Nuclear analogs of β-lactam antibiotics. XX.[1] Synthesis and X-ray structure determination of exocyclic penems: sulfur analogs of clavulanic acid

JAMES L. DOUGLAS, ALAIN MARTEL, GILLES CARON, AND MARCEL MÉNARD
Bristol Laboratories of Canada, 100 Industrial Blvd., Candiac (Qué.), Canada J5R 1J1

AND

LINDA SILVEIRA AND JON CLARDY
Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, NY 14853, U.S.A.

Received October 21, 1983

JAMES L. DOUGLAS, ALAIN MARTEL, GILLES CARON, MARCEL MÉNARD, LINDA SILVEIRA, and JON CLARDY. Can. J. Chem. **62**, 2282 (1984).

Penems **5** were converted to exocyclic analogs **6** and **10**. These served as substrates for conversion to the sulfone **11** and oxopenam **12**. None of the products showed any activity as antibiotics or as β-lactamase inhibitors. A single cyrstal X-ray diffraction analysis of compound **6***a* verified the exocyclic penem structure.

JAMES L. DOUGLAS, ALAIN MARTEL, GILLES CARON, MARCEL MÉNARD, LINDA SILVEIRA et JON CLARDY. Can. J. Chem. **62**, 2282 (1984).

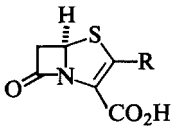
On a transformé des pénèmes **5** en analogues exocycliques **6** et **10** qui servent de substrats pour leur conversion en sulfone **11** et oxopéname **12**. Aucun de ces produits ne présente d'activité comme antibiotique ou comme inhibiteur de β-lactamase. Faisant appel à une analyse par diffraction de rayons-X sur un cristal unique, on a vérifié la structure pénème exocyclique du composé **6***a*.

[Traduit par le journal]

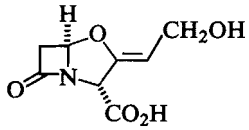
Can. J. Chem. Downloaded from www.nrcresearchpress.com by NORTHEASTERN UNIVERSITY on 11/30/14
For personal use only.

Introduction

The synthesis of simple penem structures **1** (R = H, Me) by Woodward and co-workers (1) and the modification by various groups (2–4) of their synthetic methodology to give generalized 2-substituted[2] penems **1** have made such compounds readily available as substrates for conversion to other novel β-lactams. Furthermore, the observation of β-lactamase inhibitory properties for clavulanic acid (5) provides incentive for generating structures such as **2** in which the 5-membered ring has an exocyclic double bond. One can then envisage ozonolysis of the double bond to oxopenam **3** which could be used as a substrate for further transformation.

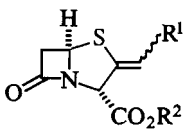


1

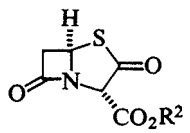


Clavulanic acid

As part of our ongoing program aimed at the discovery of β-lactam antibiotics (and (or) β-lactamase inhibitors) we set out to synthesize compounds of types **2** and **3** (and readily available) derivatives thereof).



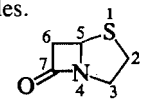
2



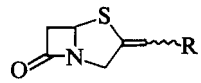
3

[1]For Part XIX, see ref. 16.

[2]The common penem numbers system as follows will be used, except in the Experimental titles.



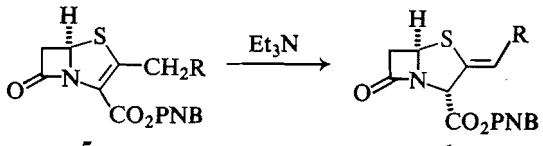
Since the inception of our work in this area, several research groups have published findings on the same or related compounds. A group at Sankyo has described the synthesis of oxopenam **3** (R^2 = H) and substituted derivatives from cephalosporins (6). Penicillin G has been converted to a 6-amido-oxopenam (7). The Glaxo research group has converted clavulanic acid into the exocyclic penem *Z*-**2** (R^1 = CH_2SAc, R^2 = H) but report it to have reduced antibacterial and β-lactamase inhibitory activity (3). Workers at Farmitalia have used a variation on the Woodward route (1) to prepare exocyclic penem **2** (R^1 = CO_2Et, R^2 = benzyl) (4). Beecham (8) and Pfizer (9) research groups have both prepared exocyclic penems **4** (lacking the important 3-carboxyl substituent) and report them to be devoid of antibacterial or β-lactamase inhibitory activity.



4

Results and discussion

The Beecham group have described the base catalyzed isomerization of the endocyclic double bond of oxapenems to the exocyclic (clavulanic acid type) position (10). Using their reaction conditions (organic base in an organic solvent) we have converted the 2-arylmethylpenems **5** (2) into the exocyclic penems **6**. In the case of R = phenyl, an equilibrium mixture of 80% **6** and 20% **5** was formed; for R = furyl or thienyl,



5 **6**

a R = phenyl *b* R = 2-furyl *c* R = 2-thienyl

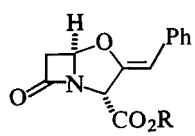
TABLE 1. Nuclear magnetic resonance spectra[a]

Compound	Vinyl	H-3	H-5	H-6α	H-6β	Other
2[b] (R^1 = CO_2Et; R^2 = benzyl)	6.14 (d, J = 1.2)	5.53 (d, J = 1.2)	5.36 (q)	3.70 (dd, J = 16 and 14)	3.20 (dd, J = 16 and 2)	1.28 (t), 4.22 (q)
6*a*	6.70 (d, J = 1)	5.58 (d, J = 1)	5.52 (q)	3.77 (dd, J = 16 and 4)	3.23 (dd, J = 16 and 2)	7.35 (s, Ph)
6*b*	6.57 (d, J = 1)	5.53 (d, J = 1)	5.50 (q)	3.77 (dd, J = 16 and 4)	3.25 (dd, J = 16 and 1.5)	7.43 and 6.4 (furyl)
6*c*	ca. 6.9	5.5–5.7	5.5–5.7	3.76 (dd, J = 16 and 5)	3.22 (dd, J = 16 and 1.8)	6.8–7.5 (thienyl)
6*d*	6.10 (d, J = 1)	5.58 (d, J = 1)	5.38 (q)	3.75 (dd, J = 16 and 4)	3.20 (dd, J = 16 and 2)	1.28 (t, J = 7, Et) 4.22 (q, J = 7, Et)
8	7.17 (d, J = 2)	5.37 (overlap with PNB)	4.68 (m)	3.6 (m)	3.6 (m)	7.4 (m, Ph)
9	—	5.17 (s)	5.57 (q)	3.97 (dd, J = 16.5 and 4)	3.45 (dd, J = 16.5 and 2)	—
10*a*	6.83 (d, J = 1)	5.48 (d, J = 1)	5.57 (q)	3.85 (dd, J = 16 and 4)	3.20 (dd, J = 16 and 1.5)	7.4 (m, Ph)
10*b*	6.75 (s)	5.53 (s)	5.55 (q)	3.87 (dd, J = 16 and 4)	3.20 (dd, J = 16 and 1.5)	7.61 and 6.5 (furyl)
10*c*	ca. 7.1	5.6–5.7	5.6–5.7	3.97 (dd, J = 16 and 4)	3.35 (dd, J = 16 and 1.5)	7.1–7.3 (thienyl)
10*d*	6.00 (s)	4.87 (s)	5.17 (m)	3.0–3.5 (m)	3.0–3.5 (m)	1.28 (t, J = 7, Et) 4.22 (q, J = 7, Et)
11	ca. 7.4	5.50 (d, J = 2)	4.83 (q)	3.82 (dd, J = 16 and 4)	3.46 (dd, J = 16 and 2)	7.35–8.0 (Ph)
12	—	5.10 (s)	5.72 (q)	4.10 (dd, J = 17 and 4)	3.47 (dd, J = 17 and 2)	—

[a]Spectra were recorded at 60 MHz and are reported in ppm downfield from TMS. All esters were in $CDCl_3$; free acids in acetone-d_6 except **10***c* in DMSO-d_6 and salt **10***d* in D_2O. Coupling constants are in Hz. All PNB esters showed doublets at δ 8.15–8.27 and 7.47–7.58 (J = 8.5) and a singlet at 5.29–5.37.
[b]Reference 4.

virtually complete conversion to the exocyclic form occurred. Minor changes in the *exo*/*endo* ratio (when R = Ph) were made by varying the reaction solvent. That the reaction only occurs when R contains a function that can conjugate with the exocyclic double bond is shown by the example of **5** (R = CH_2CO_2PNB): no isomerization was observed after prolonged treatment with base. The relative stereochemistry[3] shown for **6** (3 and 5 positions) follows from analogy to that found for **2** (R^1 = CO_2Et, R^2 = benzyl) by the Farmitalia group (4) since nmr spectra of the vinyl, H-3, and H-5 protons show a very close match between **2** and **6** both in chemical shift and coupling constants (see Table 1). The Beecham group have evidence that their isomerization product **7** (R = Me) is the *Z* isomer shown; the vinyl proton has a chemical shift of 5.57 ppm (10). If one adds a shift value of 0.6 to 0.7 ppm for going from an oxygen ring to sulfur ring (11), then one would predict a vinyl proton shift of 6.2 to 6.3 ppm for the *Z* isomer **6***a*. In fact, a vinyl proton shift of 6.70 ppm was observed (see Table 1), thus supporting the *E* assignment. However, these minor differences in chemical shift values do not provide very compelling evidence without having both isomers on hand. Molecular models of structure **6** show marked steric crowding between the aromatic ring in the *E* isomer and the ester at the 3-position, whereas the *Z* isomer shows no steric congestion. Thus, while ^1H nmr arguments favor the *E* geometry for compounds **6**, steric arguments favor the *Z* geometry.

A single crystal X-ray diffraction analysis of **6***a* conclusively verified the nmr based stereochemical assignments for the 3,5-relationship, while the double bond was shown to have the *Z* geometry. The phenyl ring, at least in the solid state conformation, is twisted slightly out of the plane of the double bond (~11°) presumably to relieve steric congestion. The molecular parameters[4] were unsurprising for a penem and the bridgehead nitrogen was 0.43 Å out of the plane of its nearest



7

[3]All compounds described are racemates; for convenience, just one enantiomer is shown.

[4]Fractional coordinates and thermal parameters, bond distances, bond angles, and observed and calculated structure factors for structure **6***a* are available, at a nominal charge, from the Depository of Unpublished Data, CISTI, National Research Council of Canada, Ottawa, Ont., Canada K1A 0S2.

Can. J. Chem. Downloaded from www.nrcresearchpress.com by NORTHEASTERN UNIVERSITY on 11/30/14
For personal use only.

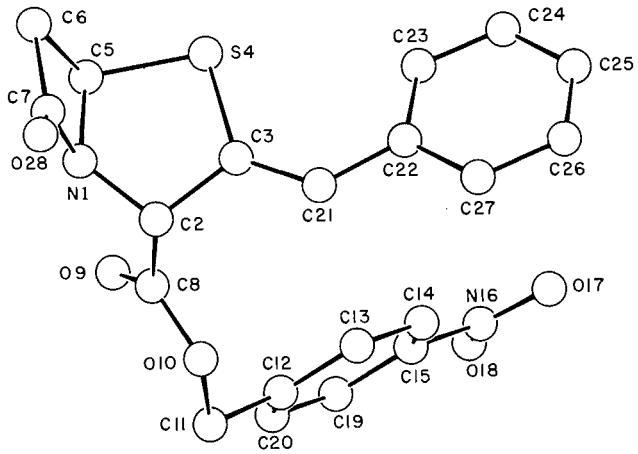
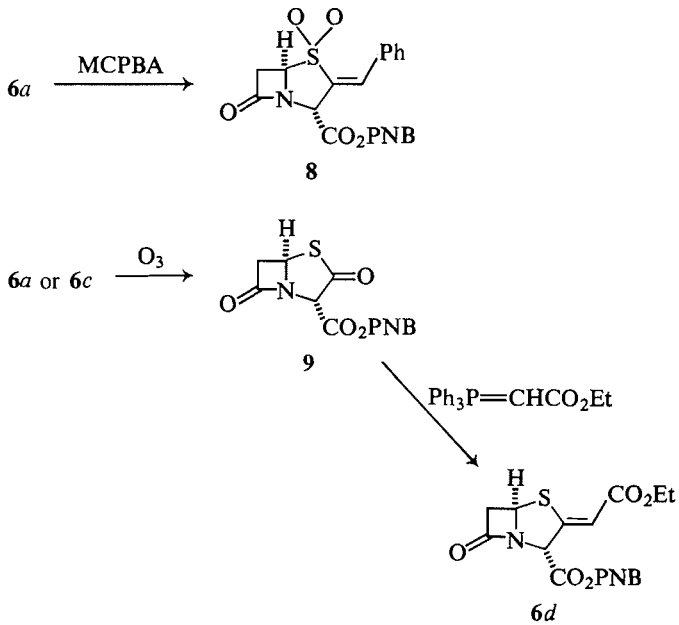


FIG. 1. A computer generated perspective drawing of the final X-ray model of **6***a*. Hydrogens are omitted.

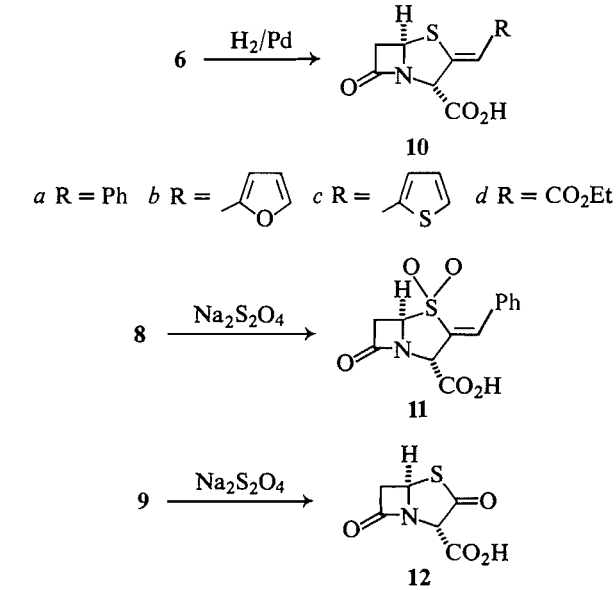


SCHEME 1

neighbors. A drawing of the final X-ray model is given in Fig. 1.

The sulfone **8** was prepared by the action of *m*-chloroperbenzoic acid on penem **6***a* (analogous to sulfone formation in the isocephems (12)) (see Scheme 1). The infrared spectrum of **8** shows strong peaks at 1320 and 1135 cm^{-1} (which do not appear in the spectrum of **6***a*), indicating the formation of the sulfone rather than the sulfoxide (ν(S=O) for sulfoxide: 1035–1070 cm^{-1}). Ozonolysis of the exocyclic double bond of **6***a* or **6***c* gave oxopenam **9**. Numerous attempts were made to carry out reactions between oxopenam **9** and Wittig reagents. All failed except for (carboxymethylene)triphenylphosphorane. This reagent gave penem **6***d* in low yield. Infrared and ^1H nmr spectra of **6***d* closely matched those reported for **2** (R^1 = CO_2Et, R^2 = benzyl) (4) (allowing for the difference between the *p*-nitrobenzyl and benzyl esters). The double bond geometry in **6***d* is uncertain but is probably *Z* in analogy with compound **6***a*.

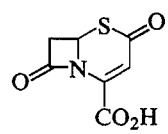
Deprotection of the esters **6** proceeded by the usual hydrogenolysis conditions (although in low yield for some) to give



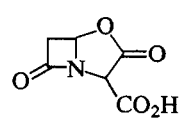
SCHEME 2

acids **10** (see Scheme 2). However, compounds **8** and **9** could not be hydrogenolyzed to their free acids due to the instability of the latter under these reaction conditions. Use of sodium dithionite (13) did give the acids **11** and **12** in good yield. The ^1H nmr spectrum of **12** was the same (allowing for the different solvents used) as the spectrum for **12** reported by the Sankyo group (6).

All of the free acids were insufficiently stable to be purified enough to give an acceptable elemental analysis (see, for example, compound **10***c* in the Experimental). However, it was felt that their level of purity (as determined by ^1H nmr) was such that microbiological evaluation would provide reliable qualitative data. In fact, none of the compounds showed any microbiological activity, either as antibacterials or as β-lactamase inhibitors. Because of concerns over stability affecting microbiological results, the chemical integrity of oxopenam **12** was determined under conditions of the β-lactamase inhibition tests: a solution of compound **12** in pH 7 buffer maintained at room temperature for 45 min showed continued presence of intact **12** (although some decomposition did occur). The lack of activity cannot be ascribed to chemical decomposition. Since oxopenem **7** (R = Na) is described as a potent β-lactamase inhibitor (10), the lack of activity in the sulfur analogs **10** must be ascribed to the replacement of oxygen by sulfur. It is interesting to note that the close analog of **12**, cephem **13**, is described as being "only marginally active against Staphylococcus aureus" (14) while the oxopenam **14** is claimed in a patent (15) as a β-lactamase inhibitor.



13



14

Experimental

Conversion of penems 5 to exocyclic penems 6

A solution of compound **5** (*a*, *b*, or *c*, 1.0 mmol), triethylamine (100 mg, 1.0 mmol), and tetrahydrofuran (4 mL) was stirred at 23°C for 15 min. The solution was concentrated *in vacuo* (40°C), the residue

Can. J. Chem. Downloaded from www.nrcresearchpress.com by NORTHEASTERN UNIVERSITY on 11/30/14
For personal use only.

Can. J. Chem. Downloaded from www.nrcresearchpress.com by NORTHEASTERN UNIVERSITY on 11/30/14
For personal use only.

was redissolved in dichloromethane (20 mL), and the solution was washed with 0.1 *M* hydrochloric acid, then water (10 mL each). The organic layer was dried and the solvent was evaporated *in vacuo* to give **6***a*, *b*, or *c*.

4-Nitrobenzyl 3-benzylidene-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate **6**a

With penem **5***a* (R = Ph) the reaction product consisted of an 80:20 mixture of **6***a* and **5***a* (as determined by ^{1}H nmr). Purification was achieved by column chromatography on silica gel: elution with ether/hexane, then with ether. The appropriate fractions were concentrated *in vacuo* to give compound **6***a* (ca. 95% pure), 65% yield; mp 110−113°C; ir (amorphous film) *ν*: 1785, 1745 cm^{-1}. A portion was recrystallized several times from benzene, the last time by very slow evaporation of solvent to give crystals suitable for X-ray diffraction analysis (see below).

4-Nitrobenzyl 3-(2-furylidene)-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate **6**b

With R = 2-furyl the reaction product consisted of almost pure **6***b* (97% yield); ir (amorphous film) *ν*: 1785, 1750 cm^{-1}.

4-Nitrobenzyl 3-(2-thienylidene)-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate **6**c

With R = 2-thienyl the reaction product consisted of pure **6***c* (99% yield); mp 103−104°C; ir ($CHCl_3$) *ν*: 1790, 1750 cm^{-1}; uv (EtOH) λ_{max}: 267 (ϵ = 15 700), 304 (ϵ = 18 300) nm. *Anal.* calcd. for $C_{18}H_{14}N_2O_5S_2$: C 53.72, H 3.51, N 6.96, S 15.93; found: C 53.77, N 3.50, N 6.90, S 16.15.

4-Nitrobenzyl 3-benzylidene-4,4,7-trioxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate **8**

A solution of compund **6***a* (198 mg, 0.50 mmol), *m*-chloroperbenzoic acid (220 mg, containing ca. 1.1 mmol), and dichloromethane (20 mL) was stirred at 23°C for 17 h. The solution was washed with 1% sodium bicarbonate (2 × 20 mL), dried, and concentrated *in vacuo*. The product was purified by chromatography on silica gel: elution with ether. Evaporation of solvent from the appropriate fractions gave the sulfone **8** as an oil; 95 mg (44% yield), in about 90% purity; ir (film) *ν*: 1800, 1750, 1320, 1135 cm^{-1}.

Ozonolysis of **6**a *and* **6**c

4-Nitrobenzyl 3,7-dioxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate **9**

A solution of compound **6***a* (396 mg, 1.0 mmol) or compound **6***c* (402 mg, 1.0 mmol) in ethyl acetate (20 mL) was ozonized at −78°C until a blue color persisted. The excess ozone was purged with oxygen and the solution was allowed to warm gradually to 23°C. The solution was washed with dilute aqueous sodium bicarbonate, then saturated sodium chloride, dried, and the solvent was evaporated *in vacuo* to give a yellow gum, 340 mg. The product was purified by column chromatography on silica gel: elution with hexane/ether 9:1 followed by ether. Evaporation of solvent from the appropriate fractions gave oxopenam **9**, 230 mg (70% yield), in greater than 90% purity. Recrystallization from benzene gave **9**; mp 114−117°C; ir (solid film) *ν*: 1790, 1750, 1710 cm^{-1}. *Anal.* calcd. for $C_{13}H_{10}N_2O_6S$: C 48.45, H 3.13, N 8.69, S 9.95; found: C 48.37, H 3.23, N 8.78, S 9.91.

4-Nitrobenzyl 3-carbethoxymethylene-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate **6**d

A solution of oxopenam **9** (97 mg, 0.30 mmol) and (carbethoxymethylene)triphenylphosphorane (111 mg, 0.32 mmol) in benzene (10 mL) was heated under reflux for 2 h. The solvent was evaporated *in vacuo* and the residue was purified by chromatography on silica gel (elution with ether) to give compound **6***d* as an oil, 30 mg (23% yield); ir ($CHCl_3$) *ν*: 1785, 1755, 1700 cm^{-1}.

Hydrogenolysis of p-*nitrobenzyl esters*

Compounds **6** were hydrogenated on a Parr apparatus (details for each compound below) at 30 to 50 psi (1 psi = 6.89 kPa) and 23°C. The catalyst was removed by filtration and the phases were separated. In the case of **6***a* and **6***b*, the aqueous phase was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with saturated sodium chloride, dried, and the solvent was evaporated *in vacuo* to give the title compounds. In the case of **6***c* and **6***d*, work-up was as given below.

3-Benzylidene-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid **10**a

Hydrogenolysis mixture: compound **6***a* (198 mg, 0.50 mmol), sodium bicarbonate (42 mg, 0.5 mmol), palladium on Celite (30%, 200 mg), tetrahydrofuran (30 mL), ether (30 mL), and water (30 mL) for 6 h. The product was obtained in 98% yield and recrystallized from ethyl acetate to give acid **10***a*; mp 153−154°C; ir (Nujol mull) *ν*: 1775, 1760, 1730 cm^{-1}; uv (EtOH) λ_{max}: 286 (ϵ = 18 100) nm.

3-(2-Furylidene)-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid **10**b

Hydrogenolysis mixture as for preparation of **10***a* except: compound **6***b* (193 mg, 0.50 mmol). The product was obtained as a brown solid, 98% yield, in about 90% purity (by nmr); ir (Nujol mull) *ν*: 1755 (very broad) cm^{-1}; uv (EtOH) λ_{max}: 296 (ϵ = 20 400), 308 (ϵ = 17 600) nm.

3-(2-Thienylidene)-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid **10**c

Hydrogenolysis mixture: compound **6***c* (344 mg, 0.855 mmol), palladium hydroxide (345 mg), tetrahydrofuran (60 mL), and water (30 mL) for 18 h. Dilute hydrochloric acid and ether were added, mixed, and the organic layer was separated and washed with water and saturated sodium chloride. The solvent was evaporated *in vacuo* and the residue was crystallized with benzene to give acid **10***c*, 100 mg (44% yield); mp 115°C (dec.); ir (Nujol) *ν*: 1775, 1765, 1730 cm^{-1}; uv (EtOH) λ_{max}: 304 (ϵ = 17 700), 315 (ϵ = 15 400) nm. *Anal.* calcd. for $C_{11}H_9NO_3S_2$: C 49.42, H 3.39, N 5.24, S 23.99; found: C 50.20, H 3.57, N 5.09, S 23.06.

Sodium 3-carbethoxymethylene-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate **10**d

Hydrogenolysis mixture: compound **6***d* (60 mg, 0.153 mmol), sodium bicarbonate (13 mg, 0.153 mmol), palladium on Celite (30%, 60 mg), tetrahydrofuran (8 mL), and water (8 mL) for 2 h. Ether was added, mixed, and the phases were separated. The aqueous phase was washed with ether, then lyophilized to give compound **10***d*, 6 mg (14% yield); ir (KBr) *ν*: 1772, 1698, 1660, 1630 cm^{-1}.

Ester cleavage by sodium dithionite

A solution of sodium dithionite (195 mg, 1.12 mmol for **8**; 260 mg, 1.5 mmol for **9**) in water (10 mL) was added to a solution of sulfone **8** (80 mg, 0.187 mmol) or oxopenam **9** (80 mg, 0.25 mmol) in tetrahydrofuran (10 mL) at 0°C. Dilute sodium bicarbonate was added until the solution was pH 7, it was stirred at 0°C for 30 min, and then it was washed with ether. The aqueous phase was acidified with dilute hydrochloric acid (0°C) to pH 2−2.5 and extracted with ethyl acetate (2 × 25 mL). The organic extracts were washed with saturated sodium chloride, dried, and the solvent was evaporated *in vacuo* to give the products as amorphous solids.

3-Benzylidene-4,4,7-trioxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid **11**

Sulfone **11**: 45 mg (82% yield); 80−90% pure (by nmr); ir (solid film) *ν*: 1800, 1750 cm^{-1}.

3,7-Dioxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid **12**

Oxopenam **12**: 39 mg (83% yield); ir (solid film) *ν*: 1790, 1730, 1718 cm^{-1}.

Stability of oxopenam **12**

The conditions of the chemical stability test were the same as those of the β-lactamase inhibition experiment with the exception of the following. Compound **12** was used in higher concentration (20 mg/mL vs. 0.1 mg/mL in the inhibition test), no bacteria were present (*Staphylococcus aureus* or *Klebsiella pneumoniae*), and no chromogenic cephalosporin indicator was present.

A solution of 5 mg of oxapenam **12** in 0.05 mL of acetonitrile plus 0.25 mL of phosphate buffer (pH 7) was maintained at 23°C for 45 min. Reversed phase thin-layer chromatography (Analtech RPSF

250-micron plates; developed with pH 7 buffer/acetonitrile 95:5; visualized with iodine; compound **12** at R_f 0.57) showed the presence of intact oxopenam **12** and some decomposition products.

Single crystal X-ray analysis of ***6***a

$C_{20}H_{16}N_2O_5S$ fw = 396.4

Triclinic, a = 5.529(2), b = 18.665(5), c = 13.481(4) Å, α = 129.04(3), β = 113.69(3), γ = 89.31(3)°, V = 931 Å^3, Z = 2, ρ_c = 1.41 g/cc, space group = $P\bar{1}$, (22°C, CuK$\bar{\alpha}$).

Preliminary X-ray photographs displayed only triclinic symmetry and accurate lattice constants, determined from a least-squares fit of fifteen diffractometer measured 2θ-values, were as above. A crystal of roughly cubic shape was used, 0.25 mm on a side. An estimated density indicated two molecules formed the unit cell and space group $P\bar{1}$ was assumed. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a computer controlled four-circle diffractometer using a variable speed, 1° ω-scan and graphite monochromated CuK$\bar{\alpha}$ radiation. After correction for Lorentz, polarization, and background effects, 1715 (74%) of the 2357 reflections were judged observed. A phasing model was readily achieved using a multisolution sign determining procedure.[5] Block diagonal least-squares refinement with anisotropic nonhydrogen atoms and isotropic hydrogens have converged to a standard crystallographic agreement factor of 0.056 for the observed data. (Quantity minimized: $\Sigma w \| F_o | - | F_c \|^2$.) Fractional coordinates and thermal parameters, bond distances, bond angles, and observed and calculated structure factors are listed in Tables 2 to 5 respectively.[4]

[5]All crystallographic calculations were done on a Prime 850 computer, operated by the Cornell Chemistry Computing Facility. Principal programs employed were as follows. REDUCE and UNIQUE, data reduction programs: M. E. Lewonowicz. Cornell University, 1978. MULTAN 78, "A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data", direct methods programs and fast Fourier transformation routine (locally modified to perform all Fourier calculations including Patterson syntheses): P. Main, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq, and M. M. Woolfson. University of York, England, 1978. NQEST, CYBER 173 version negative quartets figure of merit calculation: C. M. Weeks. Medical Foundation of Buffalo, Inc., August 1976. BLS78A, anisotropic block-diagonal least-squares refinement: K. Hirotsu and E. Arnold. Cornell University, 1980. ORTEP, crystallographic illustration program: C. K. Johnson. Oak Ridge, TN. ORNL3794, June, 1965. Scattering factors were from ref. 17.

Acknowledgements

We would like to thank Dr. B. Belleau of McGill University for advice during the course of this work. We also thank Dr. M. Misiek of the microbiological department, Bristol Laboratories, Syracuse, N.Y., for the antibacterial and β-lactamase inhibitory tests.

1. M. LANG, K. PRASAD, W. HOLICK, J. GOSTELI, I. ERNEST, and R. B. WOODWARD. J. Am. Chem. Soc. **101**, 6296 (1979).
2. M. MÉNARD and A. MARTEL. U. S. Patent 4 272 437 (1981); Chem. Abstr. **95**, 203 941 (1981); A. MARTEL, P. DEXTRAZE, J. P. DARIS, R. SAINTONGE, P. LAPOINTE, T. CONWAY, I. MONKOVIC, G. KAVADIAS, Y. UEDA, P. ELIE, S. PATIL, G. CARON, J. DOUGLAS, M. MÉNARD, and B. BELLEAU. Can. J. Chem. **60**, 942 (1982).
3. P. CHERRY, D. EVANS, C. NEWALL, and N. WATSON. Tetrahedron Lett. 561 (1980).
4. P. LOMBARDI, G. FRANCESCHI, and F. ARCAMONE. Tetrahedron Lett. 3777 (1979).
5. T. HOWARTH, A. BROWN, and T. KING. J. Chem. Soc. Chem. Commun. 266 (1976).
6. F. SHIMIZU, A. SAITO, T. NISHIMURA, and M. NAKAHARA. Japan Kokai, 79-66695 (1979); Chem. Abstr. **91**, 193 300 (1979).
7. J. MARCHAND-BRYNAEST and L. GHOSEZ. Tetrahedron Lett. 3085 (1980).
8. E. BRAIN, N. BROWN, and R. HICKLING. J. Chem. Soc. Perkin Trans. 1, 892 (1981).
9. J. ARROWSMITH and G. GREENGRASS. Tetrahedron Lett. 357 (1982).
10. P. BENTLEY, G. BROOKS, M. GILPIN, and E. HUNT. J. Chem. Soc. Chem. Commun. 905 (1977).
11. T. BRYSON. J. Org. Chem. **38**, 3428 (1973).
12. T. DOYLE, J. L. DOUGLAS, B. BELLEAU, J. MEUNIER, and B. LUH. Can. J. Chem. **55**, 2873 (1977).
13. B. JACKSON. U. S. Patent 3 799 924 (1974); Chem. Abstr. **81**, 3957 (1974); E. GUIBE-JAMPEL and M. WAKSELMAN. Synth. Commun. **12**, 219 (1982).
14. I. ERNEST, A. MAIN, and R. WOODWARD. Helv. Chim. Acta, **64**, 1303 (1981).
15. T. HOWARTH and I. STIRLING. Ger. Offen. 2 655 675 (1977); Chem. Abstr. **87**, 102 313 (1977).
16. Y. UEDA, C. E. DAMAS, and V. VINET. Can. J. Chem. **61**, 2257 (1983).
17. D. T. CROMER and J. B. MANN. Acta Crystallogr. Sect. A, **24**, 321 (1968).

Can. J. Chem. Downloaded from www.nrcresearchpress.com by NORTHEASTERN UNIVERSITY on 11/30/14
For personal use only.