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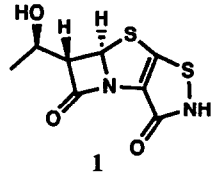
STUDIES DIRECTED TOWARDS NOVEL PENEM ANTIBACTERIALS

J.G. Phillips,*[1] D. Chu,[1] S. Spanton,[2] R. Henry,[2] and J.J. Plattner[1]
Anti-infective Research Division, Abbott Laboratories,
Abbott Park, Illinois 60064

Summary: The reaction of 2-thioxopenam esters with hydroxylamine-O-sulfonic acid leads to stable 2-sulfeneamide penem esters that do not cyclize to give the corresponding isothiazolinones.

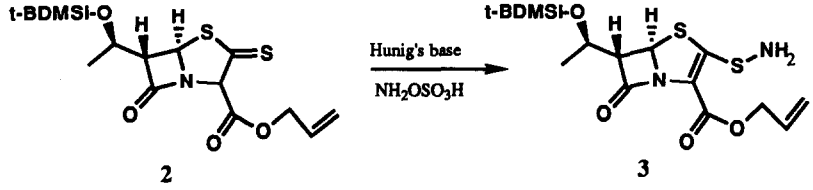
In the course of investigations toward the discovery of new structural type beta-lactam antibacterials, we decided to evaluate the possibility of substituting an isothiazolinone ring moiety for the carboxyl group in penems by undertaking the study of the preparation of penem isothiazolinone **1**. The isothiazolinone ring system possesses comparable electron withdrawing power and acidity to a carboxylic acid, and had served well as a carboxylic acid mimic in the quinolone antibacterial area.[3] Furthermore, replacement of the carboxylic acid group with a five membered lactam moiety in cephalothin has been reported to provide a cephalosporin with moderate Gram positive activity.[4] Our efforts describe the first report of the synthesis of a stable penem antibacterial containing a sulfur-nitrogen bond at C-2.



1

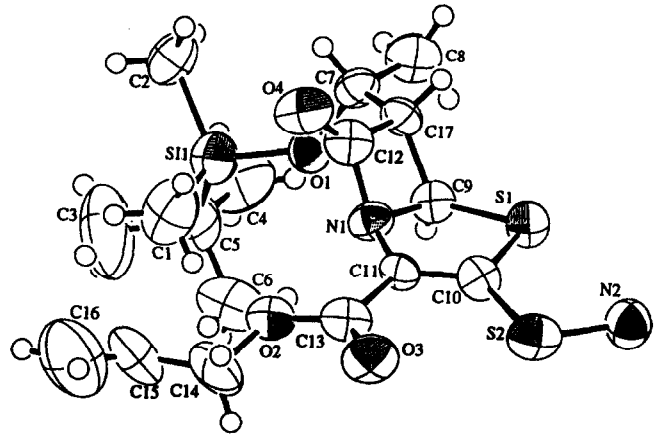
The thioxopenam **2** was prepared according to established procedures.[5] Treatment of **2** with hydroxylamine-O-sulfonic acid in the presence of Hunig's base in chloroform at 5 ° C led, after stirring for one half hour, to the formation of primary sulfeneamide **3**. (Scheme I). Isolated yields were generally 75%, and the product was purified by column chromatography (silica gel, CH_2Cl_2/hexanes 6:4). The corresponding methyl and trimethylsilylethyl esters of **2** gave similar results. Although the ^1H NMR spectrum at 300 MHz and IR spectrum of **3** supported the assigned structure, the assignment was unambiguously confirmed by X-ray crystallographic determination.[6] An ORTEP projection of **3** is shown in Figure 1.

Scheme I



2 **3**

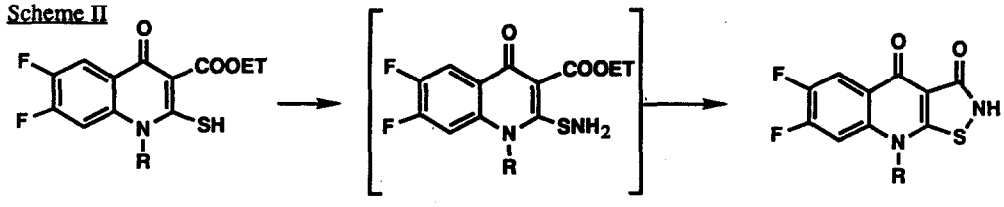
Figure 1



Ortep projection of 3. The numbering is for crystallographic purposes.

The chemistry reported here is contrasted by the facile isothiazolinone ring formation reported recently in the quinolone antibacterial area. For example, treatment of the quinolone ethyl ester **4** with hydroxylamine-O-sulfonic acid in aqueous THF in the presence of sodium bicarbonate at room temperature yielded sulfeneamide **5** which cyclized in situ to give the desired heterocycle 6,7-difluoro-9-cyclopropyl-2,3,4,9-tetrahydroisothiazolo[5,4-b]quinolone-3,4-dione **6** (85%).[3] (Scheme II).

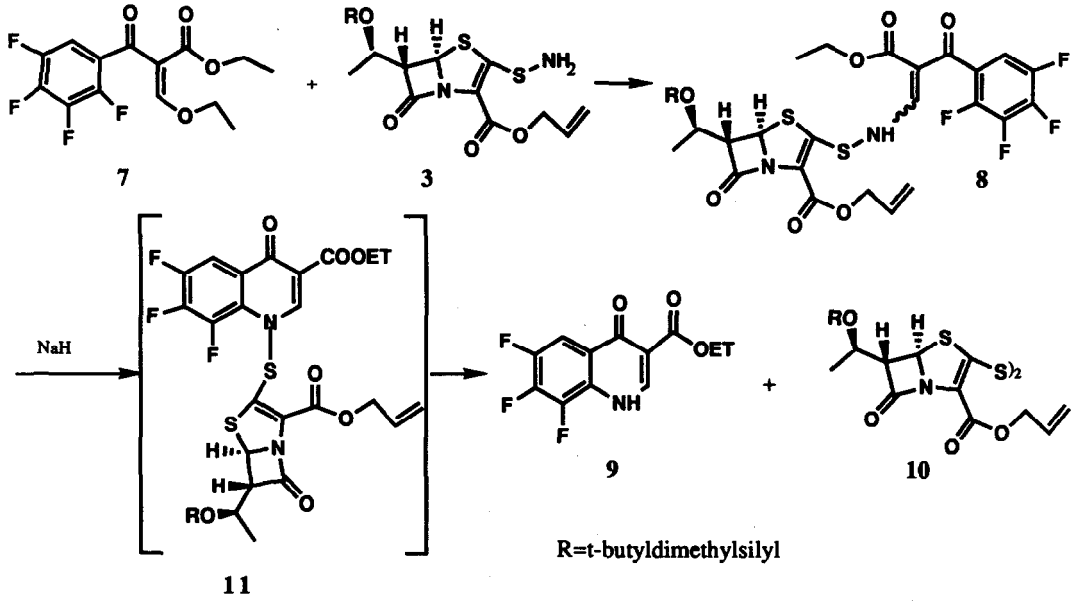
Scheme II



4 R=c-C_3H_5 **5** **6**

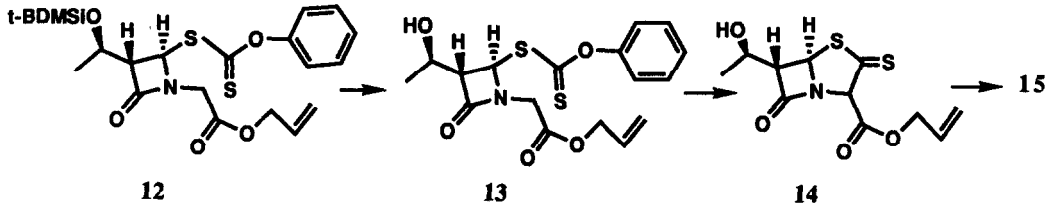
Since the sulfeneamide penem **3** failed to undergo the desired cyclization to the isothiazolinone **1**, we promptly explored the possibility of preparing a stable carboxylic acid containing penem antibacterial with sulfur-nitrogen substitution at C-2. To establish a reference point as to the chemical reactivity of these penem sulfeneamides, we decided to attempt the condensation of penem **3** with enol ether **7**. After stirring the enol ether **7** with sulfeneamide **3** in CH_2Cl_2 for two weeks[7] at room temperature in a closed vial, a 2:1 mixture of cis and trans enamines **8** was isolated in 80% yield after tlc chromatography (ethyl acetate:hexanes 3:7). Subsequently, deprotonation of the enamine nitrogen with NaH in THF at 0°C provided quinoline **9** and disulfide **10** (85% yield after tlc chromatography (ethyl acetate:hexanes 1:1).[8] Presumably, the enamine nitrogen anion selectively displaces the aromatic fluoride yielding unstable **11** which provides **9** and **10** upon workup. (Scheme III).

Scheme III



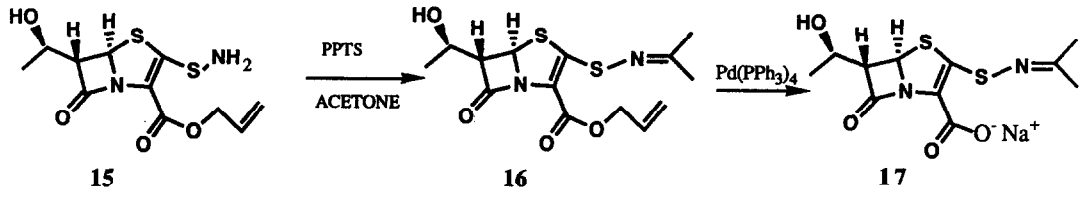
Deprotection of the t-butyldimethlysilyl protecting group of **3** with n-butyl ammonium fluoride in THF in the presence of acetic acid led to extensive decomposition. The deprotected sulfeneamide **15** could be prepared by modification of literature procedures.[5] It involves silyl deprotection[9] of **12** followed by a novel dianion cyclization[10] of **13** to thioxopenam **14** and subsequent treatment of **14** with NH_2OSO_3H. (Scheme IV)

Scheme IV



Reaction of penem **15**[11] with acetone in the presence of 5 mole percent of PPTS gave the corresponding penem sulfenimine **16** in 80% yield after filtration through florisil and tlc chromatography (ethyl acetate: hexanes 1:1).[12](Scheme V). Deprotection of the allyl ester of **16** was attempted by Pd catalysed transallylation in ethyl acetate at room temperature in the presence of sodium 2-ethyl hexanoate.[13] The crude sodium salt **17** was isolated by precipitation with ether, centrifugation, and decanting the organic layer. The ^1H NMR at 300 MHz (D_2O) and IR spectrum of the crude salt was consistent with the desired structure, but all attempts to further purify the compound by reverse phase chromatography were unsuccessful.[14]

Scheme V



15 16 17

Further studies and efforts to obtain isolable purified penems containing a S-N bond at C-2 are in progress.

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References and Notes:

1. Anti-infective Research Division
2. Single crystal X-ray crystallographic services.
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6. Complete X-ray crystallographic data are available from Abbott Laboratories Single Crystal X-ray Services. Request X-ray Structure Report 389-JP-37954-180.
7. These primary sulfeneamide penems are considerably less reactive than amines. Methods applied to drive the reaction to completion led to either decomposition or epimerization of the penem sulfenamide.The reaction was closely monitored by tlc.
8. Satisfactory spectral data (IR, ^{1}H NMR at 300 MHz, and MS) were obtained for all new compounds. Selected physical data: **3**: ^{1}H NMR ($CDCl_3$): 0.07 (6H, s), 0.88 (9H, s), 1.2 (3H, d, J= 6Hz), 2.94 (2H, s, NH_2), 3.59 (1H, dd, J= 6Hz, 1.5 Hz), 4.13 (1H, m), 4.61 (2H, m), 5.14 (1H, m), 5.32 (1H, m), 5.51 (1H, d, J= 1.5 Hz), 5.84 (1H, m). **8**: (2:1 mixture): ^{1}H NMR ($CDCl_3$): 0.07 (6H, s), 0.88 (9H, s), 1.02 (3H, t, J= 7Hz), 1.2 (3H, t, J= 7Hz), 1.24 (3H, d, J= 6 Hz), 3.77 (1H, m), 4.13 (2H, q, J= 7 Hz), 4.16 (2H, q, J= 7 Hz), 4.25 (1H, m), 4.72 (2H, m), 5.27 (1H, m), 5.43 (1H, m), 5.73 (1H, d, J= 1.5 Hz), 5.76 (1H, d, J= 1.5 Hz), 5.92 (1H, m), 7.09 (1H,m), 7.91 (1H, d, J= 13.5 Hz), 8.17 (1H, d, J= 12 Hz), 9.69 (1H, d, J= 13.5 Hz), 10.73 (1H, d, J= 12 Hz).
9. Complete silyl deprotection of **12** was obtained by use of 1.1 equivalents of n-butyl ammonium fluoride in dry THF (0.1 M) at room temperature under N_2 in the presence of 5 equivalents of acetic acid with stirring for 5-6 days. Isolated yields were generally 75% after chromatography (ethyl acetate: hexanes 1:1).
10. Thioxopenam **14** was obtained by addition of **13** to 2.1 equivalents of lithium bis (trimethylsilyl) amide in THF at -78°C with stirring for 5 minutes followed by quenching with dilute aqueous HCl. There was no evidence (^{1}H NMR at 300 MHz) of any epimerization at C-6 using this procedure. Isolated chemical yield was 80%.
11. Penem **15** exhibited no antibacterial activity, but moderate antifungal and antitumor activity when tested in vitro. MIC values against several Candida species were 12.5 ug/ml. IC_{50} values against B16F10, HT29, A549, and P388 were 2.9, 3.5, 49.2, and 6.5 ug/ml, respectively.
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13. P.D. Jeffrey and S.W. McCombie, *J. Org. Chem.*, **1982**, 47, 587.
14. **16**: ^{1} H NMR ($CDCl_3$): 1.37 (3H, d, J= 6 Hz), 2.07 (3H, s), 2.12 (3H, s), 3.72 (1H, dd, J= 6 Hz, 1.5 Hz), 4.25 (1H, m), 4.75 (2H, m), 5.26 (1H, m), 5.44 (1H, m), 5.61 (1H, d, J= 1.5 Hz), 5.97 (1H, m). MS: M+1= 343. IR: 1780, 1680. CHN: Calc.: C: 49.10, H: 5.29, N: 8.18. Found: C: 49.22, H: 5.24, N: 8.14. MP: 156-158°C. **17**: ^{1}H NMR (D_2O): 1.33 (3H, d, J= 6 Hz), 2.11 (6H, s), 3.92 (1H, dd, J= 6 Hz, 1.5 Hz), 4.26 (1H, m), 5.69 (1H, d, J= 1.5 Hz). IR: 3400, 1770, 1590. Crude penem **17** exhibited weak in vitro Gram positive activity.

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