Importance of the Substituent on C(2) in the Interconversion of the Thiazine and the Thiazolidine System of β-Lactam Antibiotics

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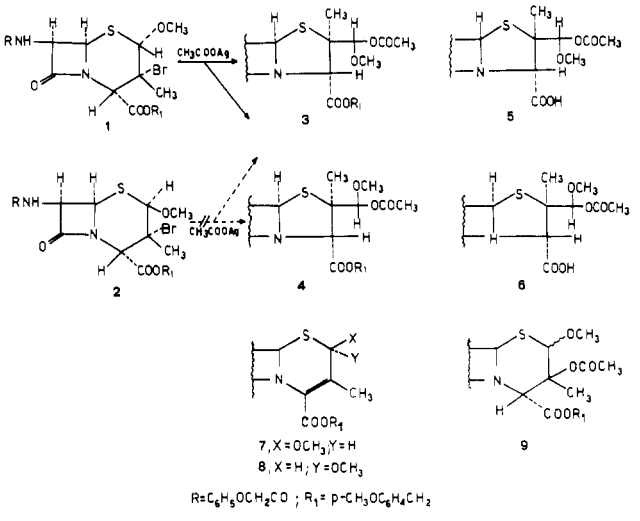
The reaction of the 2α-methoxy-3α-bromocepham derivative **1** with silver acetate in acetic acid gave a 1:1 mixture of the two penam derivatives **3** and **4**, which can be easily converted into the corresponding free acids **5** and **6**. Oxidation of **3** and **4** with *m*-chloroperoxybenzoic acid afforded equimolar mixtures of the corresponding (*R*)- and (*S*)-sulfoxides **10** and **11**, and **13** and **14**. The (*R*)-sulfoxides **10** and **13** rearranged by heating to compounds **12** and **15**, respectively, whereas the (*S*)-sulfoxides were stable under the same conditions. The structures and the configurations of all the products obtained were assigned on the basis of IR and ^{1}H NMR spectroscopy. The structure and the configuration of compound **3** have been univocally inferred by X-ray crystallographic analysis. The transformation of **1** into **3** and **4** has been rationalized through a mechanism implying the regiospecific ring opening of an intermediate episulfonium ion. The thermal rearrangements of the sulfoxides were explained through the intermediacy of a sulfenic acid.

In recent years a tremendous amount of work has been carried out in studying the interconversion reactions of the penam and the cepham skeleton.[1-3] Because the conversion of penicillins into cephalosporins offered an economic and alternative route to the synthesis of 3-substituted cephalosporins,[4] the efforts of the chemist have been devoted almost exclusively in this direction.[1-4] In contrast, few examples have been reported of the opposite transformation (cephalosporins into penicillins).[1,5]

As part of a program[6,7] aimed at developing methods for chemically modifying the dihydrothiazine ring of cephalosporins without altering the β-lactam ring, we explored the transformation of cephalosporins into penicillins in order to build up penicillin derivatives more complex than those of natural origin. Therefore, we examined the possibility of converting C(2)-substituted cephalosporins into the corresponding penam derivatives. This study should also give information on how a substituent on C(2) could influence the conversion reactions of cephalosporins into penicillins.

The treatment of a 76/24 mixture of the 2α- and 2β-methoxy-3α-bromocepham derivatives (**1** and **2**, respectively), obtained as previously described,[6] with silver acetate in glacial acetic acid at 100 °C for a few minutes[1] gave, in a good yield, a mixture of the two diastereoisomeric penam derivatives **3** and **4** in a ratio of about 1:1, together with small amounts of decomposition products. The yields of **3** and **4**, as isolated products, were 22 and 15%, respectively. From this mixture **3** can be separated by crystallization, whereas the other isomer **4** has been obtained pure by chromatography. On the other hand, the same treatment of a mixture of **1** and **2**[6] in which the latter isomer predominated (**1**/**2** ratio of 40/60) yielded, in a lower yield, an identical mixture of **3** and **4**, accompanied by markedly higher amounts of decomposition products. In the last case the yields of **3** and **4** in the pure state were 10 and 5%, respectively. Evidently only the 2α-methoxycepham derivative **1** leads to **3** and **4**, whereas the 2β-methoxy derivative **2** yields only decomposition products. Compounds **3** and **4** can be easily converted into the corresponding free acids **5** and **6** by hydrogenolysis with Pd on $CaCO_3$.



The absence of the cephem derivatives **7** and **8** from the reaction mixtures of **1** and **2** with silver acetate has been proven by comparing the ^{1}H NMR spectra of the crude products with those of authentic samples of **7** and **8**.[6] Also, **7** and **8** are not observed after treatment of the same mixtures with triethylamine. This latter experiment leads us to exclude the presence in the reaction mixture of compounds of type **9**; these products in the basic medium used should yield **7** and **8**.[3,8]

(1) S. Kukolja, S. R. Lammert, M. R. Gleissner, and A. I. Ellis, *J. Am. Chem. Soc.*, **97**, 3192 (1975).
(2) R. D. G. Cooper and D. O. Spry in "Cephalosporins and Penicillins: Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, 1972, pp 183-254.
(3) R. D. G. Cooper, L. D. Hatfield, and D. O. Spry, *Acc. Chem. Res.*, **6**, 32 (1973).
(4) S. Kukolja, S. R. Lammert, M. R. B. Gleissner, and A. I. Ellis, *J. Am. Chem. Soc.*, **98**, 5040 (1976).
(5) M. Yoshimoto, S. Ishihara, E. Nakayama, and N. Soma, *Tetrahedron Lett.*, 2923 (1972).
(6) A. Balsamo, P. Crotti, B. Macchia, F. Macchia, G. Nannini, E. Dradi, and A. Forgione, *J. Org. Chem.*, **41**, 2150 (1976).
(7) A. Balsamo, P. Crotti, B. Macchia, F. Macchia, A. Rosai, P. Domiano, and G. Nannini, *J. Org. Chem.*, **43**, 3036 (1978).
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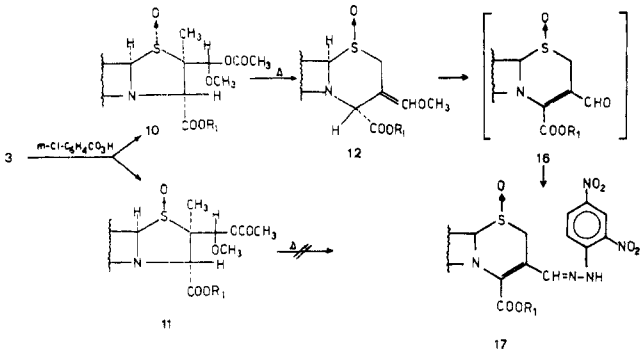
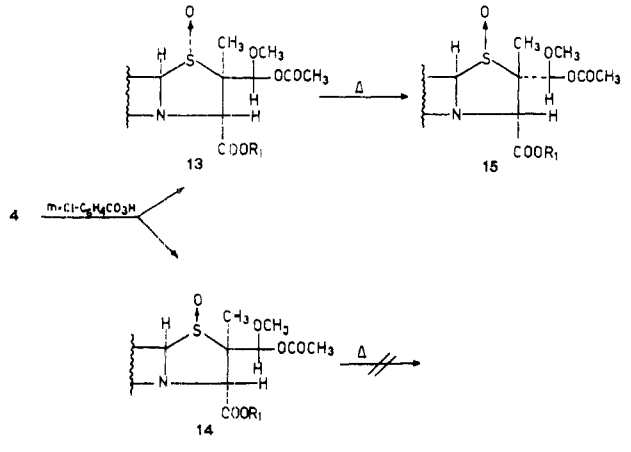
Oxidation of the penam derivatives **3** and **4** with *m*-chloroperoxybenzoic acid afforded equimolar mixtures of the corresponding (*R*)- and (*S*)-sulfoxides **10** and **11**, and **13** and **14**, respectively.



Heating the (*R*)-sulfoxide **10** in refluxing benzene resulted in rapid conversion to the cephalosporin (*S*)-sulfoxide **12**, while the corresponding (*R*)-sulfoxide **13** gave the penicillin (*S*)-sulfoxide **15**. The (*S*)-sulfoxides **11** and **14** are unreactive under the same conditions.



The structures of **3**, **4**, and **10–15** were assigned on the basis of their ^{1}H NMR, IR,[9,10] and mass spectra. Furthermore, the presence of a vinyl ether group in **12** has been proven in the following way: treatment of **12** with 2,4-dinitrophenylhydrazine in the presence of acid slowly precipitates the 2,4-dinitrophenylhydrazone of aldehyde **16** (**17**). Even though it was not isolated, the aldehyde **16** can originate from the vinyl ether **12** by acid hydrolysis.

The spectroscopic data obtained for **3** and **4** do not permit the assignment of their stereochemistry. The configuration of **3** has been inferred from its X-ray crystallographic analysis.[11] A perspective view of the molecule along the C(6)–C(7) axis is reported in Figure 1. The same chirality on C(2) in the compounds **3** and **4** has been determined by ^{1}H NMR spectroscopy through the comparison of the aromatic solvent induced shifts (ASIS)[10,12] in **3** and **4** and in the corresponding sulfoxides of *S* configuration, **11** and **14**.[10,12] Table I records the benzene-d_6-induced shift for compounds **3**, **4**, **11**, and **14** and the corresponding net ASIS [ASIS(sulfoxide) − ASIS(sulfide)]. An analogous trend can be observed for the net ASIS

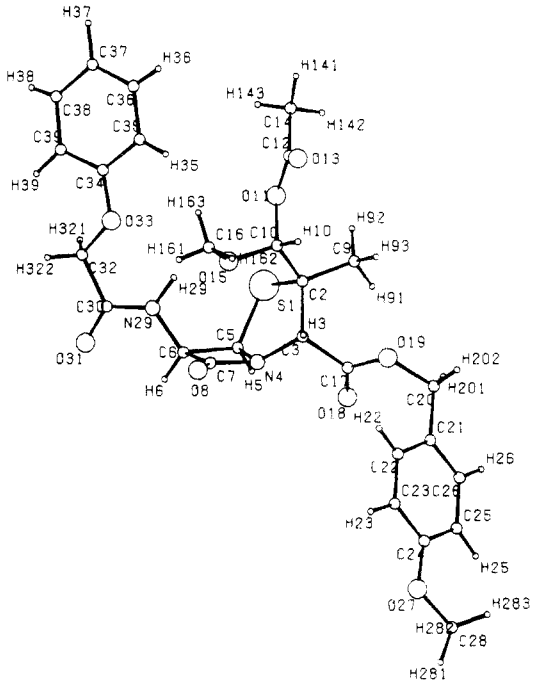


Figure 1. Perspective view of compound **3**.

Table I. Benzene-Induced Shifts in $CDCl_3$ and C_6D_6 for Compounds 3, 4, 11, and 14[a]

	H_3	H_5	H_6	2α-Me
3, $CDCl_3$	4.60	5.57	5.62	1.24
C_6D_6	4.71	5.36	5.61	1.22
Δ_3[b]	−0.11	0.21	0.01	0.02
11, $CDCl_3$	4.98	5.05	6.17	1.22
C_6D_6	5.03	4.27	5.98	1.09
Δ_{11}[b]	−0.05	0.78	0.19	0.13
$\Delta_{11} - \Delta_3$	0.06	0.57	0.18	0.11
4, $CDCl_3$	5.02	5.71	5.90	1.37
C_6D_6	5.17	5.47	5.85	1.42
Δ_4[b]	−0.15	0.24	0.05	−0.05
14, $CDCl_3$	4.97	5.06	6.14	1.22
C_6D_6	5.17	4.22	6.10	1.12
Δ_{14}[b]	−0.20	0.84	0.04	0.10
$\Delta_{14} - \Delta_4$	−0.05	0.60	−0.01	0.15

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

values [in particular for the H(5) and the 2-methyl protons] of the sulfide–sulfoxide couples **3–11** and **4–14**. This indicates that **3** and **4** must have the same configuration on C(2), which must be the one verified for **3** by X-ray crystallography. Consequently, the two penam derivatives **3** and **4** must differ only in the configuration on C(10).

The configurations of the sulfoxides **10** and **11**, **13** and **14**, and **12** and **15** have been unequivocally determined on the basis of intermolecular hydrogen-bonding studies of their amide proton using Me_2SO.[10,12] As accepted, only the oxygen of the (*S*)-sulfoxides of penicillin and cephalosporin derivatives can form an intramolecular hydrogen bond with the amide proton, and the proton resonates at a lower field than the same proton of the corresponding *R* isomer and sulfide.[10,12] It has been shown that the formation of an intermolecular hydrogen bond of type NH···O–S between the amido proton and the oxygen of the Me_2SO solvent causes a large downfield shift of this proton compared with that observed when $CDCl_3$ is used as solvent.[10,12] The formation of solute–solvent hydrogen bonding in Me_2SO is allowed only for penicillin and cephalosporin sulfoxide derivatives of *R* configuration. On the contrary, the strong intramolecular hydrogen bond

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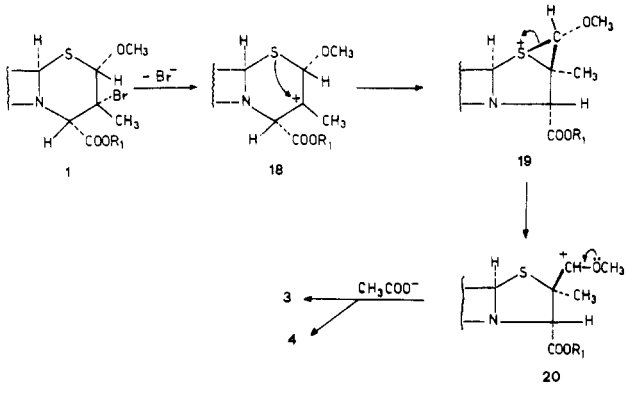
(10) P. V. Demarco and R. Nagarajan, in ref 2, p 311.
(11) P. Domiano, M. Nardelli, A. Balsamo, B. Macchia, and F. Macchia, *Acta Crystallogr., Sect. B*, 35, 1363 (1979).
(12) R. D. G. Cooper, P. V. Demarco, J. C. Cheng, and N. D. Jones, *J. Am. Chem. Soc.*, 91, 1408 (1969).

Table II. N-H Proton Shifts

compd	δ_{CDCl_3}	$\delta_{Me_2SO\text{-}d_6}$	$\Delta^{a,b}$
3	7.82	8.16	−0.34
4	7.83	7.75	0.08
10	7.40	8.98	−1.58
11	8.33	8.23	0.10
12	8.27	8.34	−0.07
13	7.48	8.87	−1.39
14	8.23	7.75	0.48
15	8.35	8.35	0.00

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

Scheme I

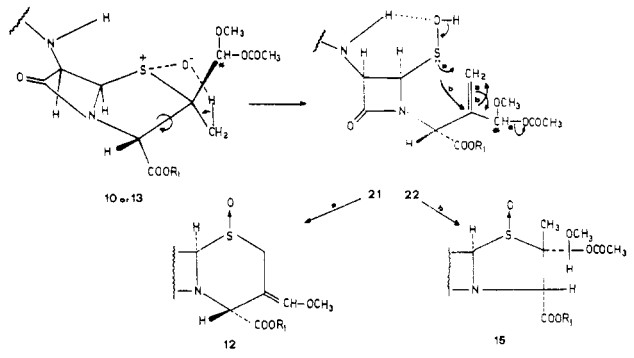


between the amide proton and the oxygen of sulfoxides of *S* configuration prevents the formation of new intermolecular bonds, and no shift or a relatively small shift is observed for this proton on going from $CDCl_3$ to $Me_2SO\text{-}d_6$.[10,12] Table II reports the amido-proton chemical shift behavior in $CDCl_3$ and $Me_2SO\text{-}d_6$ of sulfoxides **10–15** and sulfides **3** and **4**. As may be observed, only compounds **10** and **13** exhibit large solvent Δ values. This should indicate that these sulfoxides have the *R* configuration, whereas an *S* configuration must be attributed to sulfoxides **11**, **12**, **14**, and **15**. Furthermore, according to the configuration assigned to the pairs of sulfoxides **10**, **11** and **13**, **14**, the N–H proton of the *S* isomers due to the intramolecular N–H···O–S bond, resonates in $CDCl_3$ at a lower field than those of the corresponding *R* isomer and the sulfide.[10,12]

The transformation of the 3-bromocepham derivative **1** into the penam derivatives **3** and **4** can be rationalized by a mechanism (see Scheme I) implying the intermediate formation of an episulfonium ion. The formation of this type of intermediate is largely accepted in interconversion reactions of penam and cepham systems.[1-3,9] Abstraction of the halogen by the silver ion gives the carbenium ion **18** which through a nucleophilic attack of the sulfur on the electron-deficient center affords the episulfonium ion **19**. In agreement with the results of analogous reactions,[1-3,9] only the β-episulfonium ion **19** is formed, as inferred from the exclusive formation of the 2α-methyl derivatives **3** and **4**. In the previously reported reactions[1-3,9] the opening of the episulfonium ion by a nucleophile occurs on both the carbons, giving both penam and cepham derivatives. In this case the presence of the methoxy group in the 2 position of **1** determines the regiospecific ring opening of the episulfonium ion **19**, affording only the particularly stable carbenium ion **20**, which on attack by the acetate ion necessarily gives the penam derivatives **3** and **4**.

The thermal transformation of the penam sulfoxides **10** and **13** into **12** and **15**, respectively, can be explained through the intermediacy of a sulfenic acid (**21** from **10** and **22** from **13**) stabilized by an internal hydrogen bond

Scheme II



with the side-chain amide proton.[13-15] In the case of **21** the attack of the sulfur lone pair on the methylenic CH_2 (arrows a, Scheme II) leads, after elimination of $CH_3CO\text{-}OH$, to the cepham derivative **12**, whereas in the case of **22** the attack of the same lone pair on the other unsaturated carbon (arrows b, Scheme II) leads to compound **15**, the epimer of **14** on C(2). The different reactivity of the sulfenic acids **21** and **22**, and consequently the behavior of the sulfoxides **10** and **13** on heating, could be ascribed to the different steric interactions originating in the transition state relative to the recyclization of the sulfenic acids **21** and **22** to the cepham or the penam derivative.

The new penicillin derivatives **5** and **6** were tested in vitro against several strains of gram-positive and gram-negative bacteria. Both these compounds showed similar modest antibacterial activity only against gram-positive bacteria.

Experimental Section

Melting points were determined on a Kofler apparatus and are uncorrected. IR spectra for comparison of compounds were taken on paraffin oil mulls on a Perkin-Elmer Model 197 and those for the determination of C=O stretching bands with a Perkin-Elmer Model 257 double-beam grating spectrophotometer using a NaCl cell of 1-mm optical length in dried $CHBr_3$. ^1H NMR spectra were detected with a JEOL C-60 HL spectrometer in a ca. 10% solution of $CDCl_3$, in $Me_2SO\text{-}d_6$, or in C_6D_6 using Me_4Si as an internal standard. The proton magnetic resonance assignments have been firmly established on the basis of the expected chemical shift and the multiplicity of the signal.[10] The relative percentages of compounds **3** and **4**, **10** and **11**, and **13** and **14** have been calculated on the basis of the integrals of the singlets due to methyls both on C(2) and on the side chain on the same carbon. Mass spectra were registered with a Varian-Mat CH-7 spectrometer. 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 was refluxed over P_2O_5 and rectified; C_6H_6 was shaked with concentrated sulfuric acid, refluxed, and rectified over sodium.

The 76/24 and the 40/60 mixtures of the **p-methoxybenzyl 2α-methoxy- and p-methoxybenzyl 2β-methoxy-3α-bromo-3β-methyl-7-(phenoxyacetamido)cepham-4-carboxylates** (**1** and **2**, respectively) were prepared, as previously described,[6] from the corresponding 2-cephem derivative through bromination in CH_2Cl_2 and CCl_4, respectively, followed by methanolysis.

Treatment of 1 and 2 with Silver Acetate in Glacial Acetic Acid. A solution of the 76/24 mixture of **1** and **2**[6] (3.9 g, 7.6 mmol) in glacial acetic acid (170 mL) was added under stirring to silver acetate (2.2 g, 13.9 mmol) at room temperature. The resulting

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(14) R. D. G. Cooper, *J. Am. Chem. Soc.*, **92**, 5010 (1970).
(15) D. O. Spry, *J. Am. Chem. Soc.*, **92**, 5006 (1970).

stirred mixture was placed in an oil bath at 100 °C and left at the same temperature for 15 min. The suspension was allowed to cool at room temperature, filtered through asbestos to remove silver salts, and evaporated to near dryness. The residue was taken up with $CHCl_3$ and washed with 10% aqueous $NaHCO_3$ and water. Evaporation of the organic solvent yielded an oily residue (2.83 g) consisting mainly of **p-methoxybenzyl 2α-methyl-2β-[(*R*)-acetoxymethoxymethyl]-6β-(phenoxyacetamido)penam-3α-carboxylate (3) and p-methoxybenzyl 2α-methyl-2β-[(*S*)-acetoxymethoxymethyl]-6β-(phenoxyacetamido)penam-3α-carboxylate (4)** in a ratio of about 1:1 (NMR), accompanied by small amounts of decomposition products. Treatment of the crude reaction mixture with an 85/15 solution of benzene and ether yielded a solid (0.9 g) which on crystallization from acetone gave pure **3** (0.75 g): mp 168–170 °C; IR ($CHBr_3$) ν 1790.0 cm^{-1} (β-lactam C=O); ^1H NMR δ 1.24 (s, 2, 2α-CH_3), 3.32 (s, 3, $CHOCH_3$), 2.11 (s, 3, $OCOCH_3$), 5.57 (d, 1, J = 4.1 Hz, CHS), 5.62 (q, 1, J = 10.5 and 4.1 Hz, CHNH); MS m/e 558 (M^+). Anal. Calcd for $C_{27}H_{30}N_2O_9S$: C, 58.05; H, 5.41; N, 4.88. Found: C, 57.89; H, 5.39; N, 5.01.

Evaporation of the solution from which the crude **3** was obtained yielded a viscous oil (1.9 g) consisting mainly of **4** and of the decomposition products. Part of this residue (1.3 g) was chromatographed through a 3 × 36 cm column of silica gel (180 g), eluting with 85:15 benzene–ether and collecting 20-mL fractions. Fractions 54–59 yielded pure **4** (0.12 g) as an oil: IR ($CHBr_3$) ν 1788.0 cm^{-1} (β-lactam C=O); ^1H NMR δ 1.37 (s, 3, 2α-CH_3), 2.10 (s, 3, $OCOCH_3$), 3.40 (s, 3, $CHOCH_3$), 5.71 (d, 1, J = 4.0 Hz, CHS), 5.90 (q, 1, J = 4.0 and 10.3 Hz, NHCH); MS m/e 558 (M^+). Anal. Calcd for $C_{27}H_{30}N_2O_9S$: C, 58.05; H, 5.41; N, 5.01. Found: C, 57.75; H, 5.29; N, 4.71. Pure **4** (0.13 g) has been also obtained by preparative TLC of 0.4 g of the same viscous oil, eluting twice with 85:15 benzene–ether.

Treatment of the 40/60 mixture of **1** and **2**[6] (2.53 g, 4.9 mmol) as described above for the 76/24 mixture of **1** and **2** afforded a residue (1.90 g) consisting of an identical mixture of **3** and **4** (1:1), accompanied by markedly higher amounts of decomposition products (^1H NMR).

The crude reaction mixture (1.6 g) obtained from **1** and **2** (76/24) was dissolved in anhydrous benzene (70 mL), treated with triethylamine (0.87 g, 8.6 mmol), stirred 48 h at room temperature, and then washed with 3% aqueous HCl, H_2O, 5% aqueous $NaHCO_3$, and H_2O. Evaporation of the organic phase gave a residue consisting of the starting products (^1H NMR, TLC). No trace of the cephem derivatives **7** and **8**[6] could be found (^1H NMR).

2α-Methyl-2β-[(*R*)-acetoxymethoxymethyl]-6β-(phenoxyacetamido)penam-3α-carboxylic Acid (5). A solution of **3** (0.200 g) in 6:1 dioxane–water (4.2 mL) was shaken under hydrogen with 10% Pd on $CaCO_3$ (0.4 g) at room temperature, until the absorption of hydrogen ended. The reaction mixture was taken up with ethyl acetate, filtered through asbestos, washed with water, and extracted three times with 5% aqueous $NaHCO_3$. The aqueous extracts were washed with ethyl acetate, acidified at pH 3, and extracted with ethyl acetate. Evaporation of the washed (H_2O) organic solvent afforded a vitreous residue (0.076 g) consisting of practically pure **5**: ^1H NMR δ 1.50 (s, 3, 2α-CH_3), 2.20 (s, 3, $OCOCH_3$), 3.45 (s, 3, $CHOCH_3$), 5.60–6.12 [m, 3, H(5), H(6), $CHOCH_3$]. Anal. Calcd for $C_{19}H_{22}N_2O_8S$: C, 52.04; H, 5.06; N, 6.39. Found: C, 51.86; H, 4.78; N, 6.01.

2α-Methyl-2β-[(*S*)-acetoxymethoxymethyl]-6β-(phenoxyacetamido)penam-3α-carboxylic Acid (6). A solution of **4** (0.120 g) in 6:1 dioxane–water (2.5 mL) was hydrogenated exactly as described above for the preparation of **5**, yielding a residue (0.043 g) consisting of practically pure **6**: ^1H NMR δ 1.60 (s, 3, 2α-CH_3), 2.20 (s, 3, $OCOCH_3$), 3.50 (s, 3, $CHOCH_3$), 5.71–6.17 [m, 3, H(5), H(6), $CHOCH_3$]. Anal. Calcd for $C_{19}H_{22}N_2O_8S$: C, 52.04; H, 5.06; N, 6.39. Found: C, 51.94; H, 4.81; N, 6.09.

p-Methoxybenzyl 2α-Methyl-2β-[(*R*)-acetoxymethoxymethyl]-6β-(phenoxyacetamido)penam-3α-carboxylate [(*R*)-10] and (*S*)-Sulfoxide 11. A stirred solution of **3** (0.30 g, 0.53 mmol) in CH_2Cl_2 (17 mL) was cooled at 0 °C and then treated dropwise with a solution of 70% *m*-chloroperoxybenzoic acid (0.130 g, 0.53 mmol) in CH_2Cl_2 (20 mL). The resulting solution was stirred 2 h at the same temperature, washed (10% aqueous $NaHCO_3$ and H_2O), and evaporated to dryness to give a semisolid residue (0.28 g) consisting of **10** and **11** in a ratio of about 1:1. The residue was subjected to preparative TLC using a 1:1 mixture of ethyl acetate and benzene as the eluent. Elution was repeated twice. Extraction with $CHCl_3$ at room temperature of the band with lower R_f yielded, after evaporation at room temperature, a solid consisting of **10** (0.100 g), which when recrystallized from benzene yielded pure **10**: mp 147–149 °C; ^1H NMR δ 1.16 (s, 3, 2α-CH_3), 2.18 (s, 3, $OCOCH_3$), 3.38 (s, 3, $CHOCH_3$), 5.13 (d, 1, J = 4.5 Hz, CHS), 5.99 (q, 1, J = 4.5 and 10.5 Hz, NHCH); MS m/e 574 (M^+). Anal. Calcd for $C_{27}H_{30}N_2O_{10}S$: C, 56.43; H, 5.26; N, 4.88. Found: C, 56.21; H, 5.06; N, 4.60.

Extraction at room temperature with $CHCl_3$ of the band with higher R_f gave, after evaporation, an oil (0.135 g) which crystallized from acetone to yield pure **11** (0.100 g): mp 185–187 °C; IR ($CHBr_3$) ν 1799 cm^{-1} (β-lactam C=O); ^1H NMR δ 1.22 (s, 3, 2α-CH_3), 1.93 (s, 3, $OCOCH_3$), 3.55 (s, 3, $CHOCH_3$), 5.05 (d, 1, J = 4.5 Hz, CHS), 6.17 (q, 1, J = 4.5 and 10.5 Hz, NHCH); MS m/e 574 (M^+). Anal. Calcd for $C_{27}H_{30}N_2O_{10}S$: C, 56.43; H, 5.26; N, 4.88. Found: C, 56.66; H, 5.48; N, 4.93.

Thermal Transformation of the (*R*)-Sulfoxide 10. A solution of **10** (0.150 g) in anhydrous benzene (25 mL) was refluxed for 1 h. After cooling, the solution was washed with 5% aqueous $NaHCO_3$ and H_2O and then evaporated to give a residue (0.120 g) consisting of **12** which was crystallized from acetone–hexane to give pure **p-methoxybenzyl 3-*exo*-(methoxymethylene)-7β-(phenoxyacetamido)cepham-4α-carboxylate (*S*)-sulfoxide (12)**: mp 125–126 °C; IR ($CHBr_3$) ν 1783.0 cm^{-1} (β-lactam C=O); ^1H NMR δ 3.45 (m, 2, SCH_2), 3.80 (s, 3, $CHOCH_3$), 5.80 (s, 1, CHN), 6.30 (s, 1, $CHOCH_3$), 4.85 (d, 1, J = 4.5 Hz, CHS), 6.00 (q, 1, J = 4.5 and 10.7 Hz, CHNH); MS, M^+ not detectable. Anal. Calcd for $C_{25}H_{26}N_2O_8S$: C, 58.35; H, 5.09; N, 5.44. Found: C, 58.08; H, 5.12; N, 5.47.

When a solution of (*S*)-sulfoxide **11** in benzene was refluxed as described above for 4 h, the starting product was recovered completely unchanged (^1H NMR, TLC).

Treatment of a solution of **12** (0.020 g, 0.040 mmol) in ethanol (1.0 mL) with 2,4-dinitrophenylhydrazine reagent prepared with H_2SO_4 in aqueous ethanol (4.0 mL)[16] yielded after 1 h a solid precipitate (0.012 g) consisting of the **2,4-dinitrophenylhydrazone of 16 (17)**, which has been crystallized from ethanol to give pure **17**: mp 133–135 °C. Anal. Calcd for $C_{30}H_{26}N_6O_{11}S$: C, 53.09; H, 3.86; N, 12.38. Found: C, 52.81; H, 3.68; N, 12.65.

p-Methoxybenzyl 2α-Methyl-2β-[(*S*)-acetoxymethoxymethyl]-6β-(phenoxyacetamido)penam-3α-carboxylate [(*R*)-13] and (*S*)-Sulfoxide 14. A solution of **4** (0.44 g, 0.79 mmol) in CH_2Cl_2 (28 mL) was cooled at 0 °C and then treated dropwise with a solution of 70% *m*-chloroperoxybenzoic acid (0.194 g, 0.78 mmol) in CH_2Cl_2 (24 mL). The resulting solution was stirred 2 h at the same temperature, washed (10% aqueous $NaHCO_3$ and H_2O), and evaporated to dryness to yield a vitreous residue (0.40 g) consisting of an equimolar mixture of **13** and **14**. The crude product was subjected to preparative TLC (a 1:1 mixture of benzene and ethyl acetate was used as the eluent, and elution was repeated twice). Extraction with $CHCl_3$ at room temperature of the lower band yielded, after evaporation of the solvent at room temperature, a vitreous residue (0.130 g) consisting of practically pure **13**: ^1H NMR δ 1.18 (s, 3, 2α-CH_3), 2.14 (s, 3, $OCOCH_3$), 3.35 (s, 3, $CHOCH_3$), 5.07 (d, 1, J = 4.5 Hz, CHS), 5.90 (q, 1, J = 4.5 and 9.3 Hz, NHCH); MS m/e 574 (M^+). Anal. Calcd for $C_{27}H_{30}N_2O_{10}S$: C, 56.43; H, 5.26; N, 4.88. Found: C, 56.22; H, 5.01; N, 4.60.

Extraction at room temperature with $CHCl_3$ of the upper band yielded, after evaporation, a viscous liquid (0.091 g) consisting of pure **14**: IR ($CHBr_3$) ν 1797.0 cm^{-1} (β-lactam C=O); ^1H NMR δ 1.22 (s, 3, 2α-CH_3), 2.17 (s, 3, $OCOCH_3$), 3.46 (s, 3, $CHOCH_3$), 5.06 (d, 1, J = 4.5 Hz, CHS), 6.14 (q, 1, J = 4.5 and 10.5 Hz, NHCH); MS m/e 574 (M^+). Anal. Calcd for $C_{27}H_{30}N_2O_{10}S$: C, 56.43; H, 5.26; N, 4.88. Found: C, 56.15; H, 5.01; N, 4.60.

Thermal Transformation of the (*R*)-Sulfoxide (13). A solution of **13** (0.160 g) in anhydrous benzene (30 mL) was refluxed for 4 h. After the mixture cooled, the solvent was evaporated to yield an oily residue (0.155 g) consisting essentially of **15** which was purified by TLC using a 1:1 mixture of benzene and ethyl

(16) A. I. Vogel, "Practical Organic Chemistry", 3rd ed., Longmans, Green and Co., London, 1956, p 1061.

acetate as the eluent. Extraction of the main band gave pure **15** (0.090 g) as a vitreous product: IR ($CHBr_3$) ν 1796.0 cm^{-1}; ^1H NMR δ 1.66 (s, 3, 2β-CH_3), 2.13 (s, 3, $OCOCH_3$), 2.96 (s, 3, $CHOCH_3$), 5.15 (d, 1, J = 4.5 Hz, CHS), 6.04 (q, 1, J = 4.5 and 10.5 Hz, NHCH); MS m/e 574 (M^+). Anal. Calcd for $C_{27}H_{30}N_2O_{10}S$: C, 56.43; H, 5.26; N, 4.88. Found: C, 56.23; H, 5.05; N, 4.60.

When a solution of **13** in benzene was refluxed for a shorter time (1 h) some starting material was detected (^1H NMR, TLC) in the reaction mixture.

When the (*S*)-sulfoxide **14** was heated as described above for **13** or for longer times, it was recovered completely unchanged (^1H NMR, TLC).

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Approaches to Anthracyclines. 1. Conjugate Aroylation of α,β-Unsaturated Esters[1a,b]

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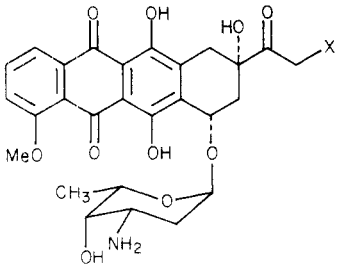
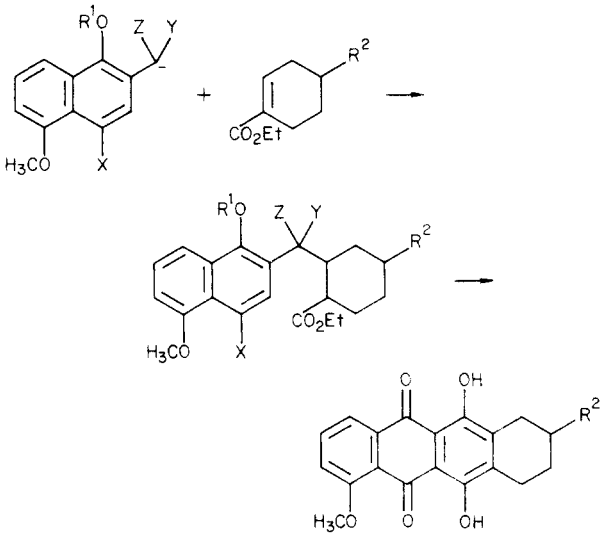
A scheme for the two-step nucleophilic aroylation of α,β-unsaturated esters has been developed. The Michael reaction of an arylacetonitrile enolate with an α,β-unsaturated ester generally proceeds in good yield. Oxidative decyanation of the adduct affords clean γ-keto esters when the aryl substituent is not electron rich.

The anthracycline antibiotics daunomycin (**1**) and adriamycin (**2**) exhibit impressively potent and broad-spectrum antitumor activity.[2] The lack of an efficient biosynthetic process, the desirabililty of analogues with improved therapeutic indices, and the challenging regio- and stereochemical features have made the anthracyclines the focus of an intense synthetic effort.[3] Accordingly, there has been a resurgence of interest in synthetic approaches to the quinone moiety and especially to the regiocontrolled elaboration of linear quinone systems.[4]



1, X = H
2, X = OH

The use of masked functionality to reverse the normal mode of reactivity of functional groups has been an area of vigorous research in recent years; the carbonyl group, because of its dominant role in organic synthesis, has received particular attention with respect to inversion of its usual electrophilic character.[5] We hoped to employ the concept of nucleophilic acylation in a construction of the anthracycline skeleton by utilizing a masked aryl aldehyde as the nucleophilic partner in a Michael-type condensation with a suitably functionalized α,β-unsaturated ester (eq 1).



(1)

While the conjugate nucleophilic acylation of enones has been extensively investigated,[6,7] the corresponding reaction

(1) (a) Abstracted from the doctoral dissertation of J.L.K., Brown University, Oct 1979. (b) For a preliminary report of this work, see K. A. Parker and J. L. Kallmerten, *Tetrahedron Lett.*, 4557 (1977). (c) Camille and Henry Dreyfus Teacher-Scholar award recipient.

(2) Several excellent reviews of the chemistry and pharmacology of the antitumor anthracyclines have appeared recently: R. K. Blum and S. K. Carter, *Ann. Intern. Med.*, **80**, 249 (1974); W. A. Remers, "The Chemistry of Antitumor Antibiotics", Vol. I, Wiley, New York, 1979, pp 63-132; F. Arcamone, *Top. Antibiot. Chem.*, **2**, 99-239 (1978).

(3) A recent review concerned with approaches to the synthesis of anthracyclines is given by T. R. Kelly, *Annu. Rep. Med. Chem.*, **14**, 288-298 (1979).

(4) For a review of quinone synthesis, see R. H. Thomas, "The Chemistry of Quinonoid Compounds", S. Patai, Ed., Wiley, New York, 1974, pp 111-61. Since we began this work, a number of methods for the regiospecific construction of the quinone moiety of fused quinone systems have been developed: (a) F. M. Hauser and R. P. Rhee, *J. Am. Chem. Soc.*, **101**, 1628 (1979); *J. Org. Chem.*, **43**, 178 (1978); F. M. Hauser and S. Prasanna, *J. Org. Chem.*, **44**, 2596 (1979); (b) G. A. Kraus and H. Sugimoto, *Tetrahedron Lett.*, 2263 (1978); (c) J. E. Baldwin and K. W. Bair, *ibid.*, 2559 (1978); I. Forbes, R. A. Pratt, and R. A. Raphael, *ibid.*, 3965 (1978); S. O. deSilva and V. Snieckus, *ibid.*, 5103 (1978); (d) K. S. Kim, E. Vanotti, A. Suaroto, and F. Johnson, *J. Am. Chem. Soc.*, **101**, 2483 (1979); (e) J. S. Swenton and P. W. Raynolds, *ibid.*, **100**, 6188 (1978). Also, a potentially regiospecific method is reported: D. K. Jackson, L. Narasimhan, and J. S. Swenton, *ibid.*, **101**, 3989 (1979).

(5) For reviews of nucleophilic acylation, see: D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969); O. W. Lever, *Tetrahedron* **32**, 1943 (1976).

(6) (a) G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **96**, 5272 (1974); (b) J. L. Herrman, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 3275 (1973); (c) R. K. Boeckman and K. J. Bruza, *ibid.*, 3365 (1974); (d) J. E. McMurry and J. Melton, *J. Am. Chem. Soc.*, **93**, 5309 (1971); (e) T. Mukaiyama, K. Narasaka, and M. Furusato, *ibid.*, **94**, 8641 (1972). See also ref 16 and references therein.

(7) J. L. Herrman, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 3271 (1973).

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