

PATENT SPECIFICATION

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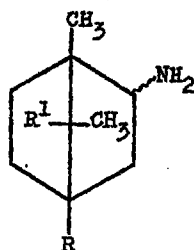
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(54) AMINES AND A PROCESS FOR THE MANUFACTURE THEREOF

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESellschaft, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to amines and a process for the manufacture thereof. More particularly, the invention is concerned with bornanamine derivatives and a process for the manufacture thereof.

The bornanamine derivatives provided by the present invention are compounds of the general formula



(I)

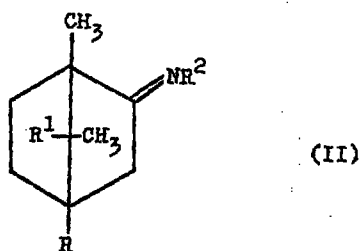
, wherein R represents a lower alkyl group or an optionally substituted phenyl group and R¹ represents a lower alkyl group — provided that at least one of R and R¹ represents a methyl group, and acid addition salts thereof.

It will be appreciated that the term "lower alkyl" as applied to the symbols R and R¹ in this description and in the accompanying claims means a straight-chain or branched-chain alkyl group containing 1 to 6 carbon atoms such as, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert.butyl, amyl and hexyl. Examples of substituents which may be present on the phenyl group are halogen (preferably chlorine or bromine), amino, hydroxy or lower alkoxy. A substituent is preferably present in the *p*-position. The term "lower alkoxy" means a lower alkyl ether group in which the lower alkyl moiety has the significance given earlier.

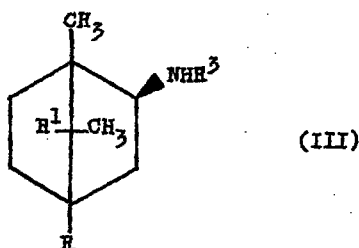
One preferred class of bornanamine derivatives provided by this invention comprises compounds of formula I in which R and R¹ each represent a methyl group, and acid addition salts thereof. Another preferred class of bornanamine derivatives provided by this invention comprises compounds of formula I in which R¹ represents a methyl group and R represents a propyl, phenyl, *p*-aminophenyl or *p*-methoxyphenyl group, and acid addition salts thereof. The especially preferred bornanamine derivatives provided by the invention are rac. 1,4,7,7-tetramethyl-2-endo-norbornanamine, rac. 4-propyl-2-exo-bornanamine, rac. 4-phenyl-2-exo-bornanamine, rac. 4-(*p*-aminophenyl)-

2-exo-bornanamine and rac. 4-(p-methoxyphenyl)-2-exo-bornanamine and acid addition salts thereof.

According to the process provided by the present invention, the bornanamine derivatives aforesaid, that is to say, the compounds of formula I hereinbefore and their acid addition salts, are manufactured by reducing a compound of the general formula



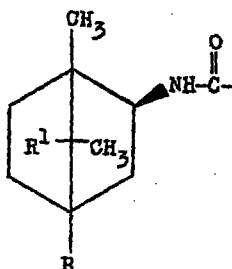
, wherein R and R¹ have the significance given earlier and R² represents a hydrogen atom or a hydroxy group, or hydrolysing a compound of the general formula



, wherein R and R¹ have the significance given earlier and R³ represents a hydrolytically-removable group,

and, if desired, resolving a stereoisomer mixture or diastereomer mixture obtained and, also if desired, converting a base obtained into an acid addition salt thereof.

The expression "hydrolytically-removable group" is used in this description and in the accompanying claims to mean all such groups which can be formed in the course of the Ritter reaction described hereinafter; for example, alkanoyl, alkenoyl, alkynoyl, aroyl, aralkanoyl, aralkenoyl and aralkynoyl groups, and thiocarboxylic acid ester groups. In this connection, the alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl and aralkynyl moieties of the aforementioned acyl groups can, in turn, be substituted by a group of the general formula



wherein R and R¹ have the significance given earlier.

It will be appreciated that this latter substitution gives rise to a dimer of a compound of formula III.

The reduction of a compound of formula II in which R² represents a hydroxy group (i.e. an oxime) to give a compound of formula I can be carried out in a manner known for the reduction of oximes to primary amines. Suitable reduction methods comprise, for example, catalytic hydrogenation. This is expediently carried out in the presence of ammonia or ammonium carbonate. and in an inert organic solvent such

as, for example, an alcohol. Especially suitable catalysts are Raney catalysts (preferably Raney-nickel), palladium/charcoal or platinum. Depending on the nature of the catalyst, the catalytic hydrogenation is expediently carried out at elevated temperature and at elevated pressure. If the hydrogenation is carried out without elevating the pressure, it is expediently carried out at a temperature of from about room temperature up to the reflux temperature of the hydrogenation mixture, preferably at the reflux temperature. If the hydrogenation is carried out under increased pressure, it can be carried out, for example, in alcohol with Raney-nickel, preferably at a temperature of about 110°C and a pressure of about 170 atmospheres.

Further suitable reduction methods comprise, for example, reduction with nascent hydrogen (e.g. with sodium in alcohol, sodium amalgam in dilute acetic acid or zinc in glacial acetic acid or in hydrochloric acid) or with complex metal hydrides (e.g. alkali metal aluminium hydrides such as lithium aluminium hydride) or with sodium dihydro-bis-(2-methoxyethoxy)-aluminate.

The preferred oxime starting materials are those in which R¹ represents a methyl group and R represents a methyl, propyl, phenyl, *p*-aminophenyl or *p*-methoxyphenyl group.

The reduction of a compound of formula II in which R² represents a hydrogen atom (i.e. an imine) to give a compound of formula I can be carried out in a manner known *per se*. In particular, the reduction of an imine of formula II can be carried out in the manner described hereinbefore for the reduction of an oxime of formula II.

One preferred class of imine starting materials comprises those in which R and R¹ each represent a methyl group. Another preferred class of imine starting materials comprises those in which R¹ represents a methyl group and R represents a propyl, phenyl, *p*-aminophenyl or *p*-methoxyphenyl group.

The hydrolysis of a compound of formula III hereinbefore can be carried out in a manner known *per se*; for example, by heating with an acid or a base, if necessary in the presence of an organic solvent such as an alcohol (e.g. methanol, ethanol or ethyleneglycol). The hydrolysis is preferably carried out with an acid, conveniently at the reflux temperature of the hydrolysis mixture.

One preferred class of starting materials of formula III comprises those in which R and R¹ each represent a methyl group. Another preferred class of starting materials of formula III comprises those in which R¹ represents a methyl group and R represents a propyl, phenyl, *p*-aminophenyl or *p*-methoxyphenyl group.

The compounds of formula I hereinbefore occur in two diastereomeric forms, namely in the *exo* and in the *endo* form. Depending on the nature of the means employed for the reduction of the oxime group or the imine group in a compound of formula II there is obtained a mixture of both forms or chiefly the *endo* or the *exo* form.

Thus, for example, where the reduction of a compound of formula II is carried out using sodium in alcohol there is chiefly obtained the *endo* form, where the reduction is carried out using lithium aluminium hydride there is obtained the practically pure *exo* form and where the reduction is carried out by catalytic hydrogenation in the presence of Raney-nickel there is obtained a mixture of the *exo* and the *endo* form in a ratio of about 3:7.

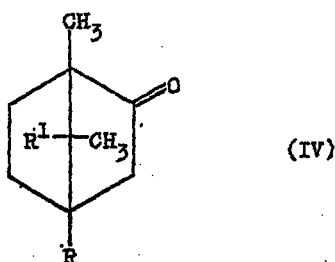
Where a mixture of the two diastereomeric forms is obtained, these forms can be separated from each other in a known manner; for example, on the basis of the different rates of crystallisation and/or different solubilities of various salts, especially the acetates.

The compounds of formula I hereinbefore are chiral and are therefore obtained in the form of racemates. These racemates can be resolved into the optical antipodes according to methods which are known *per se*; for example, by fractional crystallisation of the salts with optically active acids.

The compounds of formula I hereinbefore are bases and can be converted into acid addition salts by treatment with inorganic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid, and with organic acids such as acetic acid, tartaric acid, maleic acid, fumaric acid, citric acid, oxalic acid and toluene-sulphonic acids.

The compounds of formula II hereinbefore in which R² represents a hydrogen atom are new. The compounds of formula II hereinbefore in which R² represents a hydroxy group are also new with the exception of those in which R and R¹ each represent a methyl group and those in which R¹ represents a methyl group and R represents a propyl or phenyl group.

The compounds of formula II hereinbefore in which R² represents a hydroxy group can be prepared by heating a compound of the general formula



, wherein R and R¹ have the significance given earlier, with, for example, hydroxylamine hydrochloride and sodium ethylate in ethanol.

The compounds of the formula IV hereinbefore are likewise new with the exception of those in which R¹ represents a methyl group and R represents a methyl, ethyl, propyl or optionally substituted phenyl group.

The compounds of formula IV hereinbefore in which R represents a methyl group, the compounds of formula II hereinbefore in which R represents a methyl group and R² represents a hydrogen atom and the compounds of formula III hereinbefore in which R represents a methyl group can be prepared, for example, from fenchone in the manner described hereinafter.

The compounds of formula IV hereinbefore in which R¹ represents a methyl group, the compounds of formula II hereinbefore in which R¹ represents a methyl group and R² represents a hydrogen atom and the compounds of formula III hereinbefore in which R¹ represents a methyl group can be prepared, for example, from camphor in the manner described hereinafter.

Fenchone or camphor is reacted with a metal-organic compound of the general formula



or



, wherein R⁴ represents a methyl or optionally substituted phenyl group, R⁵ represents a lower alkyl group containing 1 to 3 carbon atoms, R⁶ represents a hydrogen atom or a lower alkyl group containing 1 to 4 carbon atoms, M represents the grouping MgX, sodium, potassium or lithium and X represents a halogen atom,

and the reaction product is hydrolysed. The hydrolysis product, if necessary after hydrogenation of any double- or triple-bond which may be present and, if desired, after dehydration, is then converted into the corresponding exo acid amide of formula III by reaction with a cyano compound [Ritter reaction: Org. Reactions: Vol. 17, 213—325 (1969)].

The foregoing exo-acid amide can then be hydrolysed to the corresponding exo amine in a manner known *per se*; for example, by heating with an acid or a base, preferably with an acid and conveniently at the reflux temperature of the hydrolysis mixture.

The foregoing exo amine can be dehydrogenated to the corresponding imine (i.e. a compound of formula II in which R² represents a hydrogen atom); for example, by reaction with tert.butyl hypochlorite in an inert organic solvent such as ether to yield the corresponding N-chloro compound and treatment of this with an inorganic base or an organic base such as, for example, sodium ethylate.

The imine aforesaid can subsequently be hydrolysed to a compound of formula IV in a manner known *per se*; for example, by treatment with a dilute mineral acid.

The compounds of formula IV in which R and R¹ each represent a methyl group can be prepared, for example, starting from fenchone and the compounds of formula IV in which R¹ represents a methyl group and R represents a methyl or phenyl group can be prepared, for example, starting from camphor as follows:

Fenchone or camphor is reacted with a Grignard compound of the general formula



or

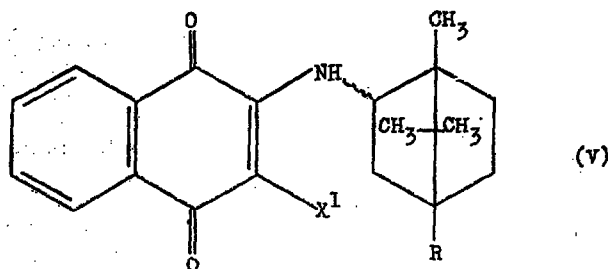


wherein R^0 represents a methyl or phenyl group, R^{10} represents a methyl group and X has the significance given earlier.

The reaction product is hydrolysed, the hydrolysis product is dehydrated and the dehydration product is subsequently treated with glacial acetic acid in the presence of an acid such as, for example, sulphuric acid, hydrochloric acid and the like to yield the corresponding R- or R^1 -substituted isobornyl acetate. This acetate is saponified with alkali and the resulting 4-R-isborneol or 7'- R^1 -norbornanol is oxidised to the 4-R-camphor or 7'- R^1 -norbornanone.

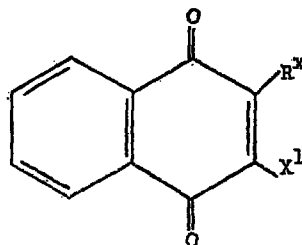
Those compounds of formula III in which R represents a substituted phenyl group can also be prepared, for example, by introducing the substituent into the unsubstituted phenyl ring of the corresponding compound of formula III in a manner known *per se*. Thus, for example, the amino group can be introduced by first introducing the nitro group by nitration with nitric acid and then reducing the nitro group in a manner known *per se*. The hydroxy group can be introduced, also in a manner known *per se*, for example, from a methoxy group by treatment with, for example, hydrobromic acid.

The compounds of formula I hereinbefore in which R^1 represents a methyl group are valuable starting materials in the manufacture of amoebicidally and bacteriostatically active compounds of the general formula



wherein R has the significance given earlier and X^1 represents a hydrogen or halogen atom or a lower alkoxy group.

The compounds of formula I in which R^1 represents a methyl group, can, for example, be converted into the compounds of formula V by reaction with a compound of the general formula



wherein X^1 has the significance given earlier and R^x represents a leaving atom or group.

Furthermore, the compounds of formula I and their acid addition salts have virucidal properties. The compounds and their pharmaceutically acceptable acid addition salts can accordingly be used against virus diseases, especially against influenza viruses.

The compounds of formula I hereinbefore and their acid addition salts also have an anti-cataleptic activity. The compounds and their pharmaceutically acceptable acid addition salts can accordingly be used for the treatment of Parkinsonism.

The anti-cataleptic activity can be determined according to the method of J. R.

Boissier et al [see C. R. Soc. Biol. (Paris), 158, 2025—2028 (1964)]. Thus, for example, in this test rac. 1,4,7,7-tetramethyl-2-endo-norbornanamine hydrochloride has an ED_{50} of 13 mg/kg i.p. and an LD_{50} of 125—250 mg/kg p.o. The corresponding exo compound has an ED_{50} of 20 mg/kg i.p. and LD_{50} of 250—500 mg/kg p.o. Rac. 4-propyl-2-exo-bornylamine hydrochloride has an ED_{50} of 18 mg/kg i.p. and an LD_{50} of 600—1200 mg/kg p.o.

The compounds of formula I hereinbefore and their pharmaceutically acceptable acid addition salts can be used as medicaments in the form of pharmaceutical preparations which contain them in admixture with a compatible pharmaceutical carrier. This carrier can be an organic or inorganic inert carrier material which is suitable for enteral or parenteral application such as, for example, water, gelatin, gum arabic, lactose, starches, magnesium stearate, talc, vegetable oils, polyalkylene glycol or petroleum jelly. The pharmaceutical preparations can be made up in solid form (e.g. as tablets, dragées, suppositories or capsules) or in liquid form (e.g. as solutions, suspensions, syrups or emulsions). The pharmaceutical preparations may be sterilised and/or may contain additives such as preserving, stabilising, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They can also contain further therapeutically valuable substances.

When the compounds of formula I and their pharmaceutically acceptable acid addition salts are used against virus diseases, the enteral and, especially, the oral form of presentation is preferred. Causules or tablets preferably contain about 50 mg to about 100 mg of active ingredient.

The dosages in which the preparations are administered are governed in each case by the requirements of the patients to be treated.

The following Examples illustrate the process provided by the invention:

Example 1

A solution of 140 g of rac. 1,4,7,7-tetramethyl-2-norbornyl oxime in 1700 ml of absolute alcohol is hydrogenated in the presence of 1.4 g of ammonium carbonate and 14 g of Raney-nickel at a hydrogen pressure of 170 atmospheres and at a temperature of 110°C for 5 hours (including heat-up time). The catalyst is subsequently separated off and the solution is made acidic to Congo-red with alcoholic hydrochloric acid and concentrated under reduced pressure.

The residue is crystallised from alcohol/ether to yield 130.6 g of crude hydrochloride salt having a melting point of over 300°C which are dissolved in water and treated with the calculated amount of sodium hydroxide to release the free amines. The base which separates out is taken up in ether and the ether solution is washed with water, dried over sodium sulphate, filtered and concentrated to yield 117.4 g of crude base nuclear magnetic resonance spectroscopy of which shows it to be a 7:3 mixture of 4-methyl-2-endo-bornanamine and 4-methyl-2-exo-bornanamine.

The two stereoisomers can be separated by fractional crystallisation of their acetate in the following manner:

117.4 g of amine are dissolved in 1000 ml of absolute ether and the solution is cooled to -20°C. 29.6 g of glacial acetic acid in 100 ml of absolute ether are added dropwise thereto with stirring over a period of 45 minutes. The resulting mixture is stirred for a further 10 minutes after the addition and the precipitated acetate is filtered off, washed with absolute ether and dried to yield 111.7 g of the acetate of the endo amine. The acetate of the exo amine remains in the mother liquor.

The 111.7 g of the acetate of the endo amine obtained as described in the preceding paragraph are dissolved in 500 ml of water and the base is released with the calculated amount of sodium hydroxide. The precipitated amine is taken up in ether and the ether solution is washed with water, dried over sodium sulphate and concentrated. Thin layer chromatography of the crude residue (86.5 g) shows it to consist of rac. 1,4,7,7-tetramethyl-2-endo-norbornanamine enriched to 90%.

These 86.5 g of amine are dissolved in 850 ml of absolute ether and the solution is cooled to -20°C. 24.82 g of glacial acetic acid in 100 ml of absolute ether are added dropwise thereto with stirring over a period of 45 minutes. The precipitated acetate is filtered off and dried to yield 93 g of the acetate of the endo amine, the acetate of the exo amine remaining in the mother liquor.

The 93 g of the acetate of the endo amine are dissolved in water and the base is released with the calculated amount of sodium hydroxide. The base is taken up in ether and the solution is washed with water, dried over sodium sulphate and filtered. The filtrate is treated with ca 100 ml of alcohol, made acidic to Congo-red with alcoholic hydrochloric acid and evaporated. The residue is crystallised from alcohol/

ether to yield 77.8 g of rac. 1,4,7,7-tetramethyl-2-endo-norbornanamine hydrochloride with a melting point of over 300°C.

The rac. 1,4,7,7-tetramethyl-2-exo-norbornanamine can be isolated from the respective mother liquors.

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Example 2

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A) The preparation of the starting material:

75 ml of glacial acetic acid are treated with 10.79 g of concentrated sulphuric acid (density=1.84 g/l). A heterogeneous mixture of 17.83 g of rac. 2-propylidene-camphane and 4.52 g of acetonitrile in 25 ml of glacial acetic acid is added. The resulting mixture is heated to 60°C, stirred for 18 hours, cooled, poured onto ca 500 g of ice and allowed to stand. The oil which separates out is taken up in 300 ml of ether and the ether solution is successively washed with two 100 ml portions of water, two 100 ml portions of saturated sodium carbonate solution and two 100 ml portions of water, dried over sodium sulphate and evaporated. The residue is chromatographed on 300 g of silica gel (0.2—0.5 mm) with methylene chloride, 136 fractions each of 20 ml being collected. Fractions 110—136 contain 13.5 g of rac. N-(4-propyl-2-exo-bornyl)-acetamide which melts at 96°—98°C after crystallisation from acetonitrile.

B) The process:

6.0 g of rac. N-(4-propyl-2-exo-bornyl)-acetamide are stirred at reflux with 30 ml of ethanol and 60 ml of 6-N hydrochloric acid for 64 hours. The alcohol-water mixture is subsequently evaporated off and the residue is dissolved in water. The aqueous solution is basified with 3-N sodium hydroxide solution and the base which separates out is extracted with ether. The ether solution is washed with saturated brine, dried over sodium sulphate, filtered and evaporated. The residue is dissolved in alcohol and the solution is treated with alcoholic hydrochloric acid. After evaporation, the residue is crystallised from alcohol/ether to yield 5.3 g of rac. 4-propyl-2-exo-bornanamine hydrochloride of melting point 294°—296°C.

Example 3

A) The preparation of the starting material:

34.5 g of 2-phenyl-borneol and 15.8 ml of acetonitrile are added dropwise over a period of a few minutes at 60°C to a solution of 32 g of concentrated sulphuric acid in 450 ml of glacial acetic acid. After 6 hours at 60°C, a further 15.8 ml of acetonitrile are added and the mixture is stirred at 60°C for a further 15 hours, then poured onto ice and extracted with methylene chloride. The combined methylene chloride phases are washed with saturated sodium hydrogen carbonate solution, dried over sodium sulphate and evaporated. The residue is crystallised from methylene chloride/hexane to yield 15.3 g of rac. N-(4-phenyl-2-exo-bornyl)-acetamide of melting point 151°—152°C. Chromatography of the mother liquors on silica gel with methylene chloride yields a further 6.6 g of pure amide, thus giving a total yield of 21.9 g.

B) The process:

5 g of rac. N-(4-phenyl-2-exo-bornyl)-acetamide, 200 ml of ethanol and 400 ml of 6-N hydrochloric acid are boiled under reflux for 72 hours. The resulting mixture is evaporated in vacuo and the residue is crystallised from methanol/water to yield 4.22 g of rac. 4-phenyl-2-exo-bornanamine hydrochloride as colourless crystals of melting point 345°—350°C.

4.2 g of rac. 4-phenyl-2-exo-bornanamine hydrochloride are treated with 16 ml of 1-N sodium hydroxide solution and the resulting mixture is extracted three times with benzene. The benzene phases are evaporated in vacuo to yield 3.7 g of rac. 4-phenyl-2-exo-bornanamine free base which distils in the bulb-tube at ca 80°C/0.05 mm Hg.

Example 4

21.6 g of rac. N-(4-phenyl-2-exo-bornyl)-acetamide (obtained as described in Example 3A) are treated with 120 ml of concentrated nitric acid. The resulting mixture is maintained at -10°C and treated dropwise with stirring with 72 ml of concentrated sulphuric acid. The mixture is kept at -10°C for a further 25 hours, then is allowed to warm to 0°C, poured onto 1 kg of ice and extracted with methylene chloride. The extract is dried with sodium sulphate and evaporated. The residue is crystallised from acetone/n-hexane to yield 14.9 g of rac. N-[4-(p-nitro-phenyl)-2-exo-bornyl]-acetamide of melting point 205°—206°C.

3.2 g of rac. N-[4-(p-nitro-phenyl)-2-exo-bornyl]-acetamide are hydrogenated in

300 ml of glacial acetic acid in the presence of 0.6 g of palladium-on-charcoal catalyst. The catalyst is subsequently filtered off and the filtrate is evaporated in vacuo. The residue is boiled under reflux with 150 ml of ethanol and 300 ml of 6-N hydrochloric acid for 72 hours, then the resulting mixture is evaporated in vacuo. The residue is crystallised from ethanol to give rac. 4-(*p*-amino-phenyl)-2-exo-bornanamine dihydrochloride of melting point 338°C.

Example 5

A) The preparation of the starting material:

5.2 g of 2-(*p*-methoxy-phenyl)-bornylene-(2) and 2.1 ml of acetonitrile, dissolved in a small amount of glacial acetic acid, are added dropwise at 60°C to a mixture of 4.26 ml of concentrated sulphuric acid and 60 ml of glacial acetic acid. After stirring at 60°C for 8 hours, a further 2.1 ml of acetonitrile are added and the mixture is stirred at 60°C for a further 13 hours, then poured onto ice and extracted with methylene chloride. The methylene chloride phase is washed with saturated sodium hydrogen carbonate solution, dried over sodium sulphate and evaporated. The residue (1.4 g) is chromatographed on 20 g of silica gel, initially with methylene chloride and subsequently with methylene chloride/methanol (98:2), fractions each of 40 ml being collected. Fractions 22—33 contain 0.6 g of a substance which is crystallised from *n*-hexane/methylene chloride to yield 0.3 g of rac. N-[4-(*p*-methoxy-phenyl)-2-exo-bornyl]-acetamide of melting point 156°—157°C.

B) The process:

603 mg of rac. N-[4-(*p*-methoxy-phenyl)-2-exo-bornyl]-acetamide are boiled under reflux with 72 ml of 6-N hydrochloric acid and 36 ml of ethanol for 72 hours. The resulting mixture is evaporated in vacuo until crystallisation begins to occur, then is allowed to stand in the refrigerator. The resulting precipitate is filtered off and crystallised from ethanol/water to yield 0.2 g of rac. 4-(*p*-methoxy-phenyl)-2-exo-bornanamine hydrochloride of melting point 309°—310°C.

Example 6

A) The preparation of the starting material:

15 g of magnesium are activated with iodine and treated with 50 ml of absolute ether, then a solution of 114.9 g of 4-bromo-chloro-benzene in 400 ml of absolute ether is added dropwise over the course of 1 hour and the resulting mixture is boiled at reflux for 14 hours, cooled to 0°C, treated dropwise over 15 minutes with a solution of 76 g of camphor in 100 ml of ether (the internal temperature not being allowed to exceed 3°C), and stirred at 3°C for 60 hours. 200 ml of saturated ammonium chloride solution are subsequently added dropwise to the resulting mixture, then the phases are separated and the aqueous phase is extracted three times with ether. The combined ether phases are washed with 5% sodium hydroxide solution and water, dried over sodium sulphate and evaporated in vacuo. Unreacted camphor is removed in a water-jet vacuum and the residue is distilled in an oil-pump vacuum to yield 27.7 g of 2-(*p*-chloro-phenyl)-borneol boiling at 115°—120°C/0.003—0.25 mm Hg.

A mixture of 22.3 g of 2-(*p*-chloro-phenyl)-borneol, 8.9 ml of acetonitrile and a small amount of glacial acetic acid is added dropwise with stirring over the course of a few minutes at 60°C to a mixture of 17.9 ml of concentrated sulphuric acid and 250 ml of glacial acetic acid. The resulting mixture is further stirred at 60°C, a further 8.9 ml of acetonitrile being added dropwise after 7 hours. After a total of 22 hours at 60°C, the mixture is poured onto ice and extracted with methylene chloride. The methylene chloride extract is shaken with water to which solid sodium hydrogen carbonate is added until evolution of carbon dioxide can no longer be observed, then is dried over sodium sulphate and evaporated. The residue is chromatographed on 420 g of silica gel, initially with methylene chloride and subsequently with methylene chloride/methanol (98:2) as solvent, fractions each of 300—450 ml being collected. Fractions 11—20 contain 12 g of pure N-[4-(*p*-chloro-phenyl)-2-exo-bornyl]-acetamide which melts at 195°—197°C after crystallisation from methylene chloride/*n*-hexane.

B) The process:

7 g of N-[4-(*p*-chloro-phenyl)-2-exo-bornyl]-acetamide are boiled under reflux with 280 ml of ethanol and 560 ml of 6-N hydrochloric acid for 96 hours. The resulting mixture is evaporated in vacuo and the residue is taken up in 140 ml of water and 210 ml of ethanol. The solution is concentrated in vacuo until unreacted starting material commences to crystallise, then is left in the cold. Crystals are filtered

off and the filtrate is again concentrated until crystallisation commences. There are thus obtained 3.1 g of 4-(*p*-chloro-phenyl)-2-exo-bornanamine hydrochloride of melting point 345°C.

Example 7

5 A) The preparation of the starting material: 5

A solution of 15.0 g of 1-methyl-camphene in 150 ml of acetonitrile is heated to 80°C and, with stirring, treated over a period of 2 hours with 11.77 g of concentrated sulphuric acid. After stirring for 3 hours, the resulting mixture is cooled and poured onto ca 300 g of ice. The oil which separates out is taken up in ether and the ether solution is washed with water, dried over sodium sulphate, filtered and evaporated. The residue is recrystallised from petroleum ether (boiling range=40°—45°C) to yield 6.55 g of rac. N-(1,4,7,7-tetramethyl-2-exo-norbornyl)-acetamide of melting point 121—123°C. 10

15 B) The process: 15

A suspension of 3 g of rac. N-1,4,7,7-tetramethyl-2-exo-norbornyl)-acetamide in 15 ml of alcohol and 30 ml of 6-N hydrochloric acid is boiled under reflux for 46 hours, then is evaporated on a rotary evaporator. The residue is dissolved in water and the aqueous solution is washed with ether and basified with sodium hydroxide. The base thus released is taken up in ether and the ether solution is washed with saturated brine, dried over sodium sulphate, filtered and evaporated. The residual base is converted into the hydrochloride with alcoholic hydrochloric acid. Recrystallisation from alcohol/ether yields 2.4 g of rac. 1,4,7,7-tetramethyl-2-exo-norbornanamine hydrochloride having a melting point of over 300°C. 20

Example 8

25 A) The preparation of the starting material: 25

15.02 g of 1-methyl-camphene are mixed with 100 ml of glacial acetic acid and 19.62 g of concentrated sulphuric acid, then treated dropwise over 15 minutes with stirring at room temperature with 8.04 g of methyl thiocyanate. After stirring for 2 hours, the mixture is diluted with 300 ml of water and extracted with three 150 ml portions of ether. The extract is successively washed with water, saturated sodium carbonate solution and water, dried over sodium sulphate, filtered and evaporated. The residue is chromatographed on 160 g of silica gel (0.2—0.5 mm) with methylene chloride as eluting agent, 170 fractions each of 10 ml being collected. Fractions 17—139 contain 12.0 g of rac. N-(1,4,7,7-tetramethyl-2-exo-norbornyl)-thiocarbamic acid S-methyl ester which distils at 100°—110°C/15 mm Hg. 30

35 B) The process: 35

A solution of 1 g of rac. N-(1,4,7,7-tetramethyl-2-exo-norbornyl)-thiocarbamic acid S-methyl ester in 5 ml of ethanol is treated with 20 ml of 6-N hydrochloric acid and boiled at reflux for 16 hours. The resulting mixture is evaporated and the residue is dissolved in water. The aqueous solution is washed with ether, then basified with sodium hydroxide. The base released is taken up in ether and the ether solution is washed with saturated brine, dried over sodium sulphate, filtered and evaporated. The residual base is converted into its hydrochloride by means of alcoholic hydrochloric acid. Recrystallisation from alcohol/ether yields 0.71 g of rac. 1,4,7,7-tetramethyl-2-exo-norbornanamine hydrochloride having a melting point of over 300°C. 40

The following Example is illustrative of the manner in which the novel derivatives provided by the invention may be converted into compounds of formula V hereinbefore: 45

A stirred suspension of 11.35 g of 2,3-dichloro-1,4-naphthoquinone in 100 ml of absolute alcohol is treated over a period of 15 minutes with 16.73 g of rac. 2-endo-1,4,7,7-tetramethylnorbornanamine in 50 ml of absolute alcohol. The resulting dark-red solution is boiled at reflux for 2 hours, then is evaporated under reduced pressure. The residue is dissolved in 200 ml of methylene chloride and the solution is successively washed with one 100 ml portion of water, three 50 ml portions of 1-N hydrochloric acid and three 100 ml portions of water, dried over sodium sulphate, concentrated, treated with active charcoal and evaporated. Crystallisation of the residue from methylene chloride/*n*-hexane yields 9.95 g of rac. 2-chloro-3-[(1,4,7,7-tetramethyl-2-endo-norbornyl)-amino]1,4-naphthoquinone of melting point 114°—115°C. 50

The following Examples are illustrative of pharmaceutical preparations containing the novel derivatives provided by the invention: 55

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Example A

Tablets of the following composition are manufactured in a conventional manner:

5	rac. 1,4,7,7-tetramethyl-2-endo-norbornanamine	50 mg	5
	lactose	89 mg	
	corn starch	50 mg	
	pregelatinized corn starch	8 mg	
	calcium stearate	3 mg	
total weight		200 mg	

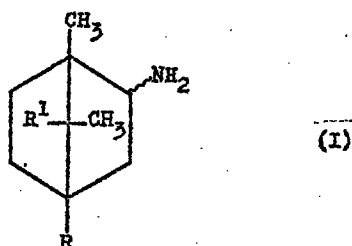
Example B

10 Capsules of the following composition are manufactured in a conventional manner:

rac. 1,4,7,7-tetramethyl-2-exo-norbornanamine	50 mg
corn starch	150 mg
talc	10 mg

15 WHAT WE CLAIM IS:—

1. Compounds of the general formula



20 , wherein R represents a lower alkyl group or an optionally substituted phenyl group and R¹ represents a lower alkyl group — provided that at least one of R and R¹ represents a methyl group, and acid addition salts thereof.

2. Compounds according to claim 1, wherein R and R¹ each represent a methyl group, and acid addition salts thereof.

25 3. Compounds according to claim 1, wherein R¹ represents a methyl group and R represents a propyl, phenyl, *p*-aminophenyl or *p*-methoxyphenyl group.

4. rac. 1,4,7,7-Tetramethyl-2-endo-norbornanamine and acid addition salts thereof.

5. rac. 1,4,7,7-Tetramethyl-2-exo-norbornanamine and acid addition salts thereof.

6. rac. 4-Propyl-2-exo-bornanamine and acid addition salts thereof.

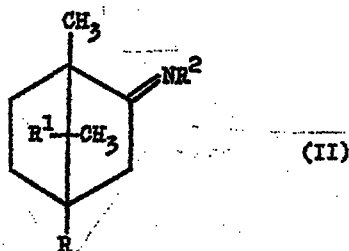
7. rac. 4-Phenyl-2-exo-bornanamine and acid addition salts thereof.

30 8. rac. 4-(*p*-Aminophenyl)-2-exo-bornanamine and acid addition salts thereof.

9. rac. 4-(*p*-Methoxyphenyl)-2-exo-bornanamine and acid addition salts thereof.

10. A pharmaceutical preparation comprising a compound of formula I as set forth in any one of claims 1 to 9 inclusive or a pharmaceutically acceptable acid addition salt thereof in admixture with a compatible pharmaceutical carrier.

35 11. A process for the manufacture of the compounds of formula I in claim 1, and acid addition salts thereof, which process comprises reducing a compound of the general formula





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Example A

Tablets of the following composition are manufactured in a conventional manner:

5	rac. 1,4,7,7-tetramethyl-2-endo-norbornanamine	50 mg	5
	lactose	89 mg	
	corn starch	50 mg	
	pregelatinized corn starch	8 mg	
	calcium stearate	3 mg	
total weight		200 mg	

Example B

10 Capsules of the following composition are manufactured in a conventional manner:

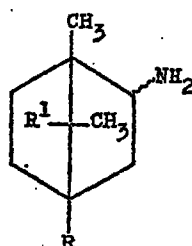
rac. 1,4,7,7-tetramethyl-2-exo-norbornanamine	50 mg
corn starch	150 mg
talc	10 mg

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WHAT WE CLAIM IS:—

1. Compounds of the general formula

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(I)

, wherein R represents a lower alkyl group or an optionally substituted phenyl group and R¹ represents a lower alkyl group — provided that at least one of R and R¹ represents a methyl group, and acid addition salts thereof.

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2. Compounds according to claim 1, wherein R and R¹ each represent a methyl group, and acid addition salts thereof.

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3. Compounds according to claim 1, wherein R¹ represents a methyl group and R represents a propyl, phenyl, *p*-aminophenyl or *p*-methoxyphenyl group.

4. rac. 1,4,7,7-Tetramethyl-2-endo-norbornanamine and acid addition salts thereof.

5. rac. 1,4,7,7-Tetramethyl-2-exo-norbornanamine and acid addition salts thereof.

6. rac. 4-Propyl-2-exo-bornanamine and acid addition salts thereof.

7. rac. 4-Phenyl-2-exo-bornanamine and acid addition salts thereof.

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8. rac. 4-(*p*-Aminophenyl)-2-exo-bornanamine and acid addition salts thereof.

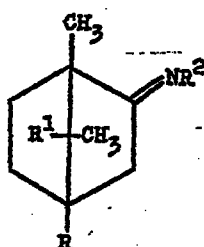
9. rac. 4-(*p*-Methoxyphenyl)-2-exo-bornanamine and acid addition salts thereof.

10. A pharmaceutical preparation comprising a compound of formula I as set forth in any one of claims 1 to 9 inclusive or a pharmaceutically acceptable acid addition salt thereof in admixture with a compatible pharmaceutical carrier.

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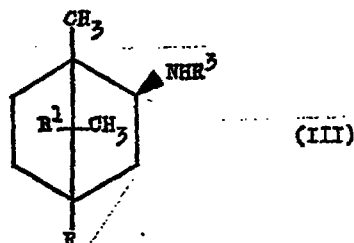
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11. A process for the manufacture of the compounds of formula I in claim 1, and acid addition salts thereof, which process comprises reducing a compound of the general formula



(II)

, wherein R and R¹ have the significance given in claim 1 and R² represents a hydrogen atom or a hydroxy group, or hydrolysing a compound of the general formula



5 , wherein R and R¹ have the significance given in claim 1 and R³ represents a hydrolytically-removable group, and, in either case, if desired, resolving a stereoisomer mixture or diastereomer mixture obtained and, also if desired, converting a base obtained into an acid addition salt thereof.

10 12. A process according to claim 11, wherein a compound of formula II in which R² represents a hydroxy group is reduced and, if desired, a stereoisomer mixture obtained is resolved and, also if desired, a base obtained is converted into an acid addition salt thereof.

15 13. A process according to claim 11, wherein a compound of formula II in which R² represents a hydrogen atom, and R and R¹ each represent a methyl group or a compound of formula III in which R and R¹ each represent a methyl group is used as the starting material.

20 14. A process according to claim 11, wherein a compound of formula II in which R² represents a hydrogen atom, R¹ represents a methyl group and R represents a propyl group or a compound of formula III in which R¹ represents a methyl group and R represents a propyl group is used as the starting material.

25 15. A process according to claim 11, wherein a compound of formula II in which R² represents a hydrogen atom, R¹ represents a methyl group and R represents a phenyl group or a compound of formula III in which R¹ represents a methyl group and R represents a phenyl group is used as the starting material.

30 16. A process according to claim 11, wherein a compound of formula II in which R² represents a hydrogen atom, R¹ represents a methyl group and R represents a *p*-aminophenyl or *p*-methoxyphenyl group or a compound of formula III in which R¹ represents a methyl group and R represents a *p*-aminophenyl or *p*-methoxyphenyl group is used as the starting material.

35 17. A process according to claim 12, wherein a starting material of formula II in which R¹ represents a methyl group and R represents a methyl, propyl, phenyl, *p*-aminophenyl or *p*-methoxyphenyl group is used as the starting material.

18. A process for the manufacture of the compounds of formula I in claim 1, and acid addition salts thereof, substantially as described with reference to Examples 1 to 8.

19. Compounds of formula I and acid addition salts thereof, when manufactured by the process claimed in any one of claims 11 to 18 inclusive.

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