Synthesis of Some Biologically Important 3-Oxacepham Derivatives

Mohammad Rafiqul Islam[1], Mohammad Nurnabi[1], A. M. Sarwaruddin Chowdhury[1], and Mohammad Mehdi Masud[2]

[1]Department of Applied Chemistry & Chemical Technology, University of Dhaka, Dhaka-1000, Bangladesh
[2]Department of Pharmaceutical Chemistry, University of Dhaka, Dhaka-1000, Bangladesh

ABSTRACT: The 6*H*-oxathiazines **1a-e** having imine moiety underwent [2+2] cycloaddition with phenoxyacetylchloride in the presence of Et_3N to give β-lactam derivatives **2a-e** in high yield. The X-ray crystallographic analysis revealed the relative stereochemistry that the substituents at *C*-2 and *C*-4 were *cis* configurated. The subtituents at *C*-6 and *C*-7 were also *cis* to each other. However, the 6*H*-oxathiazines **1f-i** containing *tert*-butyl or methyl group at *C*-4 did not undergo the cycloaddition.

Key words: Azetedinone, β-lactam, oxacepham, cycloaddition, imine, ketene, oxathiazine.

INTRODUCTION

Even more than 70 years after the discovery of penicillin, β-lactam-containing antibiotics are still in use for the treatment of infectious diseases caused by various pathogens. However, within a short time after introduction of a new antibiotic, bacterial strains become resistant to it due to the indiscriminate use and as result the antibiotics loose their activities. Moreover, the resistant bacterial strains are affecting the humans with severe damaging effects. Thus a continued effort is needed to fight the infectious diseases by extending the effectiveness of the currently available antibiotics.

The biological activity exhibited by β-lactam antibiotics is found to be associated with the β-lactam ring, the reactivity of which in turn is depend on the tail end as well as on the head of the antibiotic molecule.[1] Modification of the tail end led to the introduction of a large number of clinically useful penam and cepham derivatives.[2] Modification of the head of the antibiotic molecule involved replacement of sulfur atom of these bicyclic compounds by carbon,[2] nitrogen,[3] and oxygen[4-6] in order to enhance the reactivity of the azetedinone carbonyl function and consequently antibacterial activity. It is well accepted that the replacement of 'S' of the cepham ring with an electronegative atom such as 'O' increases the penetration of the molecule through the cell wall of the bacteria due to the greater hydrophilicity and thus imparts the greater activity.[7] Moreover, some studies showed that the oxacepham derivatives have better β-lactamase inhibitory activity, especially against cephalosporinase than the ceohem derivatives.[8] Some reports[9,10] described the synthesis of cepham derivatives containing nitrogen atom in place of C-2 of the cepham nucleus. It was documented earlier that the introduction of N, O atoms in place of C-3 activated the C=O group of the β-lactam ring through inductive effect of the highly electronegative heteroatoms.[11] However, to the best of our knowledge, only a single report on the

Correspondence to: Mohammad Nurnabi
Tel: 88029661920-73/7395
Email:nnabi@univdhaka.edu

Dhaka Univ. J. Pharm. Sci. **5**(1-2): 47-51, 2006 (June-December)

synthesis of cepham derivatives containing oxygen as third heteroatom in the head portion of the cepham derivative[11] has been disclosed. Therefore, synthesis of a wide variety of 3-oxacepham derivatives containing fluorine atom in the aromatic ring would deliver more potent drug candidates against pathogenic microorganisms.

Herein, a synthesis and detailed structural elucidation of some biologically potential 3-oxacepham derivatives are documented.

MATERIALS AND METHODS

General. All substances and reagents were commercially available and were used without further purification. Flash column chromatography was performed on Merck silica gel 60 (230-400 mesh). Melting points were determined on a Buchi 535 micro-melting point apparatus and are uncorrected. Microanalyses were obtained using a Yanagimoto CHN recorder MT-5. Proton nuclear magnetic resonance (^{1}H NMR) spectra experiments were determined at 400 MHz. on a Bruker AC-400P spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (TMS) as internal standard and coupling constants are given in Hertz (Hz). ^{13}C NMR spectra were recorded with a Bruker AC-400P (75 MHz) and chemical shift values were reported in parts per million (ppm) relative to $CDCl_3$ (δ= 77.0). Mass spectra were obtained on a Hitachi M-2000 mass spectrometer using electron impact (EI) ionization at 70 eV. Infrared spectra were recorded on a JASCO FT/IR-7300 spectrometer either by KBr pressed disks method or film (neat) method.

General procedure. To a stirred solution of **1** (1 mmol) and triethylamine (1.5 mmol) in anhydrous dichloromethane (25 ml) at 0^{o}C, was added the phenoxyacetylchloride (1.45 mmol) in anhydrous dichloromethane (10 ml) dropwise during 10 min. The stirring was continued for 2 hrs at 0-5^{o}C and then at room temperature for overnight. The reaction mixture was successively washed with water, 10% aq. sodium bicarbonate and water. The organic layer was separated, dried (Na_2SO_4) and concentrated to afford the β-lactam derivatives **2**. The compounds were purified by column chromatography.

2,4-Dimethyl-7-phenoxy-6-phenyl-3-oxa-5-thia-1-aza-bicyclo[4.2.0]octan-8-one2a): Colourless crystals (84%), mp 95-96 °C (Found: C, 66.97; H, 5.56; N, 4.10; $C_{19}H_{19}NO_3S$ requires C, 66.84; H, 5.61; N, 4.10%); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, d, J=6.0, CH_3), 1.55 (3H, d, J=6.0, CH_3), 5.18 (1H, q, J=6.0, H-2), 5.61 (1H, s, H-7), 5.72 (1H, q, J=6.0, H-4), 6.61 (2H, d, J=7.9, Ar-H), 6.86 (1H, t, J=7.3, Ar-H), 7.08–7.12 (2H, m, Ar-H), 7.19–7.25 (3H, m, Ar-H), 7.43–7.45 (2H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 21.1 (CH_3), 21.6 (CH_3), 70.1 (C-6), 75.4 (C-4), 79.5 (C-2), 93.5 (C-7), 115.3 (Ar-C), 122.2 (Ar-C), 127.4 (Ar-C), 127.5 (Ar-C), 128.3 (Ar-C), 129.2 (Ar-C), 136.9 (Ar-C), 156.2 (Ar-C) and 165.3 (C=O); *m/z* (EI) 341 (M^+ , 2%) and 121; ν_{max}/cm^{-1} (KBr) 2902, 1778, 1160, 1496, 1335 and 1116.

6-(4-Chloro-phenyl)-2,4-dimethyl-7-phenoxy-3-oxa-5-thia-1-aza-bicyclo[4.2.0]octan-8-one(**2b**): Colourless crystals (87%), mp 116-117 °C (Found: C, 60.76; H, 4.59; N, 3.64; $C_{19}H_{18}ClNO_3S$ requires C, 60.71; H, 4.83; N, 3.73%); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, J=6.0, CH_3), 1.55 (3H, d, J=6.0, CH_3), 5.15 (1H, q, J=6.0, H-4), 5.56 (1H, s, H-2), 5.69 (1H, q, J=6.0, H-6), 6.63 (2H, d, J=7.3, Ar-H), 7.11-7.15 (3H, m, Ar-H), 7.21 (2H, d, J=7.3, Ar-H), 7.41 (2H, d, J=7.3, Ar-H); δ_C (100 MHz, $CDCl_3$) 21.2 (CH_3), 21.6 (CH_3), 69.4 (C-6), 75.6 (C-4), 79.7 (C-2), 93.3 (C-7), 115.2 (Ar-C), 122.3 (Ar-C), 127.7 (Ar-C), 129.0 (Ar-C), 129.3 (Ar-C), 134.4 (Ar-C), 135.6 (Ar-C), 155.9 (Ar-C) and 165.0 (C=O); *m/z* (EI) 375 (M^+, 6%) and 155.0; ν_{max}/cm^{-1} (KBr) 2989, 1782, 1713, 1599 and 1494.

6-(4-Fluoro-phenyl)-2,4-dimethyl-7-phenoxy-3-oxa-5-thia-1-aza-bicyclo[4.2.0]octan-8-one (**2c**): Colourless oil (86%) (Found: C, 63.28; H, 4.67; N, 3.79; $C_{19}H_{18}FNO_3S$ requires C, 63.49; H, 5.05; N, 3.90%); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, J=5.9, CH_3), 1.55 (3H, d, J=5.9, CH_3), 5.15 (1H, q, J=5.9, H-4), 5.59 (1H, s, H-7), 5.68 (1H, q, J=5.9, H-2), 6.62 (2H, d, J=7.9, Ar-H), 6.86–6.93 (3H, m, Ar-H), 7.11 (2H, t, J=7.9, Ar-H), 7.43–7.46 (2H, m, Ar-H);

δ_C (100 MHz, $CDCl_3$) 19.6 (CH_3), 23.1 (CH_3), 64.8 (C-6), 70.4 (C-4), 72.8 (C-2), 96.2 (C-7), 114.2 (Ar-C), 115.4 (Ar-C), 120.1 (Ar-C), 129.1 (Ar-C), 130.5 (Ar-C), 133.9 (Ar-C), 158.8 (Ar-C), 160.5 (Ar-C) and 173.6 (C=O); *m/z* (EI) 359 (M^+, 6%) and 138.0.

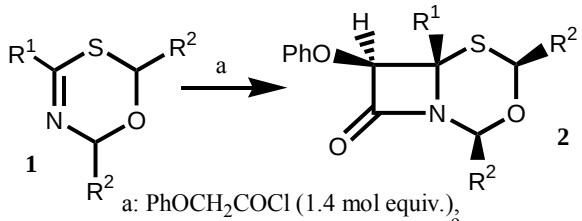
2,4-Diisopropyl-7-phenoxy-6-phenyl-3-oxa-5-thia-1-aza-bicyclo[4.2.0]octan-8-one (**2d**): Pale yellow oil (76%) (Found: C, 69.50; H, 6.80; N, 3.55; $C_{23}H_{27}NO_3S$ requires C, 69.49; H, 6.85; N, 3.52%); δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, J=6.0, CH_3), 1.03 (3H, d, J=6.0, CH_3), 1.04 (3H, d, J=5.9, CH_3), 1.08 (3H, d, J=5.9, CH_3), 1.75 (1H, m, -CH-Me_2), 2.04 (1H, m, -CH-Me_2), 4.75 (1H, d, J=6.0, H-4), 4.90 (1H, d, J=5.9, H-2), 5.55 (1H, s, H-7), 6.60 (2H,d, J=7.3, Ar-H), 7.07-7.7.11 (3H, m, Ar-H), 7.17-7.24 (3H, m, Ar-H), 7.52 (2H,d, J=7.3, Ar-H); δ_C (100 MHz, $CDCl_3$) 13.6 (CH_3), 14.0 (CH_3), 14.6 (CH_3), 16.1 (CH_3), 36.7 (CH-Me_2), 40.2 (CH-Me_2), 65.4 (C-6), 73.9 (C-4), 76.3 (C-2), 96.2 (C-7), 114.2 (Ar-C), 120.1 (Ar-C), 126.9 (Ar-C), 128.4 (Ar-C), 128.9 (Ar-C), 129.1 (Ar-C), 138.3 (Ar-C), 158.8 (Ar-C) and 173.6 (C=O); *m/z* (ES) 397.2 (M^+, 100%).

2,4-Dibutyl-7-phenoxy-6-phenyl-3-oxa-5-thia-1-aza-bicyclo[4.2.0]octan-8-one (**2e**): Colourless oil (83%) (Found: C, 70.85; H, 7.37; N, 3.39; $C_{25}H_{31}NO_3S$ requires C, 70.55; H, 7.34; N, 3.29%); δ_H (400 MHz, $CDCl_3$) 0.96 (3H, t, J=5.8, CH_3), 1.10 (3H, t, J=5.8, CH_3), 1.33 (2H, m, -CH_2-), 1.28 (2H, m, -CH_2-), 1.31 (2H, m, -CH_2-), 1.40 (2H, m, -CH_2-), 1.79 (2H, m, -CH_2-), 1.82 (2H, m, -CH_2-), 3.88 (1H, t, J=6.0, H-4), 4.94 (1H, t, J=6.0, H-2), 5.67 (1H, s, H-7), 6.61 (2H, d, J=7.9, Ar-H), 6.86 (1H, t, J=7.3, Ar-H), 7.08–7.12 (2H, m, Ar-H), 7.19–7.25 (3H, m, Ar-H), 7.43–7.45 (2H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 22.7 (CH_3), 23.1 (-CH_2-), 24.0 (-CH_2-), 25.5 (-CH_2-), 26.3 (-CH_2-), 34.2 (-CH_2-), 37.7 (-CH_2-), 65.4 (C-6), 74.2 (C-4), 76.6 (C-2), 96.2 (C-7), 114.2 (Ar-C), 120.1 (Ar-C), 126.9 (Ar-C), 128.4 (Ar-C), 128.9 (Ar-C), 129.1 (Ar-C), 138.3 (Ar-C), 158.8 (Ar-C) and 173.6 (C=O); *m/z* (EI) 397 (M^+ - CO, 3%) and 77.

RESULTS AND DISCUSSION

The synthesis of 6*H*-oxathiazines **1** have been previously reported[12] and in this study we employed the 6*H*-oxathiazines **1** having imine moiety to react with phenoxyacetylchloride in the presence of Et_3N to give β-lactam derivatives **2** in high yields. From the mechanistic point of view, deprotonation of the α-proton of phenoxyacetylchloride afforded phenoxy-ketene intermediate, which underwent a [2 + 2] cycloaddition with the imine moiety of the oxathiazine **1** to afford the β-lactam derivatives **2** (Scheme 1). To examine the versatility of the methodology a wide variety of 6*H*-1,3,5-oxathiazines were examined for the generality, scope and limitation of this approach (Table 1).

However, the [2 + 2] cycloaddition of **1f-i** with ketene did not proceed to afford the expected products. It was found that in the substrates **1,** substituents (R^1 and R^2) at C-2, C-4 and C-6 positions played vital role for the reaction. When the R^2 substituent was a bulky group (*t*-butyl), the reaction did not occur (Table 1, entry 7-9). When both R^1 and R^2 substituents were methyl group, the reaction was also unsuccessful (Table 1, entry 6), which might be due to the electron enrichment at imine moiety by methyl group (R^1), which in turn deactivated the imine moiety toward [2+2] cycloaddition with ketene.



a: $PhOCH_2COCl$ (1.4 mol equiv.), Et_3N (1.5 mol equiv.),DCM, 0-5 ^oC, 2h

Scheme 1

The relative stereochemistry of all the stereogenic centers were determined by X-ray analysis of **2a**, and the ORTEP drawing of **2a** is shown in Figure 1.[13] The X-ray crystallographic analysis revealed that the orientation of substituents at *C*-2 and *C*-4 were *cis* to each other. The substituents at *C*-6 and *C*-7 were also *cis* to each other

Table 1. Synthesis of 3-oxacepham 2

Entry	Substrate	R^1	R^2	product	yield (%)[a]
1	1a	Ph	Me	2a	84
2	1b	*p*-Cl-C_6H_4	Me	2b	87
3	1c	*p*-F-C_6H_4	Me	2c	86
4	1d	Ph	*i*-Pr	2d	76
5	1e	Ph	*n*-C_4H_9	2e	83[b]
6	1f	Me	Me	-	0
7	1g	Ph	*t*-C_4H_9	-	0
8	1h	Me	*t*-C_4H_9	-	0
9	1i	*p*-Cl-C_6H_4	*t*-C_4H_9	-	0

[a] Isolated yield, [b] Diastereomeric mixture (20:1)

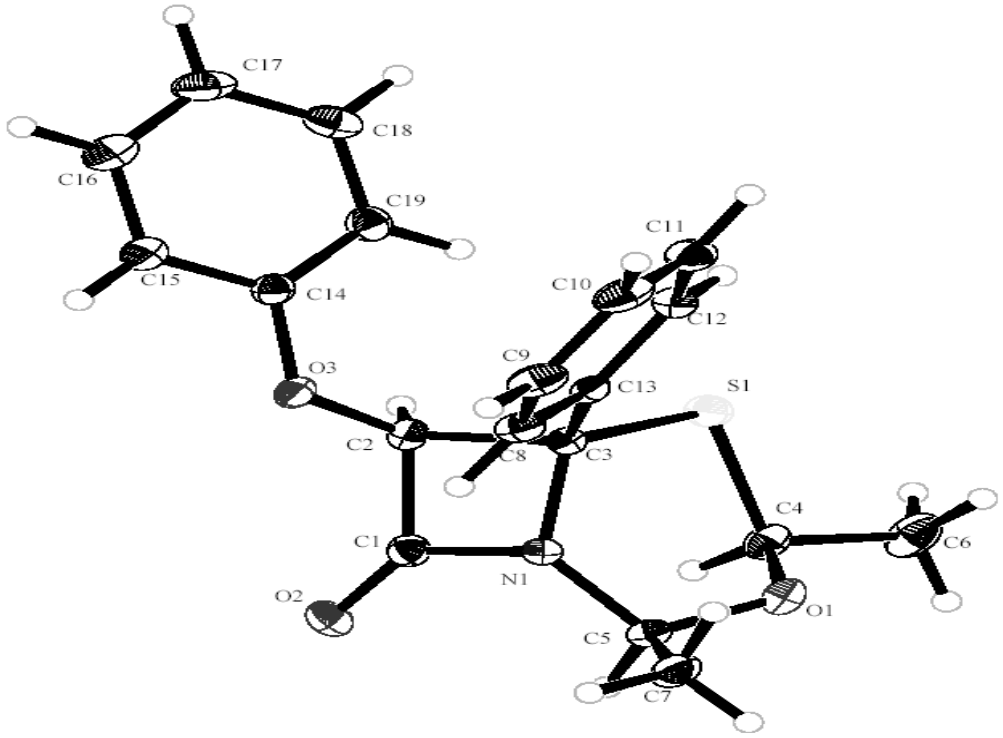


Figure 1. ORTEP Drawing of compound 2a: Selected bond lengths (A) and Angles (deg): O1-C4=1.413(2); S1-C3=1.838(2); S1-C4=1.839(2); O2-C1=1.210(2); O3-C14=1.379(2); N1-C3=1.474(2); O1-C5=1.425(2); O3-C2=1.399(2); N1-C1=1.365(2); N1-C5=1.457(2); C3-S1-C4=98.08(8); C2-O3-C14=116.8(1); C1-N1-C5=128.9(1);O2-C1-N1=131.6(2); S1-C3-N1=110.2(1); S1-C3-C13=11113.7(1); N1-C3-C13=115.6(1).

CONCLUSION

A wide variety of biologically important 3-oxacepham derivatives have been synthesized through [2+2] cycloaddition of the imine moiety of 6*H*-oxathiazines with phenoxyacetylchloride in the presence of Et_3N to give β-lactam derivatives in high yields. The scope and limitation of this approach was also explored.

REFERENCES

1. Manhas, M.S. and Bose, A.K. 1971. *Beta lactams-Natural and synthetic: Part I.* Wiley Interscience, New York, p.187.

2. Ratcliffe, R.W., Salzmann, T.N. and Christensen, B.G. 2000. A novel synthesis of the carbapen-2-em-ring system. *Tetrahedron Lett.* **21**, 31-34.

3. Brown, D., Brown, G.A., Andrews, M., Large, J.M., Urban, D., Butts, C.P., Hales, N.J. and Gallagher, M. 2002. The azomethine ylide strategy for β-lactam synthesis. Azapenams and 1-azacephams. *J. Chem. Soc., Perkin Trans.* **1**, 2014-2021.

4. Hamashima, Y., Yamamoto, S., Kubota, T., Tokura, K., Ishikura, K., Minami, K., Matsubara, F., Yamaguchi, M., Fikkawa, I. and Nagata, W. 1979. Synthesis studies on β-lactam antibiotics. 19. Synthesis of 3'-nor-type 1-oxacephems. *Tetrahedron Lett.* **20**, 4947-4950.

5. Howarth, T.T., Brown, A.G. and King, T.J. 1976. Clavulanic acid, a novel β-lactam isolated from *Streptomyces clavuligerus*; X-ray crystal structure analysis. *Chem. Commun*. 266b.

6. Furman, B., Thurmer, R., Kaluza, Z., Volter, W. and Chmielewski, M. 1999. A new acetal resin valuable for the solid-phase synthesis of 1-oxacepham via a cyclization/ cleavage step. *Tetrahedron Lett*. **40**, 5909-5912.

7. Korolkovas, A. 1988. *Essentials of medicinal Chemistry*. 2nd Ed., John Wiley and Sons, NewYork, p. 783.

8. Nishimura, S., Sasaki, H., Yasuda, N., Matsumoto, Y., Kamimura, T., Sakane, K. and Takaya, T. 1989. Synthesis and biological activity of 7 alpha-hydroxyethyl-1-oxacephem derivatives. *J. Antibiot. (Tokyo)* **42**, 1124-1132.

9. Herak, J.J., Vinkovic, M. and Lukic, I. 1995. Functional Derivatives of 4-Oxoazatidine-2-sulfinic Acids in Asymetric Synthesis of 2-Azacepham Sulfoxides and their Transformation. *Tetrahedron* **51**, 5083-5092.

10. Herak, J.J., Vinkovic, M., Mandic, Z., Lukic, I., Tomic, M. and Kovacevic, M. 1994. Synthesis, Structural Characterization and Stereocontrolled Degradation of 2-Azacephams. *Tetrahedron Assym*. **5**, 1605-1612.

11. Kar, G.K., Chatterjee, G.G. and Ray, J.K. 1988. Studies on New β-lactams: Synthesis of 3-Oxacepham Derivatives. *Ind. J. Chem.* **27B**, 786-789.

12. Islam, M.R,, Kazuaki, S., Shigenobu, A., Yuji, T. and Chizuko, K. 2004. Novel Conversion of 6*H*-1,3,5-Oxathiazine *S*-Oxides into 5-Membered Heterocyclic Compounds. *Heteroatom Chem*. **15**, 175-186.

13. X-ray crystallographic data for 2a. Colorless prism of 2a suitable for X-ray investigation was obtained from ether. Crystal data: $C_{19}H_{19}NO_3S$, FW=341.42, crystal size 0.25x0.20x0.20 mm^3, monoclinic, space group $P2_1/n$ (#14), a=12.393(4), b=8.449(3), c=16.687(6) Å, β=99.908(5)˚, V=1721.0(1) $Å^3$, Z=4, D_{calc}=1.317 g/cm^3, μ=2.04 cm^{-1}. From 16063 reflections measured 3814 were unique (R_{int}=0.025). R=0.036, R_w=0.037, MoKα (λ=0.71070 Å, T=-100.0 ˚C. The structure was solved by direct methods (SIR92).