REACTION OF β-, γ-, AND δ-CHLOROALKANAMIDES WITH POTASSIUM *tert*-BUTOXIDE IN TETRAHYDROFURAN: ELIMINATION, AND LACTAMIZATION

Eng Chi Wang* and Hucy-Jen Lin

School of Chemistry, Kaoashiung Medical College, Kaoshiung City 807, Taiwan, ROC

Abstract– γ- and δ-Chloroalkanamides were found to undergo lactamization readily when treated with potassium *tert*-butoxide in tetrahydrofuran. Raising the reaction temperature may encourage S_N2 displacement reaction. On the other hand β-chloroalkanamides only undergo elimination, followed by dimerization and trimerization of the acrylamide initially formed.

INTRODUCTION

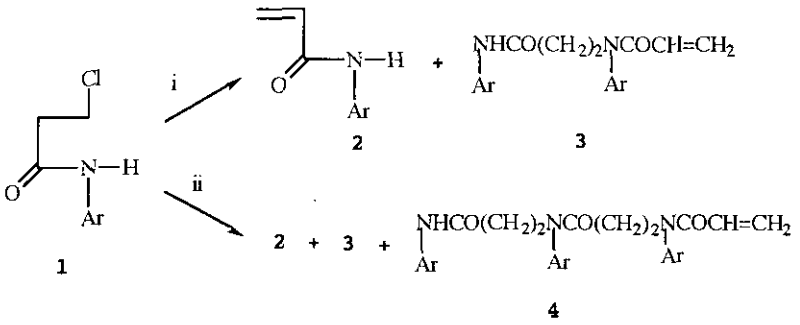
Lactams can be prepared from haloamides by treatment with a variety of bases, ranging from sodium hydride in *N,N*-dimethylformamide/dichloromethane,[1,2] sodium[3] or sodium amide[4] in liquid ammonia, dismyl ion generated from sodium hydride or potassium *tert*-butoxide in dimethyl sulfoxide,[3,5] potassium hydroxide-tetrabutylammonium bromide in mixed solvents[6] and others.[7] These methods have been used in the synthesis of 3-membered, β-, γ- and δ-lactams respectively. Surprisingly, no systematic studies on the use of potassium *tert*-butoxide in tetrahydrofuran on affecting the cyclization of β-, γ- and δ-chloroalkanamides have been reported. The potassium *tert*-butoxide-tetrahydrofuran system must certainly be more desirable than the potassium *tert*-butoxide-dimethyl sulfoxide, sodium hydride-*N,N*-dimethylformamide and sodium amide-ammonia system. We now systematically investigate the competing elimination, polymerization and lactamization reactions that take place when β-, γ- and δ-haloalkanamides were treated with potassium *tert*-butoxide at 0 °C or room temperature.

RESULTS AND DISCUSSION

Knunyants and Ganbaryan[3] have reported the lactamization of β-halopropanamide with sodium and liquid ammonia. When *N*-methoxyphenyl-β-chloropropanamide (**1a**), was treated with potassium *tert*-butoxide in tetrahydrofuran at 0 °C, no lactamization product was obtained. Instead we obtained the elimination product, *N*-(methoxyphenyl)acrylamide (**2a**) (81%) together with the dimer (**3a**) (18.5 %). The structure of **3a** can be elucidated from the ^{1}H-NMR which showed two singlet methoxy at δ 3.76 and 3.80; and three olefinic protons at δ 5.52, 6.02 and 6.34. Its ^{13}C-NMR spectrum showed two typical carbonyl carbons at δ 166.46 and 168.62. When the reaction was carried out at room temperature, we also obtained the trimer (**4a**) (27%) together with **2a** (34%) and **3a** (30%). ^{1}H-NMR of trimer **4a** showed two ($COCH_2$) signals at δ 2.29 and 2.61 as triplet, the two methoxy signals at δ 3.78 and 3.82, two (NCH_2)

signals at δ 3.94 and 3.97, together with three olefinic signals at δ 5.50, 5.99 and 6.31. The ^{13}C-NMR showed three carbonyl signals at δ 166.02, 169.46 and 171.43. This is the first time that linear polymerization products have been isolated. *N*-Phenyl-β-chloropropanamide (**1b**) had the same chemical behavior toward potassium *tert*-butoxide as comparing with **1a**. While treated with potassium *tert*-butoxide at 0 °C, it produced *N*-phenylacrylamide (**2b**) (81 %) and the dimer (**3b**) (19 %). When the reaction was run at room temperature, it gave **2b** (26 %), **3b** (38 %) and the trimer (**4b**) (16 %) (Scheme 1).

Scheme 1

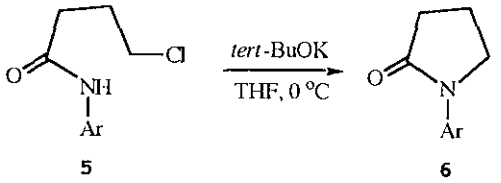


a. Ar=4-MeOPh b. Ar=Ph

i. *tert*-BuOK, THF, 0 °C ii. *tert*-BuOK, THF, rt

We next focus our attention on the reaction of γ-chlorobutyramides (**5a-e**) with potassium *tert*-butoxide in THF at 0 °C. This was found to afford *N*-substituted γ-lactams (**6a-e**) in good yield (>90 %). The reaction at room temperature did not significantly improve the yield beyond 90%. The yield of γ-lactams under our conditions is much more superior to that reported by Biswas and Miller[8] using NaH/DMF/CH_2Cl_2 for the lactamization of *N*-substituted γ-lactam which gave yield ranging from 20-60% (Scheme 2).

Scheme 2



a. Ar=Ph d. Ar=Bn

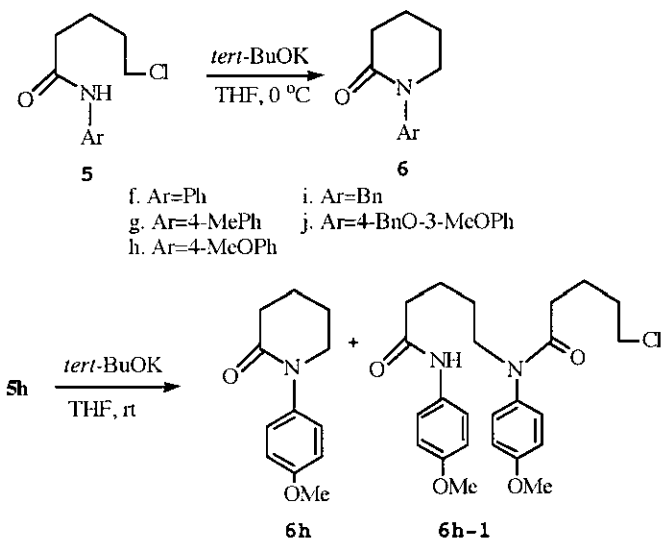
b. Ar=4-MePh e. Ar=4-BnO-3-MeOPh

c. Ar=4-MeOPh

There have been few reports on the synthesis of δ-lactam. Manhas and Jeng[4] have used sodium and ammonia for the cyclization of *N*-phenylvaleramide to give *N*-phenyl-δ-lactam in 61% yield. We have reported the diastereoselective iodine induced lactamization of δ,ε-unsaturated thioimidates to give δ-lactam in moderate yield.[9] We thus studied the lactamization of δ-chloroalkanamides with potassium *tert*-butoxide

in THF. When compounds (**5f-j**) reacted under this conditions at 0 °C, high yields of the corresponding δ-lactams (**6f-j**) were obtained. When the reaction of **5h** with potassium *tert*-butoxide was carried out at room temperature, the δ-lactam (**6h**) was obtained in 68% yield together with dimerization product (**6h-1**) (10%). The ^{1}H-NMR of **6h-1** showed four triplet signals of 2-protons at δ 2.06, 2.44, 3.42 and 3.74, indicating the presence of four methylenes having two protons in the neighbor carbons; two singlet signals of 3-protons at δ 3.79 and 3.83, indicating the presence of two methoxy groups; and no olefinic proton for the elimination product was observed. The ^{13}C-NMR of **6h-1** showed two signals of carbonyl groups at δ 171.48 and 173.30. Furthermore in MS spectra, it showed the ratio of the relative intensity of $[M+2]^+$: $[M]^+$ = 1 : 3 which confirmed the presence of a chlorine atom, and the molecular ion at m/z 446, corresponding to the molecular formula, $C_{24}H_{31}N_2O_4Cl$. These results elucidated the structure of **6h-1.** Raising the temperature thus decreased lactamization, whereby dimerization by S_N2 displacement reaction becomes competitive. In this case the δ-chloroalkanamides did not undergo elimination of the chloride to give olefin (Scheme 3).

Scheme 3



CONCLUSION

The potassium *tert*-butoxide-THF system has been found to be a good system for the synthesis of *N*-substituted γ- and δ-lactams. Raising the reaction temperature was found to encourage S_N2 displacement reaction. On the other hand, β-chloropropanamide only undergoes elimination and polymerization under this conditions.

EXPERIMENTAL SECTION

Melting points(Yanaco micro-melting-point apparatus) were uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Varian Gemini-200 or Varian Unity plus 400 spectrometer; chemical shifts are measured in ppm with respect to TMS. Elemental analyses were recorded on a Heraeus CHN-O Rapid analyzer. MS

spectra were recorded on Hewlett Packard 5989A Mass spectrometer. HRMS spectra were run on Vg 70-250s GC/MS. Silica gel(70-230 mesh suitable for column chromatography) and precoated silica gel 60 F-254 plates for thin layer chromatography were purchased from E. Merck. UV light (254 nm) was used to detect the UV-absorption spots on TLC plates after development.

General procedure for the reaction of *N*-substituted β-chloropropanamides (1a-b) with potassium *tert*-butoxide at 0 °C to give 2a-b and 3a-b.

Under dry nitrogen, the mixture of *N*-substituted β-chloropropanamide (**1a-b**) (5 mmol) and potassium *tert*-butoxide (0.57 g, 5.05 mmol) was suspended in anhydrous THF (30 mL) at 0 °C for 2 h. At the end of reaction, the solution was poured into separating funnel, mixed with ethyl acetate (100 mL), and followed by washing with brine water (10 mL X 5). The seperated organic layer was dried with anhydrous magnesium sulfate, and then filtered. The filtrates were concentrated under reduced pressure to give oily residues. The residues were eluted through silica gel column using EtOAc : Hexane (1:2) as solvent to give pure compounds (**2a-b**) and (**3a-b**) respectively.

***N*-(4-Methoxyphenyl)acrylamide (2a)**

Pure (**2a**) (0.72 g, 81%) was obtained as colorless crystals; mp 100-101 °C (EtOAc + hexane); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.78 (s, 3H, OCH_3), 5.69 (dd, *J* = 2; 10 Hz, 1H, olefinic H), 6.26 (dd, *J* = 10; 17 Hz, 1H, olefinic H), 6.40 (dd, *J* = 2; 17 Hz, 1H, olefinic H), 6.83, 7.48 (d, *J* = 9 Hz, each 2H, Ar-H), 7.91 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 43.58 (OCH_3), 126.62 (olefinic C), 127.47 (olefinic C), 127.80, 128.63, 130.65, 138.02 (Ar-C), 165.43 (C=O); MS (EI), *m/z* 177 (M^+). *Anal.* Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.71; H, 6.29; N, 7.90.

***N*-Phenylacrylamide (2b)**

Pure (**2b**) (0.60 g, 81%) was obtained as colorless crystals; mp 106-108 °C (EtOAc + hexane); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 5.75 (dd, *J* = 2; 10 Hz, 1H, olefinic H), 6.26 (dd, *J* = 10; 17 Hz, 1H, olefinic H), 6.44 (dd, *J* = 2; 17 Hz, 1H, olefinic H), 7.12 (t, *J* = 7 Hz, 1H, ArH), 7.33 (t, *J* = 8 Hz, 2H, Ar-H), 7.58 (d, *J* = 8 Hz, 2H, ArH), 7.56 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 120.03 (olefinic C), 124.56 (olefinic C), 127.76, 129.02, 131.16, 137.69 (Ar-C), 163.62 (C=O); MS (EI), *m/z* 147 (M^+). *Anal.* Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.42; H, 6.26; N, 9.35.

Dimer (3a)

Pure dimer (**3a**) (0.15 g, 18.5%) was obtained as a liquid of high viscosity; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.69 (t, *J* = 7 Hz, 2H, $COCH_2$), 3.76 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.13 (t, *J* = 7 Hz, 2H, NCH_2), 5.52 (dd, *J* = 2; 10 Hz, 1H, olefinic H), 6.02 (dd, *J* = 10; 17 Hz, 1H, olefinic H), 6.34 (dd, *J* = 2; 17 Hz, 1H, olefinic H), 6.88, 6.81 (d, *J* = 9 Hz, each 2H, Ar-H), 7.07, 7.47(d, *J* = 9 Hz, each 2H, Ar-H), 9.16 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 35.72 ($CO\underline{C}H_2$), 46.11 (NCH_2), 55.24 (OCH_3), 55.33 (OCH_3), 113.76 (olefinic C), 114.74 (olefinic C), 121.48, 127.84, 128.35, 129.06, 131.49, 133.58, 155.92, 159.07 (Ar-C), 166.46 (C=O), 168.62 (C=O). HRMS: Calcd for $C_{20}H_{22}N_2O_4$: 354.1580. Found: 354.1581.

Dimer (3b)

Pure dimer (**3b**) (0.14 g, 19%) was obtained as a liquid of high viscosity; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.73 (t, *J* = 7 Hz, 2H, $COCH_2$), 4.17 (t, *J* = 7 Hz, 2H, NCH_2), 5.53 (dd, *J* = 2; 10 Hz, 1H, olefinic H), 6.00 (dd, *J* = 10; 17 Hz, 1H, olefinic H), 6.36 (dd, *J* = 2; 17 Hz, 1H, olefinic H), 7.06-7.55 (m, 8H, Ar-H), 7.57 (d, *J* = 8 Hz, 2H, Ar-H), 9.23 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 35.97 ($CO\underline{C}H_2$), 46.20 (NCH_2), 119.83 (2 X olefinic C), 123.85, 127.94, 128.15, 128.31, 128.67, 129.68, 138.26, 141.03 (Ar-C), 166.28 (C=O), 168.87 (C=O). HRMS: Calcd for $C_{18}H_{18}N_2O_2$: 294.1368. Found: 294.1371.

General procedure for the reaction of *N*-substituted β-chloropropanamides (1a-b) with potassium *tert*-butoxide at room temperature to give 2a-b, 3a-b and 4a-b.

The procedure is the same as described above except reacting at rt (25-30 °C). Besides the products, **2a** (0.30 g, 34%) and **3a** (0.24 g, 30%); **2b** (0.27 g, 37%) and **3b** (0.28 g, 38%) were obtained, it gave pure trimer (**4a**) (27 %) and **4b** (16 %) respectively.

Trimer (4a)

Pure trimer (**4a**) (0.24 g, 27%) was obtained as a liquid of high viscosity; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.29 (t, *J* = 7 Hz, 2H, $COCH_2$), 2.61 (t, *J* = 7 Hz, 2H, $COCH_2$), 3.78 (s, 6H, 2 X OCH_3), 3.82 (s, 3H, OCH_3), 3.94 (t, *J* = 7 Hz, 2H, NCH_2), 3.97 (t, *J* = 7 Hz, 2H, NCH_2), 5.50 (dd, *J* = 2; 10 Hz, 1H, olefinic H), 5.99 (dd, *J* = 10; 17 Hz, 1H, olefinic H), 6.31 (dd, *J* = 2; 17 Hz, 1H, olefinic H), 6.78-6.91 (m, 6H, Ar-H), 7.10-7.18(m, 4H, Ar-H), 7.54(d, *J* = 9 Hz, 2H, Ar-H), 9.37(s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 32.01 ($CO\underline{C}H_2$), 36.11 ($CO\underline{C}H_2$), 46.54 (NCH_2), 47.02 (NCH_2), 55.34 (3 X OCH_3), 113.89 (olefinic C), 114.59 (olefinic C), 114.87, 121.36, 127.43, 128.44, 128.91, 129.50, 131.85, 133.87, 134.97, 155.90 and 159.01 (Ar-C), 166.02, 169.46 and 171.43 (C=O). HRMS: Calcd for $C_{30}H_{33}N_3O_6$: 531.2369. Found: 531.2366.

Trimer (4b)

Pure trimer (**4b**) (0.12 g, 16%) was obtained as a liquid of high viscosity; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.30 (t, *J* = 7 Hz, 2H, $COCH_2$), 2.65 (t, *J* = 7 Hz, 2H, $COCH_2$), 4.00 (m, 4H, 2 X NCH_2), 5.51 (dd, *J* = 2; 10 Hz, 1H, olefinic H), 5.98 (dd, *J* = 10; 17 Hz, 1H, olefinic H), 6.34 (dd, *J* = 2; 17 Hz, 1H, olefinic H), 7.08 (t, *J* = 7 Hz, 1H, Ar-H), 7.18-7.43 (m, 12H, ArH), 7.63 (d, *J* = 8 Hz, 2H, ArH), 9.41 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 32.17 ($CO\underline{C}H_2$), 36.41 ($CO\underline{C}H_2$), 46.55 (NCH_2), 47.09 (NCH_2), 119.79 (2 X olefinic C), 123.81, 127.74, 127.84, 128.02, 128.23, 128.45, 128.79 129.56, 129.88, 138.58, 141.28, 142.34 (Ar-C), 165.83, 169.76 and 171.12 (C=O). HRMS: Calcd for $C_{27}H_{27}N_3O_3$: 441.2052. Found: 441.2052.

General procedure for the reaction of *N*-substituted γ-chlorobutanamides (5a-e) and *N*-substituted δ-chloropentanamides (5f-j) with potassium *tert*-butoxide.

Under dry nitrogen, the mixture of chloroamides (**5a-j**) (5 mmol) and potassium *tert*-butoxide (0.57 g, 5.05 mmol) was suspended and stirred in anhydrous THF (30 mL) at 0 °C for 2 h. At the end of reaction, the solution was poured into separating funnel, mixed with ethyl acetate (100 mL), followed by washing

with brine water (10 mL X 5). The separated organic layer was dried with anhydrous magnesium sulfate, and then filtered. The filtrates were concentrated under reduced pressure to give oily residues. The residues were eluted through a silica gel column using EtOAc : Hexane (1:2) as solvent to give pure compounds (**6a-j**) respectively.

***N*-Phenyl-γ-butyrolactam (6a)**[10]

Pure **6a** (0.78 g, 95%) was obtained as colorless crystals; mp 67-68 °C (EtOAc + Hexane); IR (Nujol), 1691 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.16 (m, 2H, $COCH_2C\underline{H}_2CH_2$), 2.62 (t, J = 8 Hz, 2H, $COC\underline{H}_2CH_2CH_2$), 3.86 (t, J = 7 Hz, 2H, $COCH_2CH_2C\underline{H}_2N$), 7.10-7.64 (m, 5H, Ar-H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 17.99 (CH_2), 32.71 ($CO\underline{C}H_2$), 48.73 (CH_2N), 119.91, 124.44, 128.76, 139.36 (Ar-C), 174.16 (C=O); MS (EI), *m/z* 161 (M^+). *Anal.* Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.42; H, 6.91; N, 8.99.

***N*-(4-Methyl)phenyl-γ-butyrolactam (6b)**[10a, 10c]

Pure **6b** (0.79 g, 90%) was obtained as colorless crystals; mp 87-89 °C (EtOAc + Hexane); IR (Nujol), 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.14 (m, 2H, $COCH_2C\underline{H}_2CH_2$), 2.32 (s, 3H, CH_3), 2.59 (t, J = 8 Hz, 2H, $COC\underline{H}_2CH_2CH_2$), 3.83 (t, J = 7 Hz, 2H, $COCH_2CH_2C\underline{H}_2N$), 7.14-7.18 (2H, m, Ar-H), 7.45-7.51 (2H, m, Ar-H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 17.98 (CH_2), 20.81 (CH_3), 32.62 ($CO\underline{C}H_2$), 48.88 (CH_2N), 120.05, 129.29, 134.16, 136.82 (Ar-C), 174.04(C=O); MS (EI), *m/z* 175 (M^+). *Anal.* Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.35; H, 7.50; N, 8.40.

***N*-(4-Methoxy)phenyl-γ-butyrolactam (6c)**[11]

Pure **6c** (0.91 g, 95%) was obtained as colorless crystals; mp 116-117 °C (EtOAc + Hexane), IR (Nujol), 1686 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.07-2.22 (m, 2H, $COCH_2C\underline{H}_2CH_2$), 2.59(t, J = 8 Hz, 2H, $COC\underline{H}_2CH_2CH_2$), 3.79 (3H, s, OCH_3), 3.82 (t, J = 7 Hz, 2H, $COCH_2CH_2C\underline{H}_2N$), 6.90, 7.49 (d, J = 9 Hz, each 2H, Ar-H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 17.93 (CH_2), 32.37 ($CO\underline{C}H_2$), 49.10 (CH_2N), 55.37 (OCH_3), 113.93, 121.74, 132.52, 156.46 (Ar-C), 173.83 (C=O); MS (EI), *m/z* 191 (M^+). *Anal.* Calcd for $C_{10}H_{13}NO_2$: C, 69.09; H, 6.86; N, 7.33. Found: C, 68.88; H, 6.91; N, 7.65.

***N*-Benzyl-γ-butyrolactam (6d)**[12]

Pure **6d** (0.84 g, 96%) was obtained as viscous oil; IR (Nujol), 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.89-2.00 (m, 2H, $COCH_2C\underline{H}_2CH_2$), 2.38 (t, J = 8 Hz, 2H, $COC\underline{H}_2CH_2CH_2$), 3.22 (t, J = 7 Hz, 2H, $COCH_2CH_2C\underline{H}_2N$), 4.41 (s, 2H, benzylic H), 7.22-7.30 (m, 5H, Ar-H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 17.07 (CH_2), 30.27 ($CO\underline{C}H_2$), 45.85 (CH_2N), 45.95(benzylic C), 126.87, 127.41, 128.01, 135.98 (Ar-C), 174.22 (C=O); MS(EI), *m/z* 175 (M^+). *Anal.* Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.34; H, 7.49; N, 8.30.

***N*-(4-Benzyloxy-3-methoxy)benzyl-γ-butyrolactam (6e)**

Pure **6e** (1.51 g, 97%) was obtained as colorless crystals; mp 77-78 °C (EtOAc + Hexane), IR (Nujol), 1681 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.90 (m, 2H, $COCH_2\underline{C}H_2CH_2N$), 244 (m, 2H, $COCH_2$), 3.25 (m, 2H, CH_2N), 3.87 (s, 3H, OCH_3), 4.37 (s, 2H, $ArCH_2N$), 5.14 (s, 2H, $ArCH_2O$), 6.68-6.84 (m, 3H, Ar-H), 7.29-7.46 (m, 5H, Ar-H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 17.69 (CH_2), 31.02 ($CO\underline{C}H_2$), 46.55 ($Ar\underline{C}H_2N$), 51.78 (CH_2N), 56.06 (OCH_3), 71.06 ($Ar\underline{C}H_2O$), 111.90, 113.84, 120.49, 127.23, 127.82, 128.52, 129.75, 137.10, 147.66, 149.89 (Ar-C), 174.83 (C=O); MS (EI), *m/z* 311 (M^+). *Anal.* Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.21; H, 6.93; N, 4.83.

N-Phenyl-δ-valerolactam (6f)[4, 13]

Pure **6f** (0.84 g, 96%) was obtained as as colorless crystals; mp 102-103 °C (EtOAc + Hexane); IR (Nujol), 1661 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.91-1.98 (m, 4H, $COCH_2\underline{C}H_2\underline{C}H_2CH_2N$), 2.53-2.60 (m, 2H, $COCH_2$), 3.61-3.67 (m, 2H, CH_2N), 7.21-7.44 (m, 5H, Ar-H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.44 (CH_2), 23.52 (CH_2), 32.82 ($CO\underline{C}H_2$), 51.65 (CH_2N), 126.20, 126.68, 129.12, 143.35 (Ar-C), 169.95 (C=O); MS (EI), *m/z* 175 (M^+). *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.32; H, 7.50; N, 8.35.

N-(4-Methyl)phenyl-δ-valerolactam (6g)

Pure **6g** (0.83 g, 88%) was obtained as colorless crystals; mp 88-89 °C (EtOAc + Hexane); IR (Nujol), 1676 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.90-1.97 (m, 4H, $COCH_2\underline{C}H_2\underline{C}H_2CH_2N$), 2.34 (s, 3H, CH_3), 2.53-2.55 (m, 2H, $COCH_2$), 3.58-3.64 (m, 2H, CH_2N), 7.10-7.22 (m, 4H, Ar-H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.03(CH_2), 21.48 (CH_3), 23.55 (CH_2), 32.82 ($CO\underline{C}H_2$), 51.78 (CH_2N), 126.04, 129.81, 136.51, 140.80 (Ar-C), 170.02 (C=O); MS (EI), *m/z* 189 (M^+). *Anal.* Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.98; H, 8.02; N, 7.80.

N-(4-Methoxy)phenyl-δ-valerolactam (6h)

Pure **6h** (0.87 g, 85%) was obtained as colorless crystals; mp 63-64 °C (EtOAc + Hexane); IR (Nujol), 1661 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.85-2.01 (m, 4H, $COCH_2\underline{C}H_2\underline{C}H_2CH_2N$), 2.47-2.53 (m, 2H, $COCH_2$), 3.52-3.58 (m, 2H, CH_2N), 3.75 (s, 3H, OCH_3), 6.88-6.92 (m, 2H, Ar-H), 7.10-7.18 (m, 2H, Ar-H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 20.88 (CH_2), 22.96 (CH_2), 32.24 ($CO\underline{C}H_2$), 51.38 (CH_2N), 54.81 (OCH_3), 113.79, 126.81, 135.73, 157.45 (Ar-C), 169.48 (C=O); MS(EI), *m/z* 205 (M^+). *Anal.* Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.84; H, 7.36; N, 7.09.

When the reaction of **5h** (1.21 g, 5 mmol) with potassium *tert*-butoxide (0.57 g, 5.05 mmol) was carried out at rt, the δ-lactam (**6h**) (0.7 g, 68%) together with dimerization product (**6h-1**) (0.11 g, 10%) were obtained. The structure of **6h-1** has the following spectra data, ^{1}H-NMR (200 Mz, $CDCl_3$) δ: 1.64- 1.71 (m, 8H), 2.06 (t, J = 7 Hz, 2H), 2.44 (t, J = 7.5 Hz, 2H), 3.42 (t, J = 6 Hz, 2H), 3.74 (t, J = 6.5 Hz, 2H), 3.79 (s, OMe, 3H), 3.83 (s, OMe, 3H), 6.85, 6.92 (d, J = 9 Hz, each 2H, Ar-H), 7.05, 7.50 (d, J = 9 Hz, each 2H, Ar-H), 7.97 (br s, 1H, NH); ^{13}C-NMR (50 Mz, $CDCl_3$) δ: 22.74 (CH_2), 26.60 (CH_2), 29.69 (CH_2), 32.03 (CH_2), 33.48 (CH_2), 36.56 (CH_2), 44.60 (CH_2), 47.82 (CH_2), 55.49 (2 x OCH_3), 114.02, 114.99, 121.39, 129.15, 131.73, 134.81, 156.05, 159.15 (Ar-C), 171.48 (C=O),

173.30 (C=O); MS (EI) *m/z* (relative intensity, %) 448 ($M+2^+$, 5), 446 (M^+, 14), 328 (15), 309 (16), 206 (44), 205 (34), 149 (38), 136(77), 123 (100), 108(39), 91 (26), 69(13).

N-Benzyl-δ-valerolactam (6i)[12, 14a, 14b]

Pure **6i** (0.90 g, 95%) was obtained as yellow viscous oil ; IR (Nujol), 1651 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.69-1.76 (m, 4H, $COCH_2CH_2CH_2CH_2N$), 2.43 (m, 2H, $COCH_2$), 3.15 (m, 2H, CH_2N), 4.57 (s, 2H, benzylic H), 7.25-7.29 (m, 5H, Ar-H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 20.82 (CH_2), 22.59 (CH_2), 31.86 ($COCH_2$), 46.65 ($PhCH_2$), 49.45 (CH_2N), 126.70, 127.43, 127.97, 136.78 (Ar-C), 169.16 (C=O); MS (EI), *m/z* 189 (M^+). *Anal.* Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.96; H, 8.00; N, 7.56.

N-(4-Benzyloxy-3-methoxy)benzyl-δ-valerolactam (6j)

Pure **6j** (1.54 g, 95%) was obtained as colorless crystals; mp 87 °C (EtOAc + Hexane); IR (Nujol), 1656 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.74 (m, 4H, $COCH_2CH_2CH_2CH_2N$), 2.43 (m, 2H, $COCH_2$), 3.16 (m, 2H, CH_2N), 3.85 (s, 3H, OCH_3), 4.50 (s, 2H, $ArCH_2N$), 5.11 (s, 2H, $ArCH_2O$), 6.68-6.85 (m, 3H, Ar-H), 7.34-7.40 (m, 5H, Ar-H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.12 (CH_2), 22.94 (CH_2), 32.18 ($COCH_2$), 46.85 ($ArCH_2N$) 49.63 (CH_2N), 55.83 (OCH_3), 70.85 ($ArCH_2O$), 111.82, 113.65, 120.23, 127.05, 127.58, 128.29, 130.31, 136.97, 147.33, 149.63 (Ar-C), 169.61 (C=O); MS (EI), *m/z* 325 (M^+). *Anal.* Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.31. Found: C, 73.96; H, 7.25; N, 4.20.

ACKNOWLEDGMENT

We thank National Science Council of Taiwan, ROC (NSC-83-0208-M037-008) for financial support .

REFERENCES

1. H. H. Wasserman, D. J. Hlasta, A. W. Tremper, and J. S. Wu, *Tetrahedron Lett.*, 1979, 549.
2. M. J. Miller, P. G. Mattingly, M. A. Morrisson, and J. F. Kerwin Jr., *J. Am. Chem. Soc.*, 1980, **102**, 7026.
3. I. L. Knunyants and N. P. Gambaryan, *Izvest. Alkad. Nauk S.S.S.R., Otdel. Khim. Nauk.*, 1955, 1037 (*Chem. Abstr.*, 1956, **50**, 11277e).
4. M. S. Manhas and S. J. Jeng, *J. Org. Chem.*, 1967, **32**, 1246.
5. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1345.
6. H. Takahata, Y. Ohnishi, H. Takehara, K. Tsuritani, and T. Yamazaki, *Chem. Pharm. Bull.*, 1981, **29**, 1063.
7. (a). J. C. Sheehan and A. K. Bose, *J. Am. Chem. Soc.*, 1950, **72**, 5158; (b). A. K. Bose, B. N. Ghosh-Mazumdar, and B. G. Chatterjee, *J. Am. Chem. Soc.*, 1960, **82**, 2382.
8. A. Biswas and J. Miller, *Heterocycles*, 1987, **26**, 2849.
9. H. Takahata, E. C. Wang, K. Ikuro, T. Yamazaki, and T. Momose, *Heterocycles*, 1992, **34**, 435.

10. (a). M. L. Kornet, *J. Pharm. Sci.*, 1979, **68**, 350; (b). J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 1957, 4147; (c) H. Metzger and K. Seelert, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 624.
11. V. Wolfgang, L. Dieter, G. Hans, J. Helga, G. Erhard, and H. Wolfgang, Ger (East), DD 264,690, 1989 (*Chem. Abstr.*, 1989, **111**, 115028t.).
12. H. Takahata, T. Hashizume, and T. Yamazaki, *Heterocycles*, 1979, **12**, 1449.
13. E. Oliveros, M. Riviere, and A. Lattes, *J. Heterocycl. Chem.*, 1980, **17**, 1025.
14. (a). T. Fujii, Y. Takai, M. Ohba, H. Kogen, and M. Oki, *Chem. Pharm. Bull.*, 1985, **33**, 2697; (b). J. -C. Pommelet, H. Dhimane, and J. Chuche, *J. Org. Chem.*, 1988, **53**, 5680.

Received, 14th November, 1997