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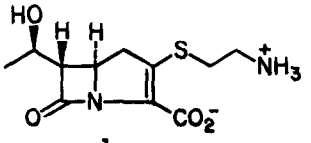
CYCLOBUTANONE ANALOGS OF β-LACTAM ANTIBIOTICS : SYNTHESIS OF N-ACETYLDEAZATHIENAMYCIN

A. J. Cocuzza* and G. A. Boswell
CENTRAL RESEARCH AND DEVELOPMENT DEPARTMENT
E. I. DU PONT DE NEMOURS AND COMPANY
EXPERIMENTAL STATION
WILMINGTON, DELAWARE 19898

Abstract: Cyclobutanone analogs of thienamycin, including N-acetyldeazathienamycin, have been synthesized and their chemical and biological properties studied.

The discovery in recent years of the non-classical β-lactams has forced a reevaluation of what structural features are required for biological activity in this important class of antibiotics. For example, the potent antibiotics thienamycin **(1)**[1] and sulfazecin **(2)**[2] differ greatly in structure from the classical penicillins and cephalosporins as well as from each other. While a reactive β-lactam ring, the one invariant structural characteristic of these compounds, may be the single structural prerequisite for antibacterial activity[3], we wondered if an activated cyclobutanone might fulfill a function similar to the β-lactam and be capable of acylating its target enzymes. To this end, we have synthesized and tested cyclobutanone analogs **(3)** of thienamycin which are activated to nucleophilic attack by appropriately placed electron-withdrawing groups (Z). During the course of this work, there have appeared four reports[4,5,6,20] of cyclobutanone analogs of β-lactams, though none of these describes compounds possessing acylating ability.



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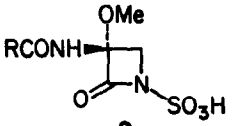

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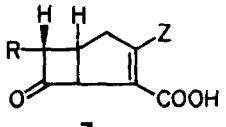

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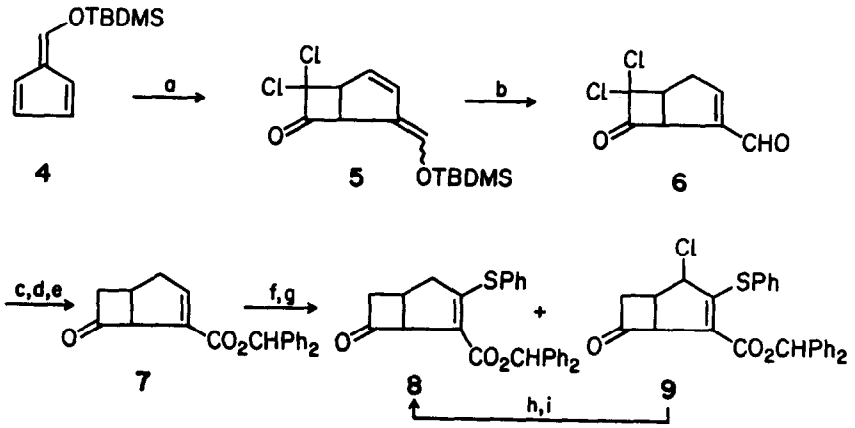
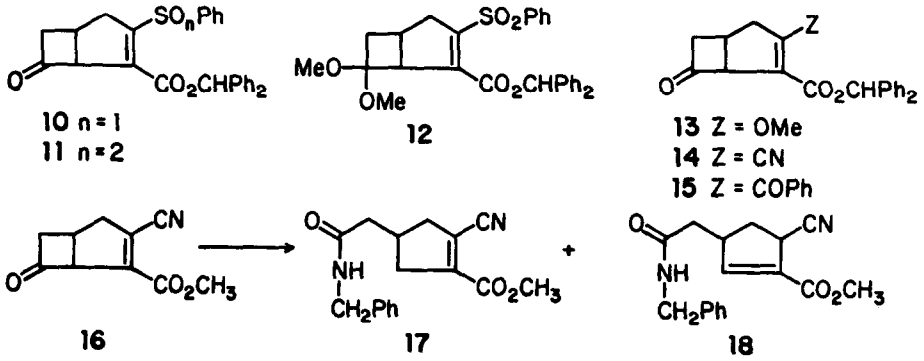
Entry into the bicyclo[3.2.0]heptenone ring system was accomplished by use of the well-known [2+2] cycloaddition of ketenes to cyclopentadiene[7]. Silyloxyfulvene **4**, prepared by sequential treatment of sodium cyclopentadienide with ethyl formate and t-butyldimethylchlorosilane, was reacted with dichloroketene to give **5** as a mixture of E and Z isomers. Hydrofluoric acid cleavage of the t-butyldimethylsilyl group afforded the α,β-unsaturated aldehyde **6**[8] (34% from cyclopentadiene) which was converted in three steps (52% yield) to the desired parent ring system **(7)** in which the free acid is protected as its benzhydryl ester[9]. Functionalization of the double bond was accomplished by Michael addition of thiophenol, followed by oxidation with sulfuryl chloride which reintroduces the double bond to give **8**[10]. The oxidation also produces a significant amount of chlorinated derivative **9**. However when this mixture was treated first with zinc to dechlorinate **9** followed by diisopropylamine to reconjugate the double bond[11], **8** alone was obtained (87.5% from **7**).



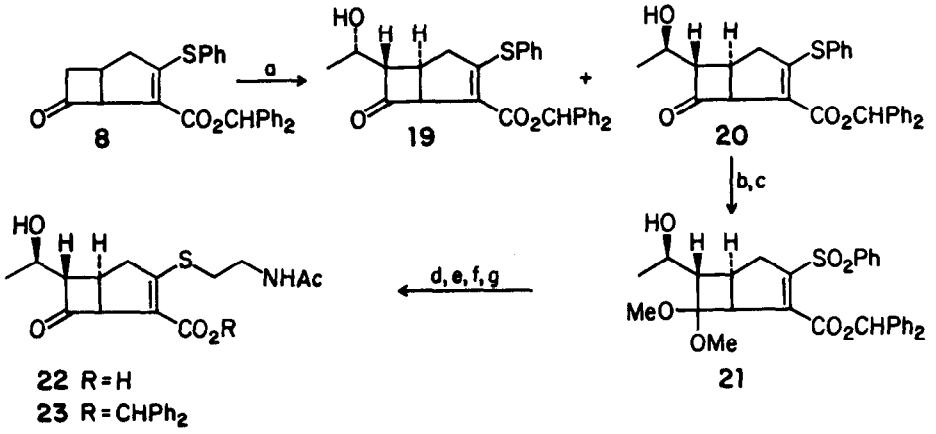
a) $Cl_2CHCOCl/Et_3N, C_6H_{12}$, RT, 1.5h; b) 50% HF, CH_3CN, reflux, 35 min; c) Jones rgnt, acetone, 20°, 45 min; d) Ph_2CN_2, EtOAc, RT, 1h; e) Zn, THF/HOAc, RT, 6h; f) $PhSH/Et_3N$, THF, RT, 1h; g) SO_2Cl_2/pyridine, CH_2Cl_2, -60°, 30 min; h) Zn, CH_2Cl_2/HOAc, RT, 30 min; i) DIA, DMSO, RT, 22h.

Compound **8** proved a useful intermediate for the preparation of a number of compounds of general class **3** bearing electron withdrawing groups. Sulfoxide **10** was prepared by m-chloroperbenzoic acid oxidation of **8** [MCPBA,CH_2Cl_2,-40°,1h,79%]. To obtain the corresponding sulfone **11**, it was necessary first to protect the ketone as its dimethyl ketal[$(MeO)_3CH/H^+$, MeOH/THF, reflux, 20 min], oxidize [MCPBA,CH_2Cl_2, reflux, 45 min, 97%] to **12** and deprotect [4NHCl, HOAc, RT, 30 min, 48%]. We were pleased to discover that the phenylsulfonyl group of **12** undergoes smooth displacement by a variety of nucleophiles. For example, reaction with methoxide and cyanide yielded after ketal hydrolysis **13** and **14** respectively. Phenylketone **15** was prepared from **12** by a 3-step sequence initiated by displacement of the phenylsulfonyl group with trimethyltinlithium[12]. The corresponding free carboxylic acids could be obtained by hydrolysis of the benzhydryl esters with anisole in trifluoroacetic acid.

To test the acylating ability of our fused cyclobutanones, we reacted them with benzylamine in methylene chloride solution at room temperature[13]. As expected, unactivated cyclobutanones **7**, **8**, and **13** were inert to these reaction conditions and were



recovered unchanged after several hours. However, sulfoxide **10**, sulfone **11**, nitrile **14**, and ketone **15** reacted quickly to acylate benzylamine. Similar treatment of methyl ester **16** afforded two ring-opened products (**17** and **18**) which could be separated and individually characterized.



a) $LiN(SiMe_3)_2/Cp_2ZrCl_2/CH_3CHO$, THF, -78° 0°, 1h, 50%; b) $(MeO)_3CH/H^+$, THF/MeOH, reflux, 1 h; c) MCPBA, CH_2Cl_2, reflux, 1.5h, 82%; d) $NaSCH_2CH_2NH_2$, MeOH/THF, RT, 15 min; e) Ac_2O, MeOH, RT, 15 min; f) 4N HCl, acetone, RT, 4.5h, 74%; g) anisole/TFA, RT, 15 min, 80%.

An important synthesis target was deazathienamycin, which required the sterospecific introduction of the hydroxyethyl side chain as well as the 2-aminoethylthio group present in thienamycin. Treatment of the lithium enolate of **8** with acetaldehyde afforded two products in which the undesired threo, trans isomer **19**[14] greatly predominated. Use of the dicylopentadienylchlorozirconium enolate[15], however, yielded the two trans aldol products in equal amounts. The natural erythro, trans isomer **20**[16] was first converted into its ketal sulfone **21**. Finally, displacement of the phenylsulfonyl group with sodium 2-aminoethylthiolate followed by acetylation and hydrolysis afforded N-acetyldeazathienamycin **22**[12,18].

While no cyclobutanone carboxylic acids (such as **22**) in the present study demonstrated any antibacterial activity, we were pleased that sulfoxide and sulfone benzhydryl esters (such as **10**,**11**, and the sulfoxides of **19** and **20**) were active against gram positive bacteria. Moreover, several sulfide, sulfoxide, and sulfone esters demonstrated anti-betalactamase activity.[19]

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8. This structure was confirmed by x-ray crystallographic analysis.

9. The free carboxylic acid corresponding to **1** has been synthesized by similar chemistry involving cycloaddition of dichloroketene to 6,6-bis(methylthio)fulvene (ref. 4).

10. ^{1}H NMR ($CDCl_3$,220 MHz) δ 2.27 (1H,dd,J=17,3.5 Hz), 2.6-3.0(3H,m), 3.18(^{1}H,ddd,J=17,8,4), 4.57 (1H,m), 6.84(1H,s), 7.0-7.5 (15H,m); IR (Nujolmull) 1625, 1715, 1785 ca^{-1}.

11. These conditions for double bond isomerization were first reported in a thienamycin total synthesis: Schmitt, S. M.; Johnston, D. B. R.; Christensen, B. G. J. Org. Chem., **1980**, 45, 1142.

12. Phenylketone **15** was prepared from **12** by: i, Me_3SnLi, -78°→ 25°, 30 min; ii, MeLi/PhCOCl, THF, -78°, 10 min; iii, 4N HCl, HOAc, 25°, 10 min.

13. For a description of rates of β-lactam hydrolysis, see ref. 3.

14. This structure was confirmed by x-ray crystallographic analysis of a derivative (sulfone dimethylketal).

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16. ^{1}H NMR ($CDCl_3$,400 MHz) δ 1.18 (3H,d,J=6.4 Hz), 1.61 (1H,s,J=4.6 Hz), 2.30 (^{1}H,dd,J=18.0,3.5 Hz), 2.83 (1H, ddd, J=8.2, 5.8, 6.4 Hz), 2.90 (1H,ddd,J=18.0, 8.2, 1.8 Hz), 3.11 (1H,ddd,J=5.8,5.2,3.0 Hz), 412 (1H, qdd, J=6.4, 4.6, 5.2 Hz), 4.54 (1H, dddd,J=6.4,3.5,3.0,1.8 Hz), 6.95 (1H,s), 7.2-7.6 (15H,m); IR (Nujolmull) 3540,1775, 1680 cm^{-1}.

17. The acetyl derivative of deazathienamycin was prepared for ease in isolation and identification. N-Acetylthienamycin is a naturally occurring substance with similar antibacterial activity to thienamycin (see ref. 1).

18. ^{1}H NMR of **23** ($CDCl_3$, 360 MHz) δ 1.29 (3H,d,J=6.4 Hz), 1.95 (3H,s), 3.05 (4H,m), 3.20 (1H,ddd,J=5.8,5.8,3.1 Hz), 3.36 (1H,ddd,H=18,8.2,2.0 Hz), 3.48 (2H,m), 4.17 (1H, qd, J=6.4,5.8 Hz), 4.51 (1H,m), 6.00 (1H, broad t), 6.88 (1H,s), 7.2-7.35 (6H,m), 7.4-7.55 (4H,m); IR ($CHCl_3$) 1498,1520, 1560,1673,1774 cm^{-1}.

19. Typical antibacterial MIC's vs. S. aureus were 25-50 μg/ml. The anti-betalactamase activity of these compounds was determined by demonstration of synergism with penicillin G against betalactamase producing strains of S. aureus.

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