Cyclic Thiosulfinates and Thiosulfonates from Oxidation of the 2-Thiacephem Ring System. Synthesis of (5*R*)-Penems by Stereospecific SO_2 Extrusion

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The MCPBA oxidation of 2-thiacephems afforded regioisomeric pairs of cyclic thiosulfinates; the 6,7-trans substrates yielded 1-oxides as the main product, while 6,7-*cis*-2-thiacephems were preferentially oxidized at the sulfur atom furthest removed from the azetidinone ring. On further MCPBA oxidation, the 6,7-*trans*-2-thiacephem 1-oxides underwent an apparent "straightforward" oxidation at the sulfinyl sulfur with formation of the 1,1-dioxides, whereas the 6,7-cis 1-oxides and all of the 2-oxides gave similar mixtures (ca. 3:1) of the two possible thiosulfonates, thus implying the intermediacy of *vic*-dioxides and *O,S*-sulfenyl sulfinates. Sodium periodate readily reacted with the 2-oxides but not with the 1-oxides or the parent disulfides, affording the 2,2-dioxides regioselectively. Stereospecific extrusion of SO_2 occurred from the 1,1-dioxides upon storage or mild heating; (5*R*)-penems were obtained even in cases where the biologically inactive 5*S* epimers had been anticipated as a consequence of the trans-directing effect of the C_7 substituent.

Chemical interest in 2-thiacephems, nuclear analogues of cephalosporins devised by Woodward[1] in the late 1960s, was recently renewed by the finding that in presence of triphenylphosphine they undergo an easy ring contraction to penems.[2,3] Further work[4] has shown the flexibility of this route for preparing highly functionalized derivatives; however, stereochemical control in the sulfur extrusion was only partially achieved, and the chemistry of this bicyclic lactam system remains largely unexplored.

Oxidation of disulfides constitutes a fascinating and controversial aspect of organosulfur chemistry;[5] chiral cyclic substrates such as 2-thiacephems appeared to us to be novel and interesting object of study. The present work describes the peracid and periodate oxidation of the disulfides **1,6**, the structure assignment of the resulting thiosulfinates and thiosulfonates, and the unique SO_2 extrusion which stereospecifically converts 2-thiacephems 1,1-dioxides into penems.

Results

MCPBA Oxidation. The readily accessible 2-thiacephem methyl ester **1a**[3] was selected as the model substrate. Oxidation of **1a** with 1 equiv of *m*-chloroperoxybenzoic acid (MCPBA) in $CHCl_3$ at −10 °C afforded two out of the four possible isomeric thiosulfinates; they were isolated after SiO_2 chromatography in an approximately 4:1 ratio and assigned (vide infra) structures **2a** and **3a**, respectively. In spite of their regioisomeric relationship, on further oxidation both **2a** and **3a** gave a single thiosulfonate, the 1,1-dioxide **4a**, which could be obtained in satisfactory yield (60%) when **1a** was directly treated with 3 mol equiv of the oxidant. In order to avoid interference from the sensitivity of the products to workup, the MCPBA oxidations were routinely repeated in $CDCl_3$ at 25 °C with ^1H NMR monitoring. The monooxides **2a** and **3a** were observed in a ca. 3:1 ratio, and some dioxide **4a** was found coexisting with the unreacted starting material **1a**; moreover, further oxidation of **3a** afforded, in addition to **4a**, a trace amount of a new product, which could subsequently be isolated (from periodate oxidation) and assigned the 2,2-dioxide structure **5a** (Chart I).

Slightly different results were obtained on varying the ester group and the C_7 substituent. Oxidation of the 6,7-trans-arranged substrates **1b** and **1c** afforded single thiosulfinates **2b** and **2c** (but the presence of an inseparable minor isomer, **3c**, was detected in the oxidation of **1c**); these were in turn converted by excess reagent into single thiosulfonates **4b** and **4c**. However, oxidation of the 6,7-cis-arranged thiacephems **6a** and **6c** was less straightforward. Treatment of **6a** with 1 mol equiv of MCPBA ($CDCl_3$, 25 °C) afforded three β-lactam products (62:26:12, NMR monitoring). After workup and chromatography the minor product was lost, while the other components could be isolated and identified as the thiosulfinates **7a** and **8a**; noticeably, the major product was in this instance the 2-oxide **8a**. On further oxidation *both* the isolated regioisomeric oxides gave similar mixtures (ca. 3:1) of the two possible thiosulfonates **9a** and **10a**, the 1,1-isomer **9a** prevailing again. Similar results were obtained from **6c**, although the products, unstable to workup and chromatography, could not be isolated pure; a ca. 3:1 mixture of monooxides **8c** and **7c**, the 2-isomer prevailing, was first obtained and then by excess reagent was converted into a mixture of dioxides **9c** and **10c**, ca. 3:1, and with inversion of the relative isomeric abundance.

$NaIO_4$ Oxidation. All of the disulfides described in our work, consistent with Oae's studies,[6] were resistant to periodate oxidation. Unexpectedly, even the 1-oxides (**2a–c**, **7a,c**) were found virtually unaffected after prolonged exposure to $NaIO_4$, with or without iodine or acetic acid catalysis, while the 2-oxides (**3a**, **8a,c**) easily and regioselectively gave the corresponding 2,2-dioxides. Thus, periodate oxidation was precious in aiding the structural discrimination between regioisomeric thiosulfinates and in affording adequate amounts of the minor thiosulfonates **5a**, and **10a,c**.

(1) (a) Heusler, K. In *Cephalosporins and Penicillins. Chemistry and Biology*; Flynn, E. H., Ed.; Academic: New York, 1972; p 275. (b) Gorman, M.; Ryan, C. W. In ref 1a; p 569.

(2) Henderson, A.; Johnson, G.; Moore, K. W.; Ross, B. C. *J. Chem. Soc., Chem. Commun.* **1982**, 809.

(3) Perrone, E.; Alpegiani, M.; Bedeschi, A.; Foglio, M.; Franceschi, G. *Tetrahedron Lett.* **1983**, *24*, 1631.

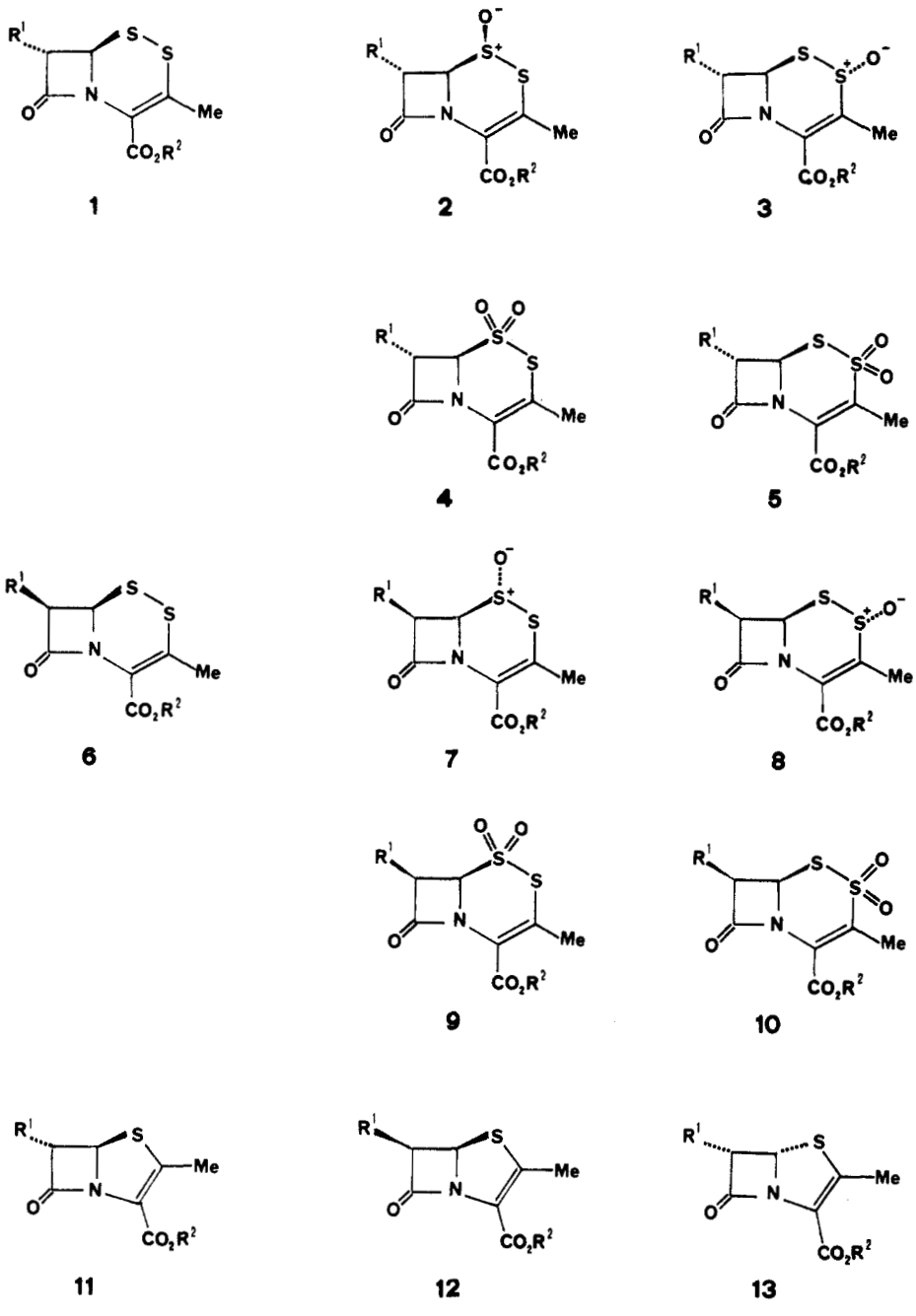
(4) (a) Perrone, E.; Alpegiani, M.; Bedeschi, A.; Foglio, M.; Franceschi, G. *Tetrahedron Lett.* **1983**, *24*, 3283. (b) Alpegiani, M.; Bedeschi, A.; Perrone, E.; Franceschi, G. *Tetrahedron Lett.* **1984**, *25*, 4167. (c) Perrone, E.; Alpegiani, M.; Battaglia, R.; Bedeschi, A.; Franceschi, G. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Brown, A. G.; Roberts, S. M., Eds.; The Royal Society of Chemistry: London, 1985, p 361.

(5) Freeman, F. *Chem. Rev.* **1984**, *84*, 117.

(6) Takata, T.; Kim, Y. H.; Oae, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1443.

0022-3263/86/1951-3413$01.50/0

Chart I



a, R^1 = OSiMe$_2$tBu / Me, R^2 = Me

b, R^1 = OCO$_2$CH$_2$CCl$_3$ / Me, R^2 = CH$_2$CCl$_3$

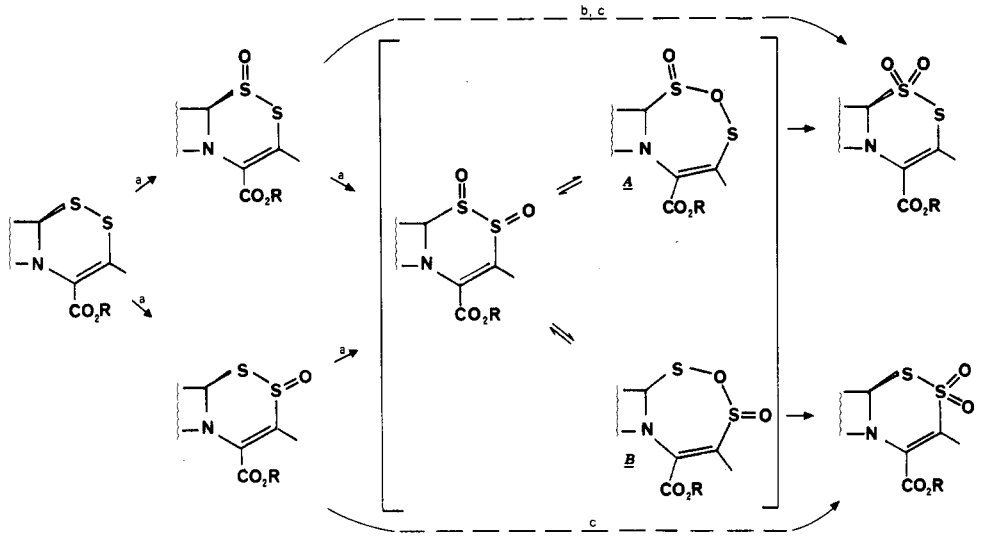
c, R^1 = 1-phthalimido, R^2 = p-nitrobenzyl

Thermolysis. From experiments carried out in refluxing benzene contrasting thermal behaviors were observed; the thiosulfinates were either chemically and configurationally stable (the 1-oxides **2a–c**, **7a,c**), or decomposed into complex mixtures of polar, non-β-lactam materials (the 2-oxides **3a,c**, **8a,c**); the 2,2-dioxides were recovered unaffected, while all of the 1,1-dioxides (**4a–c**, **9a,c**) underwent a facile, high-yield desulfonylation to 5*R* penems **11a–c**, **12a,c**, with full retention of stereochemical integrity at the azetidinone–sulfur junction. This desulfonylation, affording the biologically active penem epimers from the main products of excess MCPBA oxidation of 2-thiacephems, preparatively complements our previous desulfurative route[4] in cases where the PPh_3-mediated ring contraction occurs with unsatisfactory or adverse stereoselectivity.

Discussion

The site of first MCPBA attack on 2-thiacephems is governed by electronic and steric factors, which are respectively expected to favor 1-oxide and 2-oxide formation. Exclusive reaction at the sulfur furthest removed from the

Scheme I[a]



[a] (a) Electrophilic oxidation at sulfenyl sulfur; (b) electrophilic oxidation at sulfinyl sulfur; (c) nucleophilic oxidation at sulfinyl sulfur.

azetidinone ring was claimed in the few reported examples of peroxidation on unsymmetrical 4-azetidinyl disulfides,[7] but in thiacephems electronic deactivation of this sulfur through conjugation with the carboxy group may become determinant.[8] Our results, ranging from an almost exclusive oxidation at S_1 in 6,7-trans-arranged substrates **1a–c** to a prevailing (ca. 3:1) attack at S_2 for the 6,7-cis entries **6a,c**, presumably reflect a rather balanced situation where the amount of steric congestion at S_1 is determinant, even if the interplay of more subtle factors cannot at present be ruled out.

Further oxidation of thiosulfinates into thiosulfonates can be either the straightforward result of MCPBA attack at the sulfinyl sulfur or can occur through the intermediacy of *vic*-disulfoxides arising from preferential oxidation at the sulfenyl sulfur.[5] In acyclic substrates scrambling, disproportionation and shift of the oxidation site are often observed;[5,9] however, in unsymmetrical cyclic substrates most mechanisms put forward to account for the formation of thiosulfonates[10] would not lead to the preservation of the original ring structure, so that the conceivable ways for formation of 2-thiacephem sulfones can be reduced to Scheme I.

Similar to simple *S*-alkyl alkanesulfinothioates[11] and arenesulfinothioates,[9,12] 2-thiacephem 1-oxides are mainly or exclusively oxidized at the relatively electron-rich and sterically accessible sulfenyl sulfur (S_1) to give *vic*-dioxides, which then rearrange into a mixture of the final thiosulfonates. On the other hand the 1-oxides, like *S*-aryl alkanesulfinothioates,[13] may be competitively oxidized at S_1 or S_2. "Straightforward" oxidation at the sulfinyl sulfur (path b in Scheme I) is expected to be facilitated by relief of steric congestion at S_1; as a matter of fact, whereas the 7α-substituted 1-oxides **2a–c** almost exclusively gave the 1,1-dioxides **4a–c**, the 7β-substituted analogues **7a,c** yielded a mixture of thiosulfonates (ca. 3:1) similar to the one obtained from oxidation of the regioisomeric 2-oxides **8a,c**, again indicating the probable intermediacy of *vic*-dioxides.[14] The formation of the latter and their rearrangement into the final thiosulfonates through *O,S*-sulfenyl sulfinates which have eluded experimental observation[9] are supported by the cyclic nature of the molecule. Apparently, one type of *O,S*-sulfenyl sulfinate (A in Scheme I) is preferentially formed; old[15] and new explanations[16] may be put forward to account for this result.

The results of periodate oxidation can be easily interpreted as a straightforward nucleophilic oxidation[6,17] at the sulfinyl sulfur (path c in Scheme I). The 2-oxides, possessing a conjugated sulfinyl group, were in fact smoothly converted into the 2,2-dioxides; under the same conditions the corresponding 1-oxides were recovered unchanged. This finding points out that periodate oxidation can be used as a regioisomerism probe for thiosulfinates, the isomer bearing the more electrophilic sulfinyl sulfur being the first to react.[18,19]

(7) (a) Woodward, R. B. Ger. Offen. 2153554, 1972; *Chem. Abstr.* **1972**, *77*, 126700. (b) Chou, T. S.; Koppel, G. A.; Dorman, D. E.; Paschal, J. W. *J. Am. Chem. Soc.* **1976**, *98*, 7864.

(8) 2-Thiacephems, possessing the substructure RSSCH=CHCO$_2$R, are vinylogous to sulfenylthiocarbonates RSSCO$_2$R, which are known to undergo selective oxidation at the sulfur furthest removed from the electron-withdrawing carboxy group (Harpp, D. N.; Granata, A. *Synthesis* **1978**, 782).

(9) Freeman, F.; Angeletakis, C. N. *J. Org. Chem.* **1985**, *50*, 793 and references therein.

(10) These are: intermolecular recombination between thiyl and sulfonyl radicals, reaction between sulfinic or sulfenic acids and the starting thiosulfinate, disproportionation of sulfinic acids (see ref 5 and 9).

(11) Freeman, F.; Angeletakis, C. N. *J. Am. Chem. Soc.* **1983**, *105*, 4039 and references therein.

(12) Oae, S.; Kim, Y. H.; Takata, T.; Fukushima, D. *Tetrahedron Lett.* **1977**, 1195.

(13) (a) Bhattacharya, A. K.; Hortmann, A. G. *J. Org. Chem.* **1978**, *43*, 2728. (b) Freeman, F.; Angeletakis, C. N.; Maricich, T. J. *J. Org. Chem.* **1982**, *47*, 3403.

(14) Compounds **7a,c** are 1α-oxides; attack of the oxidant on the β-oriented lone pair of the sulfinyl sulfur ("straightforward" oxidation) is hindered by the folded geometry of the molecule and by the β-oriented C_7 substituent.

(15) Freeman, F.; Angeletakis, C. N. *J. Org. Chem.* **1981**, *46*, 3991.

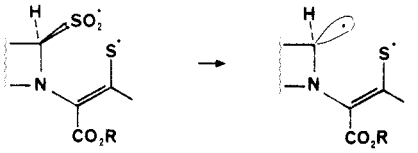
(16) It is known that vinyl sulfides are thermodynamically favored over the isomeric allyl sulfides, while for vinyl sulfoxides the reverse is true (a very popular consequence in the β-lactam area is the quantitative isomerization of Δ_2 into Δ_3 cephems occurring upon oxidation at sulfur); here we have two convergent effects, namely, the stabilization of A (see Scheme I) caused by the p–π resonance between the sulfur atom and the conjugated system and the destabilization of B due to the electron withdrawal operated by the sulfinyl group over the double bond. See: O'Connor, D. E.; Lyness, W. Y. *J. Am. Chem. Soc.* **1964**, *86*, 3840.

(17) (a) Field, L.; Barbee, R. B. *J. Org. Chem.* **1969**, *34*, 36. (b) Oae, S.; Takata, T. *Tetrahedron Lett.* **1980**, *21*, 3213.

(18) A wide range of susceptibility to periodate oxidation could be traced back in the thiosulfinate literature, although passed without comments;[19,21f] particularly significant is the contrasting behavior of *S*-phenyl 2,2-dimethylpropanethiosulfinate and its regioisomer, *S*-2,2-dimethylpropyl benzenethiosulfinate.[13b]

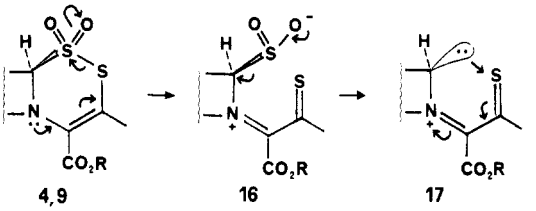
The singularities of the thermal SO_2 extrusion observed in the 2-thiacephem 1,1-dioxides deserve special comment. Ring contraction to penems, particularly fast in polar solvents, slowly occurred even in the solid state upon storage; absolute retention of configuration always ensued, irrespective of the C_7 side chain orientation.[20] Desulfonylation of thiosulfonates has precedents, but these peculiarities have never been found before.[21] Thus, arenethiosulfonates extrude SO_2 only under severe thermal conditions and in the presence of copper or copper bronze; aralkanethiosulfonates desulfonylate under milder conditions but with concomitant racemization at the carbon α to the sulfonyl group.[22]

Although the free-radical nature of thiosulfonate desulfonylations was once questioned on the basis of kinetic evidence,[21a] radicals have been detected in one recent ESR spin trap study,[23] and the radical interpretation is currently the accepted one. In this interpretation, the ring contraction is explained in terms of an easy homolytic cleavage of the S–SO_2 bond to give the relatively stable diradical **14**, which would split off SO_2 to afford a new diradical, **15**, immediately collapsing into the observed penem. This



14 **15**

hypothesis requires (a) that an unproductive homolysis and recombination takes place in the corresponding 1-oxides[24] and (b) that scavenging of the azetidinyl radical by the thiyl counterpart in species **15** intervenes at a rate fast enough to preserve the original tetrahedral geometry. The latter event in particular appears rather surprising when one considers the precedents in radical chemistry in general and azetidinone chemistry in particular.[25] Moreover, since the ring contraction could be cleanly accomplished in neat acrylonitrile, there is no evidence that radical traps might interfere. In our opinion a mechanism involving the dipolar intermediate **17**, originating after heterolytic scission of the 1,2-bond and loss of SO_2, should be preferred. The sulfinate anion is a good leaving group, and

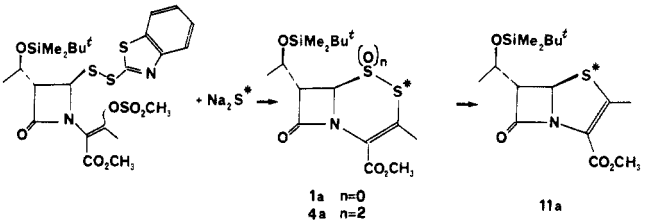


4,9 **16** **17**

hence a facile heterolytic cleavage of the S–SO_2 bond in the 1,1-dioxides promoted by the nitrogen lone pair is conceivable. Loss of SO_2 in intermediate **16** may be justified by the presence of the positive charge, which can assist the development of the adjacent carbanion; a fast intramolecular trapping of the latter species by the sulfur electrophile would follow. Clearly, a mechanism of this type cannot be operative in the 2,2-dioxides and is comparatively disfavored in the 1-oxides; this provides a rationale for the contrasting thermal behavior of the products above, while the thermal lability of the 2-oxides is presumably the consequence of a cycloeliminative pathway[26] involving the sulfinyl oxygen and the C_3-methyl hydrogens.

Structural Assignments

The 1,1-dioxide structure of the penem-yielding thiosulfonates was proved by tracer experiments[4c] aimed at determining which sulfur is extruded in the thermal and PPh_3-mediated ring contractions. Starting from the usual mesylate–disulfide azetidinone precursors and from ^{35}S-enriched Na_2S, radiolabeled **1a** was prepared, oxidized to **4a**, and thermally converted into penem **11a**; during the



1a n=0 **4a** n=2 **11a**

whole sequence the molar specific activity of the reagent was retained and finally found unchanged in the penem product. Since the ring-closing reaction requires[3] incorporation of ^{35}S at the thiacephem position 2, this result demands that the extruded "cold" SO_2 comes from position 1.

Regiochemical assignments of the thiosulfinates could be drawn from their IR, UV, and NMR spectra. When compared with their disulfide precursors, the isolable 2-oxides **3a** and **8a** showed in their IR spectrum a median 15-cm^{-1} shift toward high wavenumbers for conjugate ester CO stretching and lacked the characteristic thiacephem UV absorption at ca. 330 nm. Differences with the corresponding 1-oxides **2a** and **7a** and the remaining analogues **2b,c** were scanty but consistent, since they all showed a smaller shift (ca. 5 cm^{-1}) for ν_{CO} and a shoulder at 305–310 nm emerging from their 272–273-nm UV maximum. The best piece of spectral evidence was gathered from ^{13}C NMR spectroscopy; very significant shifts in opposite directions were observed for C_6 in the process **1a** → **2a** (13.0 ppm downfield) and **1a** → **3a** (7.7 ppm upfield).[27] Although conformational and configurational factors might play their role in determining the precise δC_6 value, such a difference in sign and magnitude can hardly be accounted for by anything other than an α_{so} vs. α_{so}'

(19) (a) Field, L.; Khim, Y. H. *J. Org. Chem.* **1972**, *37*, 2710. (b) McCormick, J. E.; McElhinney, R. S. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2795.

(20) Authentic samples of the possible penem epimers were available, so that their absence in the crude desulfonylation mixture could easily be ascertained.

(21) (a) Kice, J. L. In *The Chemistry of Organic Sulfur Compounds*; Kharasch, N., Meyers, C. Y., Eds.; Pergamon: Oxford, 1966; Vol 2, pp 115–136 and references therein. (b) Armarego, W. L. F.; Turner, E. E. *J. Chem. Soc.* **1957**, 13. (c) Padwa, A.; Gruber, R. J. *J. Org. Chem.* **1970**, *35*, 1781. (d) Fujisawa, T.; Ohta, H.; Sugimoto, K. *Chem. Lett.* **1973**, *3*, 237. (e) Meinwald, J.; Knapp, S. *J. Am. Chem. Soc.* **1974**, *96*, 6532. (f) Hortmann, A. G.; Aron, A. J.; Bhattacharya, A. K. *J. Org. Chem.* **1978**, *43*, 3374.

(22) The ring contraction of *trans*-3-phenyl-4-benzoyl-1,2-dithiolane 2,2-dioxide, occurring after 7 h of autoclave heating (230 °C), stands as the sole reported example[21c] of thiosulfonate desulfonylation resulting in retention of the stereochemical integrity at the SO_2-adjacent methine; however, this outcome may be the consequence of a trans-directing effect from the adjacent benzoyl substituent.

(23) Chatgilialoglu, G.; Gilbert, B. C.; Gill, B. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1141.

(24) Thiosulfinates undergo homolytic fission much more readily than the corresponding thiosulfonates: Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3921. Instead, the 1-oxides **2a–c** and **7a,c** were found chemically and configurationally stable under conditions promoting the quantitative desulfonylations of the corresponding 1,1-dioxides.

(25) Radicals generated at azetidinone C_4 are trapped by deuterium and allyl radicals in a nonstereoselective fashion: (a) Whitesitt, C. A.; Herron, D. K. *Tetrahedron Lett.* **1978**, *20*, 1737. (b) Blaszczak, L.; Armour, K.; Hanington, N., unpublished results (by courtesy of R. D. G. Cooper).

(26) Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3929.

(27) Unequivocal assignments for C_6, C_7, and C_8 in 2-thiacephems **1a** and **6a** and in their oxides were drawn from ^1H–^{13}C NMR heterocorrelation experiments.

Table I. ^{1}H NMR Solvent Shift Data[a] for H_6 in 2-Thiacephems and Their Monooxides

substrate	δ_{CDCl_3}	$\delta_{C_6D_6}$	ASIS[b]	net ASIS[c]
1a	4.65	4.66	−0.01	
2a	4.67	4.42	0.25	0.26
3a	5.29	5.40	−0.11	−0.10
1b	4.73	4.18	0.55	
2b	4.79	3.85	0.94	0.39
1c	4.93	4.42	0.51	
2c	5.06	3.99	1.07	0.56
3c	5.53	5.34	0.19	−0.32
6a	4.85	4.21	0.64	
7a	4.55	4.15	0.40	−0.24
8a	5.33	5.71	−0.38	−1.02
6c	5.09	4.28	0.81	
7c	4.91	4.19	0.72	−0.09
8c	5.65	5.13	0.52	−0.29

[a] In parts per million in 2% w/v solution with Me_4Si as internal reference, measured on a Varian XL-200 instrument. [b] ASIS = $\delta_{CDCl_3} - \delta_{C_6D_6}$; positive values indicate upfield shifts. [c] Net ASIS = ASIS thiosulfinate − ASIS parent disulfide.

effect,[28] which demands the 1-oxide structure for **2a** and the 2-oxide structure for **3a**. Compounds **7a** and **8a** constitute the other pair of thiosulfinates which could be isolated pure; shifts of 11.8 ppm downfield and 10.2 ppm upfield, respectively, were observed for δ_{C_6} relative to disulfide **6a**, suggesting in this case the 1-oxide structure for the minor isomer and the 2-oxide structure for the major.

The SO bond stereochemistry was inferred from ^{1}H NMR data. The thiosulfinates under study possess two spatially oriented protons, H_6 and H_7; their position is known and the former in particular occupies a pseudoaxial position on the α-face of the molecule, very close to the S–SO moiety. Under these circumstances, analysis of aromatic solvent shifts (ASIS) in ^{1}H NMR spectroscopy becomes the simplest reliable technique for determining the configuration at the sulfinyl sulfur; the use of "net ASIS" values[29] cancels out geometry effects unrelated to the spatial orientation of the SO bond. In β-oxides, benzene coordination to the positive end of the SO dipole is expected to result in large upfield shifts for the α-oriented H_6. Inspection of Table I reveals that **2a–c**, fulfilling this condition, are β-oxides and strongly suggests that the remaining 1-oxides (**7a,c**), together with all of the 2-oxides (**3a,c**, **8a,c**), are α-oriented, since they are characterized by negative net ASIS values.

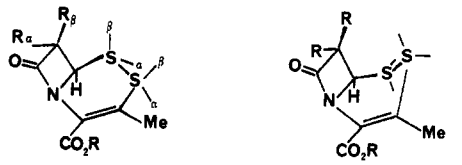
Another useful criterion for determining the SO bond configuration is the analysis of the chemical shift perturbation induced by this bond on the nearby protons;[29] in particular, it is expected that deshieldings associated with a syn-1,3 diaxal relationship are large enough to make themselves evident.[30] Table II shows that a conspicuous downfield anisotropy shift is experienced by H_6 in the 2-oxides **3a,c** and **8a,c**; they are therefore α-oriented. In 1-oxides, a similar syn-1,3 diaxal relationship holds between H_7 and the oxygen atom when both are β-oriented; the 7α-substituted 1-oxides **2a–c** share large downfield anisotropy shifts and, in agreement with the previously reported ASIS evidence, should be considered β-oriented.

Table II. ^{1}H NMR Anisotropy Shifts Induced by the Sulfoxide Bond in 2-Thiacephem Monooxides

substrate	δ_{H_6}[a]	ΔSO[b]	δ_{H_7}	ΔSO[c]
1a	4.65		3.08	
2a	4.67	0.02	3.59	0.51
3a	5.29	0.64	3.54	0.46
1b	4.73		3.33	
2b	4.79	0.06	3.81	0.48
1c	4.93		5.25	
2c	5.06	0.13	5.77	0.52
3c	5.53	0.60	5.73	0.48
6a	4.85		3.99	
7a	4.55	−0.30	3.93	(−0.06)
8a	5.33	0.48	4.11	(0.12)
6c	5.09		6.08	
7c	4.91	−0.18	6.16	(0.08)
8c	5.65	0.56	6.20	(0.12)

[a] In parts per million in $CDCl_3$ solution with Me_4Si as internal reference. [b] $\Delta SO = \delta_{thiosulfinate} - \delta_{disulfide}$; positive values indicate downfield shifts. [c] Data in brackets refer to α-oriented H_7.

It is interesting to note that the magnitude and self-consistency of the observed ASIS and ΔSO effects are best accommodated by the "open" ring conformation A,[31] although not requiring it. In the absence of samples suitable



A B

for X-ray diffraction spectra, the geometry of the bicyclic system could not be experimentally established; however, reasoning by analogy concurs in suggesting the "open" conformation as the more probable one for both the 2-thiacephem substrates[32,33] and their oxidized derivatives.[34]

The configuration at C_5 of the penem products **11a–c** and **12a,c** was determined, as usual, from the magnitude of the H_5–H_6 coupling constant. Moreover, in most instances their C_5 epimers and C_5,C_6 enantiomers, available from treatment of the 2-thiacephems **1a–c** and **6a,c** with triphenylphosphine, were used for comparison purposes; for example **13c**, the enantiomer of **12c** and C_5 epimer of **11c**, was cleanly obtained[4c] from desulfurization of **1c**.

(28) (a) Juaristi, E.; Guzman, J.; Kane, V. V.; Glass, R. S. *Tetrahedron* **1984**, *40*, 1477. (b) Bass, S. W.; Evans, S. A. *J. Org. Chem.* **1980**, *45*, 710. (c) Freeman, F.; Angeletakis, C. N. *J. Org. Chem.* **1982**, *47*, 4194. (d) Takata, T.; Iida, K.; Oae, S. *Heterocycles* **1981**, *15*, 847.

(29) (a) Demarco, P. V.; Nagarajan, R. In *Cephalosporins and Penicillins. Chemistry and Biology*; Flynn, E. H., Ed.; Academic: New York, 1972; pp 311–369. (b) Cooper, R. D. G.; Demarco, P. V.; Murphy, C. F.; Sprangle, L. A. *J. Chem. Soc. C* **1970**, 340.

(30) (a) Harpp, D. N.; Gleason, J. G. *J. Org. Chem.* **1971**, *36*, 1314 and references therein. (b) Takata, T.; Kim, Y. H.; Oae, S. *Tetrahedron Lett.* **1978**, *20*, 4303.

(31) The two geometries arising from fusion of the rigid azetidinone ring with the half-chair or twist conformation possible for the dihydrothiazine moiety are here briefly indicated as "open" (A) or "closed" (B). For a precedent, see Keith, D. D.; Tengi, J.; Rossman, P.; Todaro, L.; Weigele, M. *Tetrahedron* **1983**, *39*, 2445.

(32) Cephems[29a] and 2-isocephems,[33a] isosteric with our system, have been shown to exist in the open conformation exclusively. Although replacement of a methylene group with a sulfur atom might result in some lowering of $\Delta G^{\ddagger}$ (from reduced 1–2 rotational interactions) and of $\Delta G°$ (from a smaller space requirement),[30a] these minor effects would hardly disturb the strong conformational preference displayed by the reference structures. It may be added that the open geometry is characteristic of their 3,4-saturated analogues, 2-thiacephams,[33b] and that no conformational change occurs in cephams upon formal introduction of the 3,4-double bond.[29a]

(33) (a) Doyle, T. W.; Douglas, J. L.; Belleau, B.; Meunier, J.; Luh, B.-Y. *Can. J. Chem.* **1977**, *55*, 2873. (b) Kukolja, S.; Demarco, P. V.; Jones, N. D.; Chaney, M. O.; Paschal, J. W. *J. Am. Chem. Soc.* **1972**, *94*, 7592.

(34) Oxidation at sulfur in cephems[29a] and 2-isocephems[33a] does not entail abandon of the open geometry. In 2-thiacephem monoxides an extraeffect is introduced by the sizeable (ca. 2 kcal/mol) stabilization permitted by the axial SO conformation.[28a,b,30a] In principle, this added $\Delta G°$ might disturb the conformational preference of 1α-oxides and 2β-oxides but leaves no doubt that the 1β-oxides **2a–c** and 2α-oxides **3a,c** and **8a,c**, which are axial SO thiosulfinates in the open conformation, maintain this geometry.

Experimental Section

Melting points were taken on a Büchi 520 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 457 spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were determined on a Varian XL 200 (200 MHz, Fourier transform mode) or, when indicated, on a Varian EM 360 (60 MHz); all coupling constants (J values) are given in hertz. ^{13}C NMR spectra were taken on the former instrument at 50.3 MHz under proton noise decoupling conditions; assignments were drawn from ^{1}H–^{13}C heterocorrelation experiments. Field-desorption mass spectra were obtained on a Varian MAT 311-A spectrometer equipped with a combined FI/FD/EI ion source. Ultraviolet (UV) spectra were taken on a Carlo Erba Strumentazione Spectracomp 601 instrument.

2-Thiacephem Substrates. The starting materials **1a–c** and **6a,c** were obtained from the appropriate penicillin-derived 1-[4(*R*)-benzthiazolyldithio-2-oxo-1-azetidinyl]-2-methyl-2-butenoates through our previously published method.[3]

Methyl (6*R*,7*S*)-7-[1(*R*)-((*tert*-butyldimethylsilyl)oxy)ethyl]-3-methyl-2-thiacephem-4-carboxylate (1a): white crystals, mp 76–77 °C; IR ($CHCl_3$) 1780, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.08 (6 H, s), 0.88 (9 H, s), 1.26 (3 H, d, J = 6.2), 2.22 (3 H, s), 3.08 (1 H, dd, J = 2.3, 3.7), 3.82 (3 H, s), 4.37 (1 H, m), 4.65 (1 H, d, J = 2.3); ^{13}C NMR ($CDCl_3$) δ 19.84 (CH_3 on C_3), 22.60 (CH_3 on C_8), 53.47 (C_6), 64.44 (C_8), 66.26 (C_7), 123.79 (C_4), 128.4 (C_3); UV (95% EtOH) λ_{max} 278 nm (ϵ 6760), 327 (3118). Anal. Calcd for $C_{16}H_{27}NO_4S_2Si$: C, 49.32; N, 3.60; H, 6.99. Found: C, 49.02; N, 3.52; H, 6.96.

2,2,2-Trichloroethyl (6*R*,7*S*)-7-[1(*R*)-(((2,2,2-trichloroethoxy)carbonyl)oxy)ethyl]-3-methyl-2-thiacephem-4-carboxylate (1b): IR ($CHCl_3$) 1787, 1765 sh, 1735 sh cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.54 (3 H, d, J = 6.3), 2.33 (3 H, s), 3.33 (1 H, dd, J = 2.1, 7.3), 4.73 (1 H, d, J = 2.1), 4.85 (2 H, AB q, J = 11.7), 4.94 (2 H, AB q, J = 12), 5.37 (1 H, m); UV (95% EtOH) λ_{max} 281 nm (ϵ 6267), 330 (3892); mass spectrum, 565 (M$^+$).

***p*-Nitrobenzyl (6*R*,7*S*)-7-phthalimido-3-methyl-2-thiacephem-4-carboxylate (1c)**: white crystals, mp 142–146 °C; IR (KBr) 1790, 1775, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.30 (3 H, s), 4.93 (1 H, d, J = 2.4), 5.25 (1 H, d, J = 2.4), 5.42 (2 H, s), 7.67–8.24 (8 H, m); UV (EtOH) λ_{max} 220 nm (ϵ 49 280), 273 (16 642), 324 (4345). Anal. Calcd for $C_{22}H_{15}N_3O_7S_2$: C, 53.11; N, 8.45; H, 3.04. Found: C, 52.95; N, 8.28; H, 3.11.

Methyl (6*R*,7*R*)-7-[1(*R*)-((*tert*-butyldimethylsilyl)oxy)ethyl]-3-methyl-2-thiacephem-4-carboxylate (6a): white crystals, mp 65–66 °C; IR (KBr) 1785, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.05 (3 H, s), 0.08 (3 H, s), 0.87 (9 H, s), 1.33 (3 H, d, J = 6.3), 2.18 (3 H, s), 3.85 (3 H, s), 3.99 (1 H, dd, J = 5.5, 8.7), 4.29 (1 H, m), 4.85 (1 H, d, J = 5.5); ^{13}C NMR ($CDCl_3$) δ 19.99 (CH_3 on C_3), 23.92 (CH_3 on C_8), 57.40 (C_6), 62.57 (C_7), 64.21 (C_8); UV (95% EtOH) λ_{max} 277 nm (ϵ 6039), 331 (3066). Anal. Calcd for $C_{16}H_{27}NO_4S_2Si$: C, 49.32; N, 3.60; H, 6.99. Found: C, 49.07; N, 3.41; H, 6.83.

***p*-Nitrobenzyl (6*R*,7*R*)-7-phthalimido-3-methyl-2-thiacephem-4-carboxylate (6c)**: white powder, mp 206–208 °C; IR (KBr) 1800, 1788, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.31 (3 H, s), 5.09 (1 H, d, J = 5.0), 5.37 (2 H, s), 6.08 (1 H, d, J = 5.0), 7.60–8.25 (8 H, m); UV (EtOH) λ_{max} 271, 336 nm. Anal. Calcd for $C_{22}H_{15}N_3O_7S_2$: C, 53.11; N, 8.45; H, 3.04. Found: C, 52.88; N, 8.15; H, 3.09.

Monooxidation with MCPBA. The following general procedure was adopted unless otherwise indicated: A solution of 90% MCPBA (1.2 mmol) in CH_2Cl_2 was added to a cold (−30 °C) solution of the 2-thiacephem substrate (1 mmol) in CH_2Cl_2 (30 mL). The mixture was let rise to ambient temperature and after 30 min sequentially washed with aqueous $NaHSO_3$, aqueous $NaHCO_3$, and brine. The products were separated by flash chromatography (ethyl acetate–cyclohexane mixtures) when stable on silica gel. In parallel experiments, the reaction was run in a NMR tube and monitored by ^{1}H NMR spectroscopy at appropriate time intervals.

Oxidation of 1a. Chromatography on SiO_2 afforded, in sequence, the 1,1-dioxide **4a** (10%), the 2-oxide **3a** (16%), and the 1-oxide **2a** (58%).

Methyl (6*R*,7*S*)-7-[1(*R*)-((*tert*-butyldimethylsilyl)oxy)ethyl]-3-methyl-2-thiacephem-4-carboxylate 1β-oxide (3a): white powder, mp 90–93 °C; IR ($CHCl_3$) 1793, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.09 (6 H, s), 0.76 (9 H, s), 1.28 (3 H, d, J = 6.3), 2.24 (3 H, s), 3.59 (1 H, dd, J = 1.9, 3.5), 3.86 (3 H, s), 4.36 (1 H, m), 4.67 (1 H, d, J = 1.9); ^{13}C NMR ($CDCl_3$) δ 19.93 (CH_3 on C_3), 22.85 (CH_3 on C_8), 63.64 (C_7), 64.22 (C_8), 66.44 (C_6), 117.67 (C_3), 120.69 (C_4); UV (n-hexane) λ_{max} 273 nm (ϵ 4862), 309 sh (2721); mass spectrum, 405 (M$^+$).

Methyl (6*R*,7*S*)-7-[1(*R*)-((*tert*-butyldimethylsilyl)oxy)ethyl]-3-methyl-2-thiacephem-4-carboxylate 2α-oxide (3a): syrup, thermally unstable, slowly decomposing on silica gel; IR ($CHCl_3$) 1793, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.06 (6 H, s), 0.85 (9 H, s), 1.23 (3 H, d, J = 6.3), 2.35 (3 H, s), 3.54 (1 H, dd, J = 2.5, 3.0), 3.88 (3 H, s), 4.39 (1 H, m), 5.29 (1 H, d, J = 2.5); ^{13}C NMR ($CDCl_3$) δ 17.09 (CH_3 on C_3), 22.16 (CH_3 on C_8), 45.74 (C_6), 64.34 (C_8), 67.48 (C_7); UV (n-hexane) λ_{max} 276 nm (ϵ 5417); mass spectrum, 405 (M$^+$).

Oxidation of 1b. Full conversion of the starting material required ca. 2 mol equiv of MCPBA. The product is unstable on silica gel and was isolated crude after the standard aqueous workup as a white solid (90%), mainly consisting (≥85% by NMR integration) of **2,2,2-trichloroethyl (6*R*,7*S*)-7-[1(*R*)-(((2,2,2-trichloroethoxy)carbonyl)oxy)ethyl]-3-methyl-2-thiacephem-4-carboxylate 1β-oxide (2b)**: IR ($CHCl_3$) 1800, 1750 br cm^{-1}; ^{1}H NMR (CCl_3) δ 1.57 (3 H, d, J = 6.3), 2.37 (3 H, s), 3.81 (1 H, dd, J = 1.5, 7.5), 4.78 (2 H, AB q, J = 11.8), 4.79 (1 H, d, J = 1.5), 4.93 (2 H, AB q, J = 12.0), 5.63 (1 H, m); UV (EtOH) λ_{max} 299 nm (ϵ 5812); mass spectrum, 581 (M$^+$).

Oxidation of 1c. An inseparable mixture of the thiosulfinates **2c** and **3c** (ca. 4:1 by NMR integration) was obtained and isolated crude (95%) after aqueous workup. Both components were unstable on silica gel; brief heating (refluxing benzene) degraded **3c**, leaving **2c** as the sole β-lactam product.

***p*-Nitrobenzyl (6*R*,7*S*)-7-phthalimido-3-methyl-2-thiacephem-4-carboxylate 1β-oxide (2c)**: IR ($CHCl_3$) 1805, 1785, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.31 (3 H, s), 5.06 (1 H, d, J = 1.9), 5.42 (2 H, AB q), 5.77 (1 H, d, J = 1.9), 7.66–8.22 (8 H, m); mass spectrum, 513 (M$^+$), 465.

***p*-Nitrobenzyl (6*R*,7*S*)-7-phthalimido-3-methyl-2-thiacephem-4-carboxylate 2α-oxide (3c)**: ^{1}H NMR ($CDCl_3$) δ 2.43 (3 H, s), 5.45 (2 H, AB q), 5.53 (1 H, d, J = 2.6), 5.73 (1 H, d, J = 2.6), 7.66–8.22 (8 H, m).

Oxidation of 6a. A mixture of three β-lactam products, 62:26:12 by NMR integration, was obtained; the minor component, characterized by β-lactam protons at δ 4.02 (each 1 H, dd, J = 5.0) in the NMR spectrum ($CDCl_3$), was lost after workup and silica gel chromatography, whereupon the two major components were isolated pure.

Methyl (6*R*,7*R*)-7-[1(*R*)-((*tert*-butyldimethylsilyl)oxy)ethyl]-3-methyl-2-thiacephem-4-carboxylate 2α-oxide (8a): 55%; syrup; IR ($CHCl_3$) 1790, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.06 (3 H, s), 0.08 (3 H, s), 0.86 (9 H, s), 1.35 (3 H, d, J = 6.2), 2.35 (3 H, s), 4.11 (1 H, dd, J = 5.5, 7.1), 4.29 (1 H, m), 5.33 (1 H, d, J = 5.5); ^{13}C NMR ($CDCl_3$) δ 17.21 (CH_3 on C_3), 23.48 (CH_3 on C_8), 48.17 (C_6), 62.77 (C_7), 65.24 (C_8); UV (n-hexane) λ_{max} 277 nm (ϵ 5430); mass spectrum, 405 (M$^+$).

Methyl (6*R*,7*R*)-7-[1(*R*)-((*tert*-butyldimethylsilyl)oxy)ethyl]-3-methyl-2-thiacephem-4-carboxylate 1α-oxide (7a): 23%; syrup; IR ($CHCl_3$) 1797, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.05 (3 H, s), 0.10 (3 H, s), 0.88 (9 H, s), 1.33 (3 H, d, J = 6.2), 2.26 (3 H, s), 3.90 (3 H, s), 3.93 (1 H, dd, J = 4.9, 9.6), 4.48 (1 H, m), 4.55 (1 H, d, J = 4.9); ^{13}C NMR ($CDCl_3$) δ 63.83 (C_7), 64.33 (C_8), 69.24 (C_6); UV (n-hexane) λ_{max} 272 nm (ϵ 4140), 305 (sh); mass spectrum, 405 (M$^+$).

Oxidation of 6c. A chromatographically unstable mixture of thiosulfinates **8c** and **7c** (3:1 by NMR integration) was obtained in almost quantitative yield.

***p*-Nitrobenzyl (6*R*,7*R*)-7-phthalimido-3-methyl-2-thiacephem-4-carboxylate 2α-oxide (8c)**: IR ($CHCl_3$) (mixture of isomers) 1805, 1785, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.46 (3 H, s), 5.44 (2 H, s), 5.65 (1 H, d, J = 5.0), 6.20 (1 H, d, J = 5.0), 7.64–8.27 (8 H, m); UV (EtOH) (mixture of isomers) λ_{max} 268 nm (ϵ 14 995); mass spectrum (mixture of isomers), 513 (M$^+$), 497, 465.

***p*-Nitrobenzyl (6*R*,7*R*)-7-phthalimido-3-methyl-2-thiacephem-4-carboxylate 1α-oxide (7c)**: ^{1}H NMR δ 2.51 (3 H, s), 4.91 (1 H, d, J = 4.7), 5.36 (2 H, AB q, J = 13.0), 6.16 (1 H, J = 4.7), 7.60–8.25 (8 H, Ar).

Oxidation with Excess MCPA. Approximately 3–5 mol equiv of the oxidant was used and the reaction monitored by ^1H NMR in parallel runs. Workup with aqueous $NaHSO_3$, $NaHCO_3$ and brine, in sequence, and flash chromatography afforded the pure products, unless otherwise stated.

Oxidation of 1a. Conversion of **1a** into **2a** and **3a** and then conversion of both **2a** and **3a** into **4a** was monitored. Chromatography afforded **methyl (6*R*,7*S*)-7-[1(*R*)-((*tert*-butyldimethylsilyl)oxy)ethyl]-3-methyl-2-thiacephem-4-carboxylate 1,1-dioxide (4a)** (51%) as a syrup: IR ($CHCl_3$) 1800, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (6 H, s), 0.86 (9 H, s), 1.24 (3 H, d, J = 6.3), 2.17 (3 H, s), 3.78 (1 H, dd, J = 2.0, 2.6), 4.35 (1 H, dq, J = 2.6, 6.3), 5.07 (1 H, d, J = 2.0); UV (*n*-hexane) λ_{max} 276 nm (ϵ 5996), sh at ca. 297 (4417); mass spectrum, 357 ($M^+ - 64$). Anal. Calcd for $C_{16}H_{27}NO_6S_2Si$: C, 45.58; N, 3.32; H, 6.46. Found: C, 45.37; N, 3.18; H, 6.51. A second-eluted material was identified as the penem **11a** (11%), arising from spontaneous desulfonylation of **4a** (vide infra).

Oxidation of 2a (NMR Tube). The thiosulfonate **4a** was exclusively produced.

Oxidation of 3a (NMR Tube). A mixture (ca. 10:1) of **4a** and **5a** was obtained, the latter being identified after an independent synthesis via periodate oxidation (vide infra).

Oxidation of 1b. There was obtained **2,2,2-trichloroethyl (6*R*,7*S*)-7-[1(*R*)-(((2,2,2-trichloroethoxy)carbonyl)oxy)-ethyl]-3-methyl-2-thiacephem-4-carboxylate 1,1-dioxide (4b)**, isolated after chromatography on magnesium silicate (Florisil), owing to silica gel instability: 40%; IR ($CHCl_3$) 1805, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (3 H, d, J = 6.3), 2.35 (3 H, s), 4.0 (1 H, dd, J = 2.0, 5.0) 4.75 and 4.85 (each 2 H, AB q), 5.15 (1 H, d, J = 2.0), 5.30 (1 H, m); UV (EtOH) λ_{max} 284 nm (ϵ 4291); mass spectrum, 597 (M^+), 533.

Oxidation of 1c. There was obtained ***p*-nitrobenzyl (6*R*,7*S*)-7-phthalimido-3-methyl-2-thiacephem-4-carboxylate 1,1-dioxide (4c)**, unstable on silica, isolated as a white powder after aqueous workup and trituration with ethyl ether; 70%; mp 125 °C dec; IR (KBr) 1800, 1780, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (3 H, s), 5.42 (3 H, m), 5.98 (1 H, d, J = 2.0), 7.38–8.26 (8 H, m); UV (EtOH) λ_{max} 271 nm (ϵ 14794); mass spectrum, 529 (M^+).

Oxidation of 6a. The thiosulfonates **9a** and **10a** were formed in ca. 3:1 relative amounts (NMR monitoring), accompanied by minor, unidentified materials. Compound **9a** depleted within few hours, yielding the penem **12a**; in the presence of MCPBA, the latter could not be observed owing to its fast oxidation followed by decomposition.

Methyl (6*R*,7*R*)-7-[1(*R*)-((*tert*-butyldimethylsilyl)oxy)-ethyl]-3-methyl-2-thiacephem-4-carboxylate 1,1-dioxide (9a) (not isolated): ^1H NMR ($CDCl_3$) δ 0.07 (3 H, s), 0.10 (3 H, s), 0.88 (9 H, s), 1.33 (3 H, d, J = 6.1), 2.17 (3 H, s), 3.92 (4 H, s + AB q), 5.01 (1 H, d, J = 4.9).

Methyl (6*R*,7*R*)-7-[1(*R*)-((*tert*-butyldimethylsilyl)oxy)-ethyl]-3-methyl-2-thiacephem-4-carboxylate 2,2-dioxide (10a): yellowish syrup, 15% (after silica gel chromatography); IR ($CHCl_3$) 1790, 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (3 H, s), 0.08 (3 H, s), 0.87 (9 H, s), 1.37 (3 H, d, J = 6.3), 2.17 (3 H, s), 3.91 (3 H, s), 4.11 (1 H, t, J = 5.9), 4.32 (1 H, m), 5.77 (1 H, d, J = 5.9); mass spectrum, 364 ($M^+ - 57$). Anal. Calcd for $C_{16}H_{27}NO_6S_2Si$: C, 45.58; N, 3.32; H, 6.46; S, 15.21. Found: C, 45.31; N, 3.28; H, 6.40; S, 15.10.

Oxidation of 6c. An inseparable mixture of thiosulfonates **9c** and **10c** (3:1 relative amount by NMR integration) was formed in good yield.

***p*-Nitrobenzyl (6*R*,7*R*)-7-phthalimido-3-methyl-2-thiacephem-4-carboxylate 1,1-dioxide (9c)** (not isolated): ^1H NMR ($CDCl_3$) δ 2.47 (3 H, s), 5.20 (1 H, d, J = 4.5), 5.37 (2 H, AB q), 5.95 (1 H, d, J = 4.5), 7.55–8.20 (8 H, m). Compound **10c** was identified after an independent synthesis via periodate oxidation (vide infra).

Oxidation with Sodium Periodate. Sodium periodate (5 mmol) was added to a solution of the 2-thiacephem 2-oxide (1 mmol), either pure or in admixture with the 1-isomer, in acetonitrile (25 mL)–water (12 mL). The reaction was monitored by TLC; iodine or acetic acid was occasionally used as catalyst, as indicated. The reaction mixture was partitioned between ethyl acetate and water, and the crude product from the organic extracts was fractionated by silica gel chromatography.

Oxidation of 3a. Iodine was used as the catalyst; the reaction time was 3 h. There was obtained **methyl (6*R*,7*S*)-7-[1(*R*)-((*tert*-butyldimethylsilyl)oxy)ethyl]-3-methyl-2-thiacephem-4-carboxylate 2,2-dioxide (5a)** as an oil, 62%; IR ($CHCl_3$) 1795, 1740, 1325, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (3 H, s), 0.07 (3 H, s), 0.86 (9 H, s), 1.23 (3 H, d, J = 6.2), 2.20 (3 H, s), 3.58 (1 H, dd, J = 2.6, 3.4), 3.88 (3 H, s), 4.37 (1 H, m), 5.68 (1 H, d, J = 2.6); mass spectrum, 364 ($M^+ - 57$).

Oxidation of the Mixture of Regioisomeric Thiosulfinates 2a and 3a. Periodate oxidation of the crude mixture of **2a** and **3a** obtained after MCPBA treatment of **1a** (100 mg) afforded **5a** (11 mg) and led to the recovery of **2a** (56 mg). The pure 1-oxide **2a** was inert to metaperiodate under the above conditions. A trace amount of the 1,1-dioxide **4a** was detected after repeated additions of iodine.

Oxidation of 8a. Acetic acid was used as the catalyst; the reaction was run overnight. There was obtained the 2,2-dioxide **10a** (23%), identical with the sample isolated from MCPBA oxidation of **6a**.

Oxidation of 8c. No catalyst was needed; the reaction time was 2 h. From the chromatographically unstable mixture of thiosulfinates **8c** and **7c** (ca. 3:1) resulting after MCPBA oxidation of 125 mg of **6c**, there was obtained ***p*-nitrobenzyl (6*R*,7*R*)-7-phthalimido-3-methyl-2-thiacephem-4-carboxylate 2,2-dioxide (10c)**: 90 mg (67% based on **6c**, estimated 90% based on **8c**); IR (KBr) 1810, 1780, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.22 (3 H, s), 5.41 (2 H, s), 6.03 (1 H, d, J = 5.3), 6.14 (1 H, d, J = 5.3), 7.5–8.2 (8 H, m). Anal. Calcd for $C_{22}H_{15}N_3O_9S_2$: C, 49.90; N, 7.94; H, 2.86. Found: C, 49.73; N, 7.81; H, 2.95.

Desulfonylation to Penems. Thermolysis of 4a. The reaction was monitored by TLC (1:2 AcOEt–cyclohexane); conversion (over 90%) into penem **11a** occurred after 3.5 h in refluxing *n*-hexane, 0.5 h in refluxing benzene, or 4 h in acetonitrile at 25 °C.

Methyl (5*R*,6*S*)-6-[1(*R*)-((*tert*-butyldimethylsilyl)oxy)-ethyl]-2-methylpenem-3-carboxylate (11a): 90%, white powder; mp 82–83 °C; IR (KBr) 1775, 1710, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (6 H, s), 0.87 (9 H, s), 1.23 (3 H, d, J = 6.2), 2.34 (3 H, s), 3.61 (1 H, dd, J = 2.0, 4.5), 3.77 (3 H, s), 4 .23 (1 H, m), 5.51 (1 H, d, J = 2.0); UV (EtOH) λ_{max} 269 nm (ϵ 3701), 313 (6579); mass spectrum, 357 (M^+). Anal. Calcd for $C_{16}H_{27}NO_4SSi$: C, 53.74; N, 3.92; H, 7.61. Found: C, 53.69; N, 3.81; H, 7.65.

Thermolysis of 4b. Heating **4b** for 4 h in refluxing CCl_4 afforded, after silica gel chromatography, **2,2,2-trichloroethyl (5*R*,6*S*)-6-[1(*R*)-(((2,2,2-trichloroethoxy)carbonyl)oxy)-ethyl]-2-methylpenem-3-carboxylate (11b)**: 74%; amorphous solid; IR (KBr) 1795, 1760, 1720 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.50 (3 H, d, J = 6.2), 2.40 (3 H, s), 3.90 (1 H, dd, J = 1.9, 8.5), 4.80 (2 H, s), 4.86 (2 H, s), 5.09 (1 H, m), 5.60 (1 H, d, J = 1.9); UV (EtOH) λ_{max} 318 nm (ϵ 7790); mass spectrum, 533 (M^+).

Thermolysis of 4c. Heating **4c** for 9 h in refluxing chloroform and chromatography on silica afforded ***p*-nitrobenzyl (5*R*,6*S*)-6-phthalimido-2-methylpenem-3-carboxylate (11c)**: 48% (based on crude **4c**); white powder; $[\alpha]^{20}_D$ −86°; mp 154–156 °C dec; IR(KBr) 1818, 1765, 1710 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 2.42 (3 H, s), 540 (2 H, AB q), 5.75 (1 H, d, J = 1.8), 5.95 (1 H, d, J = 1.8), 7.6–8.3 (8 H, m); mass spectrum, 465 (M^+).

Thermolysis of 9a. The inseparable mixture of thiosulfonates **9a** and **10a** obtained after MCPBA oxidation of **6a** was converted into a mixture of **17a** and **10a** when stored for 24 h at 0 °C. Chromatography afforded **methyl (5*R*,6*R*)-6-[1(*R*)-((*tert*-butyldimethylsilyl)oxy)ethyl]-2-methylpenem-3-carboxylate (12a)**: ca. 65% (based on **9a** present in the original mixture); syrup; IR ($CHCl_3$) 1790, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (6 H, s), 0.87 (9 H, s), 1.17 (3 H, d, J = 6.1), 2.36 (3 H, s), 3.78 (3 H, s), 3.85 (1 H, dd, J = 4.3, 6.6), 4.28 (1 H, m), 5.52 (1 H, d, J = 4.3); UV (95% EtOH) λ_{max} 265 nm (ϵ 3518), 311 (6125); mass spectrum, 357 (M^+).

Thermolysis of 9c. The inseparable mixture of thiosulfonates **9c** and **10c** obtained after MCPBA oxidation of **6c** was converted into a mixture of **12c** and **10c** when heated for 3 h in refluxing $CHCl_3$. Chromatography afforded ***p*-nitrobenzyl (5*R*,6*R*)-6-phthalimido-2-methylpenem-3-carboxylate (12c)**: ca. 50% (based on **9c** present in the original oxidation mixture); white powder; $[\alpha]^{20}_D$ +148°; mp 190–192 °C dec; IR (KBr) 1805, 1772,

1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.41 (3 H, s), 5.37 (2 H, AB q, J = 13.9), 5.94 (1 H, d, J = 3.9), 6.00 (1 H, d, J = 3.9), 7.60-8.24 (8 H, m); UV ($CHCl_3$) λ_{max} 270 nm (ϵ 15927), 306 (13230). Anal. Calcd for $C_{22}H_{15}N_3O_7S$: C, 56.77; N, 9.03; H, 3.25. Found C, 56.53; N, 8.95; H, 3.31.

Registry No. **1a**, 86998-70-1; **1b**, 103304-84-3; **1c**, 103304-85-4; **2a**, 103365-75-9; **2b**, 103304-86-5; **2c**, 103304-87-6; **3a**, 103365-74-8; **3c**, 103304-88-7; **4a**, 91618-80-3; **4b**, 103321-10-4; **4c**, 103304-90-1; **5a**, 103304-89-8; **6a**, 91685-82-4; **6c**, 103365-73-7; **7a**, 103420-11-7; **7c**, 103365-78-2; **8a**, 103365-76-0; **8c**, 103365-77-1; **9a**, 103365-79-3; **9c**, 103365-81-7; **10a**, 103365-80-6; **10c**, 103304-91-2; **11a**, 86998-74-5; **11b**, 103304-92-3; **11c**, 103304-93-4; **12a**, 103320-89-4; **12c**, 103304-94-5.

Photochemical Transformations of 1-Imidazolyl-1,2-dibenzoylalkenes. Steady-State and Laser Flash Photolysis Investigations[1]

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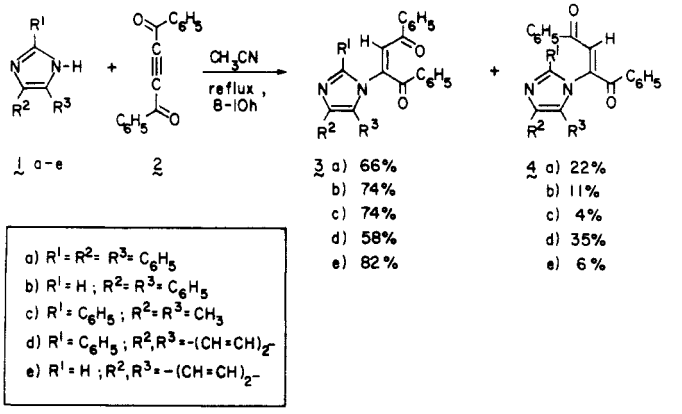
The photochemistry of a number of 1-imidazolyl-1,2-dibenzoylalkenes and 1-benzimidazolyl-1,2-dibenzoylalkenes has been investigated by steady-state photolysis combined with product analysis and laser flash photolysis. In several cases, the intramolecular phenyl group migration leading to ketene-mediated 3-butenoic acids and esters is observed. In addition, depending on the substituents present in the imidazolyl and benzimidazolyl groups, a variety of phototransformations occur; these include electrocyclic ring-closure reactions leading to dihydrophenanthrene and dihydroisoquinoline derivatives and photofragmentation reactions resulting in the loss of the imidazolyl moieties from the parent dibenzoylalkenes. Plausible mechanisms for these photoreactions are discussed. Laser flash photolysis in several cases gives rise to transient processes related to ketene and zwitterionic intermediates.

Photorearrangements of dibenzoylalkenes are known to give ketene-derived products and lactones, in addition to cis-trans isomerization products.[3-8] As a part of our continuing studies on the photorearrangements of 1,2-dibenzoylalkenes, we have recently examined the phototransformations of several substrates containing 1,2-dibenzoylalkene moieties such as 1,4- and 1,2-epoxy compounds,[9,10] dibenzobarrelenes,[11-13] 1-pyrazolyl-1,2-dibenzoylalkenes,[14,15] and 1-aziridinyl-1,2-dibenzoylalkenes.[16]

Scheme I



In general, it has been observed that photorearrangements of substituted 1,2-dibenzoylalkenes strongly depend on the nature of the substitutes present in them.

The object of the present investigation has been to examine the phototransformations of some selected 1-imidazolyl-1,2-dibenzoylalkenes and 1-benzimidazolyl-1,2-dibenzoylalkenes, containing suitably positioned substituents which are capable of undergoing other types of photoreactions, besides the 1,2-dibenzoylalkene rearrangement. In addition, laser flash photolysis studies have

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