90605-45-1; $Me(CH_2)_2CO_2Me$, 623-42-7; $Ph(CH_2)_2CO_2Me$, 103-25-3; (*E*)-$MeCH_2CH{=}CHCH_2CO_2Me$, 13894-61-6; 3-methyl-2-cyclohexen-1-ol, 21378-21-2; progesterone, 57-83-0; 5α-pregnane-3,20-dione, 566-65-4; 20β-hydroxy-4-pregnen-3-one, 145-15-3; 3-methyl-2-cyclopenten-1-one, 2758-18-1; 2-cyclohexen-1-one, 930-68-7; 3-methyl-2-cyclohexen-1-one, 1193-18-6; 3-methylcyclopentanone, 1757-42-2; cyclohexanone, 108-94-1; 3-methylcyclohexanone, 591-24-2.

Conversion Reactions of Cepham into Penam Systems. A Route To Determine the Relative Configurations of Two Diastereoisomeric 3-Bromo-4-methoxycepham Derivatives

Aldo Balsamo, Bruno Macchia, Franco Macchia,* Armando Rossello, and Patrizia Scatena

Istituto di Chimica Farmaceutica e Istituto di Chimica Organica dell'Università di Pisa, 56100 Pisa, Italy

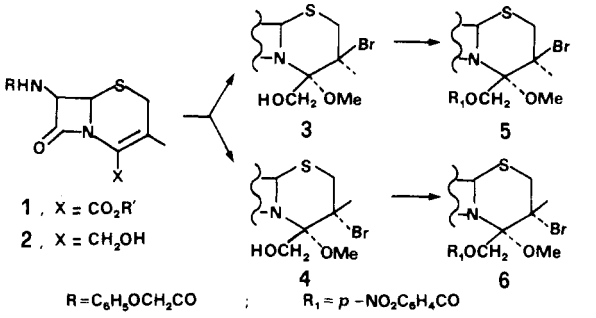
Paolo Domiano

Centro di Studio per la Strutturistica Diffrattometrica del CNR, Istituto di Strutturistica Chimica dell'Università di Parma, 43100 Parma, Italy

Received July 8, 1985

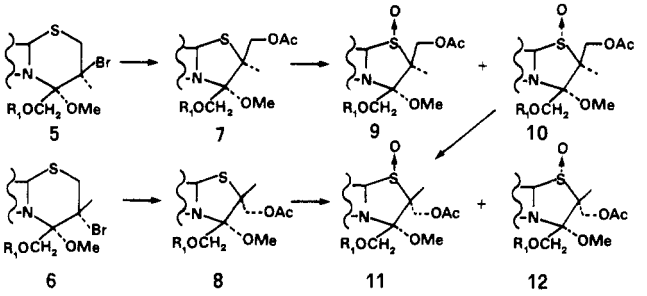
The 3-cephem double bond of cephalosporins of type **1** (R′ = H or alkyl) could appear to be a useful moiety in order to functionalize the dihydrothiazine ring of this class of β-lactam antibiotics. This double bond, however, is practically unreactive toward the classical electrophilic reagents.[1] This low reactivity could be due to the unfavorable electronic effects of the substituents on the C(3)–C(4) double bond of the cephalosporanic acid derivatives **1**. It was therefore conjectured that the electrophilic reactivity that is lacking in this unsaturated system might be restored by replacing the CO_2R' function present at C(4) of **1** with a less electron-withdrawing group such as the hydroxymethyl one. In accordance with this hypothesis, we found that the double bond of the 4-(hydroxymethyl)-3-cephem derivative **2** easily reacts with bromine in methanol, yielding a mixture of two bromomethoxy adducts **3** and **4** in a ratio of about 6:1.[2] The structure and configuration of the major product **3** was unequivocally determined by single-crystal X-ray analysis.[2] The very similar ^{13}C chemical shifts of the tetrasubstituted C(3) and C(4) carbons of both the adducts **3** and **4** led us to suggest the same regiochemistry for these compounds.[2] Unfortunately no information could be obtained about the configuration of **4**, and this did not allow us to make a complete rationalization of the formation of **3** and **4**.

It is known that 3-halosubstituted cepham derivatives can be converted by ring contraction into structurally related penam derivatives.[3,4] Bearing in mind that the



structure and configuration of compound **3** had been firmly established,[2] this kind of transformation carried out on **3** and **4** should have been able both to confirm the regiochemistry of **4** and to demonstrate its configuration. Furthermore the above-mentioned cepham–penam conversion reactions could have given β-lactam derivatives more complex than those of natural origin.

The reaction of the bromomethoxy adducts **3** and **4**, obtained by bromination of **2** in methanol,[2] with *p*-nitrobenzoyl chloride, afforded the corresponding esters **5** and **6**. The treatment of **5** and **6** with silver acetate in glacial acetic acid for a few minutes at 100 °C gave in good yields the two diastereoisomeric penam derivatives **7** and **8**, respectively. When the reaction with silver acetate was



carried out on the hydroxymethyl derivatives **3** and **4**, only complex mixtures of decomposition products were obtained. Oxidation of the penam derivatives **7** and **8** with *m*-chloroperoxybenzoic acid afforded mixtures of the corresponding *S* and *R* sulfoxides **9** and **10** and **11** and **12**, respectively, in which the *R* epimers predominated. Heating the *R* sulfoxide **10** in refluxing benzene resulted in its conversion to the penicillin *S* sulfoxide **11**. Treatment of **12** in refluxing benzene for a few hours led only to the recovery of the starting material together with small amounts of decomposition products. The *S* sulfoxides **9** and **11** were stable under these reaction conditions.

The penam nature of **7** and **8** was established on the basis both of the values of the geminal coupling constants (12.6 and 11.2 Hz, respectively) of the methylene protons of the CH_2OAc moiety, and of the high values of the stretching frequency of the β-lactam C=O (1786 and 1784 cm^{-1}, respectively).[5,6] The configurations of the sulfoxide group of **9–12** were deduced from intermolecular hydrogen-bonding studies of the amide proton using Me_2SO-d_6 (see Table I).[4,7-9] The small changes in the shift for the amide proton of the penam derivatives **9** and **11** observed on passing from $CDCl_3$ to Me_2SO-d_6 suggested the *S* con-

(1) (a) Murphy, C. F.; Webber, J. A. "Cephalosporins and Penicillins: Chemistry and Biology"; Academic Press: New York, 1972; p 134. (b) Fazakerley, H.; Gilbert, D. A.; Gregory, G. I.; Lazemby, L. K.; Long A. G. *J. Chem. Soc. C* **1967**, 1959. (c) Sammes, P. G. *Chem. Rev.* **1976**, *76*, 113. (d) Balsamo, A.; Crotti, P.; Macchia, B.; Macchia, F.; Nannini, G.; Dradi, E.; Forgione, A. *J. Org. Chem.* **1976**, *41*, 2150.

(2) Balsamo, A.; Domiano, P.; Macchia, B.; Macchia, F.; Orlandini, E.; Rosselo, A. *J. Chem. Res., Synop.* **1984**, 226; *J. Chem. Res., Miniprint* **1984**, 2155.

(3) Kukolja, S.; Lammert, S. R.; Gleissner, M. R.; Ellis, A. I. *J. Am. Chem. Soc.* **1975**, *97*, 3192.

(4) Balsamo, A.; Giorgi, I.; Macchia, B.; Macchia, F.; Rosai, A.; Domiano, P.; Nannini, G. *J. Org. Chem.* **1980**, *45*, 2610.

(5) Barton, D. H. R.; Comer, F.; Greig, D. G. T.; Sammes, P. G.; Cooper, C. M.; Hewitt, G.; Underwood, W. G. E. *J. Chem. Soc. C* **1971**, 3540.

(6) Tsushima, T.; Tanida, H. *J. Org. Chem.* **1980**, *45*, 3205.

(7) Cooper, R. D. G.; De Marco, P. V.; Cheng, J. C.; Jones, N. D. *J. Am. Chem. Soc.* **1969**, *91*, 1408.

(8) De Marco, P. V.; Nagarajan, R. In ref 1a, p 311.

(9) Balsamo, A.; Benedini, P. M.; Macchia, B.; Macchia, F.; Rossello, A. *J. Chem. Soc. Perkin Trans. 1* **1984**, 413.

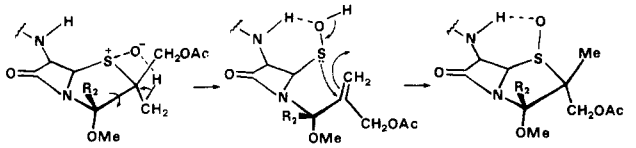
0022-3263/86/1951-0540$01.50/0

Table I. N-H Proton Shifts

compd	δ_{CDCl_3}	$\delta_{Me_2SO\text{-}d_6}$	$\Delta^{a,b}$
7	7.77	8.22	−0.45
8	7.42	8.74	−1.32
9	8.40	8.31	0.09
10	7.48	8.88	−1.40
11	8.63	8.60	0.03
12	7.37	9.35	−1.98

[a] $\Delta = \delta_{CDCl_3} - \delta_{Me_2SO\text{-}d_6}$. [b] Negative values indicate deshielding effects.

Scheme I



10 13 11

$R_2 = CH_2OR_1$

figuration for the *S*-oxide sulfoxide group; on the other hand, the larger changes obtained for the compounds **10** and **12**, indicated the *R* configuration for the same group.[4,7-9]

Unfortunately the spectroscopic data both in the case of the penam derivatives **7** and **8** and in that of the corresponding sulfoxides **9** and **10** and **11** and **12** were not sufficient to determine the configuration of these compounds. On the basis of the known transformation mechanism of 3-halocepham derivatives into penam compounds,[5] it can be assumed with certainty that the stereochemistry of the C(3) carbon of penam derivatives **7** and **8** is the same as that of the C(4) carbon of the corresponding starting cepham products **5** and **6**; the C(4) chiral centers of **5** and **6** are not involved in the reaction. The penam derivatives **7** and **8** and consequently their corresponding *S* and *R* sulfoxides **9** and **10** and **11** and **12** could differ in the stereochemistry either of one or of both of the C(2) and C(3) atoms. It is known that *R* sulfoxides which have a methyl group in the **2** position α-oriented, can be converted, by thermal isomerization which proceeds via a sulfenic acid intermediate, into the *S* sulfoxides of the corresponding C(2) epimers.[4,10,11] Therefore, if the two penam derivatives **7** and **8** differed only in their stereochemistry at C(2), both the *R* sulfoxide **10** and the *R* sulfoxide **12** could have been transformed on warming into **11** and **9**, respectively. In actual fact, the sulfoxide **10** can be converted quantitatively into **11** on heating in refluxing benzene. With the same treatment, the isomer **12** affords mostly the starting compound unchanged, in addition to some decomposition material. The conversion of **10** into **11** shows that the two diastereoisomeric penam derivatives **7** and **8** have the same configuration on C(3) and therefore must be epimers on C(2). As pointed out above, also the cepham esters **5** and **6**, and consequently the corresponding alcohols **3** and **4**, must have the same configuration on C(4) and therefore be epimers on C(3). As the configuration of **3** has been unequivocally determined by X-ray crystallography,[2] the configurations shown can be assigned to **4** and **6**.

As for the penam derivatives **7** and **8**, the relative configuration on C(2) remained to be established. However it could be assumed on the basis of mechanistic considerations based on the thermal conversion of **10** into **11**. As pointed out above, only the 2α-methyl isomer of R sulfoxides **10** and **12** should have been able to give the sulfenic acid intermediate **13**, internally stabilized by a hydrogen bond with the side-chain proton, which could rearrange to the *S* sulfoxide, which is an epimer on C(2) with respect to the starting sulfoxide (Scheme I).[12] Actually only compound **10** gave this kind of transformation, thus supporting the configuration on C(2) shown. The configurations on the C(2) carbon of **7** and **8** were confirmed by a comparison of the values of the observed sulfoxide perturbation shifts (Δ_{SO}) for corresponding protons in **7** and **8**.[7,8,13,14] It has been reported that for the penam derivatives, the H(5) proton and the 2α-methyl group, which are located vicinal and trans to the sulfoxide bond with the *S* configuration, are shielded in the sulfide → sulfoxide process.[7,8,13,14] The upfield shift recorded for the 2-methyl group in **7** and the downfield shift observed for the same group in **8** (see Table II) allowed us to confirm for the penam epimers **7** and **8** the configurations on the C(2) carbon shown.

Studies were also carried out on the aromatic solvent-induced shifts (ASIS) in **7** and **8** and in the corresponding sulfoxides with the *S* configuration **9** and **11**.[4,7,8] Even if no marked differences were observed in the trend of the net ASIS values of the sulfide–sulfoxide couples **7–9** and **8–11** (see Table III), the higher positive ASIS value observed for 2-Me protons of the couple **7–9**, further supported the 2α-methyl configuration for compound **7**.[4,7,8]

Table II. Sulfoxide Perturbation Shifts (Δ_{SO})[a] for Corresponding Protons in 7 and 8

	2α-Me	2β-Me	H-5	H-6
7	1.62		5.29	5.77
9	1.36		5.03	6.05
$(\Delta_{SO})_7$	+0.26		+0.26	−0.28
8		1.47	5.28	5.65
11		1.70	5.19	6.14
$(\Delta_{SO})_8$		−0.23	+0.09	−0.49

[a] $\Delta_{SO} = \delta_{sulfide} - \delta_{sulfoxide}$. Positive values indicate shielding effects.

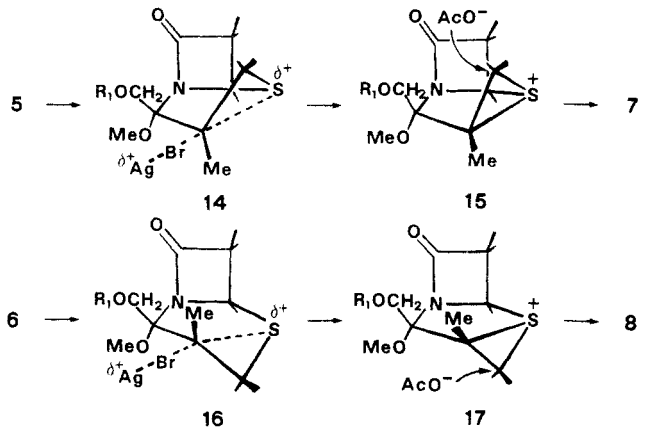
Table III. Benzene-Induced Shifts in $CDCl_3$ and C_6D_6 for Compounds 7–9 and 11[a]

	H-5	H-6	Me
7			
$CDCl_3$	5.29	5.77	1.62
C_6D_6	4.55	5.63	1.47
Δ_7[b]	0.74	0.14	0.15
9			
$CDCl_3$	5.03	6.05	1.36
C_6D_6	3.64	5.85	0.89
Δ_9[b]	1.39	0.20	0.47
$\Delta_9 - \Delta_7$	0.65	0.06	0.32
8			
$CDCl_3$	5.28	5.65	1.47
C_6D_6	4.52	5.40	1.38
Δ_8[b]	0.76	0.25	0.09
11			
$CDCl_3$	5.19	6.14	1.70
C_6D_6	4.06	5.97	1.41
Δ_{11}[b]	1.13	0.17	0.29
$\Delta_{11} - \Delta_8$	0.37	−0.08	0.20

[a] Positive values indicate shielding effects. [b] $\delta_{CDCl_3} - \delta_{C_6D_6}$.

(10) Barton, D. H. R.; Greig, D. G. T.; Lucente, G.; Sammes, P. G.; Tailor, M. V.; Cooper, C. M.; Hewit, G.; Underwood, W. G. E. *J. Chem. Soc., Chem. Commun.* **1970**, 1683.
(11) Cooper, R. D. G. *J. Am. Chem. Soc.* **1970**, *92*, 5010.
(12) Spry, D. O. *J. Am. Chem. Soc.* **1970**, *92*, 5006.
(13) Cooper, R. D. G.; De Marco, P. V.; Spry, D. O. *J. Am. Chem. Soc.* **1969**, *91*, 1528.
(14) Barton, D. H. R.; Comer, F.; Sammes, P. G. *J. Am. Chem. Soc.* **1969**, *91*, 1529.

Scheme II



The interconversion reactions of penam and cepham systems are assumed to proceed through the intermediate formation of β- and α-episulfonium ions of type **15** and **17**, respectively, which by attack of a nucleophile can afford penam or cepham derivatives usually different from the starting compounds.[3,4,6,9,15,16] The transformation of **5** and **6** with silver acetate in acetic acid into **7** and **8** can be rationalized,[3,4] as visualized in Scheme II, through abstraction of the halogen, followed by the nucleophilic attack of the sulfur on the carbon bearing the halogen, to give the episulfonium ions **15** and **17**. Attack of the nucleophile on the methylene carbon of the ions **15** and **17** affords the penam derivatives **7** and **8**. The stereospecificity of the transformation of **5** and **6** into **7** and **8**, respectively, indicates that also the formation of the intermediate episulfonium ions **15** and **17** must be stereospecific,[17] with a complete inversion of the configuration on the carbon bearing the leaving halogen.

The opening of episulfonium ions formed as intermediates in the penam–cepham interconversions by nucleophiles usually occurs on both the carbon atoms affording penam and cepham compounds. However, the presence of substituents on the two carbons different from the unusual ones can modify the regiochemistry of the ring opening. In the present case the ring opening of the episulfonium ion intermediates **15** and **17** occurs regiospecifically by the attack of the nucleophile on the methylene carbon, yielding the penam derivatives **7** and **8**, respectively. The electron-withdrawing effect of the methoxy group on the former C(4) in **15** and **17** should lower the stability of the partial positive charge on the adjacent episulfonium carbon, thus favoring the path leading to the attack of the nucleophile on the methylenic carbon.

The electrophilic additions to a double bond initiated by positive bromine are usually considered to proceed through an electrophilic step, leading to the intermediate formation of bromonium or bromocarbenium ions, followed by the attack of a nucleophile to give the addition products. In the bromination of **2** in methanol the nucleophilic step is completely regiospecific both in the formation of **3** and **4** whereas the attack of the methanol is completely anti or syn stereoselective, depending on whether the approach of the bromine occurs from the β- or from the α-side, respectively. Both the complete regiospecificity of the nucleophilic step of the reaction and the formation of the syn adduct **4** suggest that the intermediates, formed by the electrophilic attack of the bromine either from the β- or from the α-side, exhibit a fair degree of carbocation character on the carbon [C(4)] which undergoes the attack of the nucleophile. The different stereochemical behavior of the addition, depending on the direction of the attack of the bromine is, however, difficult to explain.

Experimental Section

Melting points were determined on a Kofler hot-state apparatus and are uncorrected. IR spectra for comparison of compounds were taken on paraffin oil mulls on a Perkin-Elmer Model 1310 instrument and those for the determination of C=O stretching bands with a Perkin-Elmer Model 257 double-beam grating spectrophotometer using an NaCl cell of 1-mm optical length in dried $CHBr_3$. ^1H NMR spectra were detected with a Varian CFT-20 instrument operating at 80 MHz in a ca. 2% solution of $CDCl_3$, in Me_2SO-d_6, or in C_6D_6, using Me_4Si as the internal standard.

The proton magnetic resonance assignments were firmly established on the basis of the expected chemical shift and the multiplicity of the signal. The relative percentages of compounds **9** and **10** and **11** and **12** were calculated on the basis of the integrals of the 2α-Me (for **9** and **10**) and 2β-Me (for **11** and **12**) singlets in the ^1H NMR spectra of the crude reaction mixture. ^{13}C NMR spectra were taken in $CDCl_3$ solution with a Varian CFT-20 instrument operating at 20 MHz. Preparative TLC was performed on 2-mm layer silica gel plates (Merck F_{254}) containing a fluorescent indicator; spots were detected under UV light (254 nm). Evaporations were made in vacuo (rotating evaporator). Magnesium sulfate was always used as the drying agent. CH_2Cl_2, C_6H_6, and pyridine were refluxed over P_2O_5, sodium, and KOH, respectively, and then rectified.

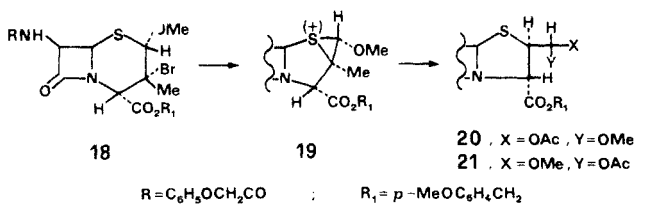
3β-Bromo-3α-methyl-4β-(hydroxymethyl)-4α-methoxy-7β-(phenoxyacetamido)cepham (3) and 3α-bromo-3β-methyl-4β-(hydroxymethyl)-4α-methoxy-7β-(phenoxyacetamido)cepham (4) were prepared from **2**, as previously described.[2]

3β-Bromo-3α-methyl-4α-methoxy-4β-[((p-nitrobenzoyl)oxy)methyl]-7β-(phenoxyacetamido)cepham (5). A stirred solution of **3**[2] (0.67 g, 1.5 mmol) in anhydrous pyridine (10 mL) was treated dropwise at 0 °C with a solution of p-nitrobenzoyl chloride (1.4 g, 7.5 mmol) in anhydrous pyridine (10 mL). The solution was stirred at room temperature for 1 h, diluted with $CHCl_3$, washed (5% aqueous HCl, 10% aqueous $NaHCO_3$, and H_2O), filtered, and evaporated to give an oily residue (1.05 g), which was crystallized from ethyl acetate–hexane to yield pure **5** (0.60 g, 67%): mp 154–155 °C; IR ($CHBr_3$) ν 1777 cm^{-1} (β-lactam C=O); ^1H NMR ($CDCl_3$) δ 2.00 (s, 3, CCH_3), 2.63 (d, 1, J = 14.7 Hz, H-2β), 3.42 (s, 3, OCH_3), 3.71 (d, 1, J = 14.7 Hz, H-2α), 5.02 (d, 1, J = 4.7 Hz, CHS), 5.32 (s, 2, CH_2OCO), 5.68 (q, 1, J = 4.7, 9.6 Hz, NHC*H*); ^{13}C NMR δ 64.92 [s, C(3)], 87.87 [s, C(4)]. Anal. Calcd for $C_{24}H_{24}BrN_3O_8S$: C, 48.50; H, 4.04; Br, 13.44; N, 7.07. Found: C, 48.39; H, 3.98; Br, 13.52; N, 6.90.

(15) See, for example: (a) Koppel, G. A.; Kinnick, M. D.; Nummy, L. J. "Recent Advances in the Chemistry of β-Lactam Antibiotics"; The Chemical Society: London, 1977; p 101. (b) Lowe, G. In "Comprehensive Organic Chemistry"; Pergamon Press: Oxford, 1979; Vol. 5, p 289 and references therein cited.

(16) Cooper, R. D. G.; Spry, D. O. In ref 1a, p 183.

(17) In previous work,[4] the supposed 2α-methoxy-3α-bromocepham derivative **18** was converted by the silver acetate–acetic acid system into the diastereoisomeric 2α-methylpenam derivatives **20** and **21**. Compounds **20** and **21** should have been formed by the attack of the nucleophile on the methoxy-substituted carbon of the β-episulfonium ion **19**. The formation of **19** from **18** was hypothesized to proceed through the intermediate formation of a C(3) carbenium ion.[4] However, if the complete stereospecificity observed in the formation of episulfonium ions **15** and **17** from the 3-bromo derivatives **5** and **6** can be extended also to the reaction of **18** with silver acetate in acetic acid, the intermediate formation of the episulfonium ion **19** could suggest for **18** an inverted stereochemistry on C(3). The stereochemistry on C(3) of **18** had previously been established on the basis of the easy dehydrobromination of **18** to the corresponding Δ^3-cephem derivative.



3α-Bromo-3β-methyl-4α-methoxy-4β-[((p-nitrobenzoyl)oxy)methyl]-7β-(phenoxyacetamido)cepham (6). This compound was synthesized from 4[2] (0.32 g) as described for **5**. Pure **6** was obtained as an oil after column chromatography on silica gel eluting with 1:1.5 ethyl acetate–hexane: yield, 0.38 g (87%); IR ($CHBr_3$) ν 1776 cm^{-1} (β-lactam C=O); ^1H NMR δ 2.08 (s, 3, CCH_3), 2.80 (d, 1, J = 13.6 Hz, H-2β), 3.51 (s, 3, OCH_3), 4.12 (d, 1, J = 13.6 Hz, H-2α), 5.10 (s, 2, CH_2OCO), 5.06 (d, 1, J = 4.9 Hz, CHS), 5.61 (q, 1, J = 4.9, 9.3 Hz, NHC*H*); ^{13}C NMR δ 62.53 [s, C(3)], 87.98 [s, C(4)]. Anal. Calcd for $C_{24}H_{24}BrN_3O_8S$: C, 48.50; H, 4.04; Br, 13.44; N, 7.07. Found: C, 48.40; H, 4.12; Br, 13.59; N, 6.85.

2β-(Acetoxymethyl)-2α-methyl-3α-methoxy-3β-[((p-nitrobenzoyl)oxy)methyl]-6β-(phenoxyacetamido)penam (7). A solution of **5** (0.93 g, 1.6 mmol) in glacial acetic acid (35 mL) was added under stirring to silver acetate (0.45 g, 2.7 mmol) at room temperature. The resulting stirred mixture was placed in an oil bath at 100 °C and left at the same temperature for 20 min. The suspension was allowed to cool at room temperature, filtered through Celite to remove silver salts, and evaporated to near dryness. The residue was taken up with $CHCl_3$, washed (10% aqueous $NaHCO_3$ and brine), filtered, and evaporated. The solid residue (0.85 g) consisting exclusively of **7** was crystallized from $CHCl_3$–hexane to yield pure **7** (0.65 g, 71%): mp 191–192 °C; IR ($CHBr_3$) ν 1786 cm^{-1} (β-lactam C=O); ^1H NMR δ 1.62 (s, 3, CCH_3), 2.07 (s, 3, $COCH_3$), 3.43 (s, 3, OCH_3), 3.95 and 4.61 (2 d, 2, J = 12.6 Hz, $SCCH_2O$)[3] 4.65 and 5.39 (2 d, 2, J = 14.0 Hz, $NCCH_2O$), 5.29 (d, 1, J = 4.3 Hz, SCH), 5.77 (q, 1, J = 4.3, 10.3 Hz, NHC*H*). Anal. Calcd for $C_{26}H_{27}N_3O_{10}S$: C, 54.46; H, 4.70; N, 7.32. Found: C, 54.38; H, 4.64; N, 7.28.

2α-(Acetoxymethyl)-2β-methyl-3α-methoxy-3β-[((p-nitrobenzoyl)oxy)methyl]-6β-(phenoxyacetamido)penam (8). This compound was prepared from **6** (0.21 g) as described for the preparation of **7**. The crude product was purified by TLC using a 1:3 mixture of ethyl acetate–benzene as the eluent. Pure **8** was obtained as a vitreous product: yield, 0.14 g (70%); IR ($CHBr_3$) ν 1784 cm^{-1} (β-lactam C=O); ^1H NMR δ 1.47 (s, 3, CCH_3), 2.09 (s, 3, $COCH_3$), 3.42 (s, 3, OCH_3), 4.38 and 4.69 (2 d, 2, J = 11.2 Hz, $SCCH_2O$), 4.85 and 5.33 (2 d, 2, J = 13.4 Hz, $NCCH_2O$), 5.28 (d, 1, J = 4.4 Hz, SCH), 5.65 (q, 1, J = 4.4, 9.6 Hz, NHC*H*). Anal. Calcd for $C_{26}H_{27}N_3O_{10}S$: C, 54.46; H, 4.70; N, 7.32. Found: C, 54.63; H, 4.57; N, 7.50.

2β-(Acetoxymethyl)-2α-methyl-3α-methoxy-3β-[((p-nitrobenzoyl)oxy)methyl]-6β-(phenoxyacetamido)penam (*S*)- and (*R*)-Sulfoxide (9 and 10). A stirred solution of **7** (0.46 g, 0.8 mmol) in anhydrous CH_2Cl_2 (25 mL) was cooled at 0 °C and then treated dropwise with a solution of 91% *m*-chloroperoxybenzoic acid (0.15 g, 0.79 mmol) in anhydrous CH_2Cl_2 (10 mL). The resulting solution was stirred 1 h at the same temperature, washed (10% aqueous $NaHCO_3$ and H_2O), filtered, and evaporated to dryness to give an oily residue (0.45 g) consisting of **7** and **8** in a ratio of about 1:4.5. The residue was subjected to preparative TLC using a 3:1 mixture of ethyl acetate and petroleum ether (bp 40–60 °C) as the eluent. Extraction with ethyl acetate at room temperature of the band with the higher R_f gave an oily residue consisting of pure **9** (0.052 g, 11%): IR ($CHBr_3$) ν 1795 (β-lactam C=O); ^1H NMR δ 1.36 (s, 3, CCH_3), 2.14 (s, 3, $OCOCH_3$), 3.50 (s, 3, OCH_3), 4.75 (s, 2, $SCCH_2O$), 4.78 and 5.86 (2 d, 2, J = 13.3 Hz, $NCCH_2$), 5.03 (d, 1, J = 4.6 Hz, SCH), 6.05 (q, 1, J = 4.6, 10.8 Hz, NHC*H*). Anal. Calcd for $C_{26}H_{27}N_3O_{11}S$: C, 52.98; H, 4.61; N, 7.13. Found: C, 53.17; H, 4.71; N, 6.89.

Extraction at room temperature with ethyl acetate of the band with the lower R_f yielded a solid residue (0.25 g) which crystallized from $CHCl_3$–hexane to yield pure **10** (0.20 g, 42%): mp 140–142 °C; IR ($CHBr_3$) ν 1792 (β-lactam C=O); ^1H NMR δ 1.54 (s, 3, CCH_3), 2.09 (s, 3, $OCOCH_3$), 3.47 (s, 3, OCH_3), 4.35 and 4.85 (2 d, 2, J = 12.9 Hz, $SCCH_2O$), 4.63 and 5.50 (2 d, 2, J = 13.8 Hz, $NCCH_2O$), 4.79 (d, 1, J = 4.5 Hz, SCH), 5.97 (q, 1, J = 4.5 and 9.2 Hz, NHC*H*). Anal. Calcd for $C_{26}H_{27}N_3O_{11}S$: C, 52.98; H, 4.61; N, 7.13. Found: C, 52.71; H, 4.55; N, 7.30.

2α-(Acetoxymethyl)-2β-methyl-3α-methoxy-3β-[((p-nitrobenzoyl)oxy)methyl]-6β-(phenoxyacetamido)penam (*S*)- and (*R*)-Sulfoxide (11 and 12). These compounds were synthesized from **8** (0.10 g) as described for **9** and **10**. The crude residue consisting of **11** and **12** in a ratio of about 1:5 was subjected to preparative TLC eluting with 65:35 ethyl acetate–petroleum ether (bp 40–60 °C). Pure **11** was obtained as an oil by extraction with $CHCl_3$ at room temperature of the upper band of the chromatogram: yield, 0.015 g (15%); IR (CHB_3) ν 1791 (β-lactam C=O); ^1H NMR δ 1.70 (s, 3, CCH_3), 2.11 (s, 3, $OCOCH_3$), 3.48 (s, 3, OCH_3), 4.28 and 4.72 (2 d, 2, J = 13.2 Hz, $SCCH_2O$), 4.93 and 5.40 (2 d, 2, J = 14.0 Hz, $NCCH_2O$), 5.19 (d, 1, J = 4.8 Hz, SCH), 6.14 (q, 1, J = 4.8 and 10.2 Hz, NHC*H*). Anal. Calcd for $C_{26}H_{27}N_3O_{11}S$: C, 52.98; H, 4.61; N, 7.13. Found: C, 53.15; H, 4.43; N, 6.92.

Pure **12** was isolated by extraction with $CHCl_3$ at room temperature of the lower band of the chromatogram: yield, 0.055 g (55%); IR ($CHBr_3$) ν 1789 (β-lactam C=O); ^1H NMR δ 1.43 (s, 3, CCH_3), 2.12 (s, 3, $OCOCH_3$), 3.43 (s, 3, OCH_3), 4.57 and 4.98 (2 d, 2, J = 12.2 Hz, $SCCH_2O$), 4.77 and 5.36 (2 d, 2, J = 13.4 Hz, $NCCH_2O$), 4.81 (d, 1, J = 4.8 Hz, SCH), 5.38 (q, 1, J = 4.8 and 10.8 Hz, NHC*H*). Anal. Calcd for $C_{26}H_{27}N_3O_{11}S$: C, 52.98; H, 4.61; N, 7.13. Found: C, 52.79; H, 4.56; N, 6.98.

Thermal Transformation of the *R* Sulfoxide 10. A solution of **10** (0.040 g) in anhydrous benzene (8 mL) was refluxed for 4 h. After the mixture cooled, the solvent was evaporated to yield an oily residue (0.038 g) consisting almost exclusively of **11** (TLC, ^1H NMR). When a solution of **10** in benzene was refluxed for a shorter time (2 h) some starting material was detected (TLC, ^1H NMR) in the reaction mixture.

When the *R* sulfoxide **12** was heated as described above for the **10**, or for longer times, it was recovered unchanged, together with some decomposition material (^1H NMR, TLC).

Acknowledgment. This work has been supported in part by a grant from the Consiglio Nazionale delle Ricerche and Ministero della Pubblica Istruzione.

Registry No. **3**, 94103-32-9; **4**, 99881-82-0; **5**, 99809-77-5; **6**, 99828-79-2; **7**, 99809-78-6; **8**, 99809-79-7; **9**, 99809-80-0; **10**, 99809-81-1; **11**, 99809-82-2; **12**, 99809-83-3.

Steric Effects of Ortho Substituents on Acid-Catalyzed Cyclization of Thiocyanatoacetophenones

Ashot Merijanian,* Gurdial M. Sharma, John Moushati, and Karl Gunderson

Department of Chemistry, William Paterson College, Wayne, New Jersey 07470

Received May 1, 1985

The synthesis of 2-chlorothiazoles by intramolecular cyclization of thiocyanatoacetophenones with HCl gas is well documented.[1,2] In this paper we report that under the same conditions thiocyanatoacetophenones can also cyclize to give 2-iminio-5-aryl-1,3-oxathiole hydrochlorides; but this mode of cyclization (Scheme I, pathway b) becomes significant only when the benzene ring of the parent compounds have substituents at the ortho positions. This observation was made by analyzing the reaction of HCl gas with thiocyanatoacetopheonones **1**, **3**, **5**, **8**, and **11** (Table I).

The thiocyanatoacetophenones **1**, **3**, **5**, **8**, and **11** were prepared by following a known sequence of reactions[1,2] outlined in Scheme I. The products obtained by saturating the solutions of these compounds in anhydrous ether with dry HCl gas are listed in Table I. A comparison of the products formed in the five reactions reveals that 2,6-di-

(1) Sharma, G. M.; Sachdev, H. S.; Narang, K. S. *J. Sci. Ind. Res., Sect. B* **1957**, *16*, 411.
(2) Bariana, D. S.; Sachdev, H. S.; Narang, K. S. *J. Indian Chem. Soc.* **1955**, *32*, 427.

0022-3263/86/1951-0543$01.50/0