IMPACT: International Journal of Research in Applied, Natural and Social Sciences (IMPACT: IJRANSS)
ISSN (E): 2321-8851; ISSN (P): 2347-4580
Vol. 4, Issue 2, Feb 2016, 111 -118

SYNTHESIS AND CHARACTERIZATION OF NEW γ -LACTAMS WHICH ARE USED TO DECRESE BLOOD GLUCOSE LEVEL

RUSUL.N.M, HAIDER.A.M & MAHMOOD.S.M

Department of Biochemistry, College of Science, University of Thi-Qar, Iraq

ABSTRACT

This study is concerned with the synthesis and characterization derivatives of the γ-lactams 2a-2c.These compounds were synthesized by reacting phenylsuccinic anhydride with the appropriate Schiff base (imines) 1a-1c in moderate yields (60-71 %). The structures of these γ-lactams were established on the basis of the spectral data like IR, ^{1}H-NMR,^{13}C-NMR, HSQC ^{1}H-^{13}C-NMR

KEYWORDS: γ - Lactams, Cycloaddition, Phenylsuccinic Anhydride, ^{13}C NMR, HSQC ^{1}H-^{13}C-NMR

INTRODUCTION

Five-membered ring lactams, which are known as γ-lactams or 2-oxopyrrolidines, are important structural motifs in biologically active natural products[1] which are also found in medicinalleads and approved drugs. Substituted γ-lactams, in particular, have potential application in drug synthesis, but the development of stereoselective synthesis of chiral γ-lactams remains a challenge [2,3].Molecules of natural origin containing a functionalized γ-lactam (pyrrolidin-2-one) ring system with a quaternary stereocenter[4] at C_5 hold a prominent position in chemistryand biology Important examples of these γ-lactams include the proteasome inhibitors lactacystin and salinosporamide , dysibetaine ,several examples from the oxazolomycin family of antibiotics.

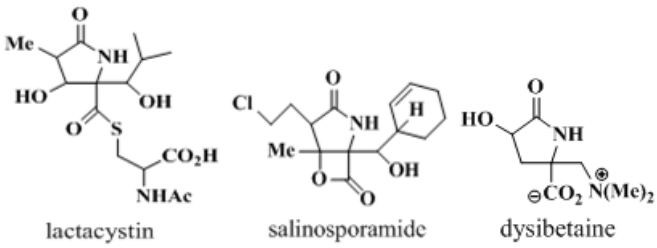


Figure 1: Some Biologically Important Γ-Lactam

Experimental

Wherever necessary, the solvents were distilled/dried prior use by standard methods. All solvent extracts were dried over anhydrous sodium sulphate unless other wise specified. The ^{1}H-NMR spectra were recorded, using VARIAN spectrophotometer (300 MHz). The ^{13}C-NMR spectra were recorded, using VARIAN spectrophotometer (75 MHz). HSQC ^{1}H-^{13}C-NMR spectra were recorded, using VARIAN spectrophotometer (600 MHz, 150 MHz), the above measurements were recorded in National Hellenic Research Foundation, Institute of Biology Medicinal Chemistry and Biotechnology, Molecular analysis Group, Athens, Greece. The chemical shift values are expressed in δ (ppm), using tetramethylsilane (TMS) as internal standard and using DMSO-d6as solvent.. IR spectra were recorded using Shimadzu FT-IR affinity

spectrophotometer as KBr disks. Only principal absorption bonds of interest are reported and are expressed in cm^{-1}.

General Procedure for the Preparation of Imines 1a-1c

Preparation of mono-imines 1a-1c. In general, the mono-imines 1a-1c were prepared [5,6] by refluxing 0.01 mol amine, 0.01 mol aldehyde and 4-6 drops of acetic acid in chloroform (25 mL) at 55-60 ˚C for 2-4 h with stirring. The progress of the reaction was followed by TLC. After completion of the reaction, the solvent evaporated and the product was recrystallized from a suitable solvent. The physical data of mono-imine (1a) and the reactants are given below.

N-(4-Chlorobenzylidene)-5-methylpyridine-2-amine (1a):It was prepared by reacting 2-amino-5-methylpyridine (0.01mole, 1.08g) with p-chlorobenzaldehyde (0.01mole, 1.40g). Yield = 68%, m.p. = 97-98ºC. IR (KBr disk): 1620 cm^{-1} (C=N).

Table 1: Physical Properties of Imine 1a

Imines2(H,I)	M.P °C	Yield %	Color
1a	150-151	85	green

Preparation of bis-imines (1b,1c). In general, the bis-imines (1b,1c) were prepared by refluxing, 0.01 mol amine, 0.02 mol aldehyde and 4-6 drops of acetic acid in chloroform (25 mL) at 55-60 ˚C for 2-20 h with stirring. The progress of the reaction was followed by TLC. After completion of the reaction, the solvent was evaporated and the product was recrystallized from a suitable solvent. The physical data of bis-imines (1b,1c) and the reactants are given below.

(N,N')-4,4'-Methylenebis(N-benzylideneaniline) (1b): It was prepared by reacting 4,4'-diphenylmethlenediamin (0.01 mol, 1.98 g) with benzaldehyde (0.02 mol, 1.12 g, 1.09 mL). Yield = 82 %, m.p. = 129-130 ºC. IR (KBr disk): 1612 cm^{-1} (C=N).

N1,N4-dibenzylidenebenzene-1,4-diamine (1c): It was prepared by reacting p-phenylenediamine (0.01 mol, 1.08 g) with benzaldehyde (0.02 mol, 2.12 g, 2.07 mL). Yield = 80%, m.p. = 141-143 0C. IR (KBr disk): 1612 cm^{-1} (C=N).

Table 2: Physical Properties of Imine 1b, 1c

imines2(h,i)	m.p °C	Yield %	Color
1b	129-130	82	White
1c	140-142	80	yellow

General Procedure of Mono and Bis Γ-Lactams (2a-2c)

Preparation of mono γ-lactams 2a In general the mono γ-lactam (2a) were prepared [7,8] by refluxing, at 55-60 ˚C, 0.01 mol mono-imine 2aand 0.01 mol of phenylsuccinic anhydride in 25 mL of chloroform for 12-17 h with stirring. The progress of the reaction was followed by TLC. After completion of the reaction, the solvent was evaporated and the product was recrystallized from a suitable solvent. The physical data of the mono γ-lactam (2a) and the reactants are given below.

2-(4-Chlorophenyl)-1-(4-methylpyridine-2-yl)-5-oxo-3-phenylpyrrolidine-3-carboxylic acid (2a): is prepared by reacting **(1a)** (0.01 mole, 2.30 g) and (0.01 mole, 1.76 g) of phenylsuccinic anhydride. Yield =68 %, m.p. = 130-131 °C. IR (KBr disk): 1681 cm^{-1} (–N–C=O), 1705 cm^{-1} (HO–C=O), ^{1}H-NMR: 3.28 (d, J= 9Hz, 1H, C_4-H), 3.67 (d, J= 9Hz, 1H, C_4-H), 4.03 (s, 1H, C_2-H), 6.46 - 8.24 (m, 12H), ^{13}C-NMR: 59.64 (C_4-H), 78.55 (C_2-H), 111.92 – 159.97 (Aromatic C), 178.39 (N-C=O), 175.15 (COOH).

Table 3: LPhysical Properties of Γ -Lactams 3a

Γ-Lactams	M.P°C	Yield %	Colour
2a	277-278	65	Wight

Preparation of bis γ-lactams (2b,2c) In general the bis γ-lactams (2b,2c) were prepared by refluxing 0.01 mol of bis-imine (1b,1c) nand 0.02 mol of phenylsuccinic anhydride in 25 mL of chloroform at 55-60 ˚C for 12-17 h with stirring. The progress of the reaction was followed by TLC. After completion of the reaction, the solvent was evaporated and the product was recrystallized from a suitable solvent. The physical data of the bis γ-lactams (2b,2c) and the reactants are given below.

1,1'-(Methylenebis(4,1-phenylene))bis(5-oxo-2,3-diphenyl pyrrolidine-3-carboxylic acid) (2b): is prepared by reacting **(1b)** (0.01 mole, 3.74 g) and phenylsuccinic anhydride (0.02 mole, 3.52 g). Yield = 60 %, m.p. = 185-186 °C. IR (KBr disk): 1651 cm^{-1} (–N–C=O), 1720 cm^{-1} (HO–C=O), ^{1}H-NMR: 2.66 (s, 1H, C_4-H), 3.07 (s, 1H, C_4-H), ^{13}C-NMR: 49.90 (C_4-H), 78.55 (C_2-H), 120.46 – 142.06 (Aromatic C), 177.24 (N-C=O), 171.95 (COOH).

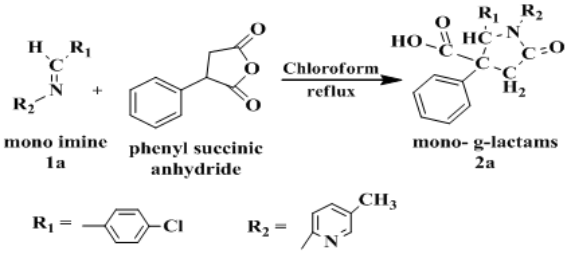
1,1'-(1,4-Phenylene)bis(5-oxo-2,3-diphenylpyrrolidine-3-carboxylic acid) (2c): is prepared by reacting **(1c)** (0.01 mole, 2.84 g) and phenylsuccinic anhydride (0.02 mole, 3.52 g). Yield = 71 %, m.p. = 187-189 °C. IR (KBr disk): 1658 cm^{-1} (–N–C=O), 1697 cm^{-1}(HO–C=O), ^{1}H-NMR: 2.71 (d, J= 6Hz, 1H, C_4-H), 3.12 (t, J= 6Hz, 1H, C_4-H), 4.06 (s, 1H, C_2-H), 6.46 - 8.24 (m, 12H), ^{13}C-NMR: 49.92 (C_4-H), 78.55 (C_2-H), 120.46 – 162.17 (Aromatic C), 177.26 (N-C=O), 172.10 (COOH).

Table 4: Physical Properties of Γ -Lactams 3b, 3c

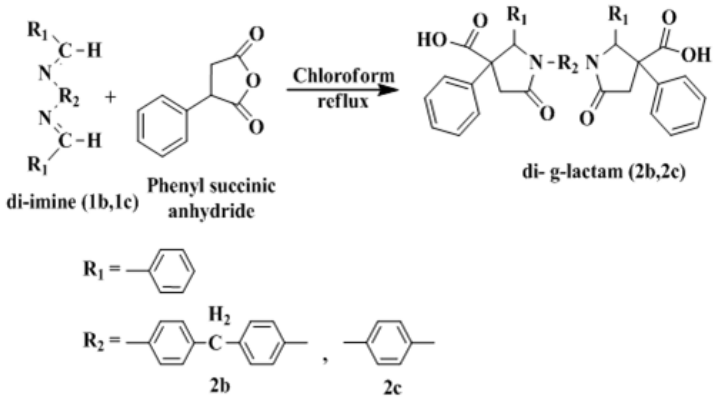
γ-lactams	m.p °C	Yield %	Color
2b	185-186	60	Wight
2c	187-189	71	Yellow

RESULTS AND DISCUSSIONS

γ-Lactams are widely found among natural products.[9-12] Biologically important lactams [13-15] are obtained from the reaction of imines with phenylsuccinic anhydride to give pure γ-lactams. The key step in the synthesis mono and bicyclic γ-lactams (2a-2c) involved the treatment of the mono or Diimines (1a-1c) with phenyl succinic anhydride in chloroform to afford γ-lactams (2a-2c)as shown in Schemes 1 and 2.

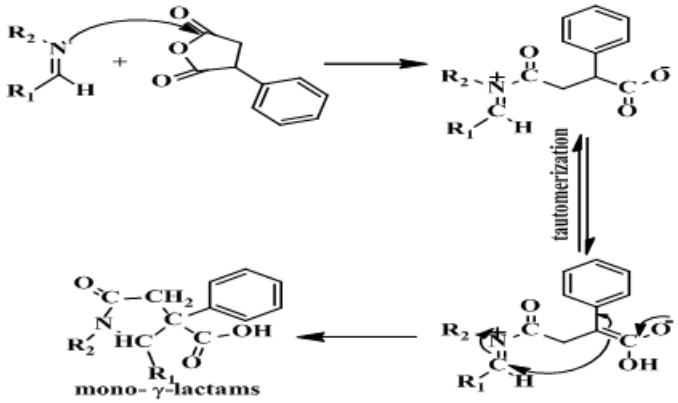


.**Scheme 1:. Synthesis of Mono Γ -Lactams**



Scheme 2: Synthesis of Bis Γ –Lactams

The general mechanism [16,17] of formation of both mono and bis-γ-lactams (Scheme3) involve formation of a zwitterionicenolate intermediate from phenylsuccinic anhydride. Formation of the enolate is favored by delocalization of negative charge by the aromatic ring if one is suitably positioned. The enolate zwitterions cyclise to form the lactam rings.



Scheme 3: Mechanism of Formation of Γ -Lactams

The structures of the mono and bicyclic γ-lactams were established on the basis of IR, ^{1}H-NMR,^{13}C-NMR, and HSQC ^{1}H-^{13}C-NMR spectral data.

IR Spectral Analysis

The IR spectra of the imines (1a-1c), in KBr disc showed absorption bond at 1612-1620 cm^{-1}corresponding to the azomethine group of imine compounds. The IR spectra of γ-lactams (2a-2c) are characterized by the seven bands corresponding to the stretching vibration of the aromatic C-H , aliphatic C-H, carbonyl carboxylic group, carbonyl amide

group, aromatic C=C, C-N band and substituted ring which occurs within the ranges 3055-3024, 2931- 2850, 1728-1697, 1674-1651, 1673-1543, 1373-1311, and 925-617 cm-1 respectively.

^{1}H-NMR Spectral Analysis

Some representative ^{1}H-NMR spectra of the γ-lactams are shown in Figure 5. The ^{1}H-NMR spectra of (2c) inpyrrolidine-2-one ring doublet signal at δ (2.71 ppm) with (J= 6 Hz) for proton **a** (d,1H,C_4-H) and triplet signal at δ (3.12 ppm) with (J= 6 Hz) for proton **b** (t, 1H, C_4-H)**.**

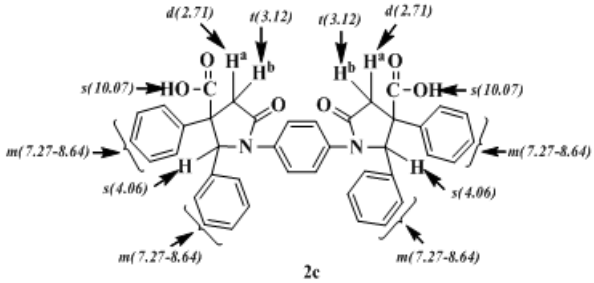


Figure 1: ^{1}H-NMR Peaks Γ -Lactum (2c)

Table 5

Mono & Di -Γ- Lactams	C_4-H, Hz C_4-H, Hz	C_2-H	COOH	Ar-H
$C_{23}H_{19}ClN_2O_3$ 2a	3.28 (d) J= 9Hz 3.67 (d) J= 9Hz	4.03 (s)	10.41 (s)	6.46 - 8.24
$C_{47}H_{38}N_2O_6$ 2b	2.66 (s) 3.07 (s)	4.02 (s)	9.91 (s)	7.09 - 7.44
$C_{40}H_{32}N_2O_6$ 2c	2.71 (d) J= 6Hz 3.12 (t) J= 6Hz	4.06 (s)	10.07 (s)	7.27 - 8.64

^{13}C-NMR Spectral Analysis

The ^{13}C-NMR spectral data of the γ-lactams have described along with syntheses of these compounds in the experimental section. The compound (2c) show in pyrolidine-2-one rings signal at 49.92 ppm for two carbon (equivalent carbon)2(C_4-H_2) respectively. The signal for carboxylic (-COOH) carbon appears at δ= 170.23 and 173.37 ppm respectively as shown in **Figure 2.**

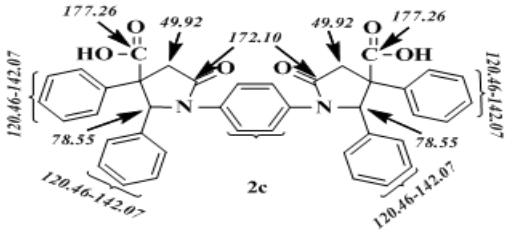


Figure 2: ^{13}C-NMR Peaks Γ -Lactum (2c)

Table 6

Γ-Lactams	C_4 Ring Ppm	C_2 Ring Ppm	N-C=O- Ppm	COOH Ppm	Ar-C
$C_{23}H_{19}ClN_2O_3$ **2a**	59.94	78.55	175.15	178.39	111.92 – 159.97
$C_{47}H_{38}N_2O_6$ **2b**	49.90	78.55	171.95	177.24	120.46 – 142.06
$C_{40}H_{32}N_2O_6$ **2c**	49.92	78.55	172.10	177.26	120.46 – 162.17

^{13}C-NMR DEPT Spectral Analysis of Γ-Lactams

The DEPT ^{13}C-NMR spectra of **(2c)** is shown in pyrrolidine-2-one rings signal at δ 47.24 (-) ppm for C_4 (CH_2) and DEPT ^{13}C-NMR spectra of the aromatic region are within therange (128.16 - 140.05) (+) ppmAnd shown signal at δ 169.30 (+) ppm for the carboxylic carbonyl group, and another signal at 174.59 (+) ppm for the amide carbonyl.

HSQC ^{1}H-^{13}C - NMR spectral analysis

The HSQC spectra of **(2c),** show pyrrolidine-2-one ring the correlation of protons signals for (CH_2) group at δ 2.70 ppm with carbon signal at δ 42.74 ppm, and correlation of protons signals for (CH_2) group at δ 3.07, 3.09, 3.11 ppm with carbon signal at δ 42.74 ppm of same group in which ledto the assignment of this signal to methylen e group, and proton signal 4.04 ppm for (CH) group with carbon signal of same group at 49.28 ppm , whichled to the assignment of this signal to (CH) group.

Anti-Hyperglycemic Activity

Serum glucose concentration is changed as shown in table (5) during the experimental period. Thus, is a significant increase($P < 0.05$) in the serumconcentration of glucose in group (**Control positive**) compared with other group whilegroups (**2c 50mg/kg)** and **(2c 100mg/kg)** do not exhibit significant differences between them.

Table 5: Serum Glucose Levels after Treatment

Groups	N	Average
Control negatev	6	99.93
Control positive	6	203.38
DMSO	6	101.01
2c (50mg/kg)	6	169.60*
2c (100mg/kg)	6	114.06*
L.S.D		6.17

REFERENCES

1. Blasdel. L.K.; Lee.D. ;Sun. B. ;Myers. A.G. ; Bioorg. Med. Chem. Lett. 23, 6905-6910, **2013**.
2. Zhao. X. ;DiRocco. D.A. ;Rovis. T. J. ,Chem.Soc.133,12466-12469,**2011**.
3. Comesse. S. ;Sanselme. M. ; Daich. A. , J. Org. Chem. 73,5566-5569, **2008**.
4. Trost. B.M. ;J.iang. C.,Chem., 115,1726,**2003**.

5. Hello. K. M., Iraqi J. Chem. , 24, 266, **2000**.
6. Krishnaswamy. D., Tetrahedron., 34, 4567,**2002**.
7. Mahmood, S. M., Abaas, T. A., Thesis, Thi-Qar University, **2012**.
8. Mahmood, S. M., Wasan, K. D., Thesis, Thi-Qar University, **2012**.
9. Feling, R. H., Buchanan, G. O., Mincer, T, J., Kauffman, C. A., Jensen, P, R. and Fenical, W., Angew. Chem., 42, 355, **2003**.
10. Guntern, A., Ioset, J. R., Queiroz,E. F., Sandor, P., Foggin, C. M. A. and Hostettman, N. K ., J. Nat. Prod. , 66, 1550, 2003.
11. Manam, R. P., Teisan, S., White, D. J., Nicholson, B., Grodberg, J., Neuteboom , S.T; Lam, K. S., Mosca, D. A., Lloyd, G. K. and Potts, B. C., J. Nat. Prod. , 68, 240, 2005.
12. Okazaki, Y., Ishizuka, A., Ishihara, A., Nishioka, T. and Iwamura, H., J. Org. Chem., 72, 3830, **2007**.
13. Stuk, T. L., Assink, B. K., Bates, R. C., Erdman, D. T., Fedij, V., Jennings, S. M., Lassig, J. A., Smith, R. J. and Smith, T. L., J. Org. Prod., 7, 851, 2003.
14. Masse, C. E., Morgan, A. J., Adams, J. and Panek, J. S., J. Org. Chem,, 13, 2528,**2000**.
15. Fenical, W., Jensen, P. R., Palladino, M. A., Lam, K. S., Lloyd, G. K. and Potts, B. C., Bio. Med. Chem. , 17, 2175, **2009**.
16. Lopez, M. G., Shaw, J. T., Chem. Rev., 109, 164, **2009**.
17. Masse, C. E., Ng, P. Y., Fukase, Y., Sanachez-Rosello, M. and
18. Shaw, J. T., J. Comb. Chem. , 8, 293, **2006**.