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US-A-4 119 710 describes inter alia the racemate 1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol (generic name: cimaterol) and its pharmaceutical properties. Thus, the compounds described in US-A-4 119 710 have, in addition to their analgesic and uterus-spasmolytic effects and their antispasmodic effects on the striated musculature, in particular β_2 -mimetic and/or β_1 -blocking effects, with one or other effect being dominant depending on the substitution. It is also established in US-A-4 119 710 that the d-(+)-compounds have in particular a selective effect on the β_1 -receptors and the l-(-)-compounds have a preferred effect on the β_2 -receptors.

Moreover, US-A-4 407 819, inter alia describes the performance-enhancing effect of cimaterol in animals.

It is also known that, normally, one of the two enantiomers of a racemate is more effective than the other enantiomer. For this reason, the present application is based on the objective of resolving the racemate known from the literature into its new enantiomers.

Surprisingly, difficulties were encountered in solving this problem, even though US-A-4 119 710 has already described two methods of separating the racemates of these compounds, namely

- a) the resolution of a mixture of diastereomeric compounds which are obtained by reacting the corresponding racemate with a chiral acyl group, and subsequently cleaving the chiral acyl group, e.g. the (-)-menthylcarbonyl group, or
- b) fractional crystallisation of a mixture of the diastereomeric salts with an optically active auxiliary acid.

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Racemate separation a) did not appear to be very promising from the start, owing to the cyano group present in the cimaterol, since this cyano group would be at least partially changed by hydrolysis or hydrogenolysis during the subsequent hydrolytic or hydrogenolytic cleavage of the chiral acyl group which would have to be carried out.

Conventional racemate separation b), which consists of dissolving a corresponding diastereomeric salt in a suitable solvent by heating and subsequently, on cooling, allowing the less soluble diastereomeric salt to crystallise out initially, a process which can be repeated several times, if necessary, until the pure, less soluble diastereomeric salt is isolated, the desired enantiomeric base subsequently being liberated from the pure diastereomeric salt thus obtained, surprisingly did not produce the desired results in the case of cimaterol, as is clear from the appended reference example.

Surprisingly, it has now been found that racemic cimaterol, which may contain one of the desired enantiomers in concentrated form, can be resolved by dissolving cimaterol and at least 2 equivalents, appropriately from 2 to 7 equivalents, but preferably 2 to 4 equivalents, of an optically active dibasic auxiliary acid such as (-)-0,0'-dibenzoyl-L-tartaric acid, (+)-0,0'-dibenzoyl-D-tartaric acid, (-)-0,0'-ditolyl-L-tartaric acid or (+)-0,0'-ditolyl-D-tartaric acid, keeping within a temperature range which is specific to each auxiliary acid and is preferably above 20°C but preferably between 25 and 30°C, in a suitable solvent, via the two diastereomeric salts thereof with subsequent liberation of the enantiomeric base. The desired diastereomeric salt is precipitated with a degree of purity of at least ee = 90% after a short time, e.g. 1 to 5 minutes, whilst the temperature must not fall below the range which is characteristic of each



auxiliary acid, which can be determined by conventional practical tests. Preferably, the two components are dissolved simultaneously, and obviously a solution of one component can be added to a solution of the other component.

It is particularly advantageous to carry out the racemate separation with 2 to 7 equivalents, preferably with 1 to 3 equivalents of (-)-0,0'-dibenzoyl-L-tartaric acid or (+)-0,0'-dibenzoyl-D-tartaric acid as the auxiliary acid at temperatures above 25°C, but preferably in a temperature range between 25 and 30°C. Thus, for example, after 1 mol of cimaterol and 1 mol of (-)-0,0'-dibenzoyl-L-tartaric acid or (+)-0,0'-dibenzoyl-D-tartaric acid have been dissolved in methanol simultaneously, pure (+)-1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol-(-)-0,0'-dibenzoyl-L-hydrogen tartrate or (-)-1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol-(+)-0,0'-dibenzoyl-D-hydrogen tartrate is obtained, and after a short time, e.g. 1 to 2 minutes, the pure diastereomeric hydrogen tartrate in question begins to crystallise out. This salt occurs in a high degree of purity of at least ee = 94% even after the first step. If even greater purity is required, the separation process can be repeated once or several times, if necessary, by dissolving the diastereomeric hydrogen tartrate obtained after a single precipitation and recrystallising it at above 25°C.

The desired pure enantiomeric base is then liberated from the diastereomeric salt thus obtained using a base, preferably dilute ammonia, and the pure base liberated is then isolated by conventional methods.

The enantiomeric bases obtained may, if desired, subsequently be converted into the acid addition salts thereof, more particularly, for pharmaceutical use, into the physiologically acceptable salts thereof with organic or inorganic acids, but preferably with organic acids. Suitable acids include, for example, hydro-



chloric, hydrobromic, sulphuric, phosphoric, fumaric, succinic, lactic, citric, tartaric or maleic acid.

However, a particularly remarkable feature of the process according to the invention is that, if the temperature is accidentally allowed to fall below the prescribed range, the racemic cimaterol-0,0'-dibenzoyl-L-hydrogen tartrate or cimaterol-0,0'-dibenzoyl-D-hydrogen tartrate obtained by way of example can be converted into the desired pure diastereomeric hydrogen tartrate, after re-suspension and heating to above 25°C.

The invention thus also relates to the use of (-)-cimaterol or of (-)-cimaterol which is substantially optically pure, i.e. has an optical purity of at least $ee = 90\%$, preferably 94 to 100%, the acid addition salts thereof, more particularly the physiologically acceptable acid addition salts thereof with organic or inorganic acids, in pharmaceutical compositions and as performance enhancers in animals.

The test report which follows shows that the L-enantiomer of cimaterol, i.e. (-)-cimaterol (the term (-)-cimaterol denoting the enantiomer which rotates the plane of oscillation of linearly polarised light of the sodium-D-line to the left) is surprisingly the only carrier of the biological effects of cimaterol:

1. The two enantiomers of cimaterol were subjected to comparative tests to investigate their β -mimetic effects on the smooth muscle of the bronchus, the skeletal musculature and the fat cells. They were also compared for their acute toxicity.

The β -mimetic effect on the smooth muscle was examined in terms of a broncholytic effect in the test designed by KONZETT and RÖSSLER (Arch. Exp. Path. Pharmacol. 195, 71-74 (1940)) compared with the acetyl choline-induced bronchospasm in guinea-pigs after i.v. administration. From the inhibition of bronchospasm



achieved with the various doses of the test substance, an ED₅₀ was calculated by linear regression analysis as the dosage which resulted in a 50% inhibition of bronchospasm.

The following Table contains the results found:

Substance	ED ₅₀ µg/kg
(-)-Cimaterol	0.27 (0.18 - 0.38)
(+)-Cimaterol	31.30 (5.50 - 48.30)

The L-enantiomer is about 100 times more effective on the β-receptors of the bronchus than the corresponding D-enantiomer.

The β-mimetic effect on the skeletal musculature was tested using the method of BOWMAN and NOTT (Pharmacol. Rev. 21, 27 (1969)). This investigates the influence on the tension of the incompletely tetanically contracting M. soleus of anaesthetised cats after i.v. administration.

The results obtained are shown in the following Table:

Substance	Dose µg/kg	n	Reduction in tension in %	
			x	SD
Cimaterol	0.5	5	38.3	10.8
(-)-Cimaterol	0.5	5	42.1	6.0
(+)-Cimaterol	50.0	5	33.7	8.0

The L-enantiomer of cimaterol is also more than 100 times more effective than the corresponding D-enantiomer on the β-receptors of the skeletal musculature.

The β-mimetic effect on the fat cells was investigated in terms of a lipolytic effect on conscious



rabbits after i.v. administration. The changes in the free fatty acids in the rabbit's blood, achieved by means of the various doses of test substances (measured by the method of DUNCOMBE: Biochem. J. 88, 8 (1963)) was used to calculate, by linear regression analysis, an ED₁₅₀, i.e. the dose which resulted in a 50% increase in the free fatty acid in the blood.

The findings obtained are shown in the following Table:

Substance	ED ₁₅₀ µg/kg
(-)-Cimaterol	0.098 (0.078 - 0.118)
(+)-Cimaterol	9.770 (7.440 - 12.700)

The doses of D-cimaterol needed to achieve a 50% increase in the free fatty acids in the rabbit's blood are about 100 times greater than those of the corresponding L-enantiomer.

The acute toxicity was measured in male and female mice weighing between 20 and 25 g after intravenous administration. An LD₅₀ was calculated by sample analysis from the percentage of animals which died within 14 days of being given the substance.

The following Table contains the results:

Substance	LD ₅₀ mg/kg
(-)-Cimaterol	74.8 (70.6 - 79.2)
(+)-Cimaterol	86.3 (80.6 - 92.3)

2. The performance enhancing effect of (-)-cimaterol was investigated on groups of 10 eight month old lambs (Suffolk x Galway wether lambs), which had been fed for 6 weeks with a feed (dry composition per kg: 145 g of crude protein + 70 g of crude fibre + 17 g of oil + 50 g of crude minerals) to which 2 mg/kg of the test



substance had been added. At the same time steps were taken to ensure that the lambs were offered at least 10% excess feed during the experimental period. The lambs were then killed and the following parameters were obtained:



	Control	(+) - Cimaterol	(-) - Cimaterol	Cimaterol
Starting weight in kg	34.4	34.8	34.2	34.9
Final weight in kg	45.4	45.7	48.0	46.0
Weight gain in g per day	259	268	324	275
Feed utilisation in g of weight gain per kg of feed	190	184	220	196
Weight of carcass in kg	22.8	22.5	24.1	24.0
Composition of carcass tissue (without bones) in g per kg:				
Fat	348	341	557	556
Protein	140	151	252	265
			177	167

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As already mentioned above, the biological data given show that, surprisingly, (-)-cimaterol is the sole carrier of the desired effects. However, since the D-enantiomer has the same toxicity as the L-enantiomer, the ratio of use to risk can be improved by a factor of 2 by using L-cimaterol instead of the racemate.

(-)-Cimaterol and the physiologically acceptable acid addition salts thereof are therefore suitable for treating obesity, obstructive lung changes, allergic bronchial asthma, spastic bronchitis, inflammations or premature labour.

In adults the single dose is between 0.01 and 50 μg , but preferably between 0.01 and 10 μg , twice to four times a day. For this purpose (-)-cimaterol or the physiologically acceptable salts thereof may be incorporated, optionally combined with other active substances, into the conventional galenic preparations such as powders, plain or coated tablets, capsules, suppositories or suspensions.

Furthermore, (-)-cimaterol and the acid addition salts thereof may be used, as mentioned hereinbefore, for treating obese animals such as dogs and, by virtue of their effect of reducing body weight (their lipolytic effect), to reduce undesirable fat deposits in animal farming, i.e. to improve the meat quality of farmed animals such as pigs, cattle, sheep and poultry. The above-mentioned compounds may be administered to the animals by oral or non-oral route, e.g. as a feed additive or by injection or by means of implants. The daily dose is between 0.01 and 100 $\mu\text{g}/\text{kg}$, but preferably between 0.01 and 10 $\mu\text{g}/\text{kg}$ of body weight.

Furthermore, (-)-cimaterol and the acid addition salts thereof may be used as performance enhancers in animals for promoting and accelerating growth, milk and wool production and in order to improve feed utilisation, carcass quality and in order to shift the meat-to-fat ratio in favour of meat. The active



substances are used in agricultural, breeding, show and pet animals.

The agricultural and breeding animals include mammals such as cattle, pigs, horses, sheep, goats, rabbits, hares, deer, fur animals such as mink and chinchilla, poultry such as chickens, geese, ducks, turkeys, fish such as carp, trout, salmon, eels, tench, yellow tails, pike, and reptiles such as snakes and crocodiles.

The show animals and pet animals include mammals such as dogs and cats, birds such as parrots and canaries and fish such as ornamental and aquarium fish, e.g. goldfish.

The active substances are used during all the growth and performance phases of the animals, irrespective of the animals' sex. Preferably, the active substances are used during the intensive growth and performance phase. Depending on the type of animal, the intensive growth and performance phase lasts from one month to 10 years.

The quantity of active substances administered to the animals in order to achieve the desired effect may vary substantially, thanks to the favourable properties of these active substances. This quantity is preferably from 0.01 to 50 $\mu\text{g/kg}$, particularly 0.01 to 25 $\mu\text{g/kg}$ of body weight per day. The correct quantity of active substance and the appropriate period of treatment depend in particular on the type of animal, its age, sex, state of health and the manner in which the animals are kept and fed and can easily be determined by anyone skilled in the art.

The active substances are administered to the animals by the usual methods. The method of administration depends in particular on the type of animal, and the behaviour and state of health of the animals.

The active substances may be administered once.



However, it is also possible to administer the active substances throughout part or all of the growth phase, temporarily or continuously. If they are administered continuously, they may be given one or several times a day at regular or irregular intervals.

The substances are administered by oral or parenteral route in suitable formulations or in pure form. Oral formulations are powders, tablets, granules, drenches, boli as well as feedstuffs, premixes for feedstuffs, and formulations for administering in drinking water.

The oral formulations contain the active substance in concentrations of 0.01 ppb - 100%, preferably 0.01 ppb - 10%.

Parenteral formulations are injections in the form of solutions, emulsions, suspensions, as well as implants.

The active substances may be present in the formulations on their own or in admixture with other active substances, mineral salts, trace elements, vitamins, proteins, colourings, fats or flavourings.

The concentration of the active substances in the finished feed is normally about 0.01 ppb to 50 ppm, preferably 0.1 ppb to 10 ppm.

The active substances may be added to the feed as they are or in the form of premixes or feed concentrates.

Thus, the feedstuffs according to the invention contain in addition to the active substance and possibly a conventional vitamin and mineral mixture, for example, for fattening pigs: barley, wheat flour, broad beans, shredded rape extract and edible fat; for broilers: maize, soya bean flour, meatmeal, edible fat and soya oil; for cattle: shredded sugar beet, maize gluten, malt germs, soya bean flour, wheat and molasses and for lambs: barley, soya bean flour, maize and molasses. To this feedstuff, one of the above-mentioned compounds of



formula I is added as active substance in a concentration of 0.01 ppb to 0.50%, but preferably from 0.1 ppb to 0.05%, the compound preferably being added in the form of an active substance premix. This premix contains, for example, 5 to 10,000 mg, but preferably 50 to 1,000 mg, expediently in 1,000 g of corn starch.

The Examples which follow are intended to illustrate the invention:



Reference example

(-)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-ethanol

a) (-)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-
ethanol-(+)-0,0'-dibenzoyl-D-hydrogen tartrate

50.0 g (0.23 mol) of cimaterol and 82.4 g (0.23 mol) of (+)-0,0'-dibenzoyl-D-tartaric acid are dissolved in 500 ml of methanol at ambient temperature. After a short time, the hydrogen tartrate of the cimaterol crystallises out. The crystalline suspension is stirred for about 2 hours at an internal temperature of 19 to 20°C, then suction filtered and the filter residue is washed with cold methanol and dried at 50°C until a constant weight is obtained.

Yield: 90 g (68.0% of theory based on the racemate used),

Melting point of the liberated base: 162.8°C

ee = 8

b) 88 g of the hydrogen tartrate obtained in a) are refluxed in 500 ml of methanol until totally dissolved and the clear solution is cooled to an internal flask temperature of about 15°C. The crystals precipitated are stirred for about 2 to 3 hours at 15 to 18°C, suction filtered, washed with cold methanol and dried.

Yield: 62 g (70.5% of the material put in),

Melting point of the liberated base: 160.9°C

ee = 24

c) 60 g of the hydrogen tartrate obtained according to b) are dissolved in 350 ml of methanol analogously to a) at boiling temperature, the crystals are stirred for about 12 hours at 10 to 15°C, suction filtered, washed



with cold methanol and dried.

Yield: 34 g (56.7% of the material put in),

Melting point of the liberated base: 151.6°C

ee = 45

After the second recrystallisation, the total yield was only 27.2% of theory, based on the racemate put in, and an enantiomeric excess (ee) of only 45 was obtained. Owing to the substantial waste, crystallisation was not continued.

Example 1

(-)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-ethanol

a) (-)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-ethanol-(+)-0,0'-dibenzoyl-D-hydrogen tartrate

50 g (0.23 mol) of 1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol and 82.4 g (0.23 mol) of (+)-0,0'-dibenzoyl-D-tartaric acid are dissolved in 500 ml of methanol in a 1 litre three-necked flask at 25 to 28°C with stirring. After about 1 to 2 minutes, the laevorotatory diastereomeric hydrogen tartrate crystallises out of the clear solution. After about 2 hours' stirring at 25 to 28°C the crystals are suction filtered, washed with a little methanol and dried at 50°C in a circulating air dryer.

Yield: 44 g (66.5% of theory),

Melting point: 140-141°C

b) 42 g of the hydrogen tartrate obtained in Example 1a are dissolved in 550 ml of methanol in a 1 litre three-necked flask at boiling temperature with stirring and the hot solution is filtered clear in a 2 litre filter



press using a Seitz-EK filter. The filtrate is evaporated down to about 100 to 150 ml of solution under a weak vacuum and the crystal suspension formed is stirred for about 1 hour at 25 to 28°C. The crystals are suction filtered, washed with a little methanol and dried at 50°C in a circulating air dryer.

Yield: 35.7 g (85% based on the hydrogen tartrate used)

Melting point: 140-141°C

c) (-)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-ethanol

36.0 g of the hydrogen tartrate obtained in Example 1b are added gradually to 50 ml of concentrated ammonia and 150 ml of water at ambient temperature. After 1 hour's stirring the crystal suspension is filtered off, washed thoroughly with deionised water and dried at ambient temperature in a circulating air dryer until a constant weight is obtained.

Yield: 11.7 g (85.6% of theory),

Melting point: 146.5°C

$\alpha = -4.37^\circ$, $[\alpha]_D^{20} = -31^\circ$

ee = 99.4

Example 2

(+)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-ethanol

a) (+)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-ethanol-(-)-0,0'-dibenzoyl-L-hydrogen tartrate

Prepared from 1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol and (-)-0,0'-dibenzoyl-L-tartaric acid analogously to Example 1a.

Yield: 69.8% of theory,



Melting point: 140-141°C

b) Purification was continued as in Example 1b.

Yield: 83% based on the hydrogen tartrate used,

Melting point: 140-141°C

c) (+)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-
ethanol

Prepared analogously to Example 1c.

Yield: 81% of theory,

Melting point: 146.5°C

$\alpha = + 4.38^\circ$, $[\alpha]_D^{20} = + 31.5^\circ$

ee = 98.2

Example 3

(+)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-
ethanol

The mother liquor obtained from the precipitation according to Example 1a is evaporated to dryness in vacuo and the residue obtained is taken up in 50 ml of concentrated ammonia and 150 ml of water and stirred for 2 hours at about 5 to 10°C. After suction filtering, the filter residue is washed thoroughly with water and dried well in a circulating air dryer at ambient temperature.

Yield: 26.5 g (53% based on the racemate used)

The crude (+)-1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol thus obtained is purified with (-)-0,0'-dibenzoyl-L-tartaric acid analogously to Example 2:

a) Yield: 39.7 g (56.8% based on the racemate/enantiomer



- mixture used),
Melting point: 140-141°C
- b) Yield: 87% based on the hydrogen tartrate used,
Melting point: 140-141°C
- c) Yield: 78.5% of theory,
Melting point: 146.5°C
 $\alpha = + 4.37^\circ$, $[\alpha]_D^{20} = + 31^\circ$
ee = 98

Example 4

(-)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-ethanol

50 g of (-)-1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol-(+)-0,0'-dibenzoyl-L-hydrogen tartrate (prepared according to Reference example a), melting point of the liberated base: 162.8°C; ee = 8) are suspended in 500 ml of methanol and stirred for 1 hour at an internal flask temperature of about 28°C. The mixture is then suction filtered, washed with a little methanol and dried at 50°C until a constant weight is obtained.
Yield: 28.0 g (56% based on the racemate/enantiomer mixture).

The hydrogen tartrate thus obtained is liberated analogously to Example 1c) using dilute ammonia.
Yield: 9.14 g (86% of theory),
Melting point: 145°C
 $\alpha = - 4.37^\circ$, $[\alpha]_D^{20} = - 31^\circ$
ee = 98



Example 5

Tablets containing 2 μ g of (-)-cimaterol

Composition:

1 tablet contains:

Active substance	0.002 mg
Lactose	82.498 mg
Potato starch	33.000 mg
Polyvinylpyrrolidone	4.000 mg
Magnesium stearate	<u>0.050 mg</u>
	120.000 mg

Method of preparation:

The active substance and polyvinylpyrrolidone are dissolved in ethanol. The mixture of lactose and potato starch is uniformly moistened with the active substance/granulating solution. Moist screening is carried out with a 1.5 mm mesh screen. The mixture is then dried at 50°C and dry screening is carried out with a 1.0 mm mesh screen. The granules thus obtained are mixed with magnesium stearate and compressed into tablets.

Weight of tablet: 120 mg

Punch: 7 mm, flat

Example 6

Coated tablets containing 1 μ g of (-)-cimaterol

Composition:

1 tablet contains:

Active substance	0.001 mg
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Lactose	82.499 mg
Potato starch	33.000 mg
Polyvinylpyrrolidone	4.000 mg
Magnesium stearate	<u>0.500 mg</u>
	120.000 mg

Method of preparation:

Tablet cores analogously to the tablets in Example 5.

Weight of core: 120 mg

Punch: 7 mm, convex

The cores are coated by known methods with a coating consisting essentially of sugar and talc. The finished coated tablets are polished with beeswax.

Weight of coated tablet: 200.0 mg

Example 7

Oblong gelatine capsules containing 1 μ g of (-)-
cimaterol

Composition:

1 tablet contains:

Active substance	0.001 mg
Lactose	59.999 mg
Corn starch	<u>60.000 mg</u>
	120.000 mg

Method of preparation:

The active substance is intensively mixed with lactose and corn starch and packed into suitably sized oblong gelatine capsules.

Capsule contents: 120.0 mg



Example 8

Ampoules containing 2 μ g of (-)-cimaterol per 2 ml

Composition:

1 ampoule contains:

Active substance	0.002 mg
Citric acid	2.500 mg
Sodium hydrogen phosphate	7.500 mg
Common salt	4.600 mg
Water for ampoules to make up to	2.000 ml

Method of preparation:

The active substance, buffer substances and common salt are dissolved in water for ampoules and then filtered to remove any pathogens.

Packaging:	in brown 2 ml ampoules under protective gas (N ₂)
Sterilisation:	20 minutes at 120°C

Example 9

Suppositories containing 2.5 μ g of (-)-cimaterol

Composition:

1 suppository contains:

Active substance	0.025 mg
Suppository mass (e.g. Witepsol W 45)	<u>1.699.975 mg</u>
	1,700.000 mg

Method of preparation:

The finely powdered active substance is stirred into the



molten suppository mass, which has been cooled to 40°C, by means of an immersion homogeniser and at 37°C the mass is poured into slightly chilled moulds.

Weight of suppository: 1.7 g

Example 10

Syrup containing 2 µg of (-)-cimaterol per 5 ml

Composition:

100 ml of syrup contains:

Active substance	0.04 mg
Benzoic acid	0.10 g
Tartaric acid	1.00 g
Sugar	50.00 g
Orange flavour	1.00 g
Red food colouring	0.05 g
Distilled water to make up to	100.00 ml

Method of preparation:

About 60 g of distilled water are heated to 80°C and the benzoic acid, tartaric acid, active substance, colouring and sugar are successively dissolved therein. After the solution has been cooled to ambient temperature the flavouring is added and the mixture is made up to the volume specified. The syrup is filtered.

Example 11

Aerosol spray delivering 1 µg of (-)-cimaterol per activation

Composition:



Active substance	0.00025 mg
Soya lecithin	0.05000 mg
Propellant gas mixture 11/12/114 (23:54:23)	<u>69.94975 mg</u>
	70.00000 mg

Example 12

Aerosol spray delivering 1 µg of (-)-cimaterol per activation

Composition:

Active substance	0.00025 mg
99.9% pure ethanol	0.87500 mg
Propellant gas mixture 11/12/114 (23:54:23)	<u>69.12475 mg</u>
	70.00000 mg

Example 13

Solution for inhalation containing 59 mg of (-)-cimaterol per 100 ml

Composition:

Active substance	0.59 mg
Sodium chloride	900.00 mg
Benzalkonium chloride	25.00 mg
Distilled water	to make up to 100.00 ml

Method of preparation:

The active substance, common salt and benzalkonium chloride are dissolved in distilled water and then filtered to remove any pathogens.



Example 14

Complete food II for fattening pigs

Barley	379 g/kg
Wheat flour	200 g/kg
Manioc flour	135 g/kg
Broad beans	100 g/kg
Shredded rape extract	100 g/kg
Edible fat	65 g/kg
Lysine-rich mineral feed for pigs	20 g/kg
Active substance premix	1 g/kg

After being carefully mixed in the quantities specified these components yield 1 kg of feed.

The 1 g of active substance premix contains for example 2 mg of active substance and 0.998 g of corn starch.

Example 15

Fattening feed II for broilers

Maize	634 g/kg
Soya bean flour	260 g/kg
Meatmeal	40 g/kg
Edible fat	25 g/kg
Soya oil	17 g/kg
Bicalcium phosphate	12 g/kg
Calcium carbonate	6 g/kg
Vitamin/mineral mix	5 g/kg
Active substance premix	1 g/kg

After being carefully mixed in the quantities specified, these components yield 1 kg of feed.

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The 1 g of active substance premix contains for example 1 mg of active substance and 0.999 g of corn starch.

Example 16

Concentrated feed for cattle

Shredded sugar beet	600.0 g/kg
Maize gluten	100.0 g/kg
Malt germs	50.0 g/kg
Soya bean flour	35.0 g/kg
Wheat	119.0 g/kg
Molasses	60.0 g/kg
Feed phosphates	12.0 g/kg
Calcium carbonate	2.5 g/kg
Salt	5.0 g/kg
Minerals	10.0 g/kg
Vitamin premix	5.5 g/kg
Active substance premix	1.0 g/kg

When carefully mixed in the quantities specified, these components yield 1 kg of feed.

The 1 g of active substance premix contains for example 2 mg of active substance and 0.998 g of corn starch.

Example 17

Fattening feed for lambs

Barley	690 g/kg
Soya bean flour	100 g/kg
Maize	159 g/kg
Molasses	30 g/kg
Vitamin/mineral mix	20 g/kg
Active substance premix	1 g/kg



When carefully mixed in the quantities specified, these components yield 1 kg of feed.

The 1 g of active substance premix contains for example 2 mg of active substance and 0.998 g of corn starch.

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Claims

1. (-)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-ethanol and the acid addition salts thereof.
2. Compound according to claim 1, characterised in that it is substantially optically pure.
3. Compound according to claim 1, characterised in that it has an optical purity of at least ee = 90%.
4. Compound according to claim 1, characterised in that it has an optical purity of at least ee = 94%.
5. Physiologically acceptable acid addition salts of the compound according to at least one of claims 1 to 4.
6. Pharmaceutical composition comprising a compound according to at least one of claims 1 to 4 or a physiologically acceptable acid addition salt according to claim 5 optionally together with one or more inert carriers and/or diluents.
7. Use of a compound according to at least one of claims 1 to 5 for preparing a pharmaceutical composition which is suitable for treating obesity, obstructive lung changes, allergic bronchial asthma, spastic bronchitis, inflammation or premature labour.
8. Process for preparing a pharmaceutical composition according to claim 6, characterised in that a compound according to at least one of claims 1 to 5 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.
9. Use of a compound according to at least one of claims 1 to 5 as a performance enhancing agent in





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animals.

10. Animal feed and premixes for producing animal feed, containing a compound according to at least one of claims 1 to 5.

11. Performance enhancing agent for animals, containing a compound according to at least one of claims 1 to 5.

12. Process for preparing performance enhancing agents for animals, characterised in that a compound according to at least one of claims 1 to 5 is mixed with extenders, diluents and nutrients and optionally other adjuvants.

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Abstract

(-)-Cimaterol and its uses in pharmaceutical compositions or as performance enhancers.

The invention relates to the use of (-)-cimaterol and its addition salts in pharmaceutical compositions or as performance enhancers.

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REPLACEMENT SHEETS SG
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SEPARATION OF ENANTIOMERS OF CIMATEROL, (-)-CIMATEROL
AND THE USE THEREOF AS PHARMACEUTICAL COMPOSITION OR
AS PERFORMANCE ENHANCERS

5 The present invention relates to an improved
process for the resolution of racemic cimaterol, to (-)-
cimaterol and derivatives thereof, to pharmaceutical
compositions containing them, and to their use as
performance enhancing agents.

US-A-4,119,710 describes inter alia the racemate 1-
(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol
(generic name: cimaterol) and its pharmaceutical
properties. Thus, the compounds described in
10 US-A-4,119,710 have, in addition to their analgesic and
uterus-spasmolytic effects and their antispasmodic
effects on the striated musculature, in particular β_2 -
mimetic and/or β_1 -blocking effects, with one or other
effect being dominant depending on the substitution. It
15 is also established in US-A-4,119,710 that the d-(+)-
compounds have in particular a selective effect on the
 β_1 -receptors and the l-(-)-compounds have a preferred
effect on the β_2 -receptors.

Moreover, US-A-4,407,819, inter alia describes the
20 performance-enhancing effect of cimaterol in animals.

It is also known that, normally, one of the two
enantiomers of a racemate is more effective than the
other enantiomer. For this reason, the present
application is based on the objective of resolving the
25 racemate known from the literature into its new
enantiomers.

Surprisingly, difficulties were encountered in
solving this problem, even though US-A-4,119,70 has
already described two methods of separating the
30 racemates of these compounds, namely

a) the resolution of a mixture of diastereomeric

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compounds which are obtained by reacting the corresponding racemate with a chiral acyl group, and subsequently cleaving the chiral acyl group, e.g. the (-)-methylcarbonyl group, or

5

b) fractional crystallisation of a mixture of the diastereomeric salts with an optically active auxiliary acid.

10 Racemate separation by method a) did not appear to be very promising from the start, owing to the cyano group present in the cimaterol, since this cyano group would be at least partially changed by hydrolysis or hydrogenolysis during the subsequent hydrolytic or hydrogenolytic cleaving of the chiral acyl group which
15 would have to be carried out.

Conventional racemate separation by method b), which consists of dissolving a corresponding diastereomeric salt in a suitable solvent by heating and subsequently, on cooling, allowing the less soluble
20 diastereomeric salt to crystallise out initially, a process which can be repeated several times, if necessary, until the pure, less soluble diastereomeric salt is isolated, the desired enantiomeric base subsequently being liberated from the pure
25 diastereomeric salt thus obtained, surprisingly did not produce the desired results in the case of cimaterol, as is clear from the appended reference example.

Surprisingly, we have now found that racemic cimaterol, which may contain one of the desired
30 enantiomers in greater concentration, can be resolved, by means of an improved process according to the present invention, which process is characterised by dissolving racemic cimaterol and at least 2 equivalents, preferably from 2 to 7 equivalents, more preferably from 2 to 4
35 equivalents, of an optically active dibasic auxiliary acid such as (-)-0,0'-dibenzoyl-L-tartaric acid, (+)-0,0'-dibenzoyl-D-tartaric acid, (-)-0,0'-ditolyl-L-

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tartaric acid or (+)-0,0'-ditolyl-D-tartaric acid, keeping within a desired predeterminable temperature range which is specific to each auxiliary acid and is preferably above 20°C, more preferably between 25° and 30°C, in a suitable solvent, obtaining the two diastereomeric salts produced thereby and subsequently liberating the corresponding enantiomeric bases thereof. The diastereomeric salt corresponding to the desired enantiomeric base is precipitated with a degree of purity of at least ee = 90% after a short time, e.g. 1 to 5 minutes. The temperature ideally must not fall below the range which is characteristic of each auxiliary acid. Preferably, the two components are dissolved simultaneously, and obviously a solution of one component can be added to a solution of the other component.

The desired temperature range in which the process according to the invention yields, in sufficient purity, the diastereomeric salt corresponding to the desired enantiomeric base may be predetermined by means of simple trial experiments for each particular auxiliary acid.

Particularly preferred for carrying out the process of the present invention is use of 2 to 7 equivalents, preferably 2 to 3 equivalents of (-)-0,0'-dibenzoyl-L-tartaric acid or (+)-0,0'-dibenzoyl-D-tartaric acid as the auxiliary acid at temperatures above 25°C, but preferably in a temperature range between 25 and 30°C.

Thus, for example, after 1 mol of cimaterol and 1 mol of (-)-0,0'-dibenzoyl-L-tartaric acid or (+)-0,0'-dibenzoyl-D-tartaric acid have been dissolved in methanol simultaneously, pure (+)-1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol-(-)-0,0'-dibenzoyl-L-hydrogen tartrate or (-)-1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol-(+)-0,0'-dibenzoyl-D-hydrogen tartrate respectively are obtained, the pure diastereomeric hydrogen tartrate in question beginning

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to crystallise after a short time, e.g. 1 to 2 minutes. This salt has been found to occur in a high degree of purity of at least $ee = 94\%$ even after the first step. If even the greater purity is required, the separation process can be repeated once or several times, if necessary, by dissolving the diastereomeric hydrogen tartrate obtained after a single precipitation and recrystallising it at above 25°C . The desired pure enantiomeric base may then be liberated from the diastereomeric salt thus obtained using a base, preferably dilute ammonia, and the pure base liberated is then isolated by conventional methods.

A particularly remarkable feature of the process according to the invention is that, if the temperature is accidentally allowed to fall below the prescribed range, the racemic cimaterol-0, 0'-dibenzoyl-L-hydrogen tartrate or cimaterol-0, 0'-dibenzoyl-D-hydrogen tartrate obtained by way of example can be converted into the desired pure diastereomeric hydrogen tartrate, after re-suspension and heating to above 25°C .

The enantiomeric bases obtained may, if desired, subsequently be converted into the acid addition salts thereof, more particularly, for pharmaceutical use, into the physiologically acceptance salts thereof with organic or inorganic acids, but preferably with organic acids. Suitable acids include, for example, hydrochloric, hydrobromic, sulphuric, phosphoric, fumaric, succinic, lactic, citric, tartaric or maleic acid.

According to the present invention there is provided (-)-1-(4'-Amino-3'-cyanophenyl)-2-isopropylaminoethanol and acid addition salts thereof or any mixture thereof with the corresponding (+) isomer and acid-addition salts thereof in which the (-)-isomer is present in excess over the (+)-isomer.

The present invention also relates to (-)-cimaterol or (-)-cimaterol which is substantially optically pure, i.e. has an optical purity of at least $ee = 90\%$, preferably 94 to 100%, the acid addition salts thereof, more particularly the physiologically acceptable acid addition acids thereof with organic or inorganic acids.

The present invention also relates to the diastereomeric salts of cimaterol with an optically active dibasic auxiliary acid, more particularly to

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those wherein the auxiliary acid is selected from (-)-0,0'-dibenzoyl-L-tartaric acid, (+)-0,0'-dibenzoyl-D-tartaric acid, (-)-0,0'-ditolyl-L-tartaric acid or (+)-0,0'-ditolyl-D-tartaric acid, most particularly to (+)- or (-)-cimaterol-0,0'-dibenzoyl-L-hydrogen tartrate or to (+)- or (-)-cimaterol-0,0'-dibenzoyl-D-hydrogen tartrate.

The test report which follows shows that the L-enantiomer of cimaterol, i.e. (-)-cimaterol (the term (-)-cimaterol denoting the enantiomer which rotates the plane of oscillation of linearly polarised light of the sodium-D-line to the left) is surprisingly the only carrier of the biological effects of cimaterol:

1. The two enantiomers of cimaterol were subjected to comparative tests to investigate their β -mimetic effects on the smooth muscle of the bronchus, the skeletal musculature and the fat cells. They were also compared for their acute toxicity.

20

The β -mimetic effect on the smooth muscle was examined in terms of a broncholytic effect in the test designed by KONSETT and RÖSSLER (Arch. Exp. Path. Pharmacol. 195, 71-74 (1940)) compared with the acetylcholine-induced bronchospasm in guinea-pigs after i.v. administration. From the inhibition of bronchospasm achieved with the various doses of the test substance, an ED_{50} was calculated by linear regression analysis as the dosage which resulted in a 50% inhibition of bronchospasm.

30

The following Table contains the results found:

Substance	ED_{50} $\mu\text{g/kg}$
(-)-Cimaterol	0.27 (0.18 - 0.38)
(+)-Cimaterol	31.30 (5.50 - 48.30)

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The L-enantiomer is about 100 times more effective on the β -receptors of the bronchus than the corresponding D-enantiomer.

The β -mimetic effect on the skeletal musculature
was tested using the method of BOWMAN and NOTT (Pharmacol. Rev. 21, 27 (1969)). This investigates the influence on the tension of the incompletely tetanically contracting M. soleus of anaesthetised cats after i.v. administration.

The results obtained are shown in the following Table:

Substance	Dose $\mu\text{g/kg}$	n	Reduction in tension in %	
			x	SD
Cimaterol	0.5	5	38.3	10.8
(-)-Cimaterol	0.5	5	42.1	6.0
(+)-Cimaterol	50.0	5	33.7	8.0

The L-enantiomer of cimaterol is also more than 100 times more effective than the corresponding D-enantiomer on the β -receptors of the skeletal musculature.

The β -mimetic effect on the fat cells was investigated in terms of a lipolytic effect on conscious rabbits after i.v. administration. The changes in the free fatty acids in the rabbit's blood, achieved by means of the various doses of test substances (measured by the method of DUNCOMBE: Biochem. J. 88, 8 (1963)) was used to calculate, by linear regression analysis, an ED_{150} , i.e. the dose which resulted in a 50% increase in the free fatty acid in the blood.

The findings obtained are shown in the following Table:

Substance	ED ₁₅₀ µg/kg
(-)-Cimaterol	0.098 (0.078 - 0.118)
(+)-Cimaterol	9.770 (7.440 - 12.700)

5

The doses of D-cimaterol needed to achieve a 50% increase in the free fatty acids in the rabbit's blood are about 100 times greater than those of the corresponding L-enantiomer.

10

The acute toxicity was measured in male and female mice weighing between 20 and 25 g after intravenous administration. An LD₅₀ was calculated by sample analysis from the percentage of animals which died within 14 days of being given the substance.

15

The following Table contains the results:

Substance	LD ₅₀ mg/kg
(-)-Cimaterol	74.8 (70.6 - 79.2)
(+)-Cimaterol	86.3 (80.6 - 92.3)

20

2. The performance enhancing effect of (-)-cimaterol was investigated on groups of 10 eight month old lambs (Suffolk x Galway wether lambs), which had been fed for 6 weeks with a feed (dry composition per kg: 145 g of crude protein + 70 g of crude fibre + 17 g of oil + 50 g of crude minerals) to which 2 mg/kg of the test substance had been added. At the same time steps were taken to ensure that the lambs were offered at least 10% excess feed during the experimental period. The lambs were then killed and the following results were obtained:

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	Control	(+)-Cimaterol	(-)-Cimaterol	Cimaterol
Starting weight in kg	34.4	34.8	34.2	34.9
Final weight in kg	45.4	45.7	48.0	46.0
Weight gain in g per day	259	268	324	275
Feed utilisation in g of weight gain per kg of feed	190	184	220	196
Weight of carcass in kg	22.8	22.5	24.1	24.0
Composition of carcass tissue (without bones) in g per kg:				
Water	501	501	557	556
Fat	348	341	252	265
Protein	140	151	177	167

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As already mentioned above, the biological data given show that, surprisingly, (-)-cimaterol is the sole carrier of the desired effects. However, since the D-enantiomer has the same toxicity as the L-enantiomer, the ratio of use to risk can be improved by a factor of 2 by using (-)-cimaterol instead of the racemate.

(-)-Cimaterol and the physiologically acceptable acid addition salts thereof are therefore therapeutically useful in the treatment of obesity, obstructive lung disorders, allergic bronchial asthma, spastic bronchitis, inflammation or premature labour.

A yet further feature of the present invention is a method of treatment of obesity, obstructive lung disorders, allergic bronchial asthma, spastic bronchitis, inflammation or premature labour in a subject which comprises administering to said subject an effective amount of (-)-cimaterol or the physiologically acceptable acid addition salts thereof.

In adults the single dose is between 0.01 and 50 μ g, but preferably between 0.01 and 10 μ g, twice to four times a day. For this purpose (-)-cimaterol or the physiologically acceptable salts thereof may be incorporated, optionally combined with other active substances, into the conventional galenic preparations such as powders, plain or coated tablets, capsules, suppositories or suspensions.

According to a yet further feature of the present invention there are provided pharmaceutical compositions comprising as active ingredient at least one compound selected from (-)-cimaterol or a physiologically acceptable acid addition salt thereof in association with one or more pharmaceutically acceptable carriers, diluents or excipients.

Furthermore, according to the present invention (-)-cimaterol and the acid addition salts thereof may be used, as mentioned hereinbefore, for treating obese animals such as dogs and, by virtue of their effect of

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reducing body weight (their lipolytic effect), to reduce undesirable fat deposits in animal farming, i.e. to improve the meat quality of farmed animals such as pigs, cattle, sheep and poultry. The above-mentioned
5 compounds may be administered to the animals by oral or non-oral route, e.g. as a feed additive or by injection or by means of implants.

The daily dose is between 0.01 and 100 $\mu\text{g/kg}$, but preferably between 0.01 and 10 $\mu\text{g/kg}$ of body weight.

10 Furthermore, according to the present invention (-)-cimaterol and the acid addition salts thereof may be used as performance enhancers in animals for promoting and accelerating growth, milk and wool production and in order to improve feed utilisation, carcass quality and
15 in order to shift the meat-to-fat ratio in favour of meat. The active substances are used in agricultural, breeding, show and pet animals.

The agricultural and breeding animals include mammals such as cattle, pigs, horses, sheep, goats,
20 rabbits, hares, deer, fur animals such as mink and chinchilla, poultry such as chickens, geese, ducks, turkeys, fish such as carp, trout, salmon, eels, tench, yellow tail, pike, and reptiles such as snakes and crocodiles.

25 The show animals and pet animals include mammals such as dogs and cats, birds such as parrots and canaries and fish such as ornamental and aquarium fish, e.g. goldfish.

30 The active substances are used during all the growth and performance phases of the animals, irrespective of the animals' sex. Preferably, the active substances are used during the intensive growth and performance phase. Depending on the type of animal, the intensive growth performance phase lasts from one
35 month to 10 years.

The quantity of active substances administered to the animals in order to achieve the desired effect may

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vary substantially, thanks to the favourable properties of these active substances. This quantity is preferably from 0.01 to 50 $\mu\text{g/kg}$, particularly 0.01 to 25 $\mu\text{g/kg}$ of body weight per day. The correct quantity of active
5 substance and the appropriate period of treatment depend in particular on the type of animal, its age, sex, state of health and the manner in which the animals are kept and fed and can easily be determined by anyone skilled in the art.

10 The active substances are administered to the animals by the usual methods. The method of administration depends in particular on the type of animal, and the behaviour and state of health of the animals.

15 The active substances may be administered once. However, it is also possible to administer the active substances throughout part or all of the growth phase, temporarily or continuously. If they are administered continuously, they may be given one or several times a
20 day at regular or irregular intervals.

The substances are administered by oral or parenteral route in suitable formulations or in pure form. Oral formulations are powders, tablets, granules, drenches, boli as well as feedstuffs, premixes for
25 feedstuffs, and formulations for administering in drinking water.

The oral formulations contain the active substance in concentrations of 0.01 ppb - 100%, preferably 0.01 ppb - 10%.

30 Parenteral formulations are injections in the form of solutions, emulsions, suspensions, as well as implants.

The active substances may be present in the formulations on their own or in admixture with other
35 active substances, mineral salts, trace elements, vitamins, proteins, colourings, fats or flavourings.

The concentration of the active substances in the

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finished feed is normally about 0.01 ppb to 50 ppm, preferably 0.1 ppb to 10 ppm.

The active substances may be added to the feed as they are or in the form of premixes or feed concentrates.

Thus, the feedstuffs according to the invention contain in addition to the active substance and possibly a conventional vitamin and mineral mixture, for example, for fattening pigs: barley, wheat flour, broad beans, shredded rape extract and edible fat; for broilers: maize, soya bean flour, meatmeal, edible fat and soya oil; for cattle: shredded sugar beet, maize gluten, malt germs, soya bean flour, wheat and molasses and for lambs: barley, soya bean flour, maize and molasses. To this feedstuff, one of the above-mentioned compounds of formula I is added as active substance in a concentration of 0.01 ppb to 0.50%, but preferably from 0.1 ppb to 0.05%, the compound preferably being added in the form of an active substance premix. This premix contains, for example, 5 to 10,000 mg, but preferably 50 to 1,000 mg, expediently in 1,000 g of corn starch.

The non-limiting Examples which follow are intended to illustrate the invention:

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Reference example

(-)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-ethanol

5

a) (-)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-ethanol-(+)-0,0'-dibenzoyl-D-hydrogen tartrate

10 50.0 g (0.23 mol) of cimaterol and 82.4 g (0.23 mol) of (+)-0,0'-dibenzoyl-D-tartaric acid are dissolved in 500 ml of methanol at ambient temperature. After briefly dissolving, the hydrogen tartrate of the cimaterol crystallises out. The crystal suspension is
15 stirred for about 2 hours at an internal temperature of 19 to 20°C, then suction filtered and the filter residue is washed with cold methanol and dried at 50°C until a constant weight is obtained.

Yield: 90 g (68.0% of theory based on the racemate
20 used),
Melting point of the liberated base: 162.8°C
ee = 8

b) 88 g of the hydrogen tartrate obtained in a) are
25 refluxed in 500 ml of methanol until totally dissolved and the clear solution is cooled to an internal flask temperature of about 15°C. The crystals precipitated are stirred for about 2 to 3 hours at 15 to 18°C, suction filtered, washed with cold methanol and dried.
30 Yield: 62 g (70.5% of the material put in),
Melting point of the liberated base: 160.9°C
ee = 24

c) 60 g of the hydrogen tartrate obtained according to
35 b) are dissolved in 350 ml of methanol analogously to a) at boiling temperature, the crystals are stirred for about 12 hours at 10 to 15°C, suction filtered, washed with cold methanol and dried.

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Yield: 34 g (56.7% of the material put in),
Melting point of the liberated base: 151.6°C
ee = 45

5 After the second recrystallisation, the total yield was
only 27.2% of theory, based on the racemate put in, and
an enantiomeric excess (ee) of only 45 was obtained.
Owing to the substantial waste, crystallisation was not
continued.

10

Example 1

(-)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-
ethanol

15

a) (-)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-
ethanol-(+)-0,0'-dibenzoyl-D-hydrogen tartrate

20 50 g (0.23 mol) of 1-(4'-amino-3'-cyano-phenyl)-2-
isopropylamino-ethanol and 82.4 g (0.23 mol) of (+)-
0,0'-dibenzoyl-D-tartaric acid are dissolved in 500 ml
of methanol in a 1 litre three-necked flask at 25 to
28°C with stirring. After about 1 to 2 minutes, the
25 laevorotatory diastereomeric hydrogen tartrate
crystallises out of the clear solution. After about 2
hours' stirring at 25 to 28°C the crystals are suction
filtered, washed with a little methanol and dried at
50°C in a circulating air dryer.

30 Yield: 44 g (66.5% of theory),
Melting point: 140-141°C

b) 42 g of the hydrogen tartrate obtained in Example 1a
are dissolved in 550 ml of methanol in a 1 litre three-
35 necked flask at boiling temperature with stirring and
the hot solution is filtered clear in a 2 litre filter
press using a Seitz-EK filter. The filtrate is
evaporated down to about 100 to 150 ml of solution under

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a weak vacuum and the crystal suspension formed is stirred for about 1 hour at 25 to 28°C. The crystals are suction filtered, washed with a little methanol and dried at 50°C in a circulating air dryer.

5 Yield: 35.7 g (85% based on the hydrogen tartrate used)
Melting point: 140-141°C

c) (-)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-ethanol

10

36.0 g of the hydrogen tartrate obtained in Example 1b are added gradually to 50 ml of concentrated ammonia and 150 ml of water at ambient temperature. After 1 hours' stirring the crystal suspension is filtered off, washed thoroughly with deionised water and dried at ambient temperature in a circulating air dryer until a constant weight is obtained.

15

Yield: 11.7 g (85.6% of theory),
Melting point: 146.5°C

20 $[\alpha]_D^{20} = -31^\circ$, ee = 99.4
 $\alpha = -4.37^\circ$

Example 2

25 (+)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-ethanol

a) (+)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-ethanol-(-)-0,0'-dibenzoyl-L-hydrogen tartrate

30

Prepared from 1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol and (-)-0,0'-dibenzoyl-L-tartaric acid analogously to Example 1a.

35 Yield: 69.8% of theory,
Melting point: 140-141°C

b) Purification was continued as in Example 1b.

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Yield: 83% based on the hydrogen tartrate used,
Melting point: 140-141°C

5 c) (+)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-
 ethanol

Prepared analogously to Example 1c.

Yield: 81% of theory,

Melting point: 146.5°C

10 $[\alpha]_D^{20} = + 31.5^\circ$, ee = 98.2
 $\alpha = + 4.38^\circ$

Example 3

15 (+)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-
 ethanol

20 The mother liquor obtained from the precipitation
 according to Example 1a is evaporated to dryness in
 vacuo and the residue obtained is taken up in 50 ml of
 concentrated ammonia and 150 ml of water and stirred for
 2 hours at about 5 to 10°C. After suction filtering,
25 the filter residue is washed thoroughly with water and
 dried well in a circulating air dryer at ambient
 temperature.

Yield: 26.5 g (53% based on the racemate used)

30 The crude (+)-1-(4'-amino-3'-cyano-phenyl)-2-
 isopropylamino-ethanol thus obtained is purified with
 (-)-0,0'-dibenzoyl-L-tartaric acid analogously to
 Example 2:

35 a) Yield: 39.7 g (56.8% based on the racemate/enantiomer
 mixture used),
 Melting point: 140-141°C

b) Yield: 87% based on the hydrogen tartrate used,
 Melting point: 140-141°C

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c) Yield: 78.5% of theory,

Melting point: 146.5°C

$[\alpha]_D^{20} = + 31^\circ$, ee = 98

$\alpha = + 4.37^\circ$

5

Example 4

(-)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-ethanol

10

50 g of (-)-1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol-(+)-0,0'-dibenzoyl-L-hydrogen tartrate (prepared according to Reference example a),
melting point of the liberated base: 162.8°C; ee = 8)
are suspended with 500 ml of methanol and stirred for 1
hour at an internal flask temperature of about 28°C.
The mixture is then suction filtered, washed with a
little methanol and dried at 50°C until a constant
weight is obtained.

20

Yield: 28.0 g (56% based on the racemate/enantiomer mixture).

The hydrogen tartrate thus obtained is liberated
analogously to Example 1c) using dilute ammonia.

25

Yield: 9.14 g (86% of theory),

Melting point: 145°C

$[\alpha]_D^{20} = - 31^\circ$, ee = 98

$\alpha = - 4.37^\circ$

Example 5

Tablets containing 2 µg of (-)-cimaterol

5

Composition:

1 tablet contains:

	Active substance	0.002 mg
10	Lactose	82.498 mg
	Potato starch	33.000 mg
	Polyvinylpyrrolidone	4.000 mg
	Magnesium stearate	<u>0.050 mg</u>
		120.000 mg

15

Method of preparation:

The active substance and polyvinylpyrrolidone are dissolved in ethanol. The mixture of lactose and potato starch is uniformly moistened with the active substance/granulating solution. Moist screening is carried out with a 1.5 mm mesh screen. The mixture is then dried at 50°C and dry screening is carried out with a 1.0 mm mesh screen. The granules thus obtained are mixed with magnesium stearate and compressed into tablets.

Weight of tablet: 120 mg

Punch: 7 mm, flat

30

Example 6

Coated tablets containing 1 µg of (-)-cimaterol

35

Composition:

1 tablet contains:

Active substance 0.001 mg

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	Lactose	82.499 mg
	Potato starch	33.000 mg
	Polyvinylpyrrolidone	4.000 mg
	Magnesium stearate	<u>0.500 mg</u>
5		120.000 mg

Method of preparation:

- Tablet cores analogously to the tablets in Example 5.
- 10 Weight of core: 120 mg
- Punch: 7 mm, convex
- The cores are coated by known methods with a coating consisting essentially of sugar and talc. The finished coated tablets are polished with beeswax.
- 15 Weight of coated tablet: 200.0 mg

Example 7

- 20 Oblong gelatine capsules containing 1 μ g of (-)-
cimaterol
-

Composition:

- 1 tablet contains:
- 25
- | | |
|------------------|------------------|
| Active substance | 0.001 mg |
| Lactose | 59.999 mg |
| Corn starch | <u>60.000 mg</u> |
| | 120.000 mg |

30

Method of preparation:

- The active substance is intensively mixed with lactose and corn starch and packed into suitably sized oblong
- 35 gelatine capsules.
- Capsule contents: 120.0 mg

Example 8

Ampoules containing 2 μ g of (-)-cimaterol per 2 ml

5

Composition:

1 ampoule contains:

	Active substance	0.002 mg
10	Citric acid	2.500 mg
	Sodium hydrogen phosphate	7.500 mg
	Common salt	4.600 mg
	Water for ampoules to	2.000 ml

15 Method of preparation:

The active substance, buffer substances and common salt are dissolved in water for ampoules and then filtered to remove any pathogens.

20	Packaging:	in brown 2 ml ampoules under protective gas (N ₂)
	Sterilisation:	20 minutes at 120°C

Example 9

25

Suppositories containing 2.5 μ g of (-)-cimaterol

Composition:

30 1 suppository contains:

	Active substance	0.025 mg
	Suppository mass (e.g. Witepsol W 45)	<u>1,699.975 mg</u>
		1,700.000 mg

35

Method of preparation:

The finely powdered active substance is stirred into the

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molten suppository mass, which has been cooled to 40°C, by means of an immersion homogeniser and at 37°C the mass is poured into slight chilled moulds.

Weight of suppository: 1.7 g

5

Example 10

Syrup containing 2 µg of (-)-cimaterol per 5 ml

10

Composition:

100 ml of syrup contains:

	Active substance	0.04 mg
15	Benzoic acid	0.10 g
	Tartaric acid	1.00 g
	Sugar	50.00 g
	Orange flavour	1.00 g
	Red food colouring	0.05 g
20	Distilled water	to 100.00 ml

Method of preparation:

About 60 g of distilled water are heated to 80°C and the benzoic acid, tartaric acid, active substance, colouring and sugar are successively dissolved therein. After the solution has been cooled to ambient temperature the flavouring is added and the mixture is made up to the volume specified. The syrup is filtered.

30

Example 11

Aerosol spray delivering 1 µg of (-)-cimaterol per activation

35

Composition:

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Active substance	0.00025 mg
Soya lecithin	0.05000 mg
Propellant gas mixture 11/12/114 (23:54:23)	<u>69.94975 mg</u>
	70.00000 mg

5

Example 12

Aerosol spray delivering 1 µg of (-)-cimaterol per
activation

10

Composition:

Active substance	0.00025 mg
99.9% pure ethanol	0.87500 mg
Propellant gas mixture 11/12/114 (23:54:23)	<u>69.12475 mg</u>
	70.00000 mg

15

Example 13

20

Solution for inhalation containing 59 mg of (-)-
cimaterol per 100 ml

25 Composition:

Active substance	0.59 mg
Sodium chloride	900.00 mg
Benzalkonium chloride	25.00 mg
Distilled water	to 100.00 ml

30

Method of preparation:

The active substance, common salt and benzalkonium
chloride are dissolved in distilled water and then
filtered to remove any pathogens.

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Example 14

Complete food II for fattening pigs

5	Barley	379 g/kg
	Wheat flour	200 g/kg
	Manioc flour	135 g/kg
	Broad beans	100 g/kg
	Shredded rape extract	100 g/kg
10	Edible fat	65 g/kg
	Lysine-rich mineral feed for pigs	20 g/kg
	Active substance premix	1 g/kg
15	After being carefully mixed in the quantities specified these components yield 1 kg of feed.	

The 1 g of active substance premix contains for example
2 mg of active substance and 0.998 g of corn starch.

20

Example 15

Fattening feed II for broilers

25	Maize	634 g/kg
	Soya bean flour	260 g/kg
	Meatmeal	40 g/kg
	Edible fat	25 g/kg
	Soya oil	17 g/kg
30	Bicalcium phosphate	12 g/kg
	Calcium carbonate	6 g/kg
	Vitamin/mineral mix	5 g/kg
	Active substance premix	1 g/kg
35	After being carefully mixed in the quantities specified, these components yield 1 kg of feed.	

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The 1 g of active substance premix contains for example 1 mg of active substance and 0.999 g of corn starch.

Example 16

5

Concentrated feed for cattle

	Shredded sugar beet	600.0 g/kg
	Maize gluten	100.0 g/kg
10	Malt germs	50.0 g/kg
	Soya bean flour	35.0 g/kg
	Wheat	119.0 g/kg
	Molasses	60.0 g/kg
	Feed phosphates	12.0 g/kg
15	Calcium carbonate	2.5 g/kg
	Salt	5.0 g/kg
	Minerals	10.0 g/kg
	Vitamin premix	5.5 g/kg
	Active substance premix	1.0 g/kg

20

When carefully mixed in the quantities specified, these components yield 1 kg of feed.

25 The 1 g of active substance premix contains for example 2 mg of active substance and 0.998 g of corn starch.

Example 17

Fattening feed for lambs

30

	Barley	690 g/kg
	Soya bean flour	100 g/kg
	Maize	159 g/kg
	Molasses	30 g/kg
35	Vitamin/mineral mix	20 g/kg
	Active substance premix	1 g/kg

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When carefully mixed in the quantities specified, these components yield 1 kg of feed.

5 The 1 g of active substance premix contains for example
2 mg of active substance and 0.998 g of corn starch.

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The claims defining the invention are as follows:

1. (-)-1-(4'-Amino-3'-cyanophenyl)-2-isopropylaminoethanol and acid addition salts thereof or any mixture thereof with the corresponding (+) isomer and acid-addition salts thereof in which the (-)-isomer is present in excess over the (+)-isomer.
5
2. A compound as claimed in claim 1 which is substantially optically pure.
3. A compound as claimed in claim 1, which has an optical purity of at least ee = 90%.
- 10 4. A compound as claimed in claim 1 which has an optical purity of at least ee = 94%.
5. Physiologically acceptable acid addition salts of a compound as claimed in any one of claims 1 to 4.
- 15 6. Pharmaceutical compositions comprising as active ingredient at least one compound as claimed in any one of claims 1 to 4 or a physiologically acceptable acid addition salt thereof in association with one or more pharmaceutically acceptable carriers, diluents or excipients.
7. Compositions as claimed in claim 6 substantially as herein described.
8. Compositions as claimed in claim 6 substantially as herein described
20 with reference to the Examples.
9. A method of treatment of obesity, obstructive lung disorders, allergic bronchial asthma, spastic bronchitis, inflammation or premature labour in a subject which comprises administering to said subject an effective amount of a compound as claimed in any one of claims 1 to 4 or a physiologically acceptable acid addition salt thereof.
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10. A process for the preparation of a pharmaceutical composition as claimed in claim 6, characterised in that a compound as claimed in any one of claims 1 to 5 is admixed with one or more pharmaceutically acceptable carriers, diluents or excipients by a non-chemical method.

11. The use of a compound as claimed in any one of claims 1 to 4, or a physiologically acceptable acid addition salt thereof as a performance enhancing agent in animals.

12. Animal feeds and premixes for producing animal feeds, containing at least one compound as claimed in any one of claims 1 to 5.

13. Animal feeds and premixes as claimed in claim 12 substantially as herein described.

14. Animal feeds and premixes as claimed in claim 12 substantially as herein described with reference to the Examples.

15. A performance enhancing agent for animals, containing at least one compound according to any one of claims 1 to 5 in association with one or more extenders, diluents, nutrients and other adjuvants.

16. A process for preparing a performance enhancing agent as claimed in claim 15, characterised in that at least one compound as claimed in any one of claims 1 to 5 is mixed with one or more extenders, diluents, nutrients and other adjuvants.

17. A process for the preparation of (-)-1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol and (+)-1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol,

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characterised in that 1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol is crystallised by dissolving 1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol and at least 2 equivalents of an optically active dibasic auxiliary acid in a suitable solvent, whilst the temperature should not fall below a desired predeterminable temperature range characteristic of each auxiliary acid, the crystallised diastereomeric salt corresponding to the desired enantiomeric base is separated off, then the desired enantiomeric base is liberated and subsequently, if desired, converted into a physiologically acceptable acid addition salt thereof.

18. A process as claimed in claim 17 wherein from 2 to 7 equivalents of the auxiliary acid are used.

19. A process as claimed in claim 17 or claim 18 wherein from 2 to 4 equivalents of the auxiliary acid are used.

20. A process as claimed in any one of claims 17 to 19 wherein the auxiliary acid used is selected from (-)-0,0'-dibenzoyl-L-tartaric acid, (+)-0,0'-dibenzoyl-D-tartaric acid, (-)-0,0'-ditolyl-L-tartaric acid or (+)-0,0'-ditolyl-D-tartaric acid.

21. A process as claimed in any one of claims 17 to 20 wherein (+)-0,0'-dibenzoyl-L-tartaric acid is used as the auxiliary acid and the process is performed at a temperature above 25°C.

22. Diastereomeric salts of 1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol with an optically active dibasic auxiliary acid.

23. Diastereomeric salts as claimed in claim 22 wherein the auxiliary acid is selected from (-)-0,0'-dibenzoyl-

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L-tartaric acid, (+)-0,0'-dibenzoyl-D-tartaric acid, (-)-0,0'-ditolyl-L-tartaric acid or (+)-0,0'-ditolyl-D-tartaric acid.

5 24. (-)-1-(4'-Amino-3'-cyano-phenyl)-2-isopropylamino-ethanol-(+)-0,0'-dibenzoyl-D-hydrogen tartrate.

10 25. A process for the preparation of the diastereomeric salts according to claim 22, characterised in that 1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol is dissolved together with at least 2 equivalents of an optically active dibasic auxiliary acid in a suitable solvent, the temperature not being allowed to fall below a desired predeterminable temperature range which is
15 characteristic of each auxiliary acid, the crystallised diastereomeric salt thereby obtained being separated off.

20 26. A process as claimed in claim 25 wherein the auxiliary acid is selected from (-)-0,0'-dibenzoyl-L-tartaric acid, (+)-0,0'-dibenzoyl-D-tartaric acid, (-)-0,0'-ditolyl-L-tartaric acid or (+)-0,0'-ditolyl-D-tartaric acid.

25 27. A process as claimed in claim 25 or claim 26, wherein the process is performed at a temperature above 20°C.

30 28. A process as claimed in claim 27 wherein the process is performed at a temperature between 25 and 30°C.

35 29. A process as claimed in any one of claims 17 to 21 and 25 to 28 substantially as herein described.

30. A process as claimed in any one of claims 17 to 21 and 25 to 28 substantially as herein described with reference to the Examples.

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REPLACED

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SEPARATION OF ENANTIOMERS OF CIMATEROL, (-)-CIMATEROL
AND THE USE THEREOF AS PHARMACEUTICAL COMPOSITION OR
AS PERFORMANCE ENHANCERS

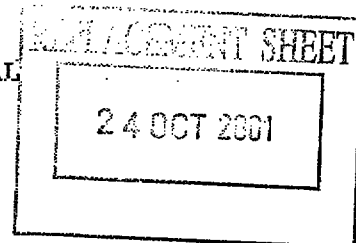
Abstract

5 The invention relates to the separation of
enantiomers of cimaterol, (-)-cimaterol, the addition
salts thereof and processes for preparing them and their
use as pharmaceutical compositions or performance
enhancers.

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(-)-CIMATEROL AND ITS USES IN PHARMACEUTICAL
COMPOSITIONS OR AS PERFORMANCE
ENHANCERS



5 The present invention relates to an improved process for the resolution of racemic cimaterol, to (-)-cimaterol and derivatives thereof, to pharmaceutical compositions containing them, and to their use as performance enhancing agents.

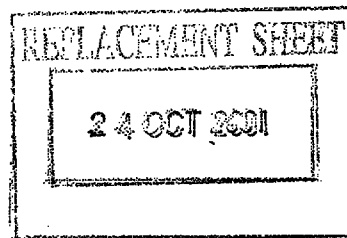
US-A-4,119,710 describes inter alia the racemate 1-(4'-amino-3'-cyano-phenyl)-2-isopropylamino-ethanol (generic name: cimaterol) and its pharmaceutical properties. Thus, the compounds described in
10 US-A-4,119,710 have, in addition to their analgesic and uterus-spasmolytic effects and their antispasmodic effects on the striated musculature, in particular β_2 -mimetic and/or β_1 -blocking effects, with one or other effect being dominant depending on the substitution. It
15 is also established in US-A-4,119,710 that the d-(+)-compounds have in particular a selective effect on the β_1 -receptors and the l-(-)-compounds have a preferred effect on the β_2 -receptors.

Moreover, US-A-4,407,819, inter alia describes the
20 performance-enhancing effect of cimaterol in animals.

It is also known that, normally, one of the two enantiomers of a racemate is more effective than the other enantiomer. For this reason, the present application is based on the objective of resolving the
25 racemate known from the literature into its new enantiomers.

Surprisingly, difficulties were encountered in solving this problem, even though US-A-4,119,70 has already described two methods of separating the
30 racemates of these compounds, namely

a) the resolution of a mixture of diastereomeric



(-)-CIMATEROL AND ITS USES IN PHARMACEUTICAL
COMPOSITIONS OR AS PERFORMANCE
ENHANCERS

Abstract

5 The invention relates to the separation of
enantiomers of cimaterol, (-)-cimaterol, the addition
salts thereof and processes for preparing them and their
use as pharmaceutical compositions or performance
enhancers.