$C_{(6\beta)}$–H)]. Reduction of **2** with sodium borohydride in methanol yielded **3**. The structure of **3** must be shown as eremophil-7(11)-ene-12,8α; 14β,6α-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, 6β-hydroxyeremophil-7(11)-en-12,8α-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-1β-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 7β-benzamido-3-methyl-3-cephem-4-carboxylate[3] (**1**) with 1.2 equivalents of *tert*-butyl hypochlorite in ethanol-containing methylene chloride (0°, 1 day, 45% yield) gave a 2α-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 2α-ethoxy-1β-oxide [**3**, mp 137—138°; IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3320, 1785, 1736, 1660, 1543; NMR ($CDCl_3$) δ ppm: 1.20 (3H, t, $J$=7, $-OCH_2\underline{C}H_3$), 2.12 (3H, s, 3-$CH_3$), 3.80 (3H, s, $-COOCH_3$), 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 2α-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 $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 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 ($CDCl_3$) $\delta$ ppm: 1.20 (6H, t, $J$=7, $-OCH_2C\underline{H}_3$), 2.27 (3H, s, $=\dot{C}-CH_3$), 3.69 (3H, s, $-COO-CH_3$), 4.87 (1H, s, $-O-\dot{C}H-O-$), 8.82 (1H, s, $=CH-S-$)] 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 $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3410, 1730, 1655, 1522; NMR ($CDCl_3$) $\delta$ ppm: 1.15 (3H, t, $J$=6.5, $-OCH_2C\underline{H}_3$), 3.24 (3H, s, $-OCH_3$), 4.68 (1H, s, $-O-\dot{C}H-O-$), 8.74 (1H, s, $=CH-S-$)] in 89% yield. On the other hand, refluxing **3** in ethyl acetate gave an isothiazolone aldehyde [**6**, syrup; IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3430, 1738, 1701, 1662, 1522; NMR ($CDCl_3$) $\delta$ ppm: 8.91 (1H, s, $=CH-S-$), 9.81 (1H, s, $-CHO$)] in 92% yield. Transformation of the 2-ethoxy-1-oxide **3** into these isothiazolones seemed to proceed through initial formation of a $\beta$-lactam-sulfenic acid intermediate[6] (**7**) arising from a cleavage of the S(1)–C(2) bond and subsequent 1,2-bond migration of the $\beta$-lactam nitrogen from the carbon atom to the sulfur atom along with dehydration.

In order to characterize the $\beta$-lactam intermediate (**7**), treatment of the 2-ethoxy-1-oxide (**3**) with 2-mercaptobenzothiazole in chloroform was attempted[8] and a $\beta$-lactam disulfide [**8**, mp 126—127.5°; IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3370, 1788, 1724, 1678, 1660, 1533; NMR ($CDCl_3$) $\delta$ ppm: 1.88 (3H, s, $=\dot{C}-CH_3$), 3.60 (3H, s, $-COOCH_3$), 5.48 (1H, dd, $J$=5 and 7, $-CONH-C\underline{H}-CO-$), 5.95 (1H, d, $J$=5, $-N-\dot{C}H-S-$), 10.20 (1H, s, $-CHO$)] 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 $\beta$-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 $\nu_{max}^{Nujol}$ $cm^{-1}$: 3250, 1744, 1663, 1644, 1584, 1508; NMR ($CDCl_3$) $\delta$ ppm: 1.76 and 1.86 (3H, s, *ca.* 5:4, $=\dot{C}-CH_3$), 2.78 (2H, t, $J$=7, $-S-C\underline{H}_2-CH_2-$), 3.81 and 3.82 (3H, s, *ca.* 4:5, $-COOCH_3$), 9.38 and 9.26 (1H, s, *ca.* 5:4, $-CHO$)] 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 $\nu_{max}^{Nujol}$ $cm^{-1}$: 3380, 1722, 1719, 1671, 1615, 1607, 1594, 1527; NMR ($CDCl_3$) $\delta$ ppm: 2.25 (3H, t, $J$=7, $-OCH_2-C\underline{H}_3$), 2.20 (3H, s, $-OCOCH_3$), 2.44 (3H, s, $=\dot{C}-CH_3$), 3.86 (3H, s, $-COOCH_3$), 5.64 (1H, s, $-O-\dot{C}H-O-$), 8.97 (1H, s, $=CH-S-$)] in 29% yield. The thiazole **12** was probably formed *via* opening of the $\beta$-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 $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1788, 1734, 1636; NMR ($CDCl_3$) $\delta$ ppm: 0.95 and 1.14 (3H, t, $J$=7, 1:1, $-OCH_2C\underline{H}_3$), 2.12 (3H, s, $=\dot{C}-CH_3$), 2.98 and 3.25 (3H, s, 1:1, $-OCH_3$), 3.67 (3H, s, $-COOCH_3$), 4.70 and 4.78 (1H, s, 1:1, $-O-\dot{C}H-O-$), 5.38 and 6.11 (1H each, ABq, $J$=3, $-\dot{C}H-\dot{C}H-$)] 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.

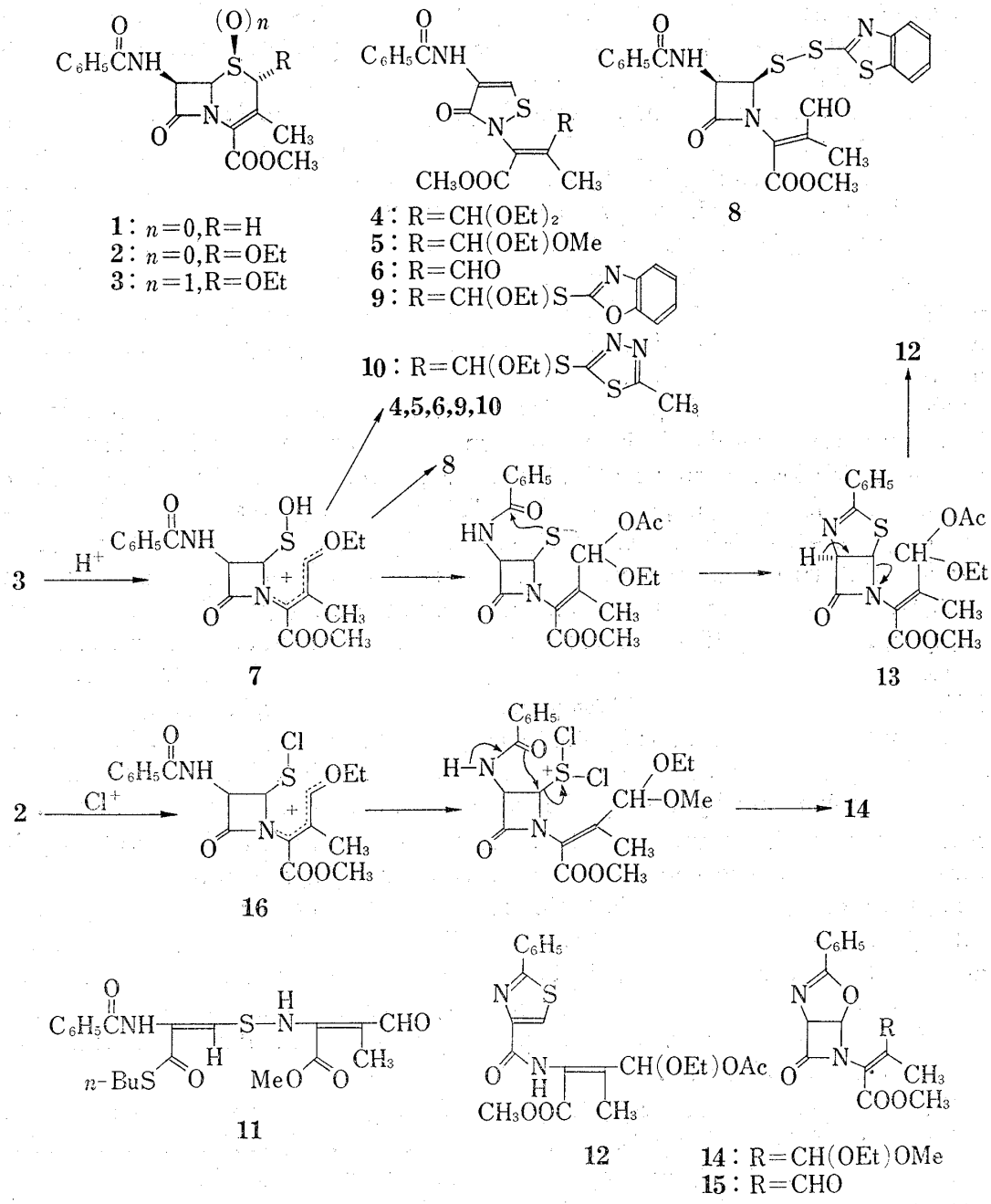


Chart 1

*p*-toluenesulfonic acid afforded the corresponding aldehyde [**15**, syrup; IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1790, 1733, 1694, 1632; NMR ($CDCl_3$) $\delta$ ppm: 5.49 and 6.30 (1H each, ABq, $J$=3, –CH–CH–), 9.67 (1H, s, –CHO)]. The acetal **14** was presumed to be formed by cleavage of the S(1)–C(2) bond yielding the cation (**16**) which sebsequently undergoes desulfurization and an intramolecular attack of the amide oxygen at C(6).

Compound **8** and **15** thus obtained retain not only the $\beta$-lactam rings intact but also have a functionallized methyl group in their $\beta,\beta$-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-6,11βH-eudesm-1-en-6,12-olide with Methanesulfonyl Chloride

An abnormal, stereospecific chlorination of 3-hydroxy-4,5-epoxy-6,11βH-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.

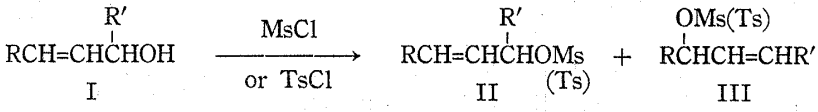


Chart 1

In this communication, we wish to report an abnormal stereospecific chlorination of 3-hydroxy-4,5-epoxy-6,11βH-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 inhibitor[1] 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 $LiAlH_4$ (tetrahydrofuran, −78°) afforded a mixture of the β-alcohol (**5**) (yield 16.7%, mp 200—202°, NMR ($CDCl_3$) δ: 4.27 (1H, d, $J$=5.0 Hz; $C_3$–H), 5.37 (1H, d, $J$=10.0 Hz; $C_1$–H), 5.65 (1H, dd, $J$=10.0, 5.0 Hz; $C_2$–H) and α-alcohol (**6**) (yield 65.6%, mp 196—197°, NMR ($CDCl_3$) δ: 4.18 (1H, dq, $J$=11.0, 2.0, 2.0 Hz; $C_3$–H), 5.26 (1H, dd, $J$=10.0, 2.0 Hz; $C_1$–H), 5.46 (1H, dd, $J$=10.0, 2.0 Hz; $C_2$–H), while reduction of **2** with $NaBH_4$ gave a mixture of **5**, **6** and corresponding dihydro derivatives (**13**, **14**).

Similar reduction of **3** with $LiAlH_4$ gave a mixture of the β-alcohol (**7**) (yield 65.9%, mp 106—107°, NMR ($CDCl_3$) δ: 4.12 (1H, m, $C_3$–H), 5.22 (1H, dd, $J$=10.5, 2.0 Hz; $C_1$–H), 5.43 (1H, dd, $J$=10.5, 2.0 Hz; $C_2$–H) and α-alcohol (**8**) (yield 15.6%, mp 158—160°, NMR ($CDCl_3$) δ: 4.20 (1H, d, $J$=5.0 Hz; $C_3$–H), 5.27 (1H, d, $J$=10.5 Hz; $C_1$–H), 5.57 (1H, dd, $J$=10.5, 5.0 Hz; $C_2$–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.