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SYNTHESIS AND BIOLOGICAL ACTIVITY OF NOVEL PENEM SULFOXIDES AND SULFONES

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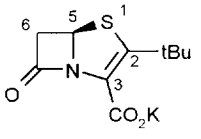
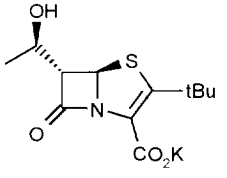
Abstract: *The first stable penem sulfoxides* ***4a, 4b*** *and the novel penem sulfone* ***6b*** *were prepared. The rates of hydrolysis and the biological activities were examined.*

In a precedent paper[1] we reported the synthesis of racemic and enantiomeric potassium 2-*tert*-butylpenem-3-carboxylates **1a** and **1b**. Interestingly, these penem salts were highly stable towards hydrolysis and, despite their low reactivity, both were found to be biologically active.

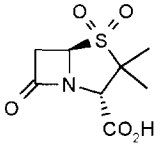


1a



1b

With the penicillins, the sulfoxides and sulfones are not significantly active as antibacterials[2]. However, the more stable penicillanic acid sulfone (sulbactam) is well known to be a clinically useful β-lactamase inhibitor[3].



Sulbactam

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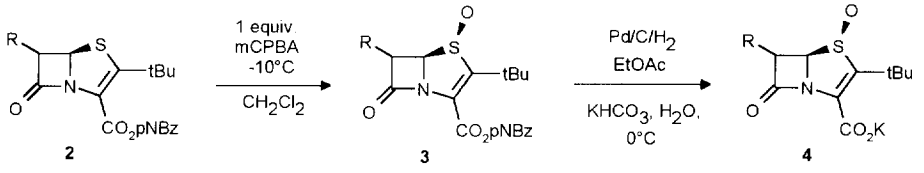
Within the cephalosporins the sulfoxides and the sulfones showed reduced activity compared to the parent sulfides[2]. However, with some derivatives, (R)-sulfoxides[4], (S)-sulfoxides or even sulfones[5] were found to be more active against Enterobacteriaceae in vitro.

With the very stable penem salts **1a** and **1b** in hand, we questioned whether the oxidation of the sulfur would eventually result in isolable sulfoxides or sulfones and whether these would be biologically active.

A penem sulfoxide ester has already been reported[6]. A penem sulfoxide sodium salt was too labile for antibacterial testing at physiological conditions[7].

The increased stability of *tert*-butyl penems **1a** and **1b** enabled us to prepare, for the first time, stable penem sulfoxide acid salts **4a** and **4b** according to the following scheme:



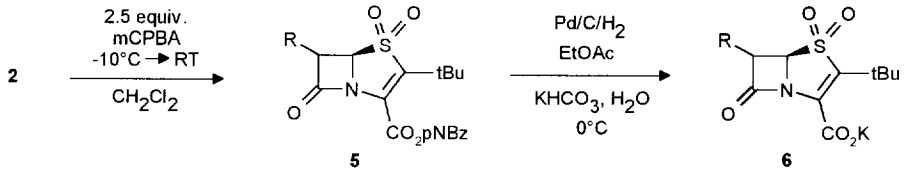
a: R = H (racemic)

b: R = 

Thus, the p-nitrobenzyl esters **2** were oxidized with 1 equiv. of *m*-chloroperbenzoic acid to **3**, which, in turn, was hydrogenated in ethyl acetate, water, 1 equiv. $KHCO_3$ and 10% Pd on C as catalyst. The latter reaction was performed at ambient pressure at 0°C within 10-20 min. The reaction mixture was filtered at 0°C and the aqueous layer separated and lyophilized in high vacuum at -30°C to give the sulfoxide salts **4a** and **4b** in 73% and 32% overall yield from **2**, as colorless non-crystalline powders[8].

Similarly, the p-nitrobenzyl esters **2** were oxidized to the corresponding sulfone esters **5**.

As **5b**, and particularly **5a**, were rather labile compounds, special care was used to remove excess of oxidant and by-product *m*-chlorobenzoic acid, by adding 2 equiv. of dimethyl sulfide prior to working up with toluene and aqueous $NaHSO_3$ and $KHCO_3$ solutions. The esters **5a** and **5b** were obtained after flash chromatography on silica gel with toluene-ethyl acetate (19:1) or (4:1) in 20% and 68% (chromatography at -10°C) yield, respectively[9].



a: R = H (racemic)

b: R = 

Hydrogenation of **5a** and work up, as described for the sulfoxides, resulted in extensive decomposition indicating that the 6-unsubstituted penem sulfone **6a** was too labile to be isolated. However, with the necessary precautions, the deprotection of **5b** was achieved and resulted in the isolation of potassium (1'R,5R,6S)-2-*tert*-butyl-6-(1'-hydroxyethyl)penem-3-carboxylate sulfone **6b** in 80% yield after lyophilisation at -30°C and 0.001 mbar[10].

The oxidation of the sulfur in the above-mentioned penems decreased the stability of the products remarkably. The augmented reactivity can be estimated from the increased β-lactam carbonyl stretching frequency of the corresponding p-nitrobenzyl esters, determined in CH_2Cl_2 solutions, starting from 1790 (sulfide **2b**) to 1805 ((S)-sulfoxide **3b**) to 1820 cm^{-1} (sulfone **5b**).

Table 1 shows the relevant half-lives of hydrolysis of the penem potassium salts, determined by UV-spectroscopy.

Compound	$T_{1/2}$	k_{rel}
1a (sulfide)	9 d	1
1b (sulfide)	16 d	0.6
4a ((S)-sulfoxide)[11]	5.5 h	39
4b ((S)-sulfoxide)	6.5 h	33
6b (sulfone)	18 min	720

Table 1: Half-lives of hydrolysis of potassium 2-*tert*-butylpenem-3-carboxylate derivatives in physiological phosphate buffer pH 7.4 at 37°C and relative hydrolysis rates.

The antibacterial activities of the penems **1a**, **1b**, penem sulfoxides **4a**, **4b** and penem sulfone **6b** were determined by the agar diffusion test as depicted in Table 2. Compared to the parent penems **1a** and **1b**[1], the (S)-sulfoxides **4a** and **4b** showed markedly decreased antibacterial activities. The sulfone **6b**, presumably because of its low stability, was inactive against all gram-positive and gram-negative bacteria tested.

	1a	**1b**	**4a**	**4b**	**6b**	**CeCl**
Staph.aur.1104	40	36	36	30	0	32
Staph.aur.res	26	35	30	27	0	19
Staph. 25768	0	31	8	24	0	13
Staph. Innsbruck	0	0	0	0	0	12
Escherichia coli 1103	11	18	10	20	0	25
E.coli TEM	0	9	0	13	0	15
Enterobacter cloacae	0	10	0	7	0	7
Enterococcus	0	11	0	0	0	15
Pseudomonas aer.	0	0	0	0	0	0
Ps.aer.res.	0	0	0	0	0	0

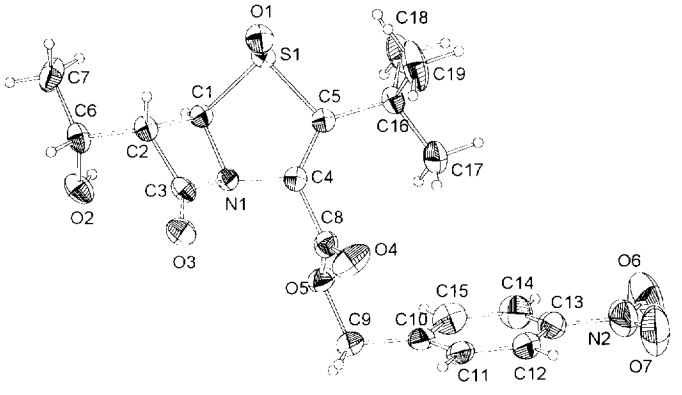
Table 2: Inhibition zone diameter in mm using 30μg of each substance or Cefaclor (CeCl). Incubation period 20 h at 37°C, DIFCO Nutrient Agar.

Because of the labile character of the novel penem sulfone **6b**, a synergy with Cefaclor or Ceftazidime against intact resistant bacteria could not be observed. However, the excellent β-lactamase inhibiting properties of **6b** could be demonstrated in the nitrocefin test, using isolated (cell free) resistance enzymes (see Table 3)[12].

Compound	IC_{50}	
	E.cloacae	E.coli TEM
1b (sulfide)	3×10^{-7}	5×10^{-5}
4b ((S)-sulfoxide)	3×10^{-7}	9×10^{-5}
6b (sulfone)	4×10^{-9}	1×10^{-5}
clavulanic acid	1×10^{-4}	4×10^{-8}
sulbactam	1×10^{-6}	8×10^{-7}

Table 3: β-Lactamase inhibition activities (IC_{50}) of potassium 2-*tert*-butylpenem-3-carboxylate derivatives after 15 min of preincubation with the enzyme at 37°C.

A remaining question about the configuration of the sulfoxides **3** and **4** was answered by an x-ray structure determination of a single crystal of compound **3b**, revealing the β-orientation of the S-O bond. As no epimeric sulfoxides were observed by NMR spectroscopy, the 1S-configuration was attached to all above-mentioned sulfoxides.



3b

Acknowledgements. We wish to thank Dr. Kurt Polborn for his x-ray structure determination. Thanks are also due to the Fonds der Chemischen Industrie for their financial support.

References and Notes

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   See also corrected configuration in *Bioorg. Med. Chem. Lett.* **1997**, *7*, 757.
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7 Tanaka R.; Oyama Y.; Ishiguro M. *J. Chem. Soc., Chem. Commun.*, **1990**, 853.
8. The reported compounds **3a** and **3b** gave correct elemental analyses and mass spectra.
   Physical data of **4a**: white powder. UV-spectrum in H_2O: λ_{max} = 271 nm ($\varepsilon \approx 5000$). ^{1}H-NMR-spectrum in D_2O/ $Me_3SiCD_2CO_2Na$: δ (ppm) = 1.37 (s, 9H, tBu), 3.40 (dd, 1H, trans 6-H, J = 2.9 Hz, J = 17.0 Hz), 3.62 (dd, 1H, cis 6-H, J = 5.6 Hz, J = 17.1 Hz), 5.11 (dd, 1H, 5-H, J = 3.0 Hz, J = 5.6 Hz).
   Physical data of **4b**: white powder. UV-spectrum in H_2O: λ_{max} = 272 nm ($\varepsilon \approx 5000$). ^{1}H-NMR-spectrum in D_2O (D_2O lock): δ (ppm) = 1.23 (d, 3H, CH_3, J = 6.5 Hz); 1.25 (s, 9H, *t*Bu), 3.64 (dd, 1H, 6-H, J = 3.1 Hz, J = 4.9 Hz); 4.34 (m, 1H, 1`-H); 5.00 (d, 1H, 5-H, J = 3.1 Hz).
9. The sulfone esters **5a** and **5b** decomposed on tlc and should be investigated by ir-spectroscopy. Column chromatography is possible with low yields at room temperature. Yields were substantially increased by low temperature chromatography.
   Mass spectra were consistent with structures **5a** and **5b**.
10. Physical data of **6b**: white powder. UV-spectrum in H_2O: λ_{max} = 265 nm ($\varepsilon \approx 5000$). ^{1}H-NMR-spectrum in D_2O (D_2O lock): δ (ppm) = 1.23 ppm (d, 3H, CH_3, J = 6.5 Hz), 1.26 (s, 9H, *t*Bu), 3.84 (dd, 1H, 6-H, J = 2.9 Hz, J = 4.8 Hz), 4.31 (m, 1H, 1`-H), 4.83 (d, 1H, 5-H, J = 2.9 Hz).
    The purity of **6b** was 80%, as determined by HPLC (Waters 3.9 x 300 mm RP-column, μBondapak C_{18}, 10 μm, H_2O:CH_3CN / 3:1).
11. Interestingly, the corresponding potassium 2-*tert*-butyl-6,6-dimethylpenem-3-carboxylate sulfoxide with $T_{1/2}$ = 2.6 h was less stable, an observation already made with *tert*-butyl penems (sulfides)[1]. The sulfide as well as the sulfoxide in this series were not significantly active, nor as antibacterials, neither as β-lactamase inhibitors.
12. The β-lactamases were available by the Sigma Chemical Co. (P 4524 type IV and P 3553).

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