

$C_{(6\beta)}-H]$. Reduction of **2** with sodium borohydride in methanol yielded **3**. The structure of **3** must be shown as eremophil-7(11)-ene-12,8 α ; 14 β ,6 α -diolide (**3**),¹⁴ since **1** was reduced with sodium borohydride to form **5** with a loss of the hydroxyl group at $C_{(8\beta)}$. The spectral data described above are compatible with the structure (**3**).

Finally, 6 β -hydroxyeremophil-7(11)-en-12,8 α -olide (**5**)⁵⁻⁷ was also isolated from the same plant.

Compounds **2** and **3** constitute the first examples of eremophilane-type sesquiterpenes having two lactone rings in their molecules.

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Opening of the Cephalosporin Dihydrothiazine Ring

2-Ethoxy-3-cephem-1 β -oxide (**3**) was found to be thermally unstable and easily converted into isothiazolones (**4**, **5**, **6**, **9**, **10**), and the β -lactam derivative (**8**) under varying reaction conditions. Furthermore, 2-ethoxy-3-cephem (**2**) was treated with *tert*-butyl hypochlorite, giving the azetidinone-oxazoline acetate (**14**).

In a previous paper,¹⁾ we described a new rearrangement reaction of 2-methylthio- or 2-methoxycephalosporins into azlactone derivatives similar to the penicillin-penicillenate rearrangement reaction.²⁾ This reaction suggested that introduction of a heteroatom substituent at C(2) of cephem molecules would facilitate ring opening of the dihydrothiazine moiety. Further, we wish to add herein other transformation reactions of 2-alkoxycephems involving S(1)-C(2) bond fission.

Treatment of methyl 7 β -benzamido-3-methyl-3-cephem-4-carboxylate³⁾ (**1**) with 1.2 equivalents of *tert*-butyl hypochlorite in ethanol-containing methylene chloride (0°, 1 day, 45% yield) gave a 2 α -ethoxy-3-cephem (**2**, mp 178—179.5°⁴⁾).⁵⁾ Successive oxidation of **2** with 1 equivalent of *meta*-chloroperbenzoic acid in chloroform (0°, 1 hr, 73% yield) afforded a 2 α -ethoxy-1 β -oxide [**3**, mp 137—138°; IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 3320, 1785, 1736, 1660, 1543; NMR (CDCl₃) δ ppm: 1.20 (3H, t, $J=7$, -OCH₂CH₃), 2.12 (3H, s, 3-CH₃), 3.80 (3H, s, -COOCH₃), 4.60 (1H, d, $J=5.5$, H-6), 4.63 (1H, s, H-2), 6.25 (1H, dd, $J=5.5$ and 10, H-7)]. The 2 α -ethoxy-1-oxide **3** thereby obtained was found to be thermally unstable in protic solvents; and **3** was easily converted into an isothiazolone diethylacetal [**4**, mp 142—143°; IR $\nu_{\max}^{\text{CHCl}_3}$ cm⁻¹: 3430, 1734, 1660, 1524;

1) A. Yoshida, S. Oida, and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **23**, 2518 (1975).

2) H. Bundgaard, *J. Pharm. Sci.*, **60**, 1273 (1971) and the related references cited therein.

3) A. Yoshida, S. Oida, and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **23**, 2507 (1975).

4) All compounds were characterized by infrared (IR), nuclear magnetic resonance (NMR) and mass spectrometry and also by elementary analysis.

5) cf. D.O. Spry, *Tetrahedron Letters*, **1972**, 3717.

NMR (CDCl_3) δ ppm: 1.20 (6H, t, $J=7$, $-\text{OCH}_2\text{CH}_3$), 2.27 (3H, s, $=\dot{\text{C}}-\text{CH}_3$), 3.69 (3H, s, $-\text{COO}-\text{CH}_3$), 4.87 (1H, s, $-\text{O}-\dot{\text{C}}\text{H}-\text{O}-$), 8.82 (1H, s, $=\text{CH}-\text{S}-$) in 69% yield on refluxing in reagent-grade chloroform (containing ethanol); while, on refluxing in methanol-containing chloroform, it afforded an isothiazolone methylethylacetal [5, syrup; IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3410, 1730, 1655, 1522; NMR (CDCl_3) δ ppm: 1.15 (3H, t, $J=6.5$, $-\text{OCH}_2\text{CH}_3$), 3.24 (3H, s, $-\text{OCH}_3$), 4.68 (1H, s, $-\text{O}-\dot{\text{C}}\text{H}-\text{O}-$), 8.74 (1H, s, $=\text{CH}-\text{S}-$) in 89% yield. On the other hand, refluxing 3 in ethyl acetate gave an isothiazolone aldehyde [6, syrup; IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3430, 1738, 1701, 1662, 1522; NMR (CDCl_3) δ ppm: 8.91 (1H, s, $=\text{CH}-\text{S}-$), 9.81 (1H, s, $-\text{CHO}$)] in 92% yield. Transformation of the 2-ethoxy-1-oxide 3 into these isothiazolones seemed to proceed through initial formation of a β -lactam-sulfenic acid intermediate⁶⁾ (7) arising from a cleavage of the S(1)-C(2) bond and subsequent 1,2-bond migration of the β -lactam nitrogen from the carbon atom to the sulfur atom along with dehydration.

In order to characterize the β -lactam intermediate (7), treatment of the 2-ethoxy-1-oxide (3) with 2-mercaptobenzothiazole in chloroform was attempted⁸⁾ and a β -lactam disulfide [8, mp 126—127.5°; IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3370, 1788, 1724, 1678, 1660, 1533; NMR (CDCl_3) δ ppm: 1.88 (3H, s, $=\dot{\text{C}}-\text{CH}_3$), 3.60 (3H, s, $-\text{COOCH}_3$), 5.48 (1H, dd, $J=5$ and 7, $-\text{CONH}-\dot{\text{C}}\text{H}-\text{CO}-$), 5.95 (1H, d, $J=5$, $-\text{N}-\dot{\text{C}}\text{H}-\text{S}-$), 10.20 (1H, s, $-\text{CHO}$)] was obtained in 74% yield.

Reaction of 3 with other mercaptans such as 2-mercaptobenzoxazole and 2-mercapto-5-methyl-1,3,4-thiadiazole did not afford β -lactam derivatives, but gave isothiazolone hemithioacetals 9, syrup, and 10, mp 181—182°, respectively. On treatment of 3 with *n*-butylmercaptan in chloroform, a thioester 11 [mp 120—122.5°; IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3250, 1744, 1663, 1644, 1584, 1508; NMR (CDCl_3) δ ppm: 1.76 and 1.86 (3H, s, *ca.* 5:4, $=\dot{\text{C}}-\text{CH}_3$), 2.78 (2H, t, $J=7$, $-\text{S}-\text{CH}_2-\text{CH}_2-$), 3.81 and 3.82 (3H, s, *ca.* 4:5, $-\text{COOCH}_3$), 9.38 and 9.26 (1H, s, *ca.* 5:4, $-\text{CHO}$)] was obtained in 53% yield as a mixture of geometrical isomers. The thioester 11 was also obtained from the isothiazolone aldehyde 6 by the same treatment with *n*-butylmercaptan.

On the other hand, treatment of the 2-ethoxy-1-oxide 3 with trimethyl phosphite^{7a)} in chloroform containing acetic acid gave a thiazole compound [12, mp 127.5—129°; IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3380, 1722, 1719, 1671, 1615, 1607, 1594, 1527; NMR (CDCl_3) δ ppm: 2.25 (3H, t, $J=7$, $-\text{OCH}_2-\text{CH}_3$), 2.20 (3H, s, $-\text{OCOCH}_3$), 2.44 (3H, s, $=\dot{\text{C}}-\text{CH}_3$), 3.86 (3H, s, $-\text{COOCH}_3$), 5.64 (1H, s, $-\text{O}-\dot{\text{C}}\text{H}-\text{O}-$), 8.97 (1H, s, $=\text{CH}-\text{S}-$)] in 29% yield. The thiazole 12 was probably formed *via* opening of the β -lactam ring in intermediate 13, azetidinone-thiazoline, which was derived from the afore-mentioned intermediate 7 by deoxygenation of sulfenic acid and subsequent cyclization to the thiazoline ring.

Further, in expectation of a S(1)-C(2) bond cleavage by electrophilic attack of chlorine at the sulfur atom of the 2-ethoxy-3-cephem 2, treatment of 2 with 2.7 equivalents of *tert*-butyl hypochlorite in methanol (0°, 30 min) was carried out and an azetidinone-oxazoline acetal [14, syrup; IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1788, 1734, 1636; NMR (CDCl_3) δ ppm: 0.95 and 1.14 (3H, t, $J=7$, 1:1, $-\text{OCH}_2\text{CH}_3$), 2.12 (3H, s, $=\dot{\text{C}}-\text{CH}_3$), 2.98 and 3.25 (3H, s, 1:1, $-\text{OCH}_3$), 3.67 (3H, s, $-\text{COOCH}_3$), 4.70 and 4.78 (1H, s, 1:1, $-\text{O}-\dot{\text{C}}\text{H}-\text{O}-$), 5.38 and 6.11 (1H each, ABq, $J=3$, $-\dot{\text{C}}\text{H}-\text{CH}-$)] was obtained in 38% yield.⁹⁾ Treatment of the acetal 14 in acetone in the presence of

- 6) The generation of sulfenic acid intermediates such as 7 from penicillin sulfoxides is postulated as taking place through a reversible six-electron electrocyclic rearrangement.⁷⁾ In this case, generation of 7 is thought to take place *via* heterolytic cleavage of the S(1)-C(2) bond and this facile bond cleavage might be attributable to stabilization of the cation 7 by delocalization of the unshared electron pairs of the oxygen in the attached alkoxy group and of the nitrogen in the enamide conjugated system.
- 7) a) R.D.G. Cooper and F.L. Jose, *J. Am. Chem. Soc.*, **92**, 2575 (1970); b) R.D.G. Cooper, *ibid.*, **92**, 5010 (1970).
- 8) cf. 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; T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi, and T. Oku, *Tetrahedron Letters*, **1973**, 3001.
- 9) The reaction product 14 was accompanied by its dimethylacetal analog which was partly formed by an acetal exchange reaction.

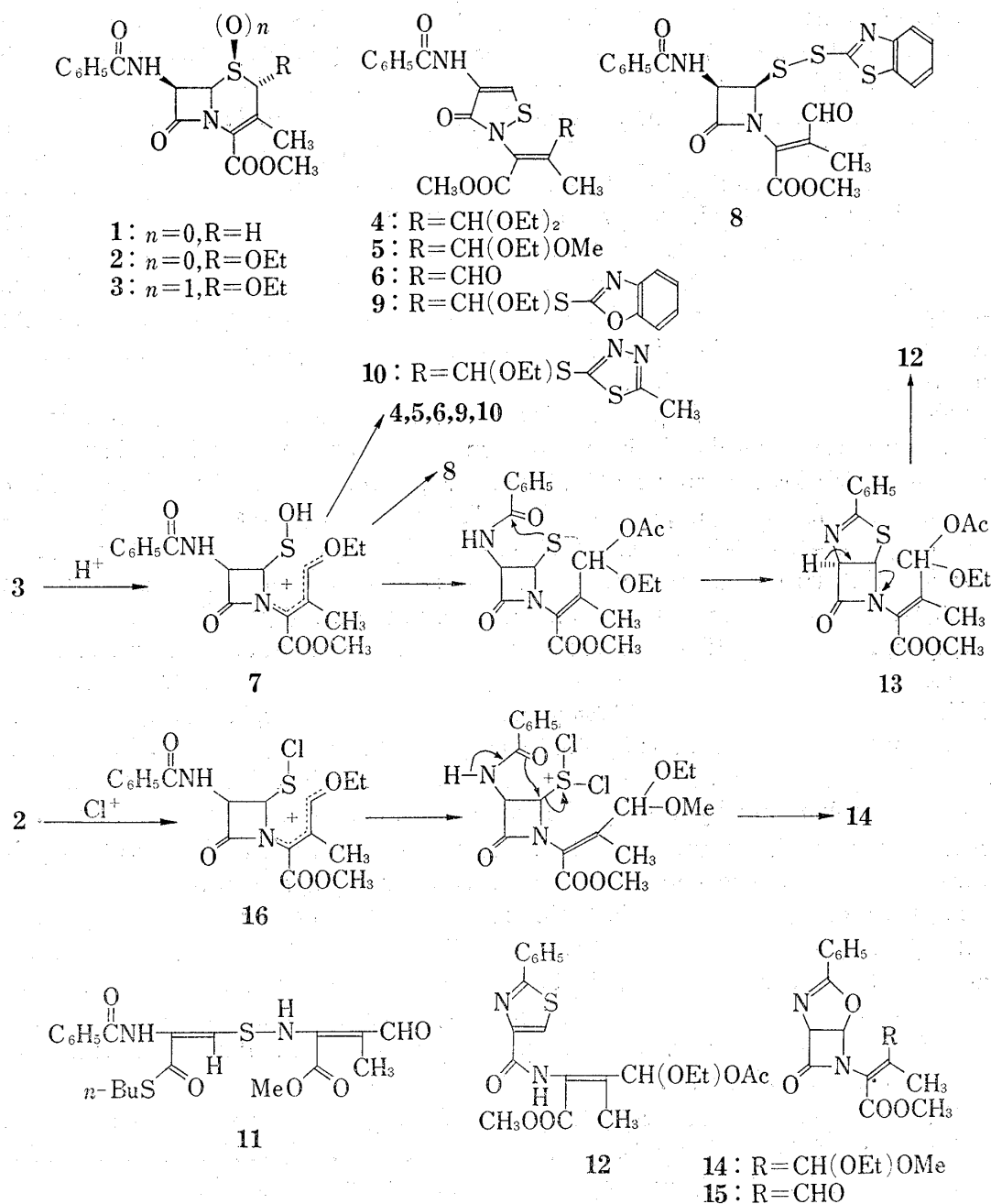


Chart 1

p-toluenesulfonic acid afforded the corresponding aldehyde [15, syrup; IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1790, 1733, 1694, 1632; NMR (CDCl_3) δ ppm: 5.49 and 6.30 (1H each, ABq, $J=3$, $-\text{CH}-\text{CH}-$), 9.67 (1H, s, $-\text{CHO}$)]. The acetal 14 was presumed to be formed by cleavage of the S(1)–C(2) bond yielding the cation (16) which subsequently undergoes desulfurization and an intramolecular attack of the amide oxygen at C(6).

Compound 8 and 15 thus obtained retain not only the β -lactam rings intact but also have a functionalized methyl group in their β,β -dimethylacrylic ester moieties; and as such they can serve as useful intermediates for the syntheses of new penam and cephem antibiotics by means of possible recyclization.¹⁰⁾

10) cf. S. Wolfe, J.B. Ducep, G. Kannengiesser, and W.S. Lee, *Can. J. Chem.*, **50**, 2902 (1972); S. Wolfe, J.B. Ducep, K.C. Tin, and S.L. Lee, *ibid.*, **52**, 3996 (1974).

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Modification of α -Santonin. I. An Abnormal Chlorination of 3-Hydroxy-4,5-epoxy-6,11 β H-eudesm-1-en-6,12-olide with Methanesulfonyl Chloride

An abnormal, stereospecific chlorination of 3-hydroxy-4,5-epoxy-6,11 β H-eudesm-1-en-6,12-olide (**5**, **6**, **7** and **8**) with methanesulfonyl chloride (or *p*-toluenesulfonyl chloride)–pyridine is described.

The stereochemistry of the chlorides (**9**, **10**, **11** and **12**) were confirmed by their nuclear magnetic resonance spectra and chemical reactions.

It is well known that mesylation (or tosylation) of an allylic alcohol (**I**) with methanesulfonyl chloride (or *p*-toluenesulfonyl chloride)–pyridine produce a mixture of the corresponding mesylate (or tosylate (**II**)) and the rearranged isomer (**III**), but there are few reports on stereospecific chlorination under these conditions.

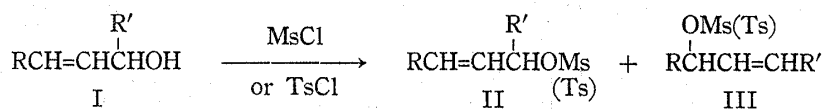


Chart 1

In this communication, we wish to report an abnormal stereospecific chlorination of 3-hydroxy-4,5-epoxy-6,11 β H-eudesm-1-en-6,12-olide (**5**, **6**, **7**, **8**) by the action of methanesulfonyl chloride (or *p*-toluenesulfonyl chloride)–pyridine.

α -Santonin (**1**) was treated with *m*-chloroperbenzoic acid in the presence of 4,4'-thiobis-(6-*t*-butyl-3-methylphenol) as a radical inhibitor¹⁾ to give the α -epoxide (**2**)^{2a-c)} (yield 38.6%), β -epoxide (**3**)^{2a,c)} (yield 43.2%) and diepoxide (**4**)^{2c)} (yield 1.8%). Selective reduction of the carbonyl group of **2** with LiAlH₄ (tetrahydrofuran, -78°) afforded a mixture of the β -alcohol (**5**) (yield 16.7%, mp $200-202^\circ$, NMR (CDCl₃) δ : 4.27 (1H, d, $J=5.0$ Hz; C₃-H), 5.37 (1H, d, $J=10.0$ Hz; C₁-H), 5.65 (1H, dd, $J=10.0, 5.0$ Hz; C₂-H) and α -alcohol (**6**) (yield 65.6%, mp $196-197^\circ$, NMR (CDCl₃) δ : 4.18 (1H, dq, $J=11.0, 2.0, 2.0$ Hz; C₃-H), 5.26 (1H, dd, $J=10.0, 2.0$ Hz; C₁-H), 5.46 (1H, dd, $J=10.0, 2.0$ Hz; C₂-H), while reduction of **2** with NaBH₄ gave a mixture of **5**, **6** and corresponding dihydro derivatives (**13**, **14**).

Similar reduction of **3** with LiAlH₄ gave a mixture of the β -alcohol (**7**) (yield 65.9%, mp $106-107^\circ$, NMR (CDCl₃) δ : 4.12 (1H, m, C₃-H), 5.22 (1H, dd, $J=10.5, 2.0$ Hz; C₁-H), 5.43 (1H, dd, $J=10.5, 2.0$ Hz; C₂-H) and α -alcohol (**8**) (yield 15.6%, mp $158-160^\circ$, NMR (CDCl₃) δ : 4.20 (1H, d, $J=5.0$ Hz; C₃-H), 5.27 (1H, d, $J=10.5$ Hz; C₁-H), 5.57 (1H, dd, $J=10.5, 5.0$ Hz; C₂-H).

- 1) Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, and H. Kakoi, *J. C. S. Chem. Comm.*, **1972**, 64.
- 2) a) E. Wedekind and K. Tettweiler, *Ber.*, **64**, 1796 (1931); b) J.B. Hendrickson and T.L. Bogard, *J. Chem. Soc.*, **1962**, 1678; c) M. Yanagita, T. Hirose, and T. Okura, The 91th Annual Meeting of Pharmaceutical Society of Japan, Fukuoka, Apr. 1971.