CHAPTER III

EXPERIMENTS

INSTRUMENTS

1. Elemental Analyzer : Perkin Elmer 240C (The Scientific and Technological Research Equipment Center, Chulalongkorn University).

2. Infrared Spectrophotometer : Shimazu IR-440 (The Scientific and Technological Research Equipment Center, Chulalongkorn University).

3. Nuclear Magnetic Resonance Spectrophotometer : Jeol FX 90 Q (90 MHz) (The Scientific and Technological Research Equipment Center, Chulalongkorn University).

4. Mass Spectrometer : Jeol FX 3000 double focusing (The Scientific and Technological Research Equipment Center, Chulalongkorn University).

5. Melting Point Apparatus : Buchi capillary melting point apparatus.

CHEMICALS

Propylbromide (Fluka chemie AG)

Diethylmalonate (Fluka chemie Co.)

2-Pyrrolidone (Synthesized by Assistant Professor Somkiat Rujirawat)

2-Dimethylaminoethanol (Fluka chemie AG.)

Formaldehyde (37% solution) (Mallinckrodt, Inc.)

Diethylamine (May & Baker Ltd.)

Urea (May & Baker Ltd.)

Thiourea (May & Baker Ltd.)

Guanidine hydrochloride (Fluka AG.)

Potassium thiocyanate (BDH chemicals Ltd.)

Ammonia Solution (25%) (Merck)

Sodium Valproate (Supported by Pharminar Co. Ltd.)

All solvents used were either B.P. or laboratory grade.

2-Propylpentanoic acid (Valproic acid)

A 12.80 g (80 mmole) of diethyl malonate was added to a solution of sodium ethoxide, which was prepared by dissolving 3.68 g (0.16 mole) of sodium metal in 80 ml absolute ethanol. The mixture was stirred for 30 minutes, then 19.68 g (0.16 mole) of propylbromide was added. The reaction vessel was fitted with a reflux condenser and the mixture was heated under gentle reflux for 3 hours. The oily liquid was separated and collected at 80 - 85^{o}C by distillation under reduced pressure (4 mmHg). The distillate was then added methanol and aqueous sodium hydroxide (1 g in 1.5 ml H_2O) and the mixture was heated under reflux for 5 hours. After cooling, most of the methanol and H_2O were removed in vacuo. Then, 50 ml of H_2O was added, the mixture was acidified by addition of 20% HCl. The aqueous phase was then extracted with

diethyl ether; dried ($MgSO_4$), and evaporated. Finally, decarboxylation of this compound was carried out under mild conditions according to the method of Touissaint *et al*. (1986). Thus, the acetonitrile was added to the obtained compound, then copper (I) oxide (10 mg) was added and the mixture was heated under reflux for 10 hours. The solvent was removed in vacuo and the crude product was treated with H_2O and the mixture was extracted with diethyl ether. Purification of this compound was carried out by distillation under reduced pressure. The oily liquid was collected at 98 - 100^oC (4 mmHg). The overall yield was approximately 4.44 g (40% yield).

The target product obtained was confirmed by comparing with authentic sample using thin-layer chromatography.

(N,N-Dimethylaminoethyl)-2-propylpentanoate

A 5.76 g (40 mmole) of 2-propylpentanoic acid was dropwisely added to a solution of 5.20 g (3.19 ml) of thionyl chloride, then the mixture was stirred at room temperature overnight. The excess thionyl chloride was removed in vacuo to yield the crude acyl chloride, which was not further purified. The acid chloride was then added dropwisely into a 3.56 g solution of N,N-dimethylaminoethanol in benzene which was already added an equimolar potassium carbonate. The mixture was refluxed for a peroid of 2 hours. The white solid was

filtered off and the excess N,N-dimethylaminoethanol was removed by distillation under reduced pressure. The oily product was added to a solution of sodium bicarbonate (3 x 50 ml). The mixture was extracted with chloroform, washed with H_2O (2 x 50 ml) and the solvent was evaporated to yield a clear oily liquid 2.58 g (30% yield).

IR (Figure 3) : 2780 - 2980 cm^{-1} (C-H)
(KBr Demountable cell) 1735 cm^{-1} (C=O)
1163 cm^{-1} (C-O)
1458 cm^{-1} ($(CH_3)_2$-N, Scissoring)

^{1}H-NMR (Figure 4) : 0.92 (m, 6H)
($CDCl_3$) 1.38 - 1.61 (m, 8H)
2.29 (s, 7H, $-N(CH_3)_2$, -CH-)
2.57 (t, 2H, J = 5.8 Hz, $-CH_2-N$)
4.19 (t, 2H, J = 5.8 Hz, $-O-CH_2-$)

2-Propylpentamide

A 5.76 g (40 mmole) of 2-propylpentanoic acid was dropwisely added to a solution of 5.20 g (3.19 ml) of thionyl chloride, then the mixture was stirred at room temperature overnight. The excess thionyl chloride was removed in vacuo to yield the crude acyl chloride, which was not further purified. The acid chloride was then

added dropwisely into an excess concentrated ammonia solution, which had been cooled in an ice bath. The mixture was stirred until the white fume was not evolved, then standed for a while. The white solid was collected by filtration, then washed with water and dried. Recrystallization from hexane gave 4.86 g (85%) of product, mp 125-126 C.

IR (Figure 5)	:	3400, 3200 cm^{-1} ($-NH_2$)
(KBr pellet)		2850 - 2980 cm^{-1} (C-H)
		1650 cm^{-1} (C=O)

(N,N-Diethylaminomethyl)-2-propylpentamide

A 5.73 g (40 mmole) of 2-propylpentamide was allowed to react with 4 ml of 37% aqueous formaldehyde and 2.88 g (40 mmole) of diethylamine with a little amount of hydrochloric acid in absolute ethanol. The mixture was stirred under reflux condition for a peroid of 10 hours and then allowed to cool. The purification was performed by column chromatographic technique, mobile phase used was ethyl acetate and stationary phase was silica gel. The overall yield was about 4.66 g (51%).

IR (Figure 6)	:	3320 cm^{-1} (NH)
(KBr Demountable cell)		1650 cm^{-1} (C=O)
		1540 cm^{-1} (NH bending)
		1200 cm^{-1} (C-N)

^{1}H-NMR (Figure 7) : 0.92 (m, 6H, 2-CH_3)

($CDCl_3$) 1.22 (t, 6H, J = 7 Hz, 2-CH_3)

1.38 - 1.61 (m, 8H, 2-CH_2-CH_2-)

5.89 (b, 1H, -NH)

4.20 (d, 2H, NH-CH_2-N)

2.50 (q, 4H, -N(CH_2)(CH_2), J=7 Hz)

2.10 (m, 1H, CH-CO-)

Mass spectrum (Figure 8)

EIMS m/e = 228 M^+ (2.04), 86 (57.25), 72 (100)

N(2'-Propylpentanoyl)-2-pyrrolidinone

A 5.76 g (40 mmole) of 2-propylpentanoic acid was dropwisely added to a solution of 5.20 g (3.19 ml) of thionyl chloride, then the mixture was stirred at room temperature overnight. The excess thionyl chloride was removed in vacuo to yield the crude acyl chloride, which was not further purified. The acid chloride was then added dropwisely into a suspension of pyrrolidinone sodium, which was prepared by treating 3.36 g (40 mmole) of pyrrolidinone with NaH in anhydrous benzene, the mixture was stirred at room temperature for 3 hours. The white solid was filtered off and the filtrate was evaporated. The oily product was added to a solution of sodium bicarbonate (3 x 50 ml). The mixture was extracted

with chloroform, washed with H_2O (2 x 50 ml) and the solvent was evaporated. The residual oily product was purified with a silica gel column, eluted with chloroform : hexane (3:1). The overall yield was about 7.60 g (90%).

IR (Figure 9) : 2890-2980 cm^{-1} (C-H)
(KBr Demountable cell) 1740 cm^{-1} (C=O lactam)
1680 cm^{-1} (C=O amide)
1350 cm^{-1} (C-N)

^{1}H-NMR (Figure 11) : 0.92 (6H, 2-CH_3)
($CDCl_3$) 1.38 - 1.61 (m, 8H, 2-CH_2-CH_2-)
2.01 (q, 2H, J = 7.3 Hz)
2.61 (t, 2H, J = 7.3 Hz)
3.81 (t, 3H, J = 7.3 Hz)

^{13}C-NMR (Figure 10)

Mass spectrum (Figure 13)
EIMS m/e = 211 M^+ (15.77), 97 (53.67),
86 (100)

N(2-Propylpentanoyl) urea

A 5.76 g (40 mmole) of 2-propylpentanoic acid was dropwisely added to a solution of 5.20 g (3.19 ml) of thionyl chloride, then the mixture was stirred at room temperature overnight. The excess thionyl chloride was removed in vacuo to yield the crude acyl chloride, which was not further purified. The acid chloride was then

added dropwisely into a mixture of 2.40 g urea and 5.50 g of potassium carbonate in dry benzene. The mixture was refluxed for about 10 hours. The mixture was filtered immediately and the white precipitate formed upon cooling was collected, then washed with cooled benzene and dried. Recrystallization from hexane yielded 5.65 g (76%) of product mp 193-194 C.

IR (Figure 15)	:	3400 cm^{-1} (NH imide)
(KBr Demountable cell)		3340, 3240 cm^{-1} (NH amide)
		1700 cm^{-1} (C=O imide)
		1680 cm^{-1} (C=O amide)
		1590 cm^{-1} (NH bending)
^{1}H-NMR (Figure 16)	:	0.90-0.97 (m, 6H, 2-CH_3)
($CDCl_3$)		1.20 - 1.66 (m, 8H, 2-CH_2-CH_2-)
		2.24 (m, 1H, -CH-)
		5.48 (b, 1H, NH)
		8.39 (b, 1H, NH)
		9.20 (b, 1H, NH)
^{1}H-NMR (Figure 18)	:	0.90 - 0.97 (m, 6H, 2-CH_3)
(DMSO-d_6)		1.20 - 1.66 (m, 8H, 2-CH_2-CH_2)
		2.24 (m, 1H, -CH-)
		5.99 (b, 1H, NH)
		8.39 (b, 1H, NH)
		9.67 (b, 1H, NH)

Mass spectrum : (Figure 19)

EIMS m/e = 187 (0.94), 157 (3.44), 144 (55.93), 115 (100)

N(2-Propylpentanoyl)thiourea

A 5.76 g (40 mmole) of 2-propylpentanoic acid was dropwisely added to a solution of 5.20 g (3.19 ml) of thionyl chloride, then the mixture was stirred at room temperature overnight. The excess thionyl chloride was removed under vacuo and the acid chloride obtained was added to a 3.88 g of potassium thiocyanate in toluene. The mixture was stirred under reflux condition for about 12 hours. After cooling, the white solid was filtered off and the slightly yellow liquid was stirred, cooled in an ice bath. Then, a little excess of concentrated ammonia solution was added for a peroid of half an hour. The mixture was stirred for one hour. Then, the mixture was washed with H_2O (3 x 30 ml), the aqueous layer was discarded and the solvent was evaporated in vacuo to yield crude product. Purification was acheived by column chromatographic technique using silica gel as a stationary phase and hexane : ethylacetate (5:1) as a mobile phase. The overall yield was 3.88 g (48%) of product mp 81 - 82 C.

IR (Figure 21) : 3350 cm^{-1} (NH)

(KBr Demountable cell) 1700 cm^{-1} (C=O)

1625 cm^{-1} (NH bending)

1300 cm^{-1} (C=S)

^{1}H-NMR (Figure 22) : 0.91-0.98 (m, 6H, 2-CH_3)

($CDCl_3$) 1.20 - 1.83 (m, 8H, 2-CH_2-CH_2-)

2.25 (m, 1H, -CH-)

7.35 (b, 1H, NH)

9.20 (b, 1H, NH)

10.02 (b, 1H, NH)

Mass spectrum : (Figure 24)

EIMS m/e = 202 M^+ (50.52), 126 (22.18),

77 (38.39), 57 (100)