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PROCESS FOR PREPARATION OF SUBSTANTIALLY OPTICALLY PURE (R)- AND (S)- ENANTIOMERS OF KETAMINE AND ITS PHARMACEUTICAL ACCEPATABLE SALTS

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ABSTRACT

A new synthesis for the preparation of optically pure (R)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone [(R)-Ketamine] as well as (S)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone [(S)-Ketamine] and its pharmaceutically acceptable salts by effectively resolving R,S-Ketamine base with Di-p-toluoyl-L-tartaric acid (DPTTA) in alcoholic solvents to separate Di-p-toluoyl-L-tartaric acid, salt of R-Ketamine and Di-p-toluoyl-L-tartaric acid salt of S-Ketamine respectively. The Di-p-toluoyl-L-tartaric acid salts of R-Ketanine and S-Ketamine are separated by crystallization process as a particular salt is soluble or less soluble in a particular alcoholic solvent system. The salt is ruptured by an alkali to get Optically Pure (R) and (S)-Ketamine Base which are treated with hydrochloric acid to get R-Ketamine hydrochloride and S-Ketamine hydrochloride without any need of purification.

KEYWORDS

INTRODUCTION

S(+)-Ketamine is approximately twice as potent as racemic Ketamine. It is eliminated from the human body more quickly than R(–)-Ketamine or racemic Ketamine, although R-Ketamine slows its elimination. A number of studies have suggested that S-Ketamine has a more medically useful pharmacological action than R-Ketamine or racemic Ketamine. S-Ketamine inhibits dopamine transporters eight times more than R-Ketamine. This increases dopamine activity in the brain. At doses causing the same intensity of effects, S-Ketamine is generally considered to be more pleasant by patients. Patients also generally recover mental function more quickly after being treated with pure S-Ketamine, which may be a result of the fact that it is cleared from their system more quickly.

S-Ketamine has an affinity for the Phencyclidine/ plasma cell pneumnia (PCP) binding site of the N-methyl-D-aspartate (NMDA) receptor 3-4 times higher than that of R-Ketamine. Unlike R-Ketamine, S-Ketamine does not bind significantly to sigma receptors. S-Ketamine increases glucose metabolism in frontal cortex, while R-Ketamine decreases glucose metabolism in the brain. This difference may be responsible for the fact that S-Ketamine generally has a more dissociative or hallucinogenic effect while R-Ketamine is reportedly more relaxing. However, another study found no difference between racemic and (S)-Ketamine on the patient's level of vigilance. Interpretation of this finding is complicated by the fact that racemic Ketamine comprises 50% (S)-Ketamine.

Similarly to racemic Ketamine and S(+) enantiomer of Ketamine, R-Ketamine is biologically active; however, it is less potent as an NMDA receptor antagonist and anesthetic and thus has never been approved or marketed for clinical use as an enantiopure drug. On the other hand, it appears to be more effective as an antidepressant. Relative to S-Ketamine, R-Ketamine possesses 4–5 times lower affinity for the PCP site of the NMDA receptor. In accordance, R-Ketamine is significantly less potent than racemic Ketamine and especially S-Ketamine in terms of anesthetic, analgesic, and sedative-hypnotic effects.

Racemic Ketamine has weak affinity for the sigma receptor, where it acts as an agonist, whereas S-Ketamine binds negligibly to this receptor, and so the sigma receptor activity of racemic Ketamine lies in R-Ketamine. It has been suggested that this action of R-Ketamine may play a role in the hallucinogenic effects of racemic Ketamine and that it may be responsible for the lowering of the seizure threshold seen with racemic Ketamine. S-Ketamine inhibits the dopamine transporter about 8-fold more potently than does R-Ketamine, and so is about 8 times more potent as a dopamine reuptake inhibitor. R-Ketamine and S-Ketamine possess similar potency for interaction with the muscarinic acetylcholine receptors.

Paradoxically, R-Ketamine shows greater and longer-lasting rapid antidepressant effects in animal models of depression relative to S-Ketamine. It has been suggested that this difference may have due to with the possibility of different activity of R-Ketamine and S-Ketamine and their respective metabolites at the α_7-nicotinic receptor, as norKetamine and hydroxy-norKetamine are potent antagonists of this receptor and markers of potential rapid antidepressant effects correlate closely with their affinity for it. In rodent studies, S-Ketamine produced hyperlocomotion, prepulse inhibition deficits, and rewarding effects, while R-Ketamine did not, in accordance with its lower potency as an NMDA receptor antagonist and dopamine reuptake inhibitor. As such, R-Ketamine may have a lower propensity for producing psychotomimetic effects and a lower abuse potential in addition to superior antidepressant efficacy.

Various methods are reported for the preparation of S(+)Ketamine and its pharmaceutically acceptable salts by resolution of racemic Ketamine with L(+)Tartaric acid[1,2], which results in low yields of the enantiomerically pure product. Feasibility of commercialization of this pure enantiomer from Ketamine, S-Ketamine, depends on the development of processes industrially efficient for its obtainment. Among the available references that present procedures of obtaining S-isomer from Ketamine, we have the procedure described in the patent DE 2062620 (Hudyma TW, Holmes SW e Hooper IR, de 1971), in which the obtainment of the S- Ketamine is effected from racemic Ketamine by means of the procedure of resolution reagent, the base racemic Ketamine and the tartaric acid are employed in equivalent amounts in moles. The diastereomer salt separated in this procedure is recrystallized twice from acetonitrile[3,] the isolated basis (S-Ketamine) is also recrystallized and its chloridrate also suffers a recrystallization to finally present a high enantiomeric purity with a low overall yield.

The consecutive recrystallization to which the several intermediate products and the final product are submitted, show a low enantiomeric purity of the tartrate salt from S-Ketamine initially

separated. Industrially, the use of this procedure presents some disadvantages, among them the extensive purifications due to the low enantiomeric purity of the S-Ketamine tartrate initially separated during the resolution process. Another disadvantage is associated to the solvent used in the purification of this salt, which is the acetonitrile, a toxic solvent which use in high proportions is not recommended. In addition to these factors, experimentally this procedure shows a great variation of the enantiomeric purity of the precipitated S-Ketamine tartrate, which interferes directly on the purification procedures for its salt.

In some cases, also, the procedure is not efficient to separate enantiomers, occurring the crystallization on both forms, i.e. the S-Ketamine and the R-Ketamine tartrates, in proportions almost equivalent. The success of the recrystallization in acetonitrile is directly dependent on the enantiomeric purity of the salt initially precipitated, which, when low, presents separation of the product in the form of oil, which crystallizes slowly, without effective increments of this enantiomeric purity, becoming an additional problem in the adequacy of the method to a industrial scale production.

The patent WO 97/43244 (Gangkafner S, Grunenwald J, Steiner K, de 1997) describes a procedure almost identical to the patent DE 2062620 mentioned above, where the author only replaces[2] the recrystallization solvent of S-Ketamine tartrate, acetonitrile, by a mix of acetone and water. It describes also some variants effected for this procedure, changing solvents used, and also the use of the resolution agent in amounts not proportional to the racemic base Ketamine molar equivalent, this resolution agent being used in amount superior to the molar equivalent amount of the base Ketamine. As in the above reference, this procedure presents large variations in the precipitated amounts and in the separated salt enantiomeric purity, the S-Ketamine tartrate. Due to the low enantiomeric purity of the precipitated salt, the product of the optical resolution needs to undergo reprocessing via recrystallization, in order to reach a higher enantiomeric purity, and this recrystallization represents the addition of one more phase in the procedure of obtaining S-Ketamine, increasing the cost for the productive process.

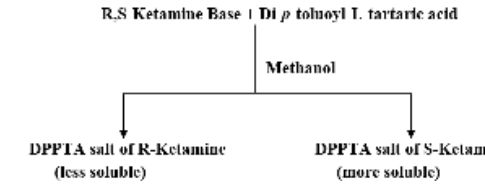
There is also the patent WO 95/08529 (Grover ER, Mazzeo JR, Merion M, Petersen JS, Schwartz ME, 1995) , where exotic chiral surfactant4 discovered by them and special equipment for the separation of the enantiomers of racemic Ketamine are used. This patent presents its application aiming at the field of Analytic Chemistry, being its use in industrial conditions not practicable, in economic terms. The patent WO 96/11894 (A' Campo CPG, Leloux MS, from 1996) describes a process for separation of enantiomers from racemic mixtures by means of procedure of extraction in countercurrent, using at least two substances, one of them being the liquid in which the racemic mixture to be separated is present and the other containing the chiral adjuvant, which is combined with a substance forming the gel in the form of discrete particles in a liquid separated from the flow counter-current liquid containing the racemate, to be separated by means of a microporous membrane[5] of pores suitable to solution passage and not to gel passage. The separation principle described in this patent is similar to the chromatography employed[6] in liquid chromatography or separation methodology of simulated movable bed[7].

The execution of these kinds of procedures at industrial level requires special industrial equipment, which are normally very complex and which cost is situated in the range of a million dollars for use in procedures requiring the production of hundreds of kilos/year. In accordance to what is described in this patent, after a complex procedure for treatment of the racemic mixture for the obtainment of S-isomer from Ketamine, the results presented by the authors showed that in the best condition found for obtainment of S-Ketamine[8,9,] this latter is separated with enantiomeric excess of only 91%. Therefore, the product obtained has to be later processed[10,11] for obtainment of S-Ketamine with higher enantiomeric excess.

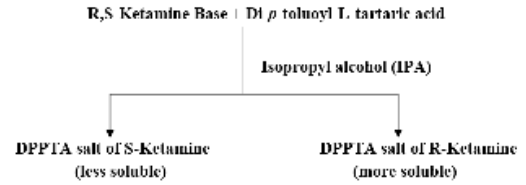
We have tried various resoluting agents like, L-Mandelic acid, D-Mandelic acid, Camphor-10-sulphonic acid, L-Lactic acid, 4-nitro tartranilic acid, Dibenzoyl-L-Tartaric acid in numerous solvents and found that only Di-p-toluoyl-L-tartaric acid was useful as it gives better separation and overall loss during the process is in very minute quantity.

EXPERIMENTAL

Di-p-toluoyl-L-tartaric acid (DPTTA) is reacted with Ketamine base in alcoholic solvent mainly methanol and refluxed for few hours. Reaction mass is cooled to room temperature and solid precipitated is filtered off. The solid obtained is DPPTA salt of R-Ketamine, the solid obtained is treated with caustic flakes in water and extracted with toluene. The toluene layer is distilled off under vacuum and degassed well, charged water. The slurry is filtered off to get R-Ketamine base which is dried under vacuum at 60-70°C. The R-Ketamine base is dissolved in Isopropyl alcohol(IPA) and pH is adjusted between 0 to 1 by IPA.HCl. The reaction mass is stirred for 30 minutes and filetered off, washed with IPA. The solid obtained is R-Ketamine Hydrochloride and it is dried under vacuum at 60-70°C.



The methanol filtrate obtained after DPTTA salt of R-Ketamine is distilled under vacuum. The solid obtained is stirred in IPA at hot condition and filtered in hot condition to get DPTTA salt of S-Ketamine. The salt obtained is treated with caustic flakes in water and extracted with toluene. The toluene layer is distilled off under vacuum and degassed well, charged water. The slurry is filtered off to get S-Ketamine base. The S-Ketamine base is dried under vacuum at 60-70°C. The S-Ketamine base is dissolved in Isopropyl alcohol(IPA) and pH is adjusted between 0 to 1 by IPA.HCl. The reaction mass is stirred for 30mins and filetered off, washed with IPA. The solid obtained is S-Ketamine Hydrochloride and it is dried under vacuum at 60-70°C.



The IPA filtrate obtained after DPTTA salt of S-Ketamine is distilled under vacuum. The solid obtained is treated with caustic flakes in water and extracted with toluene. The toluene layer is distilled off under vacuum and degassed well, charged water. The slurry is filtered off to get racemic Ketamine base. It is further used in the preparation of Ketamine hydrochloride or S and R-Ketamine hydrochloride. Hence, overall loss of material is low, the process is cost effective and time required is far less than other known process.

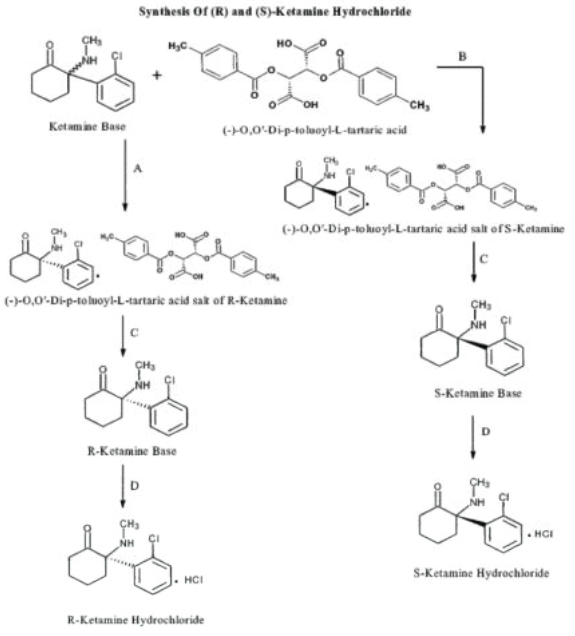
Crystallization process in this invention takes very less time and the solvents used during the process can be distilled and reused. Hence making this process commercial. Thus wastage of raw materials, reagents and solvents is not as much of other process. It is thus possible by way of the present invention to provide a commercially useful process for preparing (R)-Ketamine and (S)-Ketamine and its hydrochloride salts in good yields and using a safe and cost effective process than that of prior inventions.

Yielding reached by this process are around 80% in real yielding of S-Ketamine in its basic form and its Hydrochloride salt with enantiomeric excess higher than 99%. Factors that usually interfere on this procedures of diastereomers salt separation, as agitation speed and time required to the precipitation, were exhaustively tested and showed practically not interfere on

yielding reached and on precipitated salt quality, showing that the procedure presents enough stability and sturdiness to be industrially executed.

Pharmaceutically acceptable S-Ketamine salts, preferably the S-Ketamine Hydrochloride, can be employed for preparation of pharmaceutic compositions to be employed in Medicine and Veterinary, in analogies to exhausting pharmaceutical compositions to racemic Ketamine, as well as in new formulations, in the sense of obtained anesthesic/analgesic compositions presenting differentiate properties and with smaller side effects.

REACTION SCHEME:-



A-Methanol, 65°C, 2 hrs, RT, 5-10°C, 2 hrs
B- IPA, 50°C, 1 hr
C- DM Water, NaOH, pH=9-10, Toluene, Na_2SO_4
D-Isopropyl Alcohol, IPA.HCl, pH=0-1

1) Separation by resolution of R,S-Ketamine base:
R,S-Ketamine (50g, 0.210 moles) and (–)-O,O′-Di-p-toluoyl-L-tartaric acid (81g, 0.210 moles) were added to 500ml methanol (10 parts) under stirring. The reaction mixture was heated to 65°C with stirring for 2 hrs. The reaction mixture was cooled to room temperature and then chilled to 5-10°C for 2 hrs to crystallize (–)-O,O′-Di-p-toluoyl-L-tartaric acid salt of (R)-isomer of Ketamine and filtered the crystalline residue. The (–)-O,O′-Di-p-toluoyl-L-tartaric acid salt of (R)-isomer of Ketamine was dried under vacuum. (Yield=45.8%, M.P.=112-115°C, SOR=-26°, c=1% dimethyl formamide, chiral purity=90%).

The filtrate obtained was distilled under vacuum below 50°C and degassed well. Residue obtained is stirred with 200ml isopropyl alcohol (4 parts) at 50°C, cooled to room temperature and filtered to get (–)-O,O′-Di-p-toluoyl-L-tartaric acid salt of (S)-isomer of Ketamine. The(–)-O,O′-Di-p-toluoyl-L-tartaric acid salt of (S)-isomer of Ketamine was dried under vacuum. (Yield=84.62%, M.P.=150-155°C, SOR=-125°, c=1% dimethyl formamide, chiral purity=90%).

2) Breaking of (–)-O,O′-Di-p-toluoyl-L-tartaric acid salt of (R)-isomer of Ketamine:

30g of (–)-O,O′-Di-p-toluoyl-L-tartaric acid salt of (R)-isomer of Ketamine is treated with 5g of sodium hydroxide flakes in 300ml water under stirring for 2 hrs. The reaction mixture is then extracted with toluene (200ml x 3). The Toluene is dried over sodium sulphate and distilled off under vacuum below 60°C and degassed well for 1hr. The residue obtained is R-Ketamine Base. The R-Ketamine base is stirred with water for 30mins, filtered and dried under vacuum below 60°C. (Yield=87.49%, M.P.=120-122°C, SOR=+51°, c=2% ethanol, chiral purity=99%).

3) Preparation of R-Ketamine Hydrochloride:
10g of R-Ketamine base is dissolved in 100ml of Isopropyl alcohol. Start purging dry HCl gas till pH of reaction mass becomes between 0 to 1. Stir the reaction mass for 1hr the precipitated solid is filtered off and washed with 10ml Isopropyl alcohol to get R-Ketamine Hydrochloride. The filtered solid is dried under vacuum at 80-85°C. (Yield=86.73%, M.P.=258-261°C, SOR=-92°, c=2% water, chiral purity= 99.5%).

4) Breaking of (–)-O,O′-Di-p-toluoyl-L-tartaric acid salt of (S)-isomer of Ketamine:-
55g of (–)-O,O′-Di-p-toluoyl-L-tartaric acid salt of (S)-isomer of Ketamine is treated with 10g of sodium hydroxide flakes in 550ml water under stirring for 2hrs. The reaction mixture is then extracted with toluene (400ml x 3). The Toluene is dried over sodium sulphate and distilled of under vacuum below 60°C and degassed well for 1hr. The residue obtained is S-Ketamine Base. The S-Ketamine base is stirred with water for 30mins, filtered and dried under vacuum below 60°C. (Yield=95.46%, M.P.=120-122°C, SOR=-51°, c=2% ethanol, chiral purity=99%).

5) Preparation of (S)-Ketamine Hydrochloride:-
20g of S-Ketamine base is dissolved in 200ml of Isopropyl alcohol. Start purging dry HCl gas till pH of reaction mass becomes 0 to 1. Stir the reaction mass for 1hr the precipitated solid is filtered off and washed with 20ml Isopropyl alcohol to get S-Ketamine Hydrochloride. The filtered solid is dried under vacuum at 80-85°C. (Yield=86.7%, M.P.=258-261°C, SOR=+90°, c=2% water, chiral purity=99.9%).

RESULTS AND DISSCUSSION
Elemental composition of S-Ketamine Hydrochloride and R-Ketamine Hydrochloride, it was subjected to CHN analysis and the values obtained were compared with the theoretical values calculated from the molecular formula $C_{13}H_{17}ClNO$ of S-Ketamine Hydrochloride and R-Ketamine Hydrochloride. The data is given in Table-I.

Table-I: Elemental Composition data of R- and S- Ketamine Hydrochloride

Compound	Elemental Composition Found(Calculated)			
	C	H	N	O
S-Ketamine Hydrochloride	5.95% (5.95%)	5.86% (6.25%)	5.08% (5.11%)	5.83% (5.84%)
R-Ketamine Hydrochloride	5.94% (5.95%)	5.98% (6.25%)	5.10% (5.11%)	5.84% (5.84%)

Mass spectrum of S-Ketamine Hydrochloride and R-Ketamine Hydrochloride shows a molecular Ion Peak at 238 which is the value obtained theoretically after the protonation of one hydrogen atom in the calculated molecular mass of 237 using the molecular formula $C_{13}H_{17}ClNO$. UV spectrum of S-Ketamine Hydrochloride and R-Ketamine Hydrochloride in methanol exhibit[12] peak maxima at 130.002 nm. Assignment of various frequencies obtained from the FTIR spectrum to their corresponding functional groups is depicted in Table-II.[1]H-NMR spectral data[13] of S-Ketamine Hydrochloride and R-Ketamine Hydrochloride in DMSO-d^6 solution and the assignment of the chemical shifts and the number of protons in the molecule has been described in Table-III. [13]C-NMR spectra[13] of S-Ketamine Hydrochloride and R-Ketamine Hydrochloride in DMSO-d6 solution and the assignments of the chemical shifts and the number of protons in the molecule has been described in Table-IV.

Table-II: FTIR data of S- Ketamine Hydrochloride

Wave Number (cm^{-1})	Functional group/Band assignment
1581.84	NH Stretching Band
1722.98	C=O stretching
1410.01, 1360.01 and 1340.57	C-H Deformation
871.43 to 716.68	Aromatic C-H bending

Table-III: ^{1}H-NMR data of S-Ketamine Hydrochloride

Chemical shift (δ ppm)	Multiplicity	H atoms	Assignment
1.812	M	6H	-CH2-
2.226	S	3H	-CH3-
2.39-3.48	M	2H	-CH2-
7.620	M	3H	=CH-
7.973	M	IH	=CH-
9.186	S (Broad)	IH	-NH-

Table-IV: ^{13}C-NMR NMR data of S-Ketamine Hydrochloride

Chemical shift (δ ppm)	Assignment
21.0895	$-CH_2-$
27.5085	$-CH_3$
29.3335	$-CH_2-$
36.6084	$-CH_2-$
39.7112	$-CH_2-$
71.6159	>C<
128.2612	=CH-
128.4209	-C<
131.5894	=CH-
132.2834	=CH-
132.3878	=CH-
134.0705	=C<

CONCLUSION

1.(–)-O,O′-Di-p-toluoyl-L-tartaric gives better separation of enantiomers.

2.Racemisation process is not required as both the enantiomers are separated effectively.

3.The elemental analysis, UV, FTIR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral analysis of S-Ketamine Hydrochloride and R-Ketamine Hydrochloride confirms the chemical structure as per literature[12-14].

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