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Dihydrothiazine Ring-Opening Reactions in 2-Alkoxycephalosporin Compounds[1]

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2-Alkoxy-3-cephem-1-oxides **1b—c** were found to be thermally unstable and easily converted into isothiazolones **5a—f**, β-lactam **12** and thiazole **14** according to reaction conditions. Further, 2-alkoxy-3-cephem **4a—b** was treated with *tert*-butyl hypochlorite to give azetidinone-oxazoline acetals **18a—b**. Formation of these rearrangement products was interpreted *via* the sulfenic acid intermediate **6** or **17**.

Keywords——cephalosporin; penicillin; S–C_2 bond cleavage; isothiazolone; azetidinone; oxazoline

Numerous investigations in penicillin derivatives concerning their thiazolidine ring-opening or -expansion reactions without damage on the β-lactam parts have appeared in the literature, as exemplified in S–C(2), N–C(3), or S–C(5) bond fission,[3] and some of them were utilized to build up new β-lactam antibiotics. On the other hand, there existed only one report on bond fission of cephalosporin dihydrothiazine rings which was conducted at the S–C(2) position with ring-contraction to penam compounds.[4] A prior report[5] from this laboratory has shown that introduction of a heteroatom substituent at the C(2) position of cephalosporin molecules facilitates the dihydrothiazine ring opening; for example, 7-benzamido-3-cephem-1-oxides having a 2-methylthio or 2-methoxy substituent (**1a** or **1b**) easily underwent a cleavage of the S–C(6) bond by treatment with acetic anhydride-pyridine, giving a corresponding azlactone derivative **2a** or **2b**. In the course of this study, it was also observed that the 2-alkoxy cephem derivatives were further subjected to other transformation reactions involving the S–C(2) bond fission which form the topic of the present paper.

The starting materials, methyl 7β-benzamido-2α-methoxy-3-methyl-3-cephem-4-carboxylate-1β-oxide[5] (**1b**) and the 2α-ethoxy analog **1c** were provided by treatment of 7-benzamido-3-cephem ester[6] **3** with *tert*-butyl hypochlorite in alcohol and successive oxidation of the resulting 2α-alkoxy-3-cephem[7] **4a** or **4b** with *m*-chloroperbenzoic acid. The latter 2α-ethoxy-3-cephem-1β-oxide **1c** was prepared in quantity because of its easiness of isolation and purification with its suitable solubility in organic solvents and was mainly used for this study.

While the 2α-methylthio-1β-oxide **1a** was stable to heat in solvents, these 2α-alkoxy-1β-oxides (**1b** and **1c**) were found to be thermally unstable; and a short refluxing of **1b** or **1c** in ethyl acetate afforded the same isothiazolone aldehyde **5a**. Mass spectrum (MS) of the aldehyde **5a** showed a molecular ion peak at *m/e* 346, indicating removal of one molar methanol

1) Preliminary details of this work have been published. See A. Yoshida, S. Oida, and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **24**, 362 (1976).
2) Location: *Hiromachi, Shinagawa-ku, Tokyo.*
3) For reviews, see R.D.G. Cooper and D.O. Spry, "Cephalosporins and Penicillins, Chemistry and Biology," ed. by E.H. Flynn, Academic Press, N.Y., 1972, p. 183; D.N. McGregor, *Fortschr. Chem. Org. Naturst.*, **31**, 1 (1974); A.K. Mukerjee and A.K. Singh, *Synthesis*, **1975**, 547; R.J. Stoodley, *Tetrahedron*, **31**, 2321 (1975); P.G. Sammes, *Chem. Rev.*, **76**, 113 (1976).
4) M. Yoshimoto, S. Ishihara, E. Nakayama, and N. Soma, *Tetrahedron Letters*, **1972**, 2923.
5) A. Yoshida, S. Oida, and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **23**, 2518 (1975).
6) A. Yoshida, S. Oida, and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **23**, 2507 (1975).
7) The 2α-structure of these alkoxy group in **4a** and **4b** was based on the Spry's assignment of the preceding example. See D.O. Spry, *Tetrahedron Letters*, **1972**, 3717.

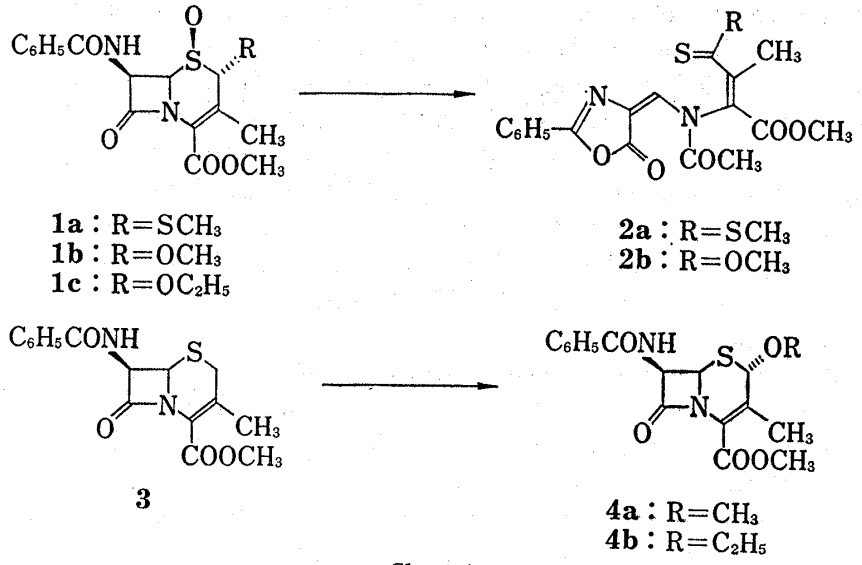

Chart 1

or ethanol from the molecule of these 2-alkoxy cephems **1b** or **1c**. The nuclear magnetic resonance (NMR) spectrum exhibited singlet absorptions at δ 9.81 and 8.91. The former indicates the existence of an aldehyde function and the latter singlet may be due to the C(5) proton of the isothiazolone ring, suggesting the structure of **5a**. Further, refluxing of the

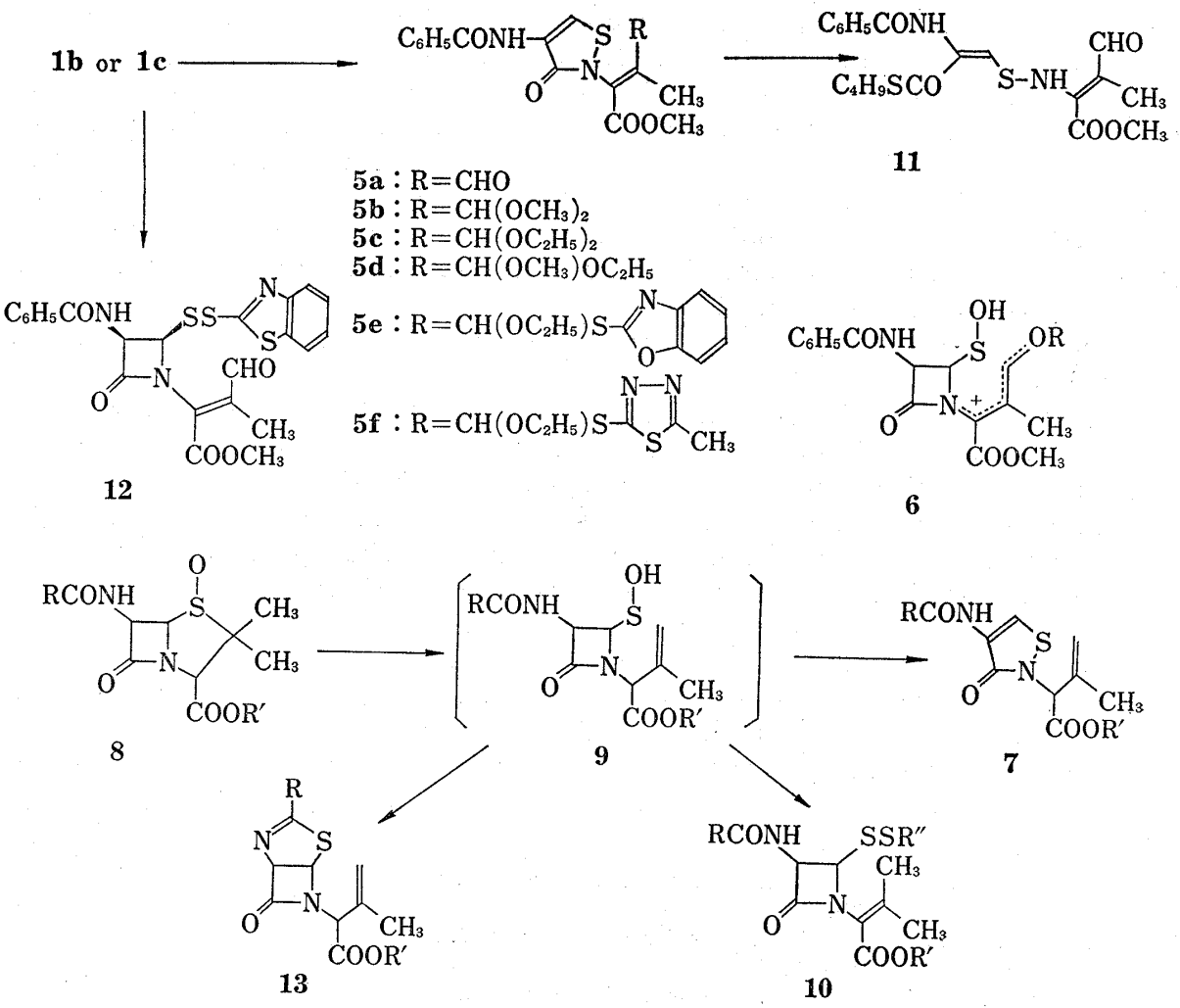

Chart 2

2α-methoxy-1-oxide **1b** in methanol or of the 2-ethoxy analog **1c** in ethanol gave an isothiazolone dimethyl or diethyl acetal (**5b** or **5c**) respectively and also treatment of **1b** in ethanol or of **1c** in methanol yielded the same ethyl methyl acetal **5d**. These acetal structures were confirmed by elementary, mass and NMR analysis. Transformation of **1b** or **1c** into these isothiazolones seems to proceed *via* formation of a β-lactam-sulfenic acid intermediate **6** arising from cleavage of the S–C(2) bond and subsequent 1,2-bond migration of the lactam nitrogen from the carbon atom to the sulfur atom along with dehydration. It might be of interest to recall that formation of the similar isothiazolone compounds **7** was observed as by-products in ring-expansion reaction of penicillin sulfoxides **8** and was interpreted as proceeding through their sulfenic acid isomers **9** which thermally equilibrate with the sulfoxides **8**.[8]

There already exists a number of successful trapping experiments on the sulfenic acid **9** retaining the β-lactam ring in penicillin sulfoxides **8**, for example, using olefin, mercaptan and so on.[3] Consequently, our attension was directed towards analogous trapping of the possible β-lactam intermediate **6** derived from 2-alkoxy-cephem-1-oxides. Considering the fact that treatment of penicillin sulfoxides **8** with mercaptans gave disulfides **10** without damage of the β-lactam rings,[9] we first attempted reaction of the 2-ethoxy-cephem-1-oxide **1c** with mercaptans. Treatment of **1c** with *n*-butylmercaptan in chloroform gave a geometrical mixture of open-chain thioesters **11** in 53% yield. The same mixture was obtained also on treatment of the afore-mentioned isothiazolone aldehyde **5a** with *n*-butylmercaptan. Elementary analysis of **11** indicated an addition of one molar mercaptan to the molecule of **5a**. A low frequency absorption at 1663 cm^{-1} in the infrared (IR) spectrum suggests the presence of β-amino-α, β-unsaturated aldehyde and the NMR spectrum showed an absorption at δ 11.85 due to the amino proton forming a hydrogen bond. These facts supported the open-chain structure for the thioester **11**. Moreover, NMR analysis of **11** indicates that the mixture is composed of two kinds of (*Z*),(*E*)-isomers.

While reaction of the 2-ethoxy-1-oxide **1c** with heteroaromatic thiols such as 2-mercaptobenzoxazole and 2-mercapto-5-methyl-1,3,4-thiadiazole resulted in a formation of isothiazolone hemithioacetals (**5e** and **5f**) respectively, treatment of **1c** with 2-mercaptobenzothiazole according to Kamiya *et al.*[10] afforded a β-lactam disulfide **12** in 74% yield. The presence of the β-lactam ring in **12** was illustrated by the IR absorption at 1788 cm^{-1} and also by the NMR absorptions containing mutually coupled doublets at δ 5.48 and 5.95, J=5 Hz, due to the azetidinone ring protons. Thus, a successful example trapping the intermediate **6** with the β-lactam ring was provided.

In 1970, Cooper *et al.*[11] reported that reaction of penicillin sulfoxide **8** with trimethyl phosphite proceeds *via* reduction of the sulfenic acid **9** and successive interaction of the formed thiol group with the side chain 6β-amido carbonyl, giving an azetidinone-thiazoline compound **13**. In view of this fact, treatment of 2-ethoxy-1-oxide **1c** with trimethyl phosphite in chloroform containing acetic acid was carried out; however, the desired bicyclic compound like **13** was not obtained and a thiazole derivative **14** was isolated in 29% yield. Elementary analysis of **14** indicates that removal of one oxygen atom from the molecule of **1c** was carried out and further was accompanied by addition of acetic acid and dehydration. The NMR spectrum of **14** reflected its structure; for example, absorptions due to acetal proton and ring proton appear at δ 5.64 and 8.97 as singlet, respectively. Formation of **14** may be rationalized by a pathway including deoxygenation of the sulfenic acid in the intermediate **6**, concomitant attack of an acetate ion, successive intramolecular attack of the formed thiol group to the

8) R.B. Morin, B.G. Jackson, R. A. Mueller, E.R. Lavagnino, W.B. Scanlon, and S.L. Andrews, *J. Am. Chem. Soc.*, **92**, 1401 (1969).
9) D.H.R. Barton, P.G. Sammes, M.V. Taylor, C.M. Cooper, G. Hewitt, B.E. Looker, and W.G.E. Underwood, *Chem. Commun.*, **1971**, 1137.
10) T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi, and T. Oku, *Tetrahedron Letters*, **1973**, 3001.
11) R.D.G. Cooper and F.L. Jóse, *J. Am. Chem. Soc.*, **92**, 2575 (1970).

side chain amido carbonyl and finally ring opening of the azetidinone-thiazoline intermediate **15** as shown in Chart 3.

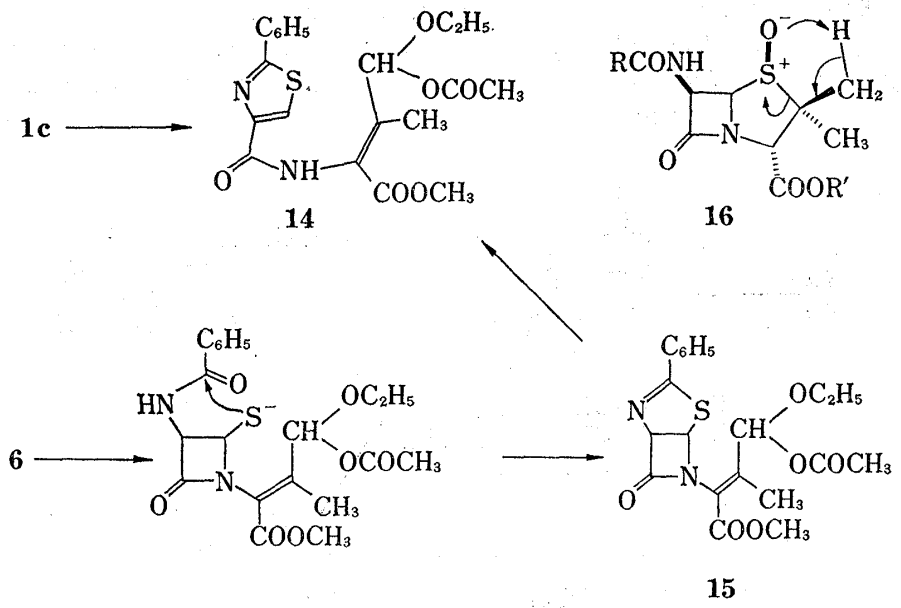

Chart 3

Thus, it might be mentioned that there exists a similarity between the chemical nature surrounding the sulfur atom of the 2-alkoxy-cephem-1-oxides and that of penicillin sulfoxides in point of the facile bond cleavage into the sulfenic acid intermediates. In penicillin sulfoxides, Cooper[11,12] has postulated that generation of the sulfenic acid **9** takes place through a reversible electrocyclic rearrangement as **16**. Different from this mechanistic pathway, generation of the intermediate **6** from the 2-alkoxy-1-oxides would be implicated in an irreversible heterolytic cleavage occurring at the S–C(2) bond of the protonated sulfoxides. In general, activation of sulfoxides and successive formation of sulfenic acids require a high acidity of the medium[13]; but generation of **6** from the 2-alkoxy-cephem-1-oxides seems to proceed under mild conditions as shown above. This facile bond cleavage might be attributable to stabilization of the formed cation **6** by delocalization of the unshared electron pairs of the oxygen in the attached alkoxy group and of the nitrogen in the enamide conjugated system. In contrast, the stability of the 2-methylthio-cephem-1-oxide **1a** to heat in protic solvents might be due to less stabilization of the corresponding cation.[14]

Based on these facts, it was also presumed that the 2-alkoxy-3-cephems (**4a** and **4b**) would generate an intermediate **17**, which is isoelectronic with **6**, under the S–C(2) bond cleavage by attack of electrophiles such as chlorine on the sulfur atom. Thus, treatment of 2-methoxy-3-cephem **4a** with *tert*-butyl hypochlorite in methanol was carried out; and an azetidinone-oxazoline acetal **18a** was obtained in 38% yield. Along with the IR absorption at 1780 cm^{-1} arising from the existence of the β-lactam ring, the NMR spectrum supported the structure

12) R.D.G. Cooper, *J. Am. Chem. Soc.*, **92**, 5010 (1972).

13) For example, racemization or fragmentation of optically-active *sec*- and *tert*-alkyl phenyl sulfoxides has been illustrated through their sulfenic acids and was experimentally conducted with a high acid medium such as 6 N perchloric acid. See G. Modena, V. Quintily, and G. Scorrano, *J. Am. Chem. Soc.*, **94**, 202 (1972).

14) Solvolysis rate of chloromethyl methyl sulfide is much lower (1/1600) than that of chloromethyl methyl ether. This is interpreted as attributed to less stability of the generated carbonium ion, $CH_2{}^+SCH_3$, which is caused by smaller 3p—2p overlapping of the sulfur and carbon orbitals in comparison with the latter case involving 2p—2p overlapping of the oxygen and carbon orbitals. See S. Oae, "Chemistry of Organosulfur Compounds," Kagaku Dojin, Kyoto, Japan, Vol. 1, 1968, p. 7.

of **18a**, exhibiting AB quartet absorptions at δ 5.38 and 6.18, J=3 Hz, due to the angular protons. Analogous treatment of the 2-ethoxy-3-cephem **4b** with *tert*-butyl hypochlorite also gave the ethyl methyl acetal **18b**.[15] These acetals were quantitatively converted into an aldehyde **18c** on treatment with *p*-toluenesulfonic acid in acetone. Formation of these acetals (**18a** and **18b**) from the 2-alkoxy-3-cephem suggests the expected cleavage of the S–C(2) bond yielding the cation **17** which subsequently undergoes desulfurization and an intramolecular attack of the side chain amide oxygen.

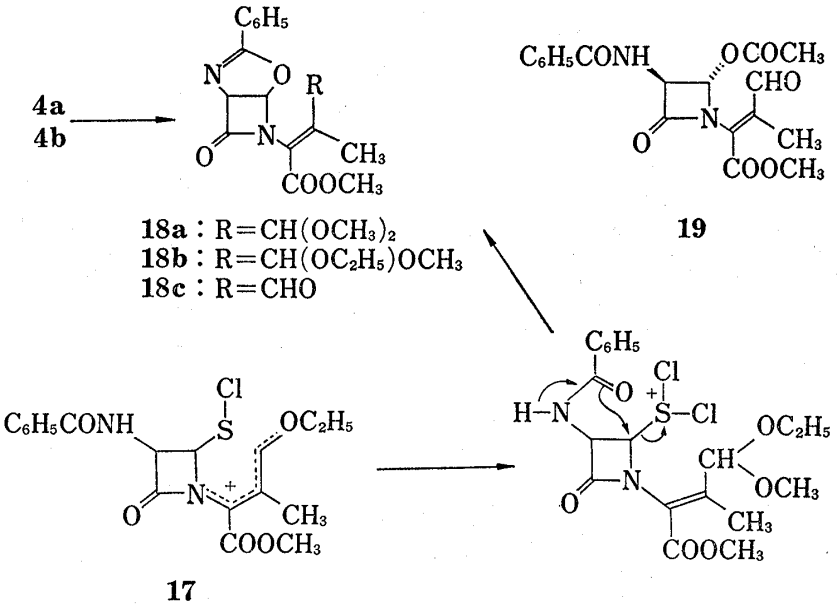

Chart 4

Moreover, hydrolysis of the dimethyl acetal **18a** with acetic acid gave a β-lactam compound **19** in 30% yield along with the aldehyde **18c**. The IR spectrum of **19** exhibited an absorption at 1792 cm^{-1} corresponding to the β-lactam carbonyl and the NMR spectrum indicated the presence of acetoxy group with a singlet absorption at δ 2.04. Absorptions due to the protons on the β-lactam ring appeared at δ 6.42 and 5.16 whose small coupling constant, J=2 Hz, suggested *trans*-orientation of the substituents on the β-lactam ring in **19**.[16]

Experimental

Melting points are not corrected. IR spectra were recorded on a JASCO A-2 spectrometer, ultraviolet (UV) spectra on a Cary 14 (Serial No. 1258) spectrometer, NMR spectra on a Hitachi Perkin-Elmer R-24 spectrometer, 60 MHz, and mass spectra (MS) on a JEOL JMS-01SG mass spectrometer. Thin-layer chromatography (TLC) was performed on TLC-plates, silica gel F_{254} precoated, layer thickness 0.25 mm (E. Merck) and spots were visualized by UV-irradiation or by spraying with vanadic acid-sulfuric acid followed by heating or with iodine. Columns for ordinary chromatography were prepared with Wakogel C-200 (WAKO Pure Chemical Industries, Ltd.). Plates for preparative TLC were provided with Silica gel $60F_{254}$ (E. Merck) and developing solvents are shown in parenthesis. Solvents were removed by a rotary flash evaporator at diminished pressure and usually at 15—35°. Chloroform was provided by passing over a column of Aluminum Oxide W-200 (ICN Pharmaceuticals GmbH Co.) in order to remove contained alcohol before use. Methyl 7β-benzamido-2α-methoxy-3-methyl-3-cephem-4-carboxylate (**4a**) and its 1β-oxide (**1b**), the starting materials, were prepared according to the preceding paper.[5] The abbreviations used are as follows: s, singlet; d, doublet; q, quartet; m, multiplet; br., broad.

Methyl 7β-Benzamido-2α-ethoxy-3-methyl-3-cephem-4-carboxylate (4b)——To a solution of 550 mg of methyl 7β-benzamido-3-methyl-3-cephem-4-carboxylate[6] (3) in a mixture of 15 ml of EtOH and 15 ml

15) The reaction product was accompanied by the dimethyl acetal **18a** which was formed by acid-catalyzed acetal exchange reaction.

16) R.J .Stoodley and N.R. Whitehouse, *J. Chem. Soc., Chem. Commun.*, **1973**, 477.

of CH_2Cl_2 was added 215 mg of *tert*-butyl hypochlorite in one portion with cooling and stirring and the mixture was further stirred at 0° overnight. Then, the mixture was poured onto a stirred mixture of CH_2Cl_2 and aq. $CaCl_2$. The organic layer was collected, washed with dil. $NaHCO_3$ and with water, dried and evaporated *in vacuo*. The residue was charged on 25 g of silica gel and eluted with $CHCl_3$–AcOEt (20: 1, v/v). Thus, 283 mg (45%) of **4b** was obtained. The analytical sample was obtained by recrystallization from $CHCl_3$–AcOEt, mp 178—179.5°, needles. IR ν_{max}^{Nujol} cm^{-1}: 3240, 1780, 1725, 1648, 1532, 1229, 1050. NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7 Hz, $-OCH_2C\underline{H}_3$), 2.15 (3H, s, 3-CH_3), 3.77 (3H, s, $-COOCH_3$), 4.88 (1H, br. s, H-2), 5.10 (1H, d, J=5 Hz, H-6), 5.98 (1H, dd, J=5, 8 Hz, H-7). MS *m/e*: 376 (M^+, $C_{18}H_{20}N_2O_5S$). *Anal.* Calcd. for $C_{18}H_{20}O_5N_2S$: C, 57.43; H, 5.35; N, 7.44; S, 8.52. Found: C, 57.12; H, 5.18; N, 7.66; S, 8.91.

Methyl 7β-Benzamido-2α-ethoxy-3-methyl-3-cephem-4-carboxylate-1β-oxide (1c)——To an ice-cold solution of 376 mg of **4b** in 10 ml of $CHCl_3$ was added dropwise a solution of 203 mg of *m*-chloroperbenzoic acid (85% purity, Aztec Chemicals) in 4 ml of $CHCl_3$ with stirring. After stirring for 1 hr with cooling, the mixture was diluted with $CHCl_3$, washed with dil. $NaHCO_3$ and with water, dried and concentrated to about 10 ml. After addition of 3 ml of EtOH, the mixture was slowly concentrated *in vacuo*, giving 285 mg (73%) of **1c**, mp 137—138°, needles. IR ν_{max}^{Nujol} cm^{-1}: 3320, 1785, 1736, 1660, 1543, 1058. NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7 Hz, $-OCH_2C\underline{H}_3$), 2.12 (3H, s, 3-CH_3), 3.80 (3H, s, $-COOCH_3$), 4.60 (1H, d, J=5.5 Hz, H-6), 4.63 (1H, s, H-2), 6.25 (1H, dd, J=5.5, 10 Hz, H-7). *Anal.* Calcd. for $C_{18}H_{20}N_2O_6S$: C, 55.10; H, 5.14; N, 7.14; S, 8.15. Found: C, 55.18; H, 5.02; N, 7.06; S, 8.32.

Methyl 2-(4-Benzamido-3-oxo-Δ^4-isothiazolin-2-yl)-3-methyl-4-oxobut-2-enoate (5a)——A solution of 400 mg of **1b** in 20 ml of AcOEt was refluxed for 30 min. After cooling, the solvent was evaporated *in vacuo* and the residue was purified by preparative TLC ($CHCl_3$–MeOH, 50: 1, v/v), giving 323 mg (92%) of **5a** as syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1738, 1701, 1662, 1522. NMR ($CDCl_3$) δ: 2.23 (3H, =C–CH_3), 3.81 (3H, s, $-COOCH_3$), 8.55 (1H, s, –NH–), 8.91 (1H, s, =CH–S–), 9.81 (1H, s, –CHO). MS *m/e*: 346 (M^+, $C_{16}H_{14}N_2O_5S$).

Analogous treatment of **1c** also gave **5a** in good yield.

Methyl 2-(4-Benzamido-3-oxo-Δ^4-isothiazolin-2-yl)-3-methyl-4-oxobut-2-enoate Acetals and Hemithioacetals (5b—f)——A solution of 100 mg of **1b** in a mixture of 0.5 ml of MeOH and 7 ml of $CHCl_3$ was refluxed for 50 min. Then, the solvent was evaporated *in vacuo* and the residue was purified by preparative TLC ($CHCl_3$–MeOH, 50: 1, v/v) to give 84 mg (81%) of dimethyl acetal **5b**. The analytical sample was obtained by recrystallization from hexane–EtOH, mp 145.5—146.5°, prisms. IR ν_{max}^{Nujol} cm^{-1}: 3380, 3300, 1730, 1651, 1526. NMR ($CDCl_3$) δ: 2.18 (3H, s, =C–CH_3), 3.27 (6H, s, $-CH(-OC\underline{H}_3)_2$), 3.67 (3H, s, $-COOCH_3$), 4.64 (1H, s, –O–CH–O–), 8.42 (1H, br. s, –NH–), 8.75 (1H, s, =CH–S–). MS *m/e*: 392 (M^+, $C_{18}H_{20}N_2O_6S$). *Anal.* Calcd. for $C_{18}H_{20}N_2O_6S$: C, 55.10; H, 5.14; N, 7.14; S, 8.16. Found: C, 54.90; H, 4.85; N, 6.90; S, 8.29.

A solution of 100 mg of **1c** in 10 ml of $CHCl_3$ (reagent-grade, containing 1% EtOH) was refluxed for 30 min. Work-up as described above gave 74 mg (69%) of the diethyl acetal **5c**. The analytical sample was obtained by recrystallization from hexane–AcOEt, mp 142—143°, prisms. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1734, 1660, 1524. NMR ($CDCl_3$) δ: 1.20 (6H, t, J=7 Hz, $-OCH_2C\underline{H}_3$), 2.27 (3H, s, =C–CH_3), *ca.* 3.5 (4H, m, $-OC\underline{H}_2CH_3$), 3.69 (3H, s, $-COOCH_3$), 4.87 (1H, s, –O–CH–O–), 8.51 (1H, br. s, –NH–), 8.82 (1H, s, =CH–S–). MS *m/e*: 420 (M^+, $C_{20}H_{24}N_2O_6S$). *Anal.* Calcd. for $C_{20}H_{24}N_2O_6S$: C, 57.13; H, 5.75; N, 6.66; S, 7.61. Found: C, 57.23; H, 5.66; N, 6.39; S, 7.64.

A solution of 100 mg of **1b** in 10 ml of $CHCl_3$ (reagent-grade, containing 1% EtOH) was refluxed for 50 min and, after work-up as described above, 94 mg (88%) of ethyl methyl acetal **5d** was obtained as syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410, 1730, 1655, 1522. NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7 Hz, $-OCH_2C\underline{H}_3$), 2.18 (3H, s, =C–CH_3), 3.24 (3H, s, $-CH(-OC\underline{H}_3)$), 3.40—3.70 (2H, m, $-OC\underline{H}_2CH_3$), 3.65 (3H, s, $-COOCH_3$), 4.68 (1H, s, –O–CH–O–), 8.44 (1H, br. s, –NH–), 8.74 (1H, s, =CH–S–). MS *m/e*: 406 (M^+, $C_{19}H_{22}N_2O_6S$).

The same ethyl methyl acetal **5d** was also obtained on refluxing of **1c** in $CHCl_3$ containing MeOH. Yield, 89%.

A mixture of 196 mg of **1c**, 151 mg of 2-mercaptobenzoxazole, and 10 ml of $CHCl_3$ was refluxed for 35 min and then was evaporated *in vacuo*. The residue was purified by preparative TLC to give 116 mg (44%) of the hemithioacetal **5e** as syrup. IR ν_{max}^{Nujol} cm^{-1}: 1735, 1657, 1530. NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7 Hz, $-OCH_2C\underline{H}_3$), 2.43 (3H, s, =C–CH_3), 3.70 (3H, s, $-COOCH_3$), 6.78 (1H, s, –S–CH–O–), 8.76 (1H, s, =CH–S–). MS *m/e*: 375 ($M^+-C_7H_4NOS$).

A mixture of 196 mg of **1c**, 128 mg of 2-mercapto-5-methyl-1,3,4-thiadiazole and 10 ml of $CHCl_3$ was treated as described above to give 92 mg of the hemithioacetal **5f**, mp 181—182° (decomp.), needles (from ether–$CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3430, 3180, 1725, 1657, 1640, 1538. NMR ($CDCl_3$) δ: 1.21 (3H, t, J=7 Hz, $-OCH_2C\underline{H}_3$), 2.43 (3H, s, =C–CH_3), 2.54 (3H, –N=C–CH_3), 3.66 (3H, s, $-COOCH_3$), 6.79 (1H, s, –S–CH–O–), 8.39 (1H, br. s, –NH–), 8.70 (1H, s, =CH–S–). MS *m/e*: 506 (M^+, $C_{21}H_{22}N_4O_5S_3$), 375 ($M^+-C_3H_3N_2S_2$). *Anal.* Calcd. for $C_{21}H_{22}N_4O_5S_3$: C, 49.80; H, 4.38; N, 11.06; S, 18.98. Found: C, 49.56; H, 4.30; N, 10.75; S, 18.77.

Methyl 3-Benzamido-2-(2-benzothiazolyldithio)-α-(1-formylethylidene)-4-oxo-1-azetidineacetate (12)—A mixture of 100 mg of **1c**, 150 mg of 2-mercaptobenzothiazole, and 8 ml of $CHCl_3$ was refluxed for 40 min and evaporated *in vacuo*. The residue was recrystallized from benzene to recover mercaptobenzothiazole. The collected mother liquor was chromatographed by preparative TLC ($CHCl_3$–AcOEt, 2: 1, v/v), giving 99 mg of **12**. The analytical sample was recrystallized from benzene–ether, mp 126—127.5°, needles.

IR ν_{max}^{Nujol} cm^{-1}: 3370, 1788, 1724, 1678, 1660, 1533. NMR ($CDCl_3$) δ: 1.88 (3H, s, =C–CH_3), 3.60 (3H, s, –$COOCH_3$), 5.48 (1H, dd, J=5, 7 Hz, –CONH–CH–CO–), 5.95 (1H, d, J=5 Hz, –N–CH–S–), 10.20 (1H, s, –CHO). *Anal.* Calcd. for $C_{23}H_{19}N_3O_5S_3$: C, 53.79; H, 3.73; N, 8.18; S, 18.73. Found: C, 53.63; H, 3.65; N, 8.05; S, 18.56.

S-Butyl 2-Benzamido-1-[N-(2-formyl-1-methoxycarbonylprop-1-enyl)sulfenamoyl]prop-1-enthioate (11)—A mixture of 200 mg of **1c**, 75 mg of *n*-butylmercaptan, and 10 ml of $CHCl_3$ was refluxed for 35 min and evaporated *in vacuo*. The residue was chromatographed over 8 g of silica gel (benzene–AcOEt, 15: 1, v/v) to give 118 mg (53%) of **11**. The analytical sample was obtained by recrystallization from AcOEt–hexane, mp 120—122.5°, needles. The NMR spectrum indicated that **11** is composed of two *Z*,*E*-isomers in relative ratio of 5: 4. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1744, 1663, 1644, 1585, 1504. UV λ_{max}^{EtOH} nm (ε): 228 (15900), 320 (16700). NMR ($CDCl_3$) δ: 1.76 and 1.86 (3H, s, *ca.* 4: 5, =C–CH_3), 2.78 (2H, t, J=7 Hz, –S–CH_2CH_2–), 3.81 and 3.82 (3H, s, *ca.* 4: 5, –$COOCH_3$), 9.38 and 9.62 (1H, s, *ca.* 5: 4, –CHO), 11.85 (1H, s, –NH–). *Anal.* Calcd. for $C_{20}H_{24}N_2O_5S_2$: C, 55.04; H, 5.04; N, 6.42; S, 14.67. Found: C, 54.97; H, 5.48; N, 6.48; S, 14.72.

A mixture of 245 mg of **5a**, 105 mg of *n*-butylmercaptan, and 10 ml of $CHCl_3$ was refluxed for 35 min and, after work-up as described above, 228 mg (74%) of **11** was obtained and identified.

N-(3-Acetoxy-3-ethoxy-1-methoxycarbonyl-2-methylprop-1-enyl)-2-phenyl-4-thiazolecarboxamide (14)—A solution of 196 mg of **1c**, 37 mg of acetic acid and 220 mg of trimethylphosphite in 10 ml of tetrahydrofuran was kept at 50° for 1.5 hr with stirring. Then, the solvent was evaporated *in vacuo* and the residue was dissolved in 30 ml of AcOEt. The solution was washed with 5% $NaHCO_3$ and with water, dried and evaporated. The syrup thus obtained was chromatographed over 6 g of silica gel, giving 61 mg of **14**, which was recrystallized from acetone–hexane, mp 127.5—129°, prisms. IR ν_{max}^{Nujol} cm^{-1}: 3380, 1722, 1719, 1671, 1615, 1607, 1594, 1527. UV λ_{max}^{EtOH} nm (ε): 282 (11800), 352 (14700). NMR ($CDCl_3$) δ: 2.25 (3H, t, J=7 Hz, –OCH_2CH_3), 2.20 (3H, s, –$OCOCH_3$), 2.44 (3H, s, =C–CH_3), *ca.* 3.8 (2H, m, –CH_2CH_3), 3.86 (3H, s, –$COOCH_3$), 5.64 (1H, s, –O–CH–O–), 8.97 (1H, s, =CH–S–). MS *m/e*: 418 (M^+, $C_{20}H_{22}N_2O_6S$). *Anal.* Calcd. for $C_{20}H_{22}N_2O_6S$: C, 57.41; H, 5.30; N, 6.70; S, 7.65. Found: C, 57.52; H, 5.25; N, 6.77; S, 7.56.

Methyl 4,4-Dimethoxy-3-methyl-2-(6-oxo-3-phenyl-2-oxa-4,7-diazabicyclo[3.2.0]hept-3-en-7-yl]but-2-enoate (18a) and Its 4-Ethoxy-4-methoxy Analog (18b)——To an ice-cold solution of 181 mg of **4a** in a mixture of 10 ml of MeOH and 10 ml of CH_2Cl_2 was added 117 mg (2.1 equiv.) of *tert*-butyl hypochlorite in one portion and the mixture was stirred for 30 min with cooling. Then, the mixture was diluted with $CHCl_3$, washed with 10% aq. $Na_2S_2O_3$, 5% aq. $NaHCO_3$, and aq. NaCl, dried and evaporated *in vacuo*. The residue was purified by preparative TLC (benzene–AcOEt, 2.5: 1, v/v), giving 70 mg (39%) of **18a** as syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1780, 1732, 1633. NMR ($CDCl_3$) δ: 2.12 (3H, s, =C–CH_3), 2.97 and 3.23 (3H, each s, –CH(OCH_3)–OCH_3), 3.66 (3H, s, –$COOCH_3$), 4.69 (1H, s, –O–CH–O–), 5.38 and 6.19 (1H each, ABq, J=3 Hz, –CH–CH–). MS *m/e*: 360 (M^+, $C_{18}H_{20}N_2O_6$).

Analogous treatment of 100 mg of **4b** with *tert*-butyl hypochlorite in MeOH–CH_2Cl_2 mixture gave 48 mg of a mixture of **18a** and **18b** as syrup. The relative ratio of **18a** and **18b** was 1: 4 on the basis of NMR analysis. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1788, 1734, 1636. MS *m/e*: 374 (M^+, $C_{19}H_{22}N_2O_6$).

The NMR spectrum of **18b** is suggested by analysis of the mixture as follows; δ ($CDCl_3$): 0.95 and 1.14 (3H, t, J=7 Hz, 1: 1, –CH_2CH_3), 2.12 (3H, s, =C–CH_3), 2.98 and 3.25 (3H, s, 1: 1, –CH–OCH_3), 3.67 (3H, s, –$COOCH_3$), 4.70 and 4.78 (1H, s, 1: 1, –O–CH–O–), 5.38 and 6.11 (1H, each, ABq, J=3 Hz, –CH–CH–).

Methyl 3-Methyl-4-oxo-2-(6-oxo-3-phenyl-2-oxa-4,7-diazabicyclo[3.2.0]hept-3-en-7-yl)but-2-enoate (18c)——A mixture of 280 mg of **18a**, 4 mg of *p*-toluenesulfonic acid and 50 ml of acetone was allowed to stand for 3 days at room temperature. Then, the mixture was concentrated *in vacuo* to about 10 ml, diluted with AcOEt, washed with 5% aq. $NaHCO_3$ and with water, dried and evaporated, giving 250 mg of **18c** as syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1790, 1733, 1694, 1632. NMR ($CDCl_3$) δ: 2.06 (3H, s, =C–CH_3), 3.85 (3H, s, –$COOCH_3$), 5.49 and 6.30 (1H, each, ABq, J=3 Hz, –CH–CH–), 9.67 (1H, s, –CHO). MS *m/e*: 314 (M^+, $C_{16}H_{14}N_2O_5$).

The crude **18b** obtained as above also gave **18c** in good yield on acid hydrolysis.

Methyl 2-Acetoxy-3-benzamido-α-(1-formylethylidene)-4-oxo-1-azetidineacetate (19)——A solution of 100 mg of **18a** in 3 ml of acetic acid was kept at 50° for 6 hr and the mixture was evaporated *in vacuo*. The residue was dissolved in AcOEt, washed with 5% aq. $NaHCO_3$ and with water, dried and concentrated *in vacuo*. The product was chromatographed on a TLC plate (benzene–AcOEt, 3: 1, v/v), giving 31 mg (30%) of **19** along with 23 mg (26%) of **18c**. IR ν_{max}^{Nujol} cm^{-1}: 3370, 1792, 1758, 1734, 1660, 1534. NMR ($CDCl_3$) δ: 2.04 (3H, s, –$COCH_3$), 2.08 (3H, s, =C–CH_3), 3.89 (3H, s, –$COOCH_3$), 5.16 (1H, dd, J=2, 7.5 Hz, –NH–CH–CO–), 6.42 (1H, d, J=2 Hz, –N–CH–O–), 9.98 (1H, s, –CHO). MS *m/e*: 374 (M^+, $C_{18}H_{18}N_2O_7$).