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# THE SYNTHESIS OF SOME DERIVATIVES OF γ-LACTONE

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**Abstract**. *A synthesis of antibacterial active polyfunctional derivatives of γ-butyric lactone is presented. The key step of the synthesis involves the Beckmann fragmentation of 3H,3aH,5H,6H,7aH-4-dichloromethyl-4-methylbenzofuran-2-one-7-one-oxime,* ***3****, with $PCl_5$ in $CH_2Cl_2$. The $^1H$ and $^{13}C$ NMR spectra of synthesized derivatives of γ-butyric lactone are also discussed.*

**Key words**: *γ-lactone, Beckmann fragmentation, synthesis.*

## 1. INTRODUCTION

α, β-Unsaturated γ-lactones are key structural subunits of natural products [1] and valuable synthetic intermediates [2]. As a consequence of the importance of unsaturated γ-lactones, many methods for the preparation of these compounds have been elaborated [2]. However, exploration of new procedures for construction of such frameworks is still required.

In our previous paper [3] we have shown that lactamic γ-lactone, 6-dichloromethyl-6-methyl-10-oxa-2-aza-bicyclo[5.3.0]dec-4-ene-3,9-dione, possesses bactericidal activity against of both $G^+$ and $G^-$ bacteria. We herein report the chemical transformation of lactone **1** in synthesis of several polyfunctional products with the γ-lactone ring (Scheme 1) in order to compare their activities with the activities of lactamic γ-lactone.

## 2. EXPERIMENTAL

The IR spectra were run on a Perkin-Elmer Grating Spectrophotometer Model 137 and model 197. The NMR spectra were recorded on a 200 Gemini Spectrophotometer, using TMS as the internal standard. The Chemical Shifts are given in δ (ppm), coupling

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constants, J, in Hz. The column chromatography was carried out using Merck Kieselgel 60.

*Preparation of trans-3H,3aH,5H,6H,7aH-4-dichloromethyl-4-methyl -2, 7-benzofurandione (**2**)*

The mixture of 1 g of the lactone **1** and 100 mg of 10% palladium/charcoal in 60 $cm^3$ of ethyl acetate was hydrogenated at room temperature and atmospheric pressure. The mixture was filtered and the filtrate was evaporated. The saturated lactone **2** was obtained by crystallization from ether (900 mg, 90%).

$^1$H NMR ($CDCl_3$), ▬: 1.18 (s, 3H, $CH_3$), 1.98 (m, 2H, 5-H), 2.21-2.73 (m, 4H, 3-H, 6-H), 5.06 (d, H, 7a-H). IR (KBr) $cm^{-1}$: 1785 (C=O, ⎯-lactone), 1720 (C=O ketone), 1180 (C-O, ⎯-lactone), 800 (C-Cl). $^{13}$C NMR: 173.8 (2-C), 34.38 (6-C), 204.6 (7-C), 82.47 (7a-C).

*Preparation of (E)-trans-3H,3aH,5H,6H,7aH-4-dichloromethyl-4-methylbenzofuran-2-one-7-one-oxime (**3**)*

Lactone **2** (249 mg), hydroxylamine hydrochloride (100 mg) and sodium acetate trihydrate (160 mg) were dissolved in methanol (10 ml) containing 2 ml water. The solution was heated under reflux for 1 h and it was evaporated, extracted with dichloromethane, dried over anhydrous sodium sulfate and subjected to column chromatography (benzene - ethyl acetate = 4 : 1) to give oxime **3** (230 mg, 87%). $^1$H NMR: 1.16 (s, 3H, $CH_3$), 1.80-1.88 (m, 2H, 5-H), 2.46-2.83 (m, 4H, 3-$H_2$ and 6-$H_2$), 3.10-3.30 (m, 1H, 3a-H), 5.10 (d, H, 7a-H, J=7.37), 6.12 (s, H,$CHCl_2$). $^{13}$C NMR: 178.2 (2-C), 17.83 (6-C), 153.5 (7-C), 80.33 (7a-C). Found: C, 45.30; H, 4.90; N, 5.28; $C_{10}H_{13}NO_3Cl_2$ requires: C, 46.17; H, 5.13; N, 5.98.

*Preparation of 4-(1′-dichloromethyl-1′-methyl-butanonitril)-5-hydroxy-oxacyclopentan-2-one (**4**)*

A solution of $PCl_5$ in 5 ml $CH_2Cl_2$ was added dropwise to a solution of the oxime **3** (266 mg) in anhydrous dichloromethane (10 ml). The solution was stirred for 1 h at room temperature. After addition of water, the solution was extracted with dichloromethane. The extract was washed successively with aq. 5% $Na_2CO_3$ and saturated sodium chloride solution, then dried over anhydrous sodium sulfate before the solvent was evaporated. The crude product was subjected to column chromatography to give compound **4** as an oil (191 mg, 72%). $^1$H NMR: 1.16 and 1.42 (s, 3H, $CH_3$), 2.05-2.29 (m, 2H, 2′-H), 2.48-2.65 (m, 2H, 3′-H), 2.68-3.10 (m, 2H, 3-H), 3.28-3.36 (m, H, 4-H), 5.71 and 5.76 (s, H, $CHCl_2$), 6.42 (br s, H, 5-H). $^{13}$C NMR: 172.8 (2-C), 128.2 (5-C), 118.8 (CN).
Found: C, 45.30; H, 4.90; N, 5.28; $C_{10}H_{13}NO_3Cl_2$ requires: C, 45.82; H, 5.10; N, 5.69.

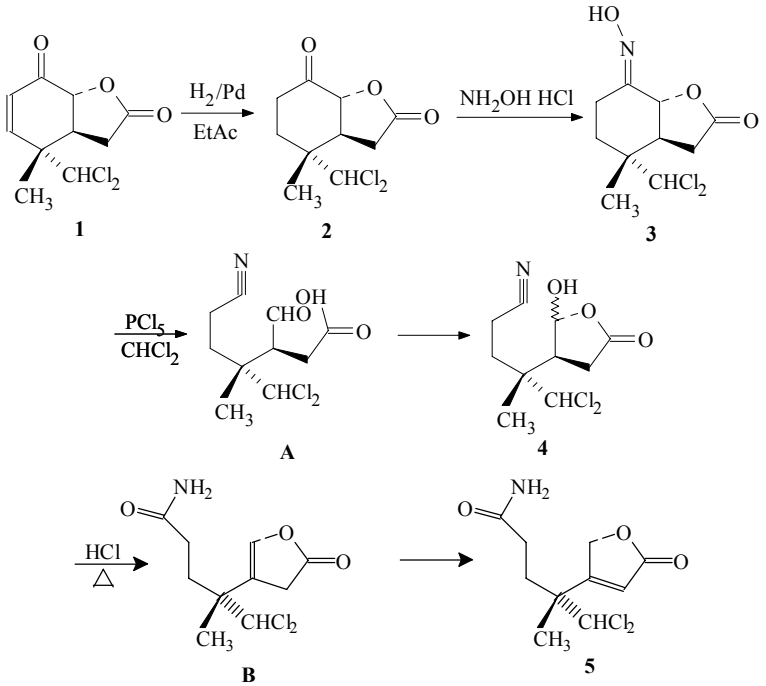
*Preparation of 4-(1′-dichloromethyl-1′-methyl-butanoamido)-oxacyclopent-3-en-2-one (**5**)*

Compound **4** (270 mg) and HCl (1:1) (8 mL) were refluxed for one hour. The reaction mixture was then cooled to room temp., extracted with chloroform, washed successively with saturated $NaHCO_3$ and NaCl and dried with anhydrous $Na_2SO_4$. The solvent was evaporated under reduced pressure and residue was subjected to column chromatography

to give compound **5** as an oil (93 mg, 35%). $^{1}$H NMR: 1.5 (s, 3H, $CH_3$), 2.15-2.25 (m, 2H, 2´-H), 2.34-2.44 (m, 2H, 3´-H), 4.96 (t, 2H, 5-H, J=2.12), 5.82 (s, H, $CHCl_2$), 6.12 (t, H, 3-H, J=1.87 and J=1.91). $^{13}$C NMR: 167.8 (2-C), 12.8 ($CH_3$), 76.7 ($CHCl_2$).
Found: C, 45.51; H, 5.15; N, 5.89; $C_{10}H_{13}NO_3Cl_2$ requires: C, 45.30; H, 4.90; N, 5.28.

## 3. RESULTS AND DISCUSSION

Hydrogenation [4] of lactone **1** with 10% Pd/C in ethyl acetate at room temperature and atmospheric pressure, gave saturated analogue, *trans*-3H,3aH,5H,6H,7aH-4-dichloromethyl-4-methyl -2,7-benzofurandione, **2** in 90% yield. The structure of lactone **2** was established on the basis of the following data: at 1.18 δ there was a singlet for three protons of the methyl group at C-4. The signal is displaced upfield in comparison with the corresponding methyl group in the unsaturated compound **1** because the anisotropic effect of the double bond was absent. Two H-5 protons give a complicated multiplet at 1.98 δ, four protons at C-6 and C-3 give a multiplet in the region 2.21-2.73 δ. The signals are overlapping. The H-7 proton appears as a doublet at 5.06 δ with coupling constant $^{3}$J=9.61. The magnitude of the coupling between the protons on C-7a and C3a indicates to their *trans*-orientation.




Scheme 1.

Treatment of lactone **2** with hydroxylamine afforded a single (E)-oxime **3** (Scheme 1). It was found that the (E)-isomer **3** did not undergo isomerisation to the (Z)-form when placed in the oximation medium. Therefore, the formation of the product must have been kinetically controlled.

It is known that oximation of methyl 4,6-O-benzyliden-2-deoxy-α-D-erythro-hexopyranosid-3-uloze whose structure is similar to lactone **2** can afford one oxime with the (E)-structure [5].

The $^{1}H$ and $^{13}C$ NMR data indicate that the hydroxyimino group had the (E)-configuration. H-7a proton of lactone **2** resonates at 5.06 δ and for oxime **3** at 5.10 δ. H-6 proton of lactone **2** resonates at 2.30-2.70 for oxime **3** it resonates at 2.46-2.83. A study of the $^{13}C$ NMR spectra confirmed the proposed structure.

As has been noted [6] the resonances of the carbonyl carbon and both ⍺ carbons all shift upfield to the oxime formation with the effect being greater for the ⍺-(Z) carbon than for the ⍺-(E) carbon. The ⍺-gauche effect observed for 7a-C is 2.14 ppm and for 6-C 16.55 ppm. Such great difference in chemical shifts for ketones and ketoximes has been published earlier [6].

Oxime **3** failed to react with $PCl_5$ and $SOCl_2$ in ethyl ether but it reacted with $PCl_5$ in $CH_2Cl_2$ and gave product of Beckmann fragmentation **4.** Relying on Beckmann fragmentation of some ⍺-hydroxy ketoximes [7] it has been supposed that primary fragmentation product, unstable cyanoaldehyde **A**, underwent, cyclization into a mixture of the stereoisomeric alcohols **4**.

Treatment of compound **4** with diluted HCl gave α, β-unsaturated γ-lactone **5** as an energetically favored conjugated system by migration of the primary formed double bond from position 4 to position 3 (Scheme 1). The structures of compounds **4** and **5** were characterized on the basis of $^{13}C$ and $^{1}H$ NMR spectral data (see experimental section).

The following compounds, which possess antibacterial activity, have been synthesized: (E)-trans-3H,3aH,5H,6H,7aH-4-dichloromethyl-4-methylbenzofuran-2-one-7-one-oxime, **3;** 4-(1′-dichloromethyl-1′-methyl-butanonitril)-5-hydroxy-oxacyclopentan-2-one, **4** and 4-(1′-dichloromethyl-1′-methyl-butanoamido)-oxacyclopent-3-en-2-one, **5.**

## REFERENCES


1. Y.S. Rao, Recent Advances in the Chemistry of Unsaturated Lactones, *Chem. Rev.* **76** (5), 625-694 (1976).
2. A. Pelter, P. Satyanarayana and R. S. Ward, An short efficient synthesis of *trans*-dibenzildutirolactones exemplified by the synthesis of di-O-methyl-compoundX (HPMF) and an anti-i-tumour extractive, *Tetrahedron Lett.,* **22** (16)**,** 1549-1550 (1981).
3. S. Sukdolak, S. Solujić and G. Stojanović, The synthesis and biological activity of 6-dichloromethyl-6-methyl-10-oxa-2-aza-bicyclo[5.3.0]dec-4-ene-3,9-dione, lactamic γ-lactone, *J. Serb. Chem. Soc.,* **62**(5), 389-392 (1997).
4. S. Sukdolak, S. Solujić, N. Manojlović and Lj. Krstić, A synthesis of benzofurane type γ-lactonic derivatives as potential antifungal and antibacteric agents, *J. Serb. Chem. Soc.,* **60**, 663-668 (1995).
5. P.J. Beynon, P.M. Collins and W.G. Overend, Aspects of the Chemistry of Oximes derived from Methyl Hexopyranosiduloses, *J. Chem. Soc.,* 272-281 (1969).
6. G.E. Hawkes, K. Herwig and J.D. Roberts, Nuclear Magnetic Resonance Spectroscopy. Use of $^{13}C$ Spectra to Establish Configurations of Oximes, *J. Org. Chem.,* **39**(8)**,** 1017-1028 (1974).
7. D. Miljković, J. Petrović, M. Stajić and M. Miljković, The Beckmann Fragmentation Reaction of Some α-Hydroxy Ketoximes, *J. Org. Chem.,* **38**, 3585-3588 (1973).

# SINTEZA NEKIH DERIVATA γ-LAKTONA

**G. Stojanović, S. Sukdolak, R. Palić**

*U radu je opisana sinteza derivata γ-laktona. Beckmann-ovom fragmentacijom 3H,3aH,5H,6H,7aH-4-dihlorometil-4-metilbenzofuran-2-on-7-on-oksima sa fosfor(V)hloridom u dihlormetanu dobiven je 4-(1`-dihlorometil-1`-metilbutanonitril)-5-hidroksioxaciklopentan-2-on koji u reakciji sa hlorovodoničnom kiselinom daje nezasićeni derivat γ-laktona 4-(1`-dihlorometil-1`-metilbutanamido)-oxaciklopent-3-en-2-on. Struktura sintetisanih jedinjenja određena je analizom IR, $^{1}H$ i $^{13}C$ NMR spektara.*