

Racemisation of Enantiomers of Nefopam and Analogues

Field of the Invention

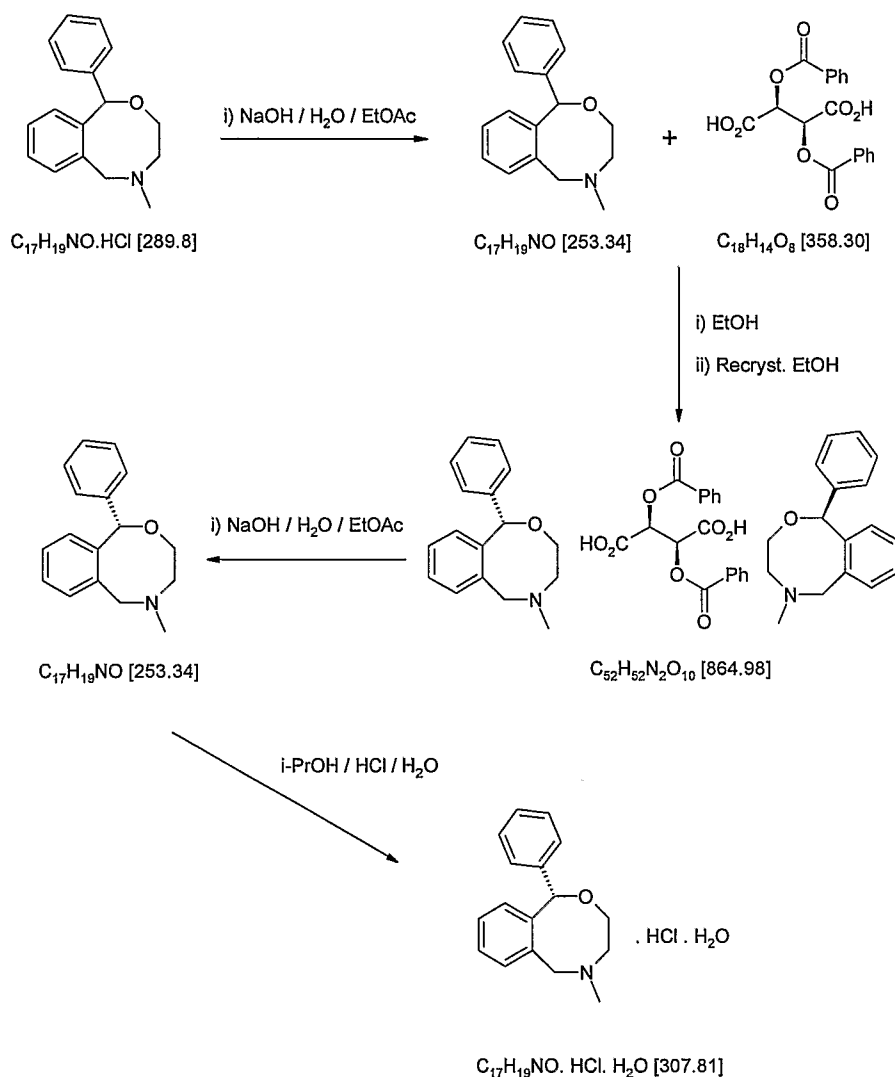
This invention relates to a racemisation and recycling process, and in particular to the racemisation of enantiomers of nefopam and analogues.

5 Background of the Invention

Nefopam (available as the hydrochloride) is a centrally acting non-narcotic analgesic. Nefopam and analogues are described in GB1148717 and in WO2004/056788. The utility of a single isomer of nefopam, i.e. (+)-nefopam, is disclosed in WO03/105832 and WO03/105833. Further, single enantiomers
10 that are analogues of nefopam, and their use, are described in WO2006/095187.

(+)-Nefopam hydrochloride monohydrate may be manufactured by resolution, as described in WO2005/056539; see Scheme 1. There is currently no defined use for the (-)-enantiomer of nefopam which is discarded as waste material.

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Scheme 1

There is no evidence in the literature that optically pure nefopam is subject to chemical racemisation nor is there any evidence of racemisation in the API stability studies carried out on the molecule to date. Literature relating to stress stability of the nefopam molecule indicates that it is chemically labile under both acid and alkaline conditions, suggesting that it would not be appropriate to attempt racemisation of nefopam under these conditions.

Summary of the Invention

The present invention is based on a finding of the utility of the mother liquors of the resolution process shown in Scheme 1, which contain enriched quantities of the (-)-nefopam enantiomer as the dibenzoyltartrate salt. These mother liquors have historically been discarded, but it has been discovered that isolation of the free base material followed by even mild acid treatment results in racemisation to material that can subsequently be recycled, e.g. into the

resolution process. This improves the efficiency of the resolution process and dramatically reduces the waste materials, enhancing the commercial attractiveness of the process.

According to the present invention, a process for the racemisation of a compound is nefopam or an analogue thereof in the form of a single enantiomer or non-racemic mixture, comprises contacting the compound with an acid.

Description of the Invention

The racemisation substrate is a single enantiomer or non-racemic mixture of enantiomers, of nefopam or an analogue, i.e. a compound having the same cyclic structure and chiral centre. Analogues are described in GB1148717, WO2004/056788 and WO2006/095187, the content of each of which is incorporated herein by reference.

The acid that is used for racemisation may be an organic or inorganic compound. Examples include alkyl and aryl-sulphonic acids. It is preferably a mineral acid such as hydrochloric acid. Other suitable acids will be readily apparent to one of ordinary skill in the art.

The racemisation reaction may be carried out in water and/or an organic solvent. For example, an alcoholic solvent, e.g. ethanol or isopropanol, may be used as a cosolvent. Other suitable solvents will be readily apparent to one of ordinary skill in the art.

The reaction is preferably carried out at from 20 to 80°C, more preferably 50 to 80°C, and most preferably 50 to 5°C. The reaction typically takes 6 to 24 hours, and usually requires at least 12 hours. For relatively dilute reaction mixtures, relatively low reaction temperatures and/or relatively low amounts of acid, the reaction may require relatively high temperature and/or time, and may require stirring. The racemic product may be isolated by procedures known to those skilled in the art; for example, dilution with isopropanol.

The following Examples illustrate the invention.

Example 1

Treatment of (-)-nefopam free base, obtained from the mother liquors of the resolution process, in ethanol (5 volumes) with dilute hydrochloric acid (1.5 volumes) results in racemisation even at low temperature. Results are shown in the following Table. Conversion was from an initial ee (enantiomeric excess) of 95.6, to 2.4 at 80°C and to 13.0 at 20-25°C.

Example 2

The mother liquors from the resolution of 300 g of nefopam racemate (WO2005/056539) were treated in the following manner:

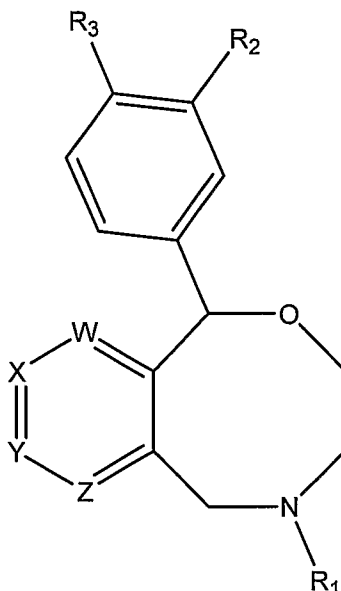
5 The mother liquors from the formation of the hydrochloride salt formation were charged to a suitable vessel and the isopropanol distilled out under vacuum. To the concentrate were added the liquors from the recrystallisation of the nefopam dibenzoyl tartrate salt and the ethanol distilled out under vacuum. To the concentrate were added the mother liquors from the initial dibenzoyl tartrate salt formation and the ethanol distilled out under vacuum. Water (100 ml) and
10 toluene (300 ml) were added to the concentrate. The mixture was heated at 50-55°C for at least 1 hour and a solution of potassium carbonate (50% w/w in water) was added over at least 1 hour. The lower aqueous layer was separated. The upper organic layer was washed with water (100 ml) and the lower aqueous layer separated. The toluene was distilled out under vacuum to leave a
15 concentrate. The isomer ratio was 25/75% in favour of the (-)-enantiomer.

36% w/w hydrochloric acid (100 ml) was added at 40-45°C and the mixture heated at 50-55°C for at least 12 hours. The isomer ratio was 52/48% (*i.e.* essentially racemic).

Isopropanol (500 ml) was added and distilled out to remove excess
20 hydrochloric acid. Isopropanol (500 ml) was added and the mixture cooled to 0 - 5°C over at least 2 hours and the mixture held for at least 2 hours. The racemic nefopam hydrochloride was isolated by filtration, washed with cold isopropanol (2 x 20 ml) and dried.

Claims

1. A process for the racemisation of a compound which is nefopam or an analogue thereof in the form of a single enantiomer or non-racemic mixture, which comprises contacting the compound with an acid.
2. A process according to claim 1, wherein the compound has the formula



wherein

- R_1 is H, C_1 - C_6 alkyl optionally substituted with F, C_3 - C_6 cycloalkyl or C_2 - C_6 alkenyl;
- either R_2 and R_3 are the same or different and are H, halogen, CN, CF_3 , C_1 - C_6 alkyl or OR_1 , or R_2 and R_3 form a five or six-membered ring which may be carbocyclic, heterocyclic (containing 1-2 heteroatoms selected from O, N and S), aromatic or heteroaromatic (containing 1-2 heteroatoms selected from O and N) ;
- one of W, X, Y and Z is N or CR_4 and the others are each CH;
- R_4 is halogen, CF_3 , CN, OR_7 , $SO_2N(R_6)_2$, COR_6 , CO_2R_6 , $CON(R_6)_2$, NR_1COR_5 , $NR_1SO_2R_5$, $NR_1CO_2R_5$, $NR_1CON(R_6)_2$, OC_1 - C_6 alkyl optionally substituted with R_4 , C_1 - C_6 alkyl optionally substituted with R_4 , C_3 - C_6 cycloalkyl optionally substituted with R_4 , C_2 - C_6 alkenyl optionally substituted with R_4 , C_2 - C_6 alkynyl optionally substituted with R_4 , aryl optionally substituted with R_4 , or a five or six-membered aromatic heterocycle containing 1-4 heteroatoms selected from N and O, linked either through carbon or nitrogen;
- R_5 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, aryl or heteroaryl;

each R₆ (which may be the same or different) is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, aryl or heteroaryl; and

R₇ is aryl or heteroaryl;

wherein aryl is an optionally substituted phenyl or naphthyl group;

5 carbocyclic is a saturated alicyclic moiety having 5 or 6 C atoms;

heterocyclic is a saturated heterocyclic moiety having 5 or 6 atoms including one or more of N, O and S; and

heteroaromatic is aromatic of 5 or 6 atoms of which at least one is N, O or S;

10 or a pharmaceutically acceptable salt thereof.

3. A process according to claim 2, wherein R₄ is present and is halogen, CN, OR₇, SO₂N(R₆)₂, COR₆, CO₂R₆, CON(R₆)₂, NR₁COR₅, NR₁SO₂R₅, NR₁CON(R₆)₂, OC₁-C₆ alkyl substituted with R₄, C₁-C₆ alkyl substituted with R₄, C₃-C₆ cycloalkyl optionally substituted with R₄, C₂-C₆ alkenyl optionally substituted with R₄, C₂-C₆ alkynyl optionally substituted with R₄, aryl optionally substituted with R₄, or a five or six-membered aromatic heterocycle containing 1-4 heteroatoms selected from N and O, linked either through carbon or nitrogen.

4. A process according to claim 3, wherein R₄ is Br, CN, CON(R₆)₂, optionally substituted cycloalkyl or aryl, or a five or six-membered aromatic heterocycle.

5. A process according to of any of claims 2 to 4, wherein R₂ is halogen, CN, CF₃, C₁-C₆ alkyl or OR₁.

6. A process according to of any of claims 2 to 4, wherein R₂ and R₃ form a ring.

7. A process according to any of claims 2 to 4, wherein R₂ or R₃ is OR₁.

8. A process according to claim 1, wherein the compound is selected from
 9-methoxy-5-methyl-1-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine
 8-methoxy-5-methyl-1-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine
 9-methoxy-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-
 2,5-oxazocine
 8-methoxy-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-
 2,5-oxazocine
 9-methoxy-5-methyl-1-(4-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-
 2,5-oxazocine and

8-methoxy-5-methyl-1-(4-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine.

9. A process according to claim 1, wherein the compound is selected from 9-cyano-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-cyano-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

9-cyclopropyl-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

10 8-cyclopropyl-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

N-(acetyl)-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-9-methylamine

15 *N*-(acetyl)-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-8-methylamine

9-cyclopropyl-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-cyclopropyl-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

20 9-cyclopropyl-5-methyl-1-(4-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine

8-cyclopropyl-5-methyl-1-(4-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine and

25 9-cyano-5-methyl-1-(4-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine.

10. A process according to claim 1, wherein the compound is selected from 9-cyano-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine 8-cyano-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine 5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-9-

30 carboxamide

5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-8-carboxamide

N-(1,1,1-trimethylmethoxycarbonyl)-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-9-methylamine

- N*-(1,1,1-trimethylmethoxycarbonyl)-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-8-methylamine
- 5-methyl-1,9-diphenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine
- 5-methyl-1,8-diphenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine
- 5 9-(3,5-dimethylisoxazol-4-yl)-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine
- 8-(3,5-dimethylisoxazol-4-yl)-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine
- 2-(5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-9-ethenyl)carboxamide
- 10 2-(5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-8-ethenyl)carboxamide
- 2-(5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-9-ethyl)carboxamide
- 15 2-(5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-8-ethyl)carboxamide
- 5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-9-methylamine
- 5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-8-methylamine
- 20 methylamine
- N*-(acetyl)-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-9-methylamine and
- N*-(acetyl)-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-8-methylamine.
- 25 11. A process according to claim 1, wherein the compound is selected from
- 9-bromo-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine
- 8-bromo-5-methyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine
- 9-bromo-5-methyl-1-(4-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine
- 30 8-bromo-5-methyl-1-(4-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine
- 9-bromo-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine and
- 8-bromo-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-
- 35 2,5-oxazocine.

12. A process according to claim 1, for racemising substantially single enantiomer (-)-nefopam.
13. A process according to claim 1, for racemising substantially single enantiomer (+)-nefopam.
- 5 14. A process according to claim 1, for the preparation of a compound selected from
- (1*S*)-8-cyano-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- (1*R*)-8-cyano-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 10 (1*S*)-8-cyclopropyl-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- (1*S*)-8-cyclopropyl-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine;
- 15 (1*S*)-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-8-carboxamide;
- (1*R*)-5-methyl-1-(3-methoxy)phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocine-8-carboxamide;
- and the salts thereof.
- 20 15. A process according to any preceding claim, wherein the racemisation is carried out using a mineral acid.
16. A process according to claim 15, wherein the mineral acid is hydrochloric acid.
17. A process according to any preceding claim, wherein the racemisation is
- 25 carried out in a solvent selected from water and organic solvents and mixtures thereof.
18. A process for the manufacture of substantially single isomer of a compound which is nefopam or an analogue thereof, which comprises resolution of the racemic compound, isolating the desired single isomer, and racemisation
- 30 of the unwanted material by a process according to any preceding claim.