CHAPTER IV

RESULTS AND DISCUSSION

In this thesis, the derivatives, *O*-alkyl or *O*-acyl-2propylpentano hydroxamate, were synthesized as novel imidooxy liked anticonvulsants. Both derivatives were prepared by alkylation, and acylation of 2-propyl pentanohydroxamic acid, respectively. 2-Propylpentanohydroxamic acid was synthesized firstly by chlorination of 2-propylpentanoic acid with thionyl chloride to obtain 2-propylpentanoyl chloride, and then the acid chloride was reacted by hydroxylamine to form 2-propylpentano hydroxamic acid. In alkylation reaction of 2-propylpentanohydroxamic acid, the alkyl halides or alkyl sulfate were used as alkylating agents. In the presence of sodium hydroxide solution and heat under reflux, the *O*-alkyl-2-propylpentanohydroxamate were formed. In contrast, the acylation reaction of 2-propylpentanohydroxamate had to avoid from base and heat. Thus, 2-propylpentanohydroxamic acid was firstly converted to sodium 2-propylpentanohydroxamate. Then the salt was acylated by using acyl halides or acid anhydride at 0-10°C. Exceptionally, 2-propylpentanohydroxamic 4-aminobenzoic anhydride was synthesized from reduction by catalytic hydrogenation of 2-propylpentanohydroxamic 4-nitrobenzoic anhydride, using palladium on activated charcoal as a catalyst. According to these synthetic pathways, the satisfactorily yield of all required compounds were obtained.

2-Propylpentanoyl Chloride.

This compound was prepared from 2-propylpentanoic acid and thionyl chloride. The reaction was the general method in the preparation of acyl halide. In the reaction when the 2-propylpentanoyl chloride had been formed, the sulfurdioxide and hydrogen chloride gas were generated. The excess thionyl chloride was easily removed by distillation, and the residue, 2-propylpentanoyl chloride, could be used without purification.

The mechanism of the reaction involved nucleophilic substitution by chloride ion on a highly reactive intermediate, an acyl chlorosulfite (See in figure 81).

Benzoyl Chloride.

Similar to the preparation of 2-propylpentanoyl chloride, the benzoyl chloride was prepared from benzoic acid and either thionyl chloride or phosphorous pentachloride. But by using phosphorous pentachloride, the higher yield of benzoyl chloride was gave. It could summarized that phosphorous pentachloride was preferred chlorinating agent for aromatic acid.

In the preparation, benzoic acid was melted with phosphorous pentachloride until the vigorous evolution of hydrogen chloride had almost cease. The impurity, phosphorous oxychloride, could be removed by distillation.

The structure of benzoyl chloride could be confirmed by IR spectrum (See in figure 20): at the wavenumber 3100-3000 CM^{-1} represented to C-H stretching of aromatic compound, 2000-1667 CM^{-1} was overtone or combination bands of aromatic compound, 1775 CM^{-1} was C=O stretching of acylchloride, 1724 was fermi resonance band (of C=O stretching, and overtone of 862 CM^{-1}), 1600, 1452 CM^{-1} were C=C stretching of aromatic ring, 862, and 765 CM^{-1} were =C-H bending (out-of-plane) of aromatic compound, and 665 CM^{-1} was C=C bending (out-of-plane) of aromatic ring.

4-Nitrobenzoyl Chloride.

This compound was prepared from 4-nitrobenzoic acid and chlorinating agent, especially, phosphorous pentachloride. 4-nitrobenzoic acid represented to aromatic acid which contain electron-withdrawing substituents, and did not react readily with thionyl chloride.

The 4-nitrobenzoic acid was melted with phosphorous pentachloride until the vigorous evolution of hydrogen chloride had almost ceased. The impurity, phosphorous oxychloride, was removed by
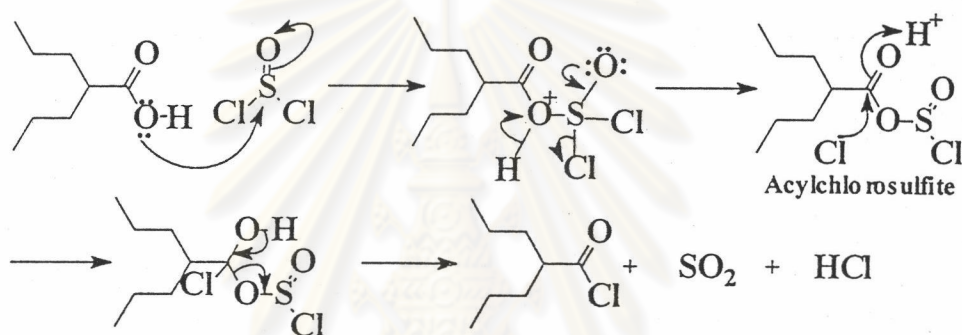
Figure 81. The reaction mechanism of the formation of
2-propylpentanoylchloride.

distillation. The 4-nitrobenzoyl chloride was purified by recrystallization from ether.

The structure of 4-nitrobenzoyl chloride could be confirmed by IR spectrum (See in figure 23): at the wavenumber 1775 CM^{-1} was C=O stretching of acylchloride, 1613, 1545 CM^{-1} were C=C stretching of aromatic ring, 842 CM^{-1} was =C-H bending (out-of-plane) of aromatic compound. The bands at 3000-2860, 1470, 1383 CM^{-1} were Nujol's.

2-Chlorotoluene.

2-Chlorotoluene was prepared from 2-toluidene and cuprous chloride by passing the intermediate, diazonium salts. These reaction called diasotisation. 2-Toluidene represented to primary aromatic amine which reacted to nitrous acid to give arenediazonium salts. Although the arenediazonium salts were unstable intermediate, but they did not decompose at an appreciate rate when the temperature of the reaction mixture was kept below 5 °C.

Diazonium salts of the type $ArN_2^+Cl^-$ were discovered by Griess. The name was based on the presence of two nitrogen atoms and on analogy to ammonium compounds. O-Toluenediazonium chloride, $CH_3-C_6H_4N_2^+Cl^-$, was the product from the reaction between O-toluidene hydrochloride and nitrous acid in the presence of excess hydrochloric acid at ice-bath temperature.

When a solution of a diazonium salt was heated, nitrogen was evolved and in the presence of cuprous chloride, the diazonium-copper(I) chloride complex was formed and decomposed by a radical mechanism see in figure 82. Copper catalyzed this decomposition because it could undergo interconversion between the +1 and +2 oxidation state as a result of electron transfer.

There were some impurities, O-cresol and a trade of azo compound that usually colors the crude product. Thus, the extraction with sodium hydroxide solution to remove O-cresol and with sulfuric acid solution to remove a trace of azo compound were necessary.
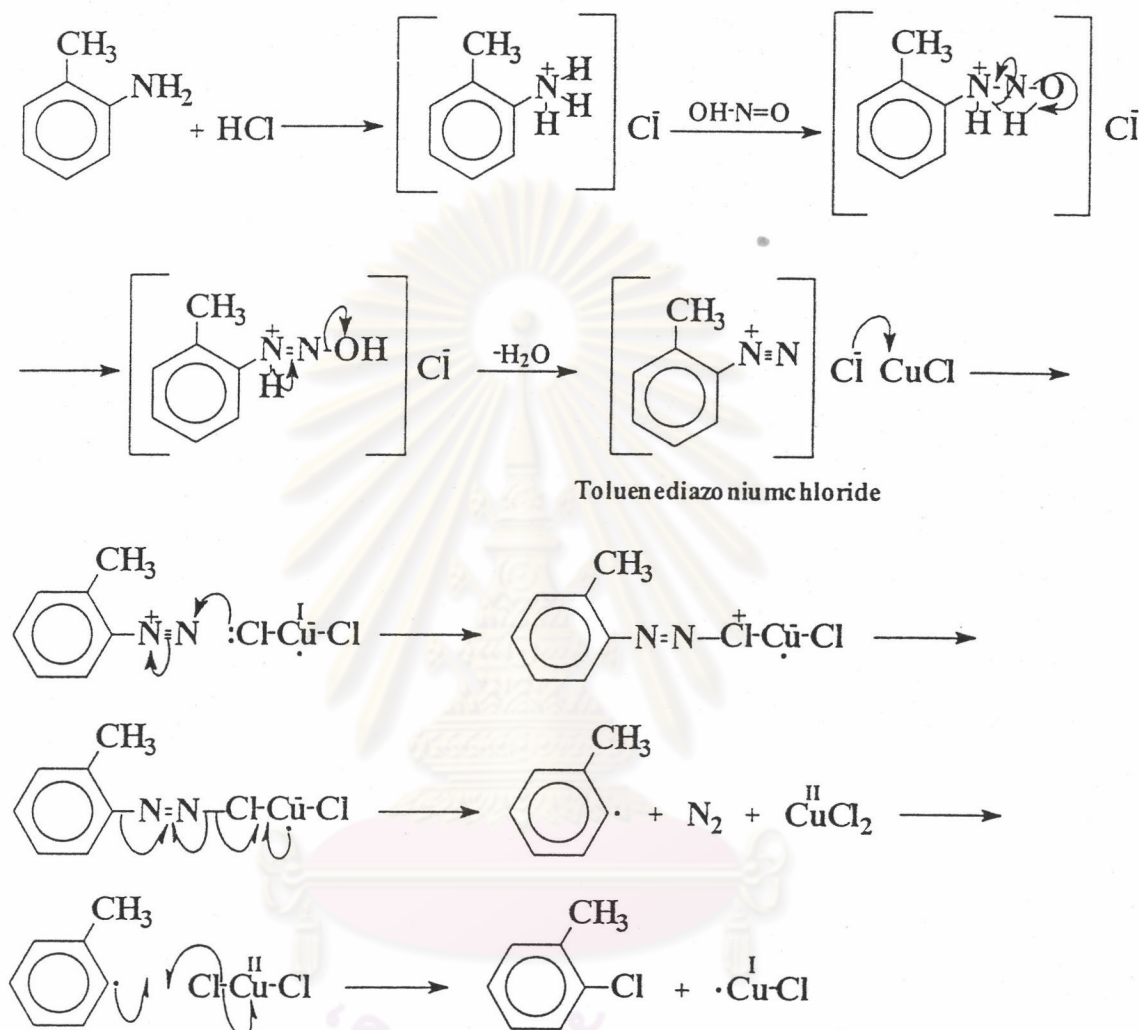
Toluenediazoniumchloride

Figure 82. The reaction mechanism of the formation of 2-chlorotoluene.

The structure of 2-Chlorotoluene was confirmed by IR spectrum (See in figure 21): at the wavenumber 3100-3000 CM^{-1} represented to C-H stretching of aromatic compound, 3000-2860 CM^{-1} was C-H stretching of aliphatic compound, 2000-1667 CM^{-1} was overtone or combination bands of aromatic compound, 1580, 1458, and 1448 CM^{-1} were C=C stretching of aromatic ring, 1052 CM^{-1} was C-Cl stretching that found in chlorobenzene, 1022 CM^{-1} was C-H bending (in plane), 720 CM^{-1} was =C-H bending (out-of-plane) of aromatic compound, and 429 CM^{-1} was C=C bending (out-of-plane) of aromatic ring.

α-Bromo-2-chlorotoluene.

In 1942, Ziegler discovered that N-bromosuccinimide reacted to a number of olefin compounds with replacement of an allylic hydrogen by bromine. Since the reaction was often catalyzed by light, or by a peroxide, it probably involved free radicals. In this synthesis α-bromo-2-chlorotoluene was prepared from 2-chlorotoluene and N-bromo-succinimide in the presence of dibenzoyl peroxide as a catalyst. Because the structure of 2-chlorotoluene like to olefin compound, it has an allyl-type hydrogen that capable of the reaction with N-bromosuccinimide. So that the 2-chlorotoluene was convertible into α-bromo-2-chlorotoluene. The mechanism of the reaction was described as follow (See the figure 83): In the initiating steps the peroxide dissociates to two benzoate radicals (1), these lose carbon dioxide to give the phenyl radical (2), which attacked N-bromosuccinimide with formation of the succimido radical (3), and abstracted an allylic hydrogen (hydrogen on methyl side chain of 2-chlorotoluene) to give an radical Ar-CH$_2$· (4), this then propagated the chain with N-bromosuccinimide to form α-bromo-2-chlorotoluene and succinido radical, which was reused (5).

The structure of α-bromo-2-chlorotoluene could be confirmed by IR spectrum (See in figure 22): at the wavenumber 3100-3000 CM^{-1} represented to C-H stretching of aromatic compound, 3000-2860 CM^{-1} was C-H stretching of aliphatic compound, 2000-1667 CM^{-1} was overtone or combination bands of aromatic compound, 1601, 1469, and 1440 CM^{-1} were C=C stretching of aromatic ring, 1222 CM^{-1} was CH$_2$ wagging for CH$_2$-Br, 1057 CM^{-1} was C-Cl stretching that found in
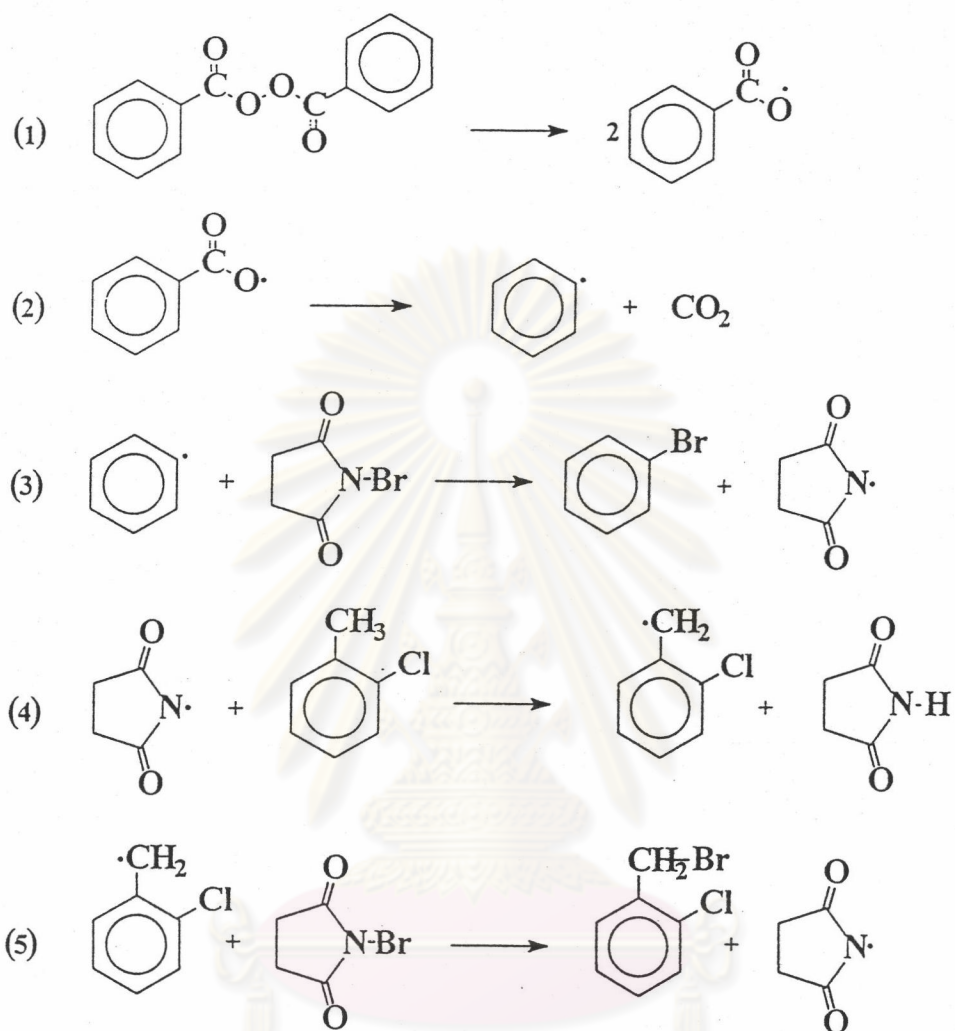
Figure 83. The reaction mechanism of the formation of
α-bromo-2-chlorotoluene.

chlorobenzene, 1038 CM^{-1} was C-H bending (in plane), and 744 CM^{-1} was =C-H bending (out-of-plane) of aromatic compound.

α-Chlorotoluene.

Similar to the chlorination of alkanes, the chlorination by using chlorine or sulfuryl chloride was a free radical chain reaction. The free radical reaction could be induced to occur in one or all of three ways: by light, by heat, and under catalyst by peroxide capable of ready homolytic decomposition to the free radical: $RO{:}OR \longrightarrow RO^{\cdot} + {}^{\cdot}OR'$. Kharasch developed a method for the low-temperature chlorination, utralizing sulfuryl chloride catalyzed by dibenzoyl peroxide. To prepare α-chlorotoluene, toluene was reacted by sulfuryl chloride in the presence of dibenzoyl peroxide as a catalyst. The mechanism of the reaction could be explained as follow (See the figure 84): In the initiating steps the peroxide dissociates to two benzoate radicals (1), these lose carbon dioxide to give the phenyl radical (2), which attacked sulfuryl chloride with formation of the radical ${}^{\cdot}SO_2Cl$ (3), In a chain propagating process, a chlorine radical was formed (4) and attacked the methyl side chain of toluene to give the radical Ar-$CH_2^{\cdot}$ (5); this attacked the reagent to produce the chlorinated hydrocarbon with regeneration of ${}^{\cdot}SO_2Cl$ for recycling (6).

The structure of α-chlorotoluene could be confirmed by IR spectrum (See in figure 24): at the wavenumber 3100-3000 CM^{-1} represented to C-H stretching of aromatic compound, 3000-2860 CM^{-1} was C-H stretching of aliphatic compound, 2000-1667 CM^{-1} was overtone or combination bands of aromatic compound, 1518, and 1452 CM^{-1} were C=C stretching of aromatic ring, 1253 was CH_2 wagging for CH_2-Cl, 1084, and 1041 CM^{-1} was C-H bending (in plane), 690 CM^{-1} was C-Cl stretching of aliphatic chloride.

2-Propylpentanohydroxamic Acid (CU-763-1201).

Similar to the amide preparation, CU-763-1201 was synthesized by using 2-propylpentanoyl chloride and hydroxylamine. This reaction was vigorously, so that the very slowly drop of 2-propylpentanoyl chloride to hydroxylamine solution may necessary. The two possible compounds could be formed: 2-propylpentanohydroxamic acid (I) and
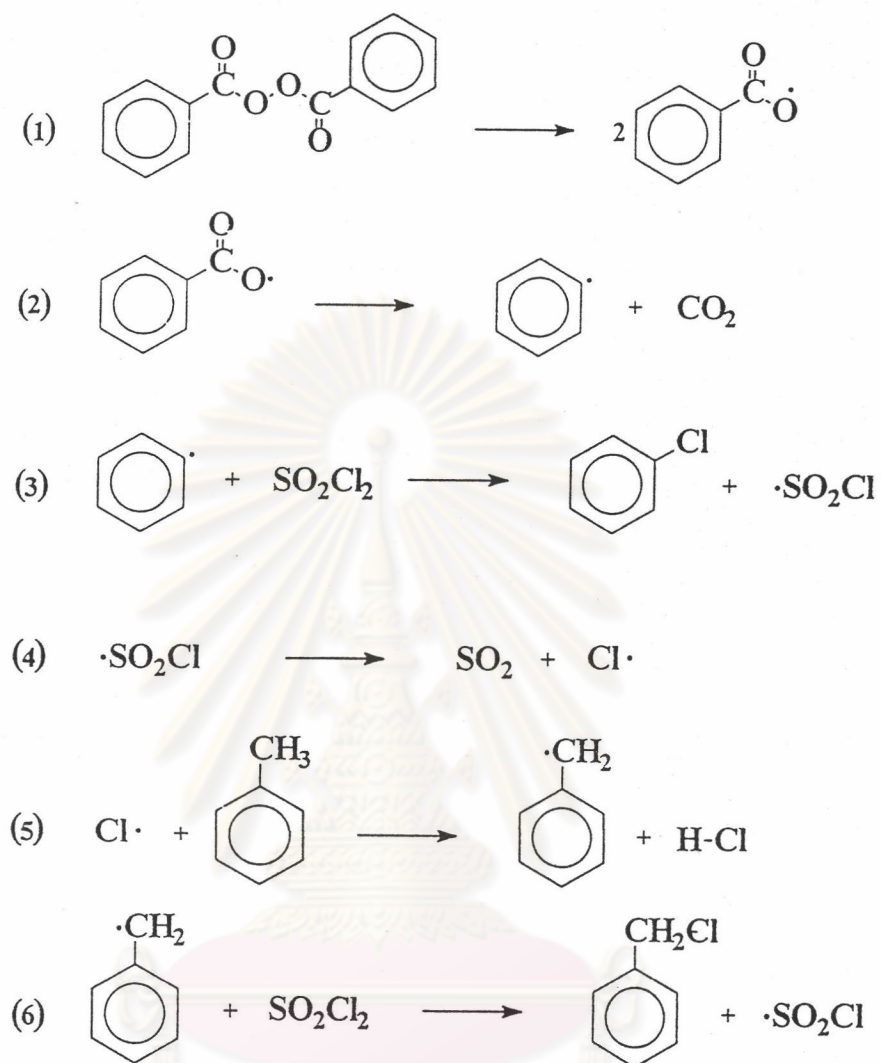
Figure 84. The reaction mechanism of the formation of α-chlorotoluene.

O-(2-propylpentanoyl)hydroxylamine (II) (See in figure 85). In this synthesis, It was found that 2-propylpentanohydroxamic acid was formed as the major product.

The esteric type of carbonyl in *O*-(2-propylpentanoyl) hydroxylamine had to show the stretching frequency considerably higher (1760 - 1730 CM^{-1}) than that for the amidic type of carbonyl in 2-propylpentanohydroxamic acid (1670 - 1640 CM^{-1}) (Bauer, L. and Exner, O. 1974). From the IR spectrum of the major product (CU-763-1201), it showed the carbonyl stretching frequency at 1629 CM^{-1}. So, the major product, CU-763-1201, from this synthesis was amide liked compound. The N-H and O-H stretching frequency showed at 3195 and 3032, respectively.

Since, the hydroxamic acid can form the coordinate complex with metal ion, therefore the color test for the presence of compound can be performed. The best known of these complexes was that with ferric chloride (Fe^{3+}) solution whose beautiful purple color formed the basis for the sensitive quantitative and qualitative determination of carboxylic acid (Yale, 1943). This quick color test retained some value in the preparative work with hydroxamic acid and was unique for hydroxamic acid of structure as 2-propylpentanohydroxamic acid. Several possible structures of this complex had been proposed (See in figure 86).

The structure of 2-propylpentanohydroxamic acid could be confirmed by:
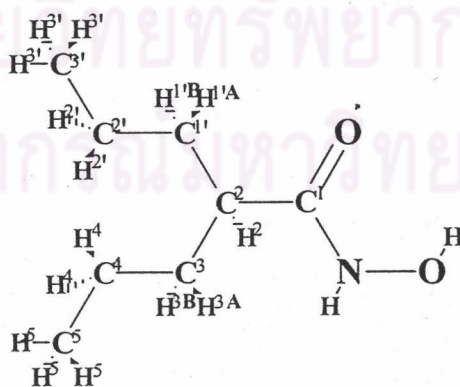
IR spectrum (Figure 26); at the wavenumber 3195 CM^{-1} represented to N-H stretching, 3032 CM^{-1} was O-H stretching, 3000-2840 CM^{-1} was C-H stretching of aliphatic compound, 1629 was C=O
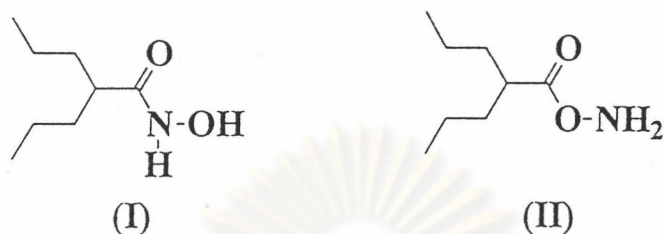
Figure 85. Two possible compounds, formed from the reaction between 2-propylpentanoylchloride and hydroxylamine.
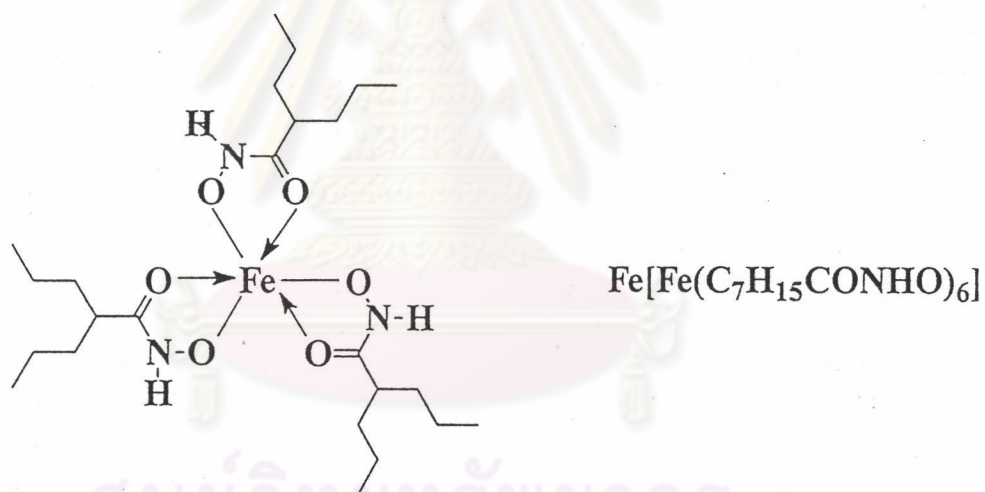

$$Fe[Fe(C_7H_{15}CONHO)_6]$$

Figure 86. The proposed structure of complex between ferric chloride and 2-propylpentanohydroxamic acid.

stretching (amide like carbonyl), 1466 CM^{-1} were N-H bending, 750-600 CM^{-1} was N-H bending (out-of-plane).

^{1}H-NMR spectrum (Figure 27); at 0.89 ppm (6H, t), these protons were assigned to six protons on C^5 and $C^{3'}$, with the coupling to two protons on C^4 and $C^{2'}$, respectively. Thus, it showed peak that was split into triplet (J = 7.32 Hz). The protons at 1.19-1.36 ppm were assigned to two protons on C^4 and two protons on $C^{2'}$ (4H, multiplet), 1.37-1.46 ppm (2H; H^{3B} and $H^{1'B}$, multiplet), 1.61 ppm (2H; H^{3A} and $H^{1'A}$, multiplet), and 1.94 ppm (1H; H^2, dddd). From the figure 87, it was showed that the proton H^{3A}, and H^{3B} were not chemical shift equivalent. The H^{3A} was strongly deshielded by O-atom of carbonyl. The proton H^2 was showed at chemical shift 1.94 ppm because it located at the C^2 that connected to carbonyl and it was split by H^{3A} (vicinal coupling; $\phi = 180°$, J ~ 14), by $H^{1'A}$ (vicinal coupling; $\phi = 180°$, J ~ 14), by H^{3B} (vicinal coupling; $\phi = 60°$, J ~ 4), and by $H^{1'B}$ (vicinal coupling; $\phi = 60°$, J ~ 4). So that the proton, H^2, had a pattern of splitting to dddd (See figure 28).

^{13}C-NMR spectrum (See in figure 28); peaks at 13.929 ppm, 20.540 ppm, 34.572 ppm, 43.604 ppm, and 174.292 ppm, represented to two carbons; C^5 and $C^{3'}$, two carbons; C^4 and $C^{2'}$, two carbons; C^3 and $C^{1'}$, a carbon; C^2, and a carbonyl carbon; C^1, respectively.

EIMS (Figure 30); since the compound represented to high electron density substance, the carbonyl connected to nitrogen which attached to oxygen, respectively. It also showed the molecular ion peak at m/z 160 $[M+1]^{·+}$. The proposed pathways of mass fragmentation of this compound were showed in figure 88: The loss of methyl radical, by $\delta\gamma$C-C cleavage to form six-membered ring with oxygen radical cation atom of hydroxy or form five-membered ring with nitrogen radical cation atom, gave a peak at m/z 144. When the five-membered ring was formed with loss of water, the lactam like substance was occurred and gave a peak at m/z 126.

A peak, showed at m/z 142 (M-17), was resulted from dehydroxylation of the parent compound. Subsequently, a proton at γ-C was shift to nitrogen cation atom with loss of propene (C_3H_6), the pentamide with a positive charge on α-C was formed and gave a peak at m/z 100. The butyl side chain migrated to nitrogen with loss of
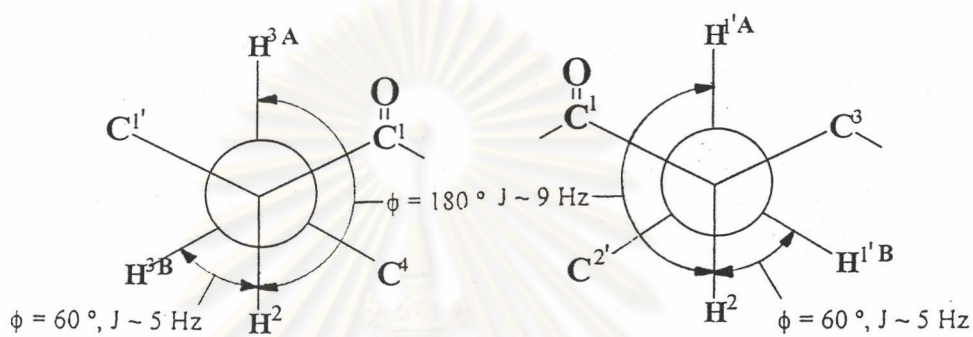
Figure 87. The Newman projections of 2-propylpentanohydroxamic acid and its derivatives, sighting along (a) C^2-C^3 bond, and (b) C^2-$C^{1'}$ bond.
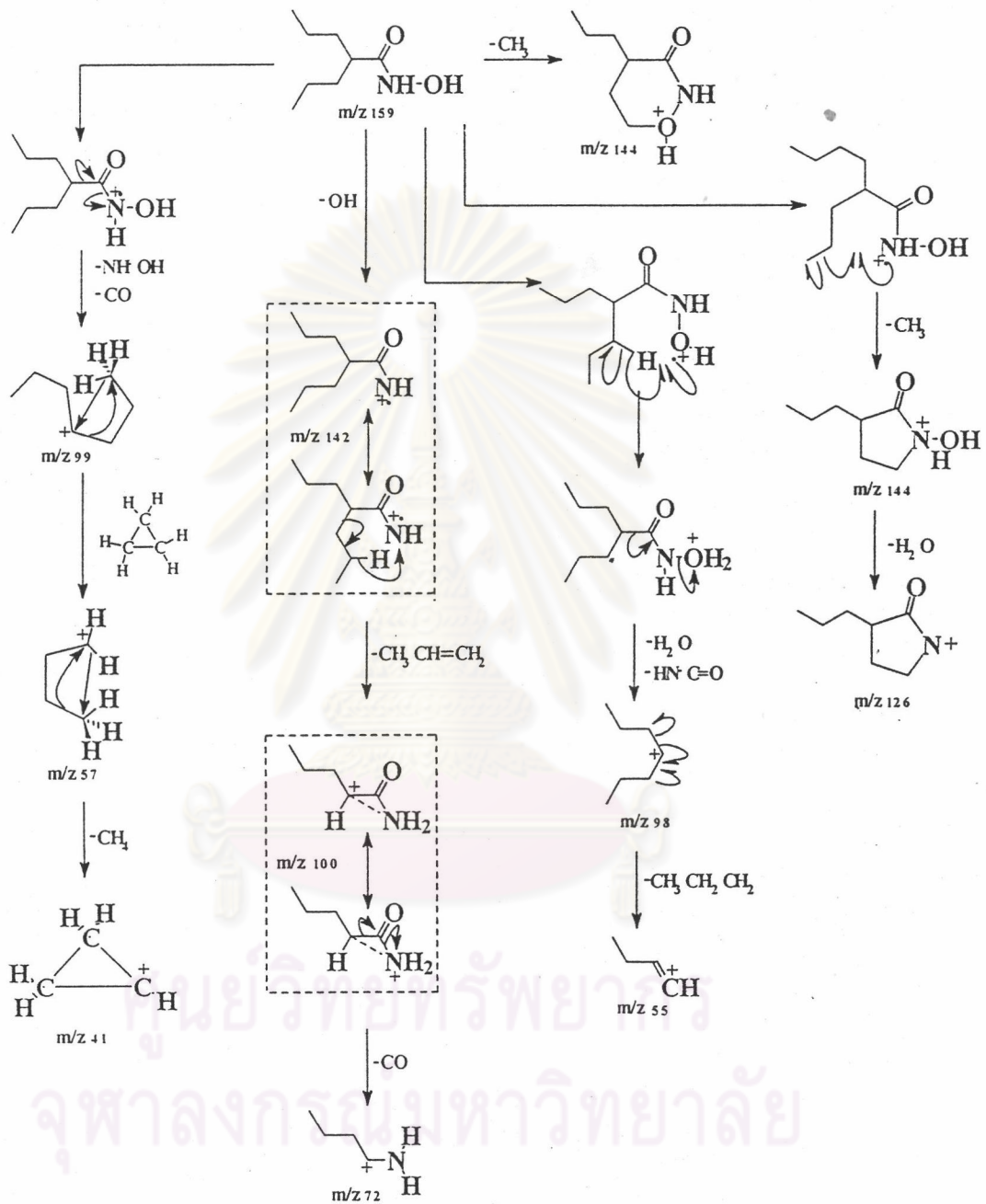
Figure 88. The proposed mass fragmentation of 2-propylpentano hydroxamic acid.

carbonmonoxide (CO), the butylamine cation was occurred and gave a peak at m/z 72.

A peak at m/z 99 represented to heptane cation $[C_7H_{15}]^+$ with a positive charge at 4-position which was resulted from elimination of OH and O=C=NH, respectively. With loss of cyclopropane (C_3H_6), the butane $[C_4H_9]^+$ with a positive charge at terminal C was formed and showed a peak at m/z 57. Then, with elimination of methane (CH_4), a cyclopropane cation $[C_3H_5]^+$ was formed and represented to a strong peak at m/z 41.

The m/z 98 fragment was probably formed by loss of proton at β-C, which connected to oxygen radical cation. With elimination of water (H_2O) and O=C=NH, the $[C_7H_{14}]^{\bullet+}$ was formed and showed on the spectrum at m/z 98, and then, it loss propyl radical, the 1-butene cation $[C_4H_7]^+$ was formed and gave a peak at m/z 55.

The Alkylation Of Hydroxamic Acid Compounds.

O-akyl hydroxamates were the major products resulting from the action of an alkylating agent on the hydroxamate ion, in spite of the fact that there are three plausible sites for alkylation (See in figure 89). One would expect the ambident anion (IV) to flavor alkylation of the nitrogen or carbonyl oxygen rather than the OH oxygen. However, the bifurcated anion species might be sufficiently hydrogen bonded or coordinated to the accompanying cation that the oxygen attached to nitrogen becomes the most nucleophilic and sterically least encumbered atom (V and VI) for attack on an eletrophilic center. The *O*-alkyl hydroxamates could be tested by using color test with ferric chloride solution. The *O*-alkyl hydroxamate could not form complex with Fe^{3+}, but the *N*-alkyl hydroxamate could.

In these syntheses, the alkylation of 2-propylpentanohydroxamic acid (CU-763-1201) with several alkylating agents in the presence of base and heat under reflux cause to form *O*-alkyl-2-propylpentanohydroxamate. There are two possible mechanisms that used to explain the alkylation of 2-propylpentanohydroxamic acid :
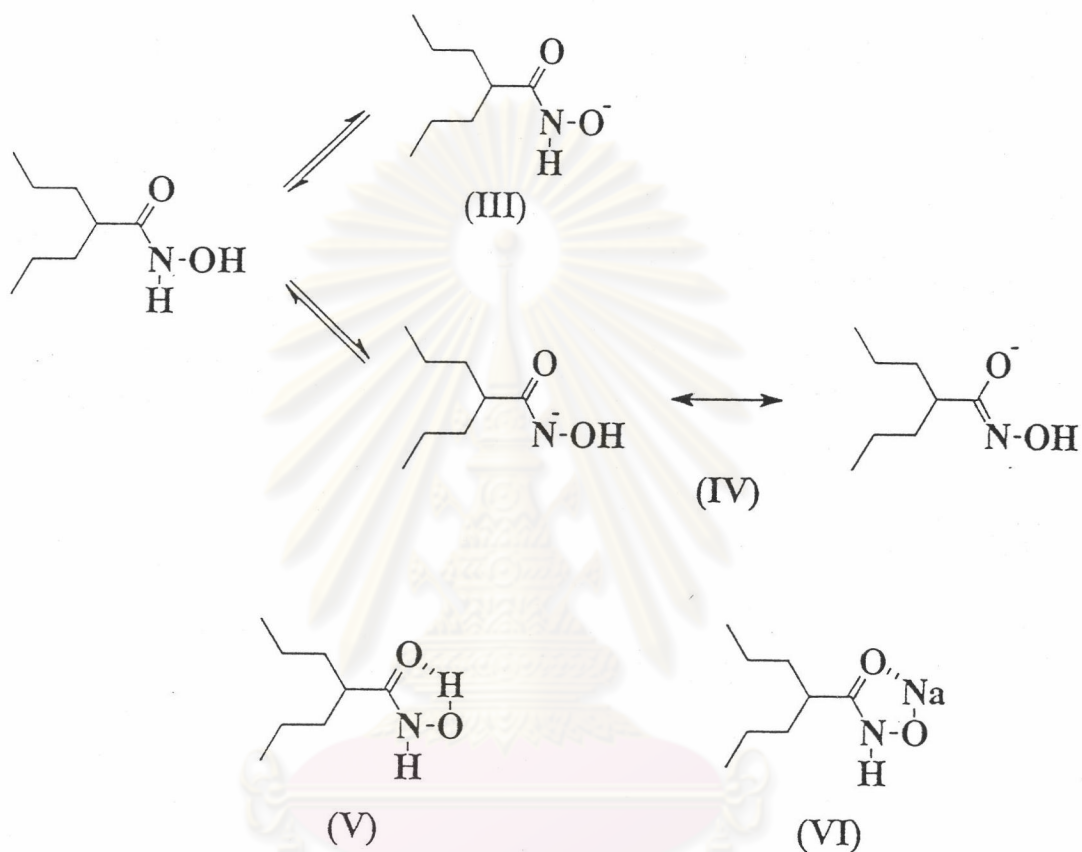
Figure 89. The possible sites, of 2-propylpentanohydroxamic acid and its salts, prefer to alkylation and acylation.

Nucleophilic substitution, bimolecular (S_N2) reaction.

According to this mechanism the sodium-2-propylpentano hydroxamate approaches the carbon bearing the leaving group from back side. It attacks from the side directly opposite the leaving group. The orbital that contains the electron pair of the nucleophile begins to overlap with the small back lobe of an orbital of the carbon bearing the leaving group. As the reaction progresses the lobe between the nucleophile and carbon atom grows and the lobe between the carbon atom and the leaving group shrinks. As this happens the leaving group is pushed away. The formation of the bond between the nucleophile and carbon provides most of the energy necessary to break the bond between the carbon atom and the leaving group.

The mechanism is a one-step displacement mechanism. There are no intermediate. The reaction proceeds through a single transition state (See in figure 90-A).

Nucleophilic substitution, unimolecular (S_N1) reaction.

The mechanism of the reaction involves two step (See in figure 90-B). The first step is the slow step, in it a molecule of alkyl halide is broken to carbocation and halide ion by heterolytic cleavage of carbon-halogen bond. Carbocation formation in general take place slow. In the last step, the intermediate carbocation reacts rapidly with sodium-2-propylpentanohydroxamate to produce O-alkyl-2-propylpentano hydroxamate.

Ethyl-α-(2-propylpentamidooxy)acetate (CU-763-1203).

The compound represented to O-alkyl-2-propylpentano hydroxamate. It was prepared from 2-propylpentanohydroxamic acid and ethyl chloro acetate in the presence of sodium hydroxide and heat under reflux. The two possible mechanisms of the reaction, S_N2 and S_N1, showed in the figure 91-A and B. However, it would expect that this reaction favored an S_N2 mechanism because ethyl chloroacetate was structurally similar to primary alkyl halide. With only one large group attached to the carbon bearing the chloride, S_N2 attack could not be prevented.
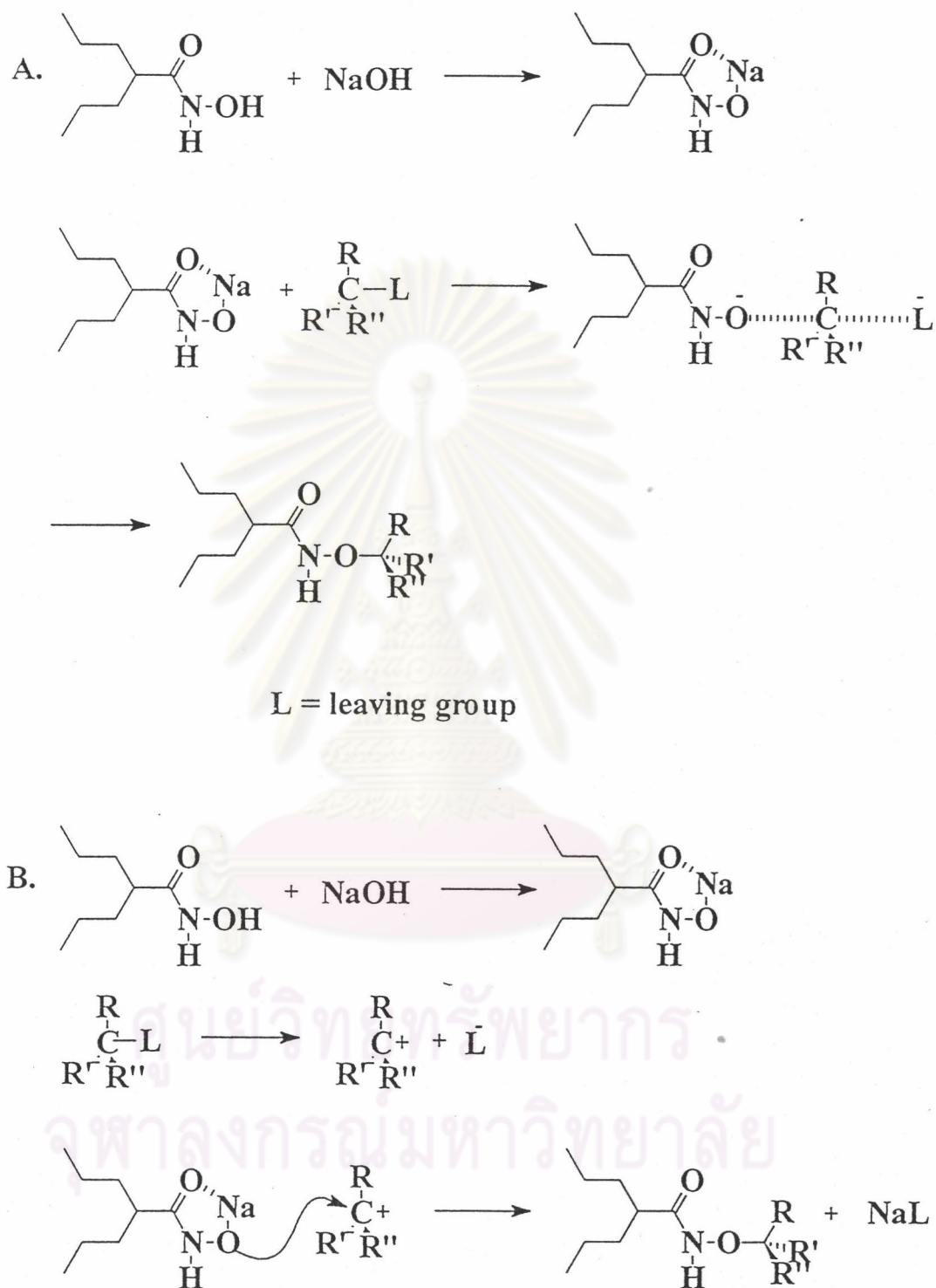
Figure 90. The proposed *O*-alkylation mechanism of 2-propylpentano
hydroxamic acid.
   A. The nucleophilic substitution, bimolecular (S_N2) reaction.
   B. The nucleophilic substitution, unimolecular (S_N1) reaction.

Figure 91. The reaction mechanism of the formation of ethyl-α-(2-propylpentamidooxy)acetate.
    A. The nucleophilic substitution, bimolecular (S_N2) reaction.
    B. The nucleophilic substitution, unimolecular (S_N1) reaction.

The structure of Ethyl-α-(2-propylpentamidooxy)acetate (CU-763-1203) could be confirmed by:
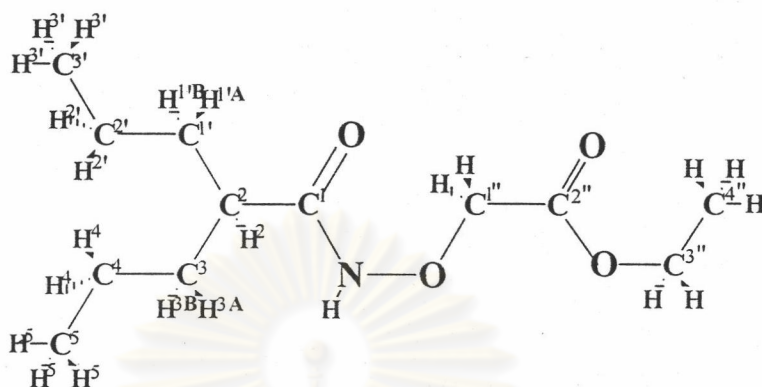
IR spectrum (Figure 31); at the wavenumber 3175 CM^{-1} represented to N-H stretching, 3000-2860 CM^{-1} was C-H stretching of aliphatic compound, 1752 CM^{-1} was C=O stretching (ester like carbonyl), 1662 was C=O stretching (amide like carbonyl), 1462 CM^{-1} were N-H bending, 1075 CM^{-1} was C-O stretching, 1215 CM^{-1} was C (C=O)-O stretching, and 750-600 CM^{-1} was N-H bending (out-of-plane).

^{1}H-NMR spectrum (Figure 32-33); at 0.86-0.91 ppm (6H, t), these protons were assigned to six protons on C^5 and $C^{3'}$, with the coupling to two protons on C^4 and $C^{2'}$, respectively. Thus, it showed peak that was split into triplet (J = 7.33, 7.33 Hz). The peaks at 1.20-1.34 ppm (4H, multiplet), were assigned to two protons on C^4 and two protons on $C^{2'}$. Similar to the protons, that were assigned in 2-propylpentanohydroxamic acid, two protons at 1.35-1.45 ppm (2H, multiplet), two proton at 1.49-1.56 ppm (2H, multiplet), and a proton at 1.31 ppm (1H, broad), were assigned to, H^{3B} and $H^{1'B}$, H^{3A} and $H^{1'A}$, and H^2, respectively. Three protons at 1.31 ppm (t, J = 7.02 Hz), two protons at 4.26 ppm (q, J = 7.02 Hz), and two protons at 4.49 ppm (singlet), were assigned to protons on the $C^{4''}$, $C^{3''}$, and $C^{2''}$, respectively.

^{13}C-NMR spectrum (Figure 34); peaks at 13.926 ppm, 20.572 ppm, 34.655 ppm, 43.703 ppm, and 173.618 ppm, represented to two carbons; C^5 and $C^{3'}$, two carbons; C^4 and $C^{2'}$, two carbons; C^3 and $C^{1'}$, a carbon; C^2, and a carbonyl carbon; C^1, respectively. Peaks, at 14.074 ppm, 61.404 ppm, 72.130 ppm, and 169.735 ppm, were assigned to a carbon; $C^{4''}$, a carbon; $C^{3''}$, a carbon; $C^{1''}$, and a carbonyl carbon; $C^{2''}$, respectively.

Figure 92. The proposed mass fragmentation of ethyl-α-(2-propylpentamidooxy)acetate.

EIMS (Figure 35) and the proposed pathways of mass fragmentation of this compound, showed in figure 92; a peak at m/z 246 represented to $[M+1]^{•+}$. Peaks, at m/z 142, 100, 99, 98, 72, 57, 55, and 41, could be resulted from the reason that was explained in EIMS of 2-propylpentanohydroxamic acid.

Peaks, at m/z 230, 216, 202, and 174, were resulted from loss of methyl radical, two methylene radicals, and carbonmonoxide, respectively.

According to Mc Lafferty rearrangement, a peak at m/z 203 and 174 were formed by elimination of propene (C_3H_6) and ethyl (C_2H_5), respectively.
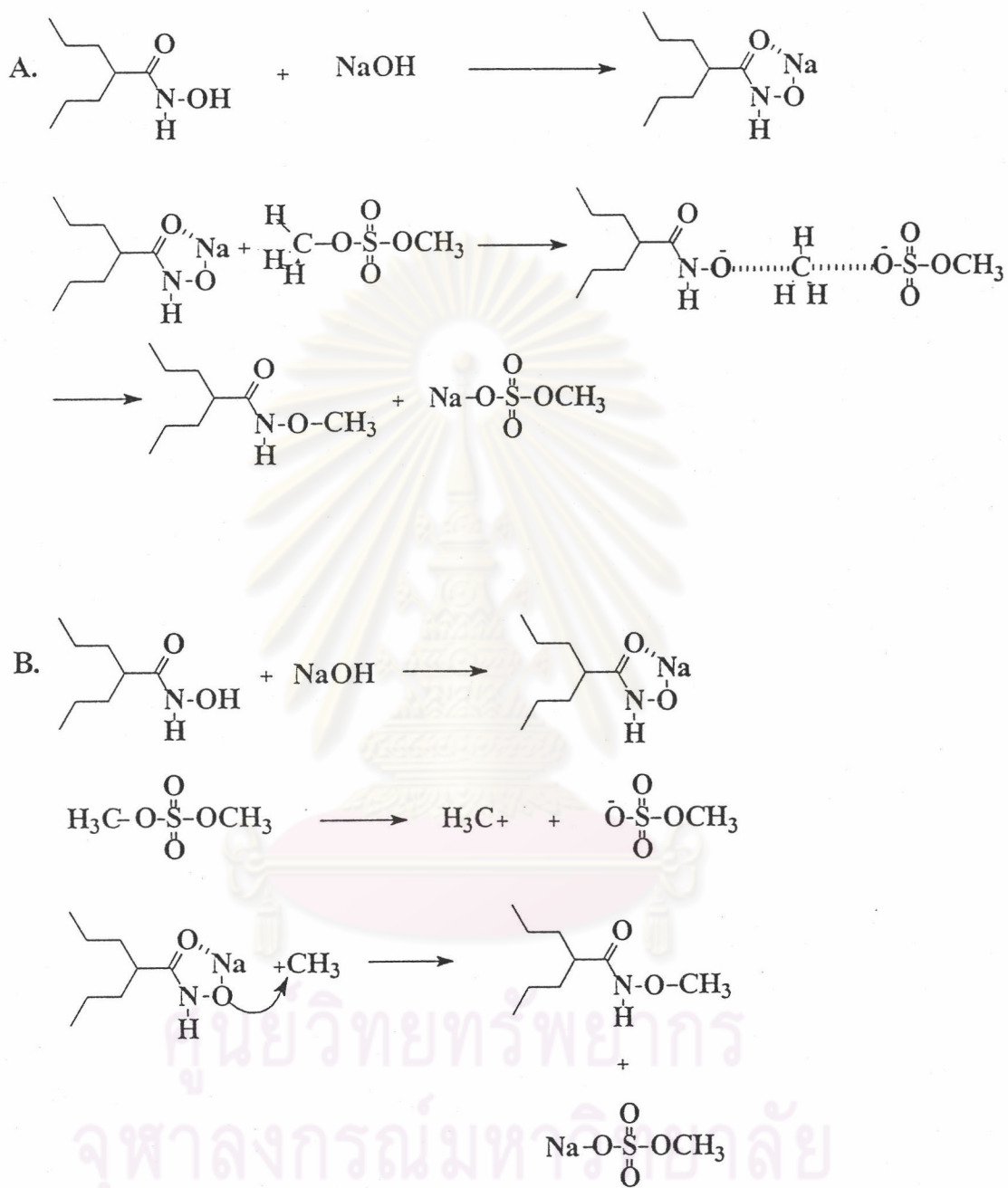
A m/z 126 fragment was probably formed by loss of ethyl hydroxyacetate (HO-CH_2-(C=O)-O-C_2H_5) after a methyl radical was eliminated by $\delta\gamma$C-C cleavage to form five-membered ring of lactam cation that gave a peak at m/z 230.
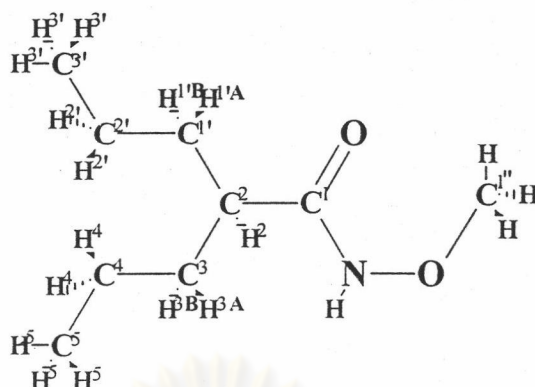
To confirm that, compound (CU-763-1203) was O-akylating compound. It was tested with ferric chloride solution. With the negative result, the color of ferric chloride solution was unchanged. It showed that the compound (CU-763-1203) represented to O-alkyl-2-propylpentanohydroxamate.

Methyl-2-propylpentanohydroxamate (CU-763-1204).

The compound represented to O-alkyl-2-propylpentano hydroxamate. It was prepared from 2-propylpentanohydroxamic acid and dimethylsulfate in the presence of sodium hydroxide and heat under reflux. The two possible mechanism of the reactions, S_N2 and S_N1, showed in the figure 93-A and B. However, it would expect that, this reaction favored an S_N2 mechanism because dimethyl sulfate was structurally similar to methylhalide. With only three small hydrogen interfere with the approaching nucleophile, S_N2 attack could not be protected.

The structure of O-methyl-2-propylpentanohydroxamate (CU-763-1204) could be confirmed by:

Figure 93. The reaction mechanism of the formation of methyl-2-
propylpentanohydroxamate.
A. The nucleophilic substitution, bimolecular (S_N2) reaction.
B. The nucleophilic substitution, unimolecular (S_N1) reaction.

IR spectrum (Figure 36); at the wavenumber 3245 CM^{-1} represented to N-H stretching, 3000-2840 CM^{-1} was C-H stretching of aliphatic compound, 1689 was C=O stretching (amide like carbonyl), 1492 CM^{-1} were N-H bending, 1085 CM^{-1} was C-O stretching, 750-600 CM^{-1} was N-H bending (out-of-plane).

^{1}H-NMR spectrum (Figure 37-38); at 0.89 ppm (6H, t), these protons were assigned to six protons on C^5 and $C^{3'}$, with the coupling to two protons on C^4 and $C^{2'}$, respectively. Thus, it showed peak that was split into triplet (J = 7.33 Hz). The peaks at 1.26-1.44 ppm were assigned to two protons on C^4, two protons on $C^{2'}$, H^{3B} and $H^{1'B}$ (6H, multiplet). Two protons at 1.55-1.68 ppm (2H, multiplet), and a proton at 2.14 ppm (1H, dddd), were assigned to H^{3A} and $H^{1'A}$, and H^2, respectively. A broad peak at 10.46 ppm represented to proton on nitrogen atom. At 3.76 ppm, the protons were assigned to three protons on $C^{1''}$ that connected to oxygen. Without coupling, a singlet peak was showed.

^{13}C-NMR spectrum (Figure 39); peaks at 13.926 ppm, 20.490 ppm, 34.786 ppm, 43.143 ppm, and 173.634 ppm, represented to two carbons; C^5 and $C^{3'}$, two carbons; C^4 and $C^{2'}$, two carbons; C^3 and $C^{1'}$, a carbon; C^2, and a carbonyl carbon; C^1, respectively. Peak, at 63.658 ppm, was assigned to a carbon; $C^{1''}$.

EIMS (Figure 40) and the proposed pathways of mass fragmentation of this compound, showed in figure 94; a peak at m/z 174 represented to [M+1]·+. Peaks, at m/z 142, 100, 99, 98, 72, 57, 55, and 41, could be resulted from the reason that was explained in EIMS of 2-propylpentanohydroxamic acid.
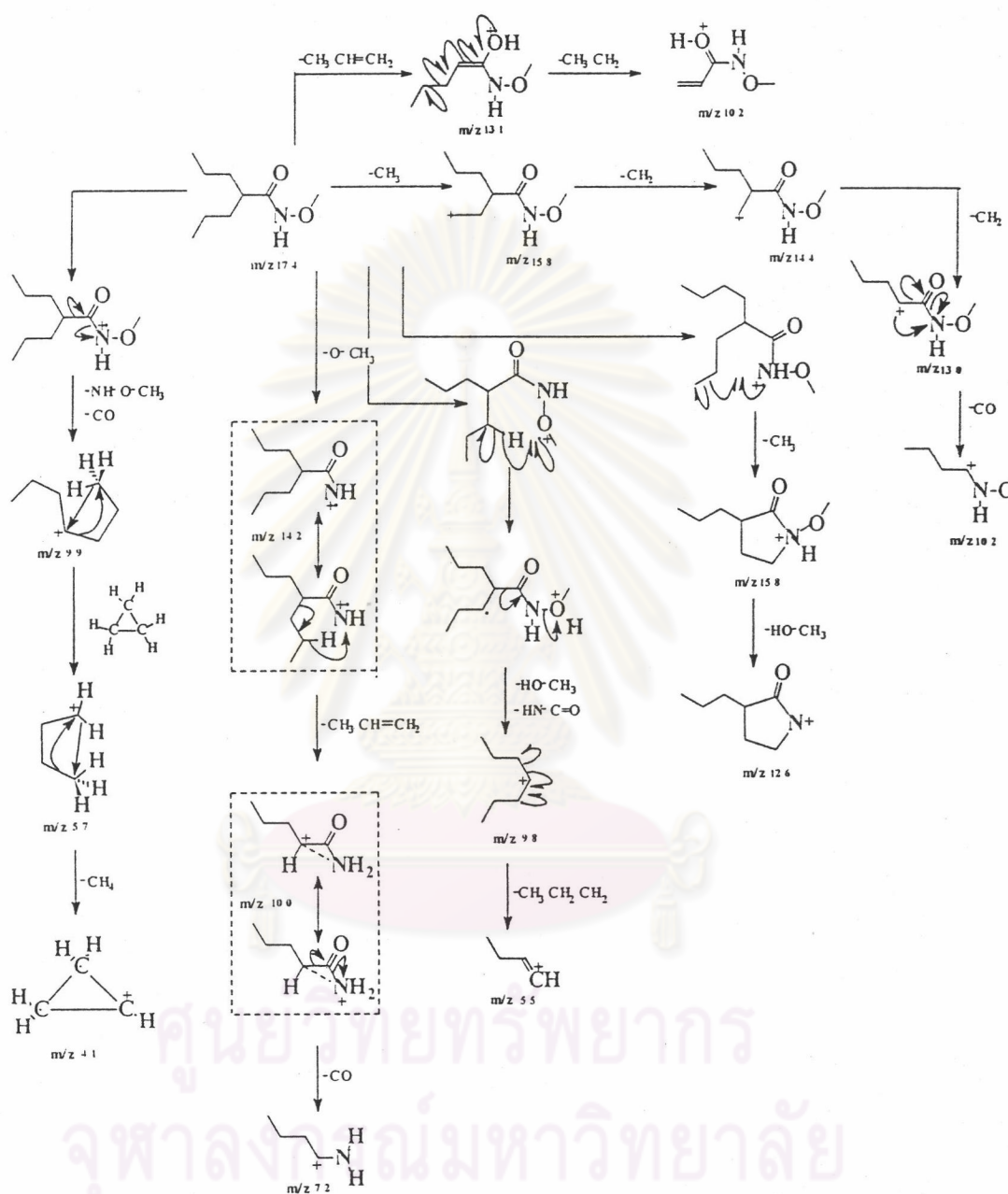
Figure 94. The proposed mass fragmentation of methyl-2-propylpentanohydroxamate.

Peaks, at m/z 158, 144,130, and 102, were resulted from loss of methyl radical, two methylene radicals, and carbonmonoxide, respectively.

According to Mc Lafferty rearrangement, a peak at m/z 131 and 102 were formed by elimination of propene (C_3H_6) and ethyl (C_2H_5), respectively.

A m/z 126 fragment was probably formed by loss of methanol (CH3-OH) after a methyl radical was eliminated by $\delta\gamma$C-C cleavage to form five-membered ring of lactam cation that gave a peak at m/z 158.

To confirm that, compound (CU-763-1204) was *O*-akylating compound. It was tested with ferric chloride solution. With the negative result, the color of ferric chloride solution was unchanged. It showed that the compound (CU-763-1204) represented to *O*-alkyl-2-propylpentanohydroxamate.

Ethyl-2-propylpentanohydroxamate (CU-763-1205).

The compound represented to *O*-alkyl-2-propylpentano hydroxamate. It was prepared from 2-propylpentanohydroxamic acid and ethyliodide in the presence of sodium hydroxide and heat under reflux. The two possible mechanisms of the reaction, S_N2 and S_N1, showed in the figure 95-A and B. However, it would expect that, this reaction favored an S_N2 mechanism because ethyl iodide was structurally similar to primary alkyl halide. With only one methyl group interfere with the approaching nucleophile, S_N2 attack could not be protected.

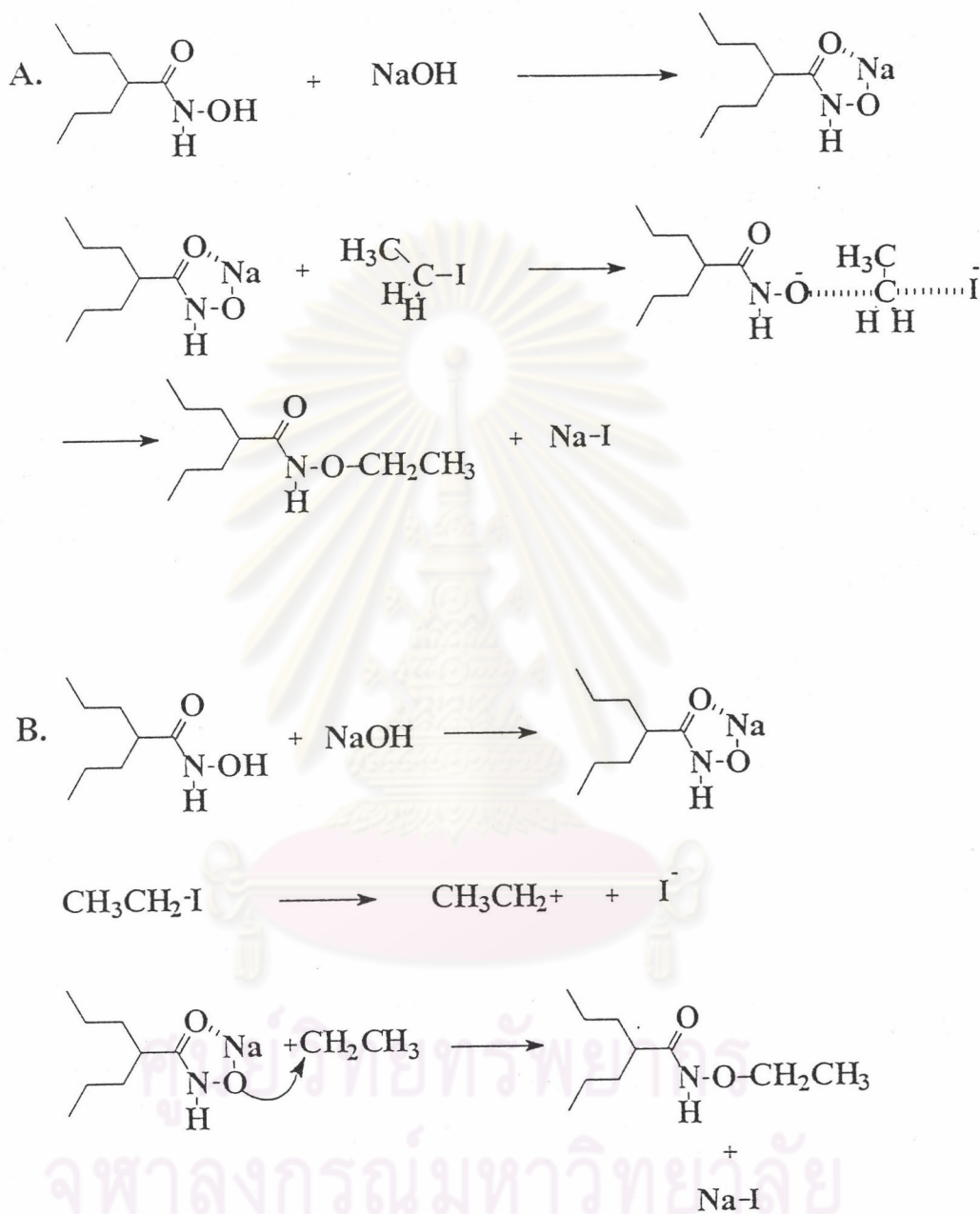The structure of *O*-ethyl-2-propylpentanohydroxamate (CU-763-1205) could be confirmed by:
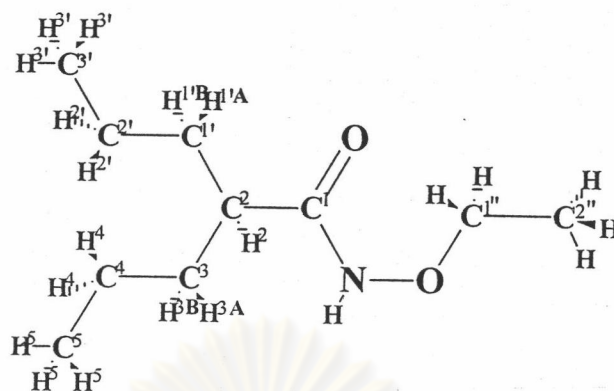
Figure 95. The reaction mechanism of the formation of ethyl-2-
propylpentanohydroxamate.
A. The nucleophilic substitution, bimolecular (S_N2) reaction.
B. The nucleophilic substitution, unimolecular (S_N1) reaction.

IR spectrum (Figure 41); at the wavenumber 3175 CM^{-1} represented to N-H stretching, 3000-2860 CM^{-1} was C-H stretching of aliphatic compound, 1660 was C=O stretching (amide like carbonyl), 1458 CM^{-1} were N-H bending, 1045 CM^{-1} was C-O stretching, 750-600 CM^{-1} was N-H bending (out-of-plane).

^{1}H-NMR spectrum (Figure 42-43); at 0.90 ppm (6H, t), these protons were assigned to six protons on C^5 and $C^{3'}$, with the coupling to two protons on C^4 and $C^{2'}$, respectively. Thus, it showed peak that was split into triplet (J = 7.33 Hz). The peaks at 1.28-1.49 ppm were assigned to two protons on C^4, two protons on $C^{2'}$, H^{3B}, and $H^{1'B}$ (6H, multiplet). Two protons at 1.55-1.75 ppm (2H, multiplet), and a proton at 2.03 ppm (1H, broad), were assigned to H^{3A} and $H^{1'A}$, and H^2, respectively. Three protons at 1.27 ppm (t, J = 7.02 Hz), and two protons at 3.99 ppm (q, J = 7.02 Hz) were represented to protons on $C^{2''}$, and $C^{1''}$, respectively.

^{13}C-NMR spectrum (Figure 44); peaks at 13.860 ppm, 20.424 ppm, 34.803 ppm, 43.045 ppm, and 173.601 ppm, represented to two carbons; C^5 and $C^{3'}$, two carbons; C^4 and $C^{2'}$, two carbons; C^3 and $C^{1'}$, a carbon; C^2, and a carbonyl carbon; C^1, respectively. Peaks, at 13.235 ppm, and 71.291 ppm, were assigned to a carbon; $C^{2''}$, and a carbon; $C^{1''}$, respectively.

EIMS (Figure 45) and the proposed pathways of mass fragmentation of this compound, showed in figure 96; a peak at m/z 188 represented to $[M+1]^{\cdot+}$. Peaks, at m/z 142, 100, 99, 98, 72, 57, 55, and 41, could be resulted from the reason that was explained in EIMS of 2-propylpentanohydroxamic acid.

Figure 96. The proposed mass fragmentation of ethyl-2-
propylpentanohydroxamate.

Peaks, at m/z 172, 158, 144, and 116, were resulted from loss of methyl radical, two methylene radicals, and carbonmonoxide, respectively.

According to Mc Lafferty rearrangement, a peak at m/z 145 and 116 were formed by elimination of propene (C_3H_6) and ethyl (C_2H_5), respectively.

A m/z 126 fragment was probably formed by loss of methanol (CH_3-OH) after a methyl radical was eliminated by $\delta\gamma$C-C cleavage to form five-membered ring of lactam cation that gave a peak at m/z 172.

To confirm that, compound (CU-763-1205) was *O*-akylating compound. It was tested with ferric chloride solution. With the negative result, the color of ferric chloride solution was unchanged. It showed that the compound (CU-763-1205) represented to *O*-alkyl-2-propylpentanohydroxamate.

Propyl-2-propylpentanohydroxamate (CU-763-1206).

The compound represented to *O*-alkyl-2-propylpentano hydroxamate. It was prepared from 2-propylpentanohydroxamic acid and propylbromide in the presence of sodium hydroxide and heat under reflux. The two possible mechanisms of the reaction, S_N2 and S_N1, showed in the figure 97-A and B. However, it would expect that, this reaction favored an S_N2 mechanism because ethyl iodide was structurally similar to primary alkyl halide. With only one ethyl group interfere with the approaching nucleophile, S_N2 attack could not be protected.

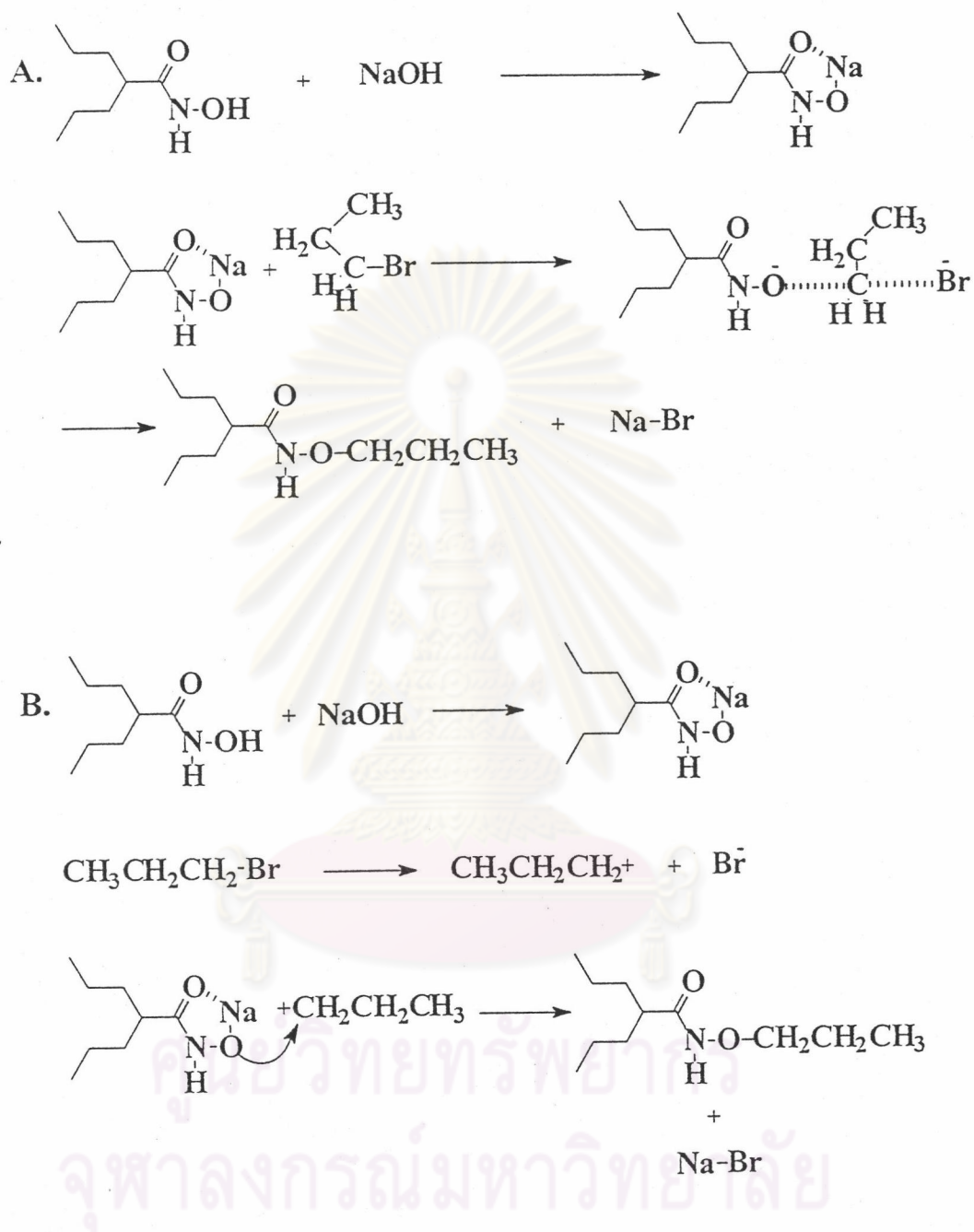The structure of *O*-propyl-2-propylpentanohydroxamate (CU-763-1206) could be confirmed by:
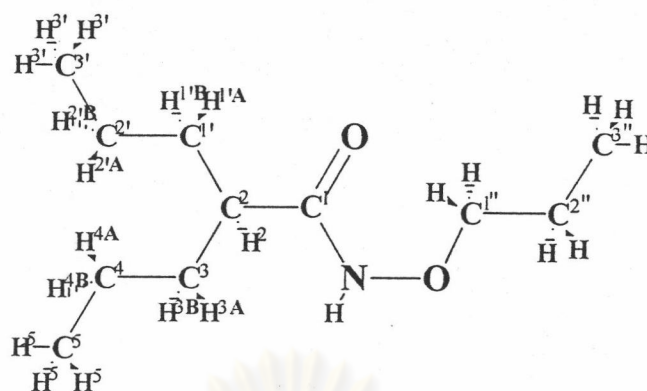
Figure 97. The reaction mechanism of the formation of propyl-2-propylpentanohydroxamate.
   A. The nucleophilic substitution, bimolecular (S_N2) reaction.
   B. The nucleophilic substitution, unimolecular (S_N1) reaction.

H$^{3'}$ H$^{3'}$
H$^{3'}$—C$^{3'}$
H$^{2'B}$—C$^{2'}$ H$^{1'B}$H$^{1'A}$
H$^{2'A}$ C$^{1'}$ O   H H
                                                                      C^{5}—H
                    C^{2}—C^{1} H H   C^{5}—H
                         H^2 H C$^{1''}$ C$^{2''}$
H^{4A} H H   H H
H^{4B}—C^4—C^3 N—O
            H^{3B}H^{3A} H
H^5—C^5
H^5 H^5

IR spectrum (Figure 46); at the wavenumber 3185 CM^{-1} represented to N-H stretching, 3000-2860 CM^{-1} was C-H stretching of aliphatic compound, 1650 was C=O stretching (amide like carbonyl), 1467 CM^{-1} were N-H bending, 1075 CM^{-1} was C-O stretching, 750-600 CM^{-1} was N-H bending (out-of-plane).

^{1}H-NMR spectrum (Figure 47-48); at 0.82 ppm (6H, t), these protons were assigned to six protons on C^5 and C$^{3'}$, with the coupling to two protons on C^4 and C$^{2'}$, respectively. Thus, it showed peak that was split into triplet (J = 7.32 Hz). The peaks at 1.16-1.34 ppm were assigned to two protons on C^4, two protons on C$^{2'}$, H^{3B}, and H$^{1'B}$ (6H, multiplet). Two protons at 1.49-1.56 ppm (2H, multiplet), and a proton at 2.01 ppm (1H, dddd), were assigned to H^{3A} and H$^{1'A}$, and H^2, respectively. Three protons at 0.88 ppm (t, J = 7.32 Hz), two protons at 1.60 ppm (qt, J = 7.32 Hz), and two protons at 3.80 ppm (t, J = 6.72 Hz), were assigned to protons on the C$^{3''}$, C$^{2''}$, and C$^{1''}$, respectively.

^{13}C-NMR spectrum (Figure 49); peaks at 13.943 ppm, 20.572 ppm, 34.819 ppm, 43.505 ppm, and 173.601 ppm, represented to two carbons; C^5 and C$^{3'}$, two carbons; C^4 and C$^{2'}$, two carbons; C^3 and C$^{1'}$, a carbon; C^2, and a carbonyl carbon; C^1, respectively. Peaks, at 10.126 ppm, 21.198 ppm, and 77.921 ppm, were assigned to a carbon; C$^{3''}$, a carbon; C$^{2''}$, and a carbon; C$^{1''}$, respectively.

EIMS (Figure 50) and the proposed pathways of mass fragmentation of this compound, showed in figure 98; a peak at m/z 202 represented to [M+1]·+. Peaks, at m/z 142, 100, 99, 98, 72, 57, 55, and 41, could be resulted from the reason that was explained in EIMS of 2-propylpentanohydroxamic acid.
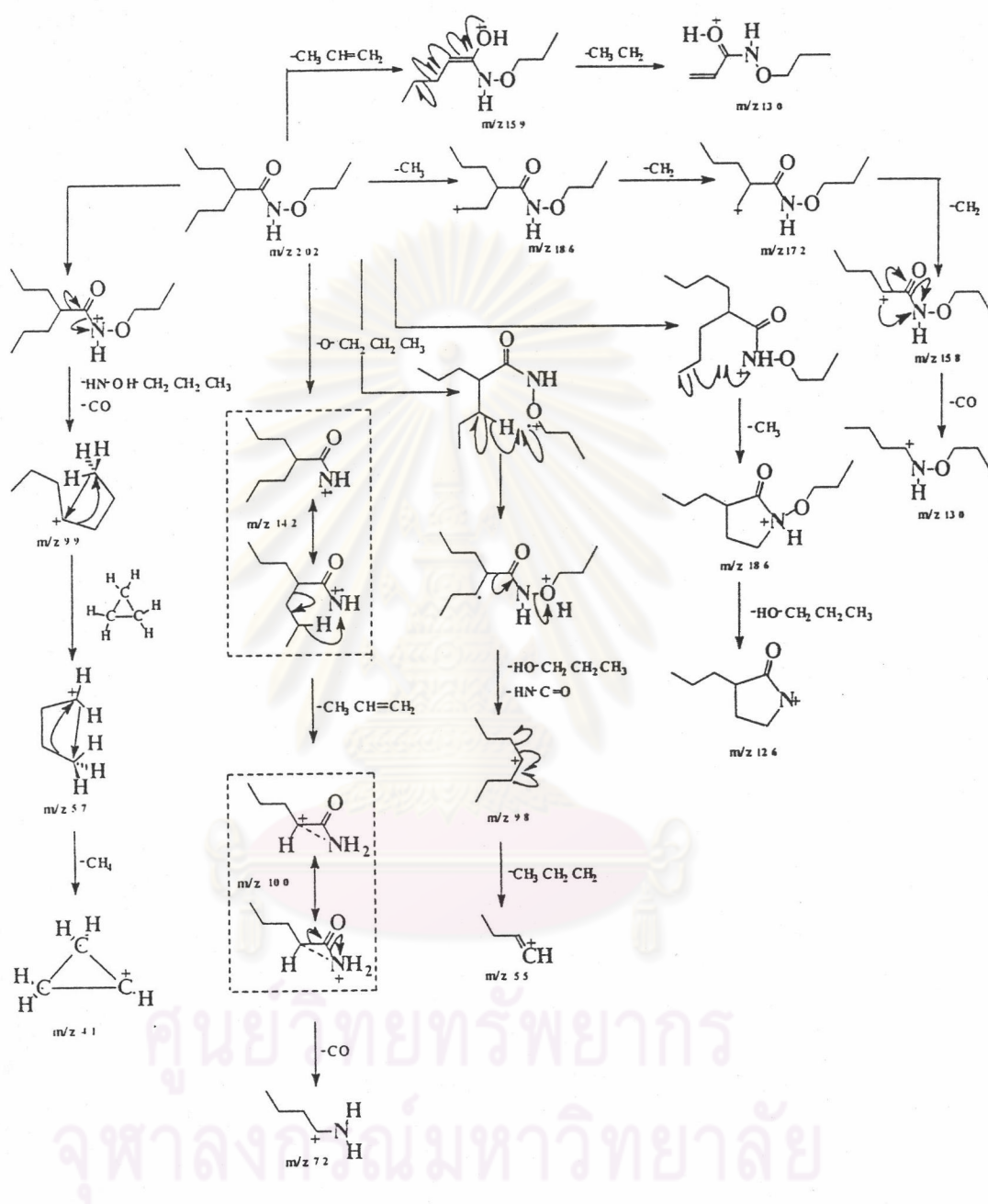
168

Figure 98. The proposed mass fragmentation of propyl-2-propylpentanohydroxamate.

Peaks, at m/z 186, 172, 158, and 130, were resulted from loss of methyl radical, two methylene radicals, and carbonmonoxide, respectively.

According to Mc Lafferty rearrangement, a peak at m/z 159 and 130 were formed by elimination of propene (C_3H_6) and ethyl (C_2H_5), respectively.
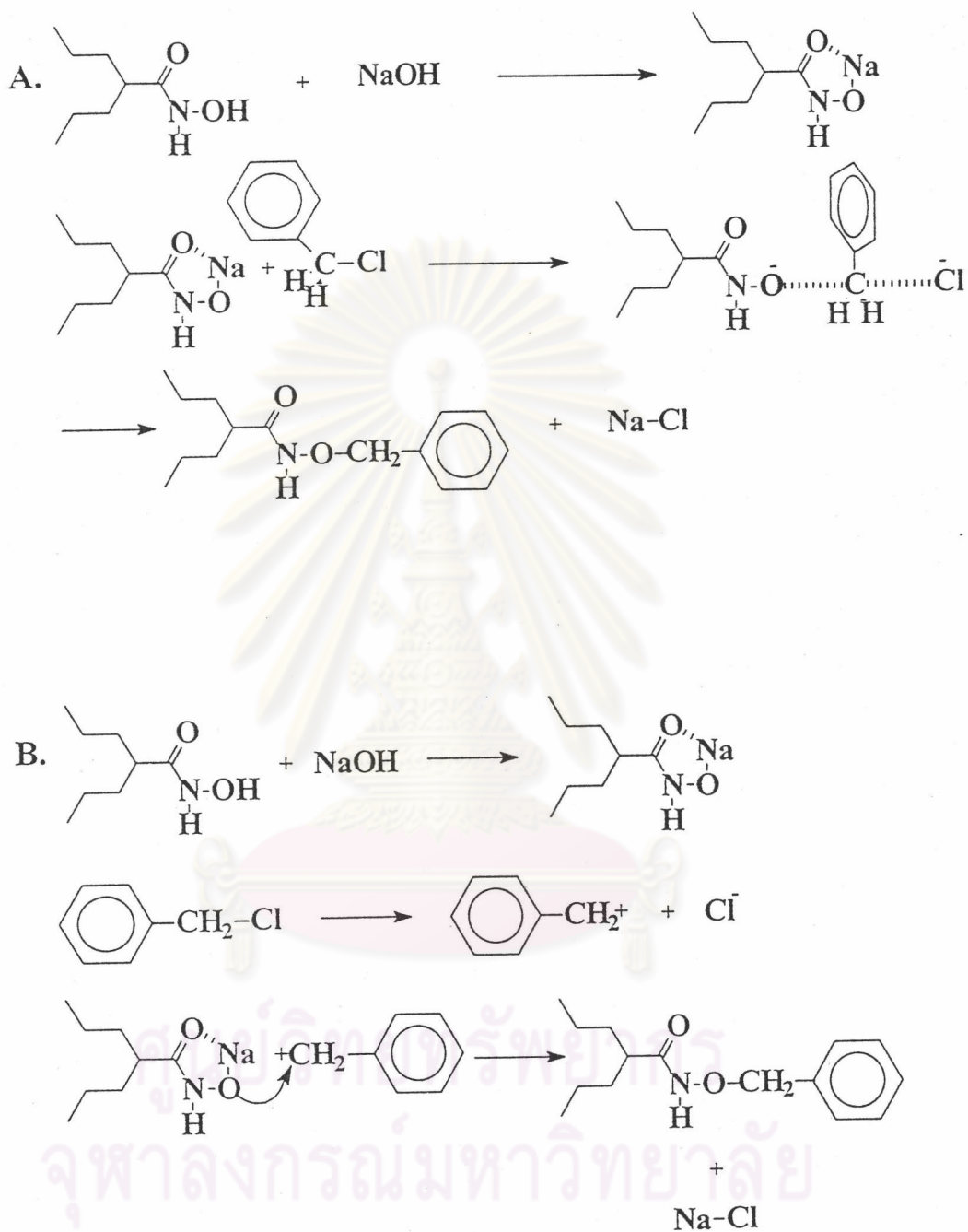
A m/z 126 fragment was probably formed by loss of methanol (CH_3-OH) after a methyl radical was eliminated by $\delta\gamma$C-C cleavage to form five-membered ring of lactam cation that gave a peak at m/z 186.
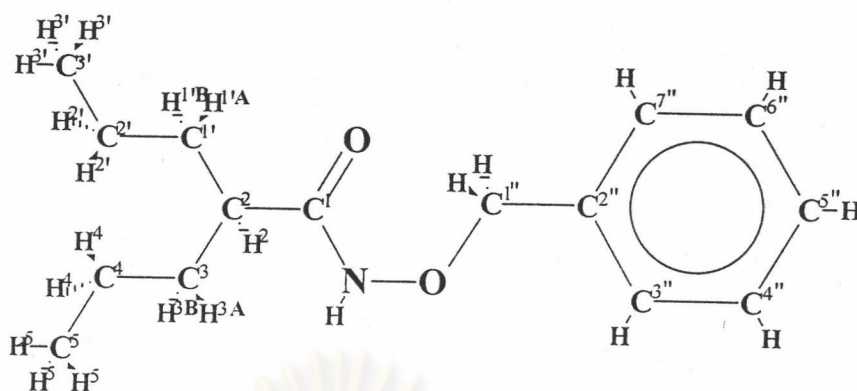
To confirm that, compound (CU-763-1206) was O-akylating compound. It was tested with ferric chloride solution. With the negative result, the color of ferric chloride solution was unchanged. It showed that the compound (CU-763-1206) represented to O-alkyl-2-propylpentanohydroxamate.

Benzyl-2-propylpentanohydroxamate (CU-763-1207).

The compound represented to O-alkyl-2-propylpentano hydroxamate. It was prepared from 2-propylpentanohydroxamic acid and benzylchloride in the presence of sodium hydroxide and heat under reflux. The two possible mechanisms of the reaction, S_N2 and S_N1, showed in the figure 99-A and B. Although benzyl chloride could react either by an S_N2 mechanism or by S_N1 mechanism because it was structurally similar to primary alkyl halide and it could form relatively stable carbocation but in nonpolar solvent, an S_N2 mechanism was expected to be a major pathway.

The structure of O-benzyl-2-propylpentanohydroxamate (CU-763-1207) could be confirmed by:

Figure 99. The reaction mechanism of the formation of benzyl-2-
propylpentanohydroxamate.
A. The nucleophilic substitution, bimolecular (S_N2) reaction.
B. The nucleophilic substitution, unimolecular (S_N1) reaction.

IR spectrum (Figure 51); at the wavenumber 3218 CM^{-1} represented to N-H stretching, 3100-3000 CM^{-1} was C-H stretching of aromatic, 3000-2860 CM^{-1} was C-H stretching of aliphatic, 2000-1667 CM^{-1} was an overtone or combination bands of aromatic, 1652 was C=O stretching (amide like carbonyl), 1514 and 1455 CM^{-1} were C=C stretching of aromatic, 738 CM^{-1} C-H bending of aromatic (out-of-plane), 697 CM^{-1} was C=C bending of aromatic, 750-600 CM^{-1} was N-H bending (out-of-plane).

^{1}H-NMR spectrum (Figure 52-53); at 0.86 ppm (6H, t), these protons were assigned to six protons on C^5 and $C^{3'}$, with the coupling to two protons on C^4 and $C^{2'}$, respectively. Thus, it showed peak that was split into triplet (J = 7.33 Hz). The peaks at 1.15-1.40 ppm were assigned to two protons on C^4, two protons on $C^{2'}$, H^{3B}, and $H^{1'B}$ (6H, multiplet). Two protons at 1.54-1.65 ppm (2H, multiplet), and a proton at 1.96 ppm (1H, broad), were assigned to H^{3A} and $H^{1'A}$, and H^2, respectively. Two protons on $C^{1''}$, connected to oxygen, were showed the absorption peak as singlet at 4.92 ppm. Five protons at 7.30-7.42 ppm (3 H, multiplet and 2H, d) were assigned to protons at meta and para, and ortho position on the benzene ring, respectively. The broad peak at 8.05 ppm referred to a proton on the nitrogen atom.

^{13}C-NMR spectrum (Figure 54); peaks at 13.992 ppm, 20.655 ppm, 34.786 ppm, 43.933 ppm, and 173.601 ppm, represented to two carbons; C^5 and $C^{3'}$, two carbons; C^4 and $C^{2'}$, two carbons; C^3 and $C^{1'}$, a carbon; C^2, and a carbonyl carbon; C^1, respectively. Peaks, at 78.234 ppm, 128.690 ppm, and 135.369 ppm, were assigned to a carbon; $C^{1''}$, a carbon; $C^{5''}$, and a carbon; $C^{2''}$, respectively. Two peaks at 128.542 ppm and 129.233 ppm were assigned to two interchangable couple carbons; $C^{3''}$, $C^{7''}$ and $C^{4''}$, $C^{6''}$.
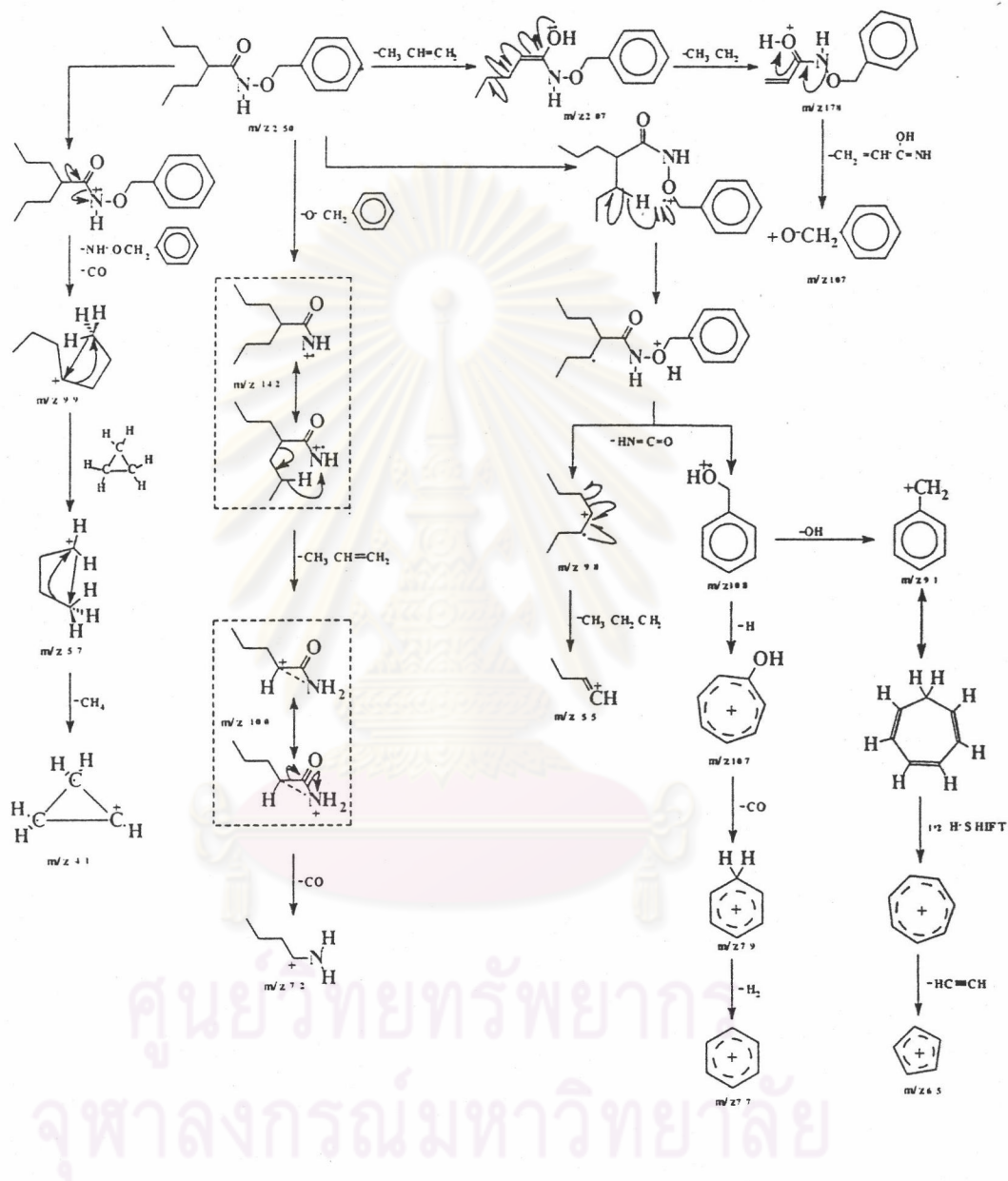
Figure 100. The proposed mass fragmentation of benzyl-2-
propylpentanohydroxamate.

EIMS (Figure 55) and the proposed pathways of mass fragmentation of this compound, showed in figure 100; a peak at m/z 250 represented to [M+1] $^{\cdot}$+. Peaks, at m/z 142, 100, 99, 72, 57, and 41, could be resulted from the reason that was explained in EIMS of 2-propylpentanohydroxamic acid.

According to Mc Lafferty rearrangement, a peak at m/z 207, 178, and 107 were formed by elimination of propene (C_3H_6), ethyl (C_2H_5), and (CH_2=CH-C(-OH)-NH), respectively.

The m/z 98 fragment was probably formed by loss of proton at β-C, which connected to oxygen radical cation. With elimination of benzyl alcohol (C_7H_7OH) and O=C=NH, the [C_7H_{14}]$^{\cdot}$+ was formed and showed on the spectrum at m/z 98, and then, it loss propyl radical, the 1-butene cation [C_4H_7]+ was formed and gave a peak at m/z 55. In contrast, when the proton at β-C was migrated to oxygen radical cation, with loss of 3-heptene ($C_7H_{14)}$ and O=C=NH, benzyl alcohol radical cation, [C_7H_7OH]$^{\cdot}$+ was formed and gave a peak at m/z 108. Benzyl alcohol itself fragmented to give sequentially the [C_7H_6OH]+, [C_6H_7]+, [C_6H_5]+ by loss of H$^{\cdot}$, CO, and H_2, respectively. The peaks of these ion presented at m/z 107, 79, and 77.

When the hydroxy was fragmented from benzyl alcohol radical cation, [C_7H_7OH]$^{\cdot}$+, the resonance-stabilized benzyl ion, [C_7H_7]+, was formed , and then fragmented to give [C_5H_5] $^{+}$ by loss of acetylene (HC≡CH), the peak were observed at m/z 91 and 65, respectively.

To confirm that, compound (CU-763-1207) was *O*-akylating compound. It was tested with ferric chloride solution. With the negative result, the color of ferric chloride solution was unchanged. It showed that the compound (CU-763-1207) represented to *O*-alkyl-2-propylpentanohydroxamate.

2-Chlorobenzyl-2-propylpentanohydroxamate (CU-763-1208).

The compound represented to *O*-alkyl-2-propylpentano hydroxamate. It was prepared from 2-propylpentanohydroxamic acid and α-bromo-2-chlorotoluene in the presence of sodium hydroxide and heat under reflux. The two possible mechanisms of the reaction, S_N2 and

S_N1, showed in the figure 101-A and B. Since α-bromo-2-chlorotoluene was structurally similar to benzyl chloride, so it could expect that the major pathway was an S_N2 mechanism.
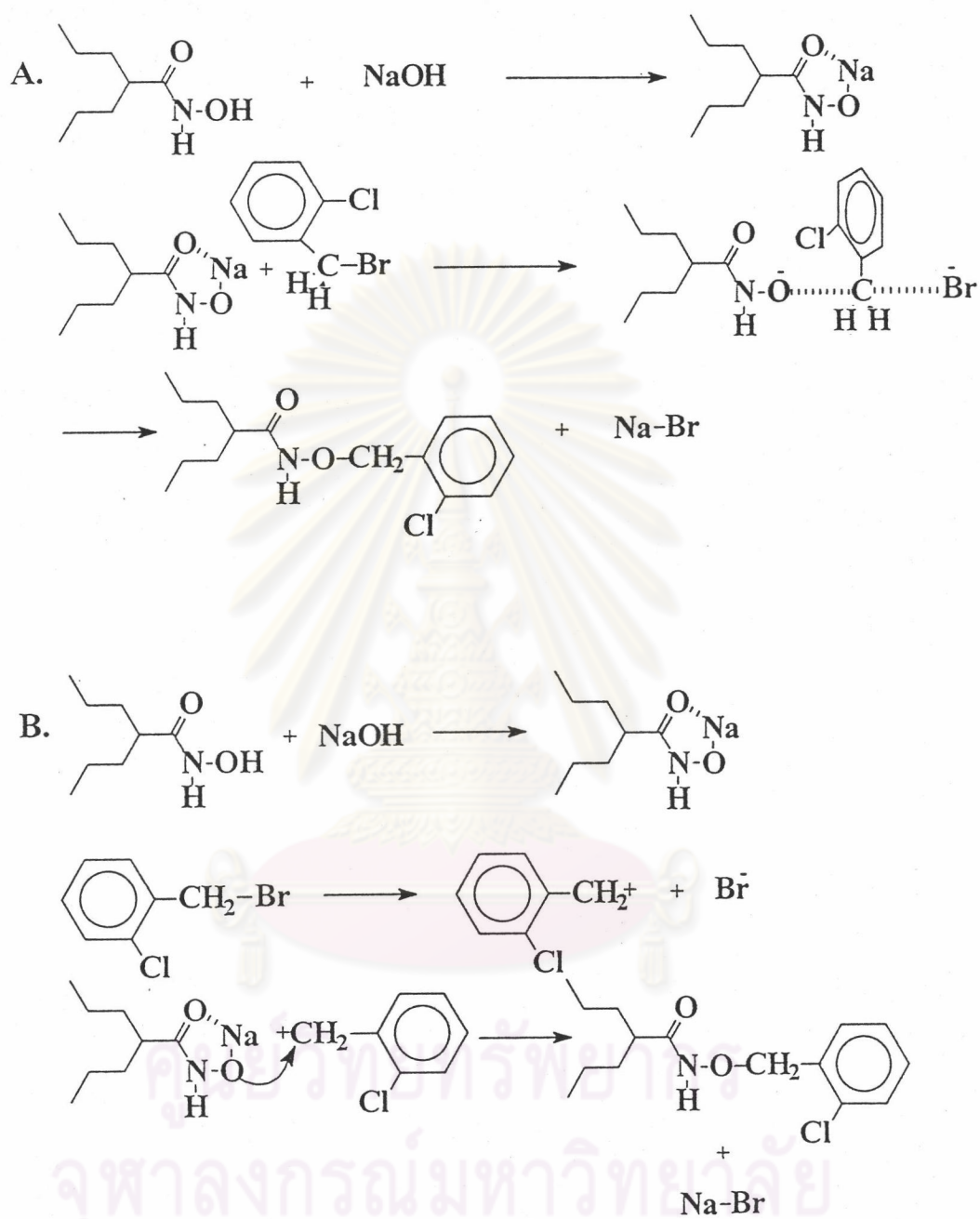
The structure of 2-Chlorobenzyl-2-propylpentanohydroxamate (CU-763-1207) could be confirmed by:
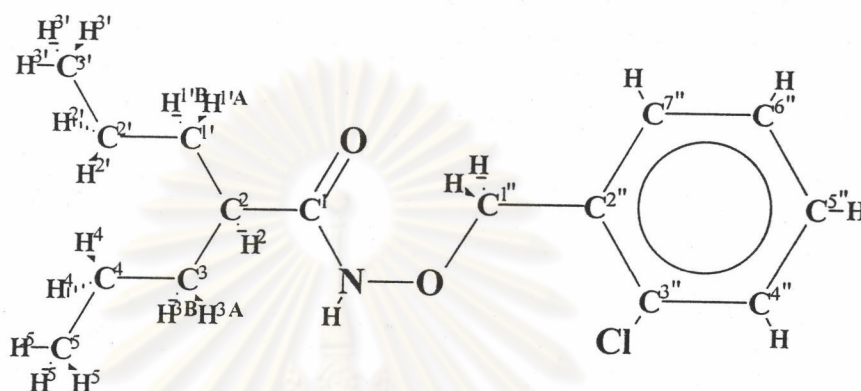
IR spectrum (Figure 56); at the wavenumber 3200 CM^{-1} represented to N-H stretching, 3100-3000 CM^{-1} was C-H stretching of aromatic, 3000-2860 CM^{-1} was C-H stretching of aliphatic, 1661 was C=O stretching (amide like carbonyl), 1520 and 1450 CM^{-1} were C=C stretching of aromatic, 1472 CM^{-1} was N-H bending, 758 CM^{-1} C-H bending of aromatic (out-of-plane), 750-600 CM^{-1} was N-H bending (out-of-plane).

^{1}H-NMR spectrum (Figure 57-58); at 0.87 ppm (6H, t), these protons were assigned to six protons on C^5 and $C^{3'}$, with the coupling to two protons on C^4 and $C^{2'}$, respectively. Thus, it showed peak that was split into triplet (J = 7.33 Hz). The peaks at 1.18-1.42 ppm were assigned to two protons on C^4, two protons on $C^{2'}$, H^{3B}, and $H^{1'B}$ (6H, multiplet). Two protons at 1.55-1.66 ppm (2H, multiplet), and a proton at 1.90 ppm (1H, dddd), were assigned to H^{3A} and $H^{1'A}$, and H^2, respectively. Two protons on $C^{1''}$, connected to oxygen, gave the absorption peak as singlet at 5.07 ppm (2H, s). Four protons at 7.27-7.54 ppm were assigned to protons at $C^{6''}$, $C^{5''}$, $C^{7''}$, and $C^{4''}$. At 8.05 ppm, the broad peak referred to a proton on the nitrogen atom.

^{13}C-NMR spectrum (Figure 59); peaks at 13.992 ppm, 20.655 ppm, 34.770 ppm, 43.900 ppm, and 173.848 ppm, represented to two carbons; C^5 and $C^{3'}$, two carbons; C^4 and $C^{2'}$, two carbons; C^3 and $C^{1'}$, a

Figure 101. The reaction mechanism of the formation of 2-chlorobenzyl-2-propylpentanohydroxamate.
A. The nucleophilic substitution, bimolecular (S_N2) reaction.
B. The nucleophilic substitution, unimolecular (S_N1) reaction.

carbon; C^2, and a carbonyl carbon; C^1, respectively. Six peaks, at 75.289 ppm, 126.847 ppm, 129.578 ppm, 129.940 ppm, 131.305 ppm, 133.197 ppm, and 134.398 ppm, were assigned to six interchangable carbons; $C^{1''}$, $C^{2''}$, $C^{3''}$, $C^{4''}$, $C^{5''}$, $C^{6''}$ and $C^{7''}$.

EIMS (Figure 60) and the proposed pathways of mass fragmentation of this compound, showed in figure 102; a peak at m/z 284 represented to $[M+1]^{\cdot+}$. Peaks, at m/z 142, 100, 99, 72, 57, and 41, could be resulted from the reason that was explained in EIMS of 2-propylpentanohydroxamic acid.

According to Mc Lafferty rearrangement, a peak at m/z 241, 212, and 141 were formed by elimination of propene (C_3H_6), ethyl (C_2H_5), and (CH$_2$=CH-C(-OH)-NH), respectively.

The m/z 98 fragment was probably formed by loss of proton at β-C, which connected to oxygen radical cation. With elimination of benzyl alcohol (C_7H_7OH) and O=C=NH, the $[C_7H_{14}]^{\cdot+}$ was formed and showed on the spectrum at m/z 98, and then, it loss propyl radical, the 1-butene cation $[C_4H_7]^+$ was formed and gave a peak at m/z 55. In contrast, when the proton at β-C was migrated to oxygen radical cation, with loss of 3-heptene ($C_7H_{14)}$ and O=C=NH, 2-chlorobenzyl alcohol radical cation, $[ClC_7H_6OH]^{\cdot+}$ was formed and gave a peak at m/z 142. 2-Chloro-benzyl alcohol itself fragmented to give sequentially the $[ClC_7H_5OH]^+$, $[ClC_6H_6]^+$, $[C_6H_5]^+$ by loss of H$^{\cdot}$, CO, and HCl, respectively. The peaks of these ion presented at m/z 141, 113, and 77.

When the hydroxy was fragmented from 2-chlorobenzyl alcohol radical cation, $[ClC_7H_6OH]^{\cdot+}$, the resonance-stabilized benzyl ion, $[ClC_7H_6]^+$, was formed by loss of hydroxy (OH). The peak was observed at m/z 125.

To confirm that, compound (CU-763-1208) was *O*-akylating compound. It was tested with ferric chloride solution. With the negative result, the color of ferric chloride solution was unchanged. It showed that the compound (CU-763-1208) represented to *O*-alkyl-2-propylpentanohydroxamate.
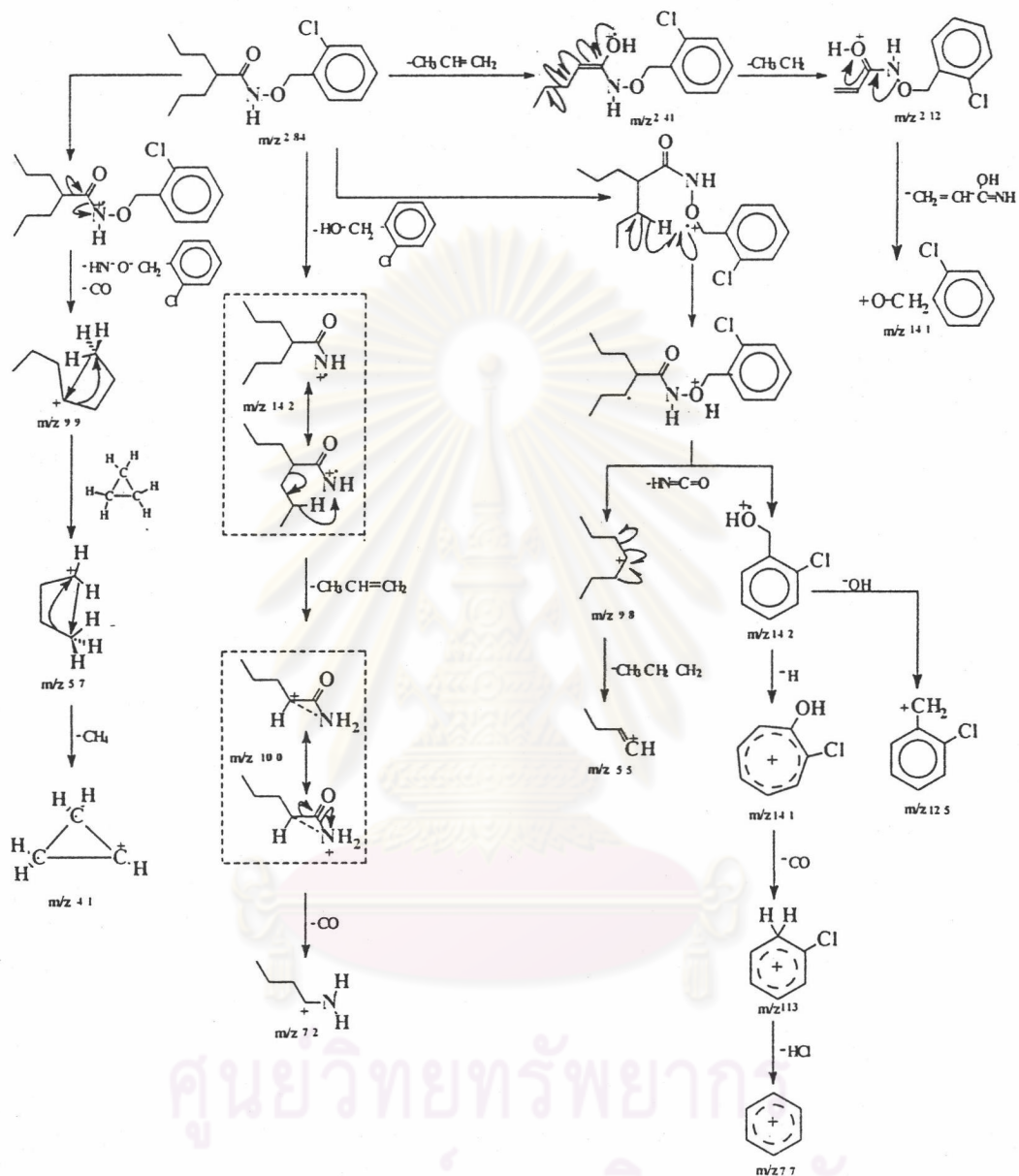
Figure 102. The proposed mass fragmentation of 2-chlorobenzyl-2-propylpentanohydroxamate.

The Acylation Of Hydroxamic Acid Compounds.

Similar to the alkylation of hydroxamic acid compounds, there were three plausible sites for acylation. But the oxygen attached to nitrogen becomes the most nucleophilic and sterically least encumbered atom for attack on an eletrophilic center. The O-acyl hydroxamates could be tested by using color test with ferric chloride solution. The O-acyl hydroxamate could not form complex with Fe^{3+}, but the N-acyl hydroxamte could.

Unlike the alkylation, the acylation of 2-propylpentano hydroxamic acid with several acyl halides or anhydride had to avoid from base or high temperature. For the reason that, all O-acyl-2-propylpentanohydroxamate easily decompose to N,N'-di(2-propylbutyl) urea (Stieglitz, J. and Stagner, B.A. 1916; Stagner, B.A. 1916; Mukaiyama, T. and Nohira, H. 1961; Zvilichovsky, G. 1969).

In the presence of base.

When O-acyl-2-propylpentanohydroxamate was reacted by base such as sodium hydroxide, the sodium salt of O-acyl-2-propylpentanohydroxamate was formed and leaded to rearrangement to form an isocyanate (Jones, L.W. and Neuffer, L. 1917; Jones, L.W. and Sneed, M.C. 1917; Jones, L.W. and Powers, D.H. 1924). According to this mechanism, there occurred first a depletion of electrons around the nitrogen atom, necessitating the migration of alkyl side chain with its pair of electrons from the adjacent carbon atom. The tendency of sodium to part from, and of carboxylate to retain, bond electrons during the formation of the ion sodium and carboxylate furnished the driving force for the reaction (Jones, L.W. and Hurd, C.D. 1921; Jones, L.W. and Scott, A.W. 1922; Jones, L.W. and Root, F.B. 1926; Berndt, D.C. and Shechter, H. 1964). In the presence of water in the solvent, the isocyanate was hydrolyzed to amine with the releasing of carbondioxide. When the amine was formed, it was then reacted by the isocyanate to form N,N'-di(1-propylbutyl)urea. The mechanism of the reaction see in figure 103-A.
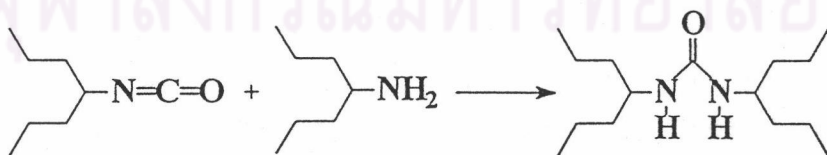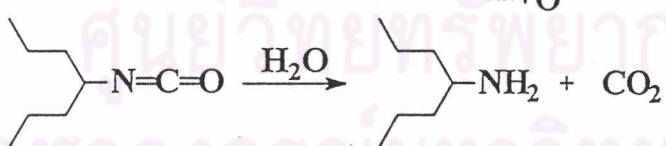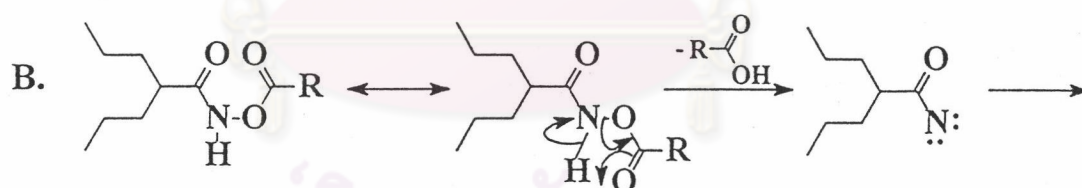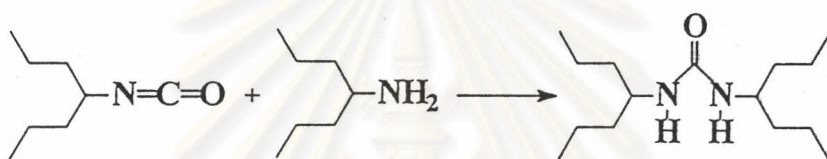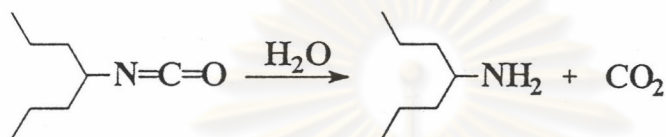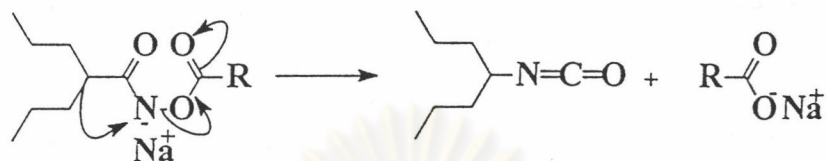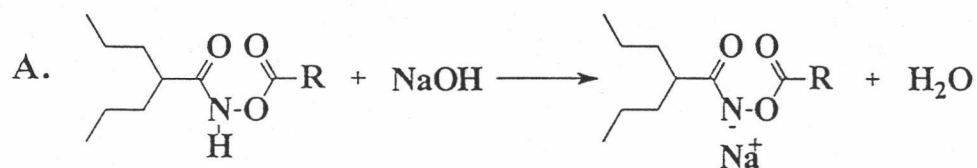
Figure 103. The proposed reaction mechanism of the formation of *N,N'*-di (1-propylbutyl)urea.
 A. In the presence of base.
 B. In the presence of heat.

In the presence of heat.

When the compound, *O*-acyl-2-propylpentano hydroxamate, was heated, the loss of carboxylic acid occurred and then leaded to rearrangement to an isocyanate. The loss of carboxylic acid gave an electronically deficient nitrogen atom which acquired stability by alkyl side chain migration. In the presence of water in the solvent, the isocyanate was then hydrolyzed into amine with the loss of carbondioxide. Suddenly, the apparent amine was reacted by the isocyanate and *N,N'*-di(1-propylbutyl)urea was formed. The mechanism of the reaction see in figure 103-B.

The structure of *N,N'*-di(1-propylbutyl)urea was identified as follow :
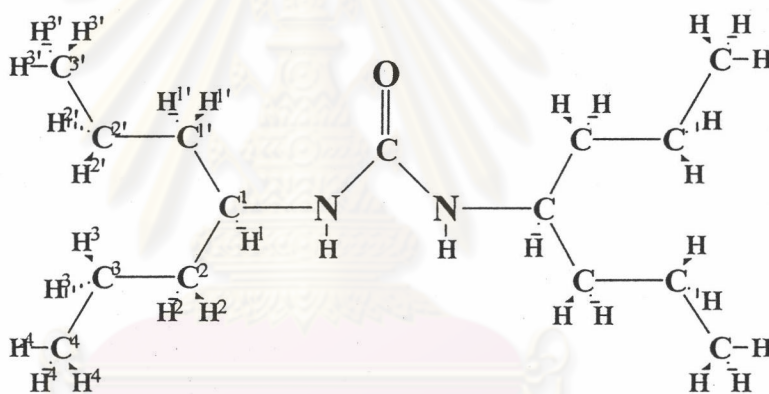
IR spectrum (Figure 104); at the wavenumber 3322 CM^{-1} represented to N-H stretching, 3000-2860 CM^{-1} was C-H stretching of aliphatic, 1625 was C=O stretching (amide like carbonyl), 1582 and 1537 CM^{-1} were N-H bending and N-C=O stretching, 1262 CM^{-1} was C-N stretching, 800-600 CM^{-1} was N-H bending (out-of-plane).

^{1}H-NMR spectrum (Figure 105-106); because both alkyl side chain of urea were symmetry, so protons of both were equivalent. At 0.91 ppm (12H, t), these protons were assigned to twelve protons of both side chain on C^4 and $C^{3'}$, with the coupling to two protons on C^3 and $C^{2'}$, respectively. Thus, it showed peak that was split into triplet (J = 7.32 Hz). The sixteen protons at 1.27-1.49 ppm were assigned to H^3, $H^{2'}$, H^2, and $H^{1'}$ of both side chain. The multiplet peak at 1.90 ppm was assigned to two protons on C^1 of both side chain. At 3.83 ppm, there was a

doublet-splited peak that referred to two protons on each nitrogen atom of urea with coupling to a H^1 (J = 9.1 Hz).

^{13}C-NMR spectrum (Figure 107); peaks at 14.058 ppm, 19.042 ppm, 38.109 ppm, 49.623 ppm, and 158.104 ppm, represented to four carbons; C^4 and $C^{3'}$, four carbons; C^3 and $C^{2'}$, four carbons; C^2 and $C^{1'}$, two carbons; C^1, and a carbonyl carbon of urea; -NH-($\underline{C}$=O)-NH-, respectively.

EIMS (Figure 108) and the proposed pathways of mass fragmentation of this compound, showed in figure 109; it showed the molecular ion peak at m/z 257, $[M+1]^{\cdot}+$. Peaks at m/z 241, 227 and 213 resulted from the loss of methyl radical, two methylene radicals, respectively.

A peak at m/z 99 referred to heptane with a positive charge at 4-position. With the loss of C_3H_6, the butane with a positive charge at terminal was formed and gave a peak at m/z 57. Subsequently, elimination of methane cause to form cyclopropane cation, m/z 41.

The loss of 3-heptene and HN-C=O caused to form 1-propylbutylamine radical cation, m/z 115. Then the propyl radical was eliminated, the butylimine cation was formed and gave a peak at m/z 72. With the loss of ethyl radical, the aminoethylene cation was occurred at m/z 43.

By cyclization to five-membered ring and loss of ethyl radical, the cyclic urea was formed and represented to a peak at m/z 227.

To avoid from base or heat in the reaction, the 2-propylpentano hydroxamic acid was firstly changed to metal salt by using sodium ethoxide. The equimolar between sodium ethoxide and 2-propyl pentanohydroxamic acid and slowly drop of sodium ethoxide to the 2-propylpentanohydroxamic acid solution were necessary to prevent the formation of N,O-disodium 2-propylpentanohydroxamate which caused to rearrangement to form isocyanate, amine, and N,N'-di(1-propylbutyl) urea, when it was reacted by several acyl halides or anhydride.
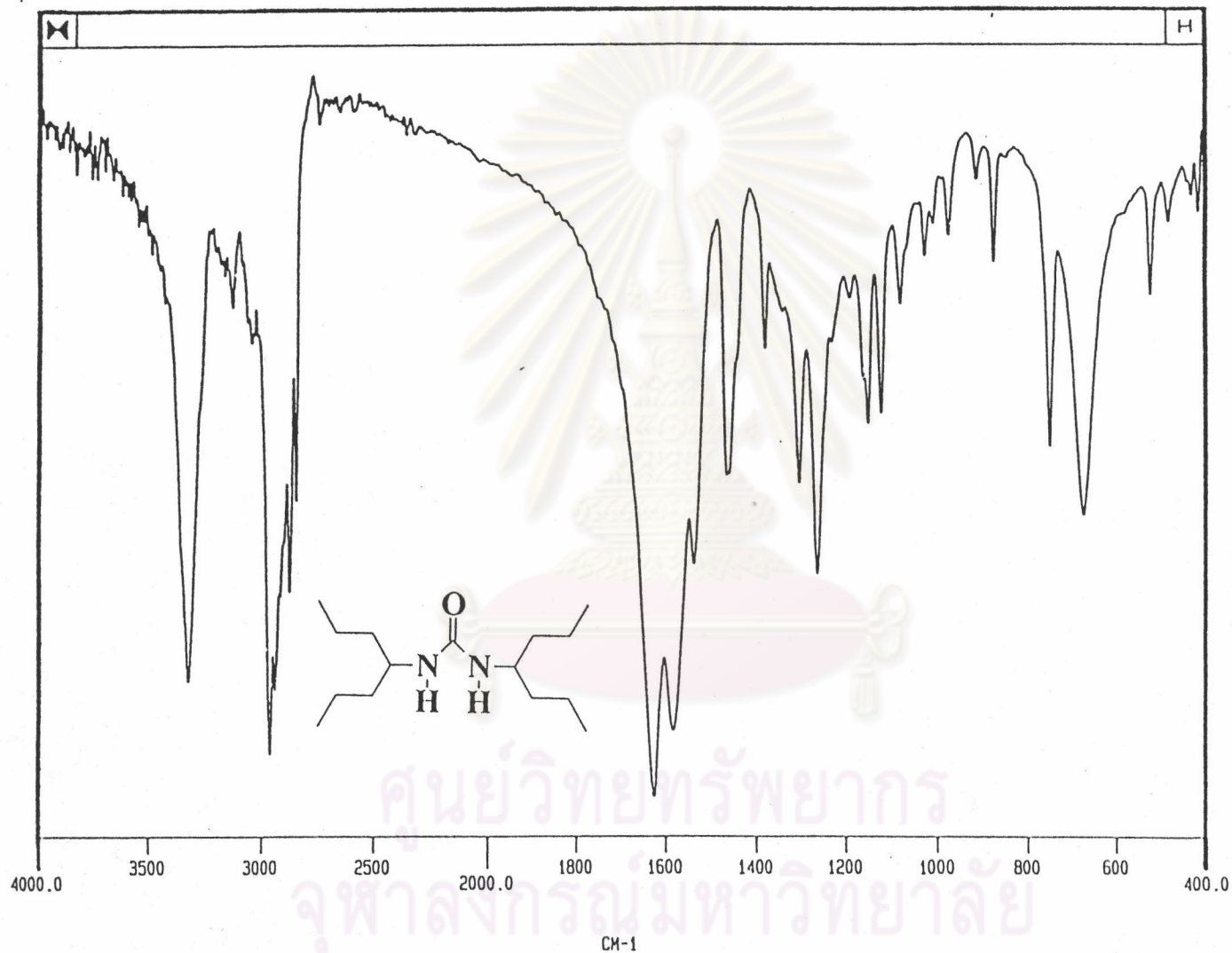
Figure 104. The IR spectrum (KBr pellet) of *N,N'*-di(1-propylbutyl)urea.

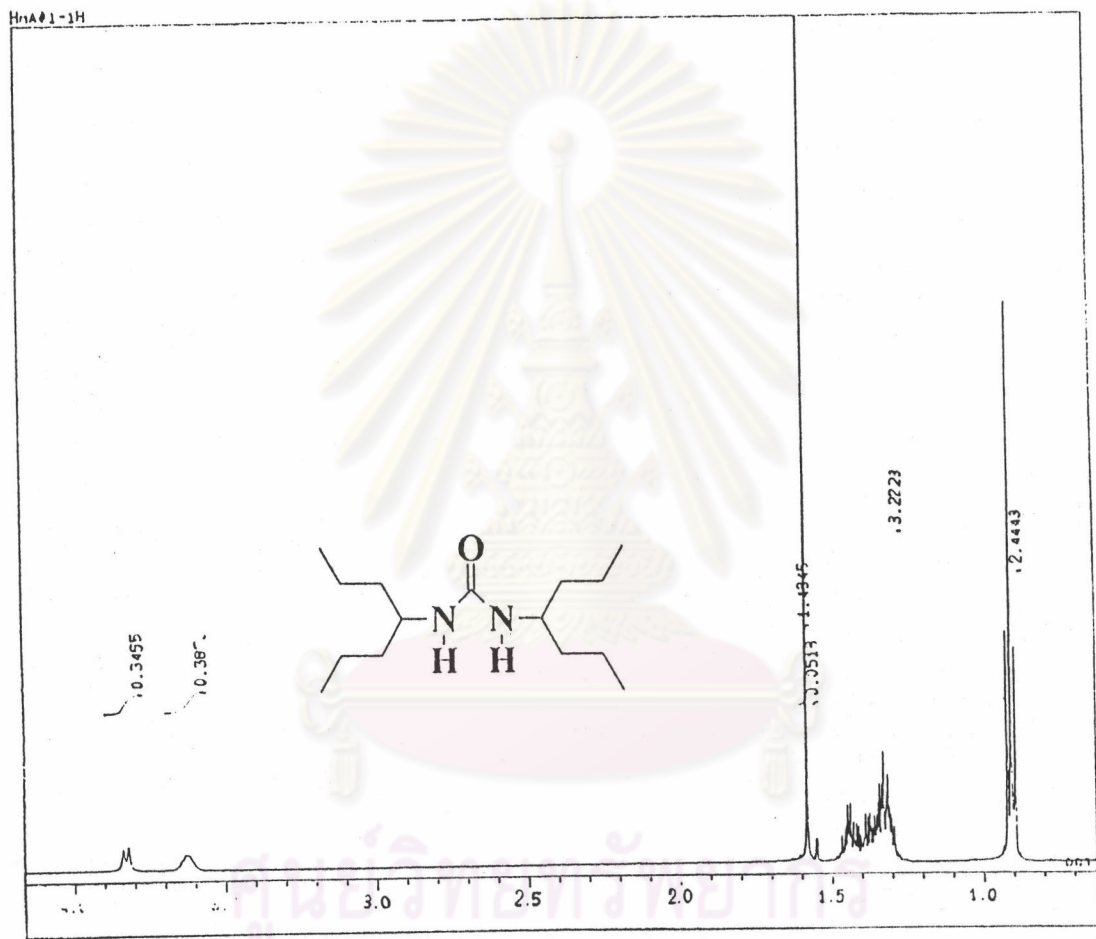Figure 105. The 500 MHz ^{1}H-NMR spectrum of N,N'-di(1-propylbutyl) urea.
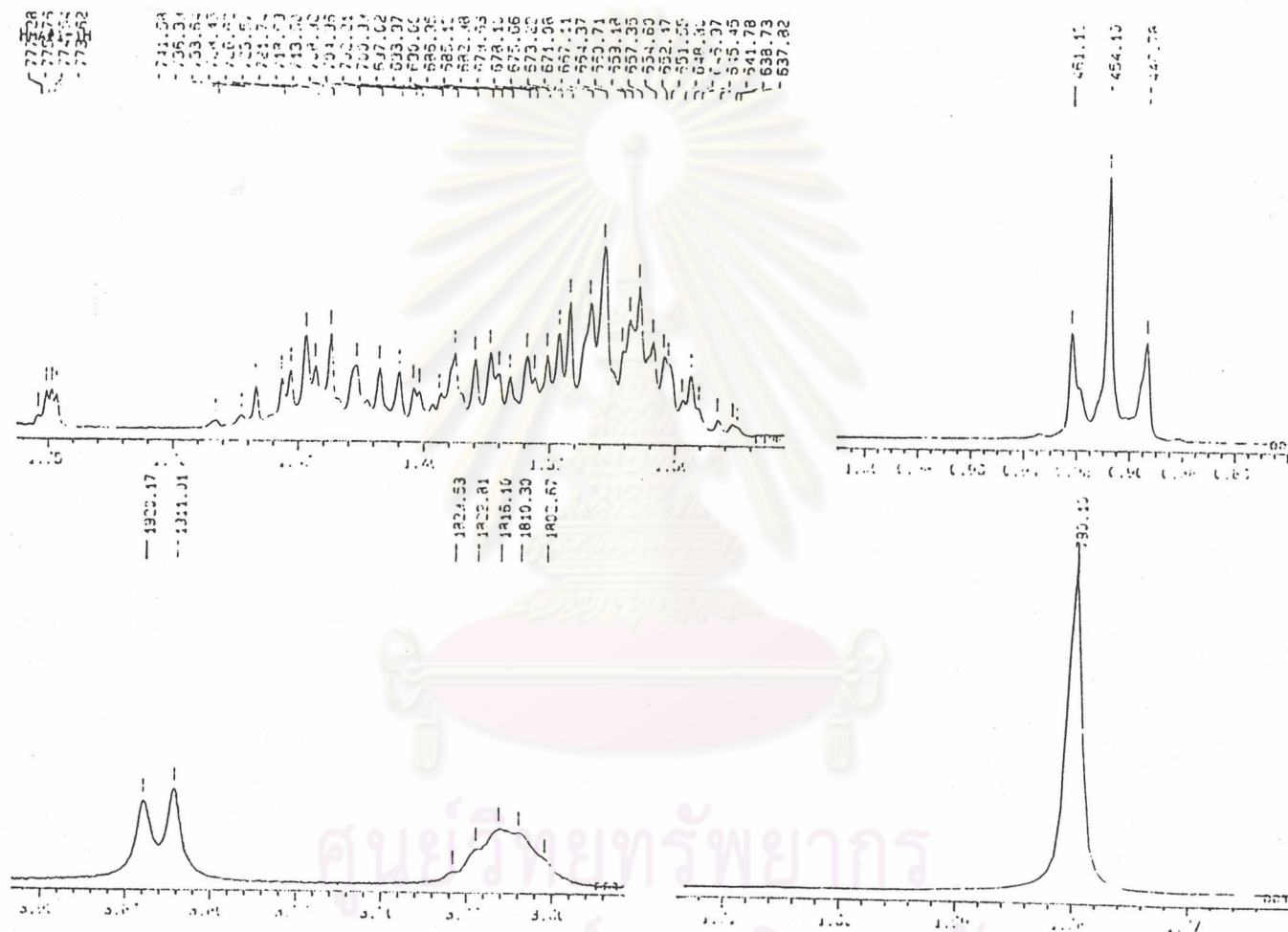
Figure 106. The 500 MHz ^{1}H-NMR spectrum N,N'-di(1-propylbutyl)urea.
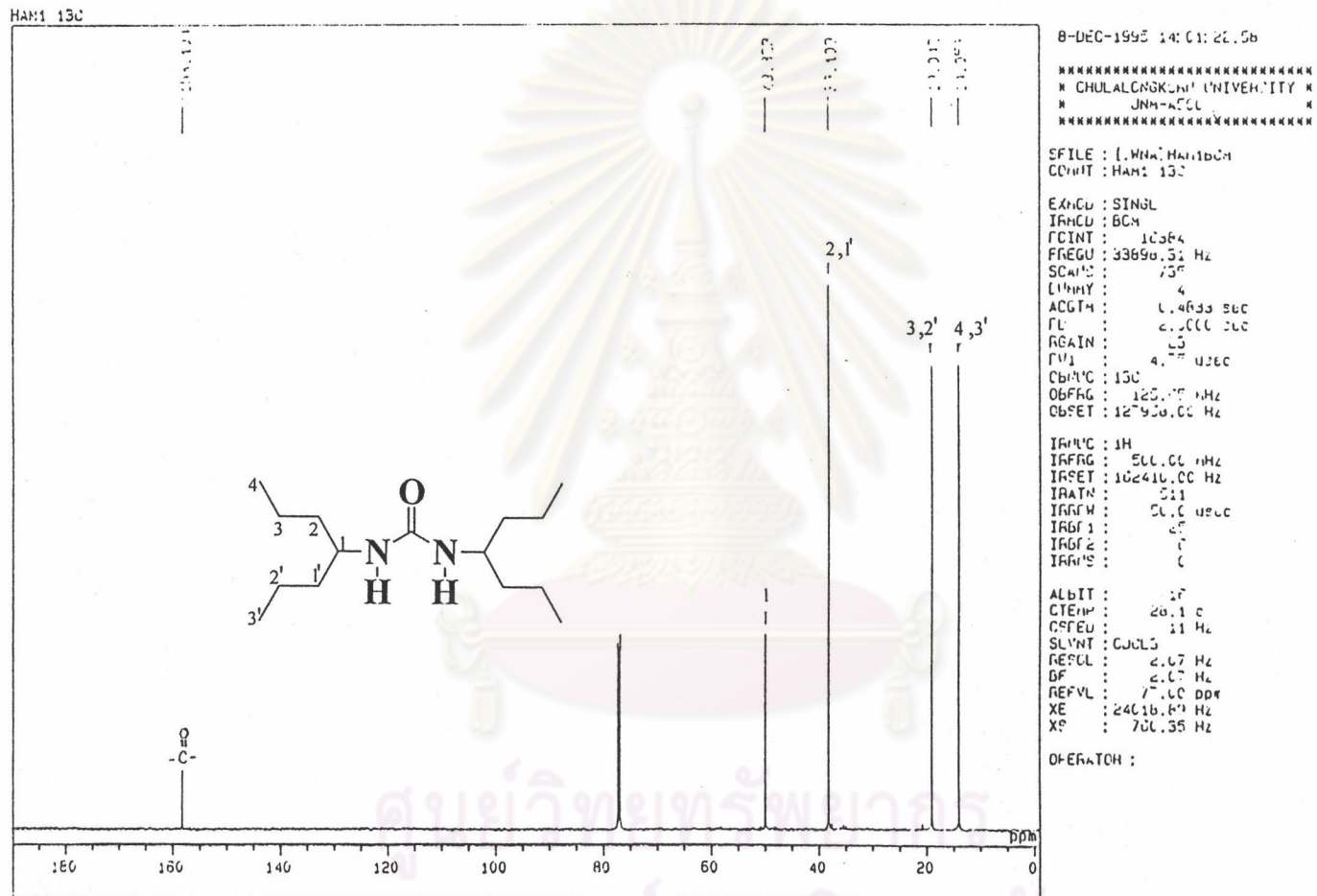(Enlarge scale : 0.86-3.90 ppm)

Figure 107. The ^{13}C-NMR decoupled spectrum of *N,N'*-di(1-propylbutyl) urea.
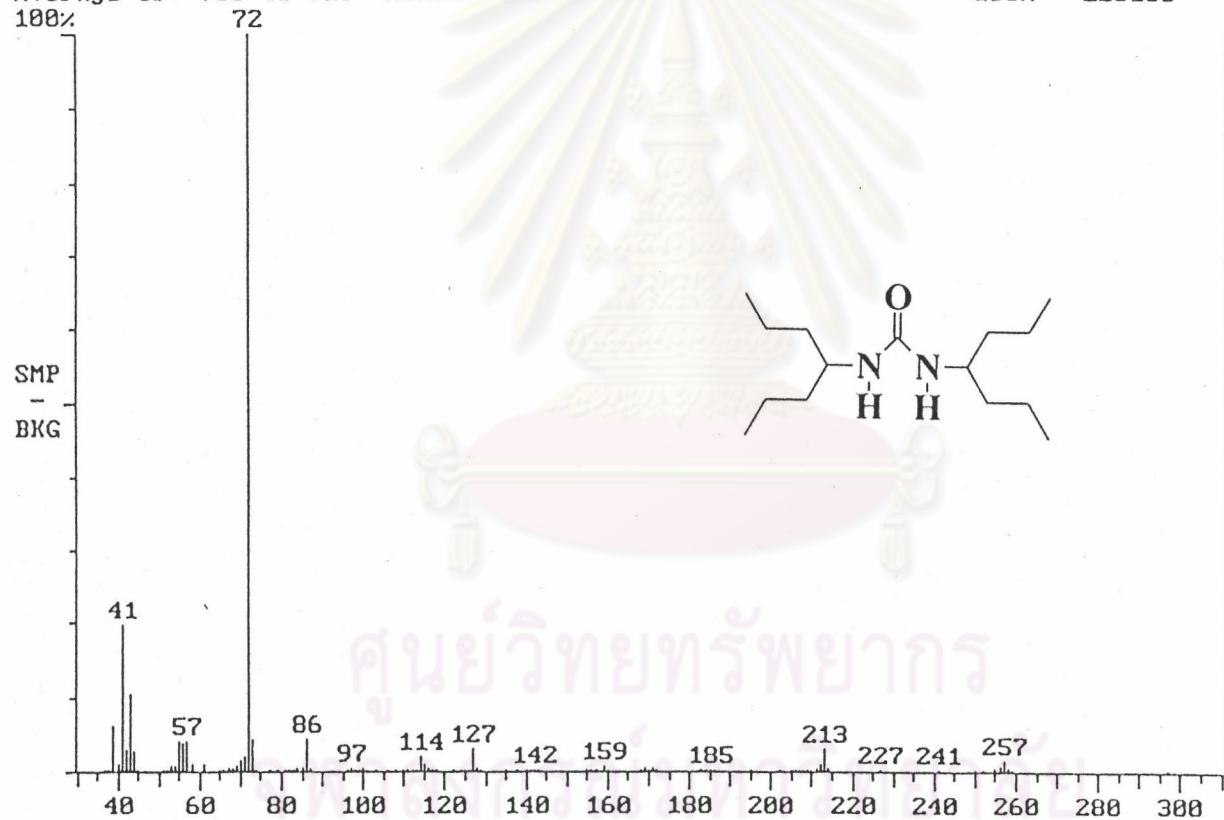
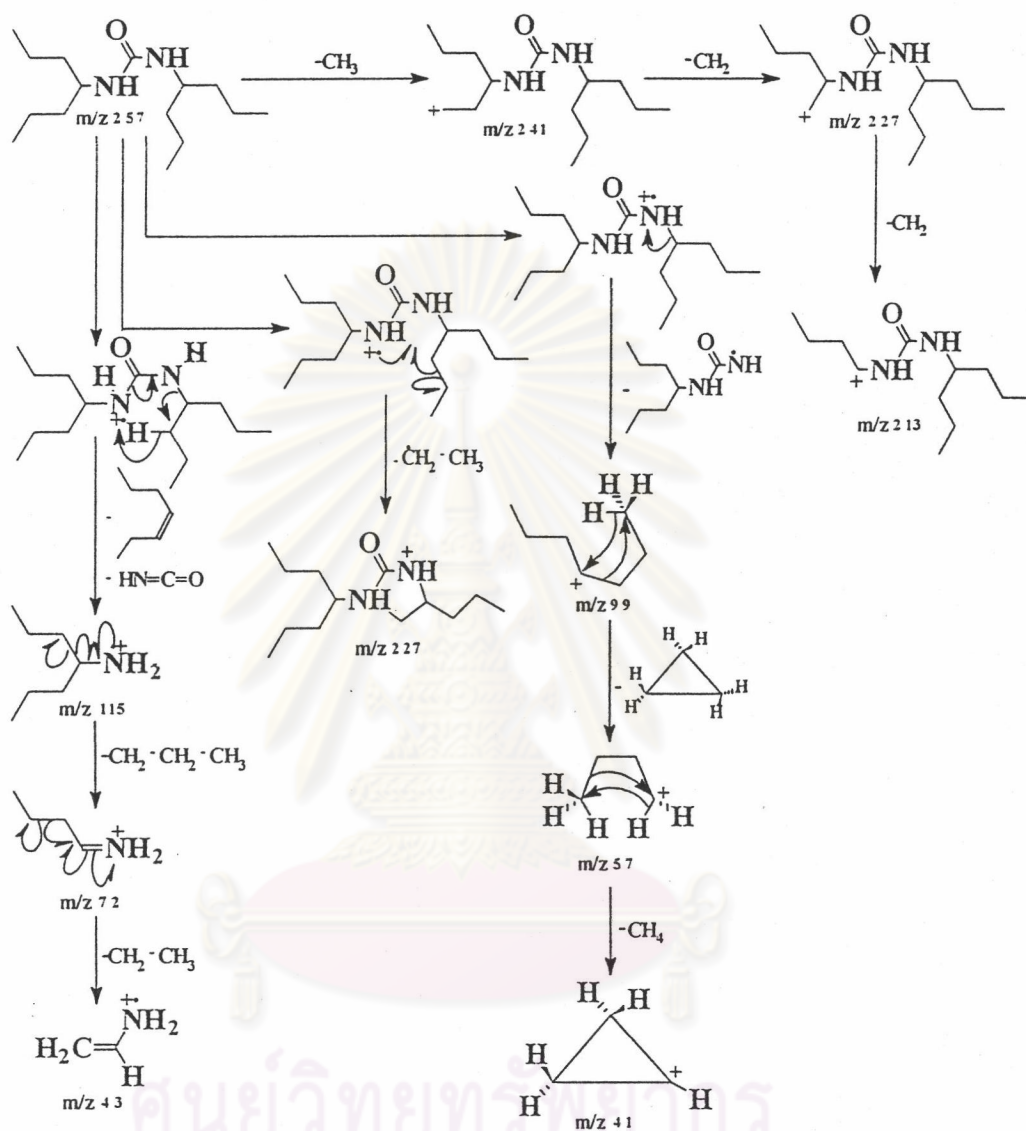Figure 108. The EIMS spectrum of *N*,*N*′-di(1-propylbutyl)urea.

Figure 109. The proposed mass fragmentation of *N*,*N'*-di(1-propylbutyl) urea.

There is a possible mechanism used to explain the acylation of *O*-sodium-2-propylpentanohydroxate (See in figure 110-A). This reaction involves nucleophilic substitution that take place at acyl carbon. The initial step, sodium-2-propylpentanohydroxamate attacks on the carbonyl carbon of acyl halide or anhydride. The initially attack is facilitated by the factor: the relative steric openness of the carbonyl carbon and the ability of the carbonyl oxygen to accommodate on electron pair of the carbon-oxygen double bond. After the initial nucleophilic attack has been taken place, the tetrahedral intermediate formed. The ejection of a leaving group, halide or carbonate, leads to regeneration of the carbonyl carbon. An *O*-acyl-2-propylpentano hydroxamate is formed.

Ethyl-2-propylpentamidooxy Formate (CU-763-1209).

This compound represented to *O*-acyl-2-propylpentano hydroxamate. It was prepared from 2-propylpentanohydroxamic acid and ethyl chloroformate, to avoid base and heat in the reaction, the 2-propylpentanohydroxamic acid was firstly formed to sodium-2-propylpentanohydroxamate. Then its salt was reacted by ethyl chloroformate with stirred at 0-10°C. It could be purified by recrystallization from the mixed solvent (to avoid high temperature).

The possible mechanism of reaction, nucleophilic substitution, showed in figure 110-B.

The structure of ethyl-2-propylpentamidooxy formate (CU-763-1209) could be confirmed by:
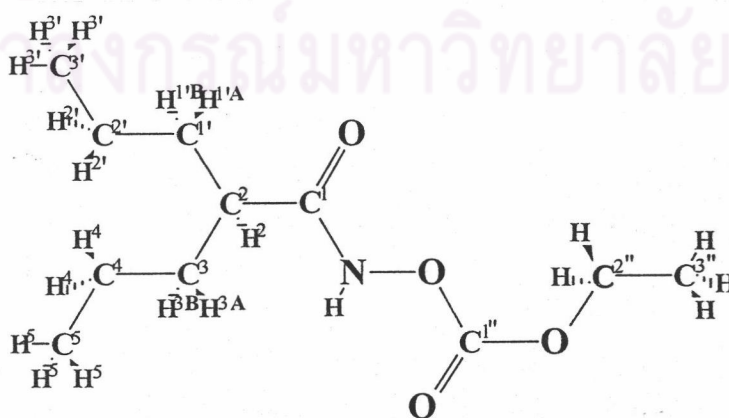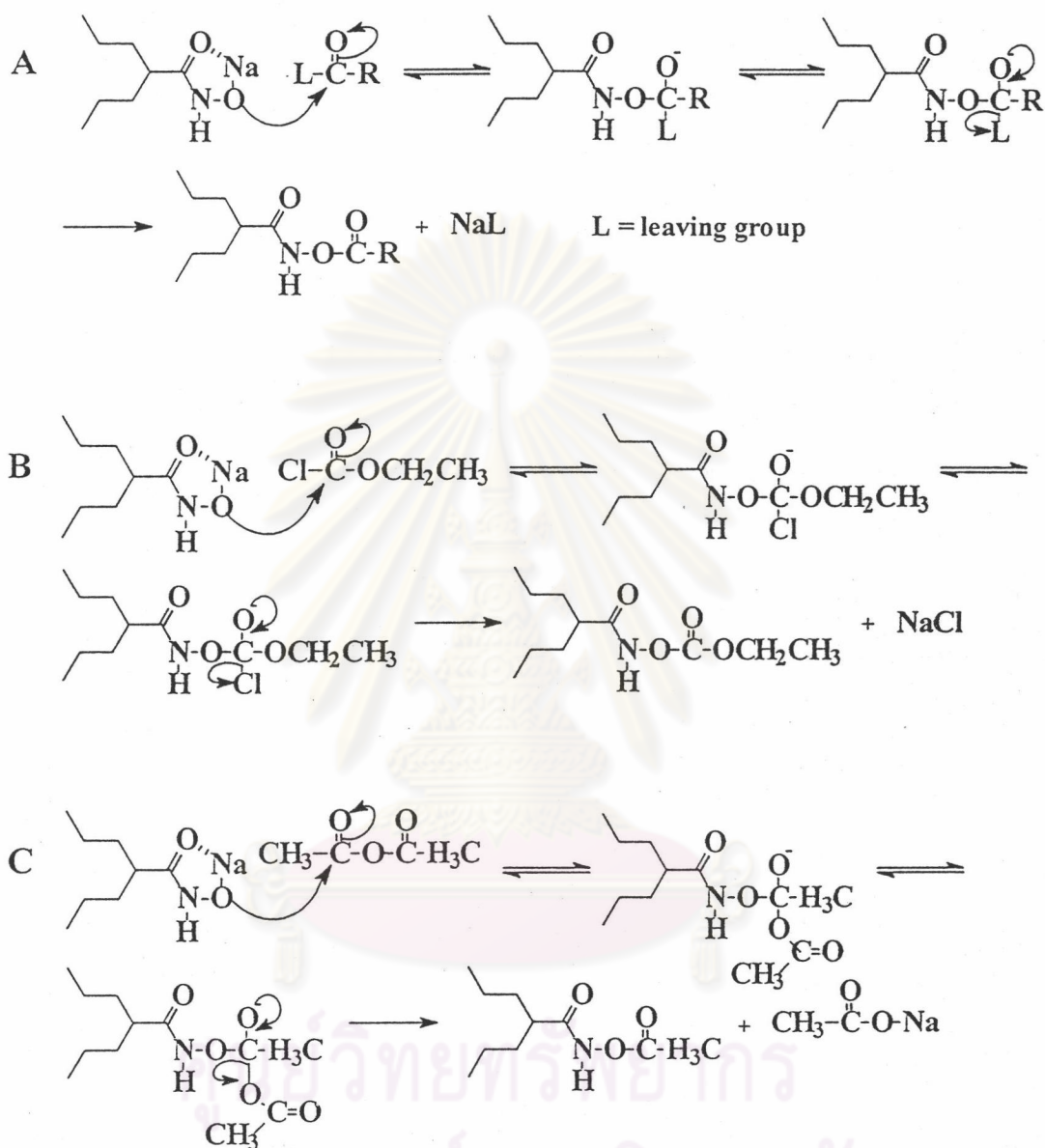
Figure 110. The *O*-acylation reaction mechanism of 2-propylpentano
hydroxamic acid.
    A. General reaction mechanism.
    B. The formation of ethyl-2-propylpentamidooxy formate.
    C. The formation of 2-propylpentanohydroxamic acetic
        anhydride.
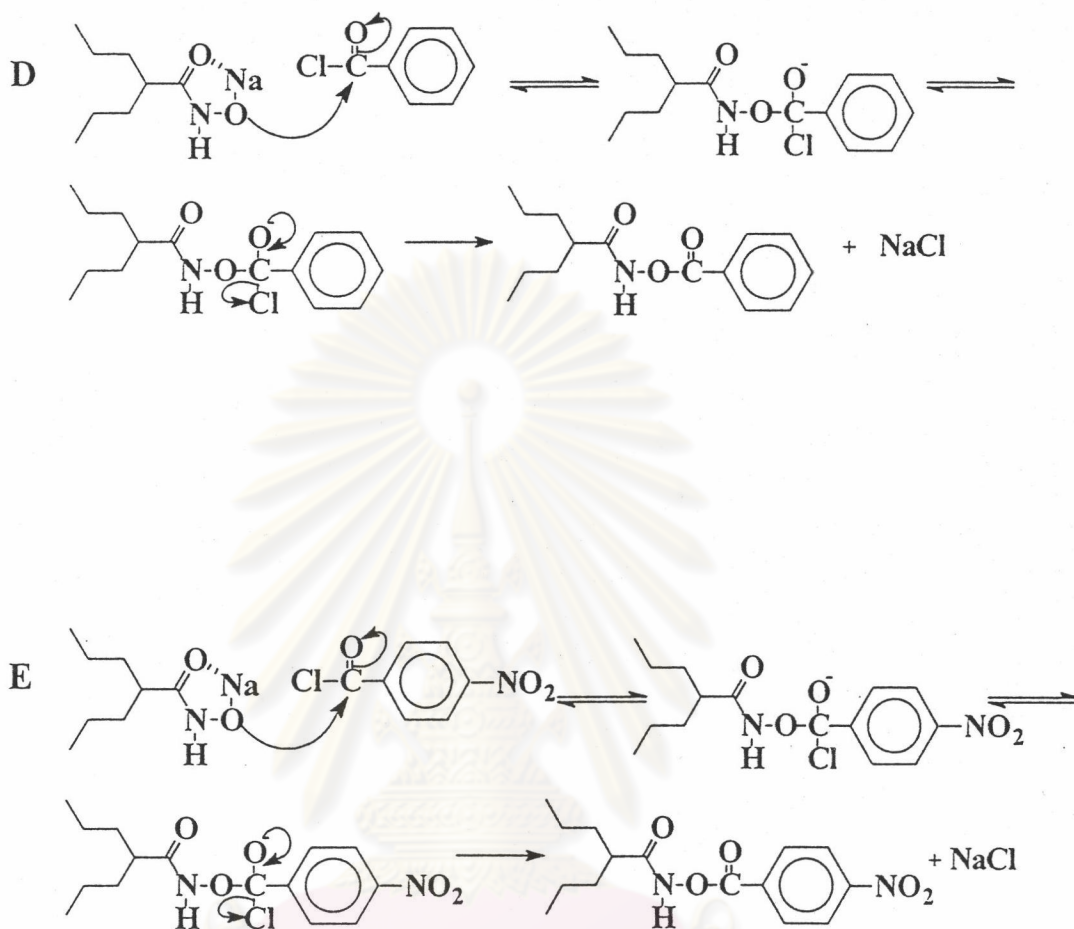
Figure 110. (Continued). The *O*-acylation reaction mechanism of
2-propylpentanohydroxamic acid.
D. The formation of 2-propylpentanohydroxamic benzoic
anhydride
E. The formation of 2-propylpentanohydroxamic
4-nitrobenzoic anhydride.

IR spectrum (Figure 61); at the wavenumber 3225 CM^{-1} represented to N-H stretching, 3000-2840 CM^{-1} was C-H stretching of aliphatic, 1798 CM^{-1} was O-(C=O)-O stretching (carbonate like carbonyl), 1667 was C=O stretching (amide like carbonyl), 1458 CM^{-1} was N-H bending, 1245 CM^{-1} was C-O stretching of ester, 750- 600 CM^{-1} was N-H bending (out-of-plane).

^{1}H-NMR spectrum (Figure 62-63); at 0.91 ppm (6H, t), these protons were assigned to six protons on C^5 and $C^{3'}$, with the coupling to two protons on C^4 and $C^{2'}$, respectively. Thus, it showed peak that was split into triplet (J = 7.32 Hz). The peaks at 1.25-1.48 ppm were assigned to two protons on C^4, two protons on $C^{2'}$, H^{3B}, and $H^{1'B}$ (6H, multiplet). Three protons at 1.37 were assigned to three protons on $C^{3''}$ that coupling to two protons on $C^{2''}$, the peak was split to triplet (J = 7.02 Hz). The multiplet peak at 1.62-1.72 ppm referred to two protons, H^{3A} and $H^{1'A}$. At 1.90 ppm showed a broad peak of a proton on C^2. At 4.33 ppm represented to two protons on $C^{2''}$ that connected to oxygen, with coupling to three protons on $C^{3''}$, the absorption peak was split to quartet (J = 7.02 Hz). At 8.52 ppm, the broad peak referred to a proton on the nitrogen atom.

^{13}C-NMR spectrum (Figure 64); peaks at 13.943 ppm, 20.490 ppm, 34.671 ppm, 43.384 ppm, and 174.539 ppm, represented to two carbons; C^5 and $C^{3'}$, two carbons; C^4 and $C^{2'}$, two carbons; C^3 and $C^{1'}$, a carbon; C^2, and a carbonyl carbon; C^1, respectively. Peaks, at 20.490 ppm, 66.142 ppm, and 54.518 ppm, were assigned to a carbon; $C^{3''}$, a carbon; $C^{2''}$, and a carbonyl carbon; $C^{1''}$, respectively.

EIMS; the mass fragmentation peak of the compound was not showed because it was easily decomposed to other compounds by highly temperature in the apparatus. Thus, the required compound could not be detected.

To confirm that, compound (CU-763-1209) was *O*-acylating compound. It was tested with ferric chloride solution. With the negative result, the color of ferric chloride solution was unchanged. It showed that the compound (CU-763-1209) represented to *O*-acyl-2-propylpentanohydroxamate.

2-Propylpentanohydroxamic Acetic Anhydride (CU-763-1210).

This compound represented to *O*-acyl-2-propylpentano hydroxamate. It was prepared from 2-propylpentanohydroxamic acid and acetic anhydride, to avoid base and heat in the reaction, the 2-propyl pentanohydroxamic acid was firstly formed to sodium-2-propyl pentanohydroxamate. Then its salt was reacted by ethyl chloroformate with stirred at 0-10°C. It could be purified by recrystallization from the mixed solvent (to avoid high temperature).

The possible mechanism of reaction, nucleophilic substitution, showed in figure 110-C.

The structure of 2-propylpentanohydroxamic acetic anhydride (CU-763-1210) could be confirmed by:
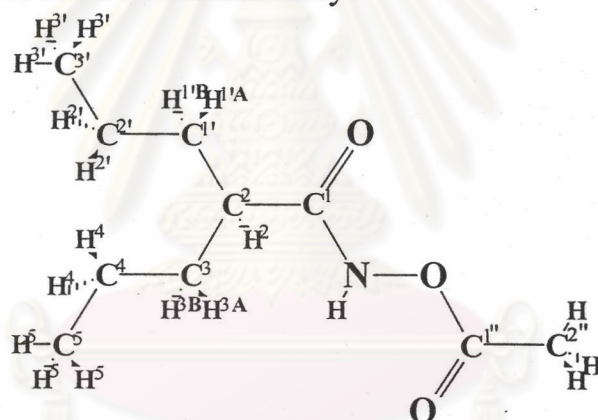
IR spectrum (Figure 65); at the wavenumber 3194 CM^{-1} represented to N-H stretching, 3000-2840 CM^{-1} was C-H stretching of aliphatic, 1793 CM^{-1} was C=O stretching (acid like carbonyl), 1658 was C=O stretching (amide like carbonyl), 1467 CM^{-1} was N-H bending, 750-600 CM^{-1} was N-H bending (out-of-plane).

^{1}H-NMR spectrum (Figure 66-67); at 0.91 ppm (6H, t), these protons were assigned to six protons on C^5 and $C^{3'}$, with the coupling to two protons on C^4 and $C^{2'}$, respectively. Thus, it showed peak that was split into triplet (J = 7.32 Hz). The peaks at 1.25-1.48 ppm were assigned to two protons on C^4, two protons on $C^{2'}$, H^{3B}, and $H^{1'B}$ (6H, multiplet). The multiplet peak at 1.58-1.70 ppm referred to two protons, H^{3A} and $H^{1'A}$. At 2.19 ppm showed a broad peak of a proton on C^2. Three protons on $C^{2''}$, connected to carbonyl, gave the absorption peak as singlet at 2.22 ppm. At 9.35 ppm, the broad peak referred to a proton on

the nitrogen atom.

^{13}C-NMR spectrum (Figure 68); peaks at 13.959 ppm, 20.540 ppm, 34.753 ppm, 43.753 ppm, and 174.177 ppm, represented to two carbons; C^5 and $C^{3'}$, two carbons; C^4 and $C^{2'}$, two carbons; C^3 and $C^{1'}$, a carbon; C^2, and a carbonyl carbon; C^1, respectively. Peaks, at 18.236 ppm, and 168.831, were assigned to a carbon; $C^{2''}$, and a carbonyl carbon; $C^{1''}$, respectively.

EIMS; the mass fragmentation peak of the compound was not showed because it was easily decomposed to other compounds by highly temperature in the apparatus. Thus, the required compound could not be detected.

To confirm that, compound (CU-763-1210) was *O*-acylating compound. It was tested with ferric chloride solution. With the negative result, the color of ferric chloride solution was unchanged. It showed that the compound (CU-763-1210) represented to *O*-acyl-2-propylpentanohydroxamate.

2-Propylpentanohydroxamic Benzoic Anhydride (CU-763-1211).

This compound represented to *O*-acyl-2-propylpentano hydroxamate. It was prepared from 2-propylpentanohydroxamic acid and benzoyl chloride, to avoid base and heat in the reaction, the 2-propyl pentanohydroxamic acid was firstly formed to sodium-2-propyl pentanohydroxamate. Then its salt was reacted by ethyl chloroformate with stirred at 0-10°C. It could be purified by recrystallization from the mixed solvent (to avoid high temperature).

The possible mechanism of reaction, nucleophilic substitution, showed in figure 110-D.

The structure of 2-propylpentanohydroxamic benzoic anhydride (CU-763-1211) could be confirmed by:
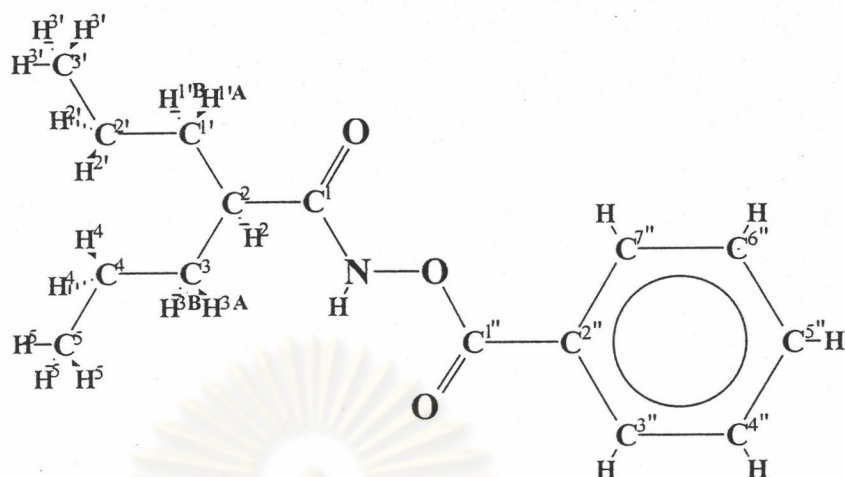
IR spectrum (Figure 69); at the wavenumber 3174 CM^{-1} represented to N-H stretching, 3100-3000 CM^{-1} was C-H stretching of aromatic, 3000-2860 CM^{-1} was C-H stretching of aliphatic, 1775 CM^{-1} was C=O stretching (acid like carbonyl), 1655 was C=O stretching (amide like carbonyl), 1600 and 1452 CM^{-1} were C=C stretching of aromatic, 1239 CM^{-1} was C-H bending (in plane), 697 CM^{-1} was C=C bending of aromatic, 750-600 CM^{-1} was N-H bending (out-of-plane).

^{1}H-NMR spectrum (Figure 70-71); at 0.92 ppm (6H, t), these protons were assigned to six protons on C^5 and $C^{3'}$, with the coupling to two protons on C^4 and $C^{2'}$, respectively. Thus, it showed peak that was split into triplet (J = 7.32 Hz). The peaks at 1.29-1.51 ppm were assigned to two protons on C^4, two protons on $C^{2'}$, H^{3B}, and $H^{1'B}$ (6H, multiplet). The multiplet peak at 1.65-1.75 ppm referred to two protons, H^{3A} and $H^{1'A}$. At 2.25 ppm showed a broad peak of a proton on C^2. Peaks, at 7.47 ppm (2H; dd, J = 7.63 Hz), 7.63 ppm (1H; dddd, J = 7.63, 1.22 Hz), and 8.10 ppm (2H; dd, J = 8.6, 1.22 Hz), were assigned to two protons; $H^{4''}$ and $H^{6''}$, a proton; $H^{5''}$, and two protons; $H^{3''}$ and $H^{7''}$, respectively. At 9.22 ppm, the broad peak referred to a proton on the nitrogen atom.

^{13}C-NMR spectrum (Figure 72); peaks at 14.008 ppm, 20.605 ppm, 34.836 ppm, 44.163 ppm, and 174.375 ppm, represented to two carbons; C^5 and $C^{3'}$, two carbons; C^4 and $C^{2'}$, two carbons; C^3 and $C^{1'}$, a carbon; C^2, and a carbonyl carbon; C^1, respectively. Peaks, at 126.666 ppm, 134.119 ppm, and 164.997 ppm, were assigned to a carbon; $C^{2''}$, a carbon; $C^{5''}$, and a carbonyl carbon; $C^{1''}$, respectively. Two peaks at

128.640 ppm and 129.956 ppm were assigned to two interchangable couple carbons; $C^{4''}$ and $C^{6''}$, $C^{3''}$ and $C^{7''}$.

EIMS; the mass fragmentation peak of the compound was not showed because it was easily decomposed to other compounds by highly temperature in the apparatus. Thus, the required compound could not be detected.

To confirm that, compound (CU-763-1211) was *O*-acylating compound. It was tested with ferric chloride solution. With the negative result, the color of ferric chloride solution was unchanged. It showed that the compound (CU-763-1211) represented to *O*-acyl-2-propylpentanohydroxamate.

2-Propylpentanohydroxamic 4-Nitrobenzoic Anhydride (CU-763-1212).

This compound represented to *O*-acyl-2-propylpentano hydroxamate. It was prepared from 2-propylpentanohydroxamic acid and 4-nitrobenzoyl chloride, to avoid base and heat in the reaction, the 2-propylpentanohydroxamic acid was firstly formed to sodium-2-propylpentanohydroxamate. Then its salt was reacted by ethyl chloroformate with stirred at 0-10°C. It could be purified by recrystallization from the mixed solvent (to avoid high temperature).

The possible mechanism of reaction, nucleophilic substitution, showed in figure 110-E.

The structure of 2-propylpentanohydroxamic 4-nitrobenzoic anhydride (CU-763-1212) could be confirmed by:

IR spectrum (Figure 73); at the wavenumber 3205 CM^{-1} represented to N-H stretching, 3100-3000 CM^{-1} was C-H stretching of aromatic, 3000-2860 CM^{-1} was C-H stretching of aliphatic, 1770 CM^{-1} was C=O stretching (acid like carbonyl), 1669 was C=O stretching (amide like carbonyl), 1608, and 1464 CM^{-1} were C=C stretching of aromatic, 1526 CM^{-1} was N-O stretching (asym), 1351 CM^{-1} was N-O stretching (sym), 1460 CM^{-1} was N-H bending, 750-600 CM^{-1} was N-H bending (out-of-plane).

^{1}H-NMR spectrum (Figure 74-75); at 0.94 ppm (6H, t), these protons were assigned to six protons on C^5 and $C^{3'}$, with the coupling to two protons on C^4 and $C^{2'}$, respectively. Thus, it showed peak that was split into triplet (J = 7.32 Hz). The peaks at 1.30-1.54 ppm were assigned to two protons on C^4, two protons on $C^{2'}$, H^{3B}, and $H^{1'B}$ (6H, multiplet), The multiplet peak at 1.66-1.76 ppm referred to two protons, H^{3A} and $H^{1'A}$. At 2.25 ppm showed a broad peak of a proton on C^2. All doublet of doublet peaks, at 8.29 ppm (J = 9.15, 1.83 Hz), and 8.34 ppm (J = 9.16, 1.83 Hz), were assigned to two interchangable couple protons; $H^{3''}$ and $H^{7''}$, and $H^{4''}$ and $H^{6''}$. At 9.00 ppm, the broad peak referred to a proton on the nitrogen atom.

^{13}C-NMR spectrum (Figure 76); peaks at 13.992 ppm, 20.605 ppm, 34.803 ppm, 44.131 ppm, and 174.588 ppm, represented to two carbon; C^5 and $C^{3'}$, two carbon; C^4 and $C^{2'}$, two carbons; C^3 and $C^{1'}$, a carbon; C^2, and a carbonyl carbon; C^1, respectively. Two peaks, at 123.787 ppm and 131.157 ppm were assigned to two interchangable couple carbons; $C^{4''}$ and $C^{6''}$, $C^{3''}$ and $C^{7''}$. Peaks at 132.128 ppm,

151.129 ppm, and 163.286 ppm, were assigned to a carbon; $C^{2''}$, a carbon; $C^{5''}$, and a carbonyl carbon; $C^{1''}$, respectively.

EIMS; the mass fragmentation peak of the compound was not showed because it was easily decomposed to other compouds by highly temperature in the apparatus. Thus, the required compound could not be detected.

To confirm that, compound (CU-763-1212) was *O*-acylating compound. It was tested with ferric chloride solution. With the negative result, the color of ferric chloride solution was unchanged. It showed that the compound (CU-763-1212) represented to *O*-acyl-2-propylpentanohydroxamate.

2-Propylpentanohydroxamic 4-Aminobenzoic Anhydride (CU-763-1213).

This compound represented to *O*-acyl-2-propylpentano hydroxamate. It was prepared by low-pressure hydrogenation of 2-propylpentanohydroxamic 4-nitrobenzoic anhydride in the presence of activated palladium carbon as catalyst (See in figure 111). It could be purified by recrystallization from the mixed solvent (to avoid high temperature).

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 desorption of the reduced molecule, an aromatic amine (House, 1972).

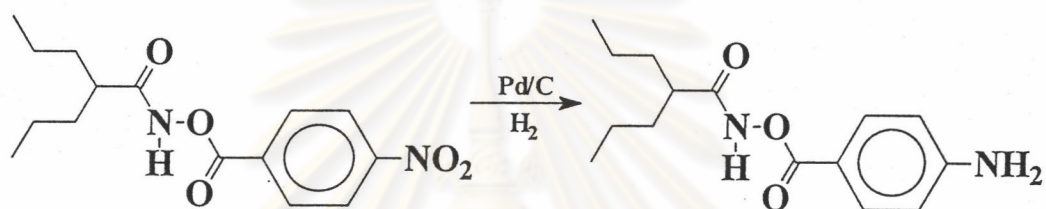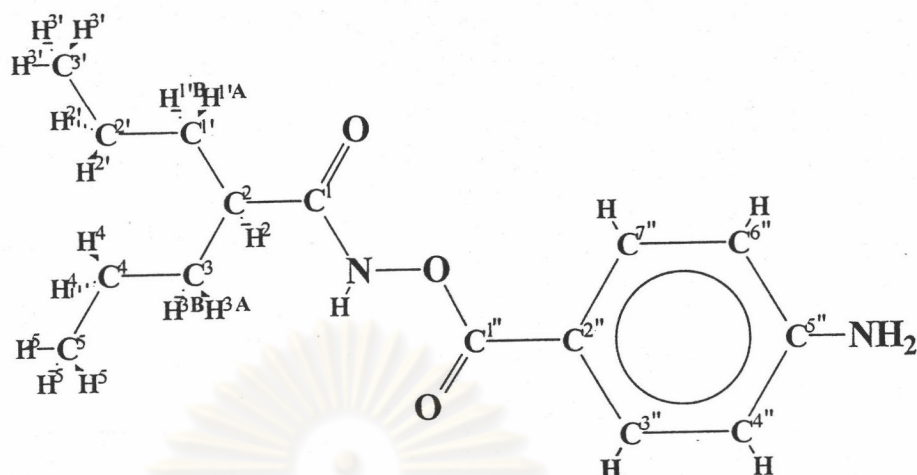The structure of 2-propylpentanohydroxamic 4-aminobenzoic anhydride (CU-763-1211) could be confirmed by:

Figure 111. The formation of 2-propylpentanohydroxamic 4-amino benzoic anhydride.

IR spectrum (Figure 77); at the wavenumber 3540 and 3460 CM^{-1} were N-H stretching of primary amine, 3248 CM^{-1} represented to N-H stretching, 3100-3000 CM^{-1} was C-H stretching of aromatic, 3000-2860 CM^{-1} was C-H stretching of aliphatic, 1774 CM^{-1} was C=O stretching (acid like carbonyl), 1670 was C=O stretching (amide like carbonyl), 1650 CM^{-1} was N-H bending of aromatic amine, 1622 CM^{-1} was C=C stretching of aromatic, 1482 CM^{-1} was N-H bending, and 1282 CM^{-1} was C-N stretching of aromatic amine.

^{1}H-NMR spectrum (Figure 78-79); at 0.86 ppm (6H, t), these protons were assigned to six protons on C^5 and $C^{3'}$, with the coupling to two protons on C^4 and $C^{2'}$, respectively. Thus, it showed peak that was split into triplet (J = 7.02 Hz). The peaks at 1.23-1.37 ppm were assigned to two protons on C^4, two protons on $C^{2'}$, H^{3B}, and $H^{1'B}$ (6H, multiplet). The multiplet peak at 1.43-1.54 ppm referred to two protons, H^{3A} and $H^{1'A}$. At 2.20 ppm showed a heptet peak (dddd) of a proton on C^2. Two doublet peaks, at 6.59 ppm (J = 8.85 Hz), and 7.77 ppm (J = 8.85 Hz), were assigned to two interchangable couple protons; $H^{4''}$ and $H^{6''}$, and $H^{3''}$ and $H^{7''}$, respectively. At 11.56 ppm, the singlet peak referred to a proton on the nitrogen atom.

^{13}C-NMR spectrum (Figure 80); peaks at 13.902 ppm, 19.956 ppm, 34.499 ppm, 42.182 ppm, and 172.212 ppm, represented to two carbons; C^5 and $C^{3'}$, two carbons; C^4 and $C^{2'}$, two carbons; C^3 and $C^{1'}$, a carbon; C^2, and a carbonyl carbon; C^1, respectively. Two peaks, at, 112.790 ppm and 131.511 ppm were assigned to two interchangable couple carbons; $C^{4''}$ and $C^{6''}$, $C^{3''}$ and $C^{7''}$. Peaks at 112.362 ppm,

154.198 ppm and 164.151 ppm, were assigned to a carbon; $C^{2''}$, a carbon; $C^{5''}$, and a carbonyl carbon; $C^{1''}$, respectively.

EIMS; the mass fragmentation peak of the compound was not showed because it was easily decomposed to other compounds by highly temperature in the apparatus. Thus, the required compound could not be detected.

To confirm that, compound (CU-763-1213) was *O*-acylating compound. it was tested with ferric chloride solution. With the negative result, the color of ferric chloride solution was unchanged. It showed that the compound (CU-763-1213) represented to *O*-acyl-2-propylpentanohydroxamate.