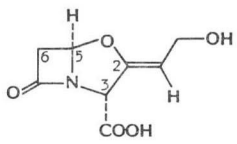
THE SYNTHESIS AND BIOLOGICAL TESTING OF 2,2-DIMETHYLPENAM SULFONE*

Sir:

In recent years a number of compounds possessing a β-lactam moiety unsubstituted at C-6, both of synthetic and natural origin, have been found to be inhibitors of β-lactamases.

The first compound of this type was clavulanic acid (**1**), a potent β-lactamase inhibitor, isolated from *Streptomyces clavuligerus*[1,2]. Later the sulfone **2**, a synthetic analogue of penicillin lacking the acylamino substituent at C-6, was also reported to be an inhibitor of several β-lactamase enzyme systems[3].



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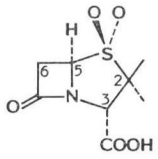

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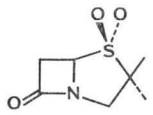
Of particular interest were subsequent reports of compounds related to clavulanic acid but lacking the C-3 carboxyl group, such as **3**[4,5], **4a**, **4b**, **4c**[6,7] and more recently **5**[8], which retained the β-lactamase inhibitory activity.

This led to the question of whether the carboxyl group at C-3 of the sulfone **2** was required for this molecule to exhibit activity as a β-lactamase inhibitor. A search of the literature failed to provide any mention of the preparation or biological testing of the sulfone **6**.

It was felt that the well known sulfenic acid-olefin cycloaddition reaction[9~12] would offer a facile route to the sulfoxide **7**, which on oxidation should afford the desired sulfone **6**, as outlined in the Scheme 1.*



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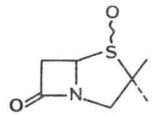

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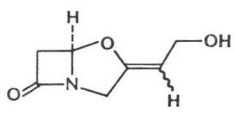
Racemic **9**, purified by flash chromatography using hexane - EtOAc and obtained as an oil: IR ($CHCl_3$) 1748, 1656 cm^{-1}; was oxidized using sodium periodate in a methanol - water mixture (8: 3) to provide the crystalline sulfoxides **10** in 90% yield, mp 57~60°C. The major isomer had mp 64~65°C; IR (KBr) 1750, 1663, 1045, 1028 cm^{-1} and the minor isomer had a mp 78~79°C; IR (KBr) 1775, 1653, 1035, 1023 cm^{-1}. Heating a mixture of these sulfoxides at reflux in toluene gave, *via* cyclization of the sulfenic acid **11** generated *in situ*, the sulfoxides **7a** and **7b** in 90% yield. The major isomer **7a**, recrystallized from EtOAc - hexane, had a mp 67~68°C; IR (KBr) 1765, 1050, 1038 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 and 1.51 (2s, 6H), 2.95 and 3.73 (2d, 2H, H-3, J=11 Hz), 3.26 (d, 2H, H-6, J=3 Hz), 4.82 (t, 1H, H-5, J=3 Hz); *Anal* C, H, N, S. Treatment of the sulfoxides **7a** and **7b** with *m*-chloroperbenzoic acid (*m*CPBA) in methylene chloride gave the racemic sulfone **6** as an oil; IR (neat) 1790, 1315, 1123 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 and 1.52 (2s, 6H), 3.20 (d, 1H, H-3, J=12 Hz), 3.42 (d, 2H, H-6, J=3 Hz), 3.82 (d, 1H, H-3, J=12 Hz), 4.46 (t, 1H, H-5, J=3 Hz); *Anal* C, H, N, S.

The sulfoxides **7** and the sulfone **6** were tested in a cell free β-lactamase test, as described in



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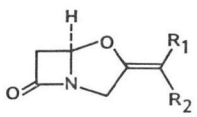
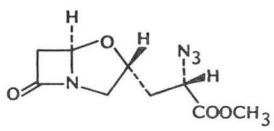


4a R_1 = $COOCH_3$, R_2 = H
4b R_1 = H, R_2 = $COOCH_3$
4c R_1 = $COOCH_3$, R_2 = Cl



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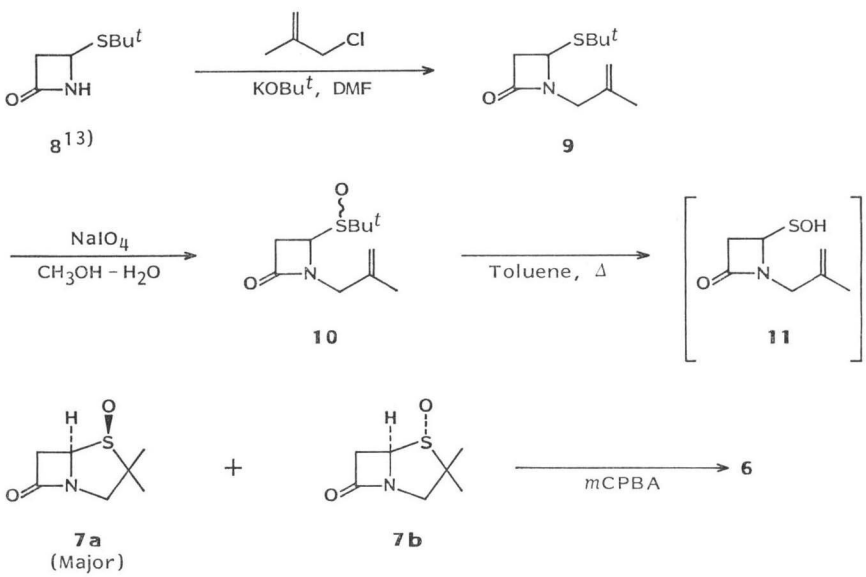
* Following the completion of this work the preparation of **8** and its use in the synthesis of 2-methylene penams was reported by ARROWSMITH and GREENGRASS[13].

* This route is nearly identical to the route used to prepare a 6-phenylacetamidopenam sulfoxide reported by KAURA *et al.*[12].

Scheme 1.



reference 8, and found to be inactive as β-lactamase inhibitors. The I_{50} values for **7** and **6** were greater than 100 μg/ml against all four β-lactamase preparations.

In vitro both **7** and **6** had no antimicrobial activity when tested in BBL seed agar against a broad spectrum of organisms (conditions under which the sulfone **2** showed weak activity).

Acknowledgments

The authors wish to express their thanks to Dr. DAVID PRUESS of the Microbiology Department of Hoffmann-La Roche Inc. for carrying out the *in vitro* testing.

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(Received June 20, 1984)

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