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A Very Mild and Quantitative Oxidation of Cephalosporins with Dimethyldioxirane.

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Abstract: The cephalosporins **1-3** and Δ^2-cephem **4** were oxidized in quantative yields to their sulfones with dimethyldioxirane. While in the case of 2-methylene-cephems (**5,6**) the exocyclic double bond oxidized simultaneously to the corresponding epoxide, the 3-vinyl derivative (**8**) or 3-methylene-cephems (**7**) gave selectively the corresponding vinyl sulfone.

The sulfoxides and sulfones of penicillin and cephalosporin derivatives were used only as synthetic intermediates in the early era ß-lactam antibiotics chemistry. The rise of these oxidized derivatives has begun when considerable effort was devoted to the human leucocyte elastase and ß-lactamase enzyme inhibitors, and several of the most useful compounds are ß-lactam sulfone derivatives.

In connection with our studies in this field our efforts were focused to an oxidation procedure which could provide cephalosporine sulfones under neutral conditions. Beyond the very generally used m-chloro-peroxybenzoic acid (MCPA), the most frequently used agents are $KMnO_4$,[1] peracetic acid or H_2O_2[2] under acidic conditions, K-persulfate (oxone),[3] and $NaIO_4$[4] for the free acids. The permanganate oxidation is generally used only with penicillin type compounds because of the possible oxidation of the double bond of the cephem ring system. Hydrogen peroxyde alone or in combination with wolframate or with an organic acid anhydride has usually been found too sluggish to obtain the sulfones (this will be the subject of a forthcoming paper), on the other hand, under slightly basic conditions a $\Delta^3 \rightarrow \Delta^2$ double bond isomerization was found to occur to some extent.

On searching for new mild oxidizing agents under neutral conditions, we came across with dimethyldioxirane (DMD). This compound (in acetone solution) has proved to be a versatile and rapid agent, with no side products and very simple work-up. Its use as oxidant for sulfur-containing compounds,[5] unsaturated ketones[6] etc has reached particular prominence. To our best knowledge DMD has never been utilized as an oxidant for cephem sulfones, therefore we studied this reaction in some detail.

The cephalosporins **1-3** were oxidized with dimethyldioxirane in acetone solution at 0-5 °C in the dark. The progress of the reaction was monitored with TLC, and dimethyldioxirane solution was added in

several batches until complete conversion of the starting material (40-60 min) to the corresponding sulfones **9-11** was reached.[7] The preparative yields of the reactions were 100% in each case, and after evaporation of the solvent the material was ready for subsequent reactions. Similarly, the Δ^2-derivative (**4**) gave quantitatively the corresponding Δ^3-conjugated ester **12** (the double bond migration is a usual phenomenon of this type of cephems). The obtained sulfones remained unchanged on further addition of dimethyldioxirane in accordance with the substantially lower reactivity of the cephem double bond toward oxidation.[12]

It is noteworthy to mention that when the oxidation was allowed to run only until the sulfoxide stage by careful addition of 1 mol of the reagent, a ca. 1:1 mixture of the two sulfoxides were obtained. In the case of **3** ^{1}H NMR investigation of the product has revealed that it is a 47:53 mixture of the S(α) and R(β)-sulfoxides. It is well known in the cephalosporin chemistry[8] that when a 7β-acylamido group is present in the molecule, oxidation to the sulfoxide gives rise to the β-sulfoxide because of the kinetic control owing to the H-bridge formation between the acylamido side chain and the peracid. Obviously the lack of such an intermolecular interaction between the dioxirane ring and the acylamido moiety results in the formation of both isomers.

Next we studied the oxidation of some different methylene and vinyl cephem derivatives as we were curiuos to know the selectivity of the oxidation if two sensitive moieties were present in the molecule. Adam *et al*[5] have found that it was possible to obtain the sulfones and epoxides selectively from 3-arylidene-1-thiochroman-4-ones by careful stepwise oxidation with DMD. In our experiments, when the exomethylene derivative **7**[10] and the 3-vinyl-cephem **8** were subjected to DMD oxidation for 2-3 hours, the sulfone derivatives **15** and **16** were isolated as the sole products in 100% yields[9] without any signs of the rupture of the double bond. This was not the case in the oxidation process with **5** and **6**.[11] Tlc monitoring showed the presence of several compounds immediately and beside the corresponding sulfone, two new compounds were formed simultaneously. However, only a long exposure (~4 days) with an excess of the oxidizing agent resulted in the complete formation of the products **13** and **14**.[9] The latter proved to be the 5:1 mixture of the C-2 isomers **14a,b**.

As the dimethyldioxirane epoxidations may show remarkable diastereoselectivity and solvent dependence[6a], further work on the structure elucidations of the isomers and influence of the reaction conditions are in progress.

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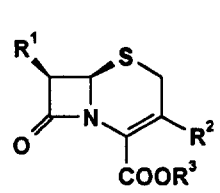
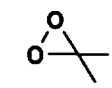
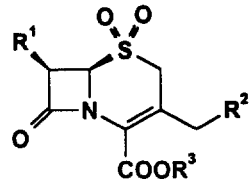






1 R^1 = V-CONH-, R^2 = -Cl, R^3 = -$CHPh_2$

2 R^1 = G-CONH-, R^2 = -CH_3, R^3 = -CH_2OAc

3 R^1 = tBocNH-, R^2 = -CH_2OCOCH_3, R^3= -CH_3

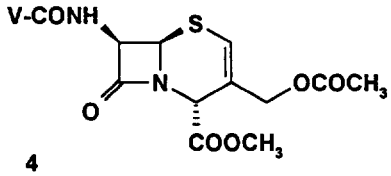
V = $C_6H_5OCH_2$-

G = $C_6H_5CH_2$-

9 100%

10 100%

11 100%



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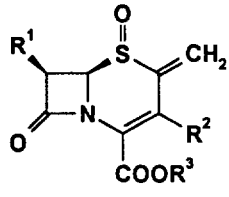
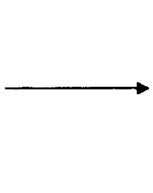
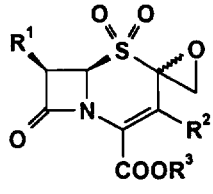
12 100%





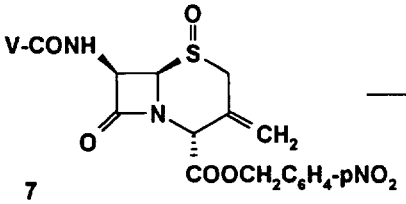


5 R^1 = V-CONH-, R^2 = -Cl, R^3 = $CHPh_2$

6 R^1 = G-CONH-, R^2 = -CH_3, R^3 = -CH_2OAc

13 95%

14a,b 85%



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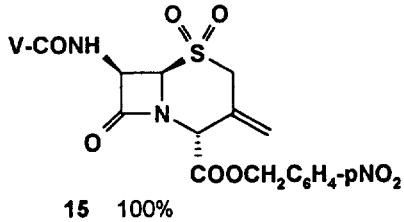
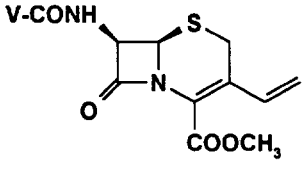


15 100%



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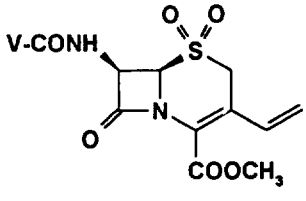

16 95%

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1. Some of the recent articles: a) Vanetswinkel, S.; Fastrez, J.; Marchand-Brynaert, J. *J. Antibiotics* **1994**, *47*, 1039-1051; b) Ziegler, Z. B.; Fields, T. L. *Tetrahedron* **1993**, *49*, 3919-3932 ; c) Maiti, S. N.; Spevak, P.; Wong, R.; Reddy, N. A. V.; Micetich, R. G.; Ogawa, K. *Heterocycles* **1991**, *32*, 1505-1515
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7. The compounds were indentical (m.p., mixed m.p., TLC) with the samples prepared by standard MCPA or H_2O_2 oxidation of the corresponding sulfides. M.p. **9**: 194-196 °C; **10**: 173-17 °C; **11**: 179-180 °C; **12**: 130-131 °C. *C.f.* lit 11.
8. Murphy, C. F. and Webber, J. A. in "Cephalosporins and Penicillins. Chemistry and Biology", pp. 135-138 (Flynn, E. H. ed.), Academic press, N.Y. 1972
9. **14a** and **14b** (separation by a Silicagel 60 column with toluene-EtOAc 5:1) major: m.p.: 174-176 °C; ^{1}H NMR (DMSO-d_6) δ 1.80 (3H, s), 2.17 (3H, s), 3.55, 3.65 (2H, ABq, J=15), 3.63, 3.78 (2H, ABq, J=4.5), 5.61 (H, d, J=4.9), 5.88, 5.91 (2H, ABq, J=6.1), 6.02 (H, dd, J=4.8 and 8.3), ~7.3 (5H, m), 9.18 (H, d, J=8.2); IR (KBr): 1764 (ß-lactam υ_{CO}), 1802, 1678, 1372, 1344 cm^{-1}
   minor: m.p.: 133-35 °C; ^{1}H NMR (DMSO-d_6) δ 2.00 (3H, s), 2.10 (3H, s), 3.56, 3.64 (2H, ABq, J=14), 4.50, 4.65 (2H, ABq, J=11.0), 5.40 (H, d, J=4.9), 5.82, 5.88 (2H, ABq, J=6.1), 6.02 (H, dd, J=4.9 and 8.5), ~7.3 (5H, m), 9.15 (H, d, J=8.5); IR (KBr): 1806 (ß-lactam υ_{CO}), 1750, 1690, 1532, 1334 cm^{-1}
   15: M.p.: 171-172 °C (EtOAc-ether); ^{1}H NMR (DMSO-d_6) δ 4.21, 4.35 (2H, ABq, J=14.1), 4.62, 4.68 (2H, ABq, J=13.5), 5.30 (H, d, J=5.0), 5.35 (2H, s), 5.53 (H, s), 5.65 (s, H), 5.73 (H, s), 6.04 (H, dd, J=8.5 and 5.3), 6.8-7.3 (5H, m), 7.6-8.3 (4H, m), 8.5 (H, d, J=8.5); IR (KBr): 1786 (ß-lactam υ_{CO}), 1740, 1696, 1522 cm^{-1}
   16: (95% after purification by passing through a short Silicagel 60 column with toluene-EtOAc 3:1) m.p.: 139-141 °C; ^{1}H NMR (DMSO-d_6) δ 3.32 (H, s), 3.82 (2H, s), 4.60 (H, d, J=13.8), 4.71 (H, d, J=13.8), 5.43 (H, d, J=2.7), 5.47 (H, d, J=3.3), 5.7 (H, d, J=17.3), 6.12 (H, dd, J=5.0 and 9.2), 6.8-7.0 (5H, m), ~7.3 (H, m), 8.7 (H, d, 9.2); IR (KBr) 1802 (ß-lactam υ_{CO}), 1724, 1684, 1526, 1492 cm^{-1}
   All of the new compounds possess satisfactory microanalitical data.
10. Thaper, R. K.; Kumar, Y.; Khanna, J. M. *Synth. Comm.*, **1995**, *25*, 883-888
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12. When **1** was allowed to stay with an excess of DMD (~3 eqs) for 5 days, TLC showed the appearence of benzophenone and another unidentified degradation products in the reaction mixture. This slow side reaction could be detected only in the case of benzhydryl esters, and presumably originates from a free radical process.

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