

PATENT SPECIFICATION

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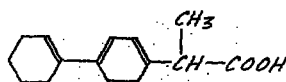
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(54) PROPIONIC ACID DERIVATIVES AND MANUFACTURE THEREOF

(71) We, CIBA-GEIGY AG, formerly known as Ciba Limited, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to propionic acid derivatives, a process for their manufacture and their use.

The present invention provides an α - [p - (1 - cyclohexenyl) - phenyl] - propionic acid of the formula



and a process for making this compound.

The compound of the invention possesses valuable pharmacological properties, especially an analgesic, for example, antinociceptive, and above all an anti-inflammatory action. Thus, in the Writhing test on mice, on oral administration of from 1 to 10 mg/kg of the compound of the invention in the form of its sodium salt, a distinct antinociceptive action was observed, and in the kaolin oedema test on the rat paw, oral administration of a dose from 1 to 10 mg/kg of the above compound produced a distinct anti-inflammatory action. Accordingly, it is useful as an anti-inflammatory and analgesic agent.

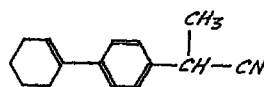
The compound of the invention is also a valuable intermediate for the manufacture of other useful substances, especially of pharmacologically active compounds.

Thus, for example, the compound of the

invention may be used for the manufacture of α - (p - cyclohexyl - phenyl) - propionic acid described in the literature by reducing the 1 - cyclohexenyl group to cyclohexyl group in known manner, for example, by catalytic reduction. The term "known" is used herein to mean in actual use in the art or described in the literature of the art.

The compound of the invention may be manufactured by known methods.

According to a preferred process, in a compound of the formula



the cyano group is hydrolysed to the carboxyl group.

The hydrolysis is carried out in known manner, for example, in the presence of a strong base, for example, an alkali metal hydroxide, for example, sodium or potassium hydroxide.

Depending on the reaction conditions and starting materials, the compound of the invention may be obtained in free form or in form of its salts with bases which can be converted in known manner one into the other or into different salts. The free acid can be converted in known manner, for example, by reaction with an appropriate basic agent, into a salt with a base, especially a physiologically tolerable salt with a base, for example, a salt with an organic amine, or into a metal salt. Suitable metal salts are in the first place alkali metal salts or alkaline earth metal salts, for example, sodium, potassium, magnesium or calcium salts. From a salt, the free acid can be liberated in known manner, for example, by reaction with an acid agent.

[Price 25p]



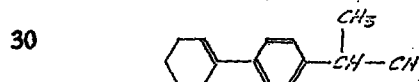
The salts are also suitable for purifying the compound of the invention, for example, by converting the free compound into a salt, isolating the salt and reconverting it into the free compound.

Depending on the chosen starting material and reaction conditions, the compound of the invention may be obtained as optical antipodes or as a racemate.

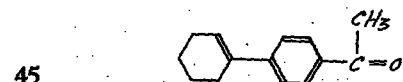
The racemate can be resolved into diastereoisomers, from which the antipodes can be liberated by treatment with suitable agents. This resolution may be carried out in known manner for example, by reaction of the free carboxylic acid with an optically active base capable of forming salts with the racemic compound and separation of the salts thus obtained, for example, on the basis of their different solubilities. A particularly frequently used optically active base is, for example, the D- and L-forms of cinchonine. It is advantageous to isolate the more active of the two antipodes.

The starting materials are known or, insofar as they are new, they may be manufactured by known methods, for example, as described in the divisional Application No. 46544/71, Serial No. 1283368.

The nitrile of the formula



preferably used as starting material is obtained, for example, when a *p*-Hal-acetophenone, wherein Hal represents a halogen atom, for example, a chlorine or bromine atom, is converted into a corresponding ketal, for example, an ethylene-ketal, the resulting compound is converted with magnesium into the corresponding Grignard reagent which is sulging [1-hydroxycyclohexyl] compound, the hydroxyl group is eliminated, advantageously in the presence of an acid, with formation of a 1,2-double bond and in the resulting compound of the formula



the oxo group is reduced to the hydroxyl group. The hydroxyl group is then converted in known manner, for example, by reaction with a halide of phosphorus or sulphur, for example, phosphorus oxychloride or thionyl chloride or a similar bromide, into a corresponding halogen atom which can then be converted into the cyano group by reaction

with a salt of hydrocyanic acid, for example, sodium cyanide.

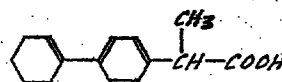
The compound of the invention can be used, for example, in the form of pharmaceutical preparations that comprise it in free form or in form of its salts, especially the physiologically tolerable alkali metal salts, in conjunction or admixture with an organic or inorganic, solid or liquid pharmaceutical carrier suitable, for example, for enteral, parenteral or topical administration. Suitable carriers are substances that do not react with the compound of the invention, for example, water, gelatin, lactose, starches, stearyl alcohol, magnesium stearate, talcum, vegetable oils, benzyl alcohols, gums, propyleneglycols, white petroleum jelly or other known medicinal carriers. The pharmaceutical preparations may be, for example, tablets, dragées, capsules, suppositories, creams or ointments, or in liquid form, solutions, for example, elixirs or syrups, suspensions or emulsions. They may be sterilized and/or comprise an assistant, for example, a preserving, stabilizing, wetting or emulsifying agent, a solubilizer, salt for regulating the osmotic pressure or buffer. They may also comprise a further pharmaceutically useful substance. The pharmaceutical preparations are formulated by known methods.

The invention also provides a method of treating commercially reared animals to relieve pain and inflammation, which comprises administering to the animal the compound of the invention.

The following examples illustrate the invention.

EXAMPLE 1

A solution of 9.5 g of α -[*p*-(1-cyclohexenyl)-phenyl]-propionitrile in a solution of 5 g of potassium hydroxide in 150 ml of ethanol and 50 ml of water is refluxed for 24 hours. The ethanol is evaporated under vacuum and the residue mixed with 200 ml of water. The insoluble phase is filtered off mixed with active carbon and filtered off. The clear aqueous solution is acidified with 2N-hydrochloric acid and extracted with methylene chloride. The methylene chloride solution is dried over magnesium sulphate and evaporated and the residue recrystallized from ether+petroleum ether, whereupon α -[*p*-(1-cyclohexenyl)-phenyl]-propionic acid of the formula



is obtained in colourless crystals melting at

106—108°C. The sodium salt is obtained by dissolving this carboxylic acid in the calculated quantity of ethanolic sodium hydroxide solution and evaporation under vacuum; decomposition point: (245°C) 248—250°C.

The α - [*p* - (1 - cyclohexenyl) - phenyl] - propionitrile used as starting material in this Example is prepared thus:

A well-stirred suspension of 9.8 g of magnesium chips (previously washed with chloroform and activated with iodine) in 150 ml of absolute tetrahydrofuran is mixed dropwise at 60°C with a solution of 96 g of 2 - (*p* - bromophenyl) - 2 - methyl - 1,3 - dioxolane in 150 ml of tetrahydrofuran. The dropwise addition is regulated so that the temperature does not rise above 60°C once the reaction has begun. Towards the end, the batch is heated for 30 minutes at 60°C, then cooled to 5°C and 35 g of cyclohexanone are stirred in dropwise. After having heated the reaction mixture for 1 hour at 50—60°C, it is filtered and evaporated in a rotary evaporator. The residue is mixed with ice and a saturated aqueous ammonium chloride solution, extracted with ether, dried over magnesium sulphate and evaporated. The residue is recrystallized from ether + petroleum ether and yields 2 - [*p* - (1' - hydroxy - 1' - cyclohexenyl) - phenyl] - 2 - methyl - 1,3 - dioxolane melting at 117—118°C.

A solution of 80 g of this compound in 200 ml of glacial acetic acid is mixed with 30 ml of concentrated hydrochloric acid and 50 ml of water, and the mixture is heated for 3 hours on a water bath at 80°C. Water is added until no more turbidity appears, and the deposited crystals are filtered off and dried and recrystallized from petroleum ether, to yield *p* - (1 - cyclohexenyl) - acetophenone melting at 76—77°C.

A solution of 7 g of sodium borohydride in 300 ml of methanol and 80 ml of water is cooled to 5°C and 50 g of *p* - (1 - cyclohexenyl) - acetophenone are stirred in portionwise. The batch is stirred on for 2 hours at room temperature, the solution is concentrated to half its volume in a rotary evaporator, mixed with 1 litre of water and extracted with 3×500 ml of methylene chloride. The methylene chloride residue is recrystallized from petroleum ether and furnishes 1 - hydroxy - 1 - [*p* - (1 - cyclohexenyl) - phenyl] - ethane melting at 60—62°C.

A solution of 20 g of 1 - hydroxy - 1 - [*p* - (1 - cyclohexenyl) - phenyl] - ethane in 300 ml of absolute benzene is stirred at room temperature in the presence of 10 ml of thionyl chloride. The batch is evaporated under vacuum and the crude, oily 1 - chloro - 1 - [*p* - (1 - cyclohexenyl) - phenyl] - ethane dissolved in 50 ml of dimethyl sulfoxide and stirred dropwise into a suspension of 15 g of sodium cyanide in 300 ml of dimethyl sulfoxide. The batch is stirred for

15 hours at 70°C, then cooled, 400 ml of water are added and the whole is extracted with a 1:1 - mixture of ether + ethyl acetate. The extract is dried over magnesium sulphate, filtered and evaporated under vacuum. Distillation of the residue under a high vacuum given α - [*p* - (1 - cyclohexenyl) - phenyl] - propionitrile as a yellow oil which boils at 125—130°C under 0.1 mm Hg pressure.

EXAMPLE 2

A hot solution of 50 g of α - [*para* - (1 - cyclohexenyl) - phenyl] - propionic acid in 1850 ml of ethanol is mixed with a hot solution of 63.9 g of cinchonidine in 1850 ml of ethanol. The mixture is allowed to cool slowly and after 16 hours, the crystals of the cinchonidine salt of the enriched (+) - α - [*para* - (1 - cyclohexenyl) - phenyl] - propionic acid that have precipitated are filtered off. Repeated fractional crystallization according to the usual scheme yields the cinchonidine salt of the dextro-rotary acid. In each case the crystals are recrystallized from a 4% ethanolic solution, while the mother liquors which contain mainly the cinchonidine salt of the levo-rotating acid are caused to crystallize by evaporation to two-thirds of their volumes. The middle fractions are separated by dissolution with the application of heat, and slow cooling.

The cinchonidine salt of the dextro-rotating acid is suspended in ether and agitated with 2N-hydrochloric acid until both phases are clear. The ethereal layer is washed with water, dried over sodium sulfate, and evaporated to obtain (+) - α - [*para* - (1 - cyclohexenyl) - phenyl] - propionic acid melting at 101—102°C; $[\alpha]_D^{20} = +53^\circ$ (ethanol, *c*=1).

In an analogous manner the dextro-rotating acid can be obtained with (−) - α - phenylethylamine instead of cinchonidine.

The fractions which contain the cinchonidine salt of the levo-rotating acid are suspended in ether and agitated with 2N-hydrochloric acid until both phases are clear. The ethereal solution is washed with water, dried over sodium sulfate, and evaporated. The residue is reacted in hot ethanol with the calculated quantity of (+) - α - phenylethylamine and the resulting salt subjected to fractional crystallization. From the pure fraction, (−) - α - [*para* - (1 - cyclohexenyl) - phenyl] - propionic acid melting at 101—102°C, $[\alpha]_D^{20} = -53^\circ$, can be isolated.

By heating a 1% solution of an antipode in 2N-sodium hydroxide solution at 100°C for 16 hours, partial racemization is achieved. The optical rotation of the (−) antipode thus drops from -53° to -24° .

EXAMPLE 3

Tablets containing 20 mg of the sodium salt of α [*p* - (1 - cyclohexenyl) - phenyl] -

propionic acid may be prepared, for example, with the following ingredients:

Ingredients	Per tablet
Active substance	20.0 mg
5 Wheat starch	45.0 mg
Lactose	60.0 mg
Coloidal silicic acid	5.0 mg
Talc	9.0 mg
Magnesium stearate	1.0 mg

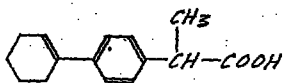
10 140.0 mg

Method

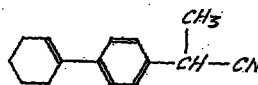
The active substance is mixed with part of the wheat starch, with lactose and colloidal silicic acid, and the mixture passed through a sieve. A further part of the wheat starch is pasted with 5 times the quantity of water on a water-bath and the powdery mixture kneaded with this paste until a weakly plastic mass is formed. The plastic mass is passed through a sieve of about 3 mm mesh, dried, and the dried granulate passed through a sieve. The remaining wheat starch, talc and magnesium stearate are added. The resulting mixture is compressed into tablets weighing 140 mg.

WHAT WE CLAIM IS:—

1. α - [*p* - (1 - Cyclohexenyl) - phenyl] - propionic acid in the form of its racemic mixture.
- 30 2. The compound as claimed in claim 1 in the free form.
3. The compound as claimed in claim 1 in the form of a salt.
- 35 4. The compound as claimed in claim 1 in the form of an alkali metal salt.
5. The compound as claimed in claim 1 in the form of a sodium salt.
6. The compound as claimed in claim 1 in the form of a physiologically tolerable salt.
- 40 7. A compound as claimed in any one of claims 1 to 6 and which is described in Example 1 herein.
8. A pharmaceutical preparation which comprises a compound as claimed in claim 1, claim 2 or any one of claims 4 to 6 in admixture or conjunction with an organic or inorganic, solid or liquid pharmaceutically suitable carrier.
- 45 9. A process for the manufacture of α - [*p* - (1 - cyclohexenyl) - phenyl] - propionic acid of formula



wherein in a compound of formula



the cyano group is hydrolysed to the carboxyl group and, if desired, resulting racemates are resolved into the optical antipodes and/or a resulting free acid converted into a salt or a resulting salt into the free acid or into another salt.

10. A process as claimed in claim 9, conducted substantially as described in Example 1 or Example 2 herein.

11. The dextrorotatory and the laevorotatory antipode of α - [*p* - (1 - cyclohexenyl) - phenyl] - propionic acid.

12. A compound as claimed in claim 11 in the free form.

13. A compound as claimed in claim 11 in the form of a salt.

14. A compound as claimed in claim 11 in the form of an alkali metal salt.

15. A compound as claimed in claim 11 in the form of the sodium salt.

16. A compound as claimed in claim 11 in the form of a physiologically tolerable salt.

17. A compound as claimed in any one of claims 11 to 16 and which is described in Example 2 herein.

18. A pharmaceutical preparation which comprises a compound as claimed in claim 11, claim 12 or any one of claims 14 to 16 in admixture or conjunction with an organic, solid or liquid pharmaceutically suitable carrier.

19. A compound as claimed in any one of claims 1 to 7 and 11 to 17, whenever prepared by a process substantially as claimed in claim 9.

20. A method of treating commercially reared animals to relieve pain, which comprises administering enterally, parenterally or topically to the animal a compound as claimed in any one of claims 1, 2, 4 to 6, 10, 11 and 14 to 16.

21. A method of treating commercially reared animals to relieve inflammation, which comprises administering enterally, parenterally or topically a compound as claimed in any one of claims 1, 2, 4 to 6, 11, 12 and 14 to 16.

ABEL & IMRAY,
Chartered Patent Agents,
Northumberland House,
303/306 High Holborn,
London, W.C.1.



propionic acid may be prepared, for example, with the following ingredients:

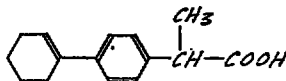
Ingredients	Per tablet
Active substance	20.0 mg
5 Wheat starch	45.0 mg
Lactose	60.0 mg
Coloidal silicic acid	5.0 mg
Talc	9.0 mg
Magnesium stearate	1.0 mg
10	140.0 mg

Method

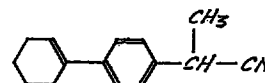
- The active substance is mixed with part of the wheat starch, with lactose and colloidal silicic acid, and the mixture passed through a sieve. A further part of the wheat starch is pasted with 5 times the quantity of water on a water-bath and the powdery mixture kneaded with this paste until a weakly plastic mass is formed. The plastic mass is passed through a sieve of about 3 mm mesh, dried, and the dried granulate passed through a sieve. The remaining wheat starch, talc and magnesium stearate are added. The resulting mixture is compressed into tablets weighing 25 140 mg.

WHAT WE CLAIM IS:—

1. α - [*p* - (1 - Cyclohexenyl) - phenyl] - propionic acid in the form of its racemic mixture.
- 30 2. The compound as claimed in claim 1 in the free form.
3. The compound as claimed in claim 1 in the form of a salt.
4. The compound as claimed in claim 1 in the form of an alkali metal salt.
- 35 5. The compound as claimed in claim 1 in the form of a sodium salt.
6. The compound as claimed in claim 1 in the form of a physiologically tolerable salt.
- 40 7. A compound as claimed in any one of claims 1 to 6 and which is described in Example 1 herein.
8. A pharmaceutical preparation which comprises a compound as claimed in claim 1, claim 2 or any one of claims 4 to 6 in admixture or conjunction with an organic or inorganic, solid or liquid pharmaceutically suitable carrier.
- 45 9. A process for the manufacture of α - [*p* - (1 - cyclohexenyl) - phenyl] - propionic acid of formula



wherein in a compound of formula



the cyano group is hydrolysed to the carboxyl group and, if desired, resulting racemates are resolved into the optical antipodes and/or a resulting free acid converted into a salt or a resulting salt into the free acid or into another salt.

10. A process as claimed in claim 9, conducted substantially as described in Example 1 or Example 2 herein.

11. The dextrorotatory and the laevorotatory antipode of α - [*p* - (1 - cyclohexenyl) - phenyl] - propionic acid.

12. A compound as claimed in claim 11 in the free form.

13. A compound as claimed in claim 11 in the form of a salt.

14. A compound as claimed in claim 11 in the form of an alkali metal salt.

15. A compound as claimed in claim 11 in the form of the sodium salt.

16. A compound as claimed in claim 11 in the form of a physiologically tolerable salt.

17. A compound as claimed in any one of claims 11 to 16 and which is described in Example 2 herein.

18. A pharmaceutical preparation which comprises a compound as claimed in claim 11, claim 12 or any one of claims 14 to 16 in admixture or conjunction with an organic, solid or liquid pharmaceutically suitable carrier.

19. A compound as claimed in any one of claims 1 to 7 and 11 to 17, whenever prepared by a process substantially as claimed in claim 9.

20. A method of treating commercially reared animals to relieve pain, which comprises administering enterally, parenterally or topically to the animal a compound as claimed in any one of claims 1, 2, 4 to 6, 10, 11 and 14 to 16.

21. A method of treating commercially reared animals to relieve inflammation, which comprises administering enterally, parenterally or topically a compound as claimed in any one of claims 1, 2, 4 to 6, 11, 12 and 14 to 16.

ABEL & IMRAY,
Chartered Patent Agents,
Northumberland House,
303/306 High Holborn,
London, W.C.1.