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CONVERSION OF CEPHAM-1-OXIDE INTO 1-OXADETHIACEPHAM

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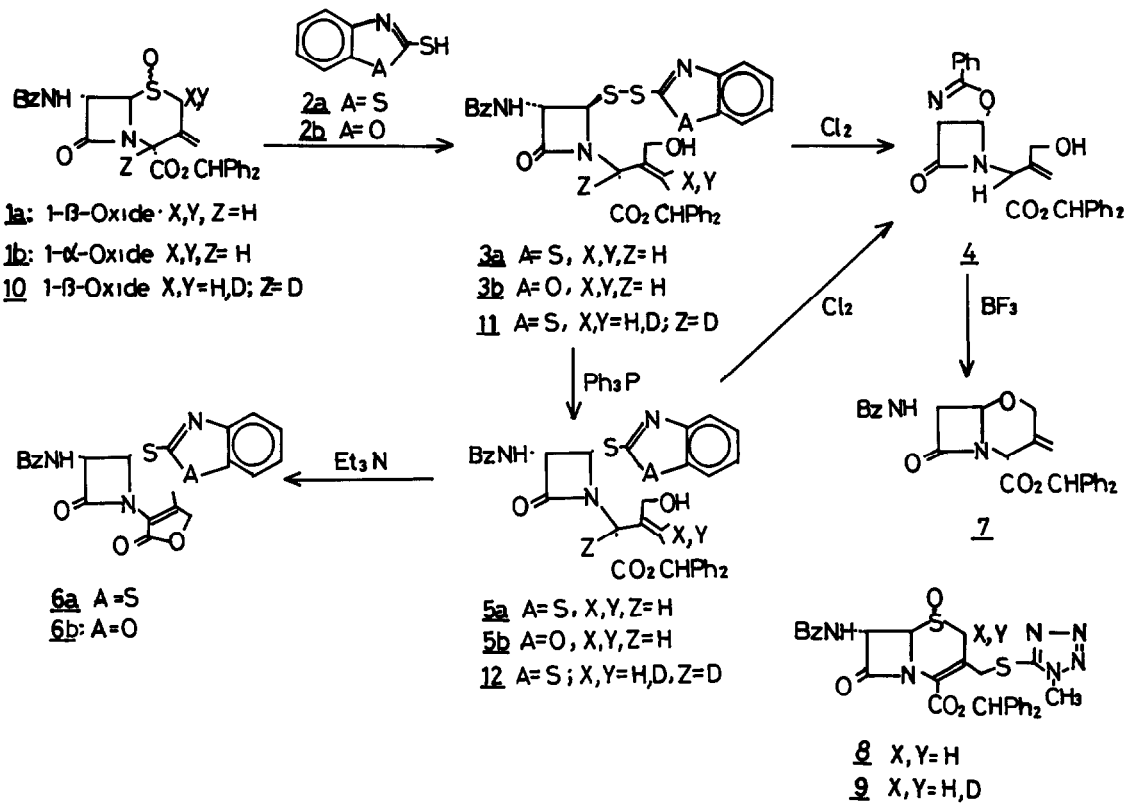
Summary 3-Exomethylenecepham-1-oxides 1 were converted into the 3-exomethylene-1-oxadethiacepham in three step process including the novel bond cleavage of the tetrahydrothiazine ring of 1 with 2-mercaptobenzothiazole or 2-mercaptobenzoxazole.

Since the antibacterial activity of the racemic 1-oxadethiacephalosporin[1] was reported, much effort[2] has been expanded to make one of the optically active constituents from penicillin and cephalosporin. Recently the industrially practical procedure[2e,f] for producing 1-oxadethiacephalosporin from penicillin was announced and the new clinically useful β-lactam antibiotic[3] was developed. We wish to describe here simple transformation of cepham-1-oxides 1a, 1b into the 1-oxadethiacepham 7 by the use of the novel ring opening reactions of 1a and 1b with the mercaptans 2a, 2b.

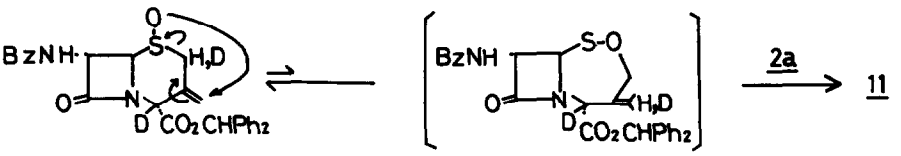
Treatment of the cepham-1β-oxide 1a and 1α-oxide 1b[4] with 2a (1.9 eq.) in benzene under reflux gave the crystalline disulfide-alcohol 3a[5] in 38% and 42% yields, respectively. Similarly the reaction of 1a with 2b afforded 3b[5] in 43% yield The structures of 3a and 3b were determined from spectral data and elemental analyses. To date there has been no report on the ring opening of the tetrahydrothiazine ring in cepham-1-oxides. The mechanism is discussed later in this report.

Conversion of 3a and 3b into the oxazoline 4,[2d] the key intermediate in the synthesis of 1-oxadethiacephalosporin, was carried out in 30% yield in both cases by treatment with chlorine (1.8 eq.) in dichloromethane (CH_2Cl_2) under -50°C in the presence of propylene oxide as a HCl scavenger The oxazoline 4 was also obtained through the sulfide-alcohols 5a , 5b. That is, desulfurization of 3a and 3b with triphenylphosphine (Ph_3P) (1.7 eq.) in CH_2Cl_2 at 25°C gave 5a and 5b[7] in quantitative and 77% yields, respectively. The cis stereochemistry at positions 3 and 4 in 5a and 5b was assigned from the NMR spectra ($J_{3\text{-}H,\ 4\text{-}H}$=5 Hz) of the γ-lactones 6a, 6b[8] prepared quantitatively by treatment of 5a and 5b with triethylamine in CH_2Cl_2 at 25°C The inversion of the stereochemistry at position 4 of the azetidinone ring by treatment of the azetidinone-disulfide with Ph_3P was previously reported.[9] Conversion of 5a and 5b into 4 was conducted in 36% and 40% yields, respectively, by the same procedure as that for the direct conversion of 3a and 3b into 4 .

Rearrangement of 4 to the 1-oxadethia-3-exomethylenecepham 7 has already been described by Nagata et al.[2e] (catalytic BF_3 Et_2O in CH_2Cl_2, 25°C).



Mechanism of the bond cleavage[10] of 1a with 2a ——— In order to investigate the mechanism, the deuterated cepham-1-oxide 10 was prepared as follows. Refluxing[11] of a solution of the 3-cephem-1-oxide 8 in methanol-d_1 and tetrahydrofuran for 2 hr gave the deuterated compound 9 which was immediately treated with zinc in acetic acid-d_4 and methanol-d_1 to afford 10. The NMR spectrum of 10 showed that deuterium was incorporated into one[12] of the two protons at position 2 and the proton at position 4. Ring opening of 10 was achieved with 2a in the same procedure as that described in conversion of 1a into 3a Treatment of 11 with Ph_3P gave the sulfide 12 The NMR spectra of 11 and 12 exhibited the signal for only one proton at the olefinic methylene group and no signal for the α proton of the but-3-enoate side chain, while the signal for the hydroxymethyl group was of normal intensity. This result indicates that the selective transformation of the CDH group (position 2) of 10 into the olefinic methylene groups of 11 and 12 and the exomethylene group at positoin 3 of 10 into the hydroxymethyl groups of 11 and 12 It is proposed that the bond cleavage process of 10 proceeds via the sulfenate intermediate 13 generated by [2,3] sigmatropic rearrangement[13] of the allylic sulfoxide. The mercaptan 2a works as the sulfenate ester trapping agent and transforms 13 into the alcohol 11.



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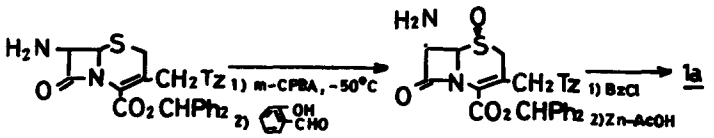
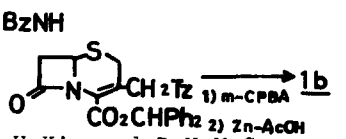
4. The oxides were prepared as follows.





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Tz=1-methyl-1H-tetrazol-5-yl

5. Mp 172-173°C (recryn. from EtOAc) IR (nujol, cm^{-1}) 3460, 3340, 1765, 1740 and 1670. NMR ($CDCl_3$;δ) 3.64 (1H, br s, OH), 5 03 (1H, br s, $NCHCO_2$), 5.08 and 5.39 (each 1H, each br s, $=CH_2$), 5.44 (1H, d, J=2 Hz, 4-H on azetidinone ring), 6.83 (1H, s, $C\underline{H}Ph_2$) and 7.0-8.0 (19H, m, phenyl protons)
6. Mp 98-100°C (recryn. from benzene). IR (nujol cm^{-1}) 3440, 3290, 1755, 1730 and 1660 . NMR (DMSO-d_6,δ). 3.62 (1H, br s, OH), 4.17 (2H, br s, $C\underline{H}_2OH$), 5.07 (1H, d,d, J=2, 8Hz, 3-H on azetidinone ring), 5.16 (1H, br s, $NC\underline{H}CO_2$), 5.20 and 5.39 (each 1H, each br s, $=CH_2$), 7.2-8.0 (19H, phenyl protons) and 9.33 (1H, d, J=8 Hz, NH).
7. 5a, amorphous powder. IR (film, cm^{-1}): 3330, 1760, 1740 and 1650. NMR ($CDCl_3$,δ) 3.07 (1H, br s, OH), 4.05 (2H, br d, J=4 Hz, $C\underline{H}_2OH$), 4.89 (1H, br s, $NCHCO_2$), 4.95 and 5.17 (each 1H, each br s,$=CH_2$), 5.8-6.05 (2-H, m, 3-H and 4-H on azetidinone ring), 6.97 (1H, s, $C\underline{H}Ph_2$), 7.0-8.0 (19H, m, phenyl protons) and 8.41 (1H, d, J=7 Hz, NH). 5b, amorphous powder. IR (nujol,cm^{-1}) 3340, 1775, 1750 and 1660. NMR ($CDCl_3$,δ) 3.10 (1H, br s, OH), 4.12 (2H, br s, $C\underline{H}_2OH$), 5.00 (2H, br s, $NCHCO_2$ and one proton of $=CH_2$), 5.20 (1H, br s, one proton of $=CH_2$), 5.65-6.05 (2H, m, 3-H and 4-H on azetidinone ring), 6.92 (1H, s, $C\underline{H}Ph_2$), 7.05-7.9 (19H, m, phenyl protons) and 8.30 (1H, d, J=8 Hz, NH).
8. 6a, amorphous powder. NMR ($CDCl_3$,δ)· 1.58 (3H, s, CH_3), 4.75 (2H, s, CH_2 on lactone ring), 6.11 (1H, d,d, J=5, 9 Hz, 3-H on azetidinone ring), 6.32 (1H, d,J=5 Hz, 4-H on azetidinone ring), 7.2-8.1 (9H, m, phenyl protons) and 9.13 (1H, d, J=9 Hz, NH). 6b, amorphous powder. NMR ($CDCl_3$,δ) 1.86 (3H, s, CH3), 4.65 (2H, s, CH_2 on lactone ring), 6.08 (1H, d, d, J=5, 9Hz, 3-H on azetidinone ring), 6.40 (1H, d, J=5 Hz, 4-H on azetidinone ring), 7.2-8.0 (9H, m, phenyl protons) and 8.63 (1H, d, J=9 Hz, NH).
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