CHAPTER IV

RESULT AND DISCUSSION

In this research, N-acyl-N′-arylurea derivatives were synthesized as compounds that expected to possess anticonvulsant activity. The reaction employed valproic acid as the starting material and progressed via isothiocyanate and isocyanate intermediates to obtain the target products.

Valproyl chloride

Valproyl chloride can be obtained from the reaction of valproic acid and thionyl chloride. This method is generally known. The excess of thionyl chloride can be distilled off and the by products, sulfer dioxide and hydrogen chloride, can also be removed during the distillation. The mechanism of this reaction can be explained in Figure 56.

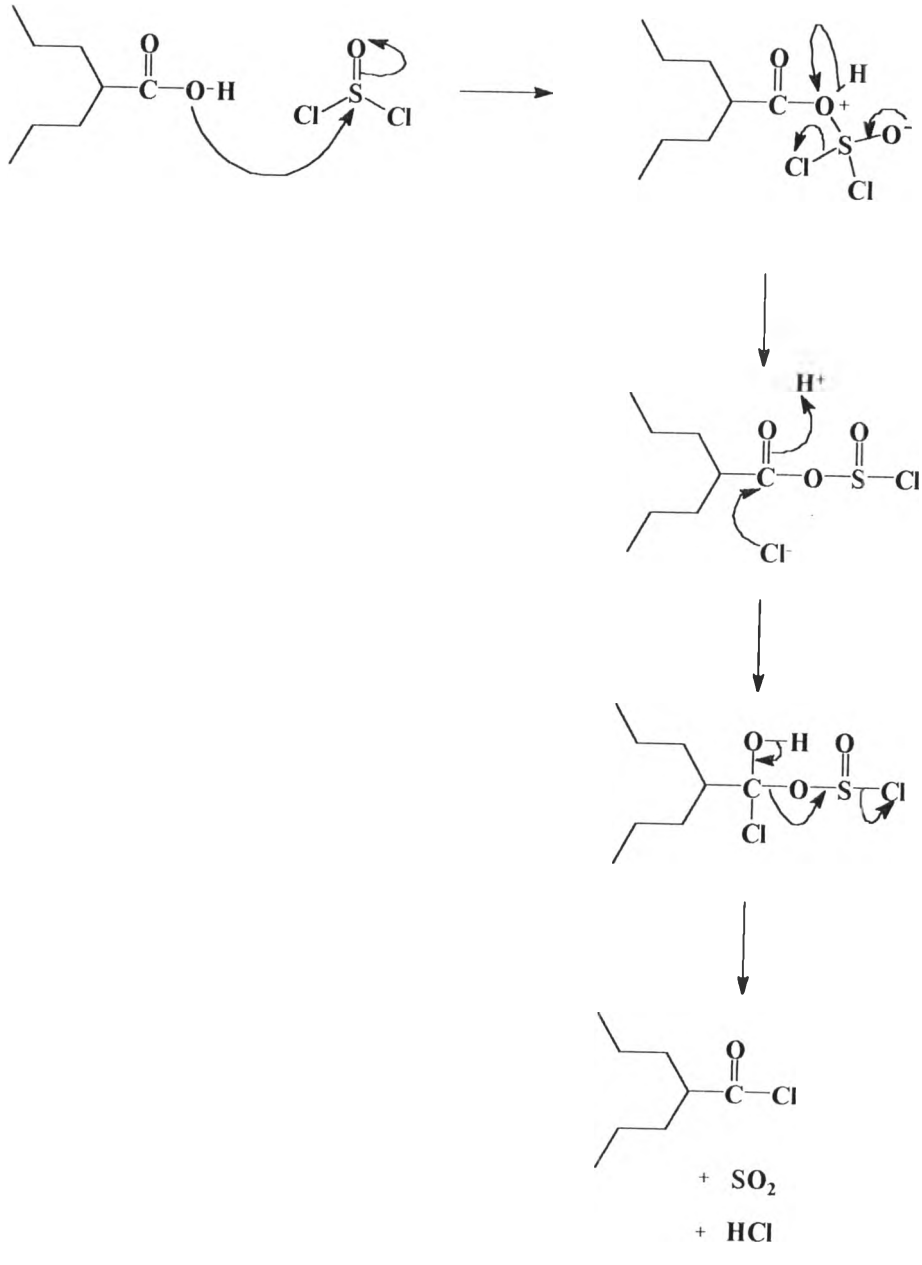
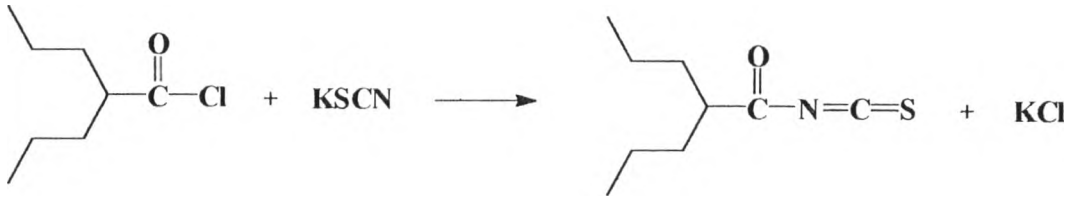


Figure 56 The reaction mechanism of formation of valproyl chloride

N-(2-Propylpentanoyl)-N'-phenylthiourea (CU-763-13-001)

This compound represents an acylthiourea compound. It was obtained by two reaction steps.

In the first step, valproyl chloride was allowed to react with potassium thiocyanate (KSCN) in dry acetone to give valproyl isothiocyanate. Acetone was selected as the solvent due to the solubility of potassium thiocyanate in this solvent is much more than its solubility in benzene or toluene which is commonly used. This reaction is a nucleophilic substitution reaction.

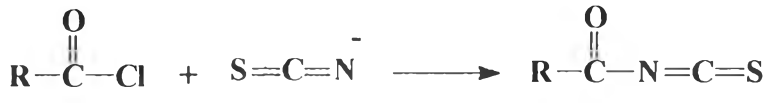


It was known that thiocyanate ion, NCS^-, is an ambident anion with the negative charge delocallized between sulfur and nitrogen atoms.

(a) (b)

In general, nucleophilic attack on the carbonyl carbon of valproyl chloride is equally possible from the S and N sites, giving rise to the thiocyanate (c) or isothiocyanate (d), respectively.

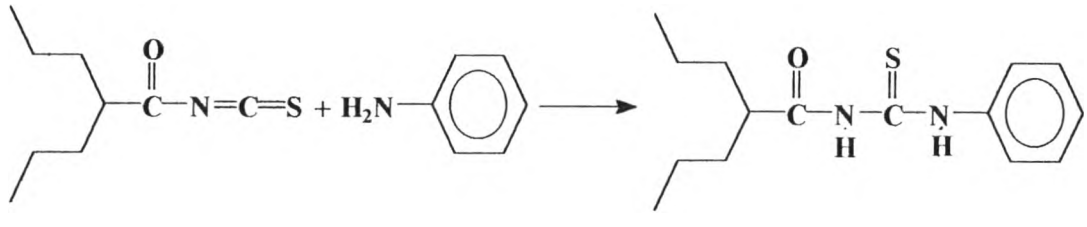
(c)



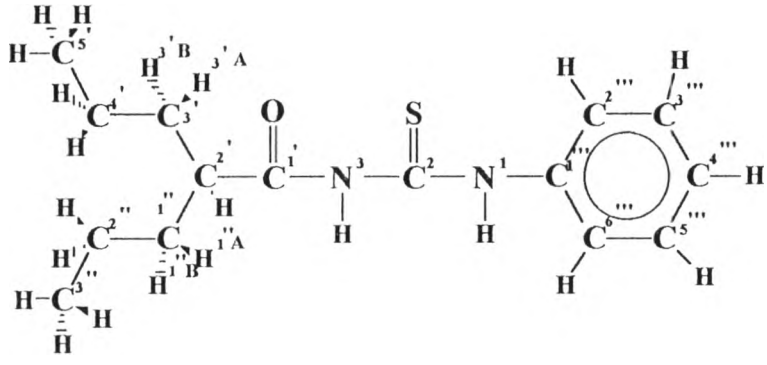
(d)

However, in this reaction, the isothiocyanate (d) was the main product obtained which can be characterized by a very strong stretching vibration peak at about 2273-2000 cm^{-1} in its IR spectrum. This crude product was used in the subsequent reaction without purification.

In the next step, aniline, as the nucleophile, was allowed to attack electrophilic carbonyl of the isothiocyanate. N-(2-Propylpentanoyl)-N′-phenylthiourea was thus formed.



The structure can be proved by IR , NMR (^{1}H, ^{13}C), mass spectroscopy and elemental anlysis as follows.



The IR spectrum of N-(2-propylpentanoyl)-N′-phenylthiourea is shown in Figure 11. The peak at 3200 cm^{-1} represents N-H stretching vibration. Many peaks in the region of 2960 - 2870 cm^{-1} represent the aliphatic C-H stretching vibration of valproyl part. The peak at 1690 cm^{-1} represents C=O stretching vibration of amide carbonyl, while stretching vibration of C=S produces a peak at 1315 cm^{-1}. The peak at 1535 cm^{-1} represents N-H bending and the peak at 1240 represents C-N stretching vibration. The aromatic part is represented by the peak at 3040-3000 cm^{-1} which shows C-H stretching, the peak at 1600 cm^{-1} representing C=C stretching vibration and at 740 cm^{-1} showing C-H out of plane bending.

The 500 MHz ^{1}H-NMR spectrum is shown in Figure 12 and 13. The signal at δ 0.93 ppm (6H, t, J = 7.3 Hz) was assigned to six protons on C-5′ and C-3″ . The signal at δ 1.36 ppm (4H, m) was assigned to four protons on C-4′ and C-2″. The signal at δ 1.48 ppm (2H, m) was assigned to H-3′B and H-1″B, while H-3′A and H-1″A appeared as the signal at δ 1.66 ppm (2H, m). The signal at δ 2.30 ppm (1H, m) could

be assigned to a proton on C-2′. The signals in range 7.20-7.70 ppm represented protons on phenyl ring. The signal at δ 7.26 ppm (1H, t, J = 7.6 Hz) was assigned as one proton on C-4‴. The signal at δ 7.40 ppm (2H, t, J = 7.9 Hz) was assigned to two protons on C-3‴ and C-5‴, while the signal at δ 7.67 ppm (2H, d, J = 8.2 Hz) was assigned to two protons on C-2‴ and C-6‴. The broad singlet signal at δ 8.96 ppm was assigned to the N-H proton at N-1. Another broad signal at δ 12.54 ppm was assigned to a proton at N-3.

The 500 MHz ^{13}C-NMR spectrum of N-(2-propylpentanoyl)-N′ phenylthiourea is shown in Figure 14. The peaks at δ 14.00, 20.60, 31.65, and 43.28 ppm were assigned to C-5′ and C-3″, C-4′ and C-2″, C-3′ and C-1″, and C-2′of the aliphatic part, respectively. Peaks in the 120 - 137 ppm region belonged to aromatic ring. The quarternary carbon, C-1‴ appeared as the pealk at δ 137.48 ppm. The peak at δ 128.80 represented C-3‴ and C-5‴. The peak at δ 126.80 represented C-4‴and the peaks at δ 124.00 ppm represented C-2‴ and C-6‴. The carbon at position C-2 and C-1′ appeared the peaks at 177.73 and 178.22 ppm, respectively.

The EIMS spectrum is of N-(2-propylpentanoyl)-N′ phenylthiourea is shown in Figure 15 . The mass fragmentation of this compound can be proposed as shown in Figure 57. A peak at m/e 278 represents M^+ peak. Cleavage between β and γ atom in aliphatic side chain, with the loss of ethyl radical ($CH_3CH_2^{\bullet}$) gave a peak at m/e 249.

Double McLafferty rearrangement can occur, resulting in the loss of 2 propene (CH_3-CH=CH_2) fragments, producing the peaks at m/e 236 and 194.

The peak at m/e 93 represents aniline cation which was propably formed by the loss of ketene and HNCS giving peaks at m/e 152 and 93 , respectively.

A peak at m/e 135 was propably formed through McLafferty rearrangement and loss of valpramide. Then, the loss of cyanate radical gave a peak at m/e 77.

The fragment at m/e 99 was 1-propylbutyl carbonium ion that would decompose by the loss of neutral molecules to give peaks at m/e 43, 57, 55 and 41.

N-(2-Propylpentanoyl)-N′-phenylurea (CU-763-13-005)

This compound is an acylurea derivative. It can be obtained from oxidation of thiocarbonyl of N-(2-propylpentanoyl)-N′-phenylthiourea by alkaline hydrogen peroxide.

The oxidation proceeds via S-oxide, and subsequently to ketone. The proposed mechanism can be explained by Figure 58. The

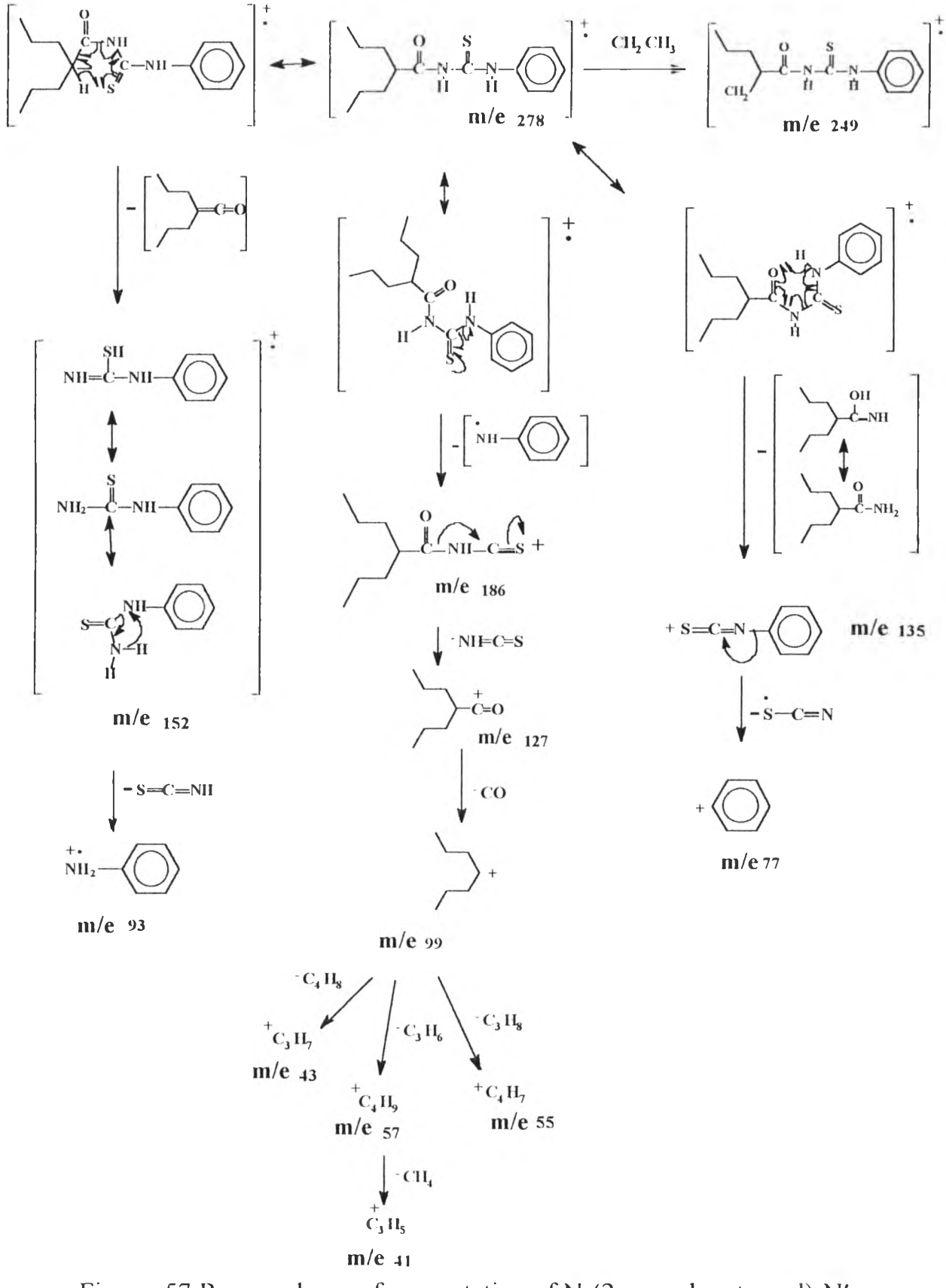
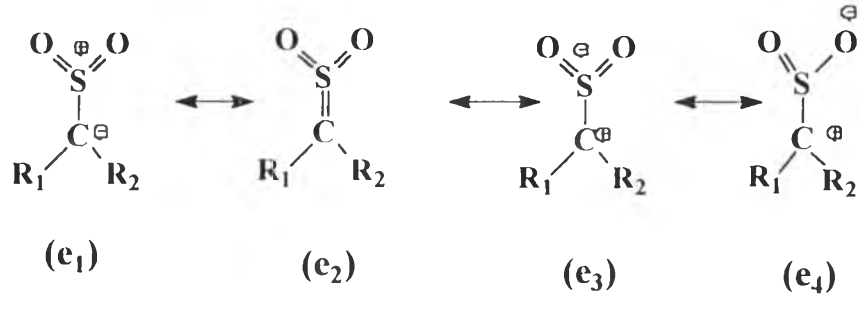


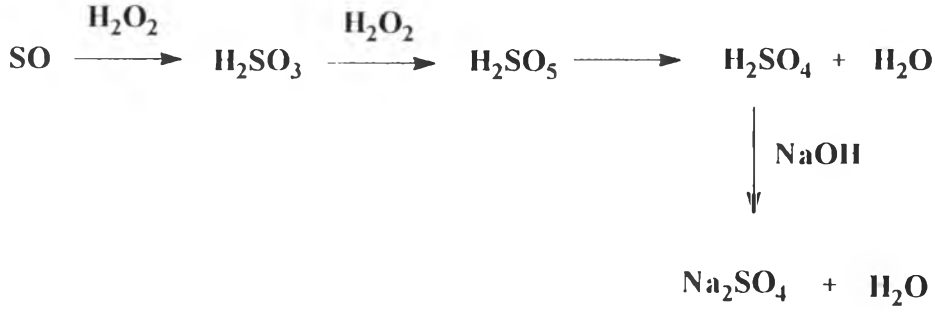
Figure 57 Proposed mass fragmentation of N-(2-propylpentanoyl)-N′-phenylthiourea

reaction started from hydrogen peroxide and hydroxide ion in the first portion to form S-oxide or S,S-dioxide compound. Since oxygen have more electronegativity than sulfur, it might be thought that the presence of O atom on S atom would increase the carbonyl reactivity, particularly since , in addition to the "carbonyl" canonical structure (e_3), a 1, 3-dipolar formulation such as (e_4) is possible, in which the oxygen has taken over the negative charge.



(e_1) (e_2) (e_3) (e_4)

SO can be further oxidised to sulfate ion. In the presence of Na^+, sodium sulfate can be precipitated off.



This compound can be proved by IR, NMR (^1H, ^{13}C), mass spectroscopy and elemental analysis as follows.

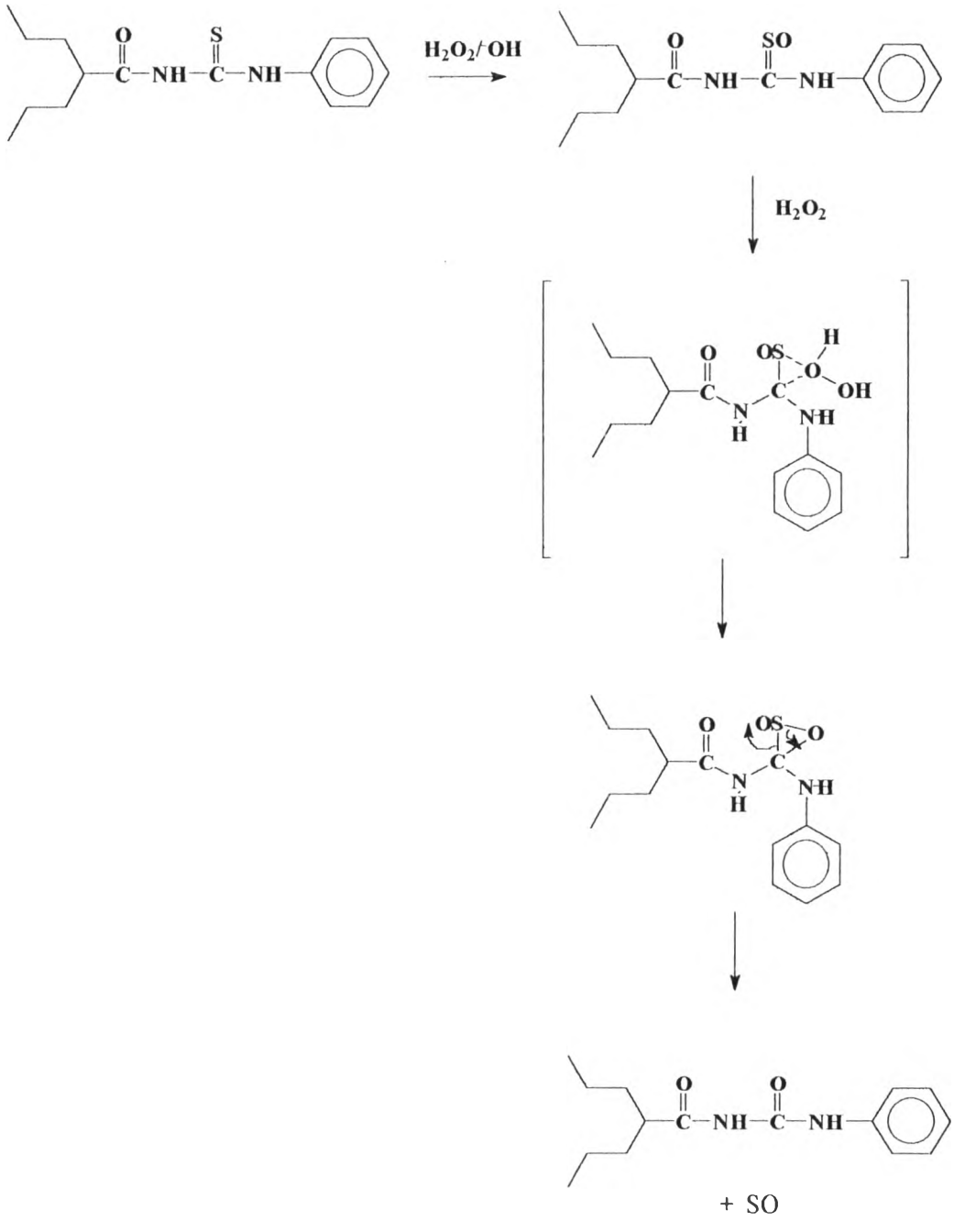
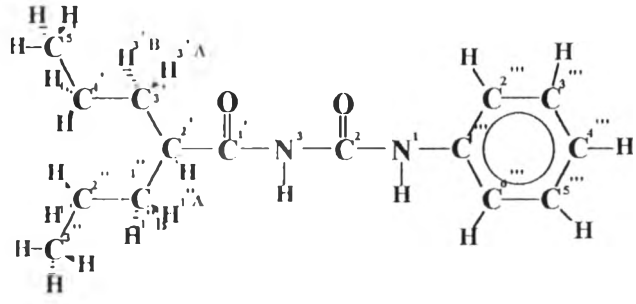


Figure 58 Proposed mechanism of the oxidation of N-(2-propylpentanoyl)-N′-phenylthiourea



The IR spectrum of N-(2-propylpentanoyl)-N′-phenylurea is shown in Figure 16. The peak at 3220 cm^{-1} represents N-H stretching vibration of imide, while N-H stretching of amide produces a peak at 3120 cm^{-1}. The peak ins the region of 2960 - 2880 cm^{-1} represents aliphatic C-H stretching vibration of valproyl part. The peaks at 1690 and 1700 cm^{-1} represent C=O stretching vibration of amide and carbamoyl carbonyl, respectively. Another peak at 1550 cm^{-1} represents N-H bending and the peak at 1230 cm^{-1} represents C-N stretching vibration. The aromatic part produces the peak at 1600 cm^{-1} representing C=C stretching vibration and at 750 cm^{-1} showing C-H out of plane bending.

The 500 MHz ^{1}H-NMR spectrum of N-(2-propylpentanoyl)-N′-phenylurea is shown in Figure 17 and 18. The signal at δ 0.93 ppm (6H, t, J = 7.3 Hz) was assigned to six protons on C-5′ and C-3″ . The signal at δ 1.36 ppm (4H, m) was assigned to four protons on C-4′ and C-2″. The signal at δ 1.50 ppm (2H, m) was assigned to H-3′B and H-1″B, while H-3′A and H-1″A appeared as signal at δ 1.70 ppm (2H, m). The signal at δ 2.42 ppm (1H, m) could be assigned to one proton on C-2′. The signals in range 7.10-7.60 ppm represented protons on phenyl ring. The signal at δ 7.12 ppm (1H, t, J = 8.2 Hz) was assigned to one proton on C-4‴. The signal at δ 7.33 ppm (2H, t, J = 8.2 Hz) was assigned to

two protons on C-3‴ and C-5‴. The signal at δ 7.54 ppm (2H, d, J = 8.2 Hz) was assigned to two protons on C-2‴ and C-6‴. The broad signal at δ 9.83 ppm was assigned as a proton at N-1. Another broad signal at δ 10.81 ppm was assigned as a proton at N-3.

The 500 MHz ^{13}C-NMR spectrum of N-(2-propylpentanoyl)-N′ phenylurea is shown in Figure 19. The peaks at 13.94, 20.60, 34.55 and 47.42 ppm were assigned to C-5′ and C-3″, C-4′ and C-2″, C-3′ and C-1″, and C-2′ of the aliphatic part, respectively. Peaks in the 120 - 138 ppm region belonged to aromatic ring. The quaternary carbon at C-1‴ appeared at 137.23 ppm. The peak at 128.92 ppm represented C-3‴ and C-5‴, while the peak at 124.23 ppm represented C-4‴. The peak at 120.17 ppm represented C-2‴ and C-6‴. Two carbonyl carbon at position C-2 and C-1′ appeared the peaks at 152.15 and 179.18 ppm, respectively.

The EIMS spectrum is shown in Figure 20. The mass fragmentation of this compound can be proposed as shown in Figure 59. A peak at m/e 262 represents M^+ peak. Cleavage between β and γ atom in aliphatic side chain, with the loss of ethyl radical ($CH_3CH_2^{\bullet}$) gave a peak at m/e 233.

The peak at m/e 93 represented aniline cation which was propably formed by the loss of ketene and isocyanic acid giving peaks at m/e 136 and 93 , respectively.

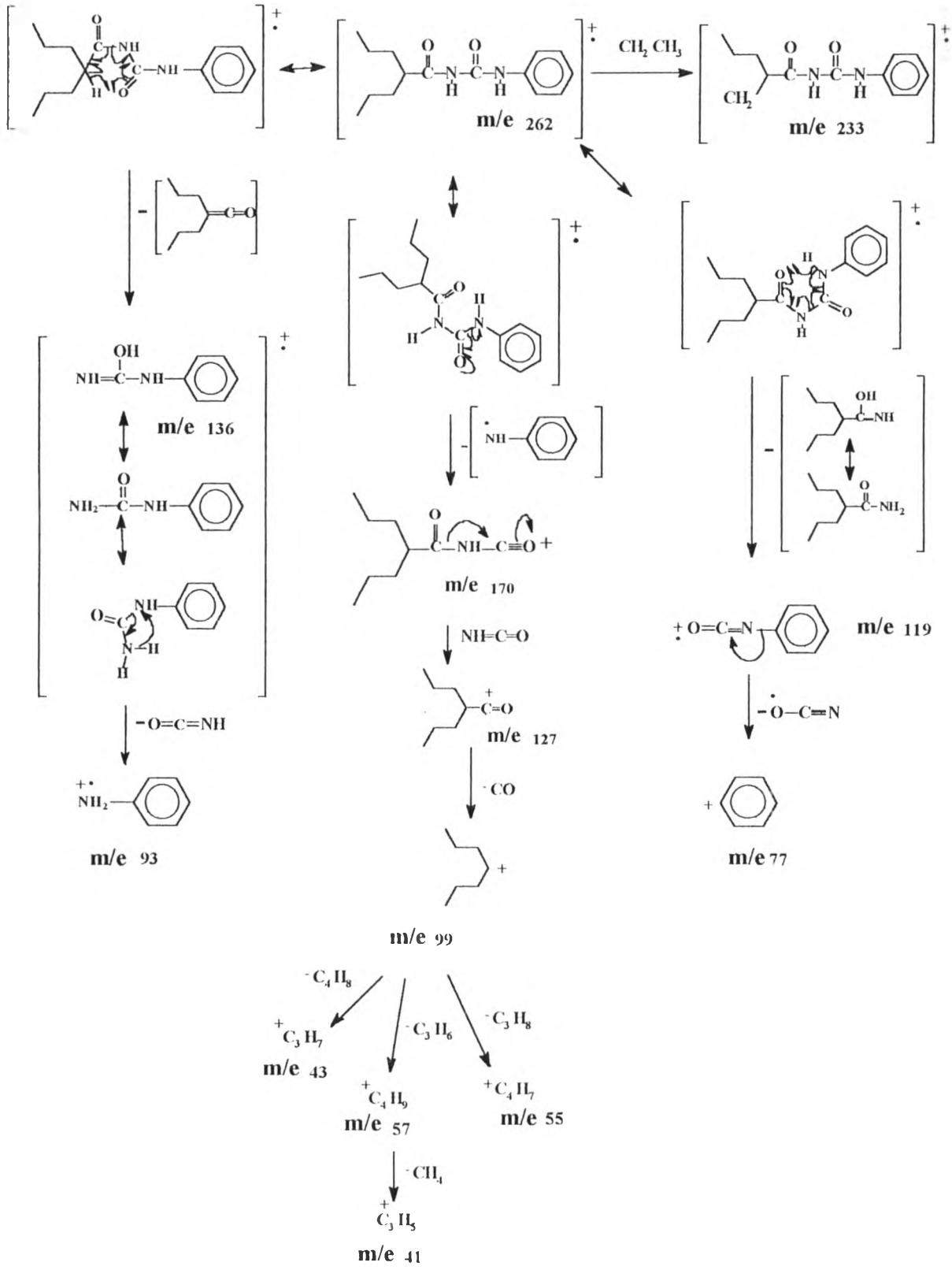


Figure 59 Proposed mass fragmentation of N-(2-propylpentanoyl)l-N′-phenylurea

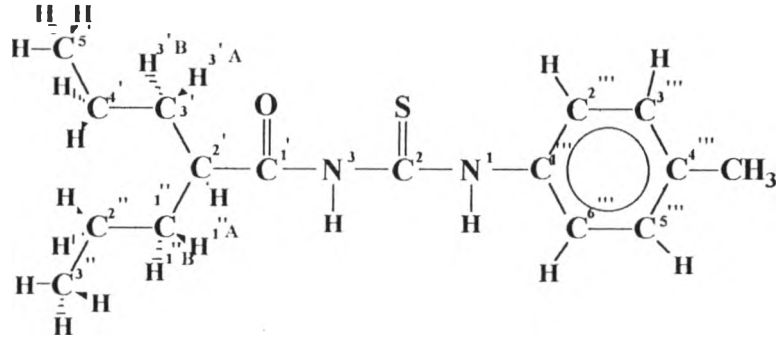
A peak at m/e 119 was propably formed through McLafferty rearrangement and loss of valpramide. Then, the loss of cyanate radical gave a peak at m/e 77.

The fragment at m/e 99 was 1-propylbutyl carbonium ion that would decompose with the loss of neutral molecules to give peaks at m/e 43, 57, 55 and 41.

N-(2-Propylpentanoyl)-N′-(4-methylphenyl)thiourea (CU-763-13-002)

N-(2-Propylpentanoyl)-N′-(4-methylphenyl)thiourea can be obtained from the similar reaction used in the preparation of N-(2-propylpentanoyl)-N′-phenylthiourea. But in this case, valproyl isothiocyanate was allowed to react with 4-toluidine in the final step instead.

This compound can be confirmed by IR, NMR (^{1}H, ^{13}C), mass spectroscopy and elemental analysis as follows.



The IR spectrum of N-(2-propylpentanoyl)-N′-(4-methylphenyl)thiourea is shown in Figure 21. The peak at 3232 cm^{-1} represents N-H stretching vibration. The peak in the region of 2962 - 2871 cm^{-1} represents the aliphatic C-H stretching vibration of valproyl part. The peak at 1684 cm^{-1} represents C=O stretching vibration of amide carbonyl, while stretching vibration of C=S appears as a peak at 1331 cm^{-1}. The peak at 1539 cm^{-1} represents N-H bending and the peak at 1250 represents C-N stretching vibration. The peak at 1600 cm^{-1} represents C=C stretching vibration of the aromatic ring and at 736 cm^{-1} shows C-H out of plane bending.

The 500 MHz ^{1}H-NMR spectrum of N-(2-propylpentanoyl)-N′-(4-methylphenyl)thiourea is shown in Figure 22 and 23. The signal at δ 0.93 ppm (H, t, *J*=7.3 Hz) was assigned to six protons on C-5′ and C-3″ . The signal at δ 1.35 ppm (4H, m) was assigned to four protons on C-4′ and C-2″. The signal at δ 1.47 ppm (2H, m) was assigned to H-3′B and H-1″B, while H-3′A and H-1″A appeared as signal at δ 1.66 ppm (2H, m). The signal at δ 2.32 ppm (1H, m) could be assigned to a proton on C-2′. The singlet signal at δ 2.35 ppm (3H) was assigned to three protons of methyl group which substituted at C-4‴. The signals in range 7.15-7.60 ppm represented protons on the phenyl ring. The signal at δ 7.20 ppm (2H, d, *J* = 7.9 Hz) was assigned to 2 protons on C-3‴ and C-5‴, whereas the signal at δ 7.51 ppm (2H, d, *J* = 8.6 Hz) could be assigned to 2 protons on C-2‴ and C-6‴. The broad singlet signal at δ 9.18 ppm

was assigned to the proton at N-1. Another broad signal at δ 12.46 ppm was assigned to the proton at N-3 position.

The 500 MHz ^{13}C-NMR spectrum of N-(2-propylpentanoyl)-N′ (4-methylphenyl)thiourea is shown in Figure 24. The peaks at 13.96 and 14.02 ppm were assigned to C-5′ and C-3″, whereas the peaks at 20.57 and 21.00 ppm were assigned to C-4′ and C-2″. The peaks at 34.66 and 43.02 ppm were assigned to C-3′ and C-1″, and C-2′ of the aliphatic part, respectively. The peak at 21.05 ppm was assigned to methyl carbon which substitued at C-4‴. Peaks in the 124-137 ppm region belonged to the aromatic ring. The peaks at 136.72 and 134.88 ppm were assigned to two quarternary carbons at C-1‴and C-4‴,respectively, which are interchangable. The peaks at 129.38 and 124.07 ppm were assigned to C-3‴ and C-5‴, C-2‴ and C-6‴. The carbonyl carbons at position C-2 and C-1′ appeared the peaks at 177.83 and 178.32 ppm, respectively.

The EIMS spectrum of N-(2-propylpenntanoyl)-N′-(4-methylphenyl)thiourea is shown in Figure 25 . The mass fragmentation of this compound can be demonstrated as in Figure 60. The thioamide cleavage produced the peak at m/e 186. The loss of HNCS led to a peak at m/e 127. Elimination of CO gave a peak at m/e 99 which is 1-propylbutyl carbonium ion that would decompose by the loss of neutral molecule to give fragment peaks at m/e 43, 57, 55 and 41.

A peak at m/e 149 was propably formed by McLafferty rearrangement and loss of valpramide. Then, the loss of thiocyanic

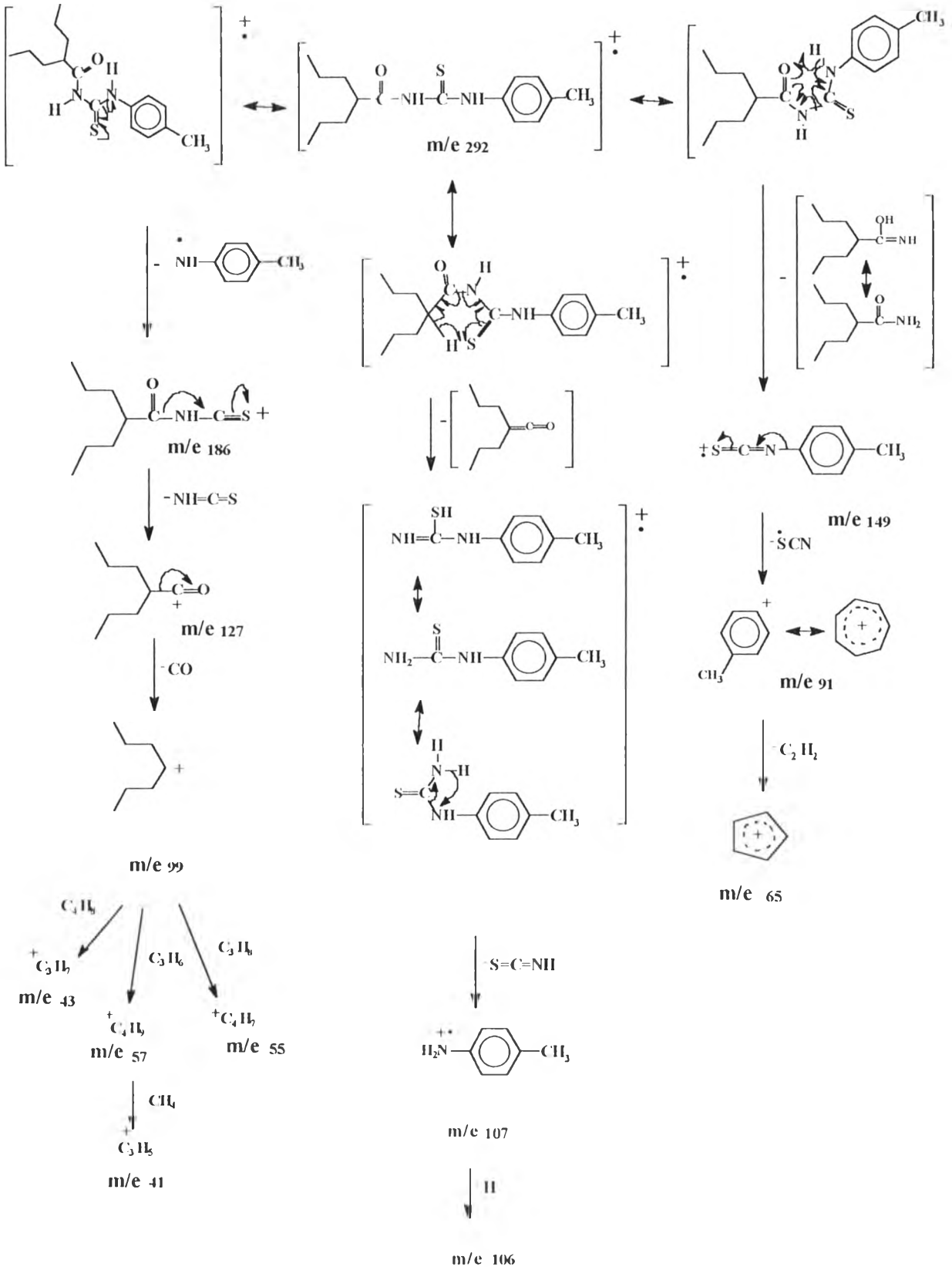


Figure 60 Proposed mass fragmentation of N-(2-propylpentanoyl)-N′-(4-methylphenyl)thiourea

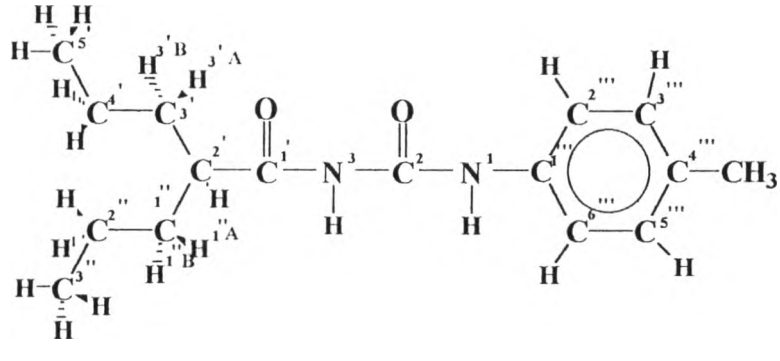
radical gave tropylium ion (m/e 91). Acetylene molecule can be eliminated from tropylium ion to give a peak at m/e 65.

A peak at m/e 107 represents 4-toluidine cation which was formed by loss of ketene and HNCS , then the loss of H gave a peak at m/e 106.

N-(2-Propylpentanoyl)-N′-(4-methylphenyl)urea (CU-763-13-006)

This compound can be obtained from oxidation of N-(2-propylpentanoyl)-N′-(4-methylphenyl)thiourea by alkaline hydrogen peroxide as explained for the first acylurea compound.

This compound can be proved by IR, NMR (^{1}H, ^{13}C), mass spectroscopy and elemental analysis as follows.



The IR spectrum of N-(2-propylpentanoyl)-N′-(4-methylphenyl) urea is shown in Figure 26. The peak at 3231 cm^{-1} represents N-H stretching vibration while N-H stretching of amide is represented at 3133

cm^{-1}. The peak in the 2980 - 2850 cm^{-1} region represents the aliphatic C-H stretching vibration of valproyl part. The peak at 1688 cm^{-1} represents C=O stretching vibration . The peak at 1551 cm^{-1} represents N-H bending and the peak at 1237 cm^{-1} represents C-N stretching vibration. The peak at 1600 cm^{-1} represents C=C stretching vibration and the peaks at 816 and 759 cm^{-1} show C-H out of plane bending.

The 500 MHz ^{1}H-NMR spectrum of N-(2-propylpentanoyl)-N′-(4-methylphenyl)urea is shown in Figure 27 and 28. The signal at δ 0.93 ppm (6H, t, *J* = 7.2 Hz) was assigned to six protons on C-5′ and C-3″ . The signal at δ 1.36 ppm (4H, m) was assigned to four protons on C-4′ and C-2″. The signal at δ 1.49 ppm (2H, m) was assigned to H-3′B and H-1″B, while H-3′A and H-1″A appeared as signal at δ 1.67 ppm (2H, m). The signal at δ 2.37 ppm (1H, m) could be assigned to a proton on C-2′. The singlet signal at at δ 2.32 ppm was assigned to three protons of methyl group which substituted at C-4‴. The signals in range 7.10-7.50 ppm represented protons on the phenyl ring. The signal at δ 7.13 ppm (2 H, d, *J* = 8.4 Hz) was assigned to two protons on C-3‴ and C-5‴, while the signal at δ 7.41 ppm (2H, d, *J* = 8.4 Hz) was assigned to two protons on C-2‴ and C-6‴. The broad singlet signal at δ 9.25 ppm was assigned to the proton at N-1. Another broad signal at δ 10.65 ppm was assigned to the proton at N-3.

The 500 MHz ^{13}C-NMR spectrum of N-(2-propylpentanoyl)-N′ (4-methylphenyl)urea is shown in Figure 29. The peaks at 13.96, 20.61,

34.57 and 47.68 ppm were assigned to C-5′ and C-3″, C-4′ and C-2″, C-3′ and C-1″, and C-2′ of the aliphatic part, respectively. The peak at 20.80 ppm could be assigned to methyl carbon that substituted on C-4‴. Peaks in the 124 - 135 ppm region belonged to aromatic ring ; at 134.65 and 133.79 ppm were assigned to two quarternary carbons, C-1‴ and C-4‴, which are interchangable. The peaks at 129.43 and 124.15 ppm were assigned to C-3‴ and C-5‴ , C-2‴ and C-6‴, respectively. The peak. The carbon at position C-2 appeared the peak at 152.12 ppm while the carbonyl carbon at C-1′ showed the peaks at 179.11 ppm.

The EIMS spectrum of N-(2-propylpentanoyl)-N′-(4-methylphenyl)urea is shown in Figure 30. The mass fragmentation of this compound can be explained as shown in Figure 61. The amide cleavage produced a peak at m/e 170. Successive loss of HNCO gave a peak at m/e 127. Elimination of CO then gave a peak at m/e 99, which is 1-propylbutyl carbonium ion that would decompose by loss of neutral molecules to give fragment peaks at m/e 43, 57, 55 and 41.

A peak at m/e 133 was propably formed through McLafferty rearrangement and loss of valpramide. Then, the loss of cyanic radical gave tropylium ion (m/e 91) . Acetylene molecule can be eliminated from tropylium ion to give a peak at m/e 65.

A peak at m/e 107 represented 4-toluidine cation which was formed by loss of ketene and HNCS , then the loss of H gave a peak at m/e 106.

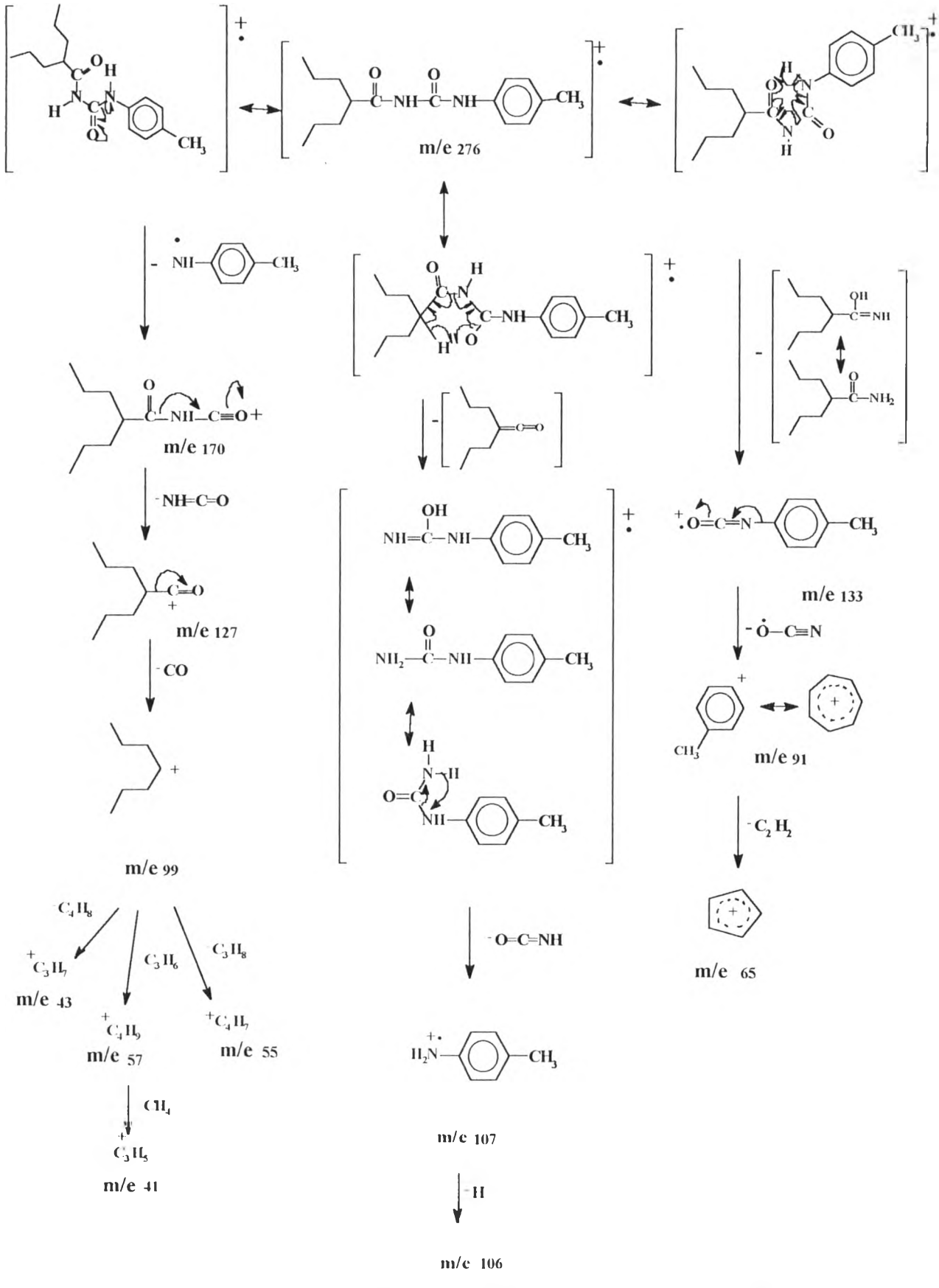
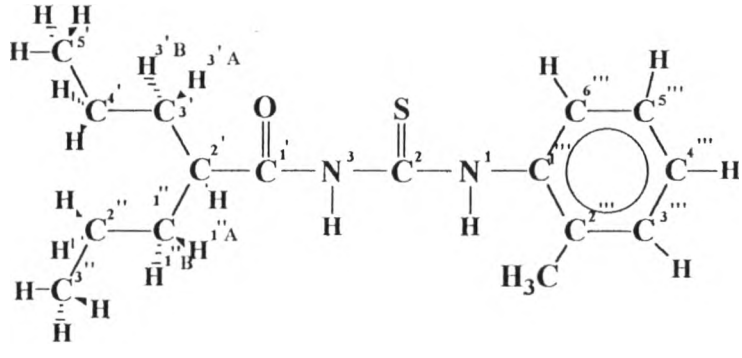


Figure 61 Proposed mass fragmentation of N-(2-propylpentanoyl)-N′-(4-methylphenyl)urea

N-(2-Propylpentanoyl)-N′-(2-methylphenyl)thiourea (CU-763-13-003)

N-(2-Propylpentanoyl)-N′-(2-methylphenyl)thiourea can be obtained from the similar reaction used in N-(2-propylpentanoyl)-N′-phenylthiourea. But in this reaction, valproyl isothiocyanate was allowed to reacted with 2-toluidine in the final step instead.

This compound can be proved by IR, NMR (^{1}H, ^{13}C), mass spectroscopy and elemental analysis as follows.



The IR spectrum of N-(2-propylpentanoyl)-N′-(2-methylphenyl) thiourea is shown in Figure 31. The peak at 3182 cm^{-1} represents N-H stretching vibration. Many peaks in the 2990 - 2871 cm^{-1} region represent the aliphatic C-H stretching vibration of valproyl part. The peak at 1692 cm^{-1} represents C=O stretching vibration of amide carbonyl, while stretching vibration of C=S produces the peak at 1321 cm^{-1}. The peak at 1535 cm^{-1} represents N-H bending and the peak at 1247 represents C-N stretching vibration. The peak at 560 cm^{-1} shows C-H out of plane bending.

The 500 MHz ^{1}H-NMR spectrum of N-(2-propylpentanoyl)-N′-(2-methylphenyl)thiourea is shown in Figure 32 and 33. The signal at δ 0.95 ppm (H, t, *J*=7.3 Hz) was assigned to six protons on C-5′ and C-3″ . The signal at δ 1.38 ppm (4H, m) was assigned to four protons on C-4′ and C-2″. The signal at δ 1.51 ppm (2H, m) was assigned to H-3′B and H-1″B, while H-3′A and H-1″A appeared as signal at δ 1.68 ppm (2H, m). The signal at δ 2.26 ppm (1H, m) could be assigned to a proton on C-2′. The singlet signal at δ 2.31 ppm was assigned to three protons of methyl group which substitued at C-2‴ position. The signals in range 7.20-7.80 ppm represented protons on the phenyl ring. The signal at δ 7.24 ppm (3H, complex) was assigned to 3 protons at C-3‴, C-4‴ and C-5‴, whereas the signal at δ 7.74 ppm (1H, d, *J* = 7.3 Hz) could be assigned to a proton on C-6‴. The broad singlet signal at δ 8.75 ppm was assigned to the N-H proton at N-1. Another broad signal at δ 12.14 ppm was assigned to the proton at N-3 position.

The 500 MHz ^{13}C-NMR spectrum of N-(2-propylpentanoyl)-N′ (2-methylphenyl)thiourea is shown in Figure 34. The peaks at 14.02, 20.62, 34.67 and 48.18 ppm were assigned to C-5′ and C-3″, C-4′ and C-2″, C-3′ and C-1″ and C-2′ of the aliphatic part, respectively. The peak at 17.89 was assigned to carbon of methyl group which substitued on C-4‴ position. Peaks in the 126 - 136 ppm region belonged to the aromatic ring. The peaks at 136.21 and 133.13 ppm were assigned to C-1‴and C-2‴ , which are interchangable. The peaks at 130.70, 127.55, 126.34

126.09 ppm were assigned to C-5‴, C-3‴, C-4‴ and C-6‴, respectively, which are interchangable. The carbons at position C-2 and C-1′ appeared the peaks at 177.83 and 178.32 ppm, respectively.

The EIMS spectrum of N-(2-propylpenntanoyl)-N′-(2-methylphenyl)thiourea is shown in Figure 35 . The mass fragmentation of this compound can be demonstrated as in Figure 62. The thioamide cleavage produced the peaks at m/e 106 and 186. The loss of HNCS led to a peak at m/e 127. Elimination of CO gave a peak at m/e 99 which is 1-propylbutyl carbonium ion that would decompose by loss the of neutral molecule to give fragment peaks at m/e 43, 57, 55 and 41.

A peak at m/e 149 was propably formed through McLafferty rearrangement and loss of valpramide. Then, the loss of thiocyanic radical gave tropylium ion (m/e 91) . Acetylene molecule can be eliminated from tropylium ion to give a peak at m/e 65.

A peak at m/e 107 represents 2-toluidine cation which was formed by the loss of ketene and HNCS , then the loss of H gave a peak at m/e 106.

N-(2-propylpentanoyl)-N′-(2-methylphenyl)urea (CU-763-13-007)

This compound can be obtained from oxidation of N-(2-propylpentanoyl)-N′-(2-methylphenyl)thiourea by alkaline hydrogen peroxide as explained in the first acylurea compound.

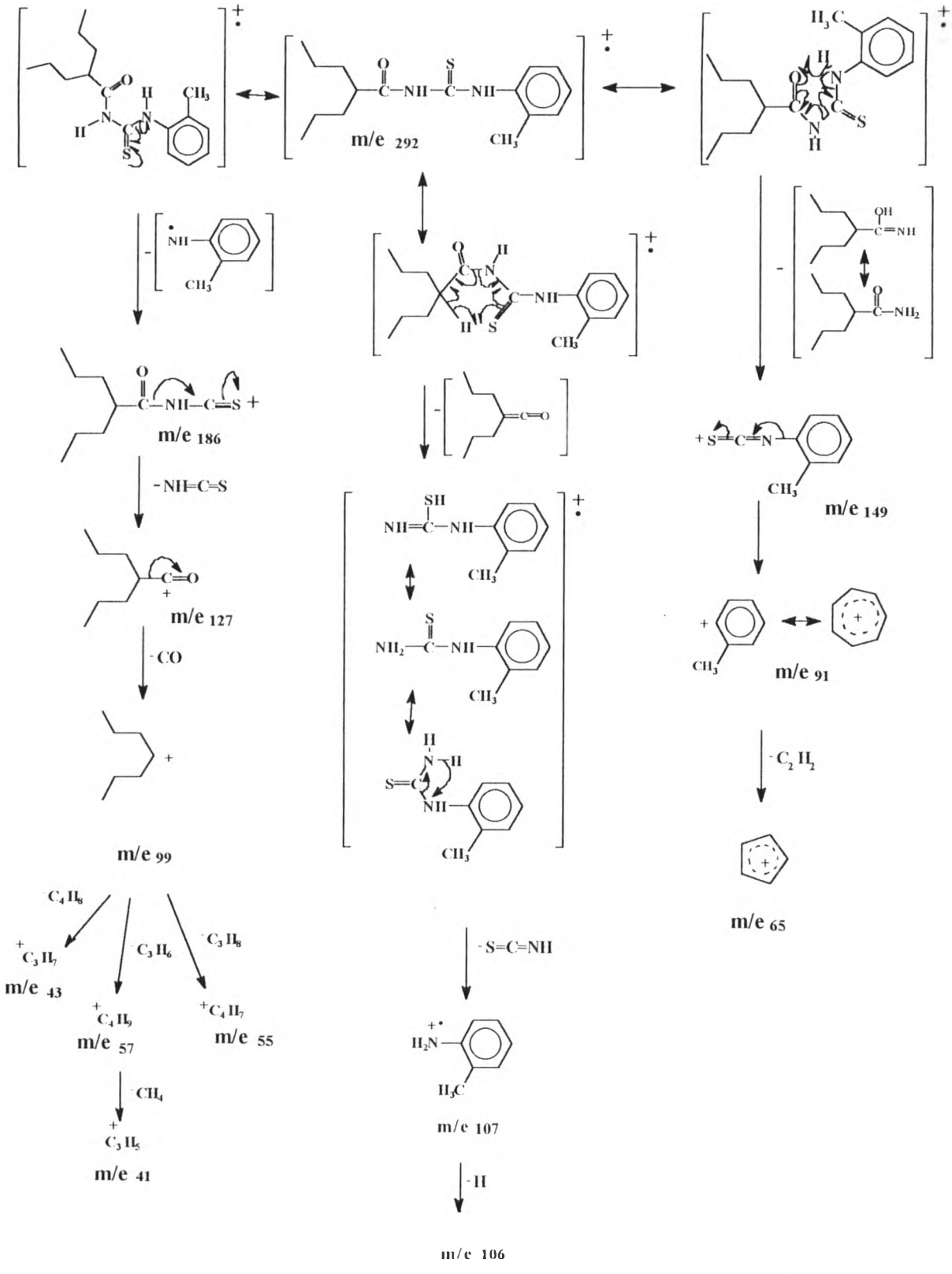
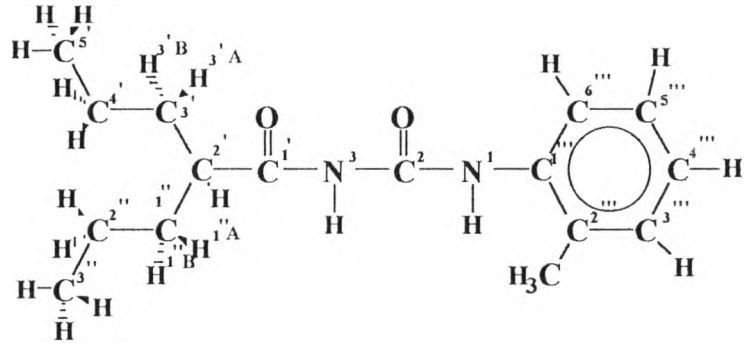


Figure 62 Proposed mass fragmentation of N-(2-propylpentanoyl)-N′-(2-methylphenyl)thiourea

This compound can be proved by IR, NMR (^{1}H, ^{13}C), mass spectroscopy and elemental analysis as follows.



The IR spectrum of N-(2-propylpentanoyl)-N′-(2-methylphenyl)urea is shown in Figure 36. The peaks at 3227 and 3135 cm^{-1} represent N-H stretching vibration of imide and amide.. The peak in the region of 3000-2940 cm^{-1}represents the aliphatic C-H stretching vibration of valproyl part. The peak at 1700 cm^{-1} represents C=O stretching vibration . The peak at 1563 cm^{-1} represents N-H bending vibration. The peak at 1616 cm^{-1} represents C=C stretching vibration and 759 cm^{-1} shows C-H out of plane bending.

The 500 MHz ^{1}H-NMR spectrum of N-(2-propylpentanoyl)-N′-(2-methylphenyl)urea is shown in Figure 37 and 38. The signal at δ 0.92 ppm (6H, t, J = 7.3 Hz) was assigned to six protons on C-5′ and C-3″ . The signal at δ 1.37 ppm (4H, m) was assigned to four protons on C-4′ and C-2″. The signal at δ 1.50 ppm (2H, m) was assigned to H-3′B and H-1″B, while H-3′A and H-1″A appeared as signal at δ 1.71 ppm (2H,

m). The signal at δ 2.46 ppm (1H, m) could be assigned to a proton on C-2′. The singlet signal at at δ 2.36 ppm was assigned to three protons of methyl group which substituted at C-2‴. The signals in range 7.00-8.10 ppm represented protons on the phenyl ring. The signal at δ 7.05 ppm (1 H, dt, J = 7.5, 0.9 Hz) was assigned to the proton on C-4‴, while the signal at δ 7.20 ppm (2H, complex) was assigned to two protons on C-3‴ and C-5‴. Another proton on C-6‴ of phenyl ring appeared at 8.06 ppm (1H, dd, J = 8.5, 0.9 Hz). The broad singlet signal at δ 10.14 and 10.77 ppm were assigned to the N-H protons at N-1 and N-3 position, respectively.

The 500 MHz ^{13}C-NMR spectrum of N-(2-propylpentanoyl)-N′ (2-methylphenyl)urea is shown in Figure 39. The peaks at 13.96, 20.62, 34.59 and 47.90 ppm were assigned to C-5′ and C-3″, C-4′ and C-2″, C-3′ and C-1″, and C-2′ of the aliphatic part, respectively. The peak at 18.06 ppm could be assigned to methyl carbon that substituted on C-2‴. Peaks in the 121 - 136 ppm region belonged to aromatic ring, The peaks at 135.76 and 130.35 ppm were assigned to two quarternary carbons, C-1‴ and C-2‴, which are interchangable. The peaks at 128.03, 126.52, 124.33 and 121.25 ppm were assigned to C-5‴, C-3‴ , C-4‴ and C-6‴, respectively. The two carbonyl carbons at position C-2 and C-1′ appeared the peak at 152.92 and 179.08 ppm, respectively.

The EIMS spectrum of N-(2-propylpentanoyl)-N′-(2-methylphenyl)urea is shown in Figure 40. The mass fragmentation of this

compound can be explained as shown in Figure 63. The amide cleavage produced peaks at m/e 106 and 170. Successive loss of HNCO gave a peak at m/e 127. Elimination of CO then gave a peak at m/e 99, which is 1-propylbutyl carbonium ion that would decompose by loss of neutral molecules to give peak fragments at m/e 43, 57, 55 and 41.

A peak at m/e 133 was propably formed by McLafferty rearrangement and loss of valpramide. Then, the loss of cyanic radical gave tropylium ion (m/e 91) . Acetylene molecule can be eliminated from tropylium ion to give a peak at m/e 65.

A peak at m/e 107 represented 2-toluidine cation which was formed by loss of ketene and HNCS , then the loss of H gave a peak at m/e 106.

N-(2-propylpentanoyl)-N′-(4-nitrophenyl)thiourea (CU-763-13-004)

N-(2-propylpentanoyl)-N′-(4-nitrophenyl)thiourea can be obtained from the reaction used in the preparation of N-(2-propylpentanoyl)-N′-phenylthiourea. But in this case, valproyl isothiocyanate was allowed to reacted with 4-nitroaniline in the final step instead.

This compound can be identified by IR, NMR (^{1}H, ^{13}C), mass spectroscopy and elemental analysis as follows.

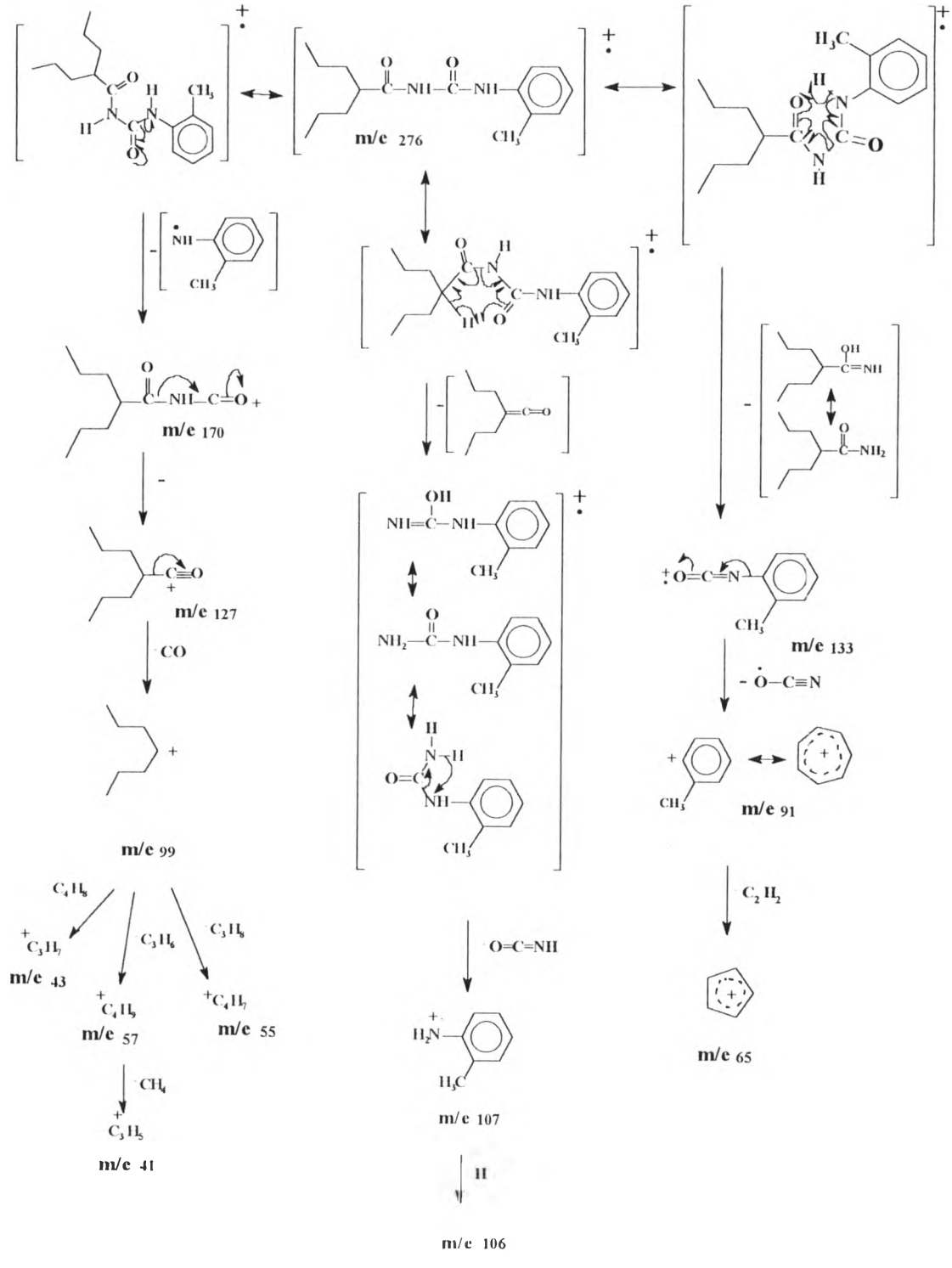
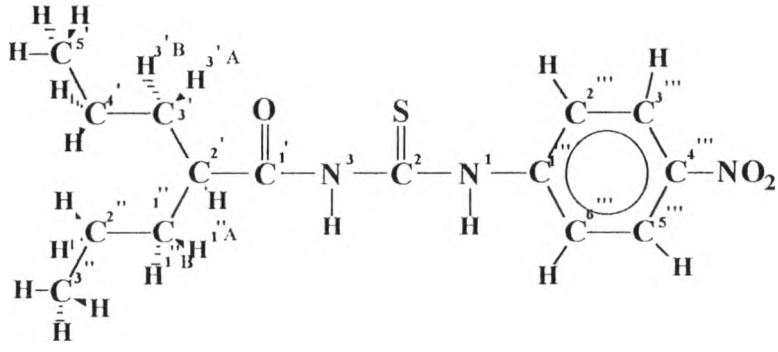


Figure 63 Proposed mass fragmentation of N-(2-propylpentanoyl)-N′-(2-methylphenyl)urea



The IR spectrum of N-(2-propylpentanoyl)-N′-(4-nitrophenyl) thiourea is shown in Figure 41. The peak at 3369 cm^{-1} represents N-H stretching vibration. The peak at region 2958 cm^{-1}represents the aliphatic C-H stretching vibration of valproyl part. The peak at 1688 cm^{-1} represents C=O stretching vibration of amide carbonyl. The peak at 1578 cm^{-1} represents N-H bending and the peak at 1510 and 1305 cm^{-1} represent asymmetric and symmetric C-NO_2 stretching vibration, respectively. The peaks at 849, 752 cm^{-1} show C-H out of plane bending.

The 500 MHz ^{1}H-NMR spectrum of N-(2-propylpentanoyl)-N′-(4-nitrophenyl)thiourea is shown in Figure 42 and 43. The signal at δ 0.94 ppm (H, t, *J*=7.3 Hz) was assigned to six protons on C-5′ and C-3″ . The signal at δ 1.38 ppm (4H, m) was assigned to four protons on C-4′ and C-2″. The signal at δ 1.52 ppm (2H, m) was assigned to H-3′B and H-1″B, while H-3′A and H-1″A appeared as signal at δ 1.68 ppm (2H, m). The signal at δ 2.34 ppm (1H, m) could be assigned to a proton on

C-2′. The signals in range 8.00-8.30 ppm represented protons on the phenyl ring. The signal at δ 8.01 ppm (2H, dd, J = 9.2, 2.1 Hz) was assigned to two protons on C-2‴ and C-6‴, whereas the signal at δ 8.27 ppm (2H, dd, J = 9.2, 2.1 Hz) could be assigned to two protons on C-3‴ and C-5‴. The broad singlet signal at δ 9.16 ppm was assigned to the N-H proton at N-1. Another broad signal at δ 13.07 ppm was assigned to the proton at N-3 position.

The 500 MHz ^{13}C-NMR spectrum of N-(2-propylpentanoyl)-N′ (4-nitrophenyl)thiourea is shown in Figure 44. The peaks at 13.91 and 13.97 ppm were assigned to C-5′ and C-3″, whereas the peaks at 20.56 was assigned to C-4′ and C-2″. The peaks at 34.55 and 48.21 ppm were assigned to C-3′ and C-1″, and C-2′ of the aliphatic part, respectively. Peaks in the 123-145 ppm region belonged to the aromatic ring. The peaks at 145.07 and 143.10 ppm were assigned to two quarternary carbons at C-1‴and C-4‴, respectively, which are interchangable. The peaks at 124.51, 124.43, 123.15, and 123.07 ppm were assigned to C-3‴ , C-5‴, C-2‴ and C-6‴, respectively, which are interchangable. The carbons at position C-2 and C-1′ appeared the peaks at 178.16 and 178.19 ppm, respectively.

The EIMS spectrum of N-(2-propylpentanoyl)-N′-(4-nitrophenyl)thiourea is shown in Figure 45 . The mass fragmentation of this compound can be proposed as shown in Figure 64. The peak at m/e 323 represents M^+ peak.

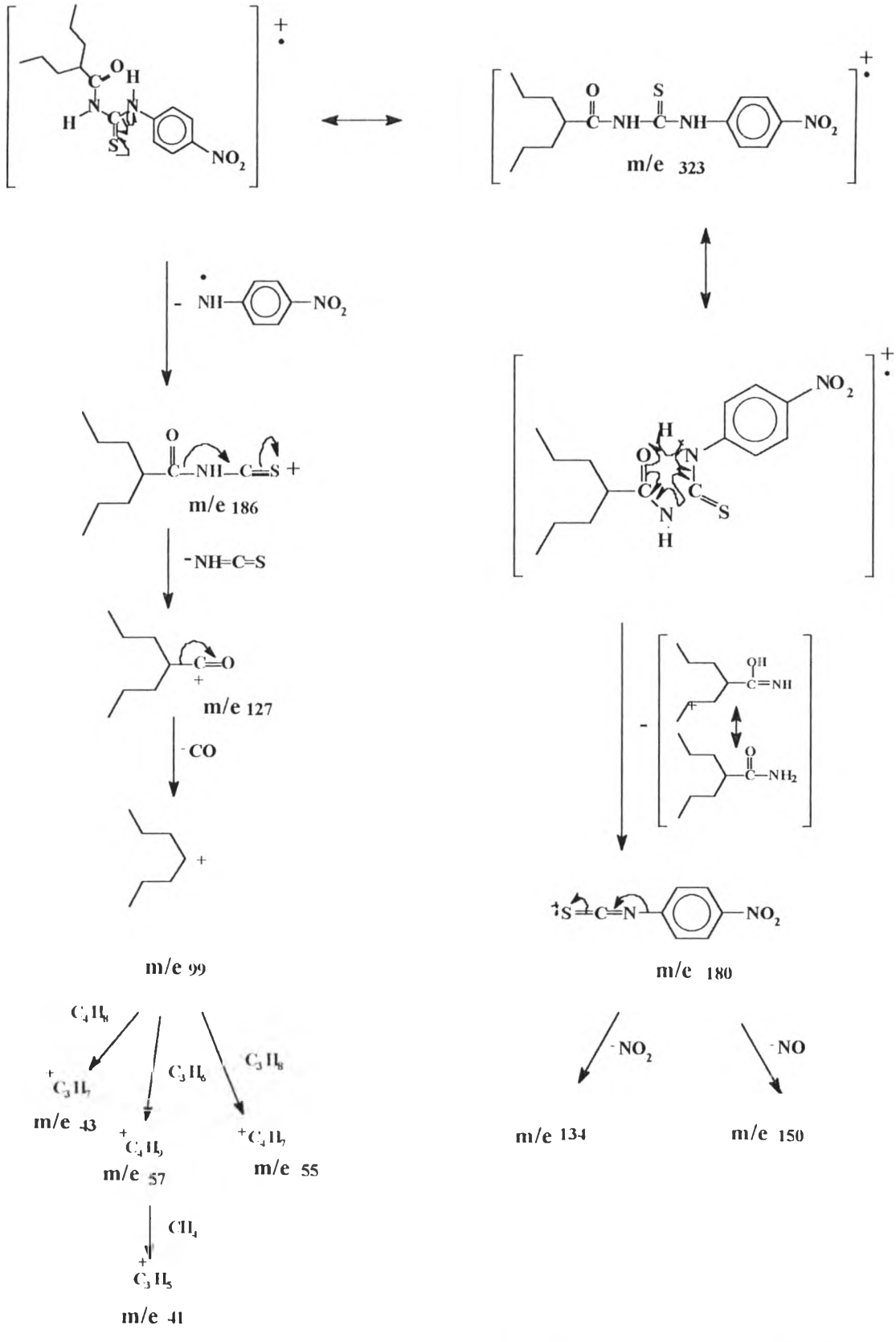


Figure 64 Proposed mass fragmentation of N-(2-propylpentanoyl)-N′-(4-nitrophenyl)thiourea

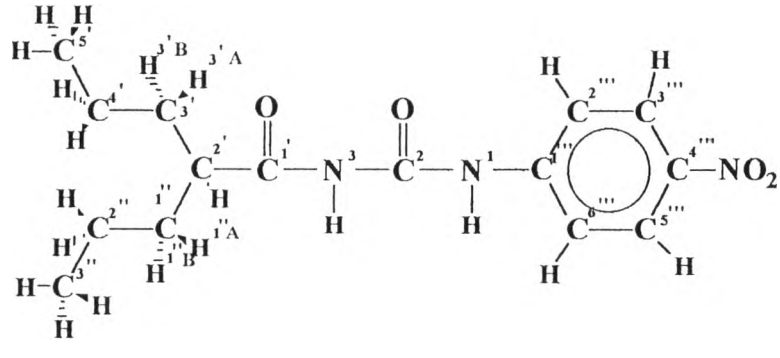
A peak at m/e 180 was propably formed through McLafferty rearrangement and loss of valpramide. Then, the loss of NO_2 produced the peak at m/e 134, while the loss of NO gave the peak at m/e 150.

The breakage of thioamide bond gave the peak at m/e 186 , then the loss of HNCS led the peak at m/e 127. The loss of CO gave 1-propylbutyl carbonium ion (m/e 99) that would decompose by the loss of neutral molecules to give peak fragments at m/e 43, 57, 55 and 41.

N-(2-propylpentanoyl)-N′-(4-nitrophenyl)urea (CU-763-13-008)

This compound can be obtained from oxidation of N-(2-propylpentanoyl)-N′-(4-nitrophenyl)thiourea by alkaline hydrogen peroxide as explained in the first acylurea compound.

This compound can be proved by IR, NMR (^1H, ^{13}C), mass spectroscopy and elemental analysis as follows.



The IR spectrum of N-(2-propylpentanoyl)-N′-(4-nitrophenyl) urea is shown in Figure 46. The peak at 3220 and 3147 cm^{-1} represents N-H stretching vibration. Many peaks in the region of 3000 - 2850 cm^{-1} represent the aliphatic C-H stretching vibration of valproyl part. The peaks at 1700 and 1697 cm^{-1} represent C=O stretching vibration . The peaks at 1513 and 1341 cm^{-1} represent asymmetric and symmetric C-NO_2 stretching vibration, respectively. The peak at 784 cm^{-1} shows C-H out of plane bending.

The 500 MHz ^{1}H-NMR spectrum of N-(2-propylpentanoyl)-N′-(4-nitrophenyl)urea is shown in Figure 47 and 48. The signal at δ 0.95 ppm (H, t, *J*=7.3 Hz) was assigned to six protons on C-5′ and C-3″ . The signal at δ 1.38 ppm (4H, m) was assigned to four protons on C-4′ and C-2″. The signal at δ 1.54 ppm (2H, m) was assigned to H-3′B and H-1″B, while H-3′A and H-1″A appeared as signal at δ 1.70 ppm (2H, m). The signal at δ 2.42 ppm (1H, m) could be assigned to a proton on C-2′. The signals in range 7.70-8.25 ppm represented protons on the phenyl ring. The signal at δ 7.71 ppm (2H, dd, *J* = 9.2, 2.1 Hz) was assigned to two protons on C-2‴ and C-6‴, whereas the signal at δ 8.23 ppm (2H, dd, *J* = 9.2, 2.1 Hz) could be assigned to two protons on C-3‴ and C-5‴. The two broad singlet at δ 9.35 and 11.24 ppm were assigned to two N-H proton at N-1 and N-3 position, respectively.

The 500 MHz ^{13}C-NMR spectrum of N-(2-propylpentanoyl)-N′ (4-nitrophenyl)urea is shown in Figure 49. The peaks at 13.94, 20.64,

34.51, and 48.05 ppm were assigned to C-5′ and C-3″, C-4′ and C-2″, C-3′ and C-1″, and C-2′ of the aliphatic part, respectively. Peaks in the 119- 144 ppm region belonged to the aromatic ring. The peaks at 143.74 and 142.13 ppm were assigned to two quarternary carbons at C-1‴and C-4‴, respectively, which are interchangable. The peaks at 125.02 and 119.62 ppm were assigned to C-3‴ , C-5‴, C-2‴ and C-6‴, respectively, which are interchangable. The two carbonyl carbons at position C-2 and C-1′ appeared the peaks at 151.74 and 179.31 ppm, respectively.

The EIMS spectrum of N-(2-propylpentanoyl)-N′-(4-nitrophenyl)urea is shown in Figure 50. The mass fragmentation of this compound can be explained as shown in Figure 65. The peak at m/e 307 represents M^+ peak. The loss of NO_2 radical gave a peak at m/e 261.

The loss of valpramide through McLafferty rearrangement produced the peak at m/e 164 and the loss of NO gave the peak at m/e 134.

Cleavage of amide bone gave the peaks at 165 and 170. The peak at m/e 127 and 99 were propably formed by loss of HNCO and CO respectively.

The fragment at m/e 99 was 1-propylbutyl carbonium ion that would decompose by the loss of neutral molecules to give peaks at m/e 43, 57, 55 and 41.

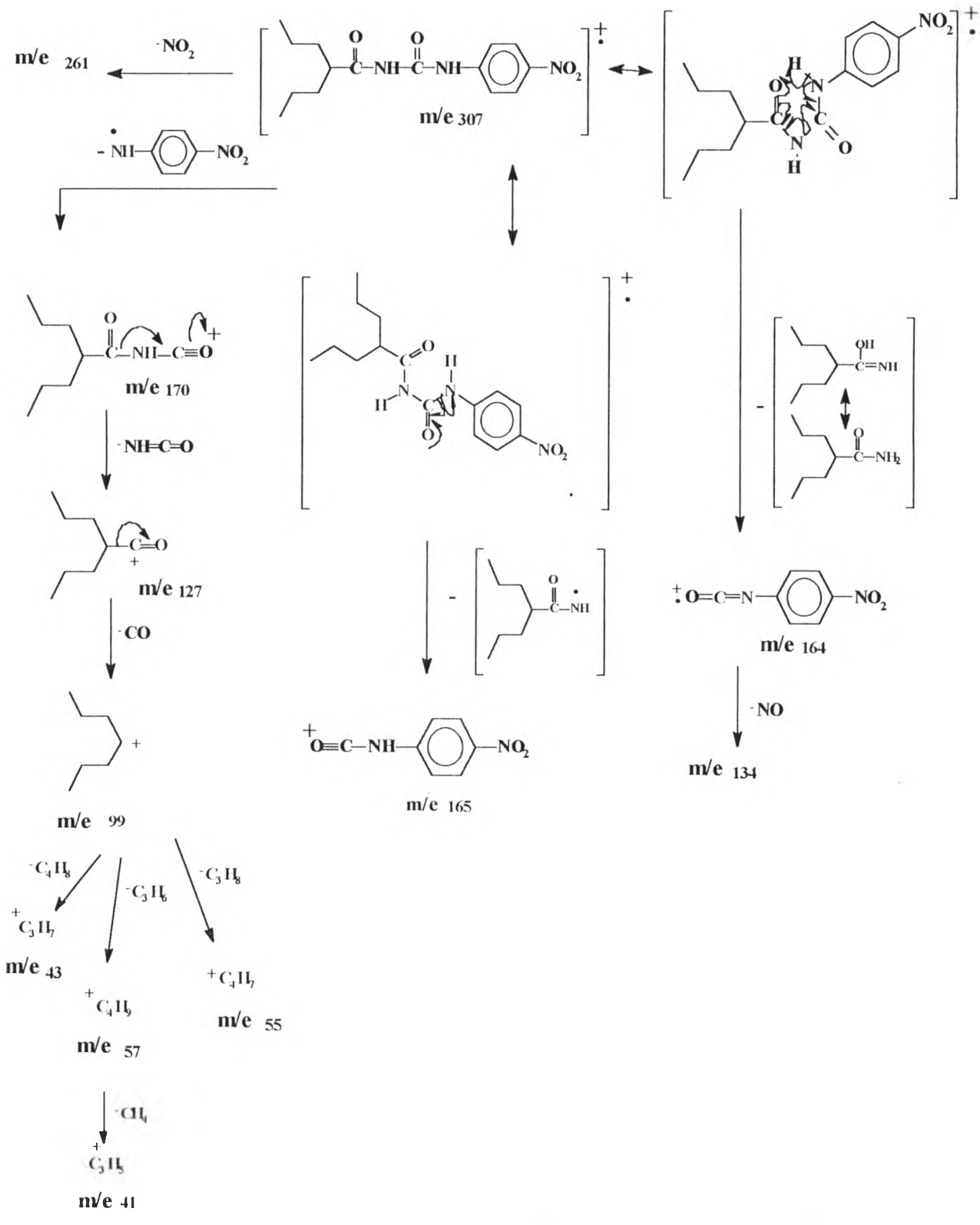


Figure 65 Proposed mass fragmentation of N-(2-propylpentanoyl)-N′-(4-nitrophenyl)urea

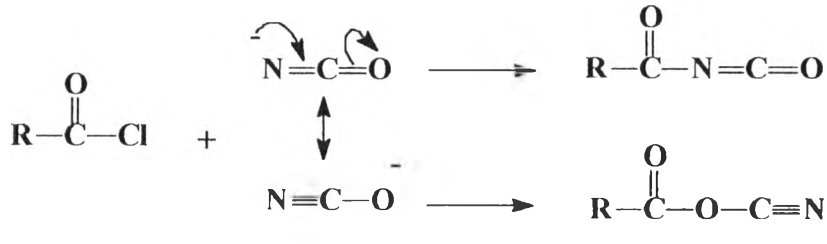
N-(2-propylpentanoyl)-N′-(4-pyridinyl)urea (CU-763-13-009)

In the first attempt, 4-aminopyridine did not react with 2-propylpentanoyl isothiocyanate in acetone to form the corresponding urea. N-(4-pyridinyl)-2-propylpentamide was obtained instead. Therefore, preparation via acylisothiocyanate intermediate had been used.

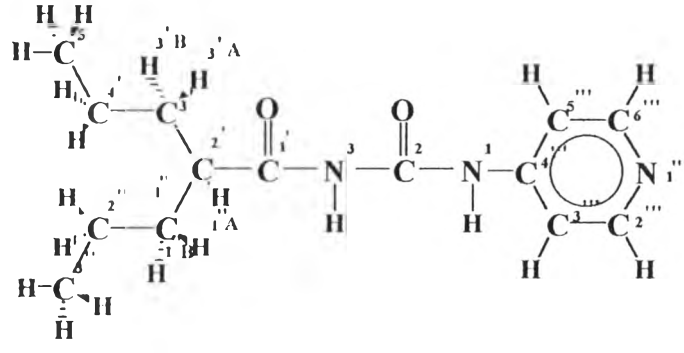
In 1988, Denz and Conben (Denz and Conben, 1988) had studied in an effluence of the catalyst and solvent in condensation of aroyl chloride on sodium cyanate. They found that special catalyst and solvent was essential for efficient satisfactory yield of aroyl urea and acyl urea derivatives.

In this work, valproyl chloride was allowed to react with potassium cyanate in dry dioxane and stannic chloride ($SnCl_4$) as catalyst to facilitating the removal of the chloride leaving group. Moreover, the reaction rate was speed up by reflux condition.

Athough isocyanate is an ambident nucleophile, it was found that reaction with cyanate ion gave only isocyanates and not the isomeric cyanate.



4-Aminopyridine was allowed to attack valproyl isocyanate by nucleophilic addition. The possible reaction can be shown as Figure 66.



The IR spectrum of N-(2-propylpentanoyl)-N′-(4-pyridinyl)urea is shown in Figure 51. The peaks at 3228 and 3148 cm^{-1} represent N-H stretching vibration of imide and amide, respectively. The peaks in the region of 2962-2870 cm^{-1} represent the aliphatic C-H stretching vibration of valproyl part. The peaks at 1734 and 1688 cm^{-1} represent C=O stretching vibration of carbamoyl carbonyl and amide carbonyl. The peak at 1385 cm^{-1} represents C-H bending vibration. The peaks at 1585 cm^{-1} represent ring stretching of pyridine.

The 500 MHz ^{1}H-NMR spectrum of N-(2-propylpentanoyl)-N′-(4-pyridinyl)urea is shown in Figure 52 and 53. The signal at δ 0.94 ppm (H, t, *J*=7.3 Hz) was assigned to six protons on C-5′ and C-3″ . The signal at δ 1.37 ppm (4H, m) was assigned to four protons on C-4′ and C-2″. The signal at δ 1.52 ppm (2H, m) was assigned to H-3′B and H-1″B, while H-3′A and H-1″A appeared as signal at δ 1.70 ppm (2H, m). The signal at δ 2.43 ppm (1H, m) could be assigned to a proton on C-2′. The

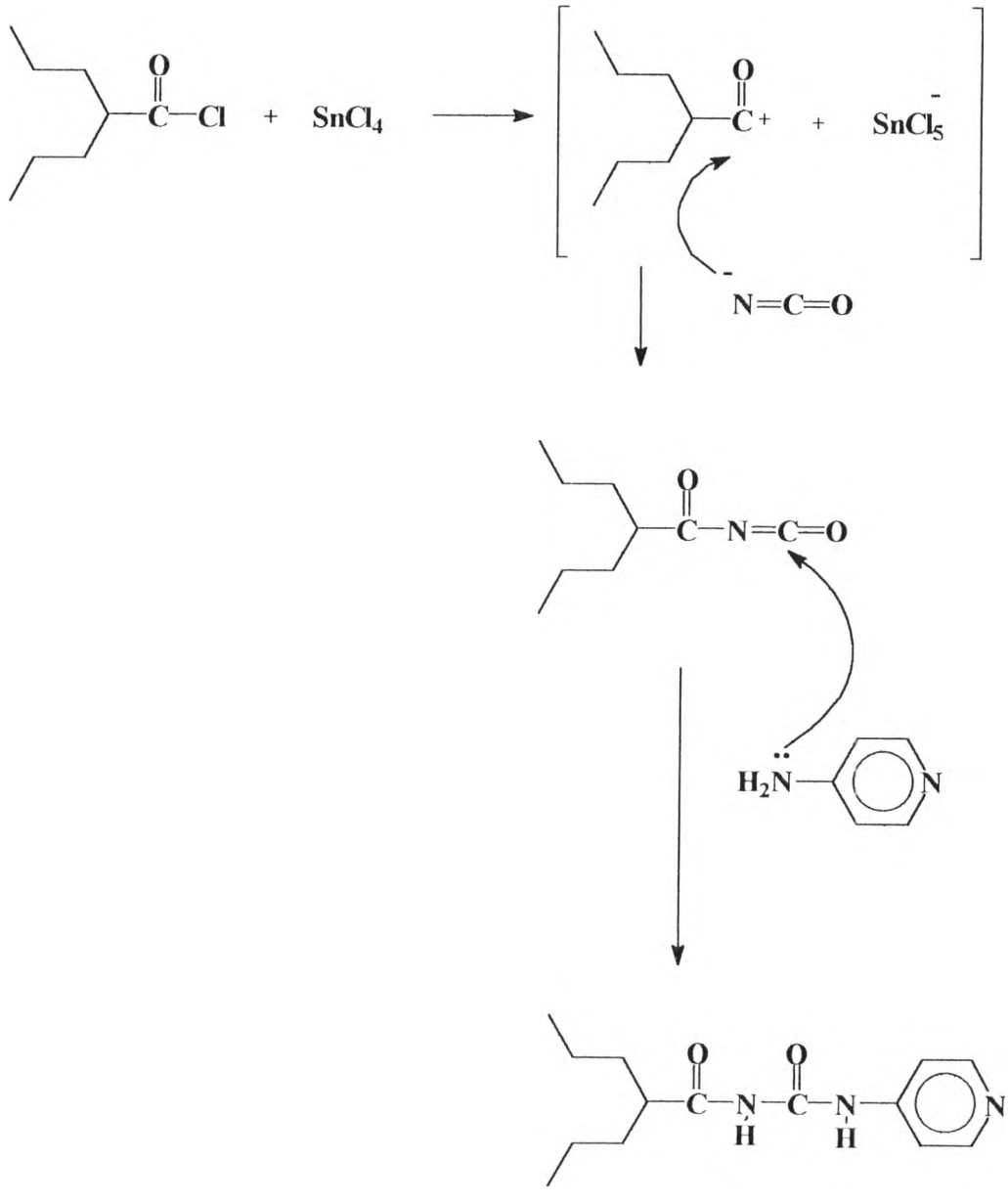


Figure 66 Synthetic pathway of N-(2-propylpentanoyl)-N′-(4-pyridinyl)urea

signals in range 7.45-8.55 ppm represented protons on the phenyl ring. The signal at δ 7.49 ppm (2H, dd, J = 5.8, 1.5 Hz) was assigned to two protons on C-3‴ and C-5‴, whereas the signal at δ 8.52 ppm (2H, d, J = 5.8 Hz) could be assigned to two protons on C-2‴ and C-6‴. The two broad singlet at δ 9.73 and 11.06 ppm were assigned to two N-H proton at N-1 and N-3 position, respectively.

The 500 MHz ^{13}C-NMR spectrum of N-(2-propylpentanoyl)-N′ (4-pyridinyl)urea is shown in Figure 54. The peaks at 13.93, 20.60, 34.52 and 47.86 ppm were assigned to C-5′ and C-3″, C-4′ and C-2″, C-3′ and C-1″, and C-2′ of the aliphatic part, respectively. Peaks in the 114-150 ppm region belonged to the aromatic ring. The peaks at 144.58 ppm was assigned to the quarternary carbon at C-4‴. The peaks at 150.44 and 114.16 ppm were assigned to C-2‴, C-6‴ and C-3‴, C-5‴, respectively, which are interchangable. The two carbonyl carbons at position C-2 and C-1′ appeared the peaks at 151.95 and 179.38 ppm, respectively.

The EIMS spectrum is shown in Figure 55. The Mass fragmentation can be proposed by Figure 67. A peak at m/e 120 is propably formed through McLafferty rearrangement to loss of valpramide. The loss of cyanic radical gave a peak at m/e 78.

Double Mclafferty rearrangement at pyridine ring and aliphatic side chain gave peak at m/e 186 and 144, respectively. Then, the loss of H_2O produced a peak at m/e 126.

The amide bond cleavage gave peak at m/e 170. Then, the loss of isocyanic acid led a peak at m/e 127. Elimination of carbon monoxide (CO) gave a peak at m/e 99 which is 1-propylbutyl carbonium ion that would decompose by loss of neutral molecules to give peaks at m/e 43, 57, 55 and 41.

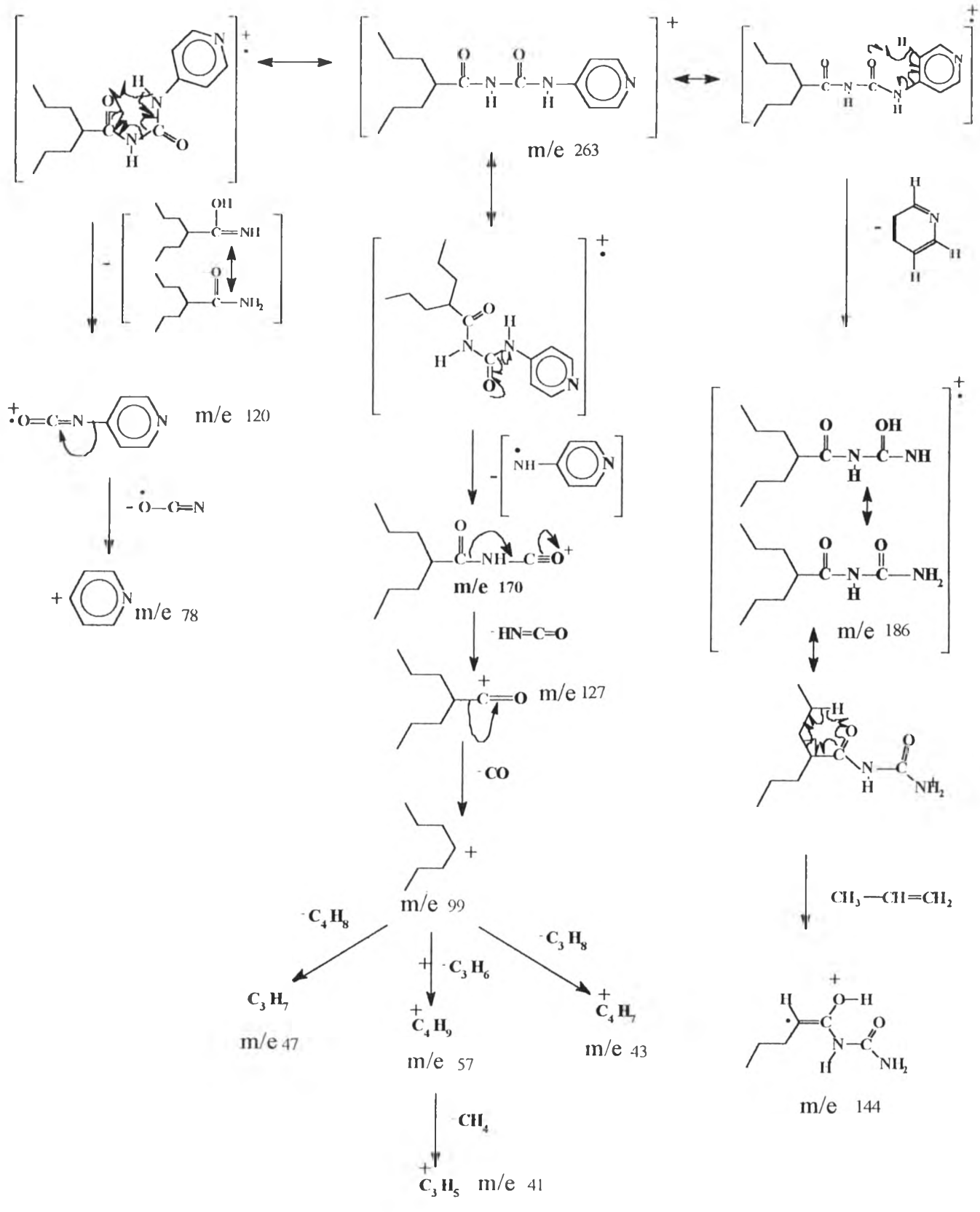


Figure 67 The proposed mass fragmentation of N-(2-propylpentanoyl)-N′-(4-pyridinyl)urea