PROCESS FOR THE PREPARATION OF 3,3-DISUBSTITUTED PIPERIDINES

A process for preparing a compound of formula (I), wherein R₁ represents hydrogen or a protecting group; and R₂ represents hydrogen or benzoyl optionally substituted in the phenyl moiety with halogen, methyl or C₁₋₄ alkoxy; which process comprises cyclising a compound of formula (II), wherein R₁ is as defined in relation to (I), to provide a cyclic lactam of formula (III), wherein R₁ is as defined in relation to (I); reducing the compound of formula (III) so formed to provide a compound of formula (I) wherein R₁ represents hydrogen; and thereafter carrying out one or more of the following optional steps: (a) N-acylating the compound of formula (I) wherein R₂ represents hydrogen to provide a compound of formula (I) wherein R₂ represents benzoyl wherein the phenyl moiety is optionally substituted with halogen, methyl or C₁₋₄ alkoxy; and (b) removing any protecting group.
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This invention relates to a novel process and to certain novel compounds prepared by such process.

European Patent Application, Publication Number 0673928 discloses certain compounds which are stated to have activity as specific antagonists of the human NK-3 receptor and in the treatment of diseases involving neurokinin B.

Example 19 of EP0673928 is the compound (+)-N-\{3-{1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl}prop-1-yl\}-4-phenylpiperidin-4-yl\}-N-methylacetamide, hereinafter also referred to as 'Compound I'.

EP0673928 also discloses certain intermediates of formula (A), used in the preparation of Compound I, which intermediates are prepared by reduction and subsequent cyclisation of a nitrile intermediate of formula (B):

In our hands the preparation of intermediate (A) proved to be difficult, mainly due to problems encountered in the reduction/cyclisation of (B). We have now found a novel and efficient method of preparing Compound I which avoids this troublesome conversion of (B) to (A) and proceeds, via a novel intermediate to give superior yields to that disclosed in EP673928. This method also utilises a novel, stereochemically efficient and high yielding resolution step to provide Compound I.

Accordingly, in a first aspect the present invention provides a process for preparing a compound of formula (I):
wherein \( R_1 \) represents hydrogen or a protecting group; and
\( R_2 \) represents hydrogen or benzoyl optionally substituted in the phenyl moiety with halogen, methyl or \( C_{1-4} \) alkoxy;
which process comprises cyclising a compound of formula (II):

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
R_1 & \quad \text{C} \quad \text{C} \\
\text{N} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

(II)

wherein \( R_1 \) is as defined in relation to (I), to provide a cyclic lactam of formula (III):

\[
\begin{align*}
\text{O} & \quad \text{O} \\
R_2 & \quad \text{C} \quad \text{C} \\
\text{NH} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

(III)

wherein \( R_1 \) is as defined in relation to (I); reducing the compound of formula (III) so formed to provide a compound of formula (I) wherein \( R_2 \) represents hydrogen; and thereafter carrying out one or more of the following optional steps:

(a) N-acylating the compound of formula (I) wherein \( R_2 \) represents hydrogen to provide a compound of formula (I) wherein \( R_2 \) represents benzoyl wherein the phenyl moiety is optionally substituted with halogen, methyl or \( C_{1-4} \) alkoxy; and
(b) removing any protecting group.

The cyclisation of the compound of formula (II) is suitably carried out by treating the compound of formula (II) with glacial acetic acid, preferably in the presence of a catalytic amount of sulphuric acid, at any temperature providing a suitable rate of formation of the required product, usually at an elevated temperature such as a temperature in the range of 85°C to 105°C, for example at 100°C.

The above mentioned reduction may be carried out using any suitable reducing reagent or procedure, including a complex metal hydride reagent or a borane reagent.

A preferred reducing agent is borane especially when complexed with a dialkysulphide, for example dimethyl sulphide.

The reduction is suitably carried out under the conditions conventionally used for the particular reduction method chosen. For example when borane/dimethyl sulphide is used the reaction is carried out in an aprotic solvent, such as
tetrahydrofuran, usually at an elevated temperature and conveniently at the reflux temperature of the solvent.

Suitably, R₁ is a protecting group, such as an acetyl or tetrahydropyran-2-yl group.

Suitably, R₂ is benzoyl.

The compounds of formula (III) are novel and are considered to form a further part of the present invention.

Accordingly, in a particular aspect the invention provides a process for the preparation of a compound of the above defined formula (III), which process comprises cyclising a compound of the above defined formula (II). The reaction conditions for this process are as described above.

In a further particular aspect, the invention provides a process for the preparation of a compound of the above defined formula (I) wherein R₂ is hydrogen, which process comprises reducing a compound of the above defined formula (III).

The reaction conditions for this process are as described above.

In yet a further aspect the invention provides a process for the preparation of a compound of the above defined formula (I) wherein R₂ represents benzoyl optionally substituted with halogen, methyl or C₁₋₄ alkoxy, which process comprises acylating a compound of formula (I) wherein R₂ represents hydrogen.

The reaction conditions for this process are as described above.

A suitable acylating agent is a benzoyle or an appropriately substituted benzoyl halide, preferably the chloride.

As aforementioned, the compounds of formula (I) are useful as intermediates for the preparation of Compound I. When used as intermediates the compounds of formula (I) are preferably used in an activated form, for example in a tosylated or mesylated form.

The activated form of the compound of formula (I) is prepared using the appropriate conventional procedure depending upon its particular nature: Thus, a mesylate is prepared by treating the compound of formula (I) with a mesyl halide, for example mesyl chloride, in an inert solvent such as dimethyl chloride.

Accordingly, in a further aspect, the invention provides a process for the preparation of a compound of formula (IV):
wherein R₂ is as defined in relation to (I), R₃ represents phenyl optionally substituted with halogen, methyl or C₁₋₄ alkoxy, R₄ represents hydrogen or -CO-C₁₋₄ alkyl and R₅ represents C₁₋₄ alkyl; which process comprises reacting a compound of the above defined formula (I), or an activated form thereof, with a compound of formula (V):

![Chemical Structure](image)

(V)

wherein R₃, R₄ and R₅ are as defined in relation to (IV), and thereafter optionally converting a compound of formula (IV) into another compound of formula (IV).

The reaction between the compounds of formulae (IV) and (V) is suitably carried out in an aprotic solvent, preferably dimethylformamide at any temperature providing a suitable rate of formation of the final product, including temperatures such as room temperature, but usually at an elevated temperature.

Generally the reaction conditions depend upon the nature of the compound of formula (V): Thus, when R₃ represents the said phenyl group and R₄ represents hydrogen, the reaction is suitably carried out at ambient temperature. Alternatively, when R₃ represents the said phenyl group and R₄ represents -CO-C₁₋₄ alkyl, then the reaction is usually effected at an elevated temperature such as a temperature in the range of 65°C to 100°C, for example 80°C, and preferably in the presence of a base such as a trialkylamine for example triethylamine.

It will be appreciated that those compounds of formula (V) wherein R₄ represents hydrogen may have been expected to react at either the ring nitrogen atom or the alkylamino nitrogen atom. It is a particularly surprising feature of the present process that reaction occurs almost exclusively at the ring nitrogen to provide the said compounds of formula (IV).
Suitable conversions of a compound of formula (IV) into another compound of formula (IV) includes the conversion of a compound of formula (IV) wherein R₄ represents hydrogen into a compound of formula (IV) wherein R₄ represents -CO-C₁₋₄ alkyl by use of an appropriate acylating agent; for example treatment with acetic anhydride smoothly converts R₄ as hydrogen into R₄ as acetyl.

The compounds of formula (IV) wherein R₃ represents phenyl optionally substituted with halogen, methyl or C₁₋₄ alkoxy, R₄ is hydrogen and R₅ is C₁₋₄ alkyl are novel compounds and are considered to form a further aspect of this invention.

Preferably, R₃ is phenyl.
Preferably, R₄ is acetyl.
Preferably, R₅ is methyl.

As indicated the compounds of formula (IV) have at least one chiral centre.

The present process provides either single isomer or racemic products depending upon the stereochemical nature of the starting materials. For example, the compounds of formula (I) can be separated into single isomers using known methodology (for example those disclosed in EP067928) which may then be used in the subsequent process steps disclosed herein.

The racemic products prepared by means of the present process can be separated into the component single isomers by using any conventional separation method, for example fractional crystallisation methods. However, in a further aspect the present invention also provides a novel, chiral high pressure liquid (HPLC) chromatographic method for resolving mixtures of optical isomers of compound (IV) which method is characterised in that the mobile phase comprises ethanol, hexane, trifluoroacetic acid and triethylamine, in particular 25% ethanol, 75% hexane, 0.5% trifluoroacetic acid and 0.1% triethylamine.

A preferred HPLC column for use in the separation is a Daicel Chiral Cell OD column.

The compounds of formula (II) are known compounds and are prepared according to literature methods, for example those disclosed in EP0673928.

Alternatively the compounds of formula (II) are prepared by reacting compounds of formula (VI):

\[
\begin{align*}
R_1 & \quad \text{Cl} \\
& \quad \text{Cl} \\
\end{align*}
\]

(VI)

wherein R₁ is as defined in relation to formula (I), with methylacrylate.
The reaction between the compounds of formula (VI) and methylacrylate is carried out in Triton B (40% in methanol) at any suitable temperature usually an elevated temperature such as the reflux temperature of the solvent.

The compounds of formula (V) may be prepared according to the procedures set out in Scheme I:

Scheme I

wherein $R_3$ is as defined in relation to formula (V), $R_{4a}$ represents $-\text{CO-C}_1\text{.}_4$ alkyl, especially acetyl, and $R_5$ represents $\text{C}_1\text{.}_4$ alkyl:

In particular the compounds of formula (V) wherein $R_3$ represents phenyl optionally substituted with halogen, methyl or $\text{C}_1\text{.}_4$ alkoxy, $R_4$ represents hydrogen and $R_5$ represents $\text{C}_1\text{.}_4$ alkyl are prepared from a compound of formula (VIII) wherein $R_3$ and $R_{4a}$ are as last defined, by removing the group $R_{4a}$ using for example acid hydrolys, to provide a compound of formula (VII) which is then alkylated using conventional methods to give, after debenzylation of the ring nitrogen, the required compound of formula (V). Any suitable alkylation method may be used, for example methylation is effected by initial formylation, by treatment with ethyl formate, followed by reduction with such as lithium aluminium hydride. Debdenylation is usually effected by catalytic hydrogenolysis, using for example palladium on carbon in ethanol.
Also the compounds of formula (V) wherein R₃ represents phenyl optionally substituted with halogen, methyl or C₁₋₄ alkoxy, R₄ represents -CO- C₁₋₄ alkyl and R₅ represents C₁₋₄ alkyl are prepared from the compound of formula (VIII) by first deprotec ting the ring nitrogen, using the procedure described above, reprotecting as a BOC derivative to give the compound of formula (IX), alkylation of the exocyclic nitrogen of (IX) to give compound (X) using the procedure described above and finally isolating (V) in stabilised form as the zinc chloride adduct.

The compounds of formula (V) wherein R₃ represents phenyl optionally substituted with halogen, methyl or C₁₋₄ alkoxy, where R₄ represents hydrogen and R₅ represents C₁₋₄ alkyl are novel compounds and form a further part of the present invention.

The compounds of formula (V) wherein R₃ represents phenyl optionally substituted with halogen, methyl or C₁₋₄ alkoxy, R₄ represents -CO-C₁₋₄ alkyl and R₅ represents C₁₋₄ alkyl in the form of a stabilised aduct, with such as zinc chloride aduct are novel compounds and form a further part of the present invention. However, the non-complexed compounds are prepared according to methods disclosed in EP0673928.

The compounds of formula (VIII) known compounds prepared according to methods such as those in EP0673928.

The compounds of formula (VI) are known compounds or they are prepared according to methods disclosed for the preparation of such compounds, for example those disclosed in EP512901.

The following Examples illustrate the invention but do not limit it in any way.
DESCRIPTION 1

4-Cyano-4-(3,4-dichloro)phenyl-7-(tetrahydropyran-2-yloxy)heptanoic acid

54.2 g (165.1 mmol) of 2-(3,4-dichloro)phenyl-5-(tetrahydropyran-2-yloxy)pentanenitrile (EP 512901) and 18.54 g (215.3 mmol) of methyl acrylate were dissolved in 90 ml (215.2 mmol) of Triton B (40\% in MeOH) and the solution was refluxed for 8 hours; 1.85 g (21.53 mmol) of methyl acrylate and 9 ml (21.52 mmol) of Triton B were added again and the reaction refluxed for additional 4 hours.

The reaction mixture was quenched with 20\% NH₄Cl, concentrated in vacuo and extracted with ether. The organic phase was extracted with 0.5N NaOH; the aqueous phase was therefore acidified to pH 5 with 1N HCl and extracted with Et₂O. The organic layer was dried over Na₂SO₄ and evaporated in vacuo to dryness to give 48.0 g of the title compound as an orange oil.

C₁₉H₂₃Cl₂NO₄
M.W. = 400.307
I.R. (nujol): 3160; 2930; 2220; 1720 cm⁻¹.
300 MHz ¹H-NMR (CDCl₃): δ 7.52 (d, 1H); 7.49 (d, 1H); 7.28 (dd, 1H); 4.51 (m, 1H); 3.87-3.65 (m, 2H); 3.53-3.32 (m, 2H); 2.61-2.50 (m, 1H); 2.45-2.32 (m, 1H); 2.28-1.98 (m, 4H); 1.85-1.65 (m, 2H); 1.60-1.40 (m, 6H).
MS (EI, TSQ 700, source 180 °C, 70 V, 200 uA): 399 (M⁺); 315; 256; 210; 197; 101; 85.

DESCRIPTION 2

3-(3,4-Dichloro)phenyl-3-(3-acethoxy)propylpiperidin-2,6-dione

52.4 g (131 mmol) of 4-cyano-4-(3,4-dichloro)phenyl-7-(tetrahydropyran-2-yloxy)heptanoic acid (compound of Description 1) were dissolved in 262 ml of acetic acid; 1.2 ml of 98\% H₂SO₄ were added dropwise and the solution was heated at 100°C for 16 hours.

The reaction mixture was concentrated in vacuo and the residue made alkaline with aqueous K₂CO₃ and extracted with Et₂O; the organic layer was separated, dried over Na₂SO₄ and evaporated in vacuo to dryness to yield 42 g of the title compound as an oil (purity: 85\% by GC).

C₁₆H₁₇Cl₂NO₄
M.W. = 358.219
I.R. (KBr): 3180; 3100; 2980; 1740; 1720; 1700 cm⁻¹.
300 MHz ¹H-NMR (CDCl₃): δ 8.05 (s br, 1H); 7.47 (d, 1H); 7.39 (d, 1H); 7.14 (dd, 1H); 4.02 (t, 2H); 2.66 (ddd, 1H); 2.45-2.20 (m,
3H); 2.08-1.89 (m, 2H); 2.03 (s, 3H); 1.73-1.47 (m, 2H).

MS (EI, TSQ 700, source 180 °C, 70 V, 200 uA): 357 (M+); 297.

DESCRIPTION 3

3-(3,4-Dichloro)phenyl-3-(3-hydroxypropyl)piperidine

36.2 g (101.0 mmol) of 3-(3,4-dichloro)phenyl-3-(3-acethoxy)propylpiperidin-2,6-dione (compound of Description 2) were dissolved, under nitrogen atmosphere, in 1000 ml of dry THF; 95.9 ml (1.01 mol) of borane dimethylsulfide complex, dissolved in 1000 ml of dry THF, were added dropwise and the solution was refluxed for 5 hours.

The reaction mixture was quenched with 610 ml of 2N HCl, refluxed 2 hours and the solvent evaporated in vacuo to dryness. The residue was treated with conc. NaOH and extracted with Et₂O; the organic layer was separated, dried over Na₂SO₄ and evaporated in vacuo to dryness. The residual oil was purified by gradient chromatography on 70-230 mesh silica gel, eluting with CH₂Cl₂/MeOH (from 0 to 20%) to afford 18.8 g of the title compound as a yellow oil.

C₁₄H₁₉Cl₂NO

M.W. = 288.215

I.R. (neat): 3300; 2920; 2880; 1555 cm⁻¹.

300 MHz ¹H-NMR (CDCl₃): 6 7.40 (d, 1H); 7.39 (d, 1H); 7.16 (dd, 1H); 3.48 (t, 2H); 3.19 (d, 1H); 2.91 (d, 1H); 2.81 (m, 2H); 2.10 (s br, 2H); 2.03 (m, 1H); 1.75 (ddd, 1H); 1.70-158 (m, 1H); 1.64 (t, 2H); 1.55-1.45 (m, 1H).

MS (EI, TSQ 700, source °180 C, 70 V, 200 uA): 288 (M+); 229.

DESCRIPTION 4

1-Benzoyl-3-(3,4-dichloro)phenyl-3-(3-hydroxypropyl)piperidine

The title compound was prepared starting from 13.55 g (47 mmol) of 3-(3,4-dichloro)phenyl-3-(3-hydroxypropyl)piperidine (compound of Description 3), 5.5 ml (47 mmol) of benzoic chloride and 7 ml (50 mmol) of TEA and following the method described in EP 512901. The crude product was purified by 70-230 mesh silica gel gradient column chromatography, eluting with CH₂Cl₂/MeOH (from 0 to 5%) to afford 18 g of the title compound.

C₂₁H₂₃Cl₂NO₂
M.W. = 392.327
DESCRIPTION 5

4-Acetylamino-4-phenyl-1-(tert-butoxycarbonyl)piperidine

15.8 g (72.5 mmol) of 4-acetylamino-4-phenylpiperidine (EP 474561 and EP 512901) were dissolved in 200 ml of dry DMF and 21.8 ml (157 mmol) of TEA were added.

The solution was cooled at 0°C and 18.3 g (84 mmol) of di-tert-butyl dicarbonate (BOC₂O), dissolved in 30 ml of dry DMF, were added dropwise; after 30 minutes at 0°C, the reaction was quenched with 50 ml of water. The reaction mixture was evaporated in vacuo to dryness; the residue was dissolved in EtOAc and washed with H₂O; the organic layer was separated, dried over Na₂SO₄ and evaporated in vacuo to dryness.

The residual oil was chromatographed on 70-230 mesh silica gel, eluting with a mixture of hexane/EtOAc 6:4 to afford 20.6 g of the title compound as a yellow oil.

C₁₈H₂₆N₂O₃
M.W. = 318.421
I.R. (neat): 3300; 3060; 2980; 1695; 1655; 1550 cm⁻¹.
300 MHz ¹H-NMR (CDCl₃): 8 7.40-7.20 (m, 5H); 5.78 (s br, 1H); 3.81 (d br, 2H);
3.09 (ddd, 2H); 2.38 (d br, 2H); 1.99 (ddd, 2H);
1.99 (s, 3H); 1.47 (s, 9H).

MS (EI, TSQ 700, source 180 °C, 70 V, 200 uA): 261; 202; 158.

DESCRIPTION 6

4-(N-Methyl-N-acetylamino)-4-phenyl-1-(tert-butoxycarbonyl) piperidine

10.35 g (32.5 mmol) of 4-acetylamino-4-phenyl-1-(tert-butoxycarbonyl)piperidine (compound of Description 5), 1.08 g (3.25 mmol) of tetrabutylammonium bromide and 5.62 g (85.24 mmol) of 85% powdered potassium hydroxide were dissolved in 100 ml of dry THF; 6.47 ml (104.0 mmol) of iodomethane, dissolved in 20 ml THF, were added dropwise and the reaction mixture was warmed at 40°C for 24 hours.

The precipitate was filtered off and the mixture was evaporated in vacuo to dryness; the residue was dissolved in EtOAc, washed with H₂O and sat. sol. NaCl; the organic layer was separated, dried over Na₂SO₄ and evaporated in vacuo to dryness.

The residue was triturated in hexane and recrystallized from Et₂O to yield 7.2 g of the title compound.

C₁₉H₂₈N₂O₃
M.P. = 127-128°C
M.W. = 332.447
I.R. (KBr): 3000-2860; 1695; 1640 cm⁻¹.
300 MHz $^1$H-NMR (CDCl$_3$): δ 7.40-7.20 (m, 5H); 3.84 (d br, 2H); 3.10 (dd br, 2H); 2.90-2.70 (m br, 2H); 2.82 (s, 3H); 2.11 (s, 3H); 2.04 (ddd, 2H); 1.45 (s, 9H).

MS (Cl, isobutane, P 4000 mTorr, source $^o$150 C): 333 (MH$^+$); 277; 260; 204.

DESCRIPTION 7

4-(N-Methyl-N-acetylamino)-4-phenylpiperidine zinc chloride complex

15.0 g (45.14 mmol) of 4-(N-methyl-N-acetylamino)-4-phenyl-1-(tert-butoxy carbonyl)piperidine (compound of Description 6) were dissolved in 900 ml of CH$_2$Cl$_2$; 12.30 g (90.28 mmol) of ZnCl$_2$ were added and the reaction mixture was stirred at room temperature for 10 days.

The solvent was evaporated in vacuo to dryness; the residue was dissolved in 400 ml of Et$_2$O and powdered with mechanical stirring. The solid was filtered, washed with Et$_2$O and dried to yield 27 g of a white powder.

C$_{14}$H$_{20}$N$_2$O · 2.5 ZnCl$_2$

M.W. = 573.023

Elemental analysis: Calcd. C, 29.34; H, 3.52; N, 4.89; Cl, 30.93;
Found C, 27.67; H, 3.95; N, 4.58; Cl, 29.43.

I.R. (KBr): 3500; 3060-3100; 1600 cm$^{-1}$.

300 MHz $^1$H-NMR (CDCl$_3$): δ 7.38-7.12 (m, 5H); 3.20 (ddd, 2H); 3.06 (ddd, 2H); 3.00-2.85 (m, 2H); 2.79 (s, 3H); 2.28-2.14 (m, 2H); 2.14 (s, 3H).

MS (Cl, isobutane, P 4000 mTorr, source $^o$150 C): 233 (MH$^+$).

EXAMPLE 1 - Method A

1-Benzoyl-3-(3,4-dichlorophenyl)-3-(3-[4-(N-methyl-N-acetylamino)-4-phenylpiperidin-1-yl]propyl)piperidine

8.8 g (22.5 mmol) of 1-benzoyl-3-(3,4-dichlorophenyl)-3-(3-hydroxypropyl) piperidine (compound of Description 4) were treated with 4.2 ml (31.25 mmol) of TEA and 2.34 ml (30.0 mmol) of methanesulfonyl chloride, according to the procedure described in EP 512901.

The crude methanesulfonyl derivative obtained and 12.5 ml (90 mmol) of TEA were dissolved in 100 ml of dry DMF and the solution was warmed at 50°C; 27 g of crude 4-(N-methyl-N-acetylamino)-4-phenylpiperidine zinc chloride complex (compound of Description 7) were added portionwise and the mixture heated at 80°C for 16 hours.
The solvent was evaporated *in vacuo* to dryness and the residue dissolved in EtOAc; the organic phase was washed with 1% HCl, 10% K₂CO₃, separated, dried over Na₂SO₄ and evaporated *in vacuo* to dryness.

The residue was purified on 70-230 mesh silica gel gradient column chromatography, eluting with CH₂Cl₂/MeOH (from 0 to 5%) to yield 2.6 g of the title compound.

C₃₅H₄₁Cl₂N₃O₂
M.P. = 77-80°C.
M.W. = 606.644

Elemental analysis:  
Calcd. C, 69.27; H, 6.81; N, 6.93; Cl, 11.69;  
Found C, 67.77; H, 6.88; N, 6.55; Cl, 12.46.

I.R. (KBr): 3060; 2940-2760; 1630 cm⁻¹.

300 MHz ¹H-NMR (CDCl₃): δ 7.40-7.20 (m, 13H); 3.60-3.20 (m, 2H); 2.80 (s, 3H); 2.75 (m, 2H); 2.60 (m, 2H); 2.25-2.05 (m, 4H); 2.10 (s, 3H); 1.85 (m, 1H); 1.70-1.10 (m, 11H).

75.47 MHz ¹³C-NMR (CDCl₃): δ 173.3, 171.3, 145.4, 137.0, 133.4, 131.1, 130.3, 129.6, 129.2, 129.2, 129.2, 129.1, 129.1, 127.6, 127.3, 127.1, 126.8, 126.8, 64.4, 59.3, 51.6, 51.4, 50.3, 49.0, 42.9, 38.9, 36.6, 36.4, 34.6, 30.3, 26.4, 22.6, 21.7 (2 aromatic quaternary carbon atoms are hidden).

MS [A] ESI POS, solvent MeOH/H₂O; B) DAU 606 ESI POS, Ar]: A) 606 (MH⁺);  
B) 606; 533; 403; 268; 105.

DESCRIPTION 8

4-Formylamino-4-phenyl-1-benzylpiperidine

10 g (37.54 mmol) of 4-amino-4-phenyl-1-benzylpiperidine (EP 673928) were dissolved in 250 ml of ethyl formate, in the presence of a catalitic amount of p-toluene sulfonic acid, and the solution was refluxed for 3 days.

The reaction mixture was evaporated *in vacuo* to dryness to afford 10.8 g of the title compound, used in the subsequent reaction without further purification.

C₁₉H₂₂N₂O
M.P. = 116-118°C.
M.W. = 294.399

I.R. (KBr): 3300; 3090-3010; 2940-2760; 1670 cm⁻¹.

300 MHz ¹H-NMR (C₆D₆): δ 7.83 (s, 1H); 7.35-7.00 (m, 10H); 4.80 (s br, 1H); 3.30 (s, 2H); 2.50 (m, 2H); 2.20-1.90 (m, 5H); 1.60 (m, 1H).
MS (EI, TSQ 700, source 180 C, 70 V, 200 uA): 294 (M+); 158.

DESCRIPTION 9

4-Methylamino-4-phenyl-1-benzylpiperidine

10.5 g (35.7 mmol) of 4-formylamino-4-phenyl-1-benzylpiperidine (compound of Description 8), dissolved in 150 ml of dry THF, were added dropwise, under nitrogen atmosphere, to a suspension of 3 g (80 mmol) of LiAlH<sub>4</sub> in 200 ml of dry THF. The reaction mixture was stirred at room temperature for 1 hour and then refluxed for 4 hours.

25 ml of H<sub>2</sub>O and 7.5 ml of 10% NaOH were added to the reaction mixture; the resulting slurry stirred 1 hour and then extracted with EtOAc; the organic layer was washed with sat. sol. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuo to dryness, to afford 9.8 g of the title compound as an oil.

C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>

M.W. = 280.415

I.R. (KBr): 3090-3020; 2940; 2800; 1500 cm<sup>-1</sup>.

300 MHz <sup>1</sup>H-NMR (C<sub>6</sub>D<sub>6</sub>): δ 7.39 (d, 2H); 7.25-7.15 (m, 8H); 3.40 (s, 3H); 2.48 (ddd, 2H); 2.38 (ddd, 2H); 1.97 (ddd, 2H); 1.87 (s, 3H); 1.69 (ddd, 2H).

MS (EI, TSQ 700, source 180 C, 70 V, 200 uA): 280 (M+); 248; 172; 158.

DESCRIPTION 10

4-Methylamino-4-phenyl-piperidine

1.4 g (5 mmol) of 4-methylamino-4-phenyl-1-benzylpiperidine (compound of Description 9) were dissolved in 38 ml of abs. EtOH and hydrogenated, in the presence of 1.4 g of 10% palladium on activated charcoal, at 30 psi for 24 hours.

The reaction mixture was evaporated in vacuo to dryness to afford 1.0 g of the crude title compound as an oil, used in the subsequent reaction without further purification.

C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>

M.W. = 190.287

DESCRIPTION 11

1-Benzoyl-3-(3,4-dichlorophenyl)-3-(3-(4-methylamino-4-phenylpiperidin-1-yl)propyl)piperidine

5 g (26.3 mmol) of 4-methylamino-4-phenyl-piperidine (compound of Description 10), 7.5 g (15.94 mmol) of 1-benzoyl-3-(3,4-dichlorophenyl)-3-(3-mesyloxypropyl)
piperidine (EP 512901) and 2.1 ml (15 mmol) of TEA were dissolved in 60 ml of
dry DMF and the solution was stirred at room temperature for 5 days.
The solvent was evaporated in vacuo to dryness and the residue dissolved in EtOAc;
the organic phase was washed with H₂O, separated, dried over Na₂SO₄ and
evaporated in vacuo to dryness.
The crude product was purified on 70-230 mesh silica gel gradient column
chromatography, eluting with CH₂Cl₂/MeOH (from 0 to 5%) to yield 7.5 g of the
title compound as an oil.
C₃₃H₃₉Cl₂N₃O
M.W. = 564.598
I.R. (KBr): 3440; 3080; 2940-2780; 1630 cm⁻¹.
MS (EI, TSQ 700, source °180 C, 70 V, 200 uA): 533; 200; 172; 158; 105.

EXAMPLE 1 - Method B
15 1-Benzoyl-3-(3,4-dichlorophenyl)-3-{3-[4-(N-methyl-N-acetylamino)-4-
phenylpiperidin-1-yl][propyl]piperidine

7.5 g (13.7 mmol) of 1-benzoxy-3-(3,4-dichlorophenyl)-3-[3-(4-methylamino-4-
phenylpiperidin-1-yl][propyl]piperidine (compound of Description 11) were
dissolved in 30 ml of acetic anhydride and the solution was stirred at room
temperature for 20 hours.
30 ml of H₂O were added and the solution was made alkaline with solid K₂CO₃ and
extracted with EtOAc; the organic layer was washed with 1N HCl, sat. sol. K₂CO₃
and sat. sol. NaCl, separated, dried over Na₂SO₄ and evaporated in vacuo to
dryness.

6.6 g of the crude product were purified on 70-230 mesh silica gel gradient column
chromatography, eluting with CH₂Cl₂/MeOH (from 0 to 5%) to yield 5 g of the title
compound.
C₃₅H₄₁Cl₂N₃O₂
M.W. = 606.644
Melting point, I.R. and N.M.R. spectroscopic data were identical to those obtained
for Example 1 - Method A.

EXAMPLE 2
35 (+)-1-Benzoyl-3-(3,4-dichlorophenyl)-3-{3-[4-(N-methyl-N-acetylamino)-4-
phenylpiperidin-1-yl][propyl]piperidine

The pure (+) enantiomer of (±)-1-benzoxy-3-(3,4-dichlorophenyl)-3-[3-[4-(N-
methyl-N-acetylamino)-4-phenylpiperidin-1-yl][propyl]piperidine (compound of
Example 1) was obtained by automated preparative chiral HPLC separation on Daicel Chiralcel OD column (10 μ, 21.2 × 250 mm), using a flux of 10 ml/min with the UV detector fixed at 280 nm, eluting with a unique mobile phase consisting of 25% EtOH, 75% hexane, 0.5% TFA and 0.1% TEA.

As an example, 2.5 g of the racemate (injection of 200 mg in 4 ml of mobile phase) gave 1.05 g of (-) stereoisomer and 1.15 g of (+) stereoisomer, both with e.e. > 99%.

Controls of the samples were made by analytical HPLC on Daicel Chiralcel OD column (10 μ, 4.6 × 250 mm) using a flux of 1 ml/min with the UV detector fixed at 254 nm.

Using these conditions, the retention time of the (+) stereoisomer was 13.0 min. and the retention time of the (-) stereoisomer was 9.8 min.

C_{35}H_{41}Cl_{2}N_{3}O_{2}

M.W. = 606.644

[α]_{D}^{25} = + 20.0 (c = 0.3, EtOH); [α]_{D}^{25} of the (-) enantiomer = -19.9 (c = 0.3, EtOH).
Claims

1. A process for preparing a compound of formula (I):

wherein \( R_1 \) represents hydrogen or a protecting group; and
\( R_2 \) represents hydrogen or benzoyl optionally substituted in the phenyl moiety with halogen, methyl or \( \text{C}_{1-4} \) alkoxy;
which process comprises cyclising a compound of formula (II):

wherein \( R_1 \) is as defined in relation to (I), to provide a cyclic lactam of formula (III):

wherein \( R_1 \) is as defined in relation to (I); reducing the compound of formula (III) so formed to provide a compound of formula (I) wherein \( R_2 \) represents hydrogen;
and thereafter carrying out one or more of the following optional steps:
(a) N-acylating the compound of formula (I) wherein \( R_2 \) represents hydrogen to provide a compound of formula (I) wherein \( R_2 \) represents benzoyl wherein the phenyl moiety is optionally substituted with halogen, methyl or \( \text{C}_{1-4} \) alkoxy; and
(b) removing any protecting group.

2. A process according to claim 1, wherein the cyclisation of the compound of formula (II) is carried out by treating with glacial acetic acid.
3. A process according to claim 1 or claim 2, wherein the reduction is carried out using borane.

4. A process according to claim 3, wherein the borane is complexed with a dialkysulphide.

5. A process according to any one of claims 1 to 4, wherein R₁ is an acetyl or tetrahydropyran-2-yl group.

6. A process according to any one of claims 1 to 5, wherein R₂ is benzoyl.

7. A process for the preparation of a compound of formula (IV):

   ![Chemical Structure](image)

   (IV)

   wherein R₂ is as defined in relation to formula (I) in claim 1, R₃ represents phenyl optionally substituted with halogen, methyl or C₁₄ alkoxy, R₄ represents hydrogen or -CO-C₁₄ alkyl and R₅ represents C₁₄ alkyl; which process comprises reacting a compound of the above defined formula (I), or an activated form thereof, with a compound of formula (V):

   ![Chemical Structure](image)

   (V)

   wherein R₃, R₄ and R₅ are as defined in relation to (IV), and thereafter optionally converting a compound of formula (IV) into another compound of formula (IV).

8. A chiral high pressure liquid (HPLC) chromatographic method for resolving mixtures of optical isomers of a compound of formula (IV) as defined in claim 7, which method is characterised in that the mobile phase comprises 25% ethanol, 75% hexane, 0.5% trifluoroacetic acid and 0.1% triethylamine.