CHAPTER IV

RESULTS AND DICUSSION

In this research, *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline and its derivatives were synthesized as potential anticonvulsants. The 1,2,3,4-tetrahydoisoquinolines can be prepared by more than one method. Bischler-Napieralski and Pictet-Spengler reactions were selected for synthesis, because these methods are widely used and substrates are available in the laboratory. 2-Phenylethylamines were utilized as the substrate in two ways. It was synthesized by three steps. First, benzaldehyde was condensed with a nitroalkane to yield the β-nitrostyrene. Second, olefinic double bond of the β-nitrostyrene was reduced by $NaBH_4$ to obtain 1-nitro-2-phenylethane. Third, 1-nitro-2-phenylethane was reduced by catalytic hydrogenation to give the corresponding 2-phenylethylamine. *N*-Acyl-2-phenylethylamine, as the substrate in the Bischler-Napieralski reaction, can be prepared by *N*-acylation of 2-phenylethylamine. In the Bischler-Napieralski reaction, *N*-acyl-2-phenylethylamine reacted with a condensing agent to obtained 3,4-dihydroisoquinoline, then 3,4-dihydroisoquinoline was reduced to give 1,2,3,4-tetrahydroisoquinoline. But in the "one pot" Pictet-Spengler reaction, 2-phenylethylamine reacted with an aldehyde to form imine compound first, then it was cyclized with acid to yield 1,2,3,4-tetrahydroisoquinoline. After the 1,2,3,4-tetrahydroisoquinoline was prepared, *N*-*p*-nitrobenzoylation of tetrahydroisoquinoline to give *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline. Finally, The nitro compound was reduced by catalytic hydrogenation, to obtain *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline was obtained.

β-Nitrostyrene and β-Methyl-β-nitrostyrene

Benzaldehyde was condensed wih nitroalkane to give the corresponding β-nitrostyrene. In the reaction, base was used to abstract acidic proton from the α-carbon of the nitroalkane to generate a nucleophile, nitroalkyl anion, and it attacked to the carbonyl carbon to give 2-nitro-1-phenylethanol. The β-nitroalcohol was dehydrated by using acid to obtain the corresponding β-nitrostyrene. (See Figure 111)

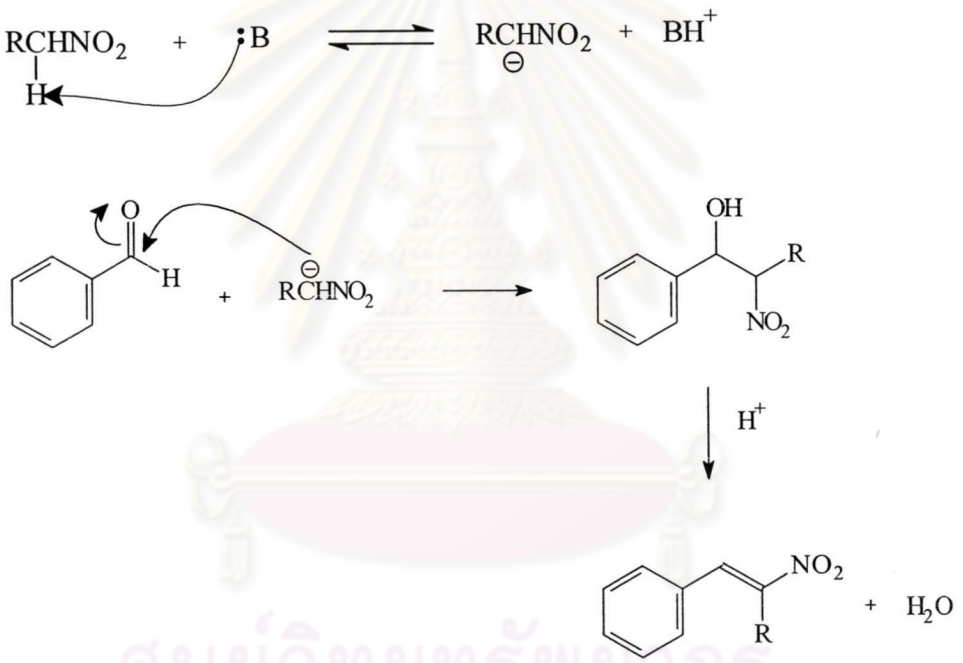

Figure 111. The mechanism of the formation β-nitrostyrene

In the synthesis of β-nitrostyrene, nitromethane and benzaldehyde were dissolved in methanol and stirred at 0°C in ice-bath, then the solution of sodium hydroxide was added to the mixture, slowly. The resultant 2-nitro-1-phenylethanol was dehydrated by added the reaction mixture in first step to the solution of hydrochloric acid at 0 °C to

obtain β-nitrostyrene. This reaction proceed so fast, and the yield was good (85%). However, when this method was used to prepare β-methyl-β-nitrostyrene, the reaction was incomplete. Experimentally, β-methyl-β-nitrostyrene can be synthisized by refluxing benzaldehyde, nitroethane and ammonium acetate in glacial acetic acid. Ammonium acetate act as base and the 2-methyl-2-nitro-1-phenylethanol was dehydrated by glacial acetic acid and heat to corresponding β-methyl-β-nitrostyrene, this reaction is "one pot" reaction and the reaction time was slower than first method, give good yield (97%).

In the first method, the strong base hydroxide ion can abstract the acidic proton at the activated methylene. The temperature of reaction must be controlled at low temperature (0-30 °C), the higher temperature force the yield of β-nitrostyrene to lower. In the higher temperature, the hydroxide ion is very active, and could also abstract the acidic proton of the intermediate "β-nitroalcohol" or "2-nitro-1-phenylethanol", and the corresponding nucleophile can react with the substrate, benzaldehyde, to generate dimeric by-product (see Figure 112).

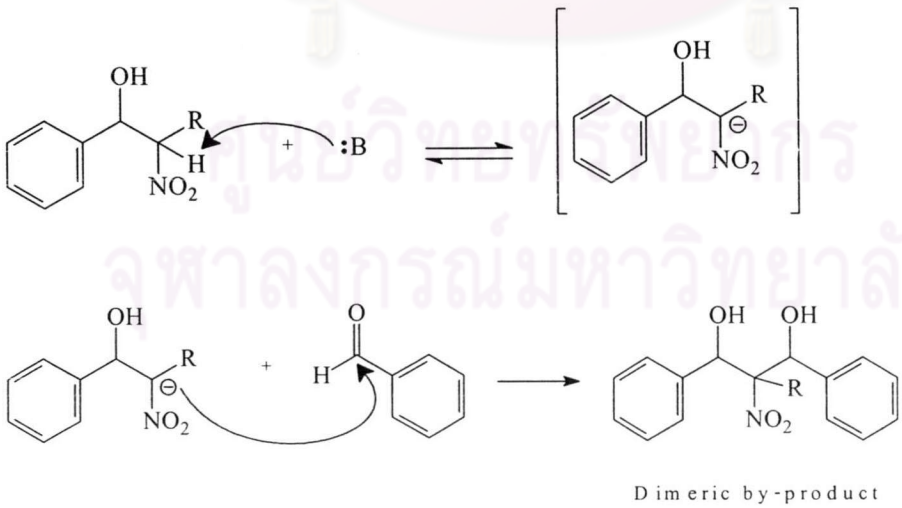

Figure 112. The mechanism of the formation of dimeric by-product in Henry condensation reaction

For β-methyl-β-nitrostyrene, the first method was unsuitable. The nitroethyl anion is stronger nucleophile than the nitromethyl anion, but in the low temperature the latter could better react with benzaldehyde due to less steric hindrance. In the second method, the experimental temperature was higher than the former. The yield of β-methyl-β-nitrostyrene was good by using this method.

The IR spectra of β-nitrostyrene and β-methyl-β-nitrostyrene are shown in Figure 32 and 34, respectively. The spectra of two compounds are similar. Aromatic and olefin displayed C-H stretching bands higher than 3000 cm^{-1}, it was occurred in 3100-300 cm^{-1} region. The C=C stretching bands of aromatic ring absorbed in the 1600-1585 cm^{-1} and 1500-1400 cm^{-1} regions. The C=C stretching bands of olefin that conjugated with aromatic absorbed near 1625 cm^{-1}. The bands of asymmetrical and symmetrical stretching of nitro group that conjugated with olefin double bond was occurred near 1550-1500 cm^{-1} and 1320-1290 cm^{-1}, respectively. The spectrum of β-methyl-β-nitrostyrene could distinguish from β-nitrostyrene by asymmetrical and symmetrical C-H stretching bands of methyl group at 2962 and 2872 cm^{-1}, respectively.

The 300 MHz ^{1}H-NMR spectrum of both compounds are shown in Figure 33 and 35, respectively. The spectrum of β-nitrostyrene showed doublet signals at δ 7.99 ppm (^{3}J = 13.5 Hz) and δ 7.57 ppm (^{3}J = 13.8 Hz), were assigned as α-H and β-H, respectively. The signals in δ 7.41-7.52 ppm region were assigned as aromatic proton. The spectrum of β-methyl-β-nitrostyrene showed singlet signals at δ 8.07 and 2.44 ppm, were assigned as α-H and β-methyl proton, respectively. The signals in δ 7.38-7.47 ppm region were assigned as aromatic proton. By computerial calculation (ChemDraw Ultra 8.0), these NMR spectrums were similar to calculated *trans*-isomer spectrums.

1-Nitro-2-phenylethane and 2-Nitro-1-phenylpropane

The corresponding 1-nitro-2-phenylethane and 2-nitro-1-phenylpropane were prepared by sodium borohydride reduction of β-nitrostyrene and β-methyl-β-nitrostyrene, respectively. This reaction is a kind of Michael nucleophilic addition. Sodium borohydride gave nucleophile, hydride anion, which attacked to the α,β-unsaturated nitro compound, the nitronate intermediate were generated. In the last step of reaction, glacial acetic acid (excess) was added to the reaction mixture, the reaction was stopped by the proton of glacial acetic acid which attached with the negative charge electorn of nitronate intermediate, the nitrophenylalkane products were obtained. (See Figure 113)

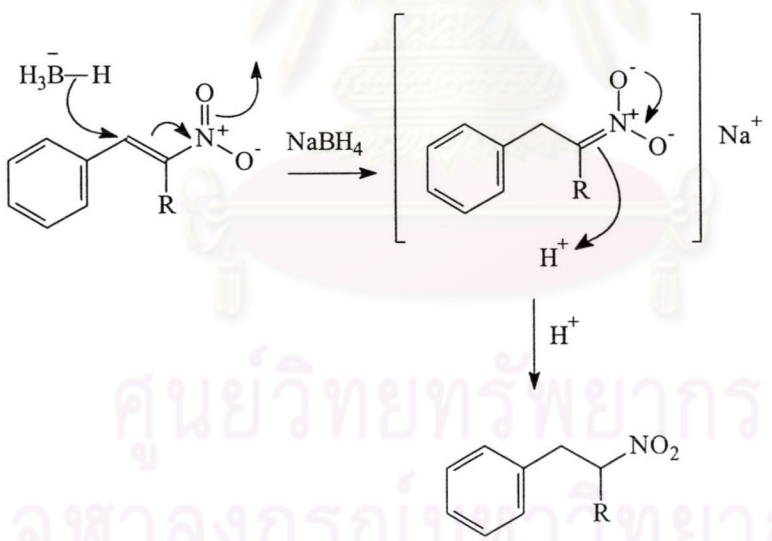

Figure 113. The mechanism of the sodium borohydride reduction of β-Nitrostyrene

Because dimeric products could possibly be produced during the borohydride reduction, these aroused from Michael addition of the nitronate intermediate with starting

nitroalkene (see Figure 114). Using low experimental temperature and silica gel in a mixed chloroform-propanol assisted the sodium borohydride reduction of nitroalkanes. The products were obtained in high yield (86-87%), and barely free of dimeric contaminants. (Barrett A.G.M. 1986)

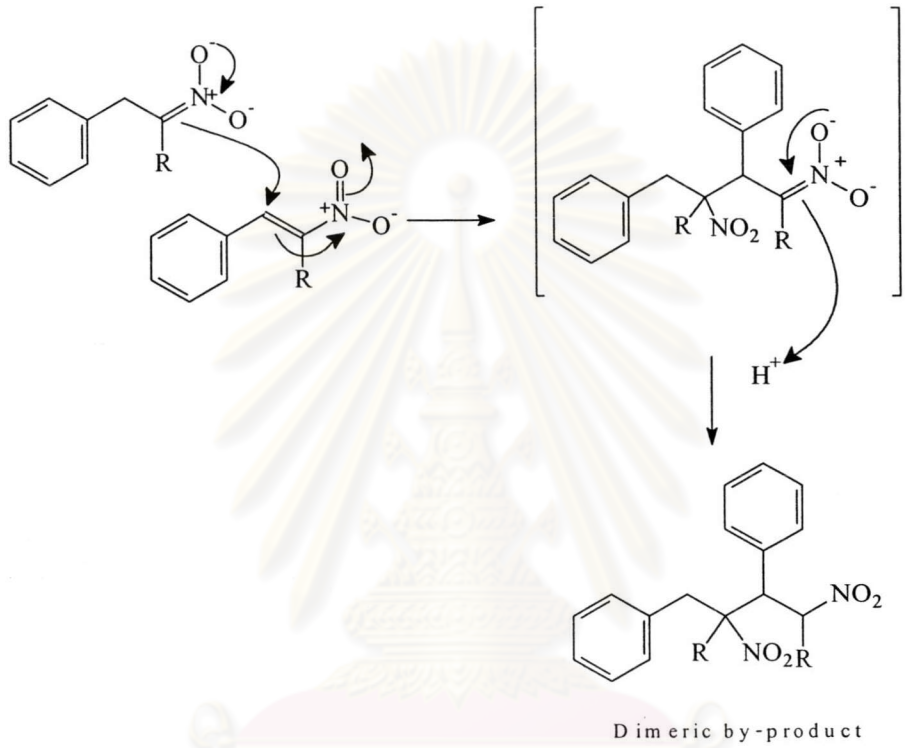

Figure 114. The formation of dimeric by-product in The sodium boerohydride reduction of β-Nitrostyrene

The IR spectra of 1-Nitro-2-phenylethane and 2-Nitro-1-phenylpropane are shown in Figures 36 and 38, respectively. The spectra of both were different from their β-nitrostyrene starting compound. The products have no olefinic chain, but they have saturated chain that link between aromatic ring and nitro group. The bands of aromatic absorption peak near 3100-300 cm^{-1}. 1-Nitro-2-phenylethane showed the C-H asymmetric and symmetric stretching bands of methylene chain at 2950 and 2920 cm^{-1}, respectively.

2-Nitro-1-phenylpropane showed C-H stretching of CH, CH_2 and CH_3. The bands of nitro group absorbed near 1550 and 1372 cm^{-1}, are O-N=O asymmetrical and symmetrical stretching, respectively.

The 300 MHz ^{1}H-NMR spectrum of 1-Nitro-2-phenylethane and 2-Nitro-1-phenylpropane are shown in Figures 37 and 39-40, respectively. 1-Nitro-2-phenylethane performed the two triplet signals at δ 3.27 and 4.56 ppm (^3J = 7.5 Hz), were assigned as methylene proton at position 2 and 1, respectively. The signals of aromatic proton were shown in δ 7.13-7.33 ppm region. In the spectrum of 2-Nitro-1-phenylpropane, signal of methyl proton (position 3) was doublet at δ 1.49 ppm that have coupling interaction with methine proton (position 2) (^3J = 6.6 Hz). The signal of 2-methine proton was multiplet at δ 4.73 ppm. The methylene proton (position 1) which as diastereotropic pair, displayed two doublet of doublets signals at δ 3.27 ppm and 2.96 ppm, respectively (^2J = 14.0 Hz and ^3J = 7.5 and 6.6 Hz, respectively). The signals of aromatic proton position (2′-6′) were in δ 7.11-7.31 ppm.

1-Amino-2-phenylethane (2-Phenylethylamine) and 2-Amino-1-phenylpropane (Amphetamine)

The corresponding amine was prepared by catalytic hydrogenation of the starting nitro compound. Palladium on activated charcoal works as catalyst. The mechanism of catalytic hydrogenation was proposed as follow. First, a reactant molecule, a aliphatic nitro compound was adsorbed on the catalyst surface. Next, the adsorption was thought to be followed by the simultaneous transfer of two or more hydrogen atoms from the catalyst to the adsorbed molecule and subsequent of the reduced molecule, an aliphatic amine.

Glacial acetic acid was added to reaction, amino product was neutralized to form salt. The result of adding glacial acetic acid was yield increasing.

The IR spectra of 2-phenylethylamine and amphetamine are shown in Figures 41 and 44, respectively. The IR spectra of compounds showed characteristic band of aliphatic primary amine, consist of N-H stretching, N-H bending and C-N stretching. The N-H asymmetrical and symmetrical stretching bands (strong) were occurred at 3400-3300 and 3330-3250 cm^{-1}. The N-H bending (scissoring) band appeared in 1650-1580 cm^{-1} region. In the 909-666 cm^{-1} regions, the medium to strong board band aroused from N-H wagging. The medium to weak C-N stretching bands were in the region of 1250-1020 cm^{-1}. The both spectra were similar. The spectrum of 2-phenylethylamine had only C-H stretching bands of methylene group at 2926 and 2853 cm^{-1}, while that of amphetamine showed C-H stretching bands of methyl at 2962 and 2872 cm^{-1}, and methylene group at 2926 and 2853 cm^{-1}. The C-H stretching bands of aromatic ring absorbed in 3100-3000 cm^{-1} region. The C=C stretching bands of aromatic were occured only in 1500-1400 cm^{-1} region.

The 300 MHz ^{1}H-NMR spectra of 2-phenylethylamine and amphetamine are shown in Figures 42-43 and 45-46, respectively. The spectrum of 2-phenylethylamine showed two triplet signals of methylene protons of position-1 and -2 at δ 2.96 and δ 2.74 ppm, respectively. The signal of amino protons is singlet and board at δ 1.60 ppm. The signals of aromatic protons were in region δ 7.18-7.32 ppm. The spectrum of amphetamine showed the doublet signal of methyl protons of position-3 at δ 1.16 ppm. The board singlet signal of amino group was at δ 1.48 ppm. The two doublet of doublets signals at δ 2.56 and 2.75 ppm were assigned as methylene protons of position-1. The multiplet signal at δ 3.20 ppm was assigned as methine proton of position-2. The aromatic protons were in region δ 7.21-7.36 ppm.

N-Acetyl-2-phenylethylamine and N-Acetylamphetamine

The corresponding *N*-acetyl-2-phenylethylamine and *N*-acetylamphetamine were prepared from 2-phenylethylamine and amphetamine, respectively. The carbonyl carbon of an acetic acid anhydride, acetylating agent, was attacked by nucleophile, primary amine. The acetate group was pushed off. The resulting acetic acid was neutralized by triethylamine to give Triethylammonium acetate. The mechanism of reaction is shown in Figure 115.

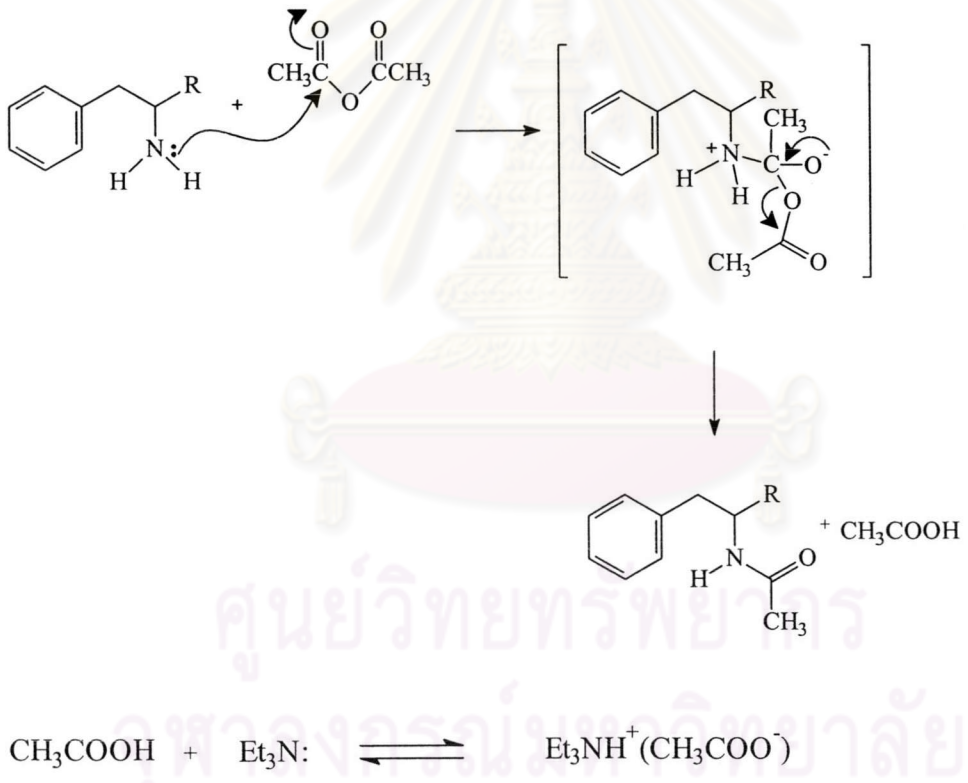

Figure 115. The mechanism of the *N*-acetylation of 2-phenylethylamine compound

The IR spectra (Neat) of *N*-Acetyl-2-phenylethylamine and *N*-Acetylamphetamine are shown in Figures 47 and 50, respectively. The two compounds are secondary amide.

The N-H stretching absorption of secondary amide was occurred in 3330-3360 cm^{-1} region. The C=O stretching of amide absorbed near 1640 cm^{-1}. (The δN-H was under the envelope of the νC=O band) Two bands at 1550 and 1250 cm^{-1}, were resulted from interaction between δN-H and νC-N of C-N-H bond.

The 300 MHz ^{1}H-NMR spectra of *N*-Acetyl-2-phenylethylamine and *N*-Acetylamphetamine are shown in Figures 48-49 and 51-52, respectively. The spectrum of *N*-acetyl-2-phenylethylamine showed the singlet signal at δ 1.92 ppm, was assigned as methyl protons of acetyl group. The triplet signal at δ 2.80 ppm was assigned as methylene protons of position-2. The quatet signal at δ 3.50 ppm was assigned as methylene proton of position-1. The board singlet signal at δ 5.39 ppm was assigned as amide proton. The aromatic protons were in δ 7.16-7.32 region. The spectrum of *N*-acetylamphetamine showed the doublet signal of methyl proton of position-3 at δ 1.44 ppm. The methyl proton of acetyl group was singlet signal at δ 1.93 ppm. The methylene protons of position-1 were diastereotropic pair, the two doublet of doublets signals of them were at δ 2.77 and δ 2.89 ppm. The multiplet signal of methine proton was at δ 4.32 ppm. The aromatic protons were in δ 7.22-7.38 ppm region.

The formation of 1,2,3,4-tetrahydroisoquinoline derivatives

There were two methods for synthesis of the 1,2,3,4-tetrahydroisoquinoline derivatives in this research. The first method, 3,4-dihydroisoquinoline was synthesized before, by Bischler-Napieralski reaction, then it was reduced by sodium borohydride reduction to yield 1,2,3,4-tetrahydroisoquinoline. And the second, 1,2,3,4-tetrahydroisoquinoline was directly prepared by Pictet-Splenger reaction. In this research,

1,2,3,4-tetrahydro-1-methylisoquinolines and 1,2,3,4-tetrahydro-1,3-dimethylisoquinoline can be prepared by the first method.

3,4-Dihydro-1-methylisoquinoline and 3,4-dihydro-1,3-dimethylisoquinoline

N-Acetyl-2-phenylethylamine and *N*-acetylamphetamine were utilized as starting agent for synthesis of 1-methyl and 1,3-dimethyl-1,2,3,4-tetrahydroisoquinolines, respectively. In the first step, *N*-acetylated compound was cyclized by refluxing with condensing agent such as phosphorus oxychloride ($POCl_3$) and phosphorus pentoxide (P_2O_5) in toluene or xylene.

The mechanism of reaction is shown in Figure 116 and 117. The condensing agents work as electrophile. Phosphorus oxychloride and phosphorus pentoxide were attacked by lone pair of amide oxygen atom. If this reaction was treated with mild condition (20-50 $^{\circ}C$), the resultant products would be imidoyl chloride or imidoyl phosphate, respectively. In the experiment, the refluxing temperature is higher than 100$^{\circ}C$ (110-140$^{\circ}C$). The high temperature enhances the formation of nitrilium ion, intermediate. The nitrilium cyclize to yield 3,4-dihydroisoquinoline. (Naubandi and Fodor 1980)

3,4-Dihydro-1-methylisoquinoline can be prepared by using only phosphorus pentoxide or the combination of phosphorus pentoxide and phosphorus oxychloride. The yield of reaction was higher when using the latter condition. The yields of two condition were 60% and 70%, respectively. While the synthesis of 3,4-dihydro-1,3-dimethylisoquinoline, the mixed condensing agents was necessary used. The yield of reaction was only 26%. The reaction could not used only phosphorus pentoxide, The poorly yield may be due to steric hindrance of α-methyl substituent.

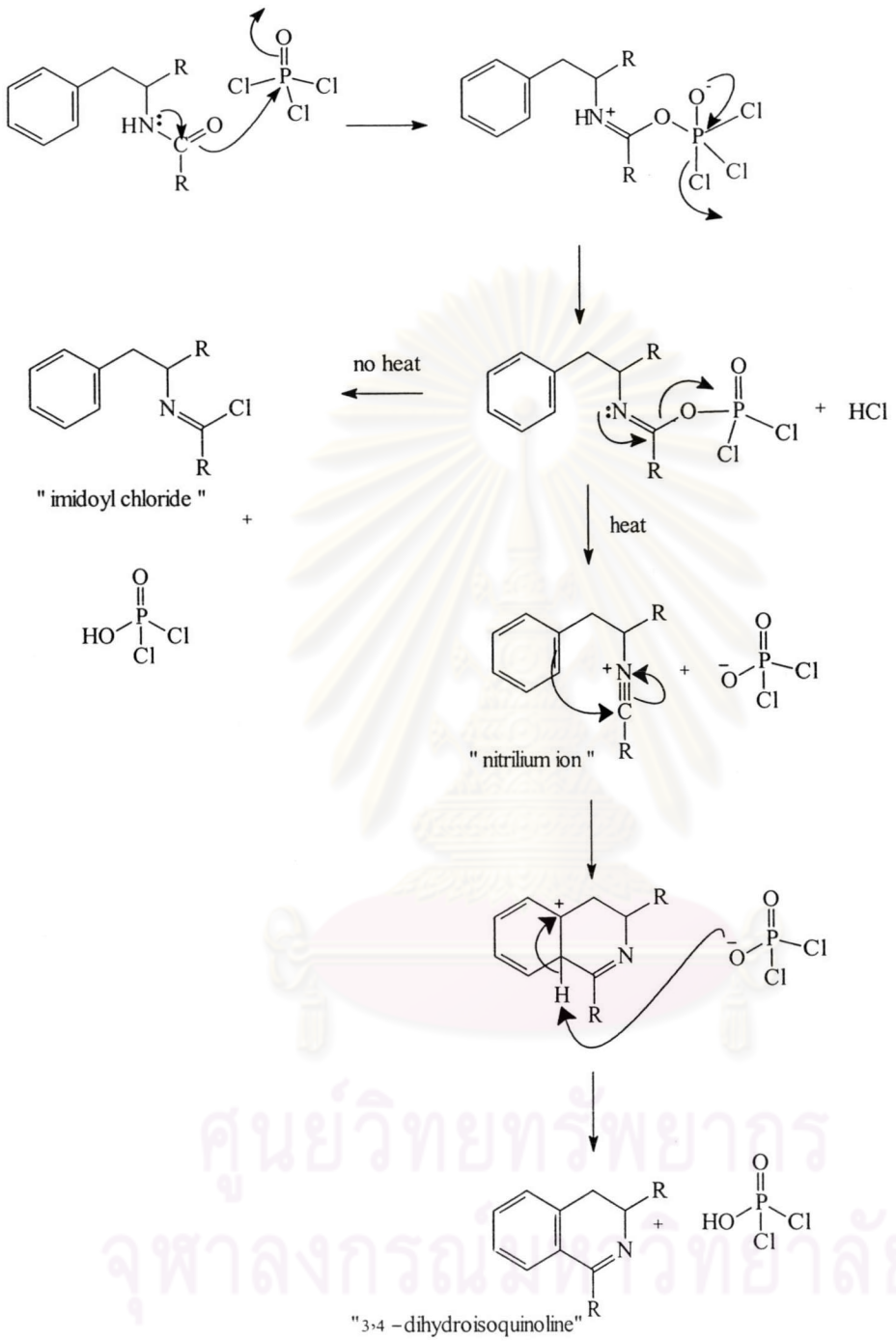

Figure 116. The mechanism of the formation of 3,4-dihydroisoquinoline by Bischler-Napieralski reaction using phosphorus oxychloride ($POCl_3$) as condensing agent

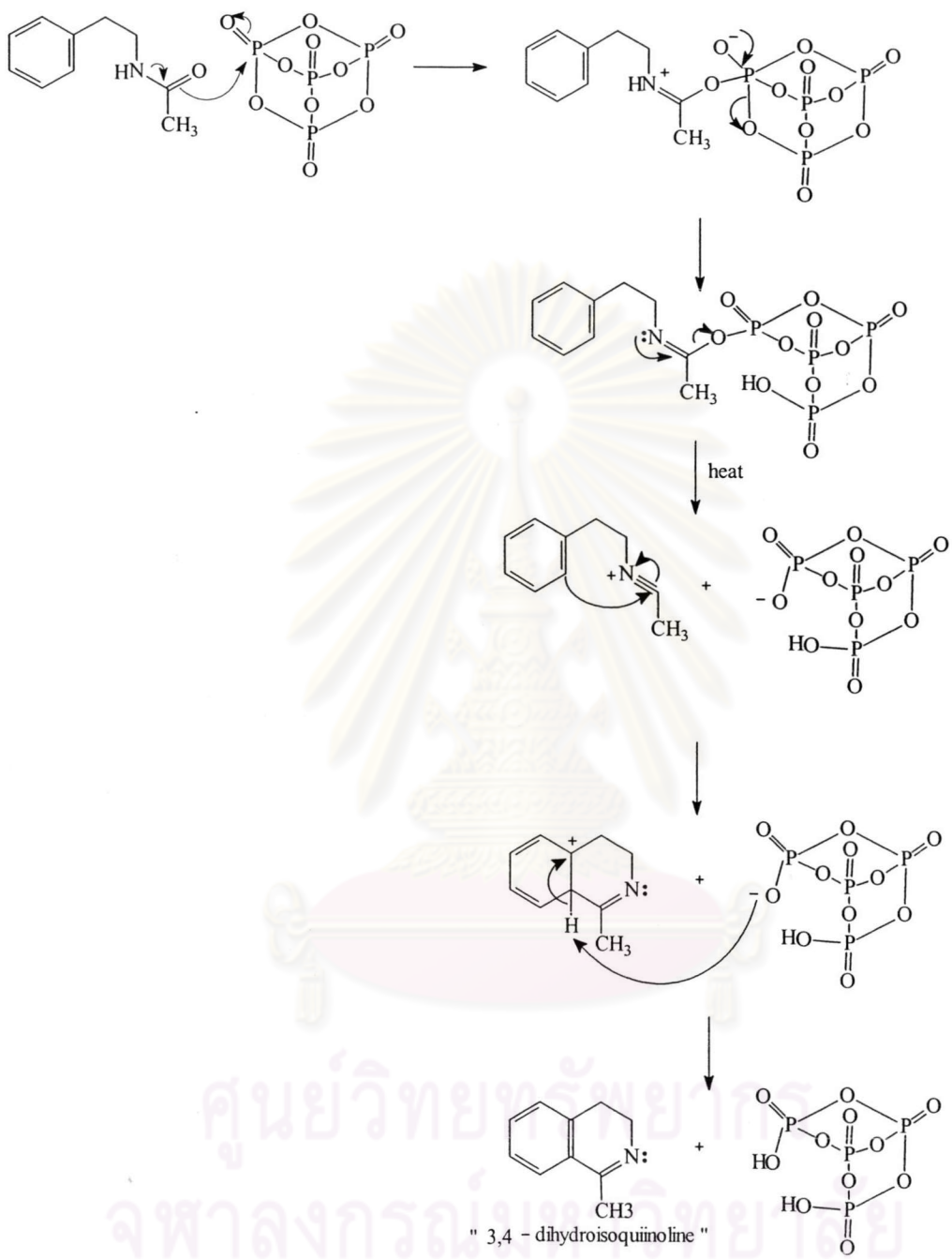

Figure 117. The mechanism of the formation of 3,4-dihydroisoquinoline by Bischler-Napieralski reaction using phosphorus pentoxide (P_2O_5) as condensing agent

The IR spectra of 3,4-Dihydro-1-methylisoquinoline and 3,4-dihydro-1,3-dimethylisoquinoline are shown in Figures 53 and 56. The ν C=N of two compounds were occurred at 1633 and 1615 cm^{-1}, respectively.

The ^{1}H-NMR spectra of 3,4-dihydro-1-methylisoquinoline and 3,4-dihydro-1,3-dimethylisoquinoline are shown in Figures 54-55 and 57-58, respectively. In the spectrum of 3,4-dihydro-1-methylisoquinoline, the singlet signal at δ 2.38 ppm was assigned as 1-methyl substituent group. The two triplet signals of 3- and 4-methylene protons appeared at δ 2.70 and δ 3.65 ppm, respectively. The two doublet signals at δ 7.17 ppm and δ 7.47 ppm were assigned as aromatic proton at positions 5 and 8, respectively.

In the spectrum of 3,4-dihydro-1,3-dimethylisoquinoline, the signal of 1-methyl substituent which as singlet, was occurred at δ 2.38 ppm. The signal of 3-methyl substituent, as doublet (^{3}J = 6.9 Hz), appeared at δ 1.36 ppm. The methine proton of position-3 occurs at δ 3.53 ppm, as multiplet. The one of methylene protons of position-4 occur at δ 2.72 ppm, the *geminal* coupling value of 15.6 Hz and the *vicinal* coupling value of 5.1 Hz, therefore the signal appears as doublet of doublets. Another one occurs at δ 2.46 ppm, the *vicinal* and the *geminal* coupling values were equal, its signal appears as triplet. These methylene protons were different in chemical shift. The characteristic of aromatic proton signals were similar to 3,4-dihydro-1-methylisoquinoline. The two doublet signals at δ 7.14 and δ 7.46 ppm are assigned as protons of position-5 and -8, respectively. The two triplet signals at δ 7.26 and δ 7.33 ppm were assigned as protons of position-7 and -6, respectively.

1,2,3,4-Tetrahydro-1-methylisoquinoline and 1,2,3,4-Tetrahydro-1,3-dimethylisoquinoline

The corresponding 1,2,3,4-tetrahydroisoquinoline was prepared by sodium borohydride reduction of the starting compound, 3,4-dihydroisoquinoline. Sodium borohydride gave a hydride ion, as a nucleophile, which attacked to the imine carbon. The acid was added to the final step of reaction to neutralize the anion intermediate. The yield of reaction was fair (55-60%). (See Figure 118)

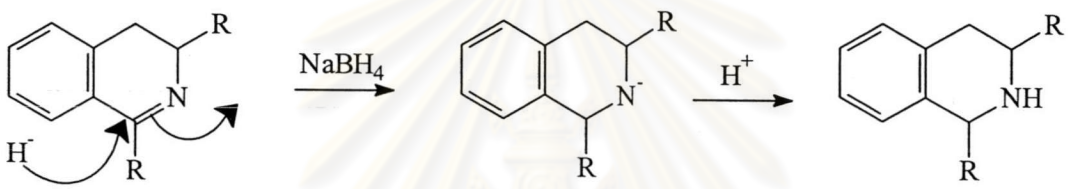

Figure 118. The mechanism of the formation of 1,2,3,4-tetrahydroisoquinoline.

The IR spectra (Neat) of 1,2,3,4-tetrahydro-1-methylisoquinoline and 1,2,3,4-tetrahydro-1,3-dimethylisoquinoline are shown in Figures 59 and 62, respectively. The two compounds showed characteristic bands of the secondary amine, as weak absorption bands in the 3350-3310 cm^{-1} region.

The 300 MHz ^{1}H-NMR spectra of 1,2,3,4-tetrahydro-1-methylisoquinoline and 1,2,3,4-tetrahydro-1,3-dimethylisoquinoline are shown in Figures 60-61 and 63-64, respectively.

In the spectrum of 1,2,3,4-tetrahydro-1-methylisoquinoline, the doublet signal at δ 1.45 ppm (^{3}J = 6.6 Hz) was assigned as 1-methyl group. The quatet at δ 4.10 ppm (^{3}J = 6.6 Hz) was assigned as 1-methine proton. The board singlet at δ 2.33 ppm was assigned

as N-H. Each of the methylene protons of positions-3 and -4 were non-equivalent. The doublet of triplets at δ 2.72 ppm (^3J = 4.5 Hz, ^2J = 16.2 Hz) was assigned as one of 3-methylene proton and another one occur at δ 2.87 ppm (^3J = 5.7 Hz, ^2J = 16.2 Hz), as doublet of doublets of doublets. The doublet of doublets at δ 3.01 ppm (^3J = 4.5 Hz, ^2J = 12.3 Hz) was assigned as one of 4-methylene proton and the doublet of triplets at δ 3.25 ppm (^3J = 5.1 Hz, ^2J = 12.3 Hz) was assigned as another one.

In the spectrum of 1,2,3,4-dihydro-1,3-dimethylisoquinoline, This compound has 2 chiral centers at position-1 and -3. The spectrum showed two signal groups of diastereomer pair (ratio 1:4). The major group of signal is assigned only. The doublet signals at δ 1.23 ppm (^3J = 6.3 Hz) and δ 1.46 ppm (^3J = 6.3 Hz), were assigned as 3-methyl and 1-methyl, respectively. The doublet of doublets signal at δ 2.56 ppm (^3J = 11.1 Hz, ^2J = 16.2 Hz) was assigned as one of 4-methylene proton, and the doublet of doublets signal at δ 2.73 ppm (^3J = 2.7 Hz, ^2J = 15.3 Hz) was assigned as another one of 4-methylene proton. The multiplet signal at δ3.05 ppm was assigned as 3-methine proton. The quartet signal at δ 4.14 ppm (^3J = 6.3 Hz) was assigned as 1-methine proton. Aromatic proton signal of major and minor diastereomer were occured in δ 7.03-7.15 ppm region.

There were two chiral centers in 1,2,3,4-tetrahydro-1,3-dimethylisoquinoline, therefore it consists of two enatiomeric pairs of two diastereomeric. The chemical shift values of the enantiomeric pairs were equivalent, but these of diastereomeric pairs were different. Figure 119 shows structures of *cis*-diastereomer and *trans*-diastereomers, 1- and 3-methyl groups of the *cis*-diasteromer preferred to be *equatorial* because of steric hindrance of two methyl groups. While, 1 and 3-methyl of *trans*-diastereomer could be *axial* and *equatorial*, equally. (Figure 120) The *geminal* coupling constant of one

methylene proton of 4-position was 11.1 Hz that indicated the 3-methine proton must be axial with this proton. ^{1}H-NMR can not determine the stereochemistry of 1,3-dimethyl substituted compound, it was recommended that the HH NOESY technique should be used to confirm the kind of stereoisomer.

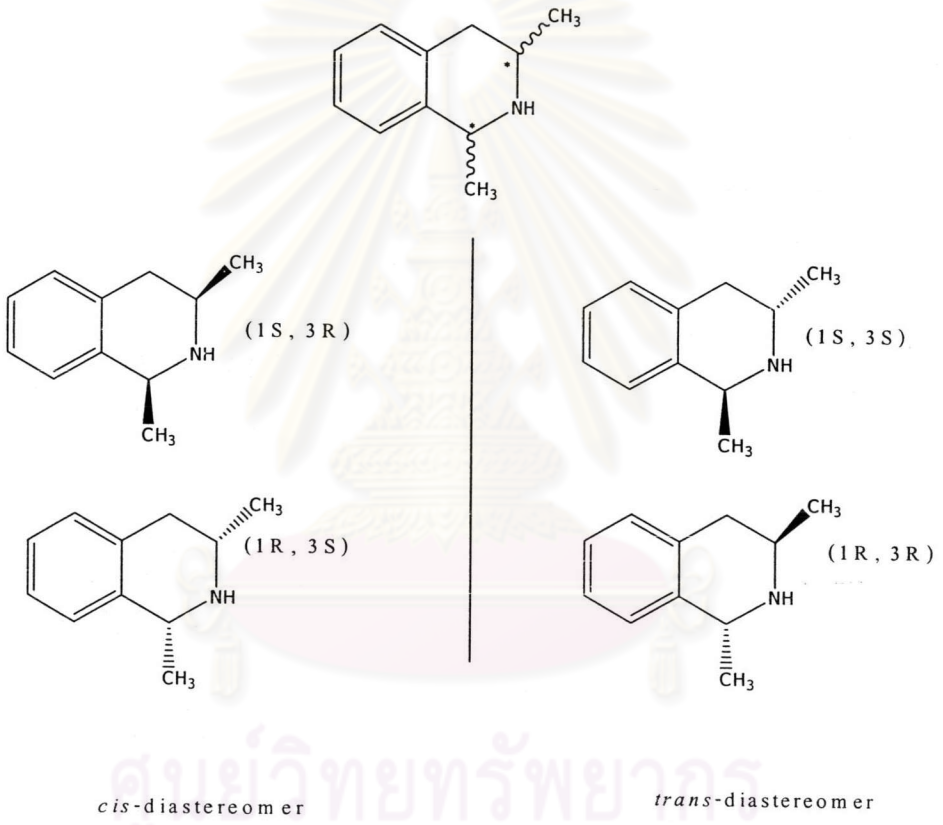

Figure 119. The representation of *cis*- and *trans*-diastereomer of 1,2,3,4-tetrahydro-1,3-dimethylisoquinoline

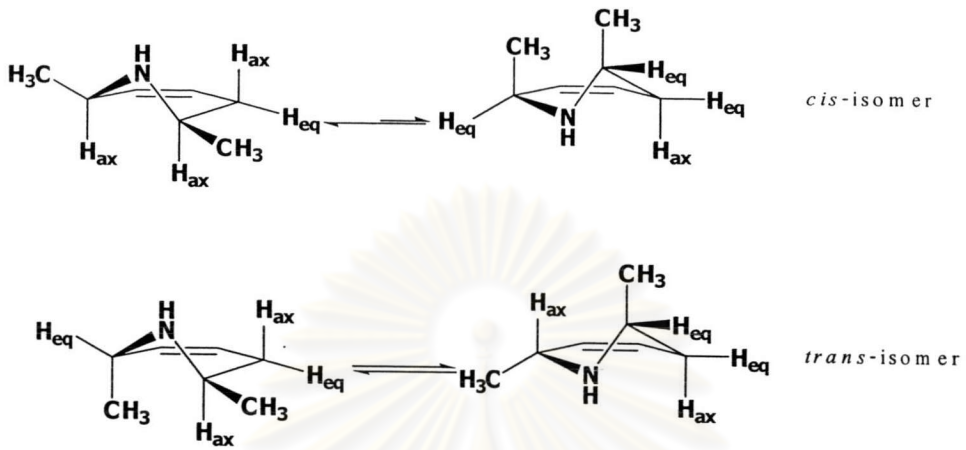

Figure 120. The conformation of pyridine part of 1,2,3,4-tetrahydro-1,3-dimethylisoquinoline

Attempt to synthesize 1,2,3,4-tetrahydro-3-methylisoquinoline

In this research, 3,4-terahydro-3-methylisoquinoline was expected to synthesize by Pictet-Splenger reaction, follow as the method of Grunewald (Grunewald, 1996). Amphetamine was condensed with formaldehyde to form shift base, then azomethine was cyclized by refluxing with concentrated hydrochloric acid. The resultant product was not the desire product, but it was a non-cyclized product, *N*-methylamphetamine (42%). The IR spectrum and ^{1}H-NMR spectrum confirmed this result. It can be described that the aromatic ring of amphetamine has no activating or electron donating group on *meta*-position to the alkyl chain which affect to the cyclization of reaction. The formation of *N*-methylamphetamine may due to phase transfer reduction. In the presence of hydrochloric acid and excess water, formaldehyde is oxidized to form formic acid. Imine-nitrogen atom is protonated by acidic proton and azomethine-carbonium is reacted with formic acid to

give *N*-methylamphetamine, this step is called "phase transfer reduction". The mechanism of reaction is shown in Figure 121.

The IR spectrum of *N*-methylamphetamine is shown in Figure 65. This compound is secondary amine, the N-H stretching band was occured at 3350-3310 cm^{-1}, and the overtone of N-H bending was shoulder at lower frequency, beside the N-H stretching band.

The 300 MHz ^{1}H-NMR spectrum of *N*-methylamphetamine is shown in Figure 66-67. The doublet signal at δ 1.11 ppm (^{3}J = 6 Hz) was assigned as methyl proton at position-3. The board singlet at δ 2.00 ppm was assigned as N-H. The sharp singlet at δ 2.44 ppm was assigned as *N*-methyl proton. The two doublet of doublets signals of 1-methylene proton were occured at δ 2.66 ppm (^{3}J = 6 Hz and ^{2}J = 12.9 Hz) and δ 2.88 ppm (^{3}J = 6.6 Hz and ^{2}J = 12.9 Hz). The multiplet signal at δ 2.84 ppm is assigned was 2-methine proton. The signals in 7.21-7.36 region were assigned as aromatic proton.

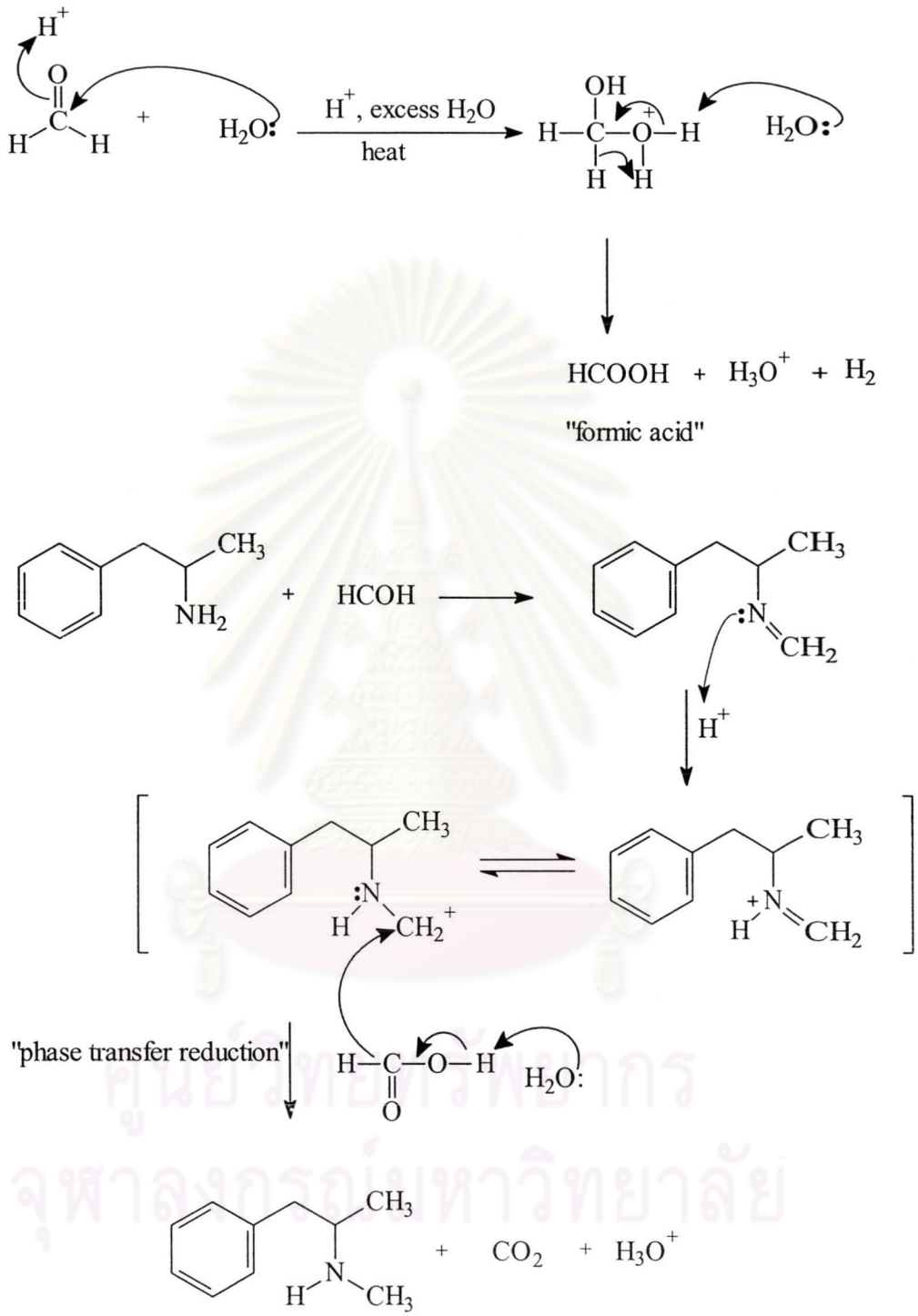

Figure 121. The mechanism of the formation *N*-methylamphetamine

N-(p-Nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline derivatives

The 1,2,3,4-tetrahydroisoquinoline compound and *p*-nitrobenzoylchloride was refluxed in the presence of potassium carbonate to give product, *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline derivative.

The reaction mechanism proceeds through nucleophilic acyl substitution. (Figure 122) This mechanism was composed of two steps, with the intermediate formation of a tetrahedral compound. The first step was the nucleophilic addition which was followed by the second step, named the beta-elimination.

Potassium carbonate added in the reaction mixture was used to neutralize hydrochloric acid occurred in the reaction. After the reaction was completed and the crude product was separated, the purification of the product was performed by recrystallization from absolute ethanol. The yields of the formation Unsubstituted and 1-methyl substituted derivatives were 85-88 %. But the yield of 1,3-dimethyl substituted compound was much less than another compounds, possibly due to steric hindrance of methyl group on 1- and 3-position.

The IR spectrum of *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline derivatives are shown in Figures 68 (unsubstituted), Figure 82 (1-methylsubstituted) and Figure 93 (1,3-dimethylsubstituted). These compounds are tertiary amide, the characteristic bands of it such as the C=O stretching vibration was occured near the 1625-1626 cm^{-1}. Because there are not N-H bond as same as the primary or secondary amide, the absorptions that involve N-H bond can not be observed. The characteristic bands of aromatic nitro group were occurred at 1520 (νas) and 1350 (νs) cm^{-1}. The other bands in spectra consisted of the

aromatic C-H stretching at 3100-3000 cm^{-1}, aliphatic C-H stretching in the 3000-2800 cm^{-1} region and aromatic C=C stretching at 1600 and 1500-1400 cm^{-1}.

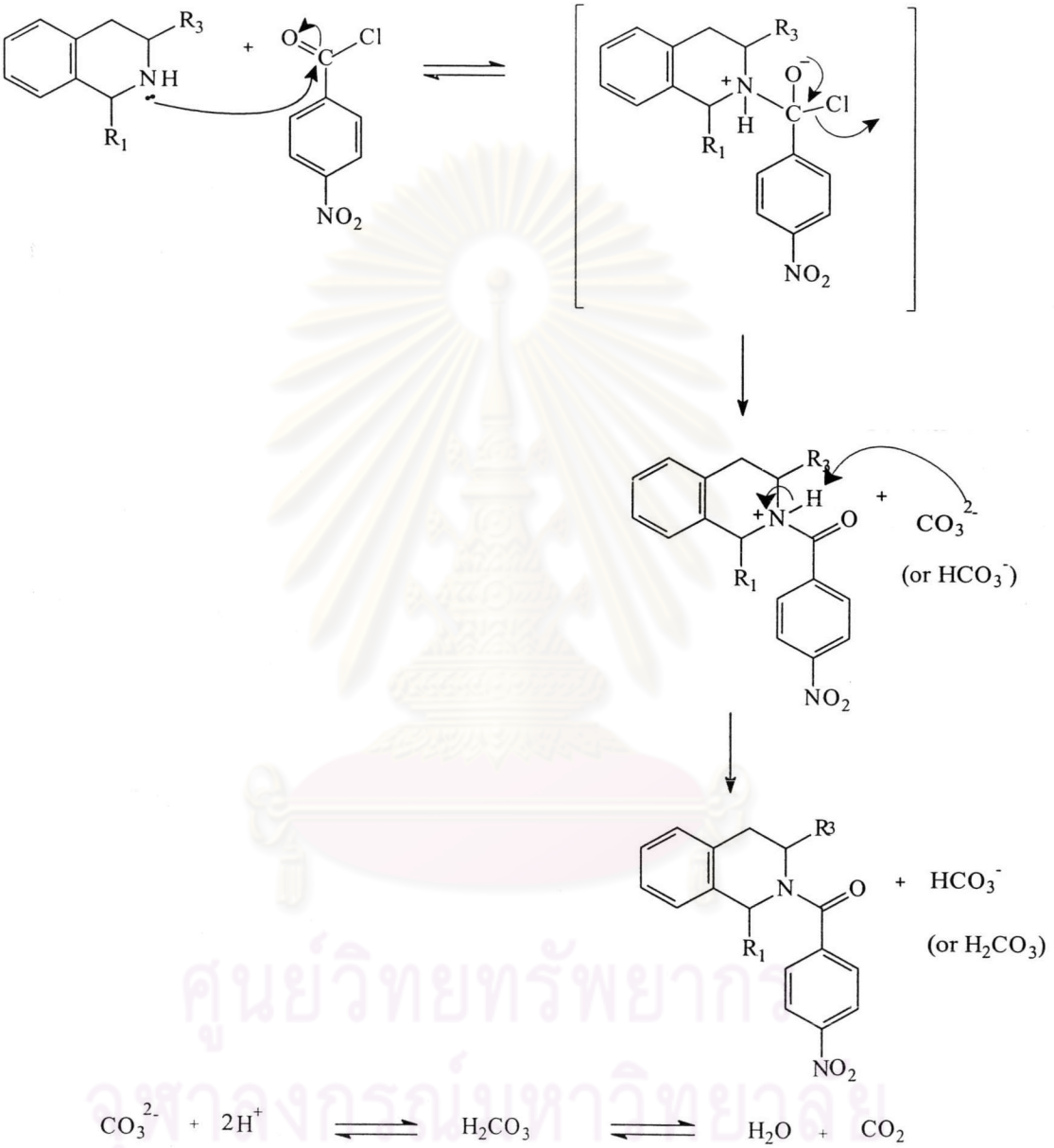

Figure 122. The mechanism of the synthesis of *N*-(*p*-Nitrobenzoyl)-1,2,3,4-tetrahydro isoquinoline derivatives.

The 300 MHz ^{1}H-NMR spectrum of *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline, at room temperature is shown in Figure 69. The signals of methylene-proton of tetrahydroisoquinoline nucleuse were all board singlet. Figure 70 show the temperature effect on 500 MHz ^{1}H-NMR spectra of this compound. But the 500 MHz ^{1}H-NMR spectrum of this compound at -10 $^{\circ}$C (Figure 71) showed the splitting of signals, clearly. The 300 MHz ^{1}H-NMR spectra of *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydro-1-methylisoquinoline and *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydro-1,3-dimethylisoquinoline are shown in Figures 83-84 and Figures 94-95, respectively)

The NMR spectra of *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline derivatives exhibited two groups of chemical shift values due to the presence of two rotameric conformation. In case of *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline, the chemical shift values of methylene protons at the same position were equivalent, each of them are enantiotropic pair. At room temperature, the tetrahydropyridine ring of tetrahydroisoquinoline exists as rapidly interconverting rotaric conformer. An axial proton becomes an equatorial proton and vice versa in the interconverting structures, and the signal of all methylene protons are singlet. As the temperature was lowered, the signals that have coupling interaction were broadened and sufficiently low temperature, the signals were split by coupling interaction with the adjacent protons.

In the case of *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydro-1-methylisoquinoline. The splitting of all ^{1}H signals was greater than the unsubstituted compound, at room temperature. Each of diastereotropic methylene protons is non-equivalent, because of 1-methylsubstituent group.

In the case of *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydro-1,3-dimethylisoquinoline. The signals of two rotamers were round at room temperature. The methylene protons at position-4 are diastereotropic pair, they are non-equivalent.

The 125 MHz ^{13}C-NMR decoupled spectrum of *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline and the 75 MHz ^{13}C-NMR decoupled spectra of *N*-(p-nitrobenzoyl)-1,2,3,4-tetrahydro-1-methylisoquinoline and *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydro-1,3-dimethylisoquinoline are shown in Figures 73-74, 85-86 and 96-97.

By the rotation and tuatomerism of amide bond, *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinolines could convert between two rotamers. Major rotamers, the ^{1}H-NMR signals of 1-position (CH_3, CH_2 or CH) were more downfield than these of minor rotamers. Inversely, the ^{1}H-NMR signals of 3- and 4-positions were more upfield than these of minor. This was described by anisotropic effect of *p*-nitrobenzoyl moiety, in the major rotamers, benzoylic phenyl ring turned to 1-positon, the chemical shift value of this position was downfield by deshielding cone of aromatic. Minor rotamer, the phenyl ring turn to the 3-position of tetrahydroisoquinoline. In addition, the ^{13}C-NMR spectrum data of the nitro compounds confirmed this phenomenon. The ^{13}C signal of 1-position was more upfield than 3-position in major rotamers and vice versa in the minor rotamers. This could be described that 1,3-interaction between benzoylic phenyl ring and 1 or 3-position of tetrahydroisoquinoline nucleuse, to make shielding effect. (see Figure 123) It was recommended that the HH NOESY should be used to confirm these structures, the correlation between 2′ and 6′-proton of benzoyl ring with 1 or 3- proton of tetrahydroisoquinoline could be occurred, which described that to be the major or minor rotamers.

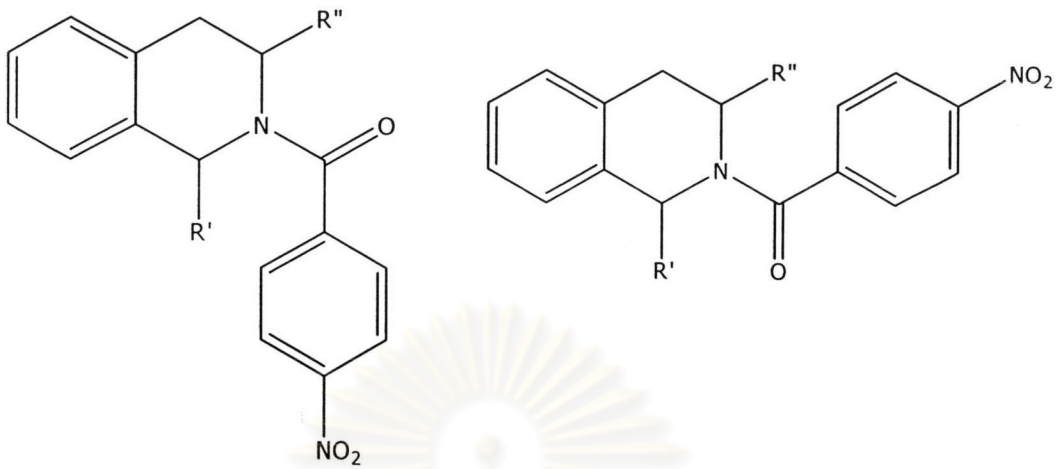

Figure 123. The representation of major and minor rotamers of N-(p-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline compounds

The peak assignment intended for ^{1}H and ^{13}C decoupled spectra were accomplished by supporting of DEPT 90, DEPT 135, HH COSY, HMQC and HMBC spectra. Table5-7 exhibit the peak assignment for ^{1}H and ^{13}C of *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinolines and long-range correlation between proton and carbon.

The 125 MHz ^{13}C-NMR, DEPT 90 and DEPT 135 spectra of *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline are compared in Figure 75. The 75 MHz DEPT 135 spectra of *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydro-1-methylisoquinoline and *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydro-1,3-dimethylisoquinoline are shown in Figure 87and 98, respectively. DEPT 90 technique gives only positive CH and CH_3 carbon signals. While DEPT135 technique gives negative CH_2 but positive CH and CH_3 carbon signals. The quaternary carbon signals are not present in these spectra.

By the 300 and 500 MHz HH COSY (Correlated Spectroscopy: HH coupling) procedure, the ^{1}H-^{1}H connectivity could be determined.

- *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline (See Figure 76)
- *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydro-1-methylisoquinoline (See Figure 88)
- *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydro-1,3-dimethylisoquinoline (See Figure 99)

The 300 and 500 MHz HMQC (Heteronuclear Multiple Quantum Correlation Spectrum) spectrum correlate the peaks between ^{1}H spectrum and the peak of ^{13}C spectrum attached together. Since the quaternary carbon atoms are not attached with proton, their peaks could not be assigned by this technique.

- *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline (See Figure 77)
- *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydro-1-methylisoquinoline (See Figure 89)
- *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydro-1,3-dimethylisoquinoline (See Figure 100)

The complete carbon assignments are achived by the analysis of the ^{1}H-detected Heteronuclear Multiple bond connectivity (HMBC) spectrum. The HMBC spectrum provides the correlations between protons and carbons through long-range coupling (2-3 bonds). The quaternary carbons are continually assigned based on the long-range coupling from the HMBC spectrum, as well as the information from their chemical shifts.

- *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline (See Figure 78-81)
- *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydro-1-methylisoquinoline (See Figure 90-92)
- *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydro-1,3-dimethylisoquinoline (See Figure101)

Table 5. ^{1}H and ^{13}C spectral assignments of *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydro isoquinoline and H,C long-range correlations.

Position Of carbon	δ ^{13}C (ppm)		δ ^{1}H (ppm)		Long-range correlation from 1H to 13C in HMBC spectrum	
	(A)	(B)	(A)	(B)	(A)	(B)
1	44.79	49.62	4.90	4.51	-	8-H
3	45.20	40.64	3.58	4.00	-	-
4	29.46	28.09	2.87	2.99	5-H	-
4a	133.34	134.45	-	-	1-H, 3-H, 4-H,8-H	1-H, 3-H, 4-H, 8-H
5	128.66	129.13	7.13-7.26	7.13-7.26	4-H, 7-H	4-H, 7-H
6	126.75	127.26			-	-
7	126.83	128.16			-	-
8	126.52	125.79		6.89	1-H	1-H
8a	132.36	132.05	-	-	1-H, 4-H, 7-H	1-H, 4-H, 7-H
1'	142.23	142.10	-	-	2' and 6'-H	
2' and 6'	127.88		7.60-7.62		6' and 2'-H	
3' and 5'	123.93		8.29-8.30		5' and 3'-H	
4'	148.43		-	-	3' and 5'-H	
C=O	168.55	168.11	-	-	1-H, 3-H, 2' and 6'-H	

Table 6. ^{1}H and ^{13}C spectral assignments of *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydro-1-methylisoquinoline and H,C long-range correlations.

Position Of carbon	δ ^{13}C (ppm)		δ ^{1}H (ppm)		Long-range correlation from 1H to 13C in HMBC spectrum	
	(A)	(B)	(A)	(B)	(A)	(B)
1-CH3	21.72	23.42	1.59	1.49	1	-
1	49.03	53.83	5.75	4.67	1-CH_3	1-CH_3
3	41.09	35.55	3.47, 3.61	3.27, 4.78	-	-
4	29.60	28.34	2.76, 2.94	2.91, 3.10	-	-
4a	132.29	133.49	-	-	3-H	-
5	-	-	7.10-7.26	7.10-7.26	-	-
6	-	-			-	-
7	-	-			-	-
8	-	-		6.87	-	-
8a	137.56	136.81	-	-	1-CH_3 and 1-H	1-CH_3 (B)
1'	142.48		-	-	3' and 5'-H	
2'+6'	127.48		7.57		6'and2'-H	
3'+5'	123.88		8.29		5' and 3'-H	
4'	148.16		-	-	2' and 6'-H	
C=O	167.62	168.92	-	-	2' and 6'-H	

Table 7. ^{1}H and ^{13}C spectral assignments of *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydro-1,3-dimethylisoquinoline of and H,C long-range correlations.
(for major conformation)

Position Of carbon	δ ^{13}C (ppm)	δ ^{1}H (ppm)	Long-range correlation from 1H to 13C in HMBC spectrum
	(A)	(A)	(A)
1-CH3	22.85	1.68	-
1	48.05	5.68	-
3-CH3	20.79	1.23	-
3	48.83	4.11	-
4	35.48	2.89 and 3.06	-
4a	136.36	-	-
5	-	7.10-7.26	-
6	-		-
7	-		-
8	-		-
8a	130.37		-
1'	143.64	-	3′ and 5′-H
2' and 6'	127.08	7.54	6′ and 2′-H
3' and 5'	124.063	8.29	5′ and 3′-H
4'	148.12	-	2′ and 6′-H
C=O	168.00	-	2′ and 6′-H

N-(*p*-Aminobenzoyl)-1,2,3,4-tetrahydroisoquinolinederivatives

A solution of *N*-(*p*-Nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline in CH_2Cl_2 was subject to low-pressure hydrogenation in the presence of palladium on activated charcoal as a catalyst.

The mechanism of catalytic hydrogenation was proposed as followed. First, a reactant molecule, an aromatic nitro compound was adsorbed on the catalyst surface. Next, the adsorption was thought to be followed by the simultaneous transfer of two or more hydrogen atoms from the catalyst to the adsorbed molecule and subsequent of the reduced molecule, an aromatic amine. The yields of all reactions were 100%. (see Figure 132)

The corresponding aromatic amine compounds were unstable when exposed to light, this problem was sloved by forming hydrochloride salt of crude product, and purified by recrystallization from methanol:diethylether.

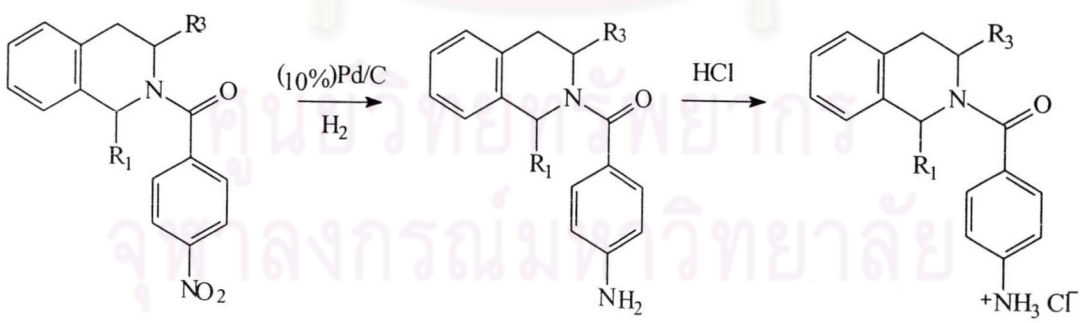

Figure 125. The formation of *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride derivatives

The IR spectrum of *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride is shown in Figure 102. Salt of primary amine shows strong, board absorption between 2800 and 2600 cm^{-1} arising from asymmetrical and symmetrical stretching in the NH_3^+ group. The asymmetrical and symmetrical N-H bending bands occur at 1570 and 1450 cm^{-1}. The C=O stretching of tertiary amide occurs at 1613 cm^{-1}. The aromatic C-H stretching bands are in the 3100-3000 cm^{-1} region.

The 300 ^{1}H-NMR spectra of *N*) -(*p*-aminobenzoyl -1,2,3,4-tetrahydroisoquinoline hydrochloride and *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydro-1-methylisoquinoline hydrochloride are shown in Figure103 and Figure108-109, respectively.

The 75 ^{13}C-NMR spectra of *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride and *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydro-1-methylisoquinoline hydrochloride are shown in Figure104 and 110, respectively.

The peak assignment for ^{1}H and ^{13}C of *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride and *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydro-1-methylisoquinoline hydrochloride are shown in Table 8 and 9.

Obviously, the NMR spectra of the final products was different from *N*-(*p*-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinolines. They have only one conformation, while the starting nitro compounds have two conformations. Because the part of primary ammonium salt can form intermolecular hydrogen bonding with amide part of molecule. This might fix the molecular structure in the only one conformation. (see Figure 126)

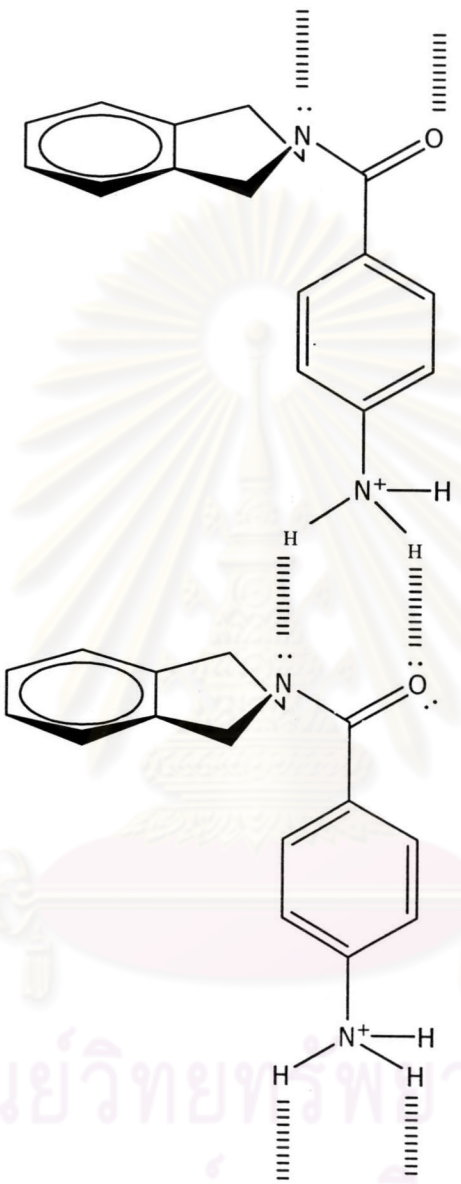

Figure 126. The representation of intermolecular hydrogen bonding of *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

Table 8. ^{1}H and ^{13}C spectral assignments of *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride.

Position Of carbon	δ 13C (ppm)	δ 1H (ppm)
1	48.0	4.66
3	45.0	3.64
4	28.51	2.84
4a	134.52	-
5	126.64	7.10-7.26
6	126.53	
7	126.36	
8	128.807	
8a	133.24	-
1'	132.88	-
2' and 6'	121.22	7.28
3' and 5'	128.71	7.48
4'	137.19	-
C=O	169.07	-

Table 9. 1H and 13C spectral assignments of *N*-(*p*-aminobenzoyl)-1,2,3,4-tetrahydro-1-methylisoquinoline hydrochloride.

Position Of carbon	δ 13C (ppm)	δ 1H (ppm)
1-CH_3	22.00	1.46
1	48.0	5.37
3	45.0	3.34
4	29.00	2.72 and 2.93
4a	138.49	-
5	127.42	7.10-7.20
6	126.80	
7	126.58	
8	129.30	
8a	133.945	-
1'	131.00	-
2' and 6'	119.45	7.09
3' and 5'	128.68	7.37
4'	141.00	-
C=O	169.0	-