(11) 1 579 879

PATENT SPECIFICATION

1 579 879

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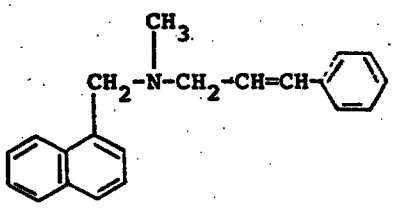
(72) Inventor DANIEL BERNEY

(54) CINNAMYL NAPHTHALENE DERIVATIVE

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, 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:—

Cinnamyl Naphthalene Derivative

This invention provides compounds of formula I,

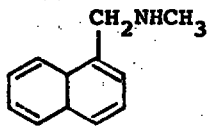


I

It will be appreciated that the compounds of the invention may be in the form of *cis* or *trans* isomers, or isomeric mixtures. It is to be understood that the invention is not intended to be limited to any particular isomeric form, although the *trans* isomeric form is preferred.

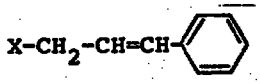
The invention also provides processes for the production of compounds of formula I, comprising

a) reacting the compound of formula II,



II

with a compound of formula III,

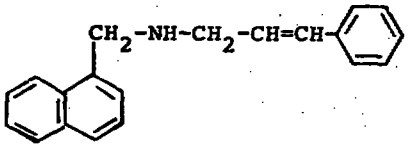


III

in which X is a leaving group,

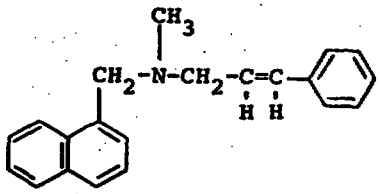
SPECIFICATION AMENDED - SEE ATTACHED SLIP

b) methylating a compound of formula IV,



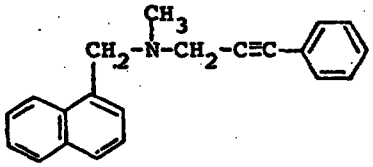
IV

c) producing a compound of formula Ia,



Ia

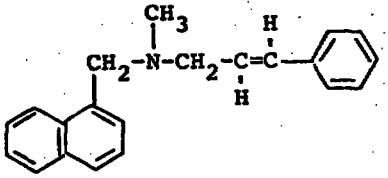
by hydrogenating a compound of formula V,



V

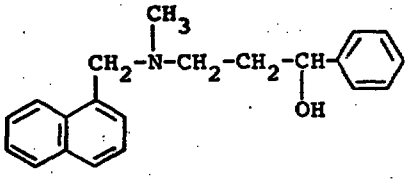
or

d) producing a compound of formula Ib,



Ib

by splitting off water from a compound of formula VI,



VI

As indicated, process c) leads to the products of the invention predominantly in *cis* isomeric form while process d) leads to the products predominantly in *trans* isomeric form. The isomeric form of the products of processes a) and b) depends on the isomeric form of the starting material which can therefore be selected in accordance with desired form of the product.

Process a) is suitably effected in an inert solvent, such as a lower alkanol, e.g. ethanol, optionally in aqueous admixture, an aromatic hydrocarbon, e.g. benzene or toluene, a cyclic ether, e.g. dioxane, or a carboxylic acid dialkylamide, e.g. dimethylformamide. The process may conveniently be carried out at a temperature of from room temperature to the boiling temperature of the reaction mixture, preferably at room temperature and is suitably effected in the presence of an acid binding agent, such as an alkali metal carbonate, e.g. sodium carbonate. The leaving group X in the compounds of formula III is suitably halogen, in particular chlorine or bromine, an organic sulphonyloxy group with 1 to 10 carbon atoms, e.g. C_{1-10}, preferably C_{1-4}, alkyl sulphonyloxy, in particular methylsulphonyloxy, or C_{1-3} alkylphenylsulphonyloxy, e.g. tosyloxy.

Process b) may be effected in manner conventional for the methylation of secondary amines, for example by direct methylation with a methylating agent, for

example a halide or sulphate, or by reductive methylation, in particular by reaction with formaldehyde and subsequent or simultaneous reduction. Reductive methylation is suitably effected in an inert organic solvent, such as a lower alkanol, e.g. methanol, and at an elevated temperature, in particular at the boiling temperature of the reaction medium. The subsequent reduction may be effected with, for example, a complex metal hydride reducing agent, e.g. $NaBH_4$ or $LiAlH_4$. The reduction may also be effected simultaneously to the methylation, for example by use of formic acid which may serve both as reducing agent and as a reaction medium.

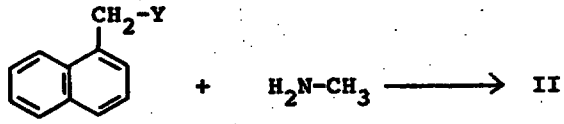
Process c) is conveniently effected in an inert solvent, e.g. a lower alkanol, such as methanol or ethanol, a chlorinated hydrocarbon, e.g. methylene chloride, pyridine or an ester, such as ethylacetate. The hydrogenation may be carried out in conventional manner, for example employing a catalyst, such as palladium or platinum, suitably on a carrier such as $BaSO_4$ or $CaCO_3$. The catalyst may also be partially inactivated, e.g. by pretreatment with lead salts (Lindlar catalysts).

Process d) may suitably be carried out using a conventional dehydrating agent, e.g. an inorganic acid, such as hydrochloric acid or sulphuric acid, an organic acid, such as methane-, benzene- or *p*-toluenesulphonic acid, or anhydrides or halides thereof. The process may suitably be effected in an inert solvent although when an acid halide is employed as dehydrating agent, an excess thereof may be used to provide a reaction medium. An acid binding agent, e.g. a tertiary amine, such as trialkylamine or pyridine, is suitably present and the reaction temperature may, for example, range from −10° to +180°C. The process may also be effected using polyphosphoric acid. In this case, the reaction temperature is conveniently from 80° to 120°C and an inert solvent, an inorganic acid, e.g. phosphoric acid or an organic acid, such as acetic acid, or an excess of the polyphosphoric acid, is suitably employed to provide a reaction medium.

The resulting compound of formula I may be isolated and purified using conventional techniques. Where the process leads to mixtures of isomers, the individual isomers may be separated in conventional manner. Where required, free base forms thereof may be converted into acid addition salt forms in conventional manner, or *vice versa*.

The starting materials for use in the processes of the invention may, for example, be produced by the following reactions:

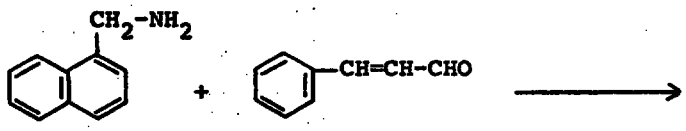
(i)



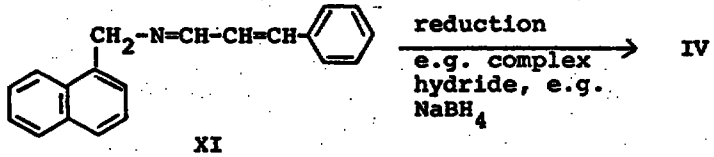
VII VIII

Y = halogen

(ii)

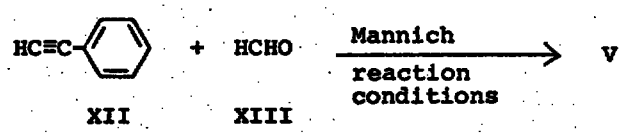


IX X

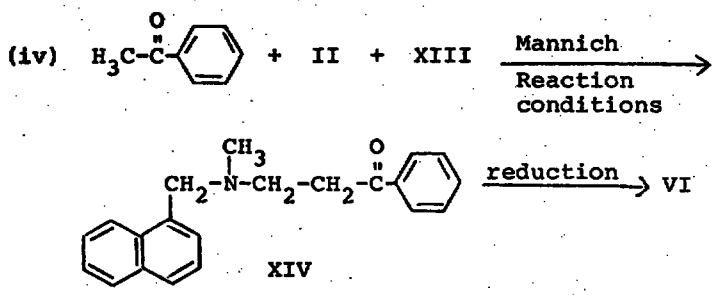


XI

(iii)



XII XIII

(iv) 

These processes may be carried out in conventional manner.

The starting materials of formulae III, VII, VIII, IX, X, XII, XIII and XV are either known or may be produced in conventional manner from available materials.

The compounds of formula I possess chemotherapeutic activity. In particular, they are indicated for use as antimycotic agents, as indicated *in vitro* in various families and types of mycetes, including Trichophyton quinkeanum, Aspergillus fumigatus, Microsporum canis, Sporotrychium schenkii and Candida albicans, at concentrations of, for example, 0.1 to 100 μg/ml, and *in vivo* in the experimental skin mycosis model in quinea pigs. In this model, guinea pigs are infected by sub-cutaneus application of Trichophyton quinkeanum. The test substance is administered once daily for 7 days beginning 24 hours after the infection either by local application by rubbing the test substances (taken up in polyethylene glycol) on the skin surface, or perorally or sub-cutaneously, the test substance being administered as a suspension. The activity is shown on local application at concentrations of for example 0.1 to 5%, in particular 0.1 to 0.5%. The oral activity is shown at dosages of, for example, 50 to 100 mg/kg.

An indicated suitable daily dosage is in the range of from 500 to 2000 mg, suitably administered in divided doses of from 125 to 1000 mg, two to four times daily, or in retard form.

The compounds may be used in free base form or in the form of chemotherapeutically acceptable acid addition salts; suitable acids for salt formation include inorganic acids, such as hydrochloric acid, and organic acids, such as naphthaline - 1,5 - disulphonic acid and fumaric acid (particularly to form the hydrogen fumarate).

The compounds may be admixed with conventional chemotherapeutically acceptable diluents and carriers, and, optionally, other excipients and administered in such forms as tablets or capsules. The compounds may alternatively be administered topically in such conventional forms as ointments or creams. The concentration of the active substance in such topical application forms will of course vary depending on the compound employed, the treatment desired and the nature of the form etc. In general, however, satisfactory results are obtained at concentrations of from 0.05 to 5, in particular 0.1 to 1 wt.%.

The following Examples illustrate the invention. All temperatures are in °C.

EXAMPLE 1

Trans-N-(cinnamylmethyl)-N-methyl-(1-naphthylmethyl)amine

[Process a)]

To a mixture of 1.42 g of methyl - (1 - naphthylmethyl)amine hydrochloride, 2.89 g of sodium carbonate and 10 ml of dimethyl formamide is added, at room temperature, 1.25 g of cinnamyl chloride, dropwise. After 18 hours stirring, at room temperature, the mixture is filtered and the filtrate is evaporated *in vacuo*. The residue is dissolved in toluene and, after drying over sodium sulphate, evaporated to obtain the heading compound, b.p. 162—167° (0.015 Torr).

The free base may be converted, with isopropanolic hydrogen chloride solution, into the hydrochloride form, m.p. 177° (from propanol).

EXAMPLE 2

Trans-N-(cinnamylmethyl)-N-methyl-(1-naphthylmethyl)amine

[Process b)]

a) *Trans*-N-(cinnamylmethyl)-(1-naphthylmethyl)amine

A mixture of 10 g of 1-aminomethylnaphthaline, 8.51 g of cinnamaldehyde and 150 ml of benzene is heated in a reaction vessel equipped with a water separator, at reflux, until the theoretical amount of water has been separated. The mixture is

cooled and evaporated to dryness. 5.78 g of the resulting Schiff's base in 60 ml of methanol, after warming to 50°, is mixed, with vigorous stirring, with 1.51 g of solid $NaBH_4$, portionwise, and the mixture is refluxed for 20 minutes. The resulting mixture may be used as such in the next stage. The title compound can be isolated as an oil, however, by evaporation and dividing the residue between aqueous $NaHCO_3$ solution and chloroform, drying the organic phase and evaporation.

b) *Trans*-N-(cinnamylmethyl)-N-methyl-(1-naphthylmethyl)amine

(i) The reaction mixture resulting from step a) is refluxed, after addition of 16 ml of 37% aqueous formaldehyde solution, for 1-1/2 hours. The mixture is cooled and mixed, portionwise, in an ice bath and with vigorous stirring, with 7.6 g of $NaBH_4$. After 4 hours, the residue is centrifugally divided between aqueous $NaHCO_3$ solution and chloroform. The organic phase is dried and centrifuged to obtain the heading compound as an oil, m.p. hydrochloride form: 177°.

(ii) The oil resulting from step a) (2.9 g) is refluxed with 3.3 g of formic acid (98—100%) and 0.81 ml of 37% aqueous formaldehyde mixture is evaporated *in vacuo*, and the residue divided between chloroform and aqueous $NaHCO_3$ solution. The aqueous phase is washed with brine, dried and evaporated to obtain the heading compound, m.p. hydrochloride form: 177°.

EXAMPLE 3

Cis-N-(cinnamylmethyl)-N-methyl-1-naphthylmethyl)amine [Process c)]

a) N-(3-phenylpropargyl)-N-methyl-(1-naphthylmethyl)amine

15 g of N - methyl - (1 - naphthylmethyl)amine, 8.97 g of phenylacetylene, 2.61 g of paraformaldehyde and 1.1 g of zinc chloride are refluxed in absolute dioxane, in the absence of water, for 3 hours. The mixture is then evaporated and the residue is divided between saturated aqueous $NaHCO_3$ solution and chloroform. The organic phase is dried and evaporated and the crude product is recrystallised from propanol/ether, m.p. 140—142°.

b) *Cis*-N-(cinnamylmethyl)-N-methyl-(1-naphthylmethyl)amine

2.68 g of N - (3 - phenylpropargyl) - N - methyl - (1 - naphthylmethyl)amine are dissolved in 50 ml of absolute pyridine. The solution is hydrogenated employing 150 mg of $Pd/BaSO_4$ (5%) until the theoretical amount of hydrogen has been taken up. The catalyst is filtered off and the mixture evaporated. The oily residue is chromatographed over silica gel using benzene/ethyl acetate (9:1) as eluant, to obtain the heading compound as an oil.

NMR ($CDCl_3$/RT/TMS): δ=8.3 (m, 1 H), δ=7.2—8.0 (m, 11 H), δ=6.60 (m, 1 H), δ=5.90 (m, 1 H), δ=3.90 (s, 2 H), δ=3.35 (m, 2 H), δ=2.25 (s, 3 H), [s=singlet, m=multiplet].

EXAMPLE 4

Trans-N-(cinnamylmethyl)-N-methyl-(1-naphthylmethyl)amine [Process d)]

a) N-Methyl-(1-naphthylmethyl)amine

17.6 g of 1 - chloromethyl - naphthalene in 40 ml of absolute ethanol is added, dropwise, at 0° to 5°, to 100 ml of a 33% solution of methylamine in absolute ethanol. The mixture is allowed to stand overnight and is then evaporated. The residue is taken up in a little chloroform and washed with 100 ml of 1 N sodium hydroxide solution and with water. The organic phase is dried and evaporated to dryness. The residue is distilled at 0.01 Torr to obtain the heading compound as main fraction, b.p. 85°—87°.

b) β-[(N-Methyl-(1-naphthylmethyl)amino]ethylphenylketone

17.1 g of N - methyl - (1 - naphthylmethyl)amine are dissolved in 200 ml of methanol and 10 ml of concentrated hydrochloric acid, 12 g of acetophenone and 100 ml of 35% formaldehyde solution are sequentially added. The mixture is refluxed for 1-1/2 hours, with stirring, cooled diluted with 1 litre of water, made alkaline with 30% sodium hydroxide solution and exhaustively extracted with chloroform. The organic extract is dried and evaporated to dryness and the oils residue is dissolved in petroleum ether and allowed to crystallise in the cold, to obtain the heading compound.

c) 3-[N-Methyl-(1-naphthylmethyl)amino]-1-phenyl)propan-1-ol

To a solution of 7.17 g of β - [N - methyl - (1 - naphthylmethyl)amino]ethyl - phenyl ketone in 400 ml of methanol is added, portionwise, at room temperature, 1

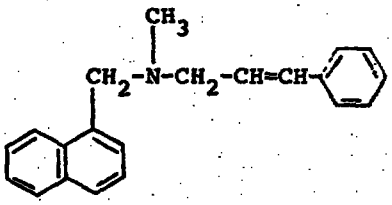
g of $NaBH_4$. The mixture is stirred for 15 minutes and the solvent is then evaporated off. The oily residue is taken up in chloroform and washed with water. The organic phase is dried and evaporated to dryness to obtain the crude heading product which is used as such in the next stage.

d) *Trans*-N-(cinnamylmethyl)-N-methyl-(1-naphthylmethyl)amine

8.03 g of 3 - [N - methyl - (1 - naphthylmethyl)amino] - 1 - phenyl - propan - 1 - ol are refluxed, with stirring, in 300 ml of 5 N hydrochloric acid for 1-1/2 hours. The mixture is isolated by addition of ice, made alkaline with 30% sodium hydroxide solution and exhaustively extracted with chloroform. The chloroform extract is dried over sodium sulphate, filtered and evaporated to dryness. The oily residue is dissolved in absolute ethanol and made acid with etheric hydrochloric acid. After addition of ether, the heading compound is obtained, m.p. hydrochloride salt form 177°.

WHAT WE CLAIM IS:—

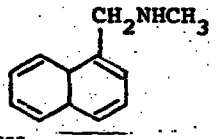
1. A process for the production of a compound of formula I,



I

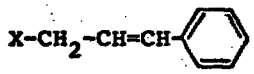
comprising

a) reacting the compound of formula II,



II

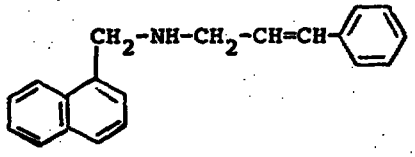
with a compound of formula III,



III

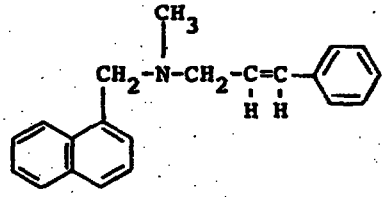
in which X is a leaving group,

b) methylating a compound of formula IV,



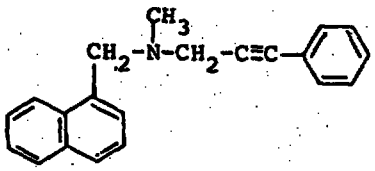
IV

c) producing a compound of formula Ia,



Ia

by hydrogenating a compound of formula V,



V

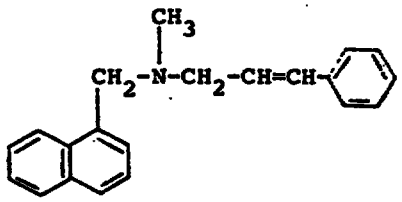
g of $NaBH_4$. The mixture is stirred for 15 minutes and the solvent is then evaporated off. The oily residue is taken up in chloroform and washed with water. The organic phase is dried and evaporated to dryness to obtain the crude heading product which is used as such in the next stage.

d) *Trans*-N-(cinnamylmethyl)-N-methyl-(1-naphthylmethyl)amine

8.03 g of 3 - [N - methyl - (1 - naphthylmethyl)amino] - 1 - phenyl - propan - 1 - ol are refluxed, with stirring, in 300 ml of 5 N hydrochloric acid for 1-1/2 hours. The mixture is isolated by addition of ice, made alkaline with 30% sodium hydroxide solution and exhaustively extracted with chloroform. The chloroform extract is dried over sodium sulphate, filtered and evaporated to dryness. The oily residue is dissolved in absolute ethanol and made acid with etheric hydrochloric acid. After addition of ether, the heading compound is obtained, m.p. hydrochloride salt form 177°.

WHAT WE CLAIM IS:—

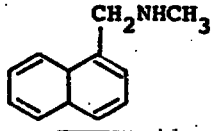
1. A process for the production of a compound of formula I,



I

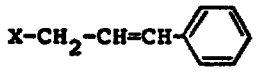
comprising

a) reacting the compound of formula II,



II

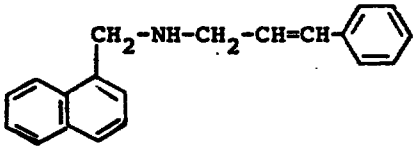
with a compound of formula III,



III

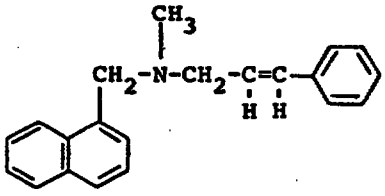
in which X is a leaving group,

b) methylating a compound of formula IV,



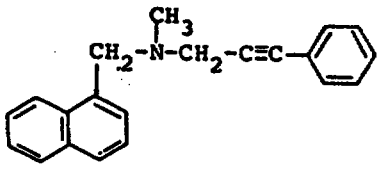
IV

c) producing a compound of formula Ia,



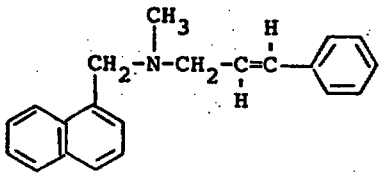
Ia

by hydrogenating a compound of formula V,



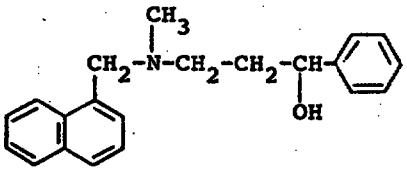
V

d) producing a compound of formula Ib,



Ib

by splitting off water from a compound of formula VI,



VI

2. A process for the production of a compound of formula I, stated in Claim 1, substantially as herein described with reference to any one of the Examples.

3. A compound of formula I, stated in Claim 1, whenever produced by a process according to Claim 1 or 2.

4. A compound of formula I, stated in Claim 1.

5. *Trans* - N - (cinnamylmethyl) - N - methyl - (1 - naphthylmethyl)amine.

6. *Cis* - N - (cinnamylmethyl) - N - methyl - (1 - naphthylmethyl)amine.

7. *Trans* - N - (cinnamylmethyl) - N - methyl - (1 - naphthylmethyl)amine hydrochloride.

8. A compound according to any one of Claims 3 to 6, in free base form.

9. A compound according to any one of Claims 3 to 6, in acid addition salt form.

10. A chemotherapeutic composition comprising a compound according to any one of Claims 3 to 6, in free base or chemotherapeutically acceptable acid addition salt form, in association with a chemotherapeutically acceptable diluent or carrier.

11. A chemotherapeutic composition comprising *trans* - N - (cinnamylmethyl) - N - methyl - (1 - naphthylmethyl)amine, in free base or chemotherapeutically acceptable acid addition salt form, in association with a chemotherapeutically acceptable diluent or carrier.

12. A chemotherapeutic composition according to Claim 11, in which the *trans* - N - (cinnamylmethyl) - N - methyl - (1 - naphthylmethyl)amine is in hydrochloride salt form.

13. A chemotherapeutic composition according to Claim 11 or 12, in a form suitable for oral administration.

14. A chemotherapeutic composition according to Claim 11 or 12, in a form suitable for topical administration.

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The following amendments were allowed under Section 29 on 8 September 1981:

Page 4, lines 37 and 48, Page 5, lines 7, 29 and 40, Page 6, line 5, Page 7, lines 10, 11, 12, 22 and 26, *for* (cinnamylmethyl)-N-methyl- *read* cinnamyl-N-methyl-N-

Page 4, line 50, *for* (cinnamylmethyl)- *read* cinnamyl-N-

Page 5, line 20, *for* (cinnamylmethyl)-N-methyl- *read* cinnamyl-N-methyl-N-(

Page 5, lines 22, 30 and 60, Page 6, line 6, *after* methyl- *insert* N-

Page 5, lines 50 and 59, *after* Methyl- *insert* N-

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