WE CLAIM:

1. A process for preparing 4-methylene piperidine hydrochloride comprising the following steps:

    a. alkylating 1-benzylpiperidine-4-one to obtain 1-benzyl-4-methylidenepiperidine;

    b. debenzylating 1-benzyl-4-methylidenepiperidine to obtain N-carbethoxy-4-methylene piperidine;

    c. deprotecting N-carbethoxy-4-methylene piperidine to obtain 4-methylidenepiperidine; and

    d. forming a salt of 4-methylidenepiperidine to obtain 4-methylene piperidine hydrochloride having purity in the range of~~greater than~~ 95% to 99%;~~.~~

    wherein the step (a) of alkylation is carried out at a temperature in the range of 60 °C to 80 °C until completion of the alkylation.

2. The process as claimed in claim 1, wherein the step (a) of alkylation is carried out using methyl triphenylphosphonium bromide as an alkylating agent; in the presence of an alkali selected from the group consisting of sodium methoxide, sodium ethoxide and sodium t-butoxide; and a first fluid medium selected from the group consisting of toluene, tetrahydrofuran and ether.

~~3. The process as claimed in claim 1, wherein the step (a) of alkylation is carried out at a temperature in the range of 60 °C to 80 °C until completion of the alkylation.~~

~~4.~~3. The process as claimed in claim 1, wherein the step (a) of alkylation comprises the step of adding 1-benzylpiperidine-4-one and the alkylating agent in parts of equal volume to a mixture comprising the alkali and the first fluid medium over a period of time in the range of 20 to 40 minutes.

~~5.~~4. The process as claimed in claim 1, wherein the molar ratio of 1-benzylpiperidine-4-one and the alkali is in the range of 1: 20 to 1: 25.

~~6.~~5. The process as claimed in claim 1, wherein the molar ratio of 1-benzylpiperidine-4-one and the alkylating agent is in the range of 1: 1 to 1: 3.

~~7.~~6. The process as claimed in claim 1, wherein the step (b) of debenzylation is carried out using ethyl chloroformate in the presence of a second fluid medium selected from the group consisting of toluene, tetrahydrofuran and ether.

~~8.~~7. The process as claimed in claim 1, wherein the step (b) of debenzylation is carried out at a temperature in the range of 0 °C to 10 °C until completion of the debenzylation.

~~9.~~8. The process as claimed in claim 1, wherein the molar ratio of 1-benzyl-4-methylidenepiperidine and ethyl chloroformate is ~~can be~~ in the range of 1: 10 to 1: 15.

~~10.~~9. The process as claimed in claim 1, wherein the step (b) of debenzylation further comprises treating N-carbethoxy-4-methylene piperidine with diethyl ether to obtain N-carbethoxy-4-methylene piperidine having purity in the range of ~~greater than~~ 95% to 99%.

~~11.~~10. The process as claimed in claim 1, wherein the step of (c) of de-protection is carried out using a base selected from sodium hydroxide and potassium hydroxide and in the presence of a third fluid medium selected from ethylene glycol and di-ethylene glycol.

~~12.~~11. The process as claimed in claim 1, wherein the step of (c) of de-protection is carried out at a temperature in the range of 100 °C to 130 °C until completion of the deprotection.

~~13.~~12. The process as claimed in claim 1, wherein the molar ratio of N-carbethoxy-4-methylene piperidine and the base is in the range of 1: 5 to 1: 10.

~~14.~~13. The process as claimed in claim 1, wherein the step (d) of salt formation is carried out using anhydrous hydrochloride gas and in the presence of a fourth fluid medium selected from the group consisting of dichloromethane, dichloroethane, and acetonitrile and at a temperature 0°C to ~~below~~ 10 °C.

~~15.~~14. The process as claimed in claim 1, wherein the step (d) of salt formation further comprises treating 4-methylene piperidine hydrochloride with acetone at a temperature 0 °C to ~~below~~ 5 °C to obtain 4-methylene piperidine hydrochloride having purity in the range of ~~greater than~~ 95% to 99%.

~~16.~~15. The process as claimed in claim 1 comprising:

i. charging a first reactor with sodium methoxide and toluene under stirring, followed by heating at 70°C to obtain a first mixture; adding methyl

triphenylphosphonium bromide and N-benzyl piperidone to said first mixture over a period of 20 minutes in 10 parts of equal volumes; and continuing heating at 70°C until complete consumption of N-benzyl piperidone to obtain a first product mixture comprising 1-benzyl-4-methylidenepiperidine;

ii. washing said first product mixture with water to obtain a first organic layer comprising 1-benzyl-4-methylidenepiperidine;

iii. cooling first organic layer comprising 1-benzyl-4-methylidenepiperidine to 5 °C in a second reactor; followed by addition of ethyl chloroformate in drop-wise manner and continuing stirring at 5 °C until complete consumption of 1-benzyl-4-methylidenepiperidine to obtain a second product mixture comparing N-carbethoxy-4-methylene piperidine;

iv. washing said second product mixture with water to obtain a second organic layer comprising N-carbethoxy-4-methylene piperidine; removing the volatiles present in said second organic layer under reduced pressure to obtain first residue comprising N-carbethoxy-4-methylene piperidine; treating said first residue with diethyl ether to obtain N-carbethoxy-4-methylene piperidine having purity in the range of ~~greater than~~ 95% to 99%;

v. charging a third reactor with N-carbethoxy-4-methylene piperidine and mono-ethylene glycol to obtain a third mixture; adding aqueous solution of potassium hydroxide in drop-wise manner to said third mixture; followed by heating at 110 °C until complete consumption of N-carbethoxy-4-methylene piperidine to obtain a third product mixture comprising 4-methylidenepiperidine; and

vi. cooling said third product mixture comprising 4-methylidenepiperidine to 10 °C; and diluting said cooled third product mixture with methylene dichloride to obtain a fourth mixture; cooling said fourth mixture to 5 °C and purging anhydrous hydrochloride gas through said cooled fourth mixture till pH of the resultant mixture is 1 to obtain a fourth product mixture comprising 4-methylene piperidine hydrochloride;

vii. removing the volatiles present in said fourth product mixture under reduced pressure to obtain a second residue comprising 4-methylene piperidine

hydrochloride; treating said second residue with acetone to obtain 4-methylene piperidine hydrochloride having purity in the range of ~~greater than~~ 95% to 99%.

Dated this 27th day of March, 2019

MOHAN RAJKUMAR DEWAN
of R.K. DEWAN & COMPANY
IN/PA-25
APPLICANT'S PATENT ATTORNEY

TO,
THE CONTROLLER OF PATENTS,
THE PATENT OFFICE, AT MUMBAI

WE CLAIM:

1. A process for preparing 4-methylene piperidine hydrochloride comprising the following steps:

    a. alkylating 1-benzylpiperidine-4-one to obtain 1-benzyl-4-methylidenepiperidine;

    b. debenzylating 1-benzyl-4-methylidenepiperidine to obtain N-carbethoxy-4-methylene piperidine;

    c. deprotecting N-carbethoxy-4-methylene piperidine to obtain 4-methylidenepiperidine; and

    d. forming a salt of 4-methylidenepiperidine to obtain 4-methylene piperidine hydrochloride having purity in the range of 95% to 99%;

    wherein the step (a) of alkylation is carried out at a temperature in the range of 60 °C to 80 °C until completion of the alkylation.

2. The process as claimed in claim 1, wherein the step (a) of alkylation is carried out using methyl triphenylphosphonium bromide as an alkylating agent; in the presence of an alkali selected from the group consisting of sodium methoxide, sodium ethoxide and sodium t-butoxide; and a first fluid medium selected from the group consisting of toluene, tetrahydrofuran and ether.

3. The process as claimed in claim 1, wherein the step (a) of alkylation comprises the step of adding 1-benzylpiperidine-4-one and the alkylating agent in parts of equal volume to a mixture comprising the alkali and the first fluid medium over a period of time in the range of 20 to 40 minutes.

4. The process as claimed in claim 1, wherein the molar ratio of 1-benzylpiperidine-4-one and the alkali is in the range of 1: 20 to 1: 25.

5. The process as claimed in claim 1, wherein the molar ratio of 1-benzylpiperidine-4-one and the alkylating agent is in the range of 1: 1 to 1: 3.

6. The process as claimed in claim 1, wherein the step (b) of debenzylation is carried out using ethyl chloroformate in the presence of a second fluid medium selected from the group consisting of toluene, tetrahydrofuran and ether.

7. The process as claimed in claim 1, wherein the step (b) of debenzylation is carried out at a temperature in the range of 0 °C to 10 °C until completion of the debenzylation.

8. The process as claimed in claim 1, wherein the molar ratio of 1-benzyl-4-methylidenepiperidine and ethyl chloroformate is in the range of 1: 10 to 1: 15.

9. The process as claimed in claim 1, wherein the step (b) of debenzylation further comprises treating N-carbethoxy-4-methylene piperidine with diethyl ether to obtain N-carbethoxy-4-methylene piperidine having purity in the range of 95% to 99%.

10. The process as claimed in claim 1, wherein the step of (c) of de-protection is carried out using a base selected from sodium hydroxide and potassium hydroxide and in the presence of a third fluid medium selected from ethylene glycol and di-ethylene glycol.

11. The process as claimed in claim 1, wherein the step of (c) of de-protection is carried out at a temperature in the range of 100 °C to 130 °C until completion of the deprotection.

12. The process as claimed in claim 1, wherein the molar ratio of N-carbethoxy-4-methylene piperidine and the base is in the range of 1: 5 to 1: 10.

13. The process as claimed in claim 1, wherein the step (d) of salt formation is carried out using anhydrous hydrochloride gas and in the presence of a fourth fluid medium selected from the group consisting of dichloromethane, dichloroethane, and acetonitrile and at a temperature 0°C to 10 °C.

14. The process as claimed in claim 1, wherein the step (d) of salt formation further comprises treating 4-methylene piperidine hydrochloride with acetone at a temperature 0 °C to 5 °C to obtain 4-methylene piperidine hydrochloride having purity in the range of 95% to 99%.

15. The process as claimed in claim 1 comprising:

    i. charging a first reactor with sodium methoxide and toluene under stirring, followed by heating at 70°C to obtain a first mixture; adding methyl triphenylphosphonium bromide and N-benzyl piperidone to said first mixture over a period of 20 minutes in 10 parts of equal volumes; and continuing heating at 70°C until complete consumption of N-benzyl piperidone to obtain a first product mixture comprising 1-benzyl-4-methylidenepiperidine;

ii. washing said first product mixture with water to obtain a first organic layer comprising 1-benzyl-4-methylidenepiperidine;

iii. cooling first organic layer comprising 1-benzyl-4-methylidenepiperidine to 5 °C in a second reactor; followed by addition of ethyl chloroformate in drop-wise manner and continuing stirring at 5 °C until complete consumption of 1-benzyl-4-methylidenepiperidine to obtain a second product mixture comparing N-carbethoxy-4-methylene piperidine;

iv. washing said second product mixture with water to obtain a second organic layer comprising N-carbethoxy-4-methylene piperidine; removing the volatiles present in said second organic layer under reduced pressure to obtain first residue comprising N-carbethoxy-4-methylene piperidine; treating said first residue with diethyl ether to obtain N-carbethoxy-4-methylene piperidine having purity in the range of 95% to 99%;

v. charging a third reactor with N-carbethoxy-4-methylene piperidine and mono-ethylene glycol to obtain a third mixture; adding aqueous solution of potassium hydroxide in drop-wise manner to said third mixture; followed by heating at 110 °C until complete consumption of N-carbethoxy-4-methylene piperidine to obtain a third product mixture comprising 4-methylidenepiperidine; and

vi. cooling said third product mixture comprising 4-methylidenepiperidine to 10 °C; and diluting said cooled third product mixture with methylene dichloride to obtain a fourth mixture; cooling said fourth mixture to 5 °C and purging anhydrous hydrochloride gas through said cooled fourth mixture till pH of the resultant mixture is 1 to obtain a fourth product mixture comprising 4-methylene piperidine hydrochloride;

vii. removing the volatiles present in said fourth product mixture under reduced pressure to obtain a second residue comprising 4-methylene piperidine hydrochloride; treating said second residue with acetone to obtain 4-methylene piperidine hydrochloride having purity in the range of 95% to 99%.

Dated this 27th day of March, 2019

MOHAN RAJKUMAR DEWAN
of R.K. DEWAN & COMPANY
IN/PA-25
APPLICANT'S PATENT ATTORNEY

TO,
THE CONTROLLER OF PATENTS,
THE PATENT OFFICE, AT MUMBAI