(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
04 **January** 2018 (04.01.2018)

W!PO | PCT

(10) International Publication Number
WO 2018/002696 A1

(51) International Patent Classification:
C07D 213/53 (2006.01)

(21) International Application Number:
PCT/IB2016/054885

(22) International Filing Date:
13 August 2016 (13.08.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
IN 201641021910 27 June 2016 (27.06.2016) IN

(71) Applicant: FLEMING LABORATORIES LIMITED [IN/IN]; 4th Floor, Madhupala Towers, Ameerpet, Hyderabad-500 016, Telangana State, India., Hyderabad 500 016 (IN).

(72) Inventors; and
(71) Applicants *(for US only):* **SHANMUGAM, Srinivasan** [IN/IN]; Fleming Laboratories Limited, Plot No. 152 & 160, Phase-V, I.D.A, Jeedimetla, Hyderabad-500 055, Telangana State, India, Hyderabad 500 055 (IN). **GOUNI, Laxma Reddy** [IN/IN]; Fleming Laboratories Limited, Plot No. 152 & 160, Phase-V, I.D.A, Jeedimetla, Hyderabad-500 055, Telangana State, India, Hyderabad 500 055 (IN). **TAMMIREDDY, Gowri Naidu** [IN/IN]; Fleming Laboratories Limited, Plot No. 152 & 160, Phase-V, I.D.A, Jeedimetla, Hyderabad-500 055, Telangana State, India, Hyderabad 500 055 (IN). **TOGATA, Madduleti** [IN/IN]; Fleming Laboratories Limited, Plot No. 152 & 160, Phase-V, I.D.A, Jeedimetla, Hyderabad-500 055, Telangana State, India, Hyderabad 500 055 (IN).

(74) Agent: SURAPUREDDY, Padmaja; iProPAT Intellectual Property Solutions, 2nd Floor, Above Apollo Clinic, Suresh Square, Plot No 1-58/91/SS, Survey No 228 & 229/1, Madinaguda, Miyapur, Hyderabad - 500 049 Hyderabad 500 049 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*

(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF AN ANTIHISTAMINE AGENT

(57) Abstract: The present invention relates to an improved process for the preparation of an antihistamine agent. The present invention particularly relates to an improved process for the preparation of Cyclizine or its salts. The present invention more particularly relates to an improved process for the preparation of Cyclizine hydrochloride. The present invention further relates to commercially feasible process for the preparation of Cyclizine hydrochloride.

WO 2018/002696 A1

AN IMPROVED PROCESS FOR THE PREPARATION OF AN ANTIHISTAMINE AGENT

FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation of an antihistamine agent.

The present invention particularly relates to an improved process for the preparation of Cyclizine or its salts.

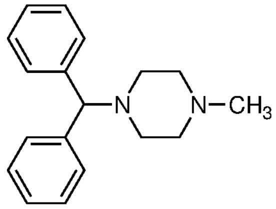
The present invention more particularly relates to an improved process for the preparation of Cyclizine hydrochloride.

The present invention further relates to commercially feasible process for the preparation of Cyclizine hydrochloride.

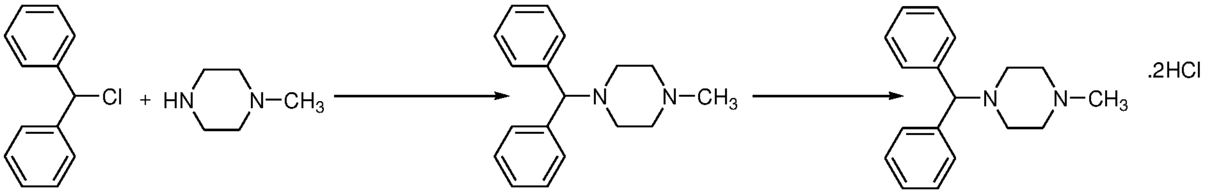
BACKGROUND OF THE INVENTION

Cyclizine is a piperazine-derivative. It is used for the prevention and treatment of nausea, vomiting, and dizziness associated with motion sickness, and vertigo. Cyclizine has also been found to inhibit cytochrome P450 CYP2D6, an important liver enzyme. Cyclizine is metabolised to its N-demethylated derivative, norcyclizine, which has little antihistaminic (HI) activity compared to Cyclizine.

Cyclizine is an orally or parenterally administered histamine HI receptor antagonist. The chemical name of Cyclizine is N-benzhydryl-N'-methylpiperazine and the molecular formula is $C_{18}H_{22}N_2$ with molecular weight of 266.38. The structural formula is:



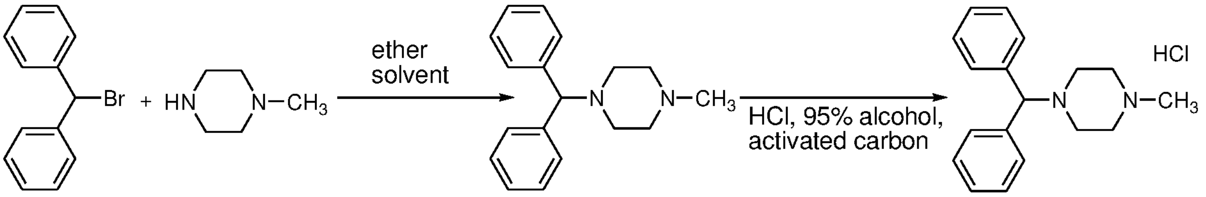
Cyclizine is first disclosed in US 2,630,435 A. This patent discloses a process for the preparation of Cyclizine dihydrochloride. The process involves the condensation reaction of benzhydryl chloride with N-methyl piperazine, followed by treating with hydrochloric acid to form Cyclizine dihydrochloride. The process is shown in the scheme given below:



Scheme I

The process enabled in US '435 is not applicable for industrial scale as the final yield is found to be very low which is commercially not viable.

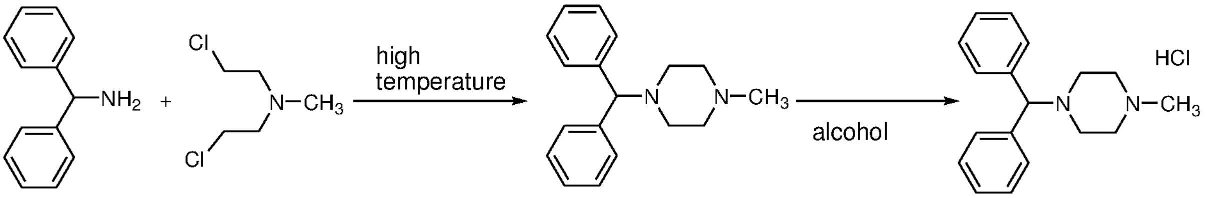
Similar to the above process, the following synthesis of Cyclizine hydrochloride is also reported in the literature, which is shown in the scheme given below:



Scheme II

In the above process benzhydryl bromide is condensed with N-methyl piperazine in the presence of ether solvent to give Cyclizine which is treated with hydrochloric acid to form Cyclizine Hydrochloride. The above process cannot be applied for Industrial scale as the reagents, reactants used in the above reaction is industrially not safe and environmentally not advisable, for example methyl piperazine used in the condensation is a costly material, further the enabled process accounts into low yield and preparation of bromo intermediate is also expensive. Hence, this process is economically not viable.

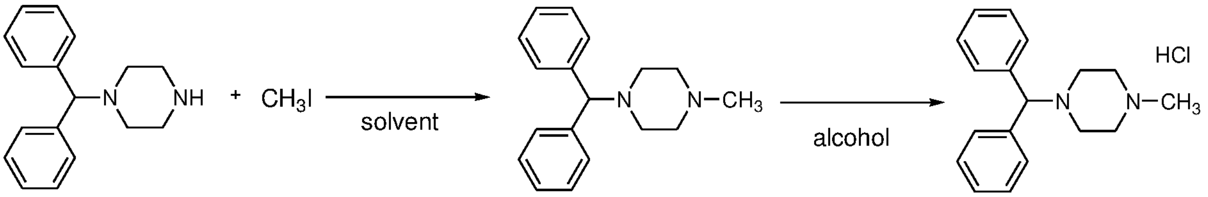
BE539693 A1 discloses a process for preparing Cyclizine, which is depicted in the scheme given below:



Scheme III

The above process has been repeated by the present inventors, which comprises reacting diphenyl methanamine with 2-chloro-N-(2-chloroethyl)-N-methylethanamine to give Cyclizine, wherein the reaction is carried out at high temperature. Cyclizine is treated with hydrochloric acid to form Cyclizine Hydrochloride. The above process cannot be applied for Industrial scale as the above cyclization reaction is carried out at very high temperature and accounts into low yielding. Hence, this process is also economically not viable.

BE539693 A1 also discloses an alternate process for preparing Cyclizine, which is shown in the scheme given below:



Scheme IV

The above process also has been repeated by the present inventors, which involves methylating benzhydryl piperazine using methyl iodide to give Cyclizine free base which is treated with carbon then the filtrate acidified with hydrochloric acid to form Cyclizine hydrochloride. This route leads to the formation of Quaternary ammonium salt due to that the above process accounts in lower yield and handling of Mel is not viable in large scale manufacturing.

Since all the above reported synthetic routes has disadvantages in terms of commercial feasibility and environmental friendly, there is consequently a need for a more advantageous alternative method of preparing Cyclizine or its salts. Said novel method should in particular be simpler and involves less number of steps, more industrially scalable, involve the use of cheaper reagents, employ mild reaction conditions, and at the same time provide Cyclizine or its salts with high yields, high chemical purity and efficiency.

The present inventors have surprisingly found an improved process for preparing Cyclizine which involves methylating DPMP (benzhydryl piperazine) using Eschweiler-Clarke reaction methodology, wherein the developed process has less number of steps, more industrially scalable with high yields.

OBJECTIVE OF THE INVENTION

The main objective of the present invention is to provide an improved process for the preparation of an antihistamine agent.

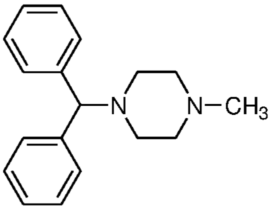
In a preferred objective of the present invention is to provide an improved process for the preparation of Cyclizine or its salts.

In a more preferred objective of the present invention is to provide an improved process for the preparation of Cyclizine hydrochloride.

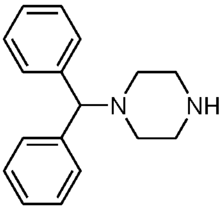
In a still more preferred objective of the present invention is to provide an improved process for the preparation of Cyclizine hydrochloride, which is commercially feasible.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides an improved process for the preparation of Cyclizine



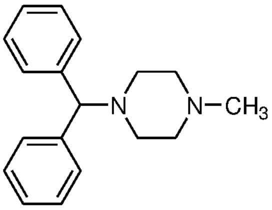
which comprises, methylating compound of Formula I or its salts



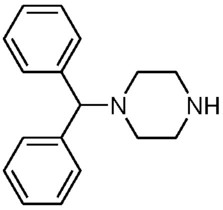
Formula I

using formaldehyde in the presence of an acid to give Cyclizine.

In preferred aspect, the present invention provides an improved process for the preparation of Cyclizine



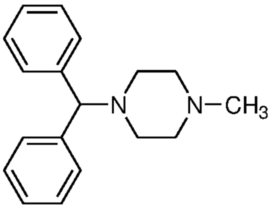
which comprises, methylating compound of Formula I or its salts



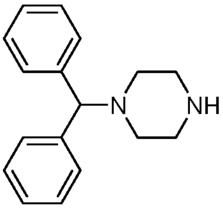
Formula I

using formaldehyde in the presence of formic acid to give Cyclizine.

In a more preferred aspect, the present invention provides an improved process for the preparation of Cyclizine



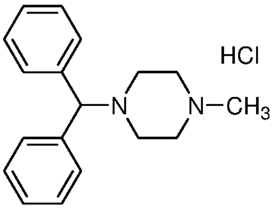
which comprises, methylating compound of Formula I or its salts



Formula I

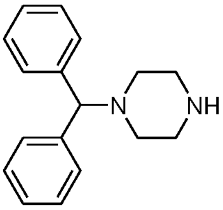
using formaldehyde and formic acid in water as a solvent medium to give Cyclizine.

In another preferred aspect, the present invention provides an improved process for the preparation of Cyclizine hydrochloride,



which comprises:

a) methylating compound of Formula I or its salts



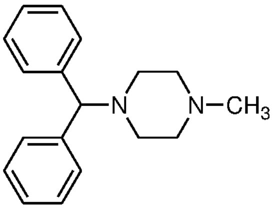
Formula I

using formic acid and formaldehyde optionally in the presence of a solvent to give Cyclizine free base,

b) optionally isolating Cyclizine free base, and

c) converting Cyclizine to its hydrochloride salt.

In still another preferred aspect, the present invention provides an improved process for the preparation of Cyclizine,



which comprises:

a) preparing a solution of formic acid and formaldehyde in water,

b) adding compound of Formula I to the solution of step a),

c) heating the reaction mass at a temperature of about 50-95°C,

d) isolating Cyclizine free base.

DETAILED DESCRIPTION OF THE INVENTION

Accordingly the present invention provides an improved process for preparing Cyclizine or its salts which is economically viable.

In a preferred embodiment the present invention provides an improved process for preparing Cyclizine free base using Eschweiler-Clarke reaction methodology. The developed process using Eschweiler-Clarke reaction methodology is commercially feasible, does not involve any side reactions, and contains fewer impurities.

Eschweiler-Clarke reaction which is also called as Eschweiler-Clarke methylation is widely used for the methylation of primary or secondary amines. Methylation using

Eschweiler-Clarke reaction will not produce quaternary ammonium salts, but instead will stop at the tertiary amine stage.

In a preferred embodiment, the present invention provides an improved process for preparing Cyclizine which comprises methylating amine of Formula I i.e DPMP (benzhydryl piperazine) with formaldehyde to give imine derivative of compound of Formula I. The imine derivative of Formula I is reduced using an acid which acts as a source of hydride to give Cyclizine free base.

In another preferred embodiment, the acid used in the present invention is selected from an acid which acts as a source of hydride. In a preferred embodiment the acid is selected from oxalic acid and its hydrates, formic acid. Preferably formic acid.

In yet another preferred embodiment, the present invention provides an improved process for preparing Cyclizine hydrochloride which comprises methylating amine of Formula I i.e DPMP (benzhydryl piperazine) with formaldehyde to give imine derivative of compound of Formula I. The imine derivative of Formula I is reduced using formic acid which acts as a source of hydride to give Cyclizine free base, followed by treating it with hydrochloric acid in the presence of a suitable solvent to give Cyclizine HC1.

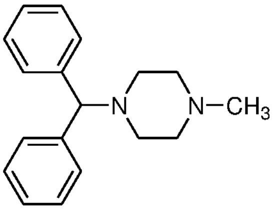
The first methylation of the amine begins with imine formation with formaldehyde. The formic acid acts as a source of hydride and reduces the imine to a secondary amine. The driving force is the formation of carbon dioxide gas. Formation of the tertiary amine is similar. From this mechanism it is clear that a quaternary ammonium salt will never form, because it is impossible for a tertiary amine to form another imine or iminium ion.

In still another preferred embodiment, the present invention provides solvent free methylation of compound of Formula I to give Cyclizine free base, wherein water alone is used in the reaction which makes the process more economical and environmental friendly. The developed process is simple and does not involve any complicated reagents. The yield of the product is very high which is commercially feasible.

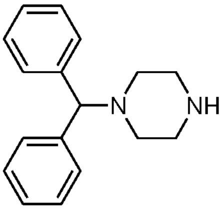
In still another preferred embodiment, the present invention provides the methylation of compound of Formula I to give Cyclizine free base in water medium to emphasize Green approach, unique, aqueous medium which is non-toxic liquid, sustainable chemistry.

According to the reported literature and the inventor's knowledge, preparation of Cyclizine free base by methylating compound of Formula I using Eschweiler-Clarke reaction methodology is not known.

In a preferred embodiment, the present invention provides an improved process for the preparation of Cyclizine,



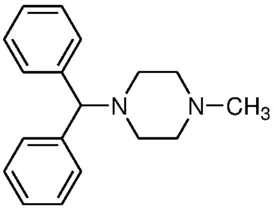
which comprises methylating compound of Formula I or its salts



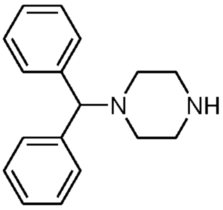
Formula I

with formaldehyde in the presence of an acid and in the absence of an organic solvent to give Cyclizine.

In a more preferred embodiment, the present invention provides an improved process for the preparation of Cyclizine,



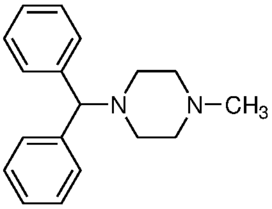
which comprises methylating compound of Formula I or its salts



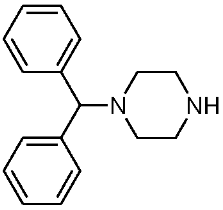
Formula I

with formaldehyde in the presence of formic acid and in the absence of an organic solvent to give Cyclizine.

In a more preferred embodiment, the present invention provides an improved process for the preparation of Cyclizine



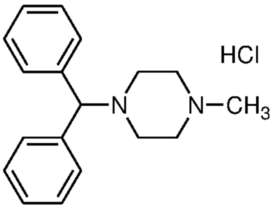
which comprises, methylating compound of Formula I or its salts



Formula I

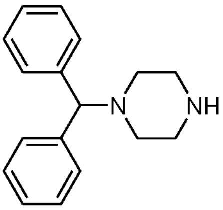
using formaldehyde and formic acid in water as a solvent medium to give Cyclizine.

In another preferred embodiment, the present invention provides an improved process for the preparation of Cyclizine hydrochloride,



which comprises:

a) methylating compound of Formula I or its salts



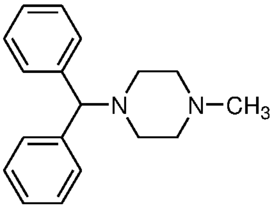
Formula I

with formic acid and formaldehyde in the absence of an organic solvent to give Cyclizine free base,

b) treating Cyclizine free base with HCI in a solvent, and

c) isolating Cyclizine hydrochloride.

In yet another preferred embodiment, the present invention provides an improved process for the preparation of Cyclizine free base,



which comprises:

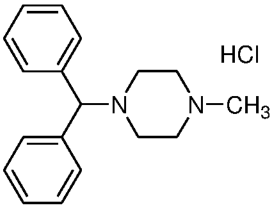
a) preparing a solution of formic acid and formaldehyde in water,

b) adding Formula I to the solution of step a),

c) heating the reaction mass at a temperature of about 50-95°C,

d) isolating Cyclizine free base.

In yet another preferred embodiment, the present invention provides an improved process for the preparation of Cyclizine hydrochloride,



comprising the following steps:

a) preparing a solution of formic acid and formaldehyde in water,

b) adding Formula I was added to the solution of step a),

c) heating the reaction mass at about 50-95°C,

d) solution of sodium hydroxide was added to the above reaction mixture,

e) isolating Cyclizine free base,

f) converting Cyclizine free base to its hydrochloride salt using HCI in methanol.

As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

The term "salts" as used herein refers to salts which are known to be non-toxic and are commonly used in the pharmaceutical literature. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric, and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenylsubstituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, beta-hydroxybutyrate, chloride, cinnamate, citrate, formate, fumarate, glycolate, heptanoate, lactate, maleate, hydroxymaleate, malonate, mesylate, nitrate, oxalate, phthalate, phosphate, monohydro genphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propionate, phenylpropionate, salicylate, succinate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzenesulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene- 1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. A preferred salt is the hydrochloride salt.

"Solvent" as defined in the presence invention is selected from water or "alcohol solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol and t-butanol and the like or "hydrocarbon solvents" such as benzene, toluene, xylene, heptane, hexane and cyclohexane and the like or "ketone solvents" such as acetone, ethyl methyl ketone, diethyl ketone, methyl tert-butyl ketone, isopropyl ketone and the like or "esters solvents" such as methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, and the like or "nitrile solvents" such as acetonitrile, propionitrile, butyronitrile and isobutyronitrile and the like or "ether solvents" such as di-tert-butylether, dimethylether, diethylether, diisopropyl ether, 1,4-dioxane, methyltert-butylether, ethyl tert-butyl ether, tetrahydrofuran, 2-methyl tetrahydrofuran, 2-methoxyethanol and dimethoxyethane, or "Amide solvents" such as formamide, DMF, DMAC, N-methyl-2-

pyrrolidone, N-methylformamide, 2-pyrrolidone, l-ethenyl-2-pyrrolidone and/or mixtures thereof.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention. The invention is illustrated below with reference to inventive and comparative examples and should not be construed to limit the scope of the invention.

EXAMPLE 1; Preparation of Cyclizine free base

To the mixture of 15.7 gm (3.0 moles) of Formic acid (assay NLT 85%), 12gm of Formaldehyde (1.5 moles, assay NLT 37%) solution in 75 ml of water, 25 gm (1.0 mole) of Diphenyl methyl-piperazine (DPMP) was added at ambient temperature under stirring. Then the reaction mixture was heated to 75-80°C and maintained at same temperature for about 3.0 hours. After completion of the reaction, the reaction mixture was cooled to the ambient temperature. 75 ml of Toluene was added to the reaction mixture, the pH was adjusted to basic pH with caustic lye solution under stirring. Reaction mixture was allowed to settle and the organic layer was separated. The organic layer was washed with water. Distilled out toluene to get the product.

Yield 23.8 gm

% of Yield: 90.5 %

Melting range 102 -104.6°C

EXAMPLE 2: Preparation of Cyclizine free base

To the mixture of 157.5 gm (3.0 moles) of Formic acid (assay NLT 85%), 120gm (1.5 moles) of Formaldehyde (assay NLT 37%) solution in 750 ml of water, 250gm (1.0 mole) of Diphenyl methyl-piperazine (DPMP) was added, and were mixed slowly with stirring at ambient temperature. Then the reaction mixture was heated 75-80°C stirred for about 3 hours at same temperature. After completion of the reaction, the reaction mixture was cooled to ambient temperature; mixture was adjusted to basic pH with caustic lye solution, at ambient temperature with stirring. The resulting compound filtered, washed with water and then dried.

Yield: 257.5 gm

% of Yield: 97.9 %

GC purity 99.19%

EXAMPLE 3: Preparation of Cyclizine free base:

11.8 gm of formic acid, 2.2 moles of, (assay NLT 85%), 9.6 gm of formaldehyde, 1.2 Moles, (assay NLT 37%), and 75 ml of water were slowly mixed with stirring by maintaining at ambient temperature. Then 25.0 gm, 1.0 mole diphenyl methyl-piperazine was added and mixed. The reaction mixture was heated 75-80°C. The reaction mixture was stirred for 2.0hours at same temperature. The reaction mixture was then cooled to ambient temperature. The reaction mixture was adjusted to basic pH with caustic lye solution, the resulting compound filtered and washed with water.

Yield: 22.8 gm

% of Yield: 86.6 %

GC purity 95.74%

EXAMPLE 4: Preparation of Cyclizine free base:

53.68 gm of formic acid 5.0 moles of (assay NLT 85%), 40.2 gm of formaldehyde 2.5 Moles, (assay NLT 37%), and 150 ml of water were slowly mixed with stirring by at ambient temperature. Then 1.0 mole 50.0 gm diphenyl methyl-piperazine 1.0 mole was added and mixed. Then reaction mixture was heated 75-80°C and stirred for 3.0 hours at same temperature. The reaction mixture was cooled ambient temperature. The pH was adjusted to basic with caustic soda solution, the resulting compound filtered and washed with water.

Output: 50.2 gm

% of Yield: 95.07 %

GC purity 97.01%

EXAMPLE 5: Preparation of Cyclizine free base:

16.0 gm of formic acid 3.0 moles (assay NLT 85%), 1.5 Moles, 12.0 gm of formaldehyde 1.5 Moles (assay NLT 37%), and 75 ml of water were slowly mixed with stirring at ambient temperature. Then added 1.0 mole 25.0 gm diphenyl methyl-piperazine added 1.0 mole was mixed. The reaction mixture was heated 85-90°C The reaction mixture was stirred for 3.0 hours at same temperature. The reaction mixture was cooled to ambient temperature. The pH was adjusted to basic with caustic soda solution, at ambient temperature. The resulting compound filtered and washed with water and dried.

Output yield: 25.3 gm

% of Yield: 96.19 %

Melting range 105 -106.5°C

EXAMPLE 6: Preparation of Cyclizine free base:

16.0 gm of formic acid 3.0 moles (assay NLT 85%), 12.0 gm of formaldehyde 1.5 Moles (assay NLT 37%), and 75 ml of water were slowly mixed with stirring at ambient temperature. Then added 25.0 gm diphenyl methyl-piperazine 1.0 mole was mixed. The reaction mixture was heated 50-55°C, and maintained 3-4 hours same temperature. The reaction mixture was cooled ambient temperature, the pH adjusted with caustic soda solution, at ambient temperature. The resulting compound filtered and washed with water and dried.

Output yield: 16.3 gm % Yield: 61.97 %

EXAMPLE 7: Preparation of Cyclizine Hydrochloride:

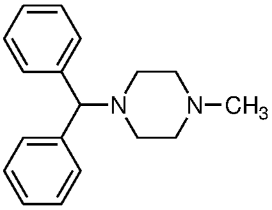
Cyclizine free base 25.0 gm (purity NLT 98.0%) dissolved in 50.0 ml of Methanol. To a clear solution added 1.0 mole of Hydrochloric acid 8.4 ml (assay NLT 35.0%) temperature in the range of 45 to 55°C. The reaction mixture was stirred for 2 hours. The resulting compound was filtered dried.

Yield: 25.70 gm

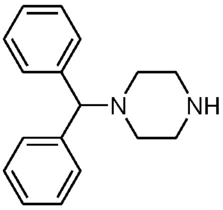
% of Yield: 90.5 % , Purity: 99.4%.

We Claim:

1. An improved process for the preparation of Cyclizine



which comprises, methylating compound of Formula I or its salts



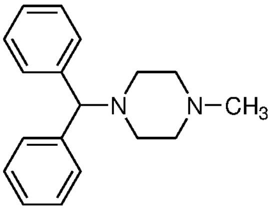
Formula I

using formaldehyde in the presence of an acid to give Cyclizine.

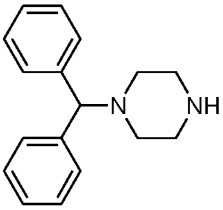
2. An improved process as claimed in claim 1, wherein the acid is selected from an acid which acts as a source of hydride.

3. An improved process as claimed in claims 1 and 2, the acid is selected from oxalic acid and its hydrates, formic acid.

4. An improved process for the preparation of Cyclizine



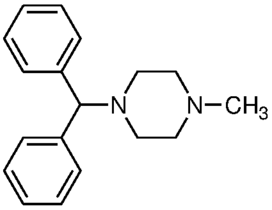
which comprises, methylating compound of Formula I or its salts



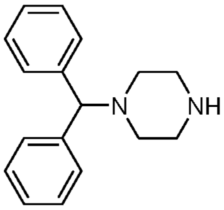
Formula I

using formaldehyde in the presence of formic acid to give Cyclizine.

5. An improved process for the preparation of Cyclizine



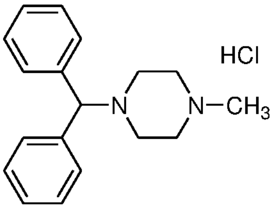
which comprises, methylating compound of Formula I or its salts



Formula I

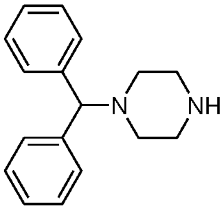
using formaldehyde and formic acid in water as a solvent medium to give Cyclizine.

6. An improved process for the preparation of Cyclizine hydrochloride,



which comprises:

a) methylating compound of Formula I or its salts



Formula I

using formic acid and formaldehyde optionally in the presence of solvent to give Cyclizine free base,

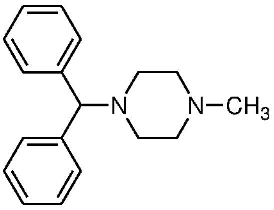
b) optionally isolating Cyclizine free base, and

c) converting Cyclizine to its hydrochloride salt.

7. An improved process as claimed in claim 6, wherein the solvent is selected from water or "alcohol solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol and t-

butanol and the like or "hydrocarbon solvents" such as benzene, toluene, xylene, heptane, hexane and cyclohexane and the like or "ketone solvents" such as acetone, ethyl methyl ketone, diethyl ketone, methyl tert-butyl ketone, isopropyl ketone and the like or "esters solvents" such as methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, and the like or "nitrile solvents" such as acetonitrile, propionitrile, butyronitrile and isobutyronitrile and the like or "ether solvents" such as di-tert-butylether, dimethylether, diethylether, diisopropyl ether, 1,4-dioxane, methyltert-butylether, ethyl tert-butyl ether, tetrahydrofuran, 2-methyl tetrahydrofuran, 2-methoxyethanol and dimethoxyethane, or "Amide solvents" such as formamide, DMF, DMAC, N-methyl-2-pyrrolidone, N-methylformamide, 2-pyrrolidone, l-ethenyl-2-pyrrolidone and/or mixtures thereof.

8. An improved process for the preparation of Cyclizine,



which comprises:

a) preparing a solution of formic acid and formaldehyde,

b) compound of Formula I was added to the solution of step a),

c) heating the reaction mass at about 50-95°C,

d) isolating Cyclizine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/054885

A. CLASSIFICATION OF SUBJECT MATTER
C07D213/53 Version=2017.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Patseer, IPO Internal Database

C. DOCUMENTS **CONSIDERED TO** BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No,
Y	BE539693 A1 (30 July 1955) whole document especially examples	1-8
Y	STANLEY H. PINE ET AL. "The Formic Acid-Formaldehyde Methylation of Amines"; J. Org. Chem.; Vol. 36, No. 6, 1971, pages 829-832. abstract, whole document	1-8

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

*	Special categories of cited documents:
"A"	document defining the general state of the art which is not considered to be of particular relevance
"E"	earlier application or patent but published on or after the international filing date
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&"	document member of the same patent family

Date of the actual completion of the international search
13-01-2017

Date of mailing of the international search report
13-01-2017

Name and mailing address of the ISA/
Indian Patent Office
Plot No. 32, Sector 14, Dwarka, New Delhi-110075
Facsimile No.

Authorized officer
Manvender Singh Dagur
Telephone No. +91-1125300200