CHAPTER IV

RESULTS AND DISCUSSION

In this research, N-(p-Aminobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline was synthesized as a potential anticonvulsant. Tetrahydrofuran ring reacted with Benzoyl chloride, by the use of zinc chloride as a catalyst, to yield 4-Chlorobutyl benzoate. Then, it was used to N-alkylate o-toluidine to acquire 4-[N-(o-Toluidino)]butyl benzoate. 4-[N-(o-Toluidino)]butanol was obtained from the alkaline hydrolysis of its benzoate ester. In order to block the amino group, formic acid was incorporated. N-(4-Hydroxybutyl)-N-(o-tolyl)formamide, the product from formylation, was chlorinated with thionyl chloride and its product was cyclized using Friedel-Craft alkylation. In this reaction, aluminium chloride was utilized as a catalyst. The formyl group was then removed by the hydrolysis in an alkaline hydroxide solution to gain 1,2,3,4-Tetrahydro-4,8-dimethylquinoline. Subsequently, it was acylated by p-nitrobenzoyl chloride. This nitro compound was then reduced by the catalytic hydrogenation to convert to the corresponding amine. The final product, N-(p-Aminobenzoyl-1,2,3,4,tetrahydro-4,8-dimethylquinoline, was obtained.

<u>p-Nitrobenzoic acid.</u>

This compound represents an aromatic acid. The reactant, p-nitrotoluene, was oxidized by the strong oxidizing agent, sodium dichromate, in an acidic solution. (Figure 78.)

Although benzene is quite unreactive toward the usual oxidizing agents ($KMnO_4$, $K_2Cr_2O_7$, etc.), the benzene ring renders an aliphatic side chain quite susceptible to oxidation. Among the variety of agents available for the oxidation of organic compounds, the most commonly used are derivatives of hexavalent chromium (Cr^{6+}) or heptavalent manganese (Mn^{7+}). In this case, the hexavalent chromium was used. Sodium dichromate ($Na_2Cr_2O_7$) was converted to the chromium (III) ion (Cr^{3+}) in the course of such oxidation, for a net transfer of three electrons to each chromium atom.

When the sulphuric acid was introduced to the reaction mixture, the heat of dilution of the acid caused the p-nitrotoluene to melt and oxidation occured. The reaction was considerably vigorous. The unchanged p-nitrotoluene was separated by dissolving the crude product in alkaline solution; the p-nitrobenzoic acid passed into solution and the p-nitrotoluene remained undissolved.

This compound was purified by recrystallisation from glacial acetic acid. The melting point was 239°c. The yield was satisfactory (86%).

The IR spectrum of p-nitrobenzoic acid is shown in figure 23. p-Nitrobenzoic acid obtained was confirmed by comparing its IR spectrum with

Figure 78. The chemical reaction of *p*-nitrotiluene with sodium dichromate in the acidic solution.
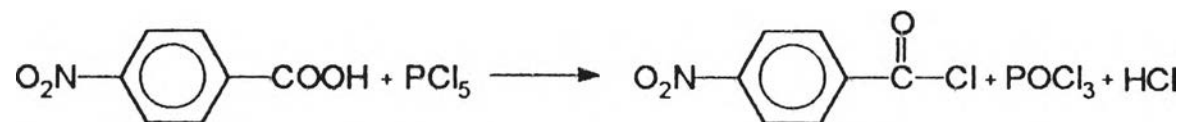

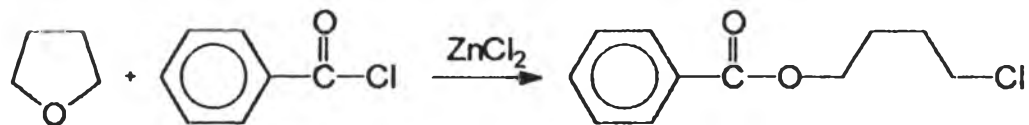Figure 79. The chemical reaction of *p*-nitrobenzoic acid with phosphorus pentachloride.

Figure 80. The chemical reaction of tetrahydrofuran with benzoyl chloride in the presence of zinc chloride.

that of authentic compound. The carboxylic acid displays very broad, intense O-H stretching absorption in the region of 3117-2840 cm^{-1}. This broad band is combined with the aromatic C-H stretching bands which present in the same region. The strong C=O stretching band occurs at 1692 cm^{-1}. The band at 1606 cm^{-1} is the result of the aromatic C-C stretching vibration. The asymmetric N-O stretching vibration absorbs at 1542 cm^{-1} while the symmetric N-O stretching vibration absorbs at 1351 cm^{-1}. The O-H bending absorption results in a band at 1429 cm^{-1}. The C-O stretching mode shows strong absorption at 1293-1279 cm^{-1}. The out-of-plane bending of the bonded O-H absorbs at 929 cm^{-1}. The band at 800 cm^{-1} shows the aromatic C-H out-of-plane bending.

<u>p-Nitrobenzoyl chloride.</u>

This compound represents an aromatic acyl halide. The p-nitrobenzoyl chloride was prepared by heating the mixture of p-nitrobenzoic acid and phosphorus pentachloride. (Figure 79.)

A carboxylic acid is perhaps more often converted into the acid chloride than into any other of its functional derivatives. From the highly reactive acid chloride, there can then be obtained many other kinds of compounds, including esters, and, in this case, amides.

An acid chloride is prepared by substitution of -Cl for the -OH of a carboxylic acid. Phosphorus pentachloride is the preferred chlorinating agent for aromatic acids which contain electron-withdrawing substituents, and which do not react readily with thionyl chloride.

The by-product, phosphorus oxychloride, can easily separated by simple distillation at ordinary pressure (b.p. 107°c). The unreacted phosphorus pentachloride was removed from the crude product by washing with diethyl ether; it can be soluble in the solvent. Then, the product was purified by recrystallising from carbon tetrachloride (m.p. 73°c).

The IR spectrum of *p*-nitrobenzoyl chloride is shown in figure 24. *p*-Nitrobenzoyl chloride obtained was confirmed by comparing its IR spectrum with that of genuine compound. The C=O stretching band of acid chloride occurs at 1775 cm^{-1}. The aromatic C-C stretching vibration absorbs at 1613 and 1545 cm^{-1}. The aromatic C-H out-of-plane bending bands appear at 842 cm^{-1}. The bands at 3000-2860, 1470, and 1383 cm^{-1} are the result of Nujol's absorption.

4-Chlorobutyl benzoate.

This compound represents a halogenated alkyl ester. The 4-Chlorobutyl benzoate was prepared by the reaction of tetrahydrofuran with benzoyl chloride in the presence of zinc chloride as a catalyst. (Figure 80.)

In spite of the fact that benzoyl chloride is highly reactive, it alone can't readily react with tetrahydrofuran. However, while zinc chloride was present in the reaction mixture, the reaction proceeded. Therefore, zinc chloride, a Lewis acid, functioned as a catalyst. The two proposed reaction mechanisms are shown in the figure 81 and the figure 82. The first mechanism occurs via nuclephilic acyl unimolecular substitution. (Figure 81.) First, the (C=O)-Cl bond breaks to produce acylium ion, R-C≡O^{+}. The acylium ion is considerably more stable
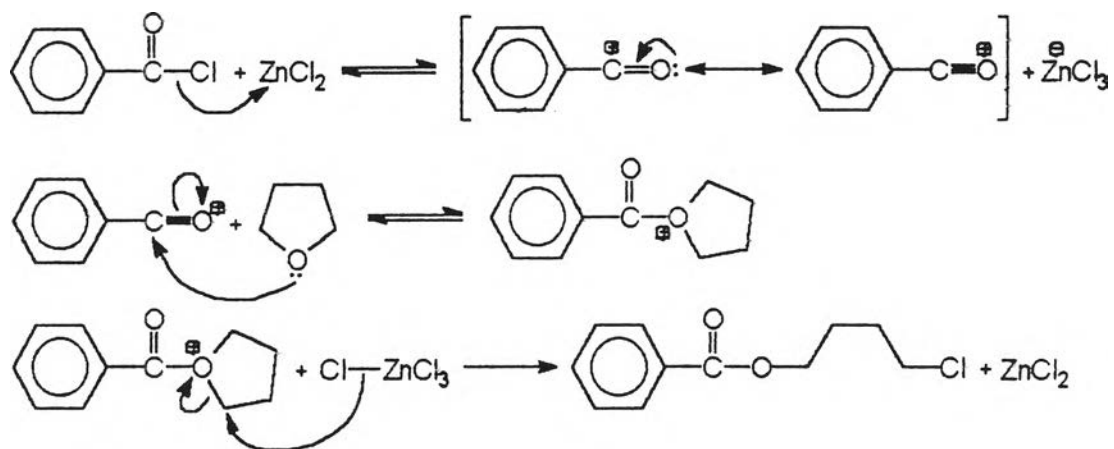
Figure 81. The proposed reaction mechanism of the formation of 4-Chlorobutyl benzoate via nucleophilic acyl unimolecular substitution.
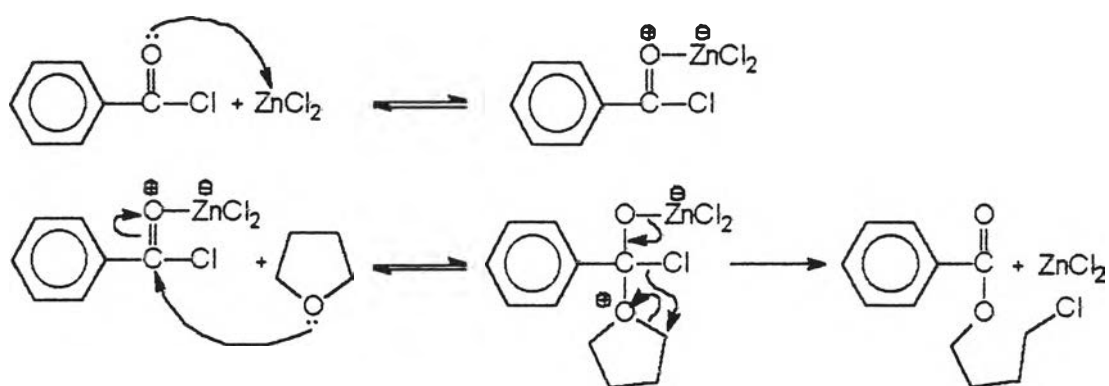

Figure 82. The proposed reaction mechanism of the formation of 4-Chlorobutyl benzoate via acid-catalysed nucleophilic acyl bimolecular substitution.

than ordinary carbocation since every atom in this ion has an octet of electrons. Second, lone pair electrons flow from the oxygen of tetrahydrofuran ring to the carbon with multiple bond, and break *pi* bond. Finally, C atom adjacent to the O atom of tetrahydrofuran is attacked by Cl from Lewis salt, then, the ring is broken to form 4-Chlorobutyl benzoate.

Alternatively, the second possible mechanism is named acid-catalysed nucleophilic acyl bimolecular substitution. (Figure 82.) It may be that the electrophile is a complex between acid chloride and Lewis acid. Zinc chloride becomes attached to carbonyl oxygen, thus making the carbonyl group even more susceptible to the nucleophilic attack; oxygen can now acquire the π electrons without having to accept a negative charge. Later, the carbonyl C is attacked by the nucleophile, tetrahydrofuran, to form the tetrahedral intermediate. Finally, the leaving group, Cl, is kicked out. Then, it attacks the C atom adjacent to O atom of tetrahydrofuran and the ring is broken to yield 4-Chlorobutyl benzoate.

After the reaction was stopped, the reaction mixture was poured into water in order to change benzoyl chloride to benzoic acid and to remove $ZnCl_2$. Then, it was washed with sodium hydroxide solution to separate benzoic acid from the product. The crude product can be easily purified by distillation through a fractionating column under reduced pressure (136°c at 2 bar). The yield was very excellent.

The IR spectrum of 4-Chlorobutyl benzoate is shown in figure 25. Aromatic C-H stretching bands occur between 3080 and 3030 cm^{-1}. Absorption arising from C-H stretching in the aliphatic part occurs in the region of 3000-

2840 cm^{-1}. The C=O absorption band of benzoate ester is at 1720 cm^{-1}. Skeletal vibrations, involving carbon-carbon stretching within the ring, absorb at 1602 and 1584 cm^{-1}. The bending vibration of the C-H bonds in the methylene group appears at 1450 cm^{-1}. The C(=O)-O stretching band of ester shows strongly at 1275 cm^{-1}. The C(alkyl)-O stretching band of ester occurs at 1115 cm^{-1}. In-plane bending bands of the ring hydrogen atom appear at 1070 and 1026 cm^{-1}, while the out-of-plane bending band occurs at 710 cm^{-1}.

The 80 MHz ^{1}H-NMR spectrum of 4-Chlorobutyl benzoate in CDCl$_3$ is shown in figure 26. The signal at $\delta 1.93$ (complex) is assigned as H$_2$-2 and H$_2$-3. The H$_2$-4 protons resonate at $\delta 3.59$ (triplet) while the H$_2$-1 resonate at lower frequency ($\delta 4.35$, triplet). The complex signal at $\delta 7.40$-7.51 is assigned as H$_2$-3' and H-4'. The remaining signal at $\delta 8.04$ (doublet of doublet) is assigned as H$_2$-2'.

4-[N-(o-Toluidino)]butyl benzoate hydrochloride salt.

This compound represents a secondary amine salt. The mixture of 4-Chlorobutyl benzoate and excess o-toluidine was heated at 125°-130°c under pressure in screwed-cap tubes. (Figure 83.)

The reaction proceeds through S$_N$2 (substitution nucleophilic bimolecular) mechanism as shown in figure 84. The 4-Chlorobutyl benzoate represents a primary alkyl halide (RCH$_2$-X) which prefers to follow S$_N$2 mechanism. The supporting evidence is that there was no rearrangement as occurring in S$_N$1 mechanism. In addition, C atom at the site of attack is less steric, so the electrophile is susceptible to be attacked by the nucleophile. After
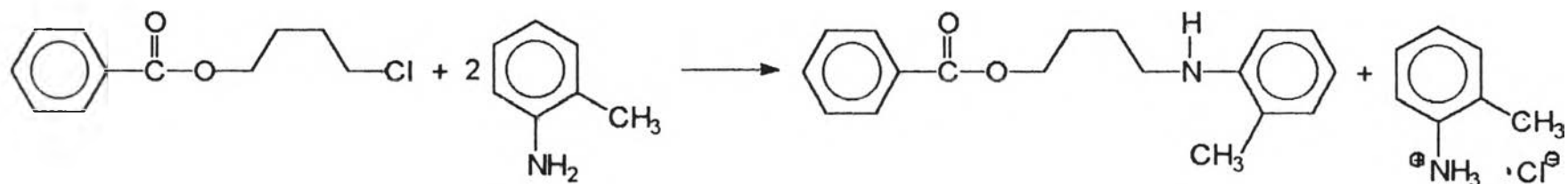
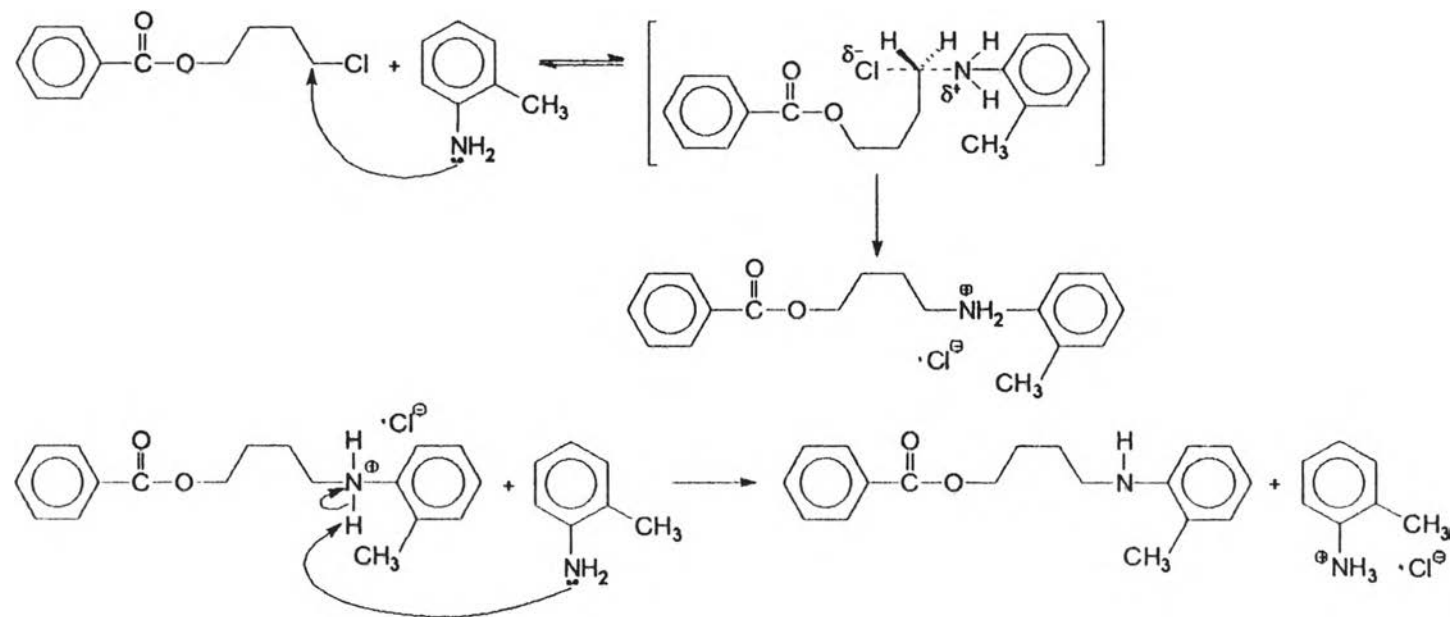Figure 83. The formation of 4-[N-(*o*-Toluidino)]butyl benzoate.

Figure 84. The reaction mechanism of the formation of 4-[N-(*o*-Toluidino)]butyl benzoate.

the salt of the product was formed, there was a proton tranfer to the excess *o*-toluidine to generate *o*-toluidine hydrochloride salt, and the product was, then, in the free-base form.

In general, there should be further alkylation of the sequentially formed products. However, in this reaction, no more alkylation occurs. Considering the structure of 4-[N-(*o*-Toluidino)]butyl benzoate, as the nucleophile becomes larger, its bulk tends to get in the way of its acting as a nucleophile. It can be concluded that steric hindrance can decrease nucleophilicity. Therefore, the nucleophile can't access to the point of attack, and the reaction is hard to proceed.

To the resulting reaction mixture, *n*-hexane was added to dissolve the crude product. The insoluble *o*-toluidine hydrochloride was filtered off. Later, the hydrochloric acid solution was added to the hexane filtrate in order to form the hydrochloride salt of the product. Surprisingly, this amine hydrochloride salt was not soluble either in hexane phase or aqueous phase and it was precipitated in the aqueous phase. This may be due to its bulky lipophilicity, which has more influence than its ionic character. (The unreacted reactant, 4-Chlorobutyl benzoate, was still dissolved in the hexane phase and could be separated.) The excess *o*-toluidine was changed to *o*-toluidine hydrochloride salt which was soluble in aqueous phase. The crude product was filtered off and purified by recrystallisation from absolute ethanol (m.p. 176-178°c).

The IR spectrum of 4-[N-(*o*-Toluidino)]butyl benzoate hydrochloride salt is shown in figure 27. Aromatic C-H stretching bands occur between 3080 and 3030 cm^{-1}. The C-H stretching vibration in the aliphatic part absorbs in the

region of 3000-2840 cm^{-1}. Salt of secondary amine absorbs strongly in the 3000-2455 cm^{-1} region because of N-H stretching vibrations. The C=O absorption band of benzoate ester is at 1716 cm^{-1}. The C-C stretching within the aromatic ring mixed with C-H bending absorbs at 1577, 1501, 1479, and 1447 cm^{-1}. The C(=O)-O stretching vibration appears at 1278 cm^{-1}. The C(alkyl)-O stretching band of ester is at 1115 cm^{-1}. The peaks at 755 and 711 cm^{-1} represent the out-of-plane aromatic C-H bending vibration.

The 500 MHz ^{1}H-NMR spectrum of 4-[N-(o-Toluidino)]butyl benzoate hydrochloride salt in CDCl$_3$ is shown in figure 28-31. The signal at δ1.79 (tt or pseudoquintet J=7.6, 7.6 Hz) is assigned as H$_2$-3. The signal at δ2.09 (tt or pseudoquintet, J=7.6, 7.6 Hz) is assigned as H$_2$-2. The singlet signal (3H) at δ 2.58 represents the aromatic methyl group. The H$_2$-4 protons resonate at δ3.35 (t, J=7.9 Hz) while the H$_2$-1 resonate at lower frequency (δ4.19, t, J=7.6 Hz). The signal at δ7.19-7.27 (complex) is assigned as H-3",H-4", and H-5". The H-6" proton, adjacent to -$^+$NH$_2$- group, resonates at δ7.73 (d, J=7.6 Hz). The multiplet signal at δ7.41 is assigned as H$_2$-3'. The signal at δ7.54 (tt, J=7.6, 1.2 Hz) is assigned as H-4'. The H$_2$-2' protons absorb at δ7.97 (dd, J=8.2, 1.2 Hz). The broad singlet signal at δ11.37 represents protons on the nitrogen atom.

4-[N-(o-Toluidino)]butanol.

This compound represents an amino alcohol. 4-[N-(o-Toluidino)]butyl benzoate was refluxed in the aqueous NaOH-alcoholic solution. (Figure 85.)

This step contains two reactions, namely neutralization and alkaline hydrolysis. (Figure 86.) The amine hydrochloride salt acts as an acid which can
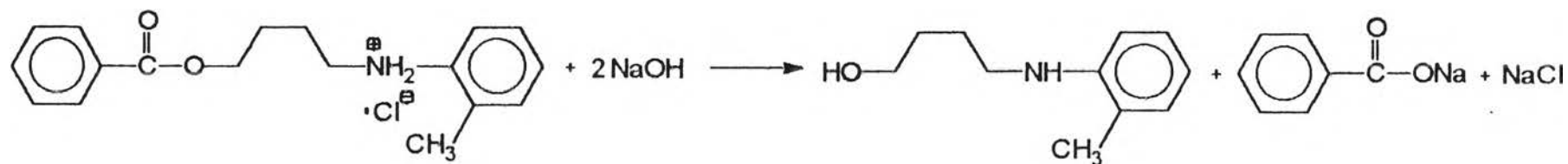
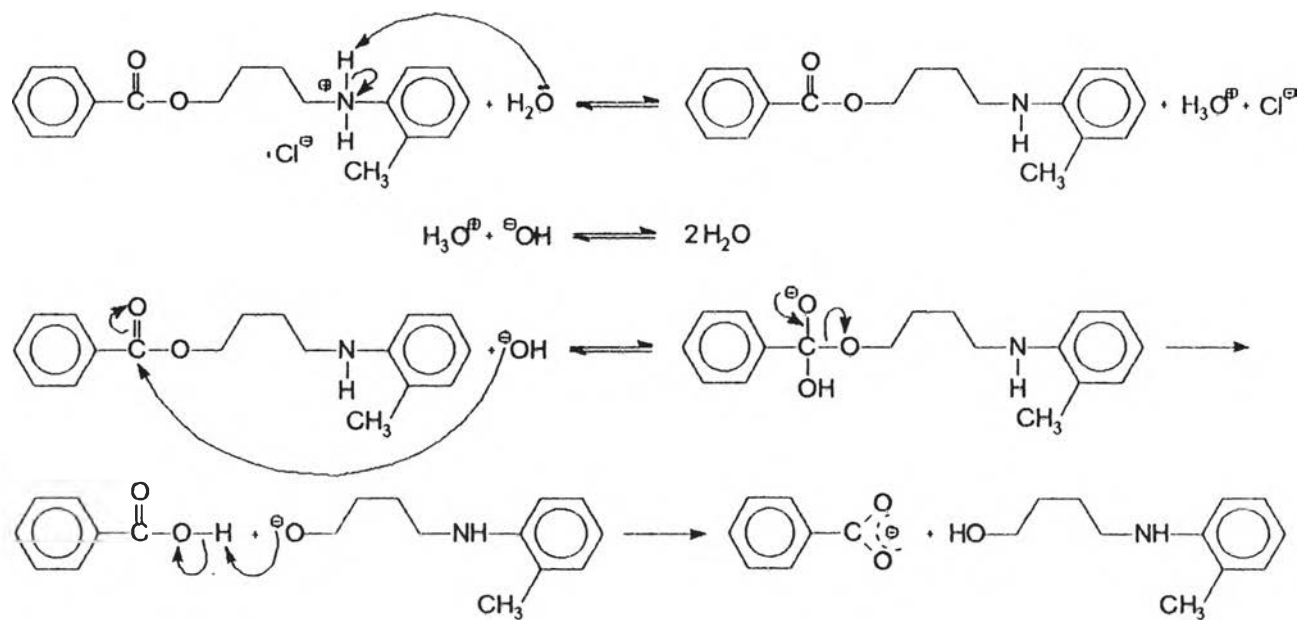Figure 85. The formation of 4-[N-(*o*-Toluidino)]butanol.

Figure 86. The reaction mechanism of the formation of 4-[N-(*o*-Toluidino)]butanol.

be neutralized by alkaline hydroxide solution to yield its corresponding free base. Ethanol was added to increase the solubility of the amine base. Succeedingly, the carboxylic ester was hydrolyzed to the carboxylic acid and the alcohol when heated in aqueous base. Under alkaline condition, of course, the carboxylic acid was obtained as its salt, sodium benzoate. Base promoted hydrolysis of esters by providing the strongly nucleophilic reagent OH⁻. This reaction was essentially irreversible, since a resonance-stabilized carboxylate anion showed little tendency to react with the alcohol.

The reaction mechanism of the hydrolysis of ester is described as followed. First, hydroxide ion attacks at the carbonyl carbon and displaces alkoxide ion. This is to say, reaction involves cleavage of the bond between oxygen and the acyl group, RCO-OR'. Attack by hydroxide ion on carbonyl carbon does not displace alkoxide ion in one step, but rather in two steps with the intermediate formation of a tetrahedral compound. Finally, there is a proton transfer from carboxylic acid to the alkoxide ion; the resulting products are carboxylate anion and alcohol.

After the hydrolysis was completed, the ethanol was evaporated out of the reaction mixture. The 4-[N-(o-Toluidino)]butanol was no longer dissolved in the reaction mixture, and separated by extraction with chloroform. The chloroform extract was washed with water to remove trace of sodium hydroxide that contaminates the extract. After the chloroform was evaporated, the crude product was purified by distillation through a fractionating column under diminished pressure (b.p. 150°c/1.5 bar).

The IR spectrum of 4-[N-(o-Toluidino)]butanol is shown in figure 32. Absorption arising from hydrogen bonded, O-H stretching occurs at 3420 cm^{-1}. The characteristic of the peak is broad and strong. Aromatic C-H stretching bands appear between 3080-3030 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The C-C stretching within the aromatic ring accompanied with C-H bending absorbs at 1618, 1600, 1521, 1482, and 1458 cm^{-1}. The C-O stretching vibration in alcohol produces a strong band at 1058 cm^{-1}. The aromatic C-H out-of-plane bending band appears at 750 cm^{-1}.

The 500 MHz ^{1}H-NMR spectrum of 4-[N-(o-Toluidino)]butanol in CDCl$_3$ is shown in figure 33-34. The signal at $\delta 1.66$ (tt or pseudoquintet, J=6.7, 6,7 Hz) is assigned as H$_2$-3. The signal at $\delta 1.72$ (tt or pseudoquintet, J=6.7, 6.7 Hz) is assigned as H$_2$-2. The singlet signal (3H) at $\delta 2.12$ represents the aromatic methyl group. The H$_2$-4 protons resonate at $\delta 3.16$ (t, J=6.7 Hz) while the H$_2$-1 protons resonate at lower frequency ($\delta 3.65$, t, J=6.1 Hz). The signals at $\delta 6.61$ (d, J=7.9 Hz), $\delta 6.65$ (ddd, J=7.3, 7.3, 0.9 Hz), δ 7.04 (d, J=7.1 Hz), and $\delta 7.11$ (ddd, J=7.9, 7.9, 0.9 Hz) are assigned as H-6', H-4', H-3',and H-5', consecutively. The very broad signal at $\delta 1.8$-3.6 (seen in figure 35.) represents the hydroxylic proton and/or NH proton which can be identified in the ^{1}H-NMR spectrum by using deuterium exchange (treatment of the sample with a small amount of D$_2$O) (Breitmaier, 1993). After the deuterium exchange (figure 36.), the signal of protons which are bonded to heteroatoms disappears.

N-(4-Hydroxybutyl)-N-(o-tolyl)formamide.

This compound represents an hydroxy amide. The mixture of 4-[N-(o-Toluidino)]butanol and formic acid was refluxed for several hours. The reaction is shown in figure 87.

The objective of this step is to block the amino group. In the next step, the hydroxy group will be chlorinated to obtain alkyl halide by the use of thionyl chloride. Nevertheless, the amino group can also react with the thionyl chloride and undesirable products are formed. Therefore, when a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, another reactive site must be temporarily blocked (Greene, 1981). The protective group used here is a formyl group. This protective group can be selectively removed by alkaline hydrolysis.

This reaction is a reversible process and proceeds very slowly. The reaction mechanism undergoes through acid-catalysed nucleophilic acyl substitution. (Figure 88.) In acidic media, the carbonyl lone pair can get protonated to produce a much better electron sink. This better electron sink can be attacked by the weaker nucleophile. Subsequently, proton transfer to the leaving group makes it a better leaving group. The reaction is reversible. According to the law of mass action, the formic acid should be excess in order to force the equilibrium shift to the right. However, in practice especially for this case, equimolecular quantities of the acid and the amine are employed. Because formic acid can react with not only the amino group, but also the hydroxy group, the acid used is limited. The mechanism of the ester formation is the same as in the amide formation which is previously described, as shown in
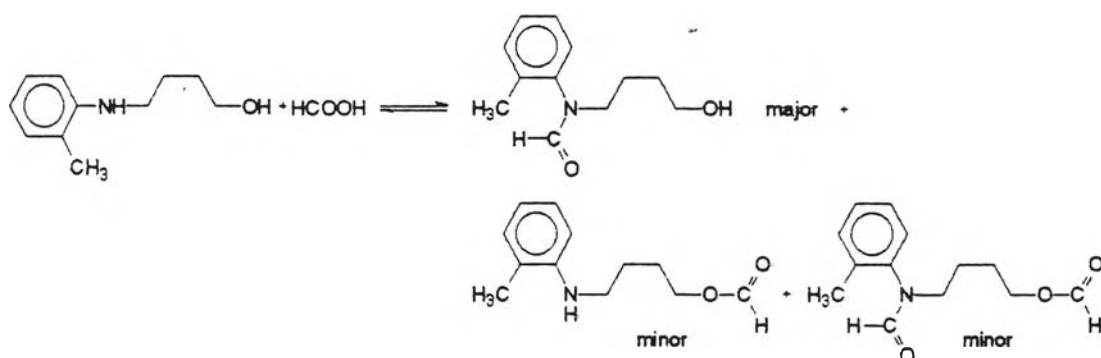
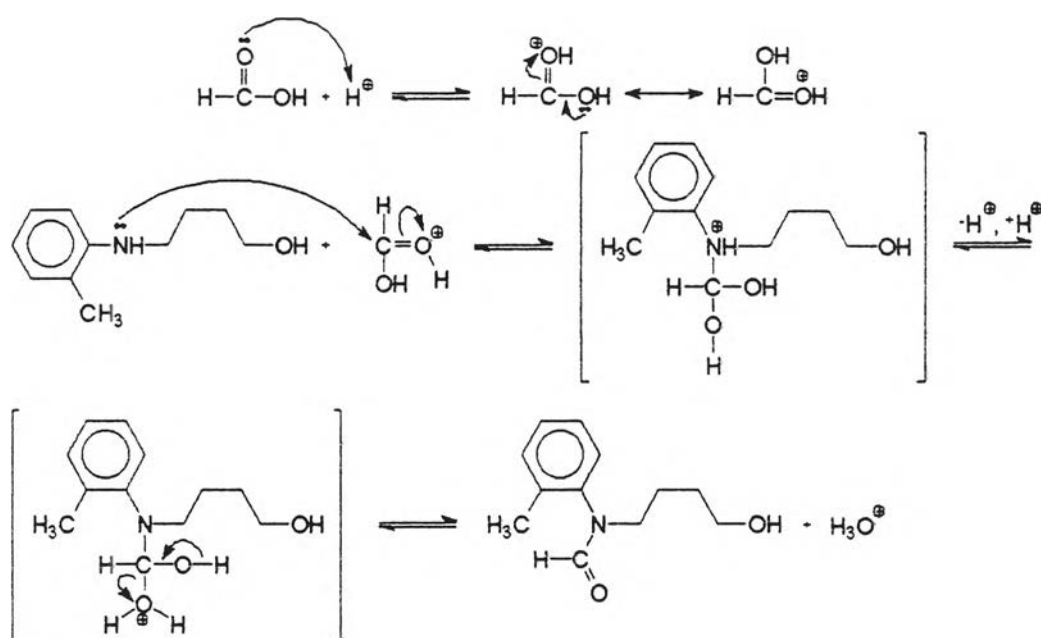Figure 87. The formation of N-(4-Hydroxybutyl)-N-(*o*-tolyl) formamide.

Figure 88. The reaction mechanism of the formation of N-(4-Hydroxybutyl)-
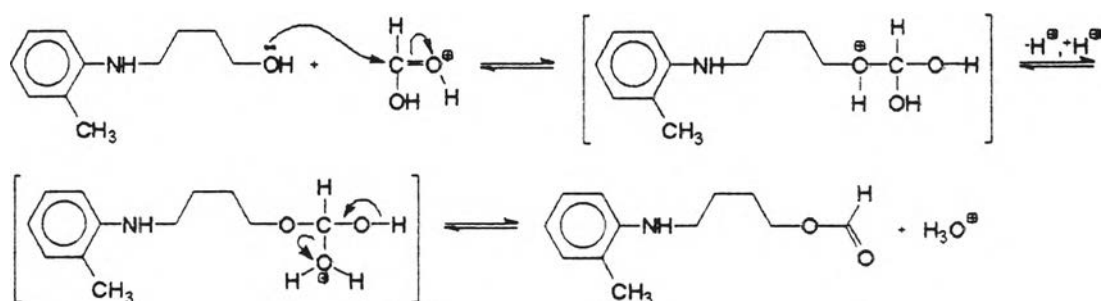N-(*o*-tolyl)formamide.

Figure 89. The reaction mechanism of the formation of the by-product,
amine-ester compound.

figure 89. The possible products of this reaction are N-(4-Hydroxybutyl)-N-(*o*-tolyl) formamide, 4-[N-(*o*-Toluidino)]butyl formate, and N-(*o*-Formyl-4-hydroxybutyl)-N-(*o*-tolyl)formamide. According to the fact that the amino group is a stronger nucleophile than the hydroxy group; therefore, the major product is the amide. The ester and the ester-amide, the minor products, can occur in little extent.

When the reaction was completed, the reaction mixture was dissolved in chloroform. Water was added to the solution to remove the unreacted formic acid, and then hydrochloric acid solution was added to extract the unreacted 4-[N-(*o*-Toluidino)]butanol from the product. When the chloroform was evaporated, the crude product was purified by column chromatography.

The IR spectrum of N-(4-hydroxybutyl)-N-(*o*-tolyl)formamide is shown in figure 37. The strong and broad band of O-H stretching vibration absorbs at 3419 cm^{-1}. Aromatic C-H stretching bands appear between 3080-3030 cm^{-1}. The aliphatic C-H stretching vibration absorbs in the region of 3000-2840 cm^{-1}. The C=O stretching absorption of amide occurs at 1668 cm^{-1}. The peaks at 1602, 1586, 1494, and 1459 cm^{-1} exhibit the absorption of aromatic C-C stretching as well as aliphatic C-H bending. The C-O stretching band appears at 1067 cm^{-1}. The aromatic C-H out-of-plane bending vibration absorbs at 769 and 731 cm^{-1}.

The 200 MHz ^{1}H-NMR spectrum of N-(4-Hydroxybutyl)-N-(*o*-tolyl)formamide in CDCl$_3$+CD$_3$OD (1:1) is shown in figure 38. The complex signal at δ1.26-1.36 represents two methylene groups (H$_2$-2 and H$_2$-3) of the alkyl part. The two singlet signals at δ1.95 and δ2.01 are assigned as the same

aromatic methyl group. The two methylene protons at position 1 resonate at δ 3.30 (t, J=5.9 Hz). The other two methylene protons at position 4 resonate at δ 3.41 (t, J=6.6 Hz). The broad singlet signal at $\delta4.14$ is the result of the hydroxylic proton absorption. The complex signal between $\delta6.81$ and $\delta7.07$ can be assigned as the four aromatic ring protons (H-3', H-4', H-5', and H-6'). The formyl proton resonates at $\delta7.79$ (s) for major conformer, and at $\delta8.03$ (s) for minor conformer.

The rotation about the C-N bond in amide is known as the hindered rotation about a partial double bond (Friebolin, 1993). At the room temperature, two resonances appear for aromatic methyl protons, as well as the formyl proton. The restricted rotation of the N-formyl group causes the geometrical difference of two conformational isomers. Since rotation around the C-N bond is slow on the NMR time scale at probe temperature, separate signals are observed for the aromatic methyl group situated *syn* and *anti* to the carbonyl oxygen (Lewin and Frucht, 1975). The structures of the two rotamers are shown in figure 90. In the more stable conformer of disubstituted formamide, the larger substituent occupies the trans-position relative to the carbonyl oxygen (Pretsch et al., 1989). Consequently, from ^{1}H-NMR spectrum, the stronger signals of the methyl protons and formyl proton represent the more stable trans-rotamer while the weaker signals represent the less stable cis-rotamer. The reason why the stronger signal of formyl proton is found more upfield than the weaker signal can be explained by the ring-current effect. When the aromatic ring rotates around the N-C(aromatic) bond, the formyl proton could be shielded by the magnetic field induced by the circulating π electrons of the aromatic ring. As a result, the formyl proton is shifted more upfield for the trans-rotamer.

cis-form   trans-form
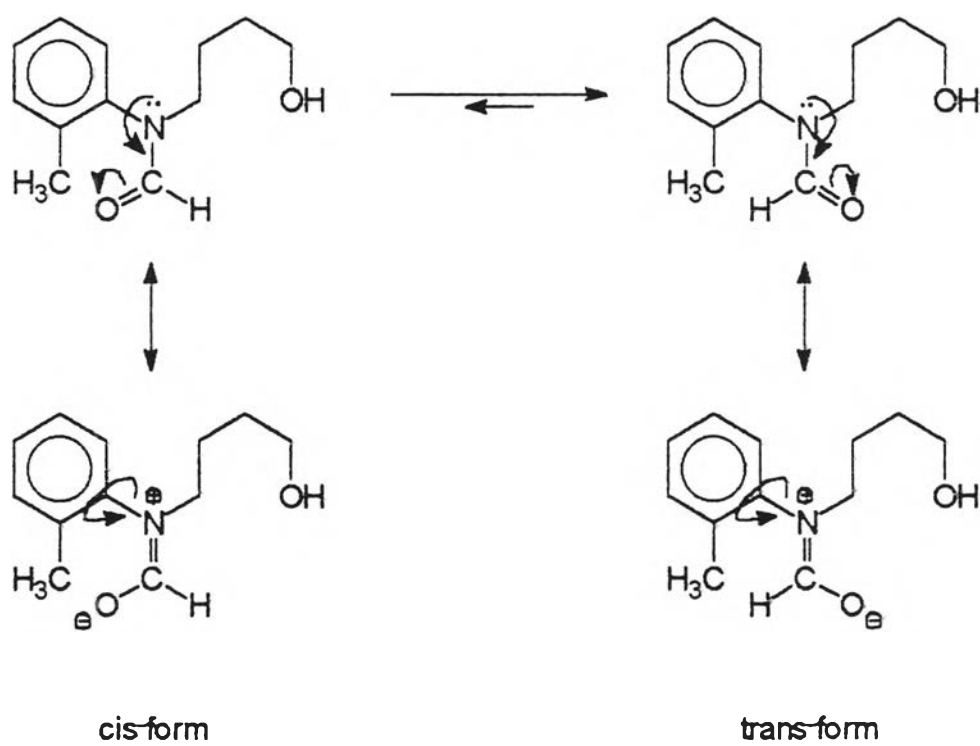
Figure 90. The chemical structures of the two rotamers of N-(4-Hydroxybutyl)-
N-(o-tolyl)formamide.

N-(4-Chlorobutyl)-N-(o-tolyl)formamide.

This compound represents a halogenated alkyl amide. N-(4-Hydroxybutyl)-N-(o-tolyl)formamide was reacted with thionyl chloride in order to change the hydroxy group to the chloro group. (Figure 91.)

One of the more usual methods of converting alcohols to alkyl chlorides is treatment with thionyl chloride, $SOCl_2$. This reaction has been shown to proceed through an alkyl chlorosulfite, an ester that can be shown to decompose upon heating to the alkyl chloride and SO_2. (Figure 92.) The chlorosulfite decomposes through a cyclic intermediate, which breaks down in a sort of "internal return" reaction, forming the chloride with retention of configuration. Since the substitution takes place through a type of "internal return" reaction, it is often referred as an S_Ni (substitution-nucleophilic-internal) reaction (Gould, 1959).

Thionyl chloride is particularly convenient, since the products formed besides the alkyl chloride are gases and thus easily separated from the alkyl chloride; any excess of the low-boiling thionyl chloride ($79^{o}c$) is easily removed by distillation. The crude product was purified by columnn chromatographic technique.

The IR spectrum of N-(4-Chlorobutyl)-N-(o-tolyl)formamide is shown at figure 39. Aromatic C-H stretching bands appear between 3080-3030 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} show the aliphatic C-H stretching vibration. The strong peak at 1678 cm^{-1} represents the C=O stretching vibration of amide. The aromatic C-C stretching vibration together with the
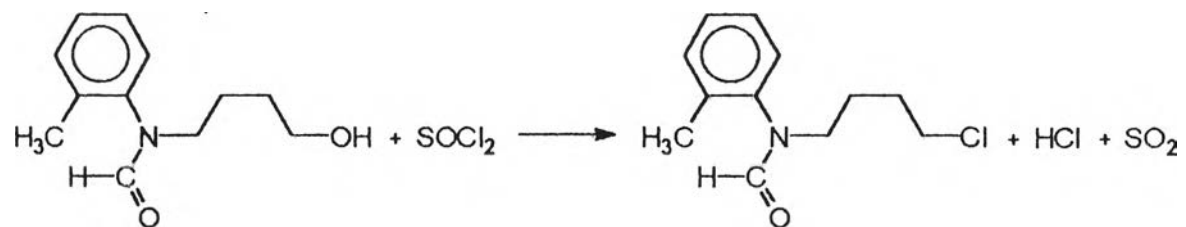
Figure 91. The formation of N-(4-Chlorobutyl)-N-(o-tolyl)formamide.
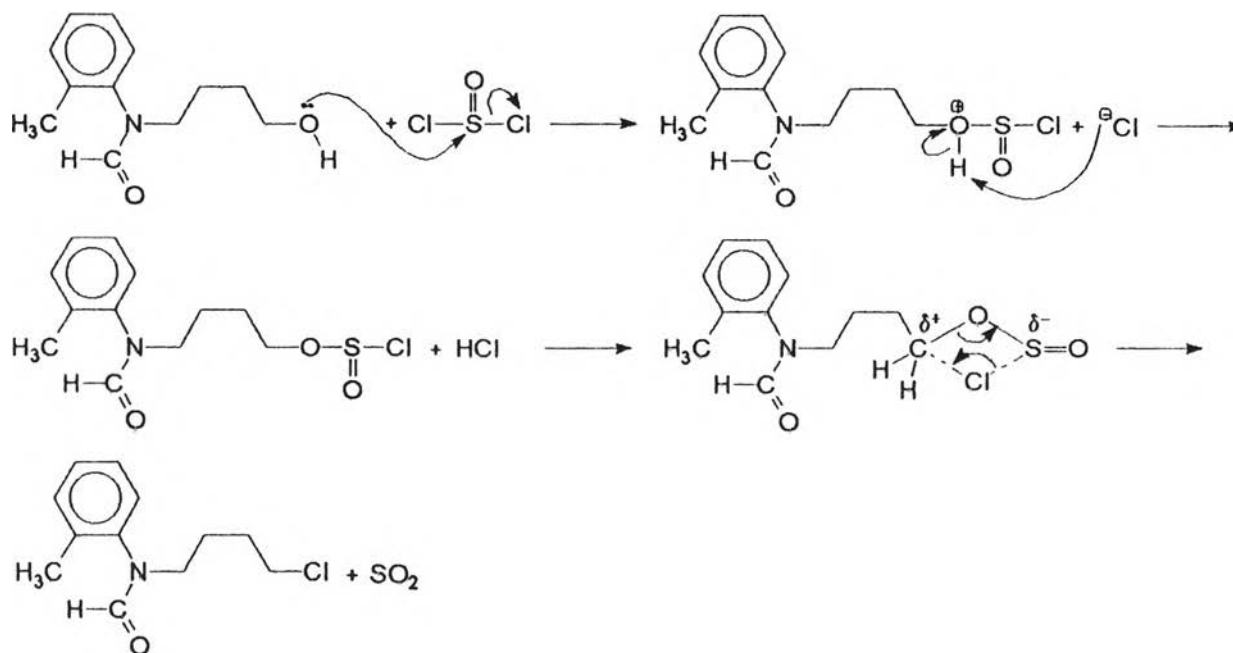

Figure 92. The reaction mechanism of the formation of N-(4-Chlorobutyl)-N-(o-tolyl)formamide.

aliphatic C-H bending vibration absorbs at 1602, 1582, 1494, and 1459 cm^{-1}. The aromatic C-H out-of-plane bending vibration shows the bands at 758 and 729 cm^{-1}.

The 200 MHz ^{1}H-NMR spectrum of N-(4-Chlorobutyl)-N-(o-tolyl)formamide in CDCl$_3$ is shown in figure 40. The signals at δ1.58-1.80 (complex) are assigned as two methylene groups at position 2 and position 3. The aromatic methyl protons resonate at δ2.18 (s) for minor conformer, and at δ 2.22 (s) for major conformer. The signal at δ3.49 (t, J=6.3 Hz) is assigned as the methylene protons at position 1. The remaining methylene protons absorb at δ3.65 (t, J=7.2 Hz). The complex signal between δ7.04 and δ7.28 can be assigned as the four aromatic ring protons (H-3', H-4', H-5', and H-6'). The two singlet signals at δ8.05 and δ8.27 are interpreted as the formyl proton. The phenomenon about the hindered rotation around the C-N partial double bond in amide can be found in ^{1}H-NMR spectrum and can be delineated as occuring in the previous compound.

N-Formyl-1,2,3,4-tetrahydro-4,8-dimethylquinoline.

This compound represents N-formyl-1,2,3,4-tetrahydro quinoline derivative. N-(4-Chlorobutyl)-N-(o-tolyl)formamide underwent the intramolecular cyclization in the presence of Lewis acid, aluminium chloride, as a catalyst. (Figue 93.)

The reaction proceeds through Friedel-Crafts alkylation. The mechanism of reaction involves the electrophilic aromatic substitution as shown in figure 94, in which the electrophile is an alkyl cation. The function of the
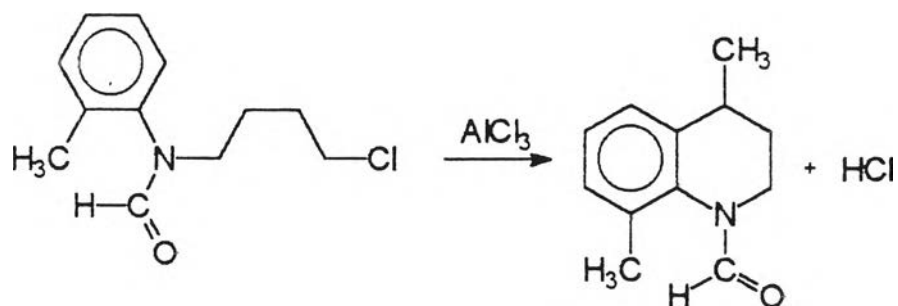
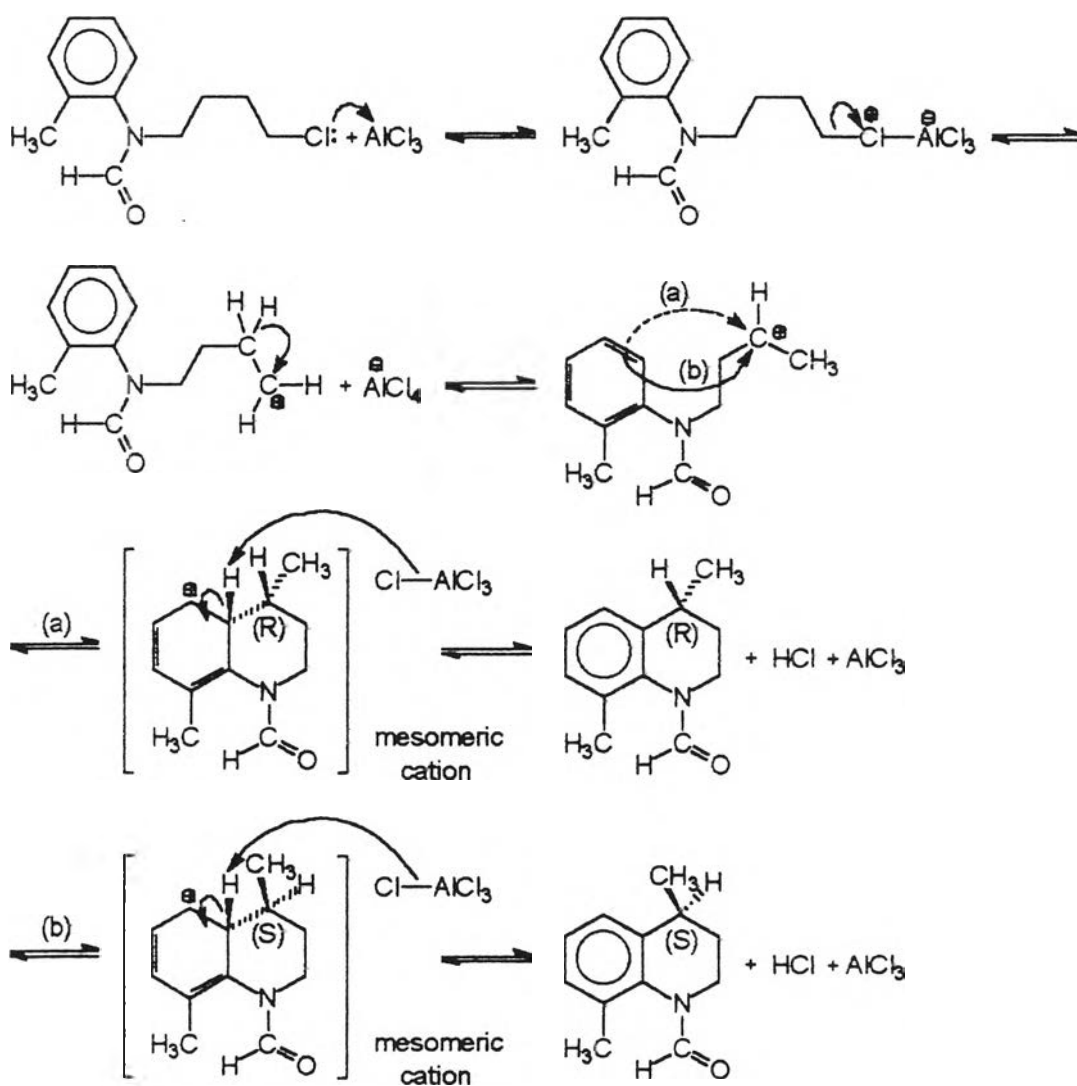Figure 93. The formation of N-Formyl-1,2,3,4-tetrahydro-4,8-dimethylquinoline.

Figure 94. The reaction mechanism of the formation of N-Formyl-1,2,3,4-tetrahydro-4,8-dimethylquinoline.

aluminium chloride is to generate this carbocation by abstracting the halogen from the alkyl halide part. Judging from the mechanism, the alkyl carbocation undergoes extensive skeletal rearrangement that is characteristic of carbocation reactions. The less stable (primary) carbocation is rearranged by a 1,2-nucleophilic shift of a hydride ion to form the more stable (secondary) carbocation. For this reaction, the sole product is the alkylbenzene containing the rearranged alkyl group while the unrearrranged product can't be detected. The reason may be that, firstly, the seven-memberred ring of the unrearranged product is more strained than the six-memberred ring of the rearranged product. Secondly, the o-position on the aromatic ring is more proper to be attacked by the rearranged alkyl group to yield six-memberred ring. Finally, the carbocation is prone to be rearranged to the stable one; therefore, the strained seven-memberred ring product is scarcely found.

It is noticeable that this reaction proceeds with racemization. The reason can be described as followed. After the chloride ion is detached from the alkyl halide molecule, the carbocation is formed. In a carbocation, the electron-deficient carbon is bonded to three other atoms, and this bonding uses sp^2 orbitals. sp^2 Orbitals lie in one plane, that of the carbon nucleus, and are directed toward the corners of an equilateral triangle. This part of a carbocation is therefore flat, the electron-deficient carbon and the three atoms attached to it lying in the same plane. Carbon still has a p orbital, with its two lobe lying on both sides of the plane of the σ bonds; however, in a carbocation, the p orbital is empty. The electrons from the aromatic ring can attack either face of this flat carbocation and, depending upon which face, yield one or the other of the two enantiomeric products. Consequently, the two enantiomers constitute the racemic modification.

In general, the reaction does not, however, stop at the stage of mono-substitution, since the alkylbenzene initially produced can undergo alkylation more easily than the original benzene derivative, owing to the electron-releasing effect of the alkyl group. Mixtures of substances, therefore, often result and extensive purification may be required in order to isolate the monosubstituted compound. To improve yield, in this experiment, the monoalkylbenzene derivative can be prepared by using an excess of the solvent, carbon disulfide, which acts as a diluent in moderating the violence of the reaction and prevents the undue formation of poly-alkylbenzene derivatives. The solvent also prevents the intermolecular alkylation; thus, the most of the products is the intramolecular alkylated product.

When the reactant was run in a large scale. A large amount of aluminium chloride was also used. Adversely, the unreacted aluminium chloride was covered with the sticky aluminium chloride complex. So, the additional aluminium chloride should be required to complete the reaction. However, after the reaction was stopped and the reaction mixture was poured onto crushed ice, a lot of heat inevitably occurred. Consequently, some of the product was destroyed by the heat. In such case, a small scale was preferable. The purification of the product was performed by column chromatography.

The IR spectrum of N-Formyl-1,2,3,4-tetrahydro-4,8-dimethylquinoline is shown in figure 41. Absorption arising from aromatic C-H stretching appears in the region of 3080-3030 cm^{-1}. The aliphatic C-H stretching vibration leads to the strong absorption in the 3000-2840 cm^{-1}. The absorption resulting from C=O stretching of amide shows the strong band at 1677 cm^{-1}. The aromatic C-C stretching vibration mixed with the aliphatic C-H bending vibration shows

the bands at 1592 cm^{-1} and in the region of 1475-1450 cm^{-1}. The bands at 783 and 755 cm^{-1} are the result of the C-H out-of-plane bending vibration.

The 200 MHz ^{1}H-NMR spectrum of N-formyl-1,2,3,4-tetrahydro-4,8-dimethylquinoline in CDCl$_3$ is shown in figure 42. The doublet signal at δ1.28 is assigned as the aliphatic methyl protons, which are coupled with the methine proton proton at position 4. The multiplet signal at δ1.58 is assigned as the axial proton at position 3 and the multiplet signal at δ2.07 is assigned as the equatorial proton at the same position. The singlet signals at δ2.19 and δ2.31 represent the aromatic methyl protons for the minor and major conformer, successively. The multiplet signal at δ2.75 represents the methine proton at position 4. The axial H-2 proton absorbs at δ3.59 (ddd, J=-12.7, 7.1, 5.3 Hz) and the equatorial H-2 proton absorbs at δ3.98 (ddd, J=-13.0, 7.7, 7.7 Hz). The next complex signals at δ7.05-7.13 are interpreted as the aromatic ring protons (H-5, H-6, and H-7). The two remaining singlet signals at δ8.24 and δ8.30 are assigned as the formyl proton which is in minor and major conformer, respectively.

The observation that an equatorial proton is consistently found further downfield by 0.4-0.6 ppm. than the axial proton on the same carbon atom in a rigid hetercyclic six-membered ring can be rationalized that the axis of the C-C bond is the axis of the deshielding cone which is the result of the σ electrons of C-C bonds (Silverstein et al.,1991).

For this compound, the major more stable conformer is still in the trans form while the minor less stable is in the cis form, but the rotation around the N-C(aromatic) is restricted because of the rigid structure fixed with the ortho

position of the aromatic ring by the alkyl chain. Thus, the aromatic ring can't rotate to the position that can shield the formyl proton. As a result, compared with the formyl proton major signal of the former compound , N-(4-Chlorobutyl)-N-(o-tolyl)formamide, the signal of this compound is located at lower field as shown in the ^{1}H-NMR spectrum.

1.2.3.4-Tetrahydro-4.8-dimethylquinoline.

This compound represents a cyclic amine. The N-Formyl-1,2,3,4-tetrahydro-4,8-dimethylquinoline was refluxed in alkaline hydroxide solution. The hydrolysis underwent to yield 1,2,3,4-Tetrahydro-4,8-dimethylquinoline as shown in figure 95.

The aim of this step is to remove the blocking formyl group. The reaction mechanism of the hydrolysis of amide is shown in figure 96. The mechanism proceeds through nucleophilic substitution, in which the amine part is replaced by hydroxy group. Under alkaline conditions, hydrolysis involves attack by the strongly nucleophilic hydroxide ion on the amide carbonyl to form the tetrahedral intermediate. Next, proton transfer can occur from water to the nitrogen lone pair. The -NHR$_2$$^+$ can serve as a fair leaving group while the unprotonated amine is not a leaving group at all. Finally, an anion undergoes beta-elimination to yield the desired amine.

In the reaction, absolute ethanol was added to produce a homogeneous solution. After the hydrolysis was completed, the ethanol was evaporated. The product, then, was extracted with chlorotorm. The chloroform extract was washed with water to remove trace of sodium hydroxide. Finally, chloroform
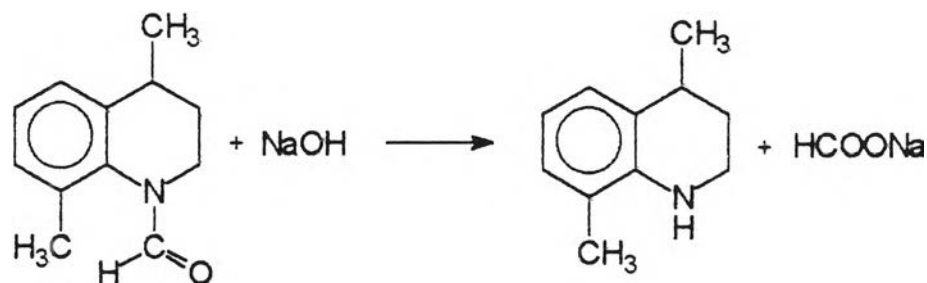
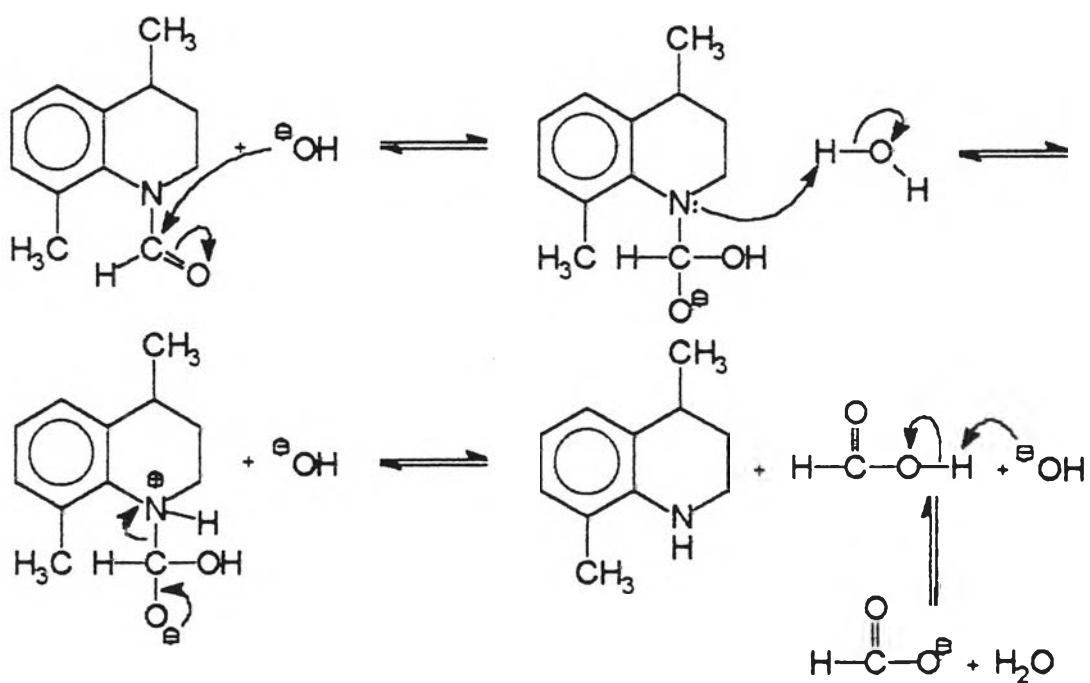Figure 95. The formation of 1,2,3,4-Tetrahydro-4,8-dimethylquinoline.

Figure 96. The reaction mechanism of the formation of 1,2,3,4-Tetrahydro-
4,8-dimethylquinoline.

was evaporated. The crude product was purified by means of column chromatography.

The IR spectrum of 1,2,3,4-Tetrahydro-4,8-dimethylquinoline is shown in figure 43. The characteristic absorption of secondary amine results from single N-H stretching at 3450 cm^{-1}. The aromatic C-H stretching bands occur between 3080 and 3030 cm^{-1}. The aliphatic C-H stretching bands appear in the region of 3000-2840 cm^{-1}. The aromatic C-C stretching vibration mixed with the aliphatic C-H bending vibration absorbs at 1610, 1505, 1491, and 1478 cm^{-1}. The aromatic C-H out-of-plane bending bands appear at 770 and 742 cm^{-1}.

The 200 MHz ^{1}H-NMR spectrum of 1,2,3,4-Tetrahydro-4,8-dimethylquinoline in CDCl$_3$ is shown in figure 44. The doublet signal at δ1.36 (J=7.4 Hz) is assigned as aliphatic methyl protons. The multiplet signals at δ 1.75 and δ2.05 are assigned as the axial and the equatorial H-3 proton, successively. The aromatic methyl protons absorb at δ2.14 (s). The multiplet signal at δ3.00 is interpreted as the methine proton at position 4. The complex signals at δ3.36-3.70 include the signals of the two methylene protons at position 2 and the NH proton at position 1. The pseudotriplet signal at δ6.65 (dd, J=7.5, 7.5 Hz) is referred to the aromatic H-6 proton. The two doublet signals at δ6.95 (J=7.3 Hz) and δ7.03 (J=7.5 Hz) are assigned as the aromatic H-7 and H-5 protons, respectively.

It is remarkable that the signals of H-2 axial and H-2 equatorial protons of 1,2,3,4-Tetrahydro-4,8-dimethylquinoline are located at similar chemical shifts whereas these signals of N-Formyl-1,2,3,4-tetrahydro-4,8-

dimethylquinoline are located at considerably different chemical shifts. The explanations for this are as followed. In 1,2,3,4-Tetrahydro-4,8-dimethylquinoline, the inversion of the heterocyclic ring is so rapid that the difference between the axial and equatorial position can't be detected by ^{1}H-NMR whereas it is slow in N-Formyl-1,2,3,4-tetrahydro-4,8-dimethylquinoline, resulting in a discrepancy between an axial and an equatorial proton. The reason for the slow inversion is that the steric hindrance due to the methyl group in position 8 makes the formyl group comparatively immobile, which is evident as a slow rate of inversion of the heterocyclic non-aromatic ring. Such a phenomenon has previously been observed by Nagarajan et al. (1967), and Svensson and Nilsson (1973).

N-(p-Nitrobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline.

This compound represents a nitrobenzoyl amide. The mixture of 1,2,3,4-Tetrahydro-4,8-dimethylquinoline and p-nitrobenzoyl chloride were refluxed in the presence of potassium carbonate. (Figure 97.)

Amides are usually prepared from the acid chloride rather than from the acid itself. Both the preparation of the acid chloride and its reaction with amine are rapid, essentially irreversible reactions. It is more convenient to carry out these two steps than the single slow, reversible reaction with the acid.

The reaction mechanism proceeds through nucleophilic acyl substitution. (Figure 98.) This mechanism is composed of two steps, with the intermediate formation of a tetrahedral compound. The first step is the nucleophilic addition which is followed by the second step, named the beta-
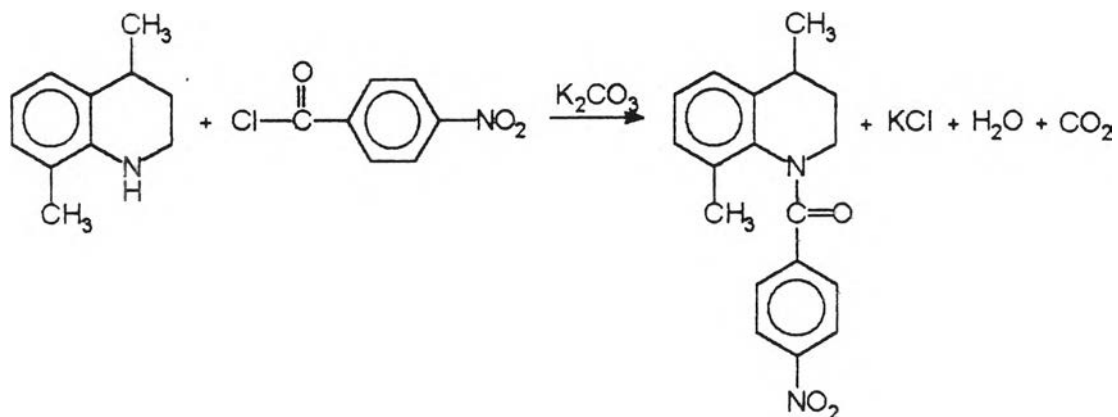
Figure 97. The formation of N-(*p*-Nitrobenzoyl)-1,2,3,4-tetrahydro-
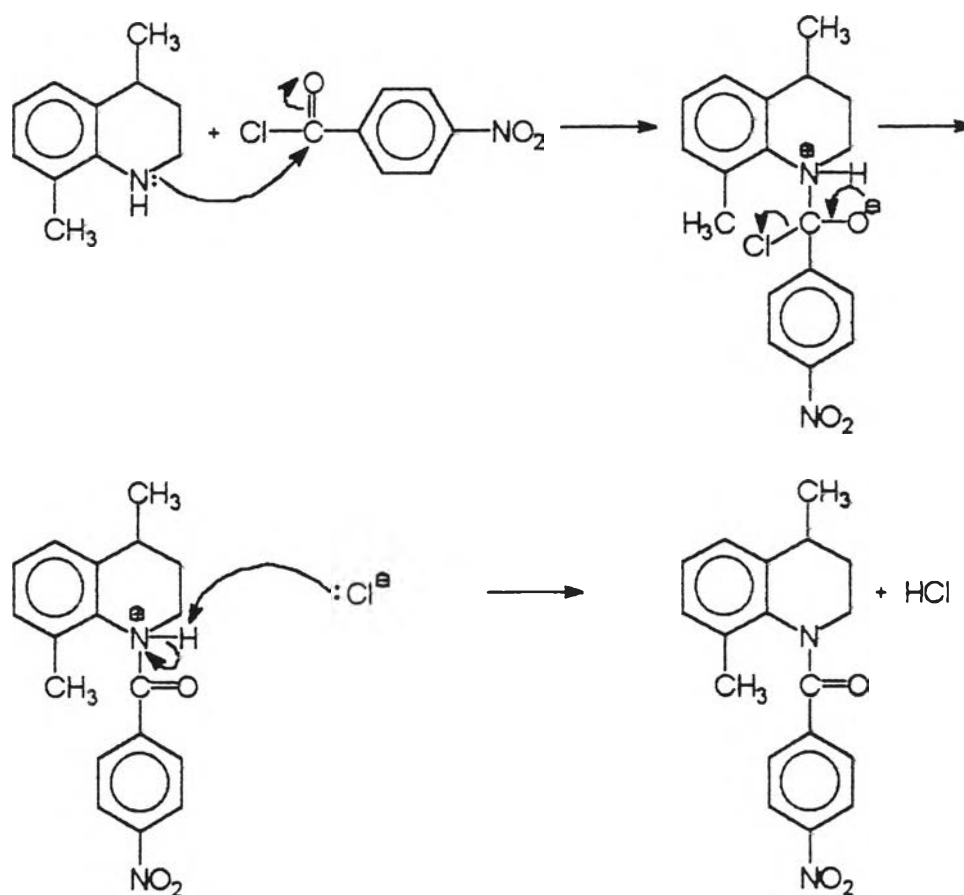4,8-dimethylquinoline.

Figure 98. The reaction mechanism of the formation of N-(*p*-Nitrobenzoyl)-
1,2,3,4-tetrahydro-4,8-dimethylquinoline.

elimination.

Potassium carbonate added in the reaction mixture was used to neutralize hydrochloric acid occured 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 (m.p. 140°-142^oc).

The IR spectrum of N-(p-Nitrobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline is shown in figure 45. Aromatic C-H stretching bands occur in the region of 3080-3030 cm^{-1}. The aliphatic C-H stretching vibration absorbs between 3000 and 2840 cm^{-1}. The C=O stretching vibration leads to the strong absorption at 1648 cm^{-1}. The bands at 1600 cm^{-1} and in the region of 1477-1409 cm^{-1} exhibit the aromatic C-C stretching vibration as well as the aliphatic C-H bending vibration. The nitro compound shows absorption due to asymmetrical and symmetrical stretching of the NO_2 group. Asymmetrical stretching absorption results in a strong band at 1517 cm^{-1}; symmetrical stretching absorption occurs at 1343 cm^{-1}. The bands in the region of 861-709 cm^{-1} show the absorption of C-H out-of-plane bending.

The 500 MHz ^{1}H-NMR spectrum of N-(p-Nitrobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline in $CDCl_3$ is shown in figure 46-49. Surprisingly, the spectrum shows many small peculiar signals excluding the expected signals. This can be rationalized as followed. In the molecule of this compound, there are many rotatable bonds such as N-C(=O) and C(=O)-C (aromatic) bonds. In addition, the aliphatic methyl group can align in either axial position or in equatorial position. As a result, this compound possesses many conformers. Protons in one conformer can position in different

environments from protons in other conformers; consequently, each conformer has its own NMR characteristic. As seen in figure 46, the ^{1}H-NMR spectrum contains the net sum of signals from each conformer. It is an arduous task to assign all the signals for all conformers. Here, only major conformer signals will be assigned.

The multiplet signal at $\delta 1.43$ represents the axial H-3 proton. The aliphatic methyl protons resonate at $\delta 1.47$ (d, J=6.7 Hz). The singlet signal at δ 1.75 is assigned as the aromatic methyl protons. The signal at $\delta 2.39$ (dddd, J= -12.8, 9.5, 4.6, 3.4 Hz) is assigned as the equatorial H-3 proton. The methine H-4 proton resonates at $\delta 2.85$ (m). The signal at $\delta 3.25$ (ddd, J=-12.8, 9.5, 3.4 Hz) is assigned as the axial H-2 proton while the signal at $\delta 4.74$ (ddd, J=-12.8, 9.5, 8.2 Hz) is assigned as the equatorial H-2 proton. The aromatic H-5, H-6, and H-7 protons absorb at $\delta 7.19$ (d, J=7.3 Hz), $\delta 7.15$ (dd, J=7.3, 7.3 Hz), and δ 6.85 (d, J=7.3 Hz), respectively. The two doublet signals at $\delta 7.35$ (d, J=8.9 Hz) and $\delta 7.98$ (d, J=8.9 Hz) are assigned as the aromatic H-2' and H-3' protons. These assignments can be accomplished by the use of the final product, N-(p-Aminobenzoyl-1,2,3,4-tetrahydro-4,8-dimethyl quinoline, as a model. Details about the assignments will be discussed in the last compound.

N-(p-Aminobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline.

This compound represent a aminobenzoyl amide. A solution of N-(p-Nitrobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethyl quinoline in absolute ethanol was subject to low-pressure hydrogenation in the presence of palladium on activated charcoal as a catalyst. (Figure 99.)
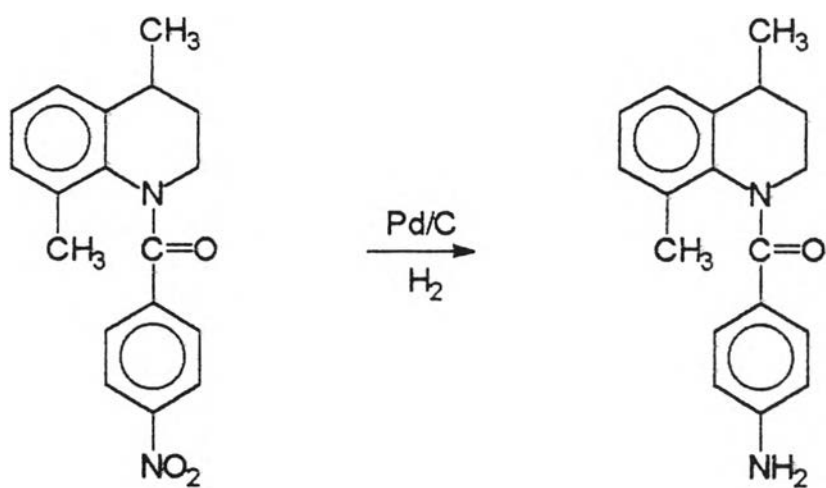
Figure 99. The formation of N-(p-Aminobenzoyl)-1,2,3,4-tetrahydro-

4,8-dimethylquinoline.

The mechanism of catalytic hydrogenation is proposed as followed. First, a reactant molecule, an aromatic nitro compound, is adsorbed on the catalyst surface. Next, the adsorption is thought to be followed by the simultaneous transfer of two or more hydrogen atoms from the catalyst to the adsorbed molecule and subsequent desorption of the reduced molecule, an aromatic amine (House, 1972).

The product was purified upon recrystallisation from benzene. the melting point was 170°-172°c.

The IR spectrum of N-(p-Aminobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline is shown in figure 50. The primary amine displays two weak absorption bands: one at 3442 cm^{-1} and the other at 3349 cm^{-1}. These bands represent, respectively, The "free" asymmetrical and symmetrical N-H stretching modes. The band at 3227 cm^{-1} arises from the overtone of the N-H bending band intensified by Fermi resonance (Colthup et al., 1990). Aromatic C-H stretching bands absorb in the region of 3080-3030 cm^{-1}. The bands between 3000 and 2840 cm^{-1} represent the aliphatic C-H stretching vibration. The strong band in the region of 1650-1604 cm^{-1} shows The C=O stretching vibration of the amide group combined with the N-H bending vibration of the primary amino group. The aromatic C-C stretching vibration mixed with the aliphatic C-H bending vibration absorbs at 1564, 1516, and 1477 cm^{-1}. The aromatic C-H out-of-plane bending bands occur at 838, 783, and 756 cm^{-1}.

The EIMS spectrum of N-(p-Aminobezoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline is shown in figure 51. This compound is confirmed by the analysis of the mass fragmentation. (See figure 100.) The peak at m/e 280
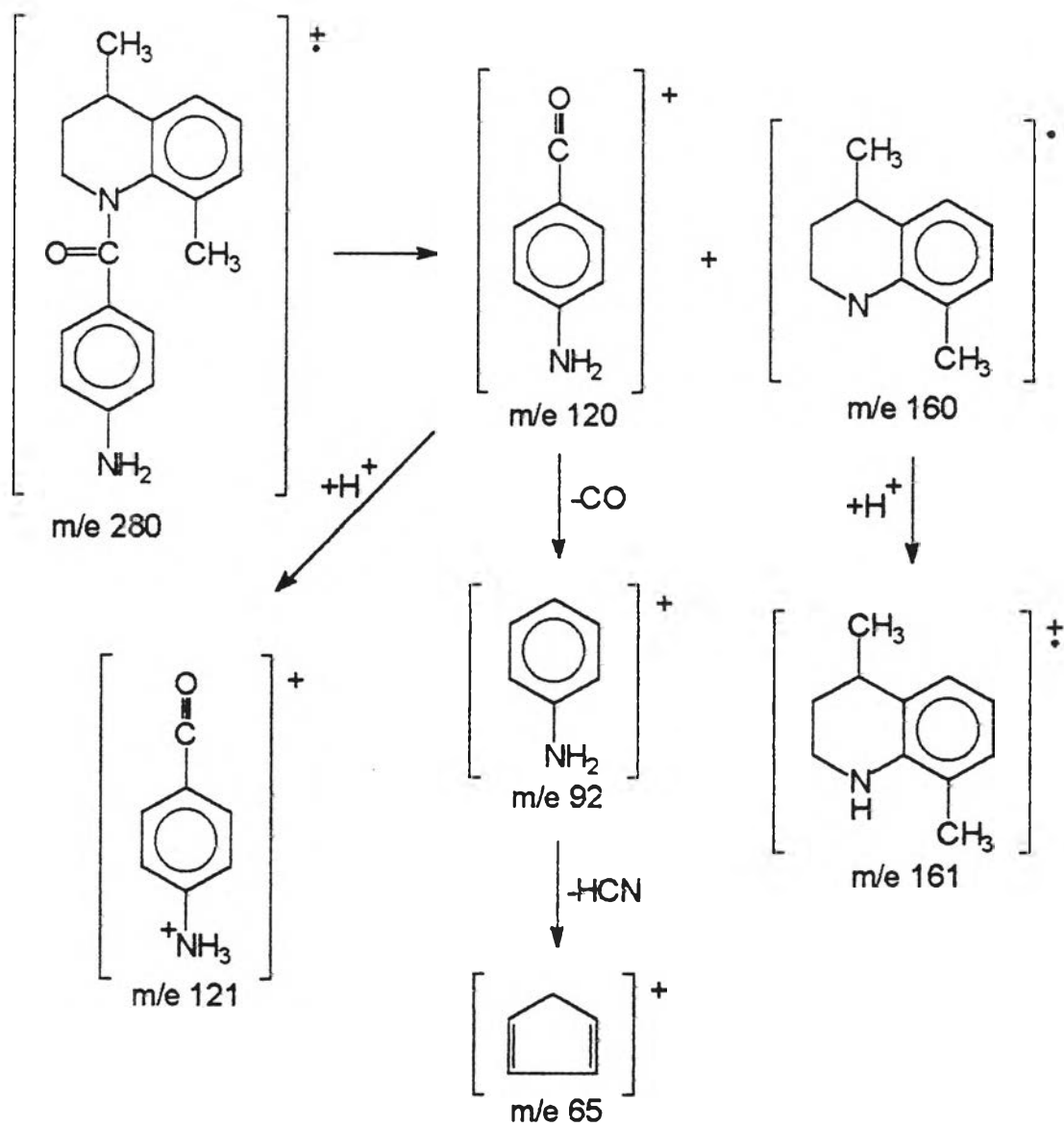
Figure 100. Mass fragmentation of N-(p-Aminobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline.

represent the molecular ion. The peak at m/e 281 is the M+1 peak which is 20.5% of the M peak. The M+1 peak can be confirmed by the calculated value from the equation, $\% (M+1) = (1.1 \times \text{number of C atoms}) + (0.36 \times \text{number of N atoms})$. For this compound, the calculated value is 20.5% that is equal to the observed value. Loss of 1,2,3,4-Tetrahydro-4,8-dimethylquinoline (m/e 160) from the molecular ion yields a resonance-stabilized p-aminobenzoyl cation (m/e 120) that in turn undergoes cleavage to an aniline cation (m/e 92). Loss of a neutral molecule of HCN gives the prominent peak at m/e 65. This pattern of fragmentation is also found in p-aminobenzoic acid as reported by El-Obeid and Al-Badr (1994). The peaks at m/e 161 and m/e 121 are the (M+H) peaks of the peak at m/e 160 and m/e 120, consecutively.

The 500 MHz ^{1}H-NMR spectrum of N-(p-Aminobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline at room temperature is shown in figure 52. Stupendously, the spectrum exhibits many broad signals. Because this molecule shows intramolecular mobility : rotations around the C(=O)-N and C(aromatic)-C(=O) bonds, and also inversion of the piperidine ring, the nuclear have different chemical environments in each conformers (Breitmaier and Voelter, 1989). As a result, interpretation of the spectrum suffers from small chemical shift differences between rotational and inversional isomers, as well as from unresolved splitting due to homonuclear spin-spin coupling. Therefore, temperature-dependent experiments was performed. An attempt to coalesce the signals of the same protons in each conformer and to resolve the average splitting pattern of each signal, the ^{1}H-NMR experiments was carried out at high temperature (40°c and 50°c). At high temperature, rotations of groups about σ bonds will become more faster and the spectrum may show the overall average chemical shifts of signals with splitting pattern of all conformers.

However, the attempt was unsuccessful. The 500 MHz ^{1}H-NMR spectrum of this compound at high temperature is shown in figure 53. The spectrum have a little change, some signals becoming sharper but still broad.

Another attempt to separate the signals of the same protons in each conformer and to resolve the splitting pattern of all signals of all conformers, the ^{1}H-NMR experiments was performed by decreasing the temperature (15°c, 0°c, -15°c, and -30°c). The 500 MHz ^{1}H-NMR spectrum of this compound at low temperature is shown in figure 54. The enlarged-scale ^{1}H-NMR is shown in figure 55 and 56. Successfully, at -30°c (figure 57), the spectrum shows the separate signals with resolved splitting patterns. The integrations of the signals are displayed in figure 58 and the expansions of the signals are illustrated in figure 59 and 60.

It is remarkable that the spectrum of this compound at -30°c is somewhat resemble the spectrum of the former nitro compound at room temperature which does not need to perform the experiment at so low temperature. The explanation for this phenomenon will be discussed. In this situation, p-substituted benzamides should give electronic effects. The barrier to rotation about the C(=O)-N bond becomes higher proceeding from electron-donating to electron-accepting substituents (Michinori, 1985). Thus, p-aminobenzamide derivative should have less rotational barrier than the corresponding nitro compound. In addition, the low value of the rotational barrier for this compound depends on the conjugative property of p-aminophenyl ring. See figure 101, the restricted motion, in fact, is due to the partial double-bond character of structure like (A) : when conjugative structure like (B) become important, thus reducing the C(=O)-N double-bond character
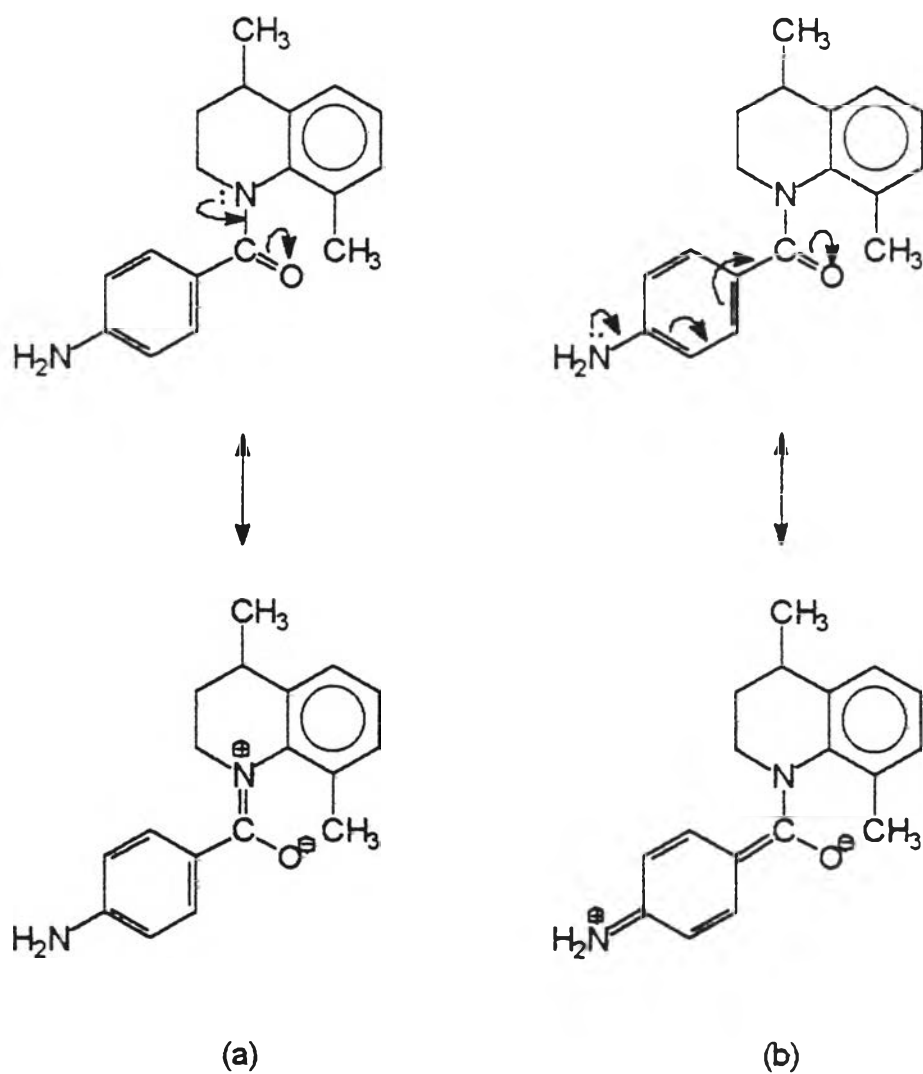
Figure 101. The chemical structures of *p*-aminobenzamide derivative illustrating

(a) partial double-bond character.

(b) conjugative property.

and, consequently, the rotational barrier (Cipiciani et al.,1979). Therefore, at room temperature, the rotation about the C(=O)-N of this compound can undergo more easily than the nitro compound.

However, it is still difficult to assign the positions of the protons by only 1D-NMR spectrum because the spectrum is composed of numerous signals and some signals overlap with the others. More data from other NMR experiments are required to clarify the spectrum.

The 125 MHz ^{13}C-NMR decoupled spectrum of this compound at room temperature is shown in figure 61. The spectrum shows some broad overlapping signals due to intramolecular mobility. Thus, the ^{13}C-NMR experiment was again accomplished at -30°c. The 125 MHz ^{13}C-NMR decoupled spectrum at -30°c is shown in figure 62. At -30°c, the ^{13}C-NMR decoupled spectrum changes from a single resonance to four separate signals (one major signal and three minor signals) with some signals overlapping with the others. This implies that this compound may have four conformers of which nuclear have differrent chemical environments. The expansions of the signals are illustrated in figure 63 and 64.

The 125 MHz DEPT135 (Distortionless Enhancement by Polarization Transfer) spectrum at -30°c is shown in figure 65. This technique gives negative CH_2 but positive CH and CH_3 carbon signals. The quaternary carbon signals are not present in this spectrum.

It is a laborious work to assign all the signals. Here, only signals of major conformers will be considered. From the ^{13}C-NMR decoupled spectrum and DEPT135 spectrum, it can be deduced that the signals at $\delta16.9$, $\delta18.1$, and $\delta30.1$ represent either alkyl CH or CH_3 carbons (C-4, C-11, or C-12), the signals at $\delta33.6$ and $\delta42.1$ represent two aliphatic CH_2 carbons (C-2, or C-3), the double-intensity signals at $\delta113.1$ and $\delta130.2$ represent a couple of two equivalent aromatic CH carbons (C_2-2', or C_2-3'), the signals at $\delta120.9$, δ 125.4, and $\delta128.8$ represent three aromatic CH carbons (C-5, C-6, or C-7), and the remaing signals at $\delta125.0$, $\delta132.0$, $\delta138.9$, $\delta139.9$, $\delta148.4$, and $\delta169.6$ represent the six quarternary carbons (C-8, C-9, C-10, C-1', C-2', or -C=O).

The 500 MHz HH COSY (COrrelated SpectroscopY : HH coupling) spectrum at -30°c and the observed correlation are shown in figure 66. The expansions of the spectrum are exhibited in figure 67 and figure 68.

The 125 MHz CH COSY (COrrelated SpectroscopY : CH coupling) spectrum at -30°c is shown in figure 69. The expansions of the spectrum are exhibited in figure 70 and figure 71. The assignments for the protonated carbons are achieved by the analysis of the CH COSY spectrum. The CH COSY spectrum provides the correlations between protons and carbons through 1-bond coupling. The correlations between each pair of proton and carbon are as followed : H-2 axial ($\delta3.24$), and H-2 equatorial ($\delta4.61$) - C-2 ($\delta42.1$); H-3 axial ($\delta2.34$), and H-3 equatorial ($\delta1.38$) - C-3 ($\delta33.6$); H-4 ($\delta2.82$) - C-4 (δ 30.1); H-6 ($\delta7.13$) - C-6 ($\delta125.0$); H_3-11 ($\delta1.45$) - C-11 ($\delta16.9$); and H_3-12 (δ 1.76) - C-12 ($\delta18.1$).

However, at the point of analysis, correlations between H-5 - C-5, H-7 - C-7, H_2-2' - C_2-2', and H_2-3' - C_2-3' are still obscure.

The complete carbon assignments are achieved by the analysis of the ^{1}H-detected Heteronuclear Multiple Bond Connectivity (HMBC) spectrum. The 125 MHz HMBC spectrum at -30°c is shown in figure 72. The expansions of the spectrum are exhibited in figure 73 and figure 74. 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. The correlations between each pair of proton and carbon are as followed : H-5 (δ7.16) - C-7 (δ128.8), and C-9 (δ138.9); H-6 (δ 7.13) - C-8 (δ132.0), and C-10 (δ139.9); H-7 (δ6.88) - C-5 (δ120.9), and C-9 (δ138.9); H_3-11 (δ1.45) - C-3 (δ33.6), C-4 (δ30.1), and C-10 (δ139.9); H_3-12 (δ1.76) - C-7 (δ128.8), C-8 (δ132.0), and C-9 (δ138.9); H-2' (δ7.03) - the other C-2' (δ130.2), C-4' (δ148.4), and C=O (169.6); H-3' (δ6.38) - C-1' (δ 125.0), and the other C-3' (δ113.1); and NH_2 (δ3.94) - C-3' (δ113.1).

The results from the analysis of HMBC spectrum can assist in the analysis of the rest correlations in CH COSY spectrum. The clarified correlations between protons and carbons are as followed : H-5 (δ7.16) - C-5 (δ 120.9); H-7 (δ6.88) - C-7 (δ128.8); H_2-2' (δ7.03) - C-2' (δ130.2); and H_2-3' (δ 6.38) - C_2-3' (δ113.1).

Now the assignments for all protons and carbons in the major conformer are complete. (See table 3.) The assignments for the protons are as followed : H-2 axial coupled with H-2 equatorial, H-3 axial, and H-3 equatorial (δ3.24,

Table 3. Carbon and proton assignments of N-(p-Aminobenzoyl)-1,2,3,4-tetra hydro-4,8-dimethylquinoline, and long-range correlations between carbons and protons.

position	δC (ppm)	δH (ppm)	long-range correlation from C to H in HMBC spectrum
1	-	-	-
2	42.1	a; 3.24, ddd (-12.5, 9.5, 2.4)	-
		e; 4.61, ddd (-12.9, 9.8, 8.6)	-
3	33.6	a; 1.38, m	H-11
		e; 2.34, dddd (-12.8, 9.8, 4.6, 2.8)	
4	30.1	2.82, m	H-11
5	120.9	7.16, d (6.3)	H-7
6	125.4	7.13, dd (7.3, 7.3)	-
7	128.8	6.88, d (6.7)	H-5, H-12
8	132.0	-	H-6, H-12
9	138.9	-	H-5, H-7, H-12
10	139.9	-	H-6, H-11
11 (4-CH₃)	16.9	1.45, d (6.7)	-
12 (8-CH₃)	18.1	1.76, s	-
1'	125.0	-	H-3'
2'	130.0	7.03, d (8.3)	H-2' (on the other C-2')
3'	113.1	6.38, d (8.9)	4'-NH₂, H-3' (on the other C-3')
4'	148.4	-	H-2'
C=O	169.6	-	H-2'
4'-NH₂	-	3.94, s	-

ddd, J =-12.5, 9.5, 2.4 Hz); H-2 equatorial coupled with H-2 axial, H-3 equatorial, and H-3 axial (δ4.61, ddd, J=-12.9, 9.8, 8.6 Hz); H-3 axial coupled with H-2 axial, H-2 equatorial, H-3 equatorial, H-4 (δ1.38, m); H-3 equatorial coupled with H-3 axial, H-2 equatorial, H-4, and H-2 axial (δ2.34, dddd, J= -12.8, 9.8, 4.6, 2.8 Hz); H-4 coupled with H-3 axial, H-3 equatorial, and H_3-11 (δ2.82, m); H-5 coupled with H-6 (δ7.16, d, J=6.3 Hz); H-6 coupled with H-5, and H-7 (δ7.13, dd, J=7.3, 7.3 Hz); H-7 coupled with H-6 (δ6.88, d, J=6.7 Hz); H_3-11 coupled with H-4 (δ1.45, d, J=6.7 Hz); H_3-12 (δ1.76, s); H-2' coupled with H-3' (δ7.03, d, J=8.3 Hz); H-3' coupled with H-2' (δ6.38, d, J=8.9 Hz); and NH_2 (δ3.94, s).

The assignments for the carbons are as follwed : C-2 (δ42.1), C-3 (δ 33.6), C-4 (δ30.1), C-5 (δ120.9), C-6 (δ125.4), C-7 (δ128.8), C-8 (δ132.0), C-9 (δ138.9), C-10 (δ139.9), C-11 (δ16.9), C-12 (δ18.1), C-1' (δ125.0), C_2-2' (δ130.2), C_2-3' (δ113.1), C-4' (δ148.4), and C=O (δ169.6).

The relative stereochemistry of this compound can be determined by the analysis of coupling constants. Vicinal coupling constants, $^3J_{HH}$, indicate the relative configuration of the coupling protons. Their contribution depends, according to Karplus-Conroy relationship, on the dihedral angle ϕ, enclosed by the CH bonds. From the coupling constants, the conformation of the piperidine ring, of which one side juxtaposed to the aromatic ring, are determined to be half-boat form with coplanarity of (C-4)-(C-10)-(C-9)-(N-1) as analyzed from the data illustrating in table 4. The Newman projections along C-2-C-3 bond and C-3-C-4 bond are exhibited in figure 102. The coupling constants and dihedral angles of H-2a, H-2e, H-3e, and H-4 are also displayed in figure 102 - (a1), (a2), (a3), and (b), respectively. The proposed conformation of the

Table 4. The analyzed data for determining the conformation of piperidine ring.

| Proton position	δH (ppm)	Coupling constants (Hz)	Proton coupled with	estimated dihedral angles
H-2 axial	3.24, ddd	-12.5 (geminal)	H-2 equatorial	-
		9.5 (vicinal)	H-3 axial	20°
		2.4 (vicinal)	H-3 equatorial	115°
H-2 equatorial	4.61, ddd	-12.9 (geminal)	H-2 axial	-
		9.8 (vicinal)	H-3 equatorial	20°
		8.6 (vicinal)	H-3 axial	145°
H-3 axial	1.38, m	-	H-3 equatorial	-
		-	H-2 axial	-
		-	H-2 equatorial	-
		-	H-4 axial	-
H-3 equatorial	2.34, dddd	-12.8 (geminal)	H-3 axial	-
		9.8 (vicinal)	H-2 equatorial	20°
		4.6 (vicinal)	H-4 axial	50°
		2.8 (vicinal)	H-2 axial	115°
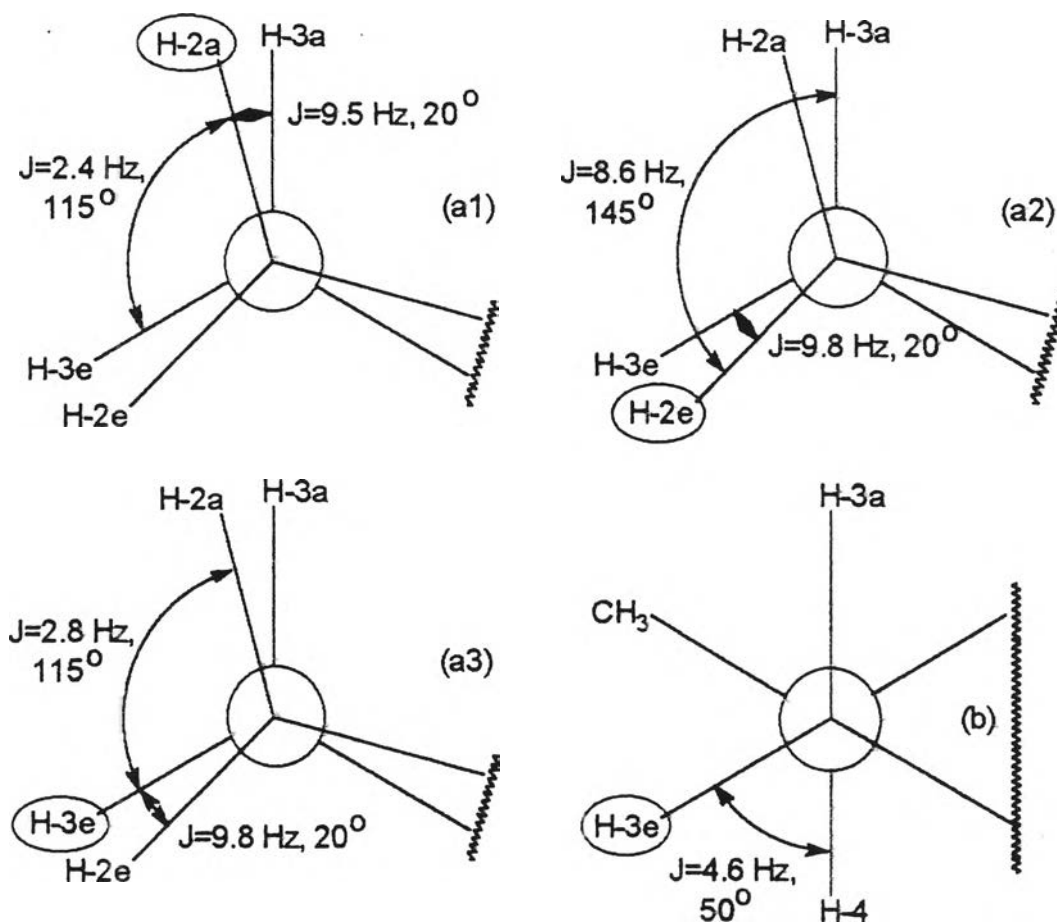
Figure 102. The Newman projections of N-(p-Aminobenzoyl-1,2,3,4-
tetrahydro-4,8-dimethylquinoline, sighting along
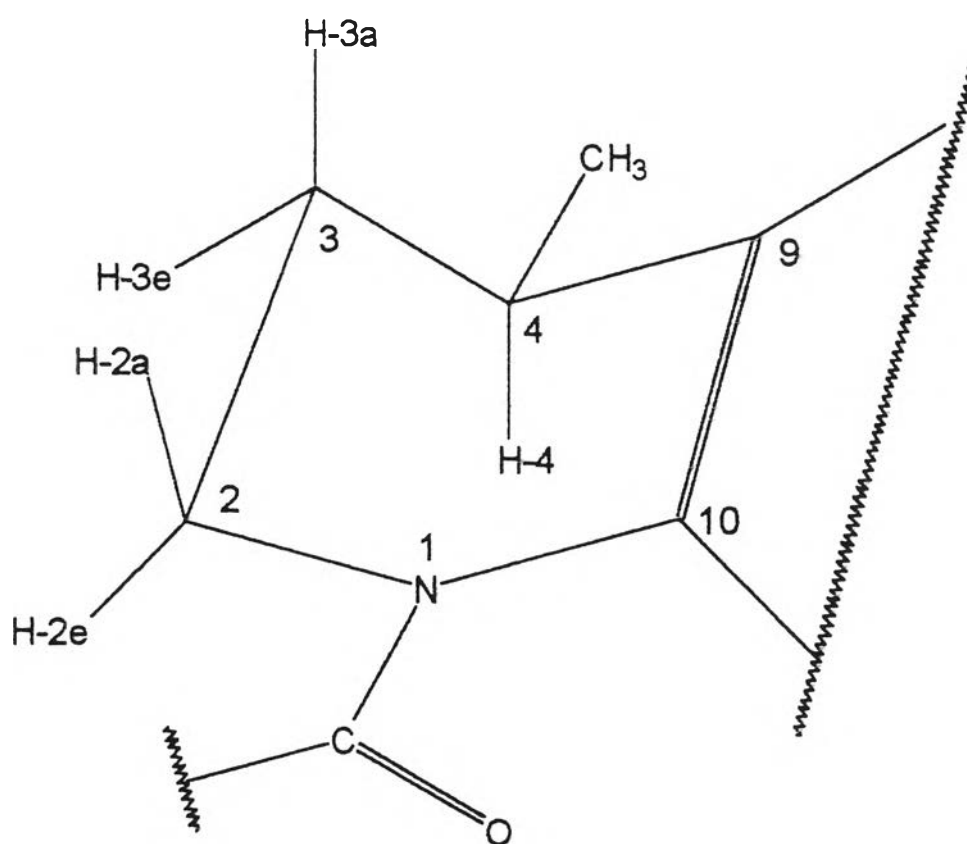(a) C-2 - C-3 bond, and (b) C-3 - C-4 bond.

Figure 103. The proposed half-boat conformation of the piperidine
ring of the major conformer of N-(p-Aminobenzoyl-
1,2,3,4-tetrahydro-4,8-dimethylquinoline.

piperidine ring of the major conformer by analyzing the coupling constants are shown in figure 103.

The other method to determine the relative stereochemistry of this compound is the analysis of NOE (Nuclear Overhauser Effect) observed from the NOESY (NOE SpectroscopY) spectrum. The 500 MHz HH NOESY spectrum at -30°c and the observed correlation are shown in figure 75. The expansions of the spectrum are exhibited in figure 76 and figure 77.

The NOESY spectrum shows the correlations between the protons as followed : H-2a - H-2e, H-2a - H-3a, H-2a - H-3e, H-2e - H-3a, H-2e - H-3e, and H-3a - H-3e. These correlations contrast to the proposed conformer from analyzing the coupling constants. The explanation for such correlations is that the piperidine ring is a flexible system. The correlations from NOESY spectrum can be depicted in figure 104.
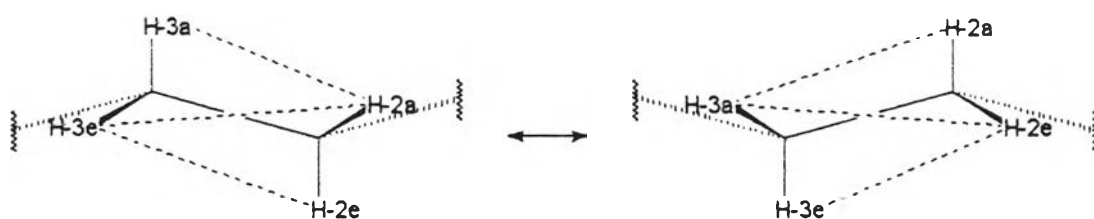

Figure 104. The NOESY correlations of the interconverting forms.

Thus, the chemical shifts and coupling constants obtained from the ^{1}H-NMR spectrum of this compound which consists of a mixture of interconverting forms are average values. It is important to realise that the average vicinal coupling constant is an average of two (or more) vicinal coupling constants and not in any way related to the coupling constant in a single intermediate

conformation with an intermediate value of dihedral angle (Jackman and Sternhell, 1969). Consequently, the proposed conformation from analyzing the coupling constants may be not correct.

By the correlations from NOESY spectrum, the conformation of the piperidine ring in a major conformer is half-chair form with interconversion of the ring. The methyl group at position 4 in a major conformer should align in the equatorial position because it is less steric; however, the explanation for this mention by the correlations from NOESY spectrum is ambiguous due to the interference from the interconverting form. In addition, the data from NOESY can't locate the p-aminobenzoyl part in the molecule.

There are many literatures reporting about the conformations of benzanilide derivatives. The study of stereochemistry of N-methylbenzanilide and benzanilide was reported by Itai et al. (1989). It indicates that the N-methyl benzanilide molecule adopts a folded cis-structure in solution with two benzene rings partially facing each other whereas the conformation of benzanilide is trans as seen in figure 105. These results are in accordance with the conformational study of N-methylamide compounds and free amide compounds reported by Toriumi et al. (1990). For the compound studied here, both conformations are possible i.e. the p-aminobenzoyl part can either fold up on the tetrahydroquinoline ring or turn away from it.
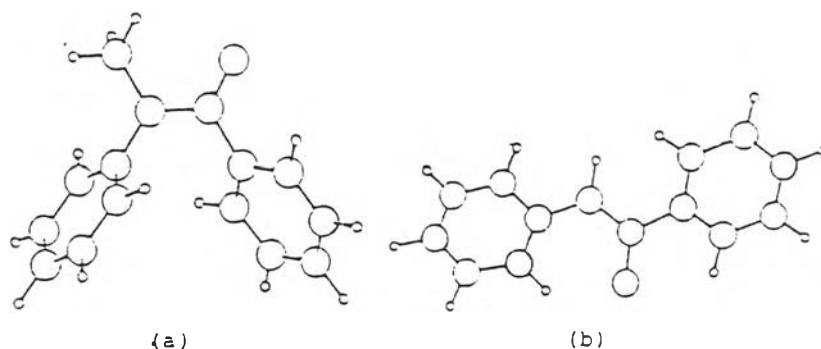
Figure 105. The conformations of (a) N-methylbenzanilide and (b) benzanilide.

To confirm the proposed conformation and to determine the conformation of *p*-aminobenzoyl part, molecular modeling was accomplished by the computer programme, CSC Chem3D Plus. After the energy was minimized, the four possible conformers are obtained as shown in figure 106. These conformers are the results of the intramolecular mobility, i.e. the interconversion of the piperidine ring and the restricted rotation of the partial C(=O)-N double bond. Although the formation of pi bonds, C=N partial double bond, requires approximate coplanarity of the reacting orbitals (Scudder, 1992), a little deformation from coplanarity, because of the steric hindrance of *p*-aminobenzoyl group or carbonyl group with the aromatic methyl group, can occur.

Here, only (R)-enantiomer was modeled. It is expected that (S)-enantiomer should give rise to another four conformers, as well. As a result, it is implied that this mixture may be composed of eight components that are not superimposible. However, NMR experiments cannot be used to discriminate the (R)- and (S)-enantiomers; therefore, only four components can be detected.
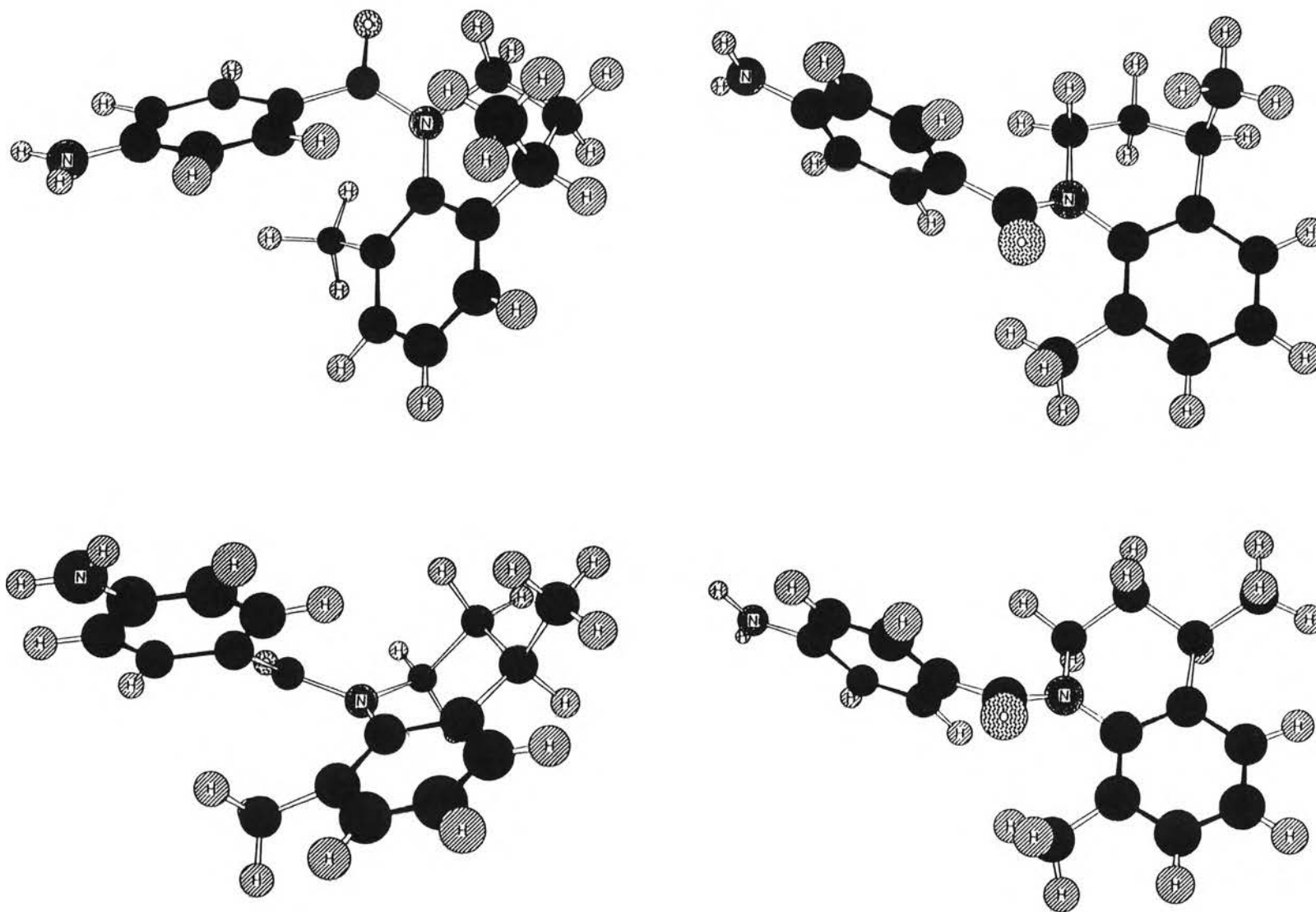
Figure 106. The four possible conformers from molecular modelling by CSC Chem3D Plus programme.

The proposed lowest energy conformer is the half-chair form that the aliphatic methyl group is in the equatorial position whereas the carbonyl group turns to the aromatic methyl group with more or less deformation of coplanarity due to steric effect. The other conformers that the methyl group is in the axial position and/or the p-aminophenyl group turn to the aromatic methyl group should have more steric hindrance.

In order to predict the most active conformer, the overlays of all conformers of N-(p-Aminobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline on the ameltolide molecule were accomplished by CSC Chem3D Plus. The conformer that lies in the closest proximity to the ameltolide molecule is expected to be the most active conformer. The investigations unviel that the conformer which has the aliphatic methyl group aligning in the equatorial position and the carbonyl group turning to the aromatic methyl group is proposed to be the active conformer. As seen in figure 107, the 2,6-dimethylphenyl region of ameltolide can be superimposed on the N-aromatic region of N-(p-Aminobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline whereas the p-aminobenzoyl region of ameltolide lie above that of the other. Interestingly, this conformer is the same as the proposed one that has the lowest energy. Therefore, because the stable conformation of this compound is similar to that of ameltolide, this compound should have pharmacological action as anticonvulsant.

N-(*p*-Aminobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline molecule.

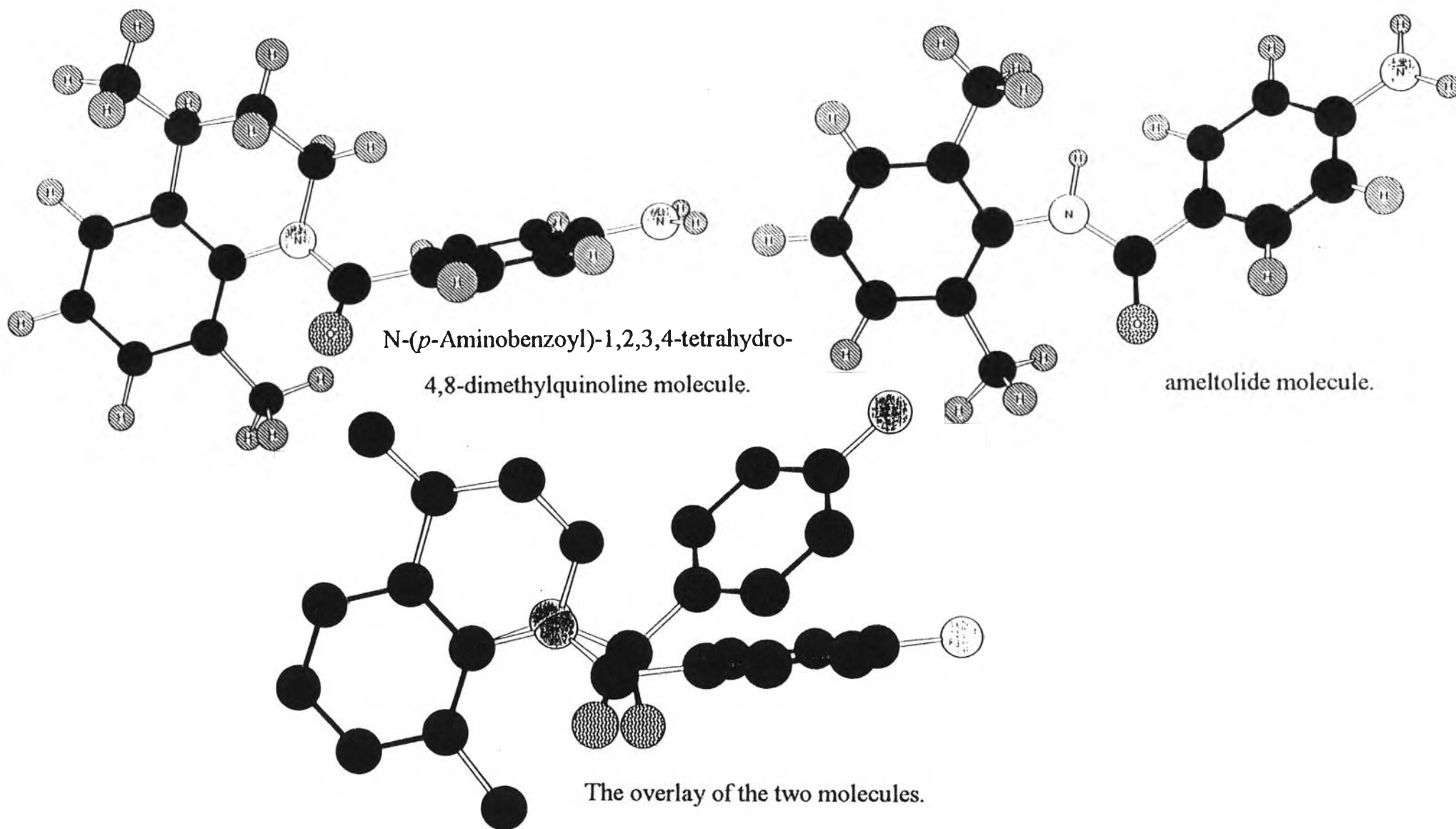ameltolide molecule.

The overlay of the two molecules.

Figure 107. The overlay of the ameltolide molecule on the N-(*p*-Aminobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline

molecule.