomethyl)cyclohexanone with the reagent 3-methoxyphenylMgX, where X is a halogen, to obtain the crude base which is then introduced to a solvent, *characterised by* contacting the crude base with water to form a hydrate of Tramadol.

2. A process according to claim 1 wherein the solvent into which the crude base is introduced is selected from ethers, aromatic solvents, aliphatic solvents, and ketones.

3. A process according to claim 1 wherein the solvent into which the crude base is introduced is selected from diethylether, di-isopropyl ether, toluene, hexane, and methyl isobutyl ketone.

4. A process for the preparation of Tramadol according to Claim 1 wherein the halogen is bromide.

5. A process for the preparation of Tramadol according to Claims 1 or 4 wherein the resulting Tramadol base hydrate is further converted to a pharmaceutically acceptable form.

6. A process for the preparation of Tramadol according to Claim 5 wherein the resulting Tramadol base hydrate is converted to Tramadol hydrochloride.

7. A process for the preparation of Tramadol according to Claim 6 wherein the resulting Tramadol base hydrate is converted to Tramadol hydrochloride by dissolving the hydrate in absolute alcohol and di-isopropyl ether and treated with gaseous hydrogen chloride.

8. A Tramadol base hydrate product formed by the process of Claim 1.

9. A pharmaceutically acceptable Tramadol hydrochloride product formed according to the process of any one of Claims 5 or 6.

10. A process for the preparation of a Tramadol pharmaceutical product comprising forming the product produced according to the process of Claim 5 into a dosage form.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C213/10 C07C215/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 652 589 A (FLICK KURT ET AL) 28 March 1972 cited in the application see column 2, line 19 - line 48 see column 3, line 46 - line 48	1-10
A	US 5 414 129 A (CHERKEZ STEPHEN ET AL) 9 May 1995 see claims	1,2
E	WO 99 03820 A (NIKOLOPOULOS ANGELO ;SCHICKANEDER HELMUT (IE); RUSSINSKY LTD (IE)) 28 January 1999 see claims	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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...ormation on patent family members

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