CHAPTER V

CONCLUSION

In this research, *N*-(*p*-Aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline and its derivatives were synthesized by the expectation that these compound will have potential anticonvulsant activity.

The synthetic pathway of them can be divided into 3 major steps, follow as:

1. The synthesis of 1,2,3,4-tetrahydroisoquinoline.
2. The synthesis of *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline.
3. The synthesis of *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline.

The first step, Bischler-Napieralski reaction and Pictet-Spengler reaction were selected to synthesize the 1 and/or 3 substituted tetrahydroisoquinoline because of available starting compounds. 1-Methyl and 1,3-dimethyl substituted 1,2,3,4-tetrahydroisouinolines were synthesized by Bischler-Napieralski. There are 6 steps to prepare this compound, such as:

1. The preparation of β-nitrostyrene and β-methyl-β-nitrostyrene by condensation of benzaldehyde and nitromethane or nitroethane.

2. The reduction of β-nitrostyrene and β-methyl-β-nitrostyrene compound by using sodium borohydride to give nitrophenylethane and nitrophenylpropane.

3. 2-Phenylethylamine and amphetamine were synthesized by catalytic hydrogenation of β-nitrostyrene and β-methyl-β-nitrostyrene, using palladium on activated charcoal as catalyst.

4. The formation of *N*-acetyl-2-phenylethylamine and *N*-acetylamphetamine by *N*-acetylation of 2-Phenylethylamine and amphetamine using acetic acid anhydride as reagent and triethylamine as catalyst.

5. 3,4-dihydro-1-methylisoquinoline and 3,4-dihydro-1,3-dimethylisoquinoline were synthesized by Bischler-Napieralski reaction. *N*-acetyl-2-phenylethylamine and *N*-acetylamphetamine were condensed to ring closure by refluxing with condensing agent in xylene or toluene at high temperature (110-140 $^{\circ}$C). 1,2,3,4-tetrahydro-1-methylisoquinoline was prepare by using phophorus pentoxide or mixed phosphorus pentoxide-phosphorus oxychloride as condensing agent. While, the preparation of 1,2,3,4-tetrahydro-1,3-dimethylisoquinoline necessary used two condensing agents; phosphorus pentoxide-phosphorus oxychloride.

6. The 1-methyl and 1,3-dimethyl substituted dihydroisoquinolines were reduced by sodium borohydride reduction to give the corresponding 1,2,3,4-tetrahydroisoquinolines.

Attempt to synthesize 1,2,3,4-tetrahydro-3-methylisoquinoline by Pictet-Spengler reaction. Amphetamine was condensed with formaldehyde to form imine, then it was cyclized by refluxing with hydrochloric acid. The resultant product was not the cyclized-compound, but it was *N*-methyl substituted amphetamine.

The second step, unsubstituted and substituted tetrahydroisoquinolines were refluxed with *p*-nitrobenzoylchloride by using potassium carbonate as catalyst, to give the corresponding *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinolines.

The final step, the nitro compounds were reduced by catalytic hydrogenation using palladium on activated charcoal to give the corresponding *N*-(*p*-aminobenzoyl)-1,2,3,4-

tetrahydroisoquinolines.The aromatic amine were rapidly decomposed when exposed to light at room temperature. The amine hydrochloride salt formation can solve this problem.

The yields of all reactions were satisfactory, except the formation of 1,2,3,4-tetrahydro-1,3-dimethylisoquinoline, so the condition should be improved for higher yield. The formation of 1,2,3,4-tetrahydro-3-methylisoquinoline by Pictet-Spengler reaction failed in this research, the Bischler-Napieralski reaction is recommended for synthesis this compound. The latter must not have the electron donating or activating group on *m*-position of aromatic ring for cyclization, the strong condensing agent and stronger condition will condense the *N*-formylamphetamine to give 3,4-dihydro-3-methylisoquinoline.

The ^{1}H and ^{13}C-NMR spectrum of *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinolines showed two groups of signals, which indicated that it consisted of major and minor rotamers. Because of the rotation of amide bond, phenyl ring of *p*-nitrobenzoyl moiety turned to 1-position of tetrahydroisoquinoline nucleus in major rotamer, and turned to 3-position in minor rotamer.

The ^{1}H and ^{13}C-NMR spectrum of *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline hydrochlorides exhibited only one group of signals, which may due to the intermolecular hydrogen bonding of ammonium hydrogen and amide part.