Research Article

A Benign Approach for Levetiracetam through Direct Crystallization of Etiracetam Acid

M. M. V. Ramana*, Rajesh K. Rao
*Department of Chemistry, University of Mumbai, Vidyanagari, Santacruz (East), Mumbai, 400098, India.
***Corresponding author's E-mail:** mmvramana@yahoo.co.in

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ABSTRACT

The compound (±)-alpha-ethyl-2-oxo-1-pyrrolidine acetic acid (Etiracetam Acid) is an important racemic precursor of Levetiracetam. The present study deals with the optical resolution of Etiracetam Acid by Direct Crystallization to afford both the antipodes. (-)-alpha-ethyl-2-oxo-1-pyrrolidine acetic acid is subsequently converted to Levetiracetam, thereby making the process simple and scalable.

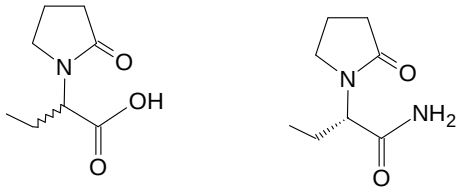
Keywords: Levetiracetam, Etiracetam acid, Resolution, Conglomerate, Direct crystallization.

INTRODUCTION

Levetiracetam is an antiepileptic chiral drug licensed for adjunctive therapy for the treatment of adults with refractory simple and partial seizure. It can also be initiated at a clinical effective dosage (500mg BD) and is patented by UCB and marketed as Keppra[1, 2]. Generic version of the drug has already hit the market. Levetiracetam is characterized by the presence of a single chiral center and is a derivative of α - amino acid i.e. 2-amino butanoic acid. The general methods of resolution of chiral drugs or intermediate include: a) Chromatographic resolution[3, 4]. b) Kinetic resolution[4] and c) Resolution by diastereomer formation[5].

Depending on the substrate, enantioselectivity and ease to handle at large scale, there differs use of resolution technology. Separation of enantiomers by Direct or Preferential Crystallization[6 - 8] generally holds true for α - amino acids[7, 8] as most of the α - amino acids are conglomerates. As per our literature study, these simple techniques of separation were very rarely applied for the resolution of chiral drugs or its chiral precursors. This approach if implemented will have a great impact on the cost of chiral life saving drugs.

To carry out separation of enantiomers by Direct Crystallization is dependent on the choice of solvents but not on the nature of the same. It also depends on the physical properties of the compound. The method of resolution by direct or preferential crystallization has been successful for *S*-methyl DOPA[3] N-acetyl-2-amino butanoic acid[9, 10], N-acetyl –DL-Norleucine[9, 10], N-acetyl-DL-Norvaline[9, 10], phenyl glycinol from glycine[11] and 2-amino butanoic acid[12]. In view of these observations in literature, we have selected a recent generic chiral drug Levetiracetam's (**IV**) racemic precursor (±)-alpha-ethyl-2-oxo-1-pyrrolidine acetic acid (**I**) which is also termed as Etiracetam Acid (**Figure 1**)[1, 2]. Etiracetam acid also happens to be α - amino acid derivative.



I **IV**

Figure 1: Etiracetam Acid (**I**), Levetiracetam (**IV**).

MATERIALS AND METHODS

All solvents were obtained from commercial sources and dried or purified by standard procedures before use. Melting points were measured on Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured using a sodium D line on Jasco DIP 370. IR spectra recorded on Shimadzu FTIR-IR-4200 spectrophotometer in KBr discs. H^1 NMR was recorded on Bucker FT-350 (350 MHz) spectrometer with TMS as an internal standard.

Resolution of (±)-alpha-ethyl-2-oxo-1-pyrrolidine acetic acid (I) (Etiracetam acid) by Direct Crystallization

Compound I (2 gm) was stirred in 2-propyl alcohol (16ml). This was heated to reflux on water bath for 30mins. The reaction mass was made clear by passing the reaction mass through filter bed. The clear filtrate thus obtained was stirred with magnetic stirrer at lower speed at 60^0 C to 70°C for 1hr. It was gradually cooled to temperature 35°C - 40°C under stirring, added seed of compound II (0.02 gm). The stirring was continued for another 90 min. The solid separated was filtered, washed with 2-propyl alcohol (2 ml) to afford crude white solid of compound **II**, 0.405gm, (yield : 20.25%), m.p.132°C - 133°C, $[\alpha]_D^{25}$, -18°, (c 1.00, acetone).

The mother liquor or the filtrate was preserved for the isolation of compound III.

After separation of compound **II**, 2-propyl alcohol (about 1ml) was added to the preserved mother liquor, and was heated to 65° C- 70°C for 30min. under stirring. It was

gradually cooled to temperature 35°C, stirred for 90 min at low speed. The solid separated was filtered and washed with 2-propyl alcohol (2 ml) to get crude white solid of compound **III**, 0.365gm (yield : 18.25%) m.p.130°C, $[\alpha]_D^{25}$, +15°, (c 1.00, acetone).

The mother liquor or the filtrate was preserved for the isolation of compound II.

After separation of compound **III**, 2-propyl alcohol (about 1ml) was added to the preserved mother liquor or the filtrate and was heated to 65° C - 70°C for 30min under stirring. The clear filtrate thus obtained was gradually cooled to 35°C and stirred for 90 min at low speed. The solid separated was filtered and washed with 2-propyl alcohol (2 ml) to get crude white solid of compound **II** 0.385gm (yield : 19.25%), m.p.128° C - 129°C, $[\alpha]_D^{25}$, -16°, (c 1.00, acetone).

Filtrate on evaporation of solvent afforded white solid of compound **III** 0.710gm (yield : 35.5%) m.p.125° C - 132°C, $[\alpha]_D^{25}$, +13°, (c 1.00, acetone).

The crude compounds **II** and **III** obtained in the above steps were combined separately and crystallized from 2-propyl alcohol to afford compound **II**, 1.6gm (yield : 80%), m.p.123° C - 124°C, (lit. [1, 2, 13, 14], m.p.122° C - 125° C), $[\alpha]_D^{25}$, -26°, (c 1.00, acetone), (lit. [1, 2, 13, 14], $[\alpha]_D^{25}$, -26°, c 1.00, acetone), and compound **III**, 1.5gm (yield : 75%), m.p.123° C - 125° C, (lit. [1, 2, 13, 14], m.p.122° C - 125° C), $[\alpha]_D^{25}$, +26° (c 1.00, acetone, (lit. [1, 2, 13, 14], $[\alpha]_D^{25}$, +26°, c 1.00, acetone). The spectral data (H^1 NMR and IR) was also consistent with the reported data[1, 2, 13, 14].

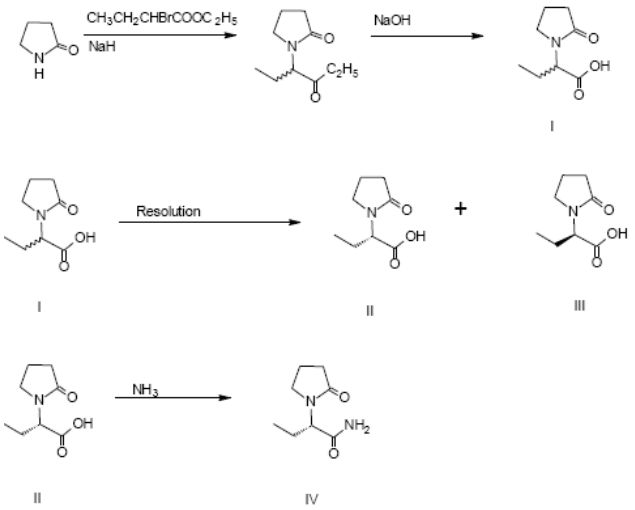
Preparation[13, 14] of (-)-alpha-ethyl-2-oxo-1-pyrrolidine acetamide (IV) (Levetiracetam).

(-)-Alpha-ethyl-2-oxo-1-pyrrolidine acetic acid (**II**) (0.002 mole) was taken in dichloromethane and cooled to –40° C to –30° C. Triethyl amine (0.002 mole) and ethyl chloroformate (0.002 mole) were added followed by aminolysis as per the process given in literature. The reaction on workup as described afforded semi-solid residue, which was dispersed in toluene, filtered and was crystallized from ethyl acetate to afford white crystalline (-)-alpha-ethyl-2-oxo-1-pyrrolidine acetamide (**IV**) (Levetiracetam), (yield : 70%), m.p.112° C - 116° C, $[\alpha]_D^{25}$, -90°, (c 1.00, acetone). The spectral data (H^1 NMR and IR) was also consistent with the reported data[1, 2, 13, 14].

RESULTS AND DISCUSSION

For optical resolution of Etiracetam Acid, required (±)-alpha-ethyl-2-oxo-1-pyrrolidine acetic acid (**I**), (-)-alpha-ethyl-2-oxo-1-pyrrolidine acetic acid (**II**) and (+)-alpha-ethyl-2-oxo-1-pyrrolidine acetic acid (**III**), were synthesized according to the literature procedure [1,2, 13, 14] and is depicted in **Scheme 1.**

The compound **I** has a melting point of 150 -153°C. The compounds **II** and **III** have a melting point of 121 -123°C. The difference in melting point between the racemate and its enantiomers is around 30 – 31°C. The solubility of compounds **I**, **II** and **III** in most of the solvents were identical except in 2-propyl alcohol. This melting point and solubility differences points towards the possibility of compound **I** being a conglomerate. Hence it should be possible to resolve compound **I** by direct crystallization.



Scheme 1 Synthetic approach for compounds **I**, **II**, **III** and **IV.**

We attempted direct resolution of compound **I** using 2-propyl alcohol as the solvent. This process sequence is depicted in **Figure 2**, which afforded compounds **II** and **III**.

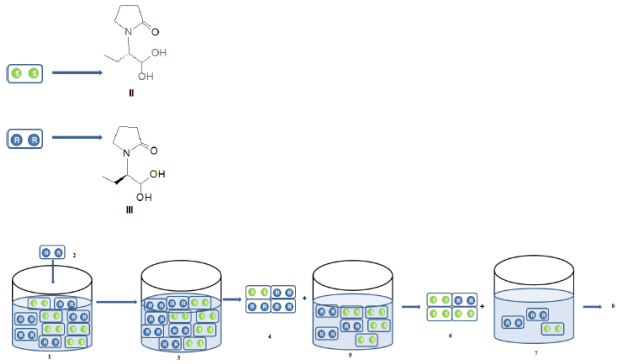


Figure 2: 1- Compound **I** dissolved in solvent at elevated temperature. 2- Seed of pure compound **III** added to the saturated solution for crystal growth at ambient temperature. 3- Saturated solution with seed of pure compound **III** at ambient temperature. 4- First crop of crude compound **III** was filtered from the saturated solution. 5- First filtrate was heated to get clear solution and allowed to cool. 6- Crystals of crude compound **II** collected by filtration. 7- Second filtrate was heated to get clear solution. 8- The steps 3 to 6 are repeated, till the compound **I** gets exhausted.

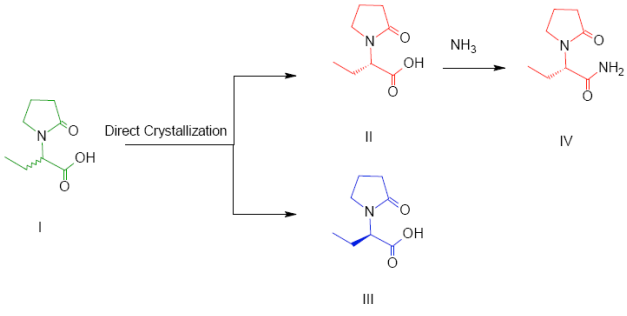


Figure 3: Direct Crystallization of Etiracetam acid (**I**) to afford compound **II** followed by its conversion to Levetiracetam (**IV**).

This process is more convenient and economical in comparison with the reported methods[1, 2, 13 – 19]. Compound **II**, thus obtained was then converted into Levetiracetam as depicted in **Figure 3**.

CONCLUSION

It was for the first time an important chiral drug intermediate Etiracetam Acid (**I**) of Levetiracetam has been resolved by Direct Crystallization to afford (-)-alpha-ethyl-2-oxo-1-pyrrolidine acetic acid (**II**) and (+)-alpha-ethyl-2-oxo-1-pyrrolidine acetic acid (**III**). (-)-alpha-ethyl-2-oxo-1-pyrrolidine acetic acid (**II**) was subsequently treated with ammonia as per the reported procedure to afford Levtiracetam[1, 2, 13, 14]. The method developed is short efficient, economical and amenable to large scale synthesis in comparison with the reported methods[1, 2, 13 - 19].

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