CHAPTER IV

RESULT AND DISCUSSION

In this research, the unsaturated $\underline{N}$-(2-propylpentanoyl) urea derivatives i.e. $\underline{N}$-(4-methyl-2-propyl-4-pentenoyl) urea, $\underline{N}$-(2-propyl-4-pentenoyl) urea, $\underline{N}$-(4-methyl-2-(2'-methyl-2'-propenyl)-4-pentenoyl) urea and $\underline{N}$-(2-allyl-4-pentenoyl) urea were synthesized as potential anticonvulsants. The designed compounds was expected to possess the potent, broad spectrum and higher margin of safety anticonvulsants. Since the structures of the final products are in the acylurea class, it would be expected to be a potent and broad spectrum anticonvalsants. The aliphatic side chain of these compounds are resemble to 4-methyl-2-propyl-4-pentenoic acid, which is an anticonvulsant with the the higher margin of safety. As this reason, the synthesized compounds should be a safety anticonvulsants too. The synthetic methods for the target compounds were described below.

Diethyl malonate was reacted with n-propyl bromide by the use of the sodium ethoxide as a base to yield diethyl propylmalonate. Then, it was alkylated with 3-chloro-2-methyl-1-propene or allylbromide to obtain diethyl (2-methyl-2-propenyl)propylmalonate or diethyl allyl(propyl) malonate, repectively. Diethyl di-(2-methyl-2-propenyl)malonate and

diethyl diallyl malonate were synthesized by using 2-equivalent of the base and 2-equivalent of suitable alkylhalides, 3-chloro-2-methyl-1-propene or allyl bromide to react with diethyl malonate. The disubstituted malonic esters were refluxed with lithium chloride-water-dimethylsulfoxide to give the decarbethoxylated products, monoesters. The monoesters were hydrolyzed in ethanolic potassium hydroxide solution to convert to the corresponding monocarboxylic acid. Then, they were heated with thionyl chloride at 50 °C to acquire the acid chlorides which were refluxed with urea in dry benzene using potassium carbonate as a base. The final products N-(4-methyl-2-propyl-4-pentenoyl) urea, N-(2-propyl-4-pentenoyl) urea, N-(4-methyl-2-(2′-methyl-2′-propenyl)-4-pentenoyl) urea and N-(2-allyl-4-pentenoyl) urea were obtained.
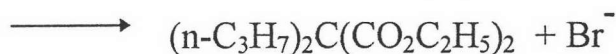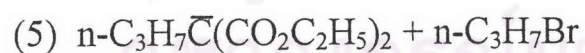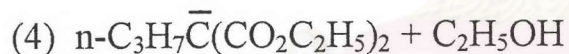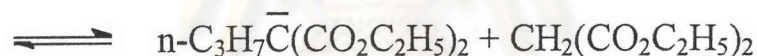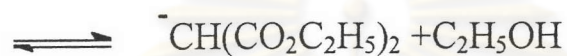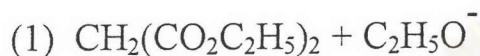
1. Synthesis of N-(4-Methyl-2-propyl-4-pentenoyl) urea. (CU-763-11-01).

1.1. Synthesis of Diethyl propylmalonate.

This compound represents an monoalkyl malonic ester. The reactant which was an active methylene compound, diethylmalonate, was alkylated with alkylating agent, n-propyl bromide, in ethanol by the use sodium ethoxide as a base to obtain the product, diethyl propyl malonate.

This reaction always gives dialkylated product, diethyl dipropylmalonate, as a by-product. During the alkylation of diethyl

sodium malonate with n-propyl bromide, the diethyl propylmalonate that is formed (reaction 2) is in equilibrium with its anion (reaction 3 and 4). The question, therefore, arises as to why little diakylation (reation 5) is observed.

(1) $CH_2(CO_2C_2H_5)_2 + C_2H_5O^-$

$$\rightleftharpoons \quad {}^-CH(CO_2C_2H_5)_2 + C_2H_5OH$$

(2) $^-CH(CO_2C_2H_5)_2 + n\text{-}C_3H_7Br \longrightarrow n\text{-}C_3H_7CH(CO_2C_2H_5)_2 + Br^-$

(3) $n\text{-}C_3H_7CH(CO_2C_2H_5)_2 + {}^-CH(CO_2C_2H_5)_2$

$$\rightleftharpoons \quad n\text{-}C_3H_7\bar{C}(CO_2C_2H_5)_2 + CH_2(CO_2C_2H_5)_2$$

(4) $n\text{-}C_3H_7\bar{C}(CO_2C_2H_5)_2 + C_2H_5OH$

$$\rightleftharpoons \quad n\text{-}C_3H_7CH(CO_2C_2H_5)_2 + C_2H_5O^-$$

(5) $n\text{-}C_3H_7\bar{C}(CO_2C_2H_5)_2 + n\text{-}C_3H_7Br$

$$\longrightarrow \quad (n\text{-}C_3H_7)_2C(CO_2C_2H_5)_2 + Br^-$$

The IR spectrum of diethyl propylmalonate is shown in figure 10. Diethyl propylmalonate obtained was confirmed by comparing its IR spectrum with that authentic compound.

The 500 MHz ^{1}H-NMR spectrum of diethyl propylmalonate is shown in figure 11. The signal at δ 0.94 ppm (3H, t, J=7.3 Hz) is assigned as a methyl group (CH_3-CH$_2$-CH$_2$-). The signal at δ 1.27 ppm (6H, t, J=7.3 Hz) is assigned as two methyl groups (CH_3-CH$_2$-O-). The signal at δ 1.36 ppm (2H, m) is assigned as a methylene group (CH$_3$-CH_2-CH$_2$-). The signal at δ 1.88 ppm (2H, m) is assigned as a methylene group (CH$_3$-CH$_2$-CH_2-). The signal at δ 3.33 ppm (1H, t, J=7.3 Hz) is assigned as a methine proton (-CH-). The signal at δ 4.20 ppm (4H, m) is assigned as two methylene groups (CH$_3$-CH_2-O-). The proton resonated at the most downfield because they were adjacent to oxygen atom.

1.2. Synthesis of Diethyl (2-methyl-2-propenyl)propylmalonate.

This compound represents an disubstituted malonic ester. The reactant, diethyl propylmalonate, was alkylated with alkylating agents, 3-chloro-2-methyl-1-propene, in ethanol by the use of sodium ethoxide as a base leading to the product.

The mechanism of alkylation of diethyl propylmalonate was shown in figure 82 (R= CH$_2$=C(CH$_3$)-CH$_2$-).

$$n\text{-}C_3H_7CH(CO_2C_2H_5)_2 + C_2H_5O^- \rightleftharpoons n\text{-}C_3H_7\overset{-}{C}(CO_2C_2H_5)_2 + C_2H_5OH$$

$$\downarrow RX$$

$$\underset{R}{\overset{CH_3CH_2CH_2}{>}}C\underset{COOCH_2CH_3}{\overset{COOCH_2CH_3}{<}} \quad + X^-$$
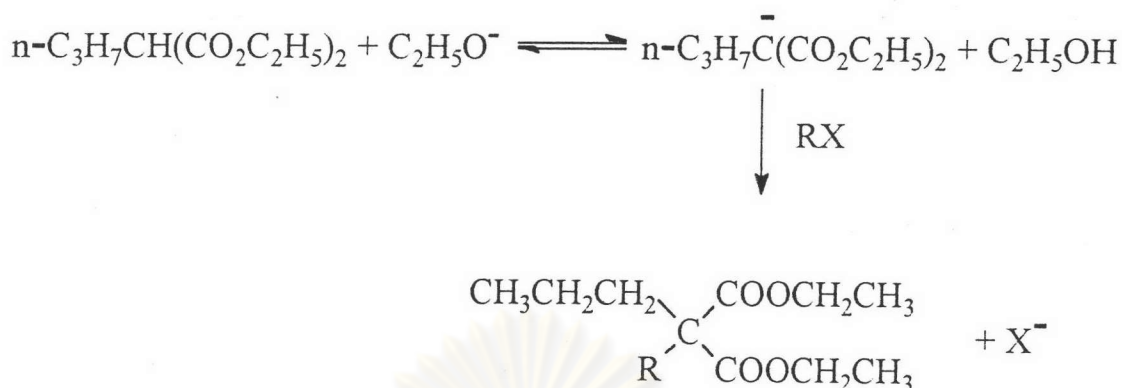
Figure 82. Alkylation of diethyl propylmalonate

In the dialkylation of malonic ester the introduction of a primary alkyl group should always precede the introduction of a secondary alkyl groups. If this precaution is not observed, the introduction of a second alkyl group is often unsucessful because of the low acidity of the intermediate alkylmalonic ester and the sterically hindered nature of the corresponding enolate anion. This difficulty accompanying the alkylation of alkyl malonic esters has occasionally been overcome by the use of a strong base such as sodium t-butoxide in t-butyl alcohol or the use of concentrated NaOEt in ethanol or NaOEt in an aprotic solvent. In this research, concentrated sodium ethoxide in ethanol were used.

The IR spectrum of diethyl (2-methyl-2-propenyl)propyl malonate is shown in figure 14. The C-H stretching of alkene absorbs at 3076 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The C=O absorption bands of esters are at 1736 and 1732 cm^{-1}. The C=C stretching absorbs at 1646 cm^{-1}. The

C(=O)-O stretching vibration appears at 1186 cm⁻¹. The C(alkyl)-O stretching band of ester is at 1028 cm⁻¹. The out-of-plane bending of alkene is shown at 898 cm⁻¹.

The 500 MHz ¹H-NMR spectrum of diethyl (2-methyl-2-propenyl)propylmalonate is shown in figure 15-17. The signal at δ 0.91 ppm (3H, t, J=7.3 Hz) is assigned as a methyl group (*CH₃*-CH₂-CH₂-). The signal at δ 1.18-1.27 ppm (8H, complex) is assigned as two methyl groups (*CH₃*-CH₂-O) and one methylene group (CH₃-*CH₂*-CH₂-). The signal at δ 1.66 ppm (3H, m) is assigned as a methyl group adjacent to alkene (CH₂=C(*CH₃*)-). The signal at δ 1.84-1.89 ppm (2H, m) is assigned as a methylene group (CH₃-CH₂-*CH₂*-). The signal at δ 2.70 ppm (2H, s) is assigned as a methylene group adjacent to alkene (CH₂=C(CH₃)-*CH₂*-). The signal at δ 4.17 ppm (4H, 2q, J=7.2 Hz) is assigned as two methylene groups (CH₃-*CH₂*-O). The signal at δ 4.72 ppm (1H, s) and δ 4.85 ppm (1H, s) are assigned as two methylene protons of alkene (*CH₂*=C(CH₃-)-).

1.3. Synthesis of Ethyl 4-methyl-2-propyl-4-pentenoate.

This compound represents an unsaturated carboxylic ester. The decarbalkoxylation of diethyl (2-methyl-2-propenyl)propylmalonate by heating with LiCl-H₂O-DMSO gives monocarboxylic ester, ethyl 4-methyl -2-propyl-4-pentenoate.

Several advantages of this procedure include the facts that functional groups such as ketals, ester or alkene which are sensitives to acidic or basic conditions survive the reaction and isomerizations of double bonds do not occur.

The decarbalkoxylation of disubstituted malonic ester proceeds readily in water-dimethylsulfoxide with sodium chloride, lithium chloride or potassium cyanide. Although the most effective decarbalkoxylation reagent system is the potassium cyanide-water-dimethylsulfoxide combination, lithium chloride and sodium chloride were used in this experiment to avoid the hazardous use of potassium chloride. Since lithium chloride is more effective than sodium chloride, which is probably due to the greater solubility of lithium chloride in dimethylsulfoxide in comparison to sodium chloride (heterogeneous), lithium chloride is an excellent salt for use in preparative decarbalkoxylation.

As the reaction proceeds with lithium chloride as the salts, lithium carbonate (Li_2CO_3) precipitates during the reaction and exhibits little effect on the rate of decarbalkoxylation. The remainder of CO_2 is evolved.

The decarbalkoxylation mechanism is dependent on substrate structure. Substituted diethyl malonates exhibit dual pathways in which disubstituted in diethyl malonates react predominantly via the $B_{AL}2$ route (figure 8) while monosubstituted malonates react predominantly via the $B_{AC}2$ route (figure 9) (Krapcho et al., 1978)

Diethyl (2-methyl-2-propenyl)propylmalonate represents disubstituted malonic ester which prefers to follow the $B_{AL}2$ mechanism while the $B_{AC}2$ mechanism is competitive.

The IR spectrum of ethyl 4-methyl-2-propyl-4-pentenoate is shown in figure 18. The C-H stretching of alkene absorbs at 3076 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The C=O absorption bands of ester is at 1732 cm^{-1}. The C=C stretching absorbs at 1652 cm^{-1}. The C(=O)-O stretching vibration appears at 1160 cm^{-1}. The C(alkyl)-O stretching band of ester is at 1032 cm^{-1}. The out-of-plane C-H bending of alkene show at 892 cm^{-1}.

The 500 MHz ^{1}H-NMR spectrum ethyl 4-methyl-2-propyl-4-pentenoate is shown in figure 19-21. The signal at δ 0.90 ppm (3H, t, J=7.3 Hz) is assigned as a methyl group (CH_3-CH$_2$-CH$_2$-). The signal at δ 1.22-1.35 ppm (5H, complex) is assigned as one methyl group (CH_3-CH$_2$-O-) and one methylene group (CH$_3$-CH_2-CH$_2$-). The signal at δ 1.40-1.45 ppm (1H, m) and δ 1.56-1.63 ppm (1H, m) are assigned as a two protons of methylene group (CH$_3$-CH$_2$-CH_2-). The signal at δ 1.72 ppm (3H, s) is assigned as a methyl group adjacent to alkene (CH$_2$=C(CH_3)-). The signal at δ 2.10-2.15 ppm (1H, m) and δ 2.32-2.37 ppm (1H, m) are assigned as two protons of methylene group which is adjacent to alkene (CH$_2$=C(CH$_3$)-CH_2-). The signal at δ 2.53-2.60 ppm (1H, m) is assigned as a methine proton(-CH-). The signal at δ 4.09-4.14 ppm (2H, q, J=7.3 Hz) is assigned as a methylene group adjacent to oxygen atom (CH$_3$-CH_2-O-).

The signal at δ 4.70 ppm (1H, s) and δ 4.74 ppm (1H, s) are assigned as two methylene protons of alkene (CH_2=C(CH$_3$)-).

1.4. Synthesis of 4-Methyl-2-propyl-4-pentenoic acid.

This compound represents an unsaturated carboxylic acid. The reactant, ethyl 4-methyl-2-propyl-4-pentenoate, was refluxed in the aqueous potassium hydroxide-alcoholic solution.

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, potassium 4-methyl-2-propyl-1-pentenoate. Base promoted hydrolysis of esters by providing the strongly necleophilic reagent OH$^-$. This reaction was essentially irreversible, since a resonance stabilized carboxylic 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 involved 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.

After the hydrolysis was completed, the ethanol was evaporated out of the reaction mixture as much as possible. The mixture was washed with hexane to remove unreacted ester. the aqueous layer was acidified by addition of 20 % hydrochloric acid to convert the carboxylate salt into the carboxylic acid. Then, it was separated by extraction with hexane. The hexane extract was washed with water to remove trace of hydrochloric acid and potassium chloride that contaminate the extract. After hexane was evaporated. The product was pure enough to continue the further reaction.

The IR spectrum of 4-methyl-2-propyl-4-pentenoic acid is shown in figure 22. Absorption arising from hydrogen bonded, O-H stretching occurs in the region of 3300-2500 cm^{-1}. The characteristic of peak is broad and strong. The C-H stretching of alkene absorbs at 3078 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The C=O absorption band of acid is at 1710 cm^{-1}. The C=C stretching absorbs at 1652 cm^{-1}. The O-H bending absorption of carboxylic acid appears at 1422 cm^{-1}. The C-O stretching absorbs at 1288 cm^{-1}. The out-of-plane O-H bending and out-of-plane C-H bending of alkene show the peaks at 942 and 894 cm^{-1}, respectively.

The 500 MHz ^{1}H-NMR spectrum 4-methyl-2-propyl-4-pentenoic acid is shown in figure 23-25. The signal at δ 0.92 ppm (3H, t, J=7.3 Hz) is assigned as a methyl group (CH_3-CH$_2$-CH$_2$-). The signal at δ 1.30-1.65 ppm (4H, m) is assigned as two methylene groups (CH$_3$-CH_2-CH_2-). The signal at δ 1.73 ppm (3H, s) is assigned as a methyl group

adjacent to alkene (CH_2=C(CH_3)-). The signal at δ 2.13-2.18 ppm (1H, m) and δ 2.35-2.40 ppm (1H, m) are assigned as two protons of methylene group adjacent to alkene (=C(CH_3)-CH_2-). The signal at δ 2.56-2.62 ppm (1H, m) is assigned as a methine proton (-CH-). The signal at δ 4.70 ppm (1H, s) and δ 4.74 ppm (1H, s) are assigned as two methylene protons of alkene (CH_2=C(CH_3)-). The signal at δ 11.1 ppm (1H, s, broad) is assigned as a proton of carboxylic acid (-$COOH$).

1.5. Synthesis of N-(4-Methyl-2-propyl-4-pentenoyl) urea.

This compound represents monoureide analog or acylurea derivative. The synthesis of this compound was accomplished by the reaction of 4-methyl-2-propyl-4-pentenoyl chloride and urea in dry benzene with the present of potassium carbonate granules.

It was known that ordinary amides are neutral or weakly basic. On the other hand, they are poor nucleophiles. Urea is such a compound, the chemical struture of urea is a symmetric primary diamide. However, urea is stronger base than ordinary amide which is attributed to resonance stabilization of the cation.

The reaction proceeds simple nucleophilic substitution. Since potassium carbonate was added to the mixture to neutralize hydrogen chloride which was evolved in the reaction. Since urea was slighly soluble in benzene (hetorogeneous), it was used as a powder to increase the surface area.

$$\underset{\substack{\| \\ O}}{R-\overset{O}{\overset{\|}{C}}-Cl} \;+\; NH_2-\overset{O}{\overset{\|}{C}}-NH_2 \longrightarrow R-\overset{O}{\overset{\|}{C}}-NH-\overset{O}{\overset{\|}{C}}-NH_2 \;+\; HCl$$

$$2HCl + K_2CO_3 \longrightarrow 2KCl + H_2O + CO_2$$
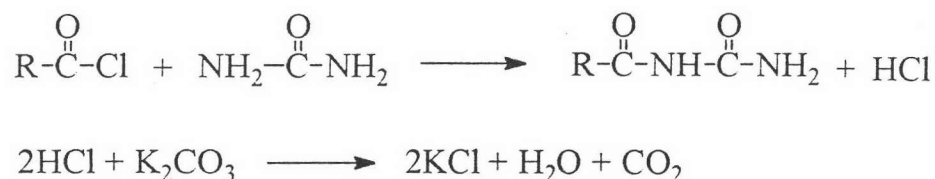
The target compound was obtained in a low yield because many by products occured in the reaction. The solid product was difficult to crystallize from the crude oily mixture. Therefore, the use of column chromatography was necessary to purified the final product for this reaction.

The IR spectrum of N-(4-methyl-2-propyl-4-pentenoyl) urea is shown in figure 26. The peaks at 3398 cm^{-1} and 3246 cm^{-1} represent the asymmetric and symmetric N-H stretching vibration of primary amide, respectively. The strong sharp peak at 3334 cm^{-1} represents the N-H stretching vibration of imide. The C-H stretching of alkene absorbs at 3088 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The strong peak at 1716 cm^{-1} represents C=O stretching vibration (amide I) of imide and the strong peak at 1678 cm^{-1} represents C=O stretching vibration (amide I) of primary amide. The C=C stretching absorbs at 1624 cm^{-1}. The C-N bending absorption appears at 1410 cm^{-1}.

The 500 MHz ^{1}H-NMR spectrum N-(4-methyl-2-propyl-4-pentenoyl) urea is shown in figure 27-29. The signal at δ 0.92 ppm (3H, t,

J=7.3 Hz) is assigned as a methyl group (CH_3-CH$_2$-CH$_2$-). The signal at δ 1.30-1.50 ppm (4H, m) is assigned as two methylene group (CH$_3$-CH_2-CH_2-). The signal at δ 1.73 ppm (3H, s) is assigned as a methyl group adjacent to alkene (CH$_2$=C(CH_3)-). The signal at δ 2.10-2.18 ppm (1H, m) and δ 2.33-2.40 ppm (1H, m) are assigned as two protons of methylene group adjacent to alkene (CH$_2$=C(CH$_3$)-CH_2-). The signal at δ 2.49-2.54 ppm (1H, m) is assigned as a methine proton(-CH-). The signal at δ 4.72 ppm (1H, s) and δ 4.78 ppm (1H, s) are assigned as two methylene protons of alkene (CH_2=C(CH$_3$)-). . The three broad peaks at δ 5.16 ppm (1H, s, broad), δ 8.35 ppm (1H, s, broad), and δ 9.32 ppm (1H, s, broad) represent N-H protons. The peak at 9.32 ppm located at the most down field should be the N-H proton of imide NH proton which was most deshielded by the two carbonyl groups. The signal at 8.35 and 5.16 ppm represent the NH protons of primary amide. The NH protons of primary amides usually show chemical shifts in the region 5-7 ppm and the two NH protons should appear at the same chemical shift or may appear at a little different signals due to the rotation around the CO-N bond which is so slow that the two separated signals observed for the two conformers. In this case, the two NH protons, which should be the proton of primary amide moiety, showed two separated signal at chemical shifts 5.16 ppm and 8.35 ppm. This phenomena can be explained by the intramolecular hydrogen bonding. The N-H proton, which forms the intramolecular hydrogen bonding, of the primary amide shows the signal at the higher chemical shift than the others (see figure 83). The detail was described by Wichan Jawitayanuchit, 1992.
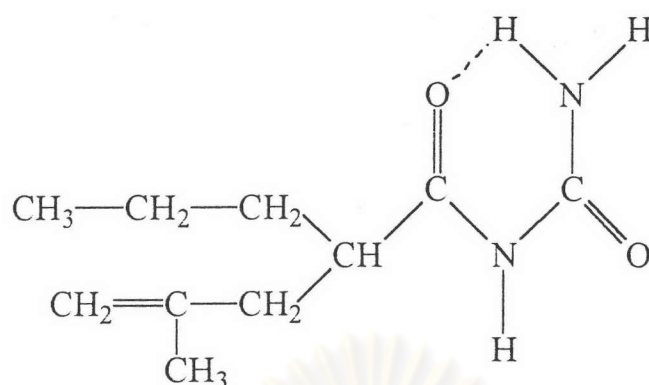
Figure 83. Proposed structure of N-(4-methyl-2-propyl-4-
pentenoyl) urea showing intramolecular
hydrogen bonding.

The 500 MHz ^{13}C-NMR spectrum of N-(4-methyl-2-propyl-4-pentenoyl) urea is shown in figure 30. The assignment is also described in this figure.

The EIMS spectrum of N-(4-methyl-2-propyl-4-pentenoyl) urea is shown in figure 31. This compound is confirmed by the analysis of the mass fragmentation (see figure 84).
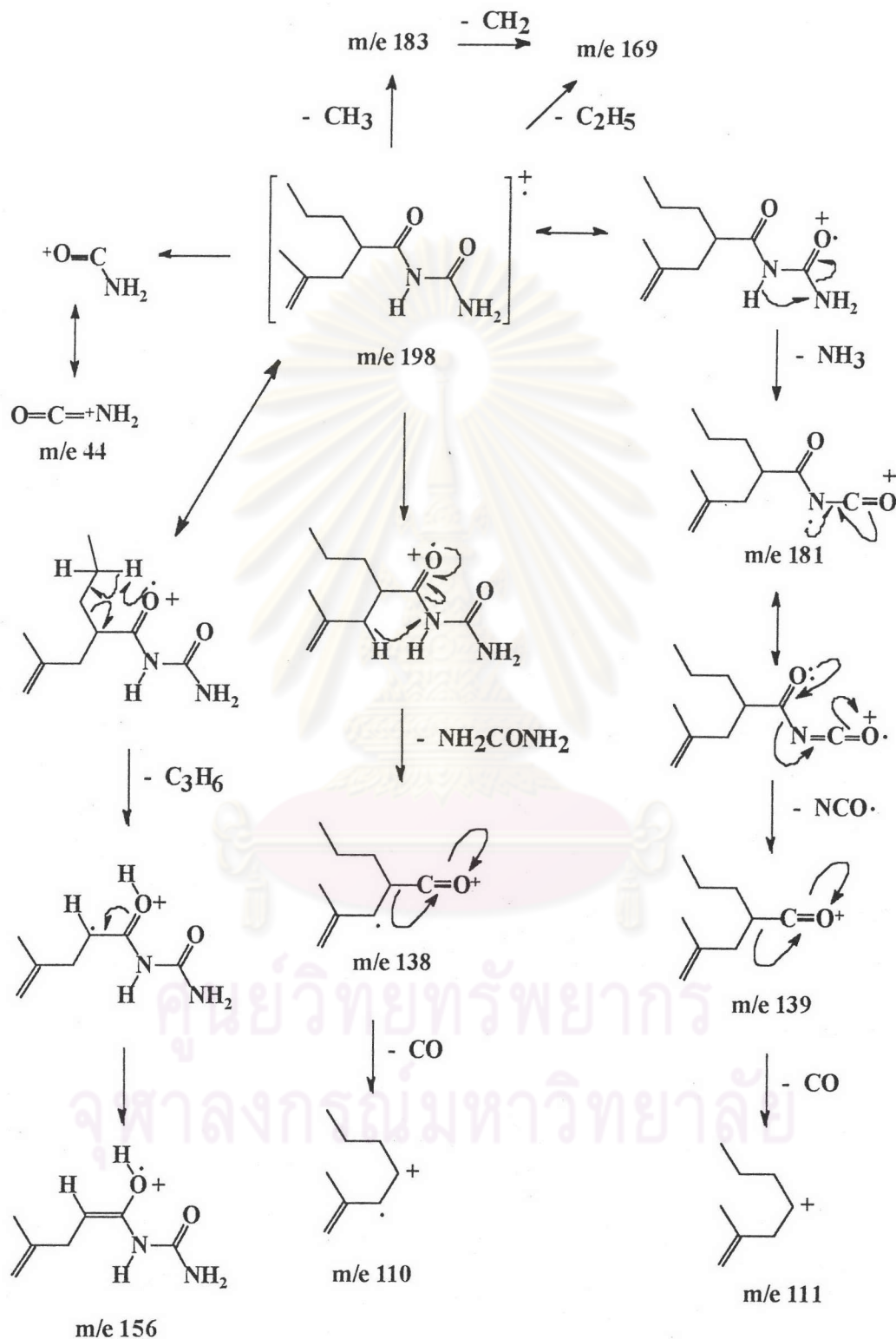
Figure 84. Mass fragmentation of N-(4-methyl-2-propyl-
4-pentenoyl) urea

2. Synthesis of <u>N</u>-(2-Propyl-4-pentenoyl) urea (CU-763-11-02).

2.1. Synthesis of Diethyl allyl(propyl)malonate.

This compound represents an disubstituted malonic ester. The reactant, diethyl propylmalonate, was alkylated with alkylating agents, allyl bromide, in ethanol by the use of sodium ethoxide as a base leading to the product.

The mechanism of alkylation of diethyl propylmalonate was shown in figure 82 (R= CH_2=CH_2-CH_2-).

The IR spectrum of diethyl allyl(propyl)malonate is shown in figure 32. The C-H stretching of alkene absorbs at 3080 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The C=O absorption bands of esters are at 1736 and 1732 cm^{-1}. The C=C stretching absorbs at 1642 cm^{-1}. The C(=O)-O stretching vibration appears at 1196 cm^{-1}. The C(alkyl)-O stretching band of ester is at 1040 cm^{-1}. The out-of-plane bending of alkene is shown at 918 cm^{-1}.

The 500 MHz ^{1}H-NMR spectrum of diethyl allyl(propyl) malonate is shown in figure 33-35. The signal at δ 0.92 ppm (3H, t, J=7.3 Hz) is assigned as a methyl group (*CH₃*-CH$_2$-CH$_2$-). The signal at δ 1.17-1.26 ppm (8H, complex) is assigned as two methyl groups (*CH₃*-CH$_2$-O-) and one methylene group (CH$_3$-*CH₂*-CH$_2$-). The signal at δ 1.82-1.87

ppm (2H, m) is assigned as a methylene group (CH$_3$-CH$_2$-*CH$_2$*-). The signal at δ 2.63-2.66 ppm (2H, ddt, J=7.3, 1.2 Hz) is assigned as a methylene group (CH$_2$=CH-*CH$_2$*-). This signal is downfield because the methylene group is adjacent to alkene. The signal shown the long lenght coupling with methylene protons of alkene. The signal at δ 4.15-4.20 ppm (4H, 2q, J=7.2 Hz) is assigned as two methylene groups (CH$_3$-*CH$_2$*-O-). The signal at δ 5.05-5.12 ppm (2H, m) is assigned as methylene protons of alkene (*CH$_2$*=CH-) and the signal at δ 5.61-5.70 ppm (1H, m) is assigned as methine proton of alkene (CH$_2$=*CH*-CH$_2$-).

2.2. Ethyl-2-propyl-4-pentenoate.

This compound represents an unsaturated carboxylic ester. The decarbalkoxylation of diethyl allyl(propyl)malonate by heating with LiCl-H$_2$O-DMSO gives monocarboxylic ester, ethyl 2-propyl-4-pentenoate.

Diethyl allyl(propyl)malonate represents disubstituted malonic ester which prefers to follow the B$_{AL}$2 mechanism (figure 8) while the B$_{AC}$2 mechanism (figure 9) is competitive.

The IR spectrum of ethyl 2-propyl-4-pentenoate is shown in figure 36. The C-H stretching of alkene absorbs at 3080 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The C=O absorption bands of ester is at 1732 cm^{-1}. The C=C stretching absorbs at 1642 cm^{-1}. The C(=O)-O stretching

vibration appears at 1178 cm^{-1}. The C(alkyl)-O stretching band of ester is at 1032 cm^{-1}. The out-of-plane bending C-H of alkene show at 916 cm^{-1}.

The 500 MHz ^{1}H-NMR spectrum ethyl 2-propyl-4-pentenoate is shown in figure 37-39. The signal at δ 0.90 ppm (3H, t, J=7.3 Hz) is assigned as a methyl group (*CH$_3$*-CH$_2$-CH$_2$-). The signal at δ 1.18-1.35 ppm (5H, complex) is assigned as one methyl group (*CH$_3$*-CH$_2$-O-) and one methylene group (CH$_3$-*CH$_2$*-CH$_2$-). The signal at δ 1.41-1.49 ppm (1H, m) and δ 1.57-1.65 ppm (1H, m) are assigned as a two protons of methylene group (CH$_3$-CH$_2$-*CH$_2$*-). The signal at δ 2.19-2.25 ppm (1H, m) and δ 2.32-2.39 ppm (1H, m) are assigned as two protons of methylene group which is adjacent to alkene (CH$_2$=CH-*CH$_2$*). The signal at δ 2.40-2.46 ppm (1H, m) is assigned as a methine proton (-*CH*-). The signal at δ 4.11-4.16 ppm (2H, q, J=7.3 Hz) is assigned as a methylene group adjacent to oxygen atom (CH$_3$-*CH$_2$*-O-). The signal at δ 4.98-5.05 ppm (2 H, s) is assigned as methylene protons of alkene (*CH$_2$*=CH-CH$_2$-) and the signal at δ 5.70-5.79 ppm (1H, m) are assigned as methine proton of alkene (CH$_2$=*CH*-CH$_2$-).

2.3. 2-Propyl-4-pentenoic acid.

This compound represents an unsaturated carboxylic acid. The reactant, ethyl 2-propyl-4-pentenoate, was refluxed in the aqueous potassium hydroxide-alcoholic solution.

The IR spectrum of 2-propyl-4-pentenoic acid is shown in figure 40. Absorption arising from hydrogen bonded, O-H stretching occurs in the region of 3300-2500 cm^{-1}. The characteristic of peak is broad and strong. The C-H stretching of alkene absorbs at 3080 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The C=O absorption band of acid is at 1708 cm^{-1}. The C=C stretching absorbs at 1642 cm^{-1}. The O-H bending absorption of carboxylic acid appears at 1420 cm^{-1}. The C-O stretching absorbs at 1280 cm^{-1}. The out-of-plane O-H bending and out-of-plane C-H bending of alkene show the peaks at 938 and 918 cm^{-1}, respectively.

The 500 MHz ^{1}H-NMR spectrum 2-propyl-4-pentenoic acid is shown in figure 41-43. The signal at δ 0.92 ppm (3H, t, J=7.3 Hz) is assigned as a methyl group (CH_3-CH$_2$-CH$_2$-). The signal at δ 1.30-1.67 ppm (4H, m) is assigned as two methylene groups (CH$_3$-CH_2-CH_2-). The signal at δ 2.22-2.29 ppm (1H, m) and δ 2.36-2.42 ppm (1H, m) are assigned as two protons of methylene group adjacent to alkene (CH$_2$=CH-CH_2-). The signal at δ 2.43-2.50 ppm (1H, m) is assigned as a methine proton (-CH-). The signal at δ 5.04 ppm (1H, dt) and δ 5.09 ppm (1H, dt) are assigned as two methylene protons of alkene (CH_2=CH-CH$_2$-). The signal at δ 5.72-5.82 ppm (1H, m) is assigned as methine proton of alkene (CH$_2$=CH-CH$_2$-) The signal at δ 10.92 ppm (1H, s, broad) is assigned as a proton of carboxylic acid (-$COOH$).

2.4. <u>N</u>-(2-Propyl-4-pentenoyl) urea.

This compound represents monoureide analog or acylurea derivative. The synthesis of this compound was accomplished by the reaction of 2-propyl-4-pentenoyl chloride and urea in dry benzene with the present of potassium carbonate granules.

The IR spectrum of <u>N</u>-(2-propyl-4-pentenoyl) urea is shown in figure 44. The peaks at 3394 cm^{-1} and 3240 cm^{-1} represent the asymmetric and symmetric N-H stretching vibration of primary amide, respectively. The strong sharp peak at 3330 cm^{-1} represents the N-H stretching vibration of imide. The C-H stretching of alkene absorbs at 3084 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The strong peak at 1702 cm^{-1} represents C=O stretching vibration (amide I) of imide and the strong peak at 1688 cm^{-1} represents C=O stretching vibration (amide I) of primary amide. The N-H stretching absorbs at 1592 cm^{-1}. The C-N bending absorption appears at 1390 cm^{-1}.

The 500 MHz ^{1}H NMR spectrum <u>N</u>-(2-propyl-4-pente-noyl) urea is shown in figure 45-47. The signal at δ 0.92 ppm (3H, t, J=7.3 Hz) is assigned as a methyl group (CH_3-CH$_2$-CH$_2$-). The signal at δ 1.27-1.68 ppm (4H, m) is assigned as two methylene group (CH$_3$-CH_2-CH_2-). The signal at δ 2.20-2.28 ppm (1H, m) and δ 2.33-2.41 ppm (1H, m) is assigned as one proton of methylene group adjacent to alkene (CH$_2$=CH-CH_2-). Another proton shows the signal which combined to the

signal of methine proton at δ 2.33-2.41 ppm (2H, m, -CH-). The signal at δ 5.02-5.11 ppm (2H, complex) is assigned as two methylene protons of alkene (CH_2=CH-CH$_2$-).   The signal at δ 5.69-5.78 ppm (1H, m) is assigned as methine proton of alkene (CH$_2$=CH-CH$_2$-). The three broad peaks at δ 5.45 ppm (1H, s, broad), δ 8.34 ppm (1H, s, broad), and δ 9.17 ppm (1H, s, broad) represent N-H protons. The peak at 9.17 ppm located at the most down field should be the N-H proton of imide NH proton which was most deshielded by the two carbonyl groups. The signal at 8.34 and 5.45 ppm represent the NH protons of primary amide.

The 500 MHz ^{13}C-NMR spectrum of N-(2-propyl-4-pentenoyl) urea is shown in figure 48. The assignment is also described in this figure.

The EIMS spectrum of N-(2-propyl-4-pentenoyl) urea is shown in figure 49. This compound is confirmed by the analysis of the mass fragmentation (see figure 85).
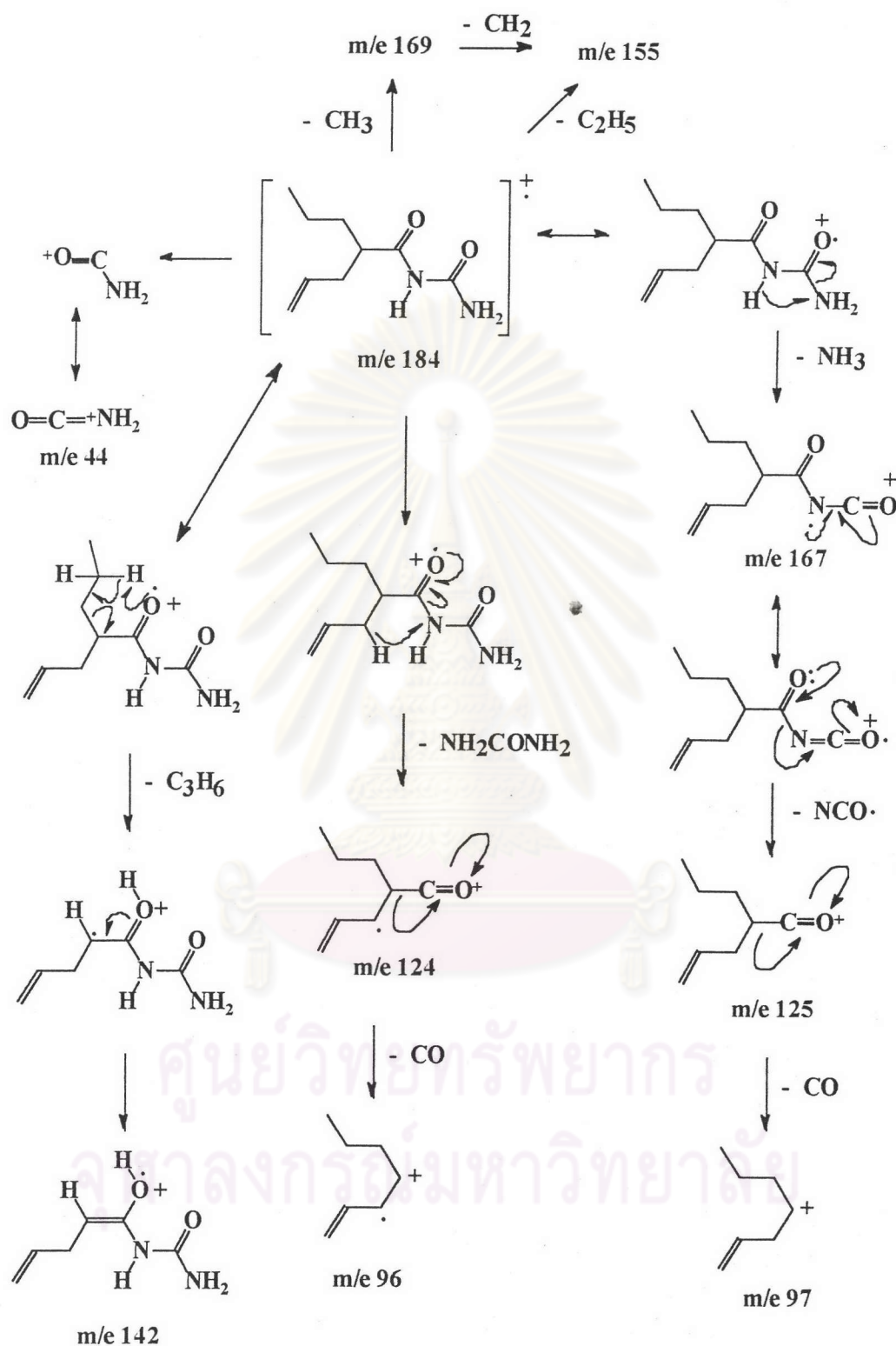
Figure 85. Mass fragmentation of N-(2-propyl-4-pentenoyl) urea

3.. <u>N</u>-(4-Methyl-2-(2′-methyl-2′-propenyl)-4-pentenoyl) urea. (CU-763-11-03)

3.1. Diethyl di-(2-methyl-2-propenyl)malonate.

This compound represents an disubstituted malonic ester. The reactant, diethyl malonate, was alkylated with 2-equivalent of alkylating agents, 3-chloro-2-methyl-1-propene, in ethanol by the use of 2-equivalent of sodium ethoxide as a base leading to the product.

The IR spectrum of diethyl di-(2-methyl-2-propenyl) malonate is shown in figure 50. The C-H stretching of alkene absorbs at 3070 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The C=O absorption bands of esters are at 1736 and 1732 cm^{-1}. The C=C stretching absorbs at 1644 cm^{-1}. The C(=O)-O stretching vibration appears at 1182 cm^{-1}. The C(alkyl)-O stretching band of ester is at 1036 cm^{-1}. The out-of-plane bending of alkene is shown at 896 cm^{-1}.

The 500 MHz ^{1}H-NMR spectrum of diethyl di-(2-methyl-2-propenyl)malonate is shown in figure 51-52. The signal at δ 1.25 ppm (6H, t, J=7.3 Hz) is assigned as two methyl groups (*CH₃*-CH$_2$-O-). The signal at δ 1.69 ppm (6H, t, J=0.7 Hz) is assigned as two methyl groups adjacent to alkene (CH$_2$=C(*CH₃*)-). The signal at δ 2.74 ppm (4H, d, J=0.9 Hz) is assigned as two methylene groups adjacent to alkene (CH$_2$=C (CH₃)-*CH₂*-). The signal at δ 4.14-4.19 ppm (4H, 2q, J=7.3 Hz) is

assigned as two methylene groups (CH$_3$-CH_2-O-) adjacent to oxygen atom. The signal at δ 4.74 ppm (2H, s) and δ 4.85 ppm (2H, s) are assigned as two methylene groups of alkene (CH_2=C(CH$_3$)-CH$_2$-). The signal splits with a little J-value due to the long lenght coupling.

3.2. Ethyl 4-methyl-2-(2′-methyl-2′-propenyl)-4-pentenoate.

This compound represents an unsaturated carboxylic ester. The decarbalkoxylation of diethyl di-(2-methyl-2-propenyl)malonate by heating with LiCl-H$_2$O-DMSO gives monocarboxylic ester, ethyl 4-methyl-2-(2′-methyl-2′-propenyl)-4-pentenoate.

Diethyl di-(2-methyl-2-propenyl)malonate represents disubstituted malonic ester which prefers to follow the B$_{AL}$2 mechanism (figure 8) while the B$_{AC}$2 mechanism (figure 9) is competitive.

The IR spectrum of ethyl 4-methyl-2-(2′-methyl-2′-propenyl)-4-pentenoate is shown in figure 53. The C-H stretching of alkene absorbs at 3078 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The C=O absorption bands of ester is at 1732 cm^{-1}. The C=C stretching absorbs at 1650 cm^{-1}. The C(=O)-O stretching vibration appears at 1174 cm^{-1}. The C(alkyl)-O stretching band of ester is at 1032 cm^{-1}. The out-of-plane C-H bending of alkene show at 894 cm^{-1}.

The 500 MHz ^{1}H NMR spectrum ethyl 4-methyl-2-(2′-methyl-2′-propenyl)-4-pentenoate is shown in figure 54-56. The signal at δ 1.23 ppm (3H, t, J=7.3 Hz) is assigned as a methyl group (CH_3-CH$_2$-O). The signal at δ 1.73 ppm (6H, s) is assigned as two methyl groups adjacent to alkene (CH$_2$=C(CH_3)-). The signal at δ 2.12-2.17 ppm (2H, 2 d, J=5.8, 5.8 Hz) and δ 2.30-2.37 ppm (2H, 2d, J=9.2, 9.2 Hz) are assigned as two methylene groups adjacent to alkene(CH$_2$=C(CH$_3$)-CH_2-). The signal at δ 2.74-2.81 ppm (1H, m) is assigned as a methine proton (-CH-). The signal at δ 4.08-4.13 ppm (2H, q, J=7.3 Hz) is assigned as a methylene group adjacent to oxygen atom (CH$_3$-CH_2-O). The signal at δ 4.73 ppm (2H, s) and δ 4.76 ppm (2H, s) are assigned as two methylene protons of alkene (CH_2=C(CH$_3$)-).

3.3. 4-Methyl-2-(2′-methyl-2′-propenyl)-4-pentenoic acid.

This compound represents an unsaturated carboxylic acid. The reactant, ethyl 4-methyl-2-(2′-methyl-2′-propenyl)-4-pentenoate , was refluxed in the aqueous potassium hydroxide-alcoholic solution.

The IR spectrum of 4-methyl-2-(2′-methyl-2′-propenyl)-4-pentenoic acid is shown in figure 57. Absorption arising from hydrogen bonded, O-H stretching occurs in the region of 3300-2500 cm^{-1}. The characteristic of peak is broad and strong. The C-H stretching of alkene absorbs at 3076 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The C=O absorption band of acid is at 1712 cm^{-1}. The C=C stretching absorbs at 1652 cm^{-1}. The C-

O stretching absorbs at 1290 cm^{-1}. The out-of-plane O-H bending and out-of-plane C-H bending of alkene show the peaks at 942 and 894 cm^{-1}, respectively.

The 500 MHz ^{1}H-NMR spectrum 4-methyl-2-(2′-methyl-2′-propenyl)-4-pentenoic acid is shown in figure 58-59. The signal at δ 1.74 ppm (6H, s) is assigned as two methyl groups adjacent to alkene (CH$_2$=C(_CH$_3$_)-). The signal at δ 2.14-2.20 ppm (2H, 2d, J=6.1, 5.8 Hz) and δ 2.33-2.38 ppm (2H, 2d, J=9.2, 8.9 Hz) are assigned as two of methylene group adjacent to alkene (CH$_2$=C(CH$_3$)-_CH$_2$_-). The signal at δ 2.76-2.82 ppm (1H, m) is assigned as a methine proton (-_CH_-). The signal at δ 4.75 ppm (2H, s) and δ 4.79 ppm (2H, s) are assigned as two methylene groups of alkene (_CH$_2$_=C(CH$_3$)-).

3.4. N-(4-Methyl-2-(2′-methyl-2′-propenyl)-4-pentenoyl) urea.

This compound represents monoureide analog or acylurea derivative. The synthesis of this compound was accomplished by the reaction of 4-methyl-2-(2′-methyl-2′-propenyl)-4-pentenoyl chloride and urea in dry benzene with the present of potassium carbonate granules.

The IR spectrum N-(4-methyl-2-(2′-methyl-2′-propenyl)-4-pentenoyl) urea is shown in figure 60. The peaks at 3396 cm^{-1} and 3250 cm^{-1} represent the asymmetric and symmetric N-H stretching vibration of primary amide, respectively. The strong sharp peak at 3336 cm^{-1} represents the N-H stretching vibration of imide. The C-H stretching of

alkene absorbs at 3084 and 2976 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The strong peak at 1708 cm^{-1} represents C=O stretching vibration (amide I) of imide and the strong peak at 1678 cm^{-1} represents C=O stretching vibration (amide I) of primary amide. The C=C stretching absorbs at 1620 cm^{-1}. The C-N bending absorption appears at 1400 cm^{-1}.

The 500 MHz ^{1}H-NMR N̲-(4-methyl-2-(2′-methyl-2′-propenyl)-4-pentenoyl) urea is shown in figure 61-62. The signal at δ 1.74 ppm (6H, s) is assigned as two methyl groups adjacent to alkene (CH$_2$=C(*CH$_3$*)-). The signal at δ 2.14-2.19 ppm (2H, 2d, J=5.5, 5.8 Hz) and δ 2.33-2.38 ppm (2H, 2d, J=9.2, 8.9 Hz) are assigned as two methylene group adjacent to alkene (CH$_2$=C(CH$_3$)-*CH$_2$*-). The signal at δ 2.65-2.72 ppm (1H, m) is assigned as a methine proton (-*CH*-). The signal at δ 4.74 ppm (2H, dd, J=0.92 Hz) and δ 4.82 ppm (2H, t, J=1.53 Hz) are assigned as two methylene groups of alkene (*CH$_2$*=C(CH$_3$)-). The three broad peaks at δ 5.27 ppm (1H, s, broad), δ 8.27 ppm (1H, s, broad), and δ 8.93 ppm (1H, s, broad) represent N-H protons. The peak at 8.93 ppm located at the most down field should be the N-H proton of imide NH proton which was most deshielded by the two carbonyl groups. The signal at 8.27 and 5.27 ppm represent the NH protons of primary amide.

The 500 MHz ^{13}C-NMR spectrum N̲-(4-methyl-2-(2′-methyl-2′-propenyl)-4-pentenoyl) urea is shown in figure 63. The assignment is also described in this figure.

The   EIMS   spectrum   <u>N</u>-(4-methyl-2-(2′-methyl-2′-propenyl)-4-pentenoyl) urea is shown in figure 64.   This compound is confirmed by the analysis of the mass fragmentation (see figure 86).
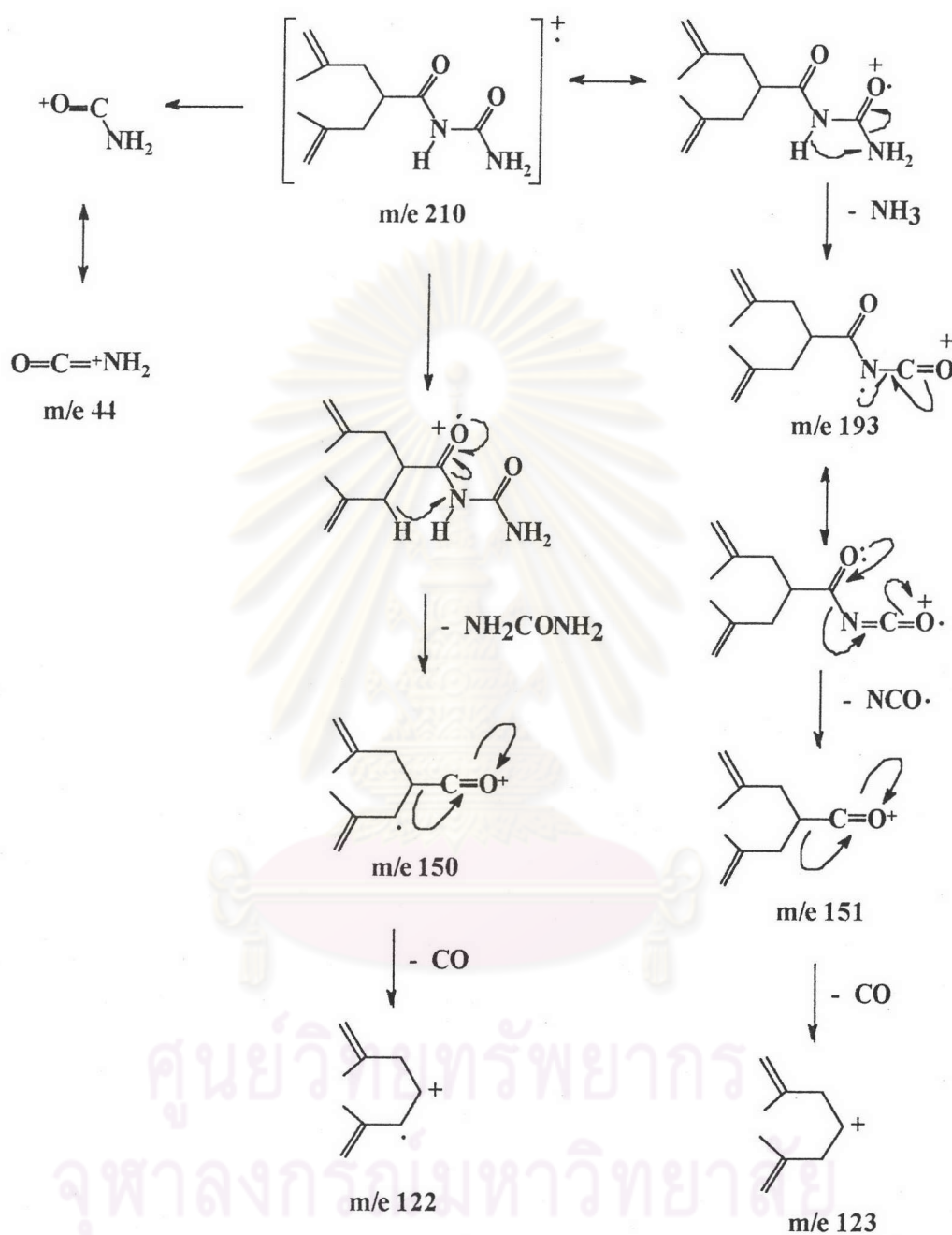
Figure 86. Mass fragmentation <u>N</u>-(4-methyl-2-(2′-methyl-2′-
propenyl)-4-pentenoyl) urea.

4. <u>N</u>-(2-Allyl-4-pentenoyl) urea (CU-763-11-04).

4.1. Diethyl diallylmalonate.

This compound represents an disubstituted malonic ester. The reactant, diethyl malonate, was alkylated with 2-equivalent of alkylating agents, allyl bromide, in ethanol by the use of 2-equivalent of sodium ethoxide as a base leading to the product.

The IR spectrum of diethyl diallylmalonate is shown in figure 65. The C-H stretching of alkene absorbs at 3080 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The C=O absorption bands of esters are at 1736 and 1732 cm^{-1}. The C=C stretching absorbs at 1642 cm^{-1}. The C(=O)-O stretching vibration appears at 1196 cm^{-1}. The C(alkyl)-O stretching band of ester is at 1036 cm^{-1}. The out-of-plane bending of alkene is shown at 920 cm^{-1}.

The 500 MHz ^{1}H-NMR spectrum of diethyl diallyl malonate is shown in figure 66-68. The signal at δ 1.25 ppm (6H, t, J=7.3 Hz) is assigned as two methyl groups (<u>CH₃</u>-CH₂-O-). The signal at δ 2.63-2.66 ppm (4H, ddt, J=7.3, 1.2 Hz) is assigned as two methylene groups adjacent to alkene (CH₂=CH-<i>CH₂</i>-). The signal shown the long lenght coupling with methylene protons of alkene. The signal at δ 4.16-4.21 ppm (4H, 2q, J=7.2 Hz) is assigned as two methylene groups (CH₃-<i>CH₂</i>-O-). The signal at δ 5.08-5.14 ppm (4H, m) is assigned as two

methylene groups of alkene (CH_2=CH-). The signal at δ 5.60-5.71 ppm (2 H, m) is assigned as two methine groups of alkene (CH$_2$=CH-CH$_2$-).

4.2. Ethyl-2-allyl-4-pentenoate.

This compound represents an unsaturated carboxylic ester. The decarbalkoxylation of diethyl diallylmalonate by heating with LiCl-H$_2$O-DMSO gives monocarboxylic ester, ethyl 2-allyl-4-pentenoate.

Diethyl diallylmalonate represents disubstituted malonic ester which prefers to follow the B$_{AL}$2 mechanism (figure 8) while the B$_{AC}$2 mechanism (figure 9) is competitive.

The IR spectrum of ethyl 2-allyl-4-pentenoate is shown in figure 69. The C-H stretching of alkene absorbs at 3080 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The C=O absorption bands of ester is at 1734 cm^{-1}. The C=C stretching absorbs at 1642 cm^{-1}. The C(=O)-O stretching vibration appears at 1196 cm^{-1}. The C(alkyl)-O stretching band of ester is at 1036 cm^{-1}. The out-of-plane C-H bending of alkene show at 920 cm^{-1}.

The 500 MHz ^{1}H-NMR spectrum of ethyl 2-allyl-4-pentenoate is shown in figure 70-72. The signal at δ 1.24 ppm (3H, t, J=7.3 Hz) is assigned as a methyl group (CH_3-CH$_2$-O-). The signal at δ 2.22-2.29 ppm (2H, m) and δ 2.33-2.41 ppm (2H, m) are assigned as two methylene groups adjacent to alkene (CH$_2$=CH-CH_2-). The signal at δ

2.48-2.54 ppm (1H, m) is assigned as a methine proton (-*CH*-). The signal at δ 4.11-4.16 ppm (2H, q, J=7.3 Hz) is assigned as a methylene group adjacent to oxygen atom (CH_3-*CH$_2$*-O-). The signal at δ 5.01-5.09 ppm (4H, complex) is assigned as two methylene groups of alkene (*CH$_2$*=CH-). The signal at δ 5.70-5.79 ppm (2H, m) are assigned as two methine protons of alkene (CH_2=*CH*-CH_2-).

4.3. 2-Allyl-4-pentenoic acid.

This compound represents an unsaturated carboxylic acid. The reactant, ethyl 2-allyl-4-pentenoate, was refluxed in the aqueous potassium hydroxide-alcoholic solution.

The IR spectrum of 2-allyl-4-pentenoic acid is shown in figure 73. Absorption arising from hydrogen bonded, O-H stretching occurs in the region of 3300-2500 cm^{-1}. The characteristic of peak is broad and strong. The C-H stretching of alkene absorbs at 3080 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The C=O absorption band of acid is at 1712 cm^{-1}. The C=C stretching absorbs at 1644 cm^{-1}. The C-O stretching absorbs at 1282 cm^{-1}. The out-of-plane C-H bending of alkene show the peaks at 894 cm^{-1}, respectively.

The 500 MHz ^{1}H-NMR spectrum 2-allyl-4-pentenoic acid is shown in figure 74-75. The signal at δ 2.26-2.33 ppm (2H, m) and δ 2.36-2.44 ppm (2H, m) are assigned as two methylene groups adjacent to

alkene (CH$_2$=CH-CH_2-). The signal at δ 2.52-2.59 ppm (1H, m) is assigned as a methine proton (-CH-). The signal at δ 5.05-5.12 ppm (4H, complex) is assigned as two methylene groups of alkene (CH_2=CH-). The signal at δ 5.73-5.82 ppm (2H, m) is assigned as two methine protons of alkene (CH$_2$=CH-CH$_2$-).

4.4. N-(2-Allyl-4-pentenoyl) urea.

This compound represents monoureide analog or acylurea derivative. The synthesis of this compound was accomplished by the reaction of 2-allyl-4-pentenoyl chloride and urea in dry benzene with the present of potassium carbonate granules.

The IR spectrum of N-(2-allyl-4-pentenoyl) urea is shown in figure 76. The peaks at 3378 cm^{-1} and 3218 cm^{-1} represent the asymmetric and symmetric N-H stretching vibration of primary amide, respectively. The strong sharp peak at 3330 cm^{-1} represents the N-H stretching vibration of imide. The C-H stretching of alkene absorbs at 3078 cm^{-1}. The peaks in the region of 3000-2840 cm^{-1} represent the aliphatic C-H stretching vibration. The strong peak at 1702 cm^{-1} represents C=O stretching vibration (amide I) of imide and the strong peak at 1687 cm^{-1} represents C=O stretching vibration (amide I) of primary amide. The C=C stretching absorbs at 1640 cm^{-1}. The N-H bending absorbs at 1592 cm^{-1}. The C-N bending absorption appears at 1400 cm^{-1}.

The 500 MHz ^{1}H-NMR spectrum $\underline{N}$-(2-allyl-4-pentenoyl) urea is shown in figure 77-79. The signal at δ 2.24-2.34 ppm (2H, m) and δ 2.36-2.46 ppm (3H, complex) are assigned as two methylene groups adjacent to alkene (CH$_2$=CH-CH_2-) and one methine proton (-CH-). The signal at δ 5.06-5.12 ppm (4H, complex) is assigned as two methylene groups of alkene (CH_2=CH-) . The signal at δ 5.70-5.79 ppm (2H, m) is assigned as two methine protons of alkene (CH$_2$=CH-CH$_2$-) . The three broad peaks at δ 5.38 ppm (1H, s, broad), δ 8.27 ppm (1H, s, broad), and δ 8.92 ppm (1H, s, broad) represent N-H protons. The peak at 8.92 ppm located at the most down field should be the N-H proton of imide NH proton which was most deshielded by the two carbonyl groups. The signal at 8.27 and 5.38 ppm represent the NH protons of primary amide.

The 500 MHz ^{13}C-NMR spectrum of $\underline{N}$-(2-allyl-4-pentenoyl) urea is shown in figure 80. The assignment is also described in this figure.

The EIMS spectrum of $\underline{N}$-(2-allyl-4-pentenoyl) urea is shown in figure 81. This compound is confirmed by the analysis of the mass fragmentation (see figure 87).
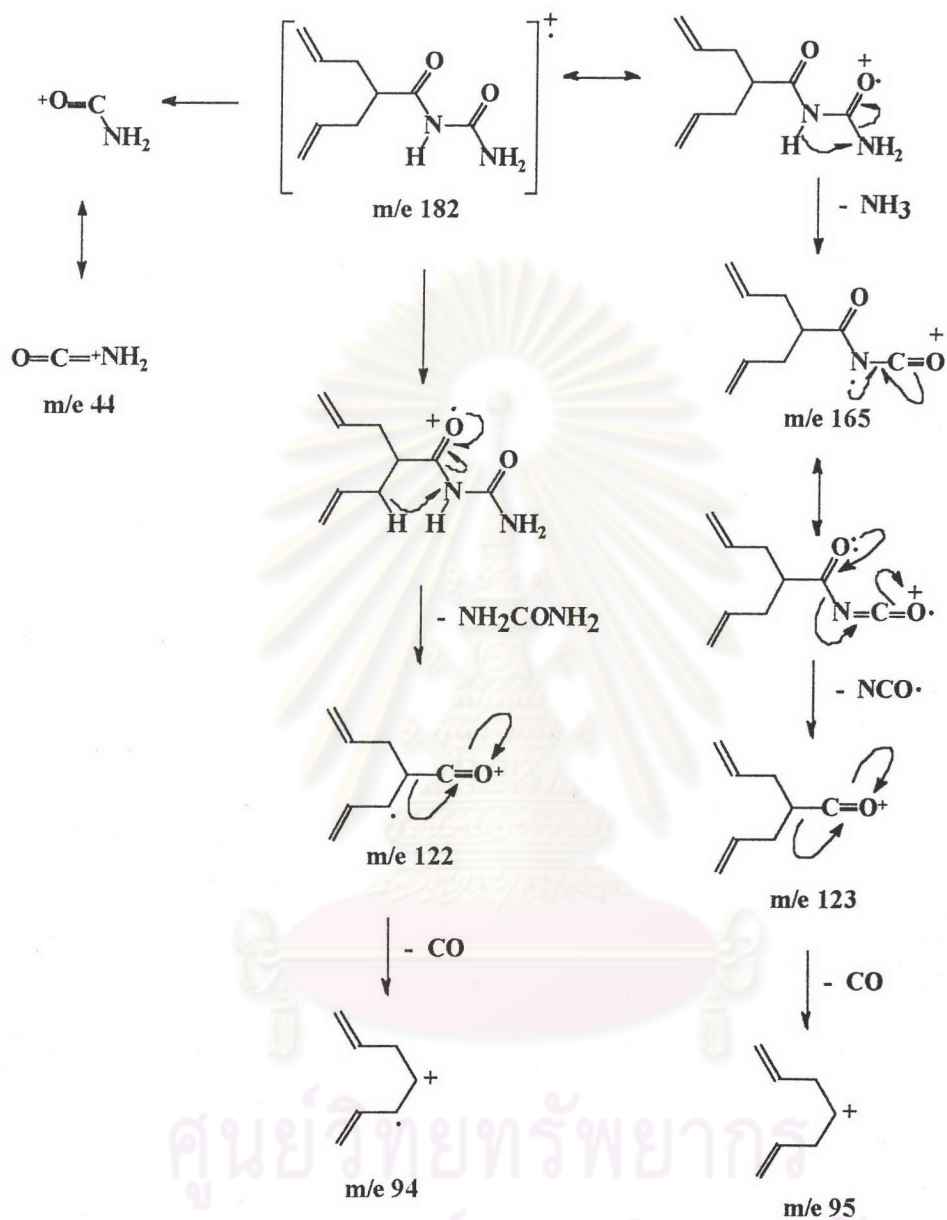
Figure 87. Mass fragmentation <u>N</u>-(2-allyl-4-pentenoyl) urea