through the above reaction sequence. Preparative gas chromatography (2 m × 10 mm column packed with 6% SE-30 on Gas Chrom Q) gave a sample of pure (4a*S*,4*R*)-plagiolactone: NMR (90 MHz) δ 6.53 (1 H, d, J = 3 Hz), 5.73 (1 H, s), 3.35 (1 H, complex multiplet), 2.91 (1 H, d of q, J = 5.3, 6.8 Hz, C*H*CH$_3$), 2.40 (2 H, multiplet, CH$_2$C=C), 1.76 (3 H, br s, CH$_3$C=C), 1.08 (3 H, d, J = 6.8 Hz, C*H*$_3$CH); ORD (*c* 3.2 mg/10 mL) (ethanol) Φ_{278nm} − 9200, Φ_{243nm} + 40 300.

Autoxidation of Chrysomelidial. A solution containing 100 mg of chrysomelidial (isomeric mixture from (*R*)-limonene) in 0.5 mL of benzene was stirred vigorously in an open vessel for 4 days. The reaction was followed by TLC until starting material could not be detected. The solution was then diluted with 5 mL of benzene, and treated with 1.0 mL of acetic anhydride and a few crystals of *p*-toluenesulfonic acid. After stirring overnight, 1.0 g of sodium acetate was added and the solvents were removed in vacuo. The residue was taken up in ether, filtered, and examined by GC/MS.

In the multicomponent product mixture, the next to the largest component (comprising ca. 5% of the mixture) was identified as plagiolactone by its characteristic mass spectrum. The largest component, 4,4a,5,6-tetrahydro-4,7-dimethylcyclopenta[*c*]pyran-1,3-dione (**11**) (ca. 80% of the mixture) was purified by preparative GLC (2 m × 10 mm column packed with 6% SE-30 on Gas Chrom Q) and had the following spectral data: IR 1790, 1745, 1640, 1428, 1372, 1340, 1260, 1232, 1215, 1170, 1140, 1118, 1104, 1070, and 980 cm^{-1}; NMR (90 MHz) δ 3.3 (1, m, C=C(CH)CO), 2.9 (1, m, C*H*CH$_3$), 2.62 (2, br t, CH$_2$C=C), 2.28 (3, br s, CH$_3$C=C), 1.30 and 1.14 (3, a pair of doublets, J = 7 Hz, C*H*$_3$CH); MS *m/e* (rel intensity) 180 (8), 152 (3), 136 (47), 121 (44), 108 (25), 107 (22), 94 (10), 93 (100), 91 (37), 80 (11), 79 (50), 78 (10), 77 (39), 65 (11), 51 (10); calcd *m/e* for C$_{10}$H$_{12}$O$_3$, 180.0786 (found, 180.0783).

References and Notes

(1) Partial support of this research by the National Institutes of Health (Grant AI-12020 and Fellowship I-F32-CA05139 to T.H.J.) is gratefully acknowledged. We thank Marcia Cohen for valuable technical assistance.

(2) This is Report No. 58 of the series "Defense Mechanisms of Arthropods". Report No. 57: T. Eisner, T. H. Jones, D. J. Aneshansley, W. R. Tschinkel, R. E. Silberglied, and J. Meinwald, *J. Insect Physiol.*, in press.

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(21) The natural chrysomelidial isolated by us from *Plagiodera versicolora* was also a mixture of these same diastereomers, but in the reverse (1:4) ratio. It is likely that our natural material was partially epimerized in the course of isolation,[3] since Blum et al.[4] isolated a *single* chrysomelidial isomer (from the larvae of *Gastrophysa cyanea*) whose ^{1}H NMR spectrum was identical to that of the major isomer from *P. versicolora*.

(22) Since 1 and **2** are almost certain to be closely related biosynthetically, it is likely that these two compounds also have the same absolute configurations. (This is our third argument for the configuration of 1.)

(23) Interestingly enough, no other C$_{10}$H$_{12}$O$_2$ product, such as the enol lactone found in *Gastrophysa cyanea*,[4] was detected in this reaction mixture.

Synthesis of Mercury Mercaptide Azetidinones via 2- and 4-Methylthio-Substituted Cephalosporins

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Abstract: Treatment of 4β-methylthio-Δ^2-cephalosporins with methanol in the presence of mercuric acetate yields 4α-methoxy-Δ^2-cephalosporins and allylic rearrangement products including 2α- and 2β-methylthio-Δ^3-cephalosporins, 2α-acetoxy-Δ^3-cephalosporins, and bis[(4-oxo-2-azetidinyl)thio]mercury derivatives. The latter, which can also be obtained from 2α- and 2β-methylthio-Δ^3-cephalosporins, undergo ring closures to 2α- and 2β-methoxycephalosporins upon treatment with hydrogen sulfide.

We and other researchers have reported the conversion of 7α-methylthiocephalosporins to 7α-methoxycephalosporins by mercury(II)-mediated methanolysis.[2] We now report that mercuric acetate solvolysis of 2α- or 2β-methylthio-Δ^3- and 4β-methylthio-Δ^2-cephalosporins leads to various rearrangement products, including mercury mercaptide azetidinones that undergo facile ring closures to 2α- and 2β-alkoxy-Δ^3-cephalosporins when treated with H$_2$S.

Treatment of the 4β-methylthio-Δ^2-cephem **1a**[3,4] with 1.5 equiv of Hg(OAc)$_2$ in CH$_3$OH (30 min, 25 °C) afforded compounds **2a–6a** after isolation [TLC, silica gel, CHCl$_3$–EtOAc (9:1)]. The yields of most of these compounds were slightly lower with 1 equiv of Hg(OAc)$_2$. ^{1}H NMR spectral assignments of these and other compounds are indicated in Tables I and II.

The epimers **2a** [11%; amorphous; IR (CHCl$_3$) 1778 and 1740 cm^{-1}] and **3a** [7%; mp 97–99 °C; IR (CHCl$_3$) 1780 and 1745 cm^{-1}] both contained conjugated ester groups and were differentiated by the occurrence of a five-bonded coupling ($J_{2,7}$ = 0.5 Hz) in the 2α epimer.[5] The 2α-acetoxycephem **6a** [7%; amorphous; IR (CHCl$_3$) 1792 and ~1750 cm^{-1}] also exhibited in its ^{1}H NMR spectrum a five-bonded coupling ($J_{2,7}$ = 0.5

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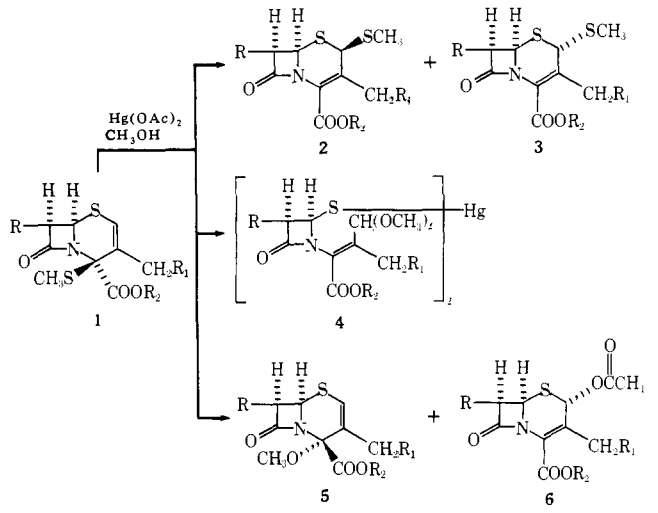
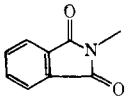


	R	R_1	R_2
a	$PhCH_2\overset{O}{\overset{\|\|}{C}}NH$	H	CH_2CCl_3
b	$PhCH_2\overset{O}{\overset{\|\|}{C}}NH$	H	CH_3
c	$PhCH_2\overset{O}{\overset{\|\|}{C}}NH$	H	$CHPh_2$
d	Ph_3CNH	H	CH_2CCl_3
e	Ph_3CNH	OAc	$C(CH_3)_3$
f		H	$C(CH_3)_3$

Hz) similar to that observed by Spry.[6] The 4α-methoxy-Δ^2-cephem **5a**[7] [2%; amorphous; IR ($CHCl_3$) 1788 and 1765 (sh) cm^{-1}] was assigned its structure on the basis of spectral evidence.

The configuration of the 4-methoxy group in **5a** followed, by analogy, from europium shift reagent studies on **5b,** obtained from **1b** (9%). In studies of epimeric 7β-benzamido analogues of **1b,** Yoshida et al.[4] have reported with $Eu(fod)_3$ a downfield shift of the CO_2CH_3 proton resonance in the 4α-methylthio epimer and an upfield shift of the CO_2CH_3 proton resonance in the epimeric 4β-methylthio analogue. In our studies with 7β-phenylacetamido derivatives, we have observed with $Eu(fod)_3$ an upfield shift of the CO_2CH_3 proton resonance in the 4β-methylthio derivative **1b** (Figure 1) and a downfield shift of the CO_2CH_3 proton resonance in the 4-methoxy **5b** (Figure 2). Analogous results were observed with **1b** and **5b** in the presence of $Eu(dmp)_3$ (Figures 3 and 4). The downfield shift of the CO_2CH_3 proton resonance in our 4-methoxycephem methyl ester is consistent with a 4β-orientation of the CO_2CH_3 group as shown in structure **5b.**

The most polar component formed in the methanolysis reaction was assigned the mercury mercaptide structure **4a** [26%; amorphous; IR ($CHCl_3$) 1775 and 1755 (sh) cm^{-1}] having a dimethyl acetal group.[8] Treatment of **4a** with a catalytic amount of $TsOH{\cdot}H_2O$ (3% by weight) in acetone-H_2O (25 °C, 1 h) provided the chromatographically unstable aldehyde **7a** [~100%; IR ($CHCl_3$) 1785, 1750, and 1690-1660 (broad) cm^{-1}].

Treatment of mercury mercaptides of structure **4** with H_2S resulted in ring closures to 2-alkoxy-Δ^3-cephems. For example, when **4a** was treated with H_2S in CH_2Cl_2 (0 °C, 15 min), **9a** 16%; amorphous; IR ($CHCl_3$) 1790 and 1738 cm^{-1}] and **10a** [34%; mp 133-134 °C; ^1H NMR $J_{2,7}$ = 0.5 Hz; IR ($CHCl_3$) 1784 and 1738 cm^{-1}] were isolated after preparative TLC [silica gel, $CHCl_3$-EtOAc (4:1)].[9] Treatment of **4b** with H_2S in commercial $CHCl_3$ containing 0.75% EtOH (0 °C, 1 h),

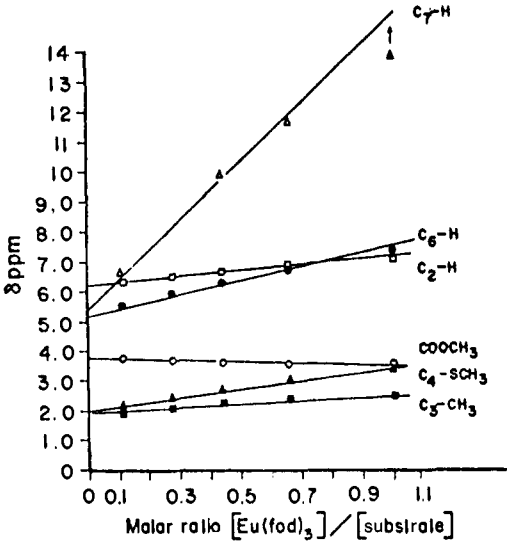
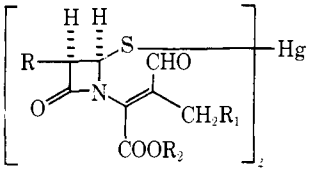


Figure 1. Chemical shifts of 4β-methylthioester **1b** in the presence of $Eu(fod)_3$.

however, provided the 2α-alkoxycephems **10b** (7%) and **10c** (12%); both compounds exhibited $J_{2,7}$ = 0.5 Hz and IR ($CHCl_3$) 1780 and 1730 cm^{-1}.

We have also found that mercury mercaptides can be obtained from either 2α- or 2β-methylthio-Δ^3-cephems as well as from 4β-methylthio-Δ^2-cephems. Treatment of **2b** and **3b** with $Hg(OAc)_2$-CH_3OH under conditions already mentioned provided **4b** (11 and 10%, respectively) after isolation [TLC, silica gel, $CHCl_3$-EtOAc (9:1)]. Similar treatment of **6b** with $Hg(OAc)_2$-CH_3OH, however, yielded decomposition products



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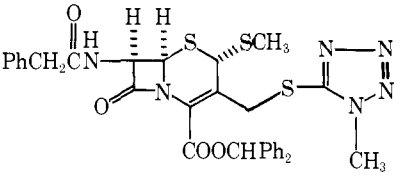

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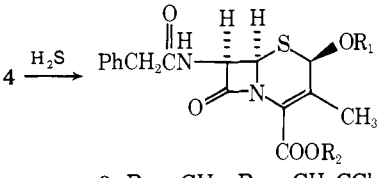
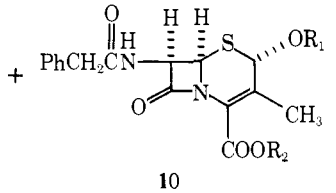


9, R_1 = CH_3; R_2 = CH_2CCl_3



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	R_1	R_2
a	CH_3	CH_2CCl_3
b	CH_3	CH_3
c	CH_2CH_3	CH_3

Table I. Chemical Shift Values ($DCCl_3$, δ, (J), Me_4Si, 60 MHz)

C-2(4) substituent	Compd	H_2	H_6	H_7	C-2(4) subst	C-3 methyl	Ester CH_2CCl_3 CH_3, $C(CH_3)_3$, $CHPh_2$	Yield,[a] %
4β-CH_3S	**1a**	6.33, d (1.5)	5.30, d (4.5)	5.49, q (4.5, 8)	2.03, s	1.98, d (1.5)	4.72, 4.95, q (12)	
4β-CH_3S	**1b**[e]	6.25, d (1.5)	5.20, d (5)	5.42, q (5, 8)	1.97, s	1.92, d (1.5)	3.80, s	
4β-CH_3S	**1c**	6.22, d (0.5)	5.15, d (5)	5.33, q (5, 8)	1.93, s	1.82, d (0.5)	6.88, s	
4β-CH_3S	**1d**	6.15, d (0.5)	4.50, bs	4.50, bs	2.10, s	1.93, d (0.5)	4.73, s	
4β-CH_3S	**1e**	6.57, bs	4.48, d (4)	4.62, q (4, 9)	2.08, s	4.80, bs, 2.02, s	1.43, s	
4β-CH_3S	**1f**	6.33, d (1)	5.40, d (4.5)	5.63, d (4.5)	2.30, s	2.00, bs	1.53, s	
2β-CH_3S	**2a**[e]	4.17, s	5.22, d (4.5)	5.68, q (4.5, 8)	1.94, s	2.39, s	4.83, s	11, 33[b]
2β-CH_3S	**2b**	4.17, s	5.18, d (4.5)	5.65, q (4.5, 9)	1.95, s	2.33, s	3.82, s	8
2α-CH_3S	**3a**[e]	4.34, d (0.5)	5.32, d (5)	5.92, m (0.5, 5, 9)	2.30, s	2.28, s	4.77, 4.95, q (11)	7, 9[b]
2α-CH_3S	**3b**[e]	4.32, d (0.5)	5.26, d (5)	5.87, m (0.5, 5, 8)	2.25, s	2.20, s	3.80, s	10, 22[c]
4α-CH_3O	**5a**	6.30, d (1.5)	5.03, d (4)	5.76, q (4, 8)	3.42, s	1.83, d (1.5)	4.42, 4.98, q (12)	2
4α-CH_3O	**5b**[e]	6.20, m	4.97, d (4)	5.65, q (4, 8.5)	3.35, s	1.78, d (1)	3.74, s	9
4α-CH_3O	**5c**	6.28, d (1)	5.02, d (4)	5.63, q (4, 8)	3.40, s	1.63, d (1)	6.87, s	7
4α-CH_3O	**5e**	6.50, d (0.5)	4.30, d (4)	4.28, q (4, 9)	3.33, s	4.60, bs, 2.03, s	1.52, s	13
4α-CH_3O	**5f**	6.20, d (1.5)	5.17, d (4.5)	5.78, d (4.5)	3.52, s	1.87, d (1.5)	1.63, s	23
2α-OAc	**6a**[e]	6.30, d (0.5)	5.15, d (5)	5.91, m (0.5, 5, 8)	2.12, s	2.14, s	4.82, 5.00, q (11)	7
2α-OAc	**6b**[e]	6.27, d (0.5)	5.08, d (4.5)	5.84, m (0.5, 4.5, 8)	2.04, s	2.10, s	3.84, s	5
2β-OCH_3	**9a**[e]	4.60, s	5.18, d (4)	5.79, q (4, 9)	2.94, s	2.40, s	4.83, s	16[d]
2α-OCH_3	**10a**[e]	4.77, d (0.5)	5.05 (5)	5.88, m (0.5, 5, 8)	3.44, s	2.18, s	4.77, 4.97 (11)	34[d]
2α-OCH_3	**10b**	4.75 (0.5)	5.02 (5)	5.84, m (0.5, 5, 8)	3.43, s	2.13, s	3.82	7[d]
2α-OCH_2CH_3	**10c**	4.85 (0.5)	5.05 (5)	5.84, m (0.5, 5, 8)	1.22, t, 3.55, q (8)	2.13, s	3.82, s	12[d]

[a] From 4β-methylthiocephem, unless indicated otherwise. [b] From 4β-methylthiocephem in dimethoxyethane. [c] From 2β-methylthiocephem in dimethoxyethane. [d] From mercury mercaptide. [e] 100 MHz.

and recovered starting material (50%); no **4b** was detected. When **2b** was treated with 1 equiv of $Hg(OAc)_2$ in the absence of an alcohol (dimethoxyethane, 25 °C, 30 min), **3b** was obtained in 22% yield along with recovered **2b**. When **1a** was treated under these conditions, **2a** and **3a** were isolated in 33 and 9% yield, respectively.

Mercury mercaptide azetidinones were obtained from 2- and 4-methylthiocephalosporins possessing a variety of substituents, including compounds having triphenylmethylamino or phthalimido groups at position 7, methyl or acetoxymethyl groups at position 3, and *tert*-butyl or benzhydryl ester groups at position 4 (i.e., compounds **1c–f**, Tables I and II). Yields of mercury mercaptide azetidinones obtained from 4-methylthiocephalosporins were found to vary with reaction time and number of equivalents of $Hg(OAc)_2$. Higher yields were obtained when more than 1, but less than 2, equiv of $Hg(OAc)_2$ was used, and lower yields were observed, in most instances, with reaction times of more than 30 min. The product distribution of 4α-methoxy-, 2α-acetoxy-, and, especially, 2α-methylthio- and 2β-methylthiocephems was also found to vary. Yields of 4α-methoxycephems appeared to decrease with increasing size and electronegativity of the ester group, although in the case of methanolysis of the 7β-phthalimido *tert*-butyl ester **1f**, a comparatively high yield (23%) of 4α-methoxy-Δ^2-cephem (**5f**) was obtained. Surprisingly, the 2α-methylthio-3′-(1-methyl-1*H*-tetrazol-4-yl)thio-Δ^3-cephem **8**[10] was recovered (TLC, silica gel, >90%) after treatment with $Hg(OAc)_2$ in CH_3OH (1 equiv, 25 °C, 30 min); no mercury mercaptide azetidinone was detected.

The mercury mercaptides of general structure **4** and the corresponding aldehydes **7** represent functionalized azetidinones that are readily obtainable and useful as intermediates in preparing new cephalosporin derivatives.[11] Modifications with these intermediates are in progress.

Experimental Section

The ^1H NMR spectra were obtained on Varian nuclear magnetic resonance spectrometers (Models T-60 and XL-100-15), and the infrared spectra were recorded on Perkin-Elmer spectrometers (Models 257 and 621). Mass spectra were obtained from an AEI-MS-902 mass spectrometer. Melting points are uncorrected.

Reaction of 1a with Mercuric Acetate in Methanol. A mixture of 4β-methylthiotrichloroethyl ester **1a** (1.80 g, 3.52 mmol) and $Hg(OAc)_2$ (1.68 g, 5.28 mmol) in 25 mL of dry CH_3OH was stirred

Table II. Chemical Shift Values ($DCCl_3$, δ, Me_4Si, 60 MHz)

Compd	Ester	H_2	H_3	CHOO	$>C(OCH_3)_2$	Vinyl CH_3	$ArCH_2$	CHO	Yield,[a] %
4a	4.78, s	5.70, d (5)	5.29, q (5, 7)	4.98, s	3.38, s; 3.12, s	2.23, s	3.70, s		26
4b	3.78, s	5.65, d (5)	5.34, q (5, 7)	4.92, s	3.38, s	2.12, s	3.70, s		27, 11,[c] 10[b]
4c	6.92, s (*CH*)	5.18, q (5, 8)	5.53, d (5)	4.97, s	3.35, s, 3.38, s	2.12, s	3.60		7
4d	4.88, 4.53, q (12)	~4.8 q (5)	6.84, bd	4.97, s	3.30, s, 3.43, s	2.20, s			46
4e	1.42, s	4.68, q, 4.58 (5, 8)	5.27, d (5)	4.98, s	3.20, s 3.42, s	4.80, bs 1.98, s			21
4f	1.53, s	5.63, d (5)	5.83, d (5)	5.53, s	3.50, s 3.58, s	2.19, s			49
7a	4.83, 5.10, q (12)	6.13, d (5)	5.11 q (5, 7)			2.22, s	3.73, d	9.97, s	91[d]
7b[e]	3.92, s	6.00, d (5)	5.13, q (5, 8)			2.07, s	3.68, d	9.95, s	95[d]
7f	1.60, s	6.28, s (5)	5.75, d (5)			2.08, s		10.27, s	77[d]

[a] From 4β-methylthiocephem, unless indicated otherwise. [b] From 2α-methylthiocephem. [c] From 2β-methylthiocephem. [d] From mercury mercaptide. [e] 100 MHz.

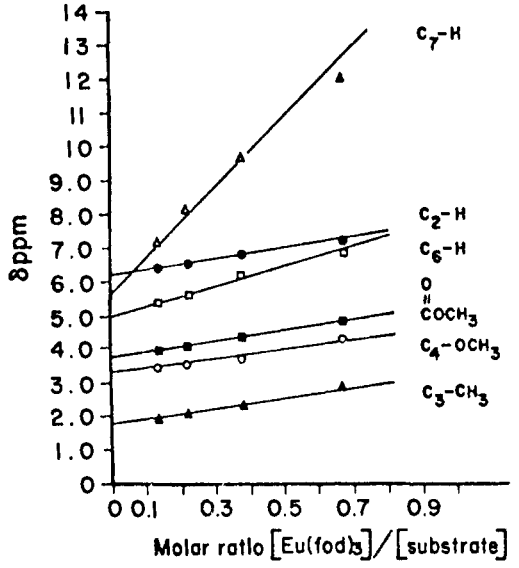

Figure 2. Chemical shifts of 4α-methoxy ester **5b** in the presence of $Eu(fod)_3$.

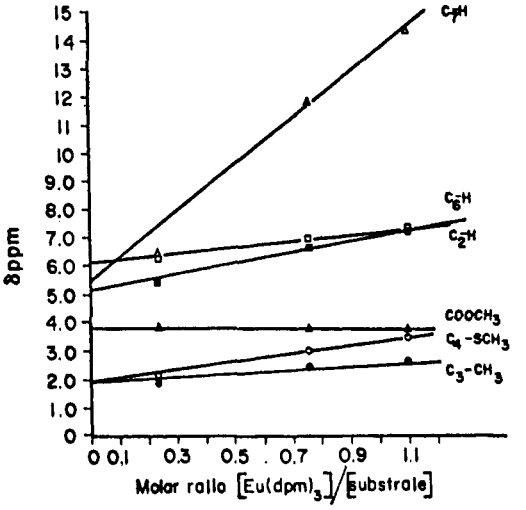

Figure 3. Chemical shifts of 4β-methylthioester **1b** in the presence of $Eu(dpm)_3$.

at 25 °C under N_2 for 30 min. After removal of the solvent in vacuo, the residue was taken up in $CHCl_3$–H_2O, and the $CHCl_3$ layer was washed with water three times, dried (Na_2SO_4), and evaporated to a residue. Fractionation of this residue by silica gel TLC in the system $CHCl_3$–EtOAc (9:1) provided the following compounds in decreasing order of R_f.

3a: 124 mg (7%); mp 97–99 °C (from benzene–hexane); IR ($CHCl_3$) 1780, 1745, and 1680 cm^{-1}; mass spectrum *m/e* 508 (M^+), 461 ($M - SCH_3$), and 333 ($M - COOCH_2CCl_3$).

Anal. ($C_{19}H_{19}N_2O_4S_2Cl_3$) C, H, N, S.

6a: 132 mg (7%); amorphous; IR ($CHCl_3$) 1792, 1750, and 1658 cm^{-1}; mass spectrum *m/e* 520 (M^+); mol wt (calcd for $C_{20}H_{19}N_2O_6SCl_3$, 520.0029) 519.9997.

2a: 193 mg (11%); amorphous; IR ($CHCl_3$) 1778, 1740, and 1680 cm^{-1}; mass spectrum *m/e* 508 (M^+), 461 ($M - SCH_3$), and 333 ($M - COOCH_2CCl_3$); mol wt (calcd for $C_{19}H_{19}N_2O_4S_2Cl_3$, 507.9852) 507.9869.

5a: 41 mg (2%); amorphous; IR ($CHCl_3$) 1788, 1765 (sh), and 1680 cm^{-1}; mass spectrum *m/e* 492 (M^+), 461($M - OCH_3$), and 317 ($M - COOCH_2CCl_3$); mol wt (calcd for $C_{19}H_{19}N_2O_5SCl_3$, 492.0080) 492.0036.

4a: 583 mg (26%); amorphous;[11] IR ($CHCl_3$), 1775, 1755 (sh), and 1685 cm^{-1}.

Hydrolysis of Dimethyl Acetal 4a. *p*-Toluenesulfonic acid monohydrate (1.5 mg) was added to a solution of dimethyl acetal **4a** (50 mg) in 0.4 mL of deuterioacetone and 40 μL of D_2O containing 1 drop of tetramethylsilane. Examination of the ^1H NMR spectrum of this solution after 20 min indicated almost 50% conversion to aldehyde **7a**, and examination after 1 h indicated essentially complete conversion of starting material to **7a**. In another run, a solution of dimethyl acetal **4a** (583 mg, 0.47 mmol) and 15 mg of $TsOH{\cdot}H_2O$ in 4 mL of acetone and 0.4 mL of water was stirred at 25 °C for 1.5 h under N_2. The solvent was removed in vacuo, and the residue was taken up in EtOAc–H_2O. The EtOAc layer was washed with dilute aqueous $NaHCO_3$ at pH 7.2 and then water, and finally dried (Na_2SO_4) and evaporated to give 513 mg (91%) of **7a** as a residue[11] having IR ($CHCl_3$) 1785, 1750, and 1690–1660 (broad) cm^{-1}.

Reaction of 1a with Mercuric Acetate in Dimethoxyethane. To a stirred solution of 200 mg (0.39 mmol) of **1a** in 2 mL of dimethoxyethane under N_2 at 25 °C was added 125 mg of $Hg(OAc)_2$. The mixture was stirred for 30 min and evaporated to a residue. The residue was taken up in $CHCl_3$–water, and the $CHCl_3$ layer was washed with water, dried (Na_2SO_4), and evaporated to a residue. Preparative TLC on silica gel in the system $CHCl_3$–EtOAc (9:1) gave 18 mg (9%)

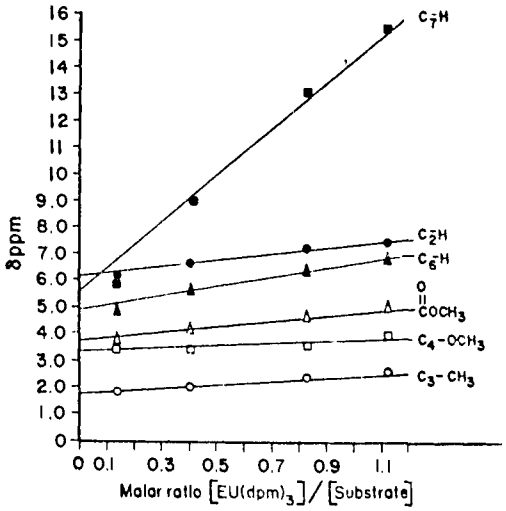

Figure 4. Chemical shifts of 4α-methoxy ester **5b** in the presence of $Eu(dpm)_3$.

of 2α-methylthiocephem **3a** and 66 mg (33%) of 2β-methylthiocephem **2a.**

Reaction of 1b with Mercuric Acetate in Methanol. A mixture of 1.45 g (3.70 mmol) of 4β-methylthiocephem **1b** and 1.18 g (3.70 mmol) of $Hg(OAc)_2$ in 30 mL of dry CH_3OH was stirred at 25 °C for 30 min under N_2. After removal of the solvent in vacuo, the residue was taken up in benzene–water, and the benzene layer was washed with water, dried (Na_2SO_4), and evaporated to a residue. Preparative TLC of this residue on PQIF silica gel in the system $CHCl_3$–EtOAc (9:1) provided the following compounds in order of decreasing R_f.

3b: 150 mg (10%); mp 173–174 °C (from CH_2Cl_2–petroleum ether); IR ($CHCl_3$) 1785, 1732, and 1680 cm^{-1}; mass spectrum m/e 392 (M^+), 345 ($M - SCH_3$), and 333 ($M - COOCH_3$).

Anal. ($C_{18}H_{20}N_2O_4S_2$) C, H, N.

6b: 76 mg (5%); amorphous; IR ($CHCl_3$) 1788, 1745, 1738 (sh), and 1680 cm^{-1}; mass spectrum m/e 404 (M^+); mol wt (calcd for $C_{19}H_{20}N_2O_6S$, 404.1042) 404.1028.

2b: 118 mg (8%); amorphous; IR ($CHCl_3$) 1775, 1720, and 1675 cm^{-1}; mass spectrum m/e 392 (M^+), 345 ($M - SCH_3$), 333 ($M - COOCH_3$); mol wt (calcd for $C_{18}H_{20}N_2O_4S_2$, 392.0864) 392.0861.

5b: 132 mg (9%); amorphous; IR ($CHCl_3$) 1788, 1760, and 1680 cm^{-1}; mass spectrum m/e 376 (M^+) and 317 ($M - COOCH_3$); mol wt (calcd for $C_{18}H_{20}N_2O_5S$, 376.1092) 376.1101.

4b: 500 mg (27%); amorphous (EtOAc–hexane); mp 85–87°; IR ($CHCl_3$) 1770, 1730, and 1685 cm^{-1}. Anal. Calcd for $C_{38}H_{46}N_4O_{12}S_2Hg$: C, 44.95; H, 4.57; N, 5.52; Hg, 19.76. Found: C, 45.49; H, 4.89; N, 5.53; Hg. 19.40.

Isomerization of 2β-Methylthiocephem 2b to 2α-Methylthiocephem 3b. A mixture of 50 mg (0.128 mmol) 2β-methylthiocephem **2b** and $Hg(OAc)_2$ (41 mg, 0.128 mmol) in 3 mL of dry dimethoxyethane was stirred under N_2 at 25 °C for 30 min. The solvent was removed in vacuo, and the residue was taken up in benzene–water. The benzene layer was washed with water, dried (Na_2SO_4), and evaporated to a residue (55 mg). Preparative TLC of this residue on PQIF silica gel in the system $CHCl_3$–EtOAc (9:1) provided 11 mg (22%) of 2α-methylthiocephem **3b** and 11 mg of recovered cephem **2b**, as determined from ^1H NMR spectral comparisons.

Mercury Mercaptide Azetidinone 4b from 2β-Methylthiocephem 2b. A mixture of 65 mg (0.166 mmol) of 2β-methylthiocephem **2b** and 53 mg (0.166 mmol) of $Hg(OAc)_2$ in 3 mL of dry CH_3OH was stirred at 25 °C for 30 min under N_2. Workup with benzene–water and preparative TLC as described above provided 9 mg (11%) of azetidinone **4b** as determined from TLC and ^1H NMR comparisons with authentic material.

Mercury Mercaptide Azetidinone 4b from 2α-Methylthiocephem 3b. Treatment of 82 mg (0.21 mmol) of 2α-methylthiocephem **3b** with 67 mg (0.21 mmol) of $Hg(OAc)_2$ in 3 mL of dry CH_3OH for 30 min at 25 °C under N_2 provided, after TLC chromatography as described above, 11 mg (10%) of azetidinone **4b** and 12 mg of cephem **3b**, as determined from ^1H NMR spectral comparisons.

Attempted Solvolysis of 2α-Acetoxycephem 6b with Mercuric Acetate in Methanol. Treatment of 65 mg (0.16 mmol) of 2α-acetoxycephem **6b** with 51 mg (0.16 mmol) of $Hg(OAc)_2$ in 3 mL of dry CH_3OH for 30 min at 25 °C under N_2 provided, after workup with benzene–water and preparative TLC on silica gel as described above, 30 mg of 2α-acetoxycephem **6b** (IR and ^1H NMR comparisons with authentic material) and no major identifiable product.

2α-Methoxycephem 10a and 2β-Methoxycephem 9a from Treatment of 4a with Hydrogen Sulfide. Hydrogen sulfide was bubbled through a solution of **4a** (1.00 g, 0.80 mmol) in 50 mL of dry CH_2Cl_2 for 15 min at room temperature with care being taken to exclude moisture. Precipitated HgS was removed by filtration through Celite, and the filtrate was evaporated to a residue, which was taken up in benzene and washed with water to give, after drying, a second residue (641 mg). Purification of this residue by TLC on silica gel in the system $CHCl_3$–EtOAc (4:1) yielded 266 mg (34%) of 2α-methoxycephem **10a** and 129 mg (16%) of the slower moving component, **9a.** The former had mp 133.5–134 °C (from acetone–hexane) and IR ($CHCl_3$) 1784, 1738, and 1680 cm^{-1}. Anal. ($C_{19}H_{19}N_2O_5SCl_3$) C, H, N, S. The latter was amorphous and had IR ($CHCl_3$) 1790, 1738, and 1675 cm^{-1}; mass spectrum m/e 492 (M^+), 461 ($M - OCH_3$), 344 ($M - HOCH_2CCl_3$), and 317 ($M - COOCH_2CCl_3$); mol wt (calcd for $C_{19}H_{19}N_2O_5SCl_3$, 492.0080) 492.0060.

2α-Ethoxycephem 10c and 2α-Methoxycephem 10b from Treatment of 4b with Hydrogen Sulfide. Hydrogen sulfide was bubbled through a solution of 200 mg (0.20 mmol) of azetidinone **4b** in 15 mL of 1% ethanolic chloroform for 1 h, with care being taken to exclude atmospheric moisture. The mixture was filtered through Celite and evaporated to a residue, which was chromatographed by TLC on silica gel in the system $CHCl_3$–EtOAc (9:1) to give 29 mg of a residue consisting of 19 mg (12%) of 2α-ethoxycephem **10c** and 10 mg (7%) of 2α-methoxycephem **10b,** as determined from integration of the ^1H NMR spectrum of the mixture. The ratio (2:1) of **10c** to **10b** in the mixture permitted assignment of chemical shifts to protons of each component. The mixture had IR ($CHCl_3$) 1780, 1730, and 1680 cm^{-1} and a mass spectrum consistent with both compounds being present including m/e 390 (M^+), 331 ($M - COOCH_3$), 345 ($M - OCH_2CH_3$) and mol wt (calcd for $C_{19}H_{22}N_2O_5S$, 390.1246) 390.1207 for **10c** and m/e 376 (M^+), 317 ($M - COOCH_3$), 345 ($M - OCH_3$), and mol wt (calcd for $C_{18}H_{20}N_2O_5S$, 376.1092) 376.1055 for **10b.**

Reaction of 1c with Mercuric Acetate in Methanol. Treatment of 1.04 g (1.91 mmol) of 4β-methylthiocephem **1c** with 851 mg (2.69 mmol) of $Hg(OAc)_2$ in 8 mL of CH_3OH for 1 h, according to the procedure for solvolysis of **1a,** provided after preparative TLC on silica gel in the system $CHCl_3$–EtOAc (9:1), 66 mg (7%) of 4α-methoxycephem **5c** having IR ($CHCl_3$) 1780, 1755, and 1680 cm^{-1} and 88 mg (7%) of dimethyl acetal **4c**[11] having IR ($CHCl_3$) 1770, 1720, and 1680 cm^{-1}.

Reaction of 1d with Mercuric Acetate in Methanol. Treatment of 537 mg (0.85 mmol) of 4β-methylthio-7-triphenylmethylaminocephem **1d** with 271 mg (0.85 mmol) of $Hg(OAc)_2$ in 15 mL of CH_3OH and 3 mL of dimethoxyethane according to the procedure described for solvolysis of **1a** provided, after preparative TLC on silica gel in the system $CHCl_3$–hexane (4:1), 293 mg (46%) of **4d**[11] having IR ($CHCl_3$) 1773 and 1760 cm^{-1} (sh).

Reaction of 1e with Mercuric Acetate in Methanol. Reaction of 308 mg (0.5 mmol) of 4β-methylthio-7-triphenylmethylaminocephem **1e** with 160 mg (0.5 mmol) of $Hg(OAc)_2$ in CH_3OH according to the procedure described for solvolysis of **1a** provided, after preparative TLC on silica gel in the system $CHCl_3$–hexane (4:1), 39 mg (13%) of 4α-methoxycephem **5e**, having IR ($CHCl_3$), 1780 and 1740 (intense) cm^{-1}; mass spectrum m/e 600 (M^+), 544 [loss of $H_2C{=}C(CH_3)_3$], 513 [loss of $H_2C{=}C(CH_3)_3$ and OCH_3], and 243 [base, $(C_6H_5)_3C^+$]; mol wt (calcd for $C_{36}H_{36}N_2O_6S$, 600.2294) 600.2365; and 150 mg (21%) of amorphous[11] (EtOAc–hexane) dimethyl acetal **4e** having mp 83–86 °C; IR ($CHCl_3$) 1760, 1730, and 1710 (sh) cm^{-1}.

Reaction of 1f with Mercuric Acetate in Methanol. Treatment of 700 mg (1.57 mmol) of 4β-methylthio-7-phthalimidocephem **1f** with 501 mg (1.57 mmol) of $Hg(OAc)_2$ in 7 mL of CH_3OH according to the procedure described for solvolysis of **1a** afforded after preparative TLC on silica gel in the system $CHCl_3$–EtOAc (9:1) 158 mg (23%) of 4α-methoxycephem **5f**, having IR ($CHCl_3$), 1798, 1780, 1745, and 1730 cm^{-1} and mass spectrum m/e 430 (M^+), 399 ($M - OCH_3$), and 329 [$M - COOC(CH_3)_3$], and 427 mg (49%) of dimethyl acetal **4f**[11]

having IR ($CHCl_3$) 1785, 1775, 1725, and 1700 (sh) cm^{-1}.

Acid Hydrolysis of Acetal 4f. Treatment of 39 mg (0.035 mmol) of acetal **4f** with 2.5 mg of *p*-toluenesulfonic acid monohydrate in 2.5 mL of acetone and 0.25 mL of water according to the procedure described for the hydrolysis of **4a** yielded 29 mg (77%) of aldehyde **7f**[11] having IR ($CHCl_3$) 1780 (broad), 1720 (broad), and 1685 cm^{-1}.

References and Notes

(1) A preliminary account of this study, including the synthesis of 4β-methylthiocephalosporins, was presented at the Symposium on Recent Advances in the Chemistry of β-Lactam Antibiotics, Cambridge, England, June 28–30, 1976, and has been reported elsewhere: W. A. Slusarchyk, H. E. Applegate, C. M. Cimarusti, J. E. Dolfini, P. T. Funke, W. H. Koster, M. S. Puar, and M. Young, "Recent Advances in the Chemistry of β-Lactam Antibiotics," *Chem. Soc., Spec. Publ.*, **No. 28**, 129 (1977).

(2) (a) W. A. Slusarchyk, H. E. Applegate, P. Funke, W. Koster, M. S. Puar, M. Young, and J. E. Dolfini, *J. Org. Chem.*, **38**, 943 (1973); (b) T. Jen, J. Frazee, and J. R. E. Hoover, *ibid.*, **38**, 2857 (1973); (c) H. E. Applegate, J. E. Dolfini, M. S. Puar, W. A. Slusarchyk, B. Toeplitz, and J. Z. Gougoutas, *ibid.*, **39**, 2794 (1974).

(3) A manuscript describing various syntheses of 2-, 4-, and 7-thio-substituted cephalosporins is in preparation.

(4) Compound **1a** was obtained by methylthiolation of 7-triphenylmethylaminodeacetoxycephalosporanic acid trichloroethyl ester (as described for the preparation of 4β-methylthio-7-phthalimido esters including **1f** [J. E. Dolfini, W. A. Slusarchyk, and M. Young, U.S. Patent 3 941 779 (1976)]), detritylation and acylation with phenylacetyl chloride. The 4β-methylthio configuration in **1a** was assigned by similar acylation with benzoyl chloride, deesterification (1 equiv of NaOH, dioxane–H_2O, 25 °C), and methylation (CH_2N_2) to give 7-benzamido-4-β-methylthio-3-methyl-Δ^2-cephem-4-carboxylic acid methyl ester, identical with an authentic sample [A. Yoshida, S. Oida, and E. Ohki, *Chem. Pharm. Bull.*, **23**, 2507 (1975)].

(5) Yoshida et al. (ref 4) have recently reported the synthesis of 2α- and 2β-methylthiocephems via base-catalyzed methylthiolation of cephalosporin sulfoxides.

(6) D. O. Spry, *Tetrahedron Lett.*, 3717 (1972).

(7) Although 4-methoxy-3-methylene-7-acylaminocephams have been reported, the stereochemistry at position 4 was not elucidated: M. Ochai, O. Aki, A. Morimoto, T. Okada, and T. Kaneko, *Tetrahedron Lett.*, 2345 (1972).

(8) Totally synthetic, racemic mercury mercaptide azetidinones have been reported: R. Lattrell, *Angew. Chem., Int. Ed. Engl.*, **12**, 925 (1973); R. Lattrell, *Justus Liebigs Ann. Chem.*, 1361 (1974); M. D. Bachi and K. J. Ross-Petersen *J. Chem. Soc., Chem. Commun.*, 2525 (1975).

(9) 2α- and 2β-Methoxycephems have recently been reported: A. Balsamo, P. Crotti, B. Macchia, F. Macchia, G. Nannini, E. Dradi, and A. Forgioni, *J. Org. Chem.*, 41, 2150 (1976).

(10) Compound **8** was prepared via methylthiolation of the parent cephem sulfoxide and subsequent reduction: W. H. Koster and J. E. Dolfini, German Offen. 2455-358 (1975); U.S. Patent 3 968 109 (1976).

(11) In the amorphous state, these mercury mercaptide azetidinones were found to be unstable on storage, even at −20 °C, and generally unsuitable for elemetal analysis. (Their mass spectra yielded little useful information, other than confirmation of the presence of mercury.) Their ^1H NMR spectra, following initial isolation, indicated only signals expected for the titled compounds. After storage for several days below 0 °C, these mercury mercaptides, with the exception of the aldehydes, could be repurified by chromatography on silica gel.

Kinetics of Epimerization of 15(*R*)-Methylprostaglandin E_2 and of 15(*S*)-Methylprostaglandin E_2 as a Function of pH and Temperature in Aqueous Solution

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Abstract: The kinetics of epimerization of 15(*R*)-methylprostaglandin E_2 (*R*) and 15(*S*)-methylprostaglandin E_2 (*S*) allylic alcohols have been studied in aqueous solution as a function of pH and temperature via high-performance liquid chromatography (HPLC) of their *p*-nitrophenacyl esters. The equilibrium constant was found to be unity within experimental error. The effective rate of epimerization at 37.2 °C was found to be 4.45 $[H^+]$ min^{-1}; the activation energy, E_a, was found to be 20.6 ± 0.4 kcal mol^{-1}. No evidence of reactions competing significantly with epimerization was detected.

Introduction

A number of naturally occurring prostaglandins have been shown to inhibit gastric secretion in animals[1,2] and in man[3-5] and to prevent ulcer formation in rats.[6]

The rapid inactivation of these compounds via oxidation by 15-prostaglandin dehydrogenase limits their therapeutic potential.[7] Incorporation of an alkyl group in place of the C-15 hydrogen in the prostaglandin blocks the action of this enzyme.[8a,b] Synthetic C-15 alkyl substituted prostaglandins have exhibited enhanced potency and duration of action for a number of biological activities. In its antisecretory properties in dogs, 15(*S*)-methylprostaglandin E_2 (*S*) was found to be 30–50 times more potent than prostaglandin E_2 when given intravenously, was active on oral administration, and had a longer duration of activity than prostaglandin E_2.[9] Robert and Yankee have demonstrated that the observed antisecretory activity of the methyl ester of 15(*R*)-methylprostaglandin E_2 (*R*) given orally results from the acid-promoted conversion of this compound to the 15(*S*) epimer.[10] The former compound has no antisecretory activity when administered intravenously.

Robert's and Yankee's observation suggests that the inactive methyl ester of *R* serves as a pro-drug for delivering the epimer active as an antisecretory to its site of action, the gastric mucosa, and only when needed, during the overproduction of gastric acid and pepsin. This delivery system should minimize the side effects associated with the *S* epimer; the most serious of these is the ability to stimulate smooth muscle, particularly the uterus. Karim has demonstrated that *R* is only one-tenth as potent as *S* in its uterine stimulating ability.[11]

The free acid *R* has similar properties to its methyl ester in its ability to inhibit gastric acid secretion and promote the healing of ulcers.[12] The crystallinity of the acid makes this compound easier to formulate as a drug for oral administration than the methyl ester, a viscous oil. The efficacious use of 15(*R*)-methylprostaglandin E_2 clearly is dependent upon its rate of conversion to the active epimer. We report here on the kinetics of this epimerization as a function of temperature and hydrogen ion concentration.

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