



## Reactions of Cephalosporin Sulphones 1. Rearrangement of the $\beta$ -Lactam Ring to a Triazole Derivative

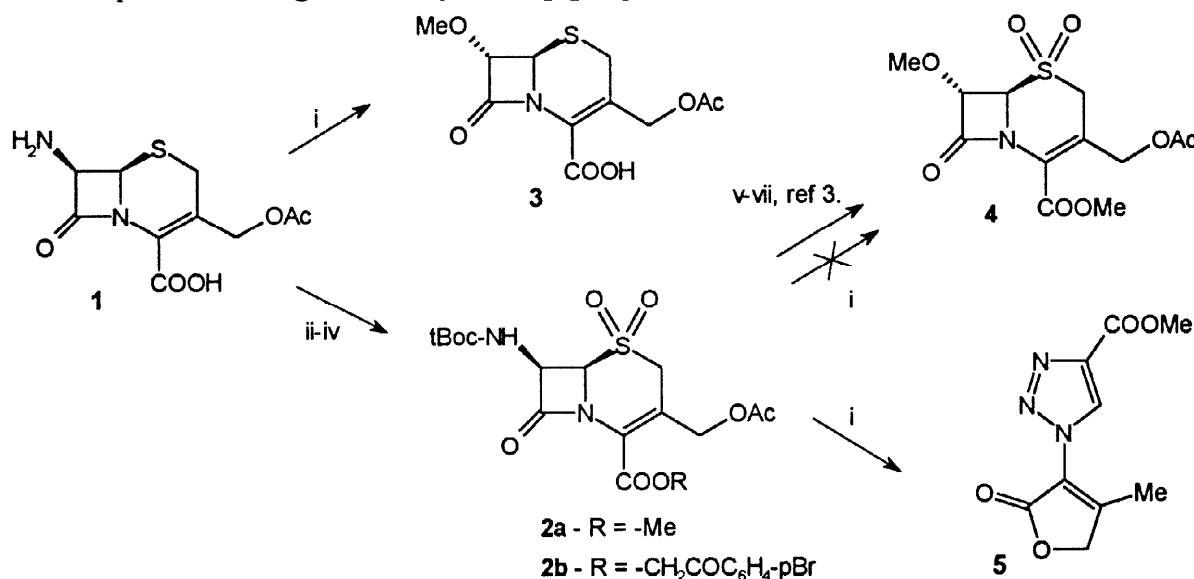
Tamás E. Gunda<sup>†</sup>, László Tamás<sup>†</sup> and Szabolcs Sályi<sup>†</sup>

Research Group for Antibiotics, Hungarian Academy of Sciences, P.O.Box 70, H-4010 Debrecen, Hungary

Received 8 January 1998; revised 10 February 1998; accepted 13 February 1998

**Abstract:** The 7 $\beta$ -amino-cephalosporin sulphones, generated *in situ* from the appropriate 7 $\beta$ -tBoc-amino derivative and diazotized in a one-pot reaction in aq. HClO<sub>4</sub> - MeOH - NaNO<sub>2</sub>, rearrange exclusively to the triazoles **5** in a multistep reaction. © 1998 Elsevier Science Ltd. All rights reserved.

Several 7 $\alpha$ -alkyloxy- or halogenocephalosporin sulphone derivatives are known to possess  $\beta$ -lactamase<sup>1</sup> or human leukocyte elastase<sup>2</sup> inhibitory properties. The main route to these 7 $\alpha$ -derivatives involves diazotisation of the corresponding amine and exchange of the diazo function under appropriate conditions and subsequent oxidation of the sulphur. This is usually a one-pot reaction of inadequate yield, and several attempts have been made recently to optimize this process (see ref. 3 and the literature cited therein). In our approach we have chosen oxidation prior to diazotisation, assuming that the sulphone is more resistant to the reaction conditions of diazotisation. In a previous paper<sup>3</sup> we described the conversion of **2a** to **4** by using distinct steps for removing the tBoc protecting group, diazotisation and rhodium(II)-catalysed exchange

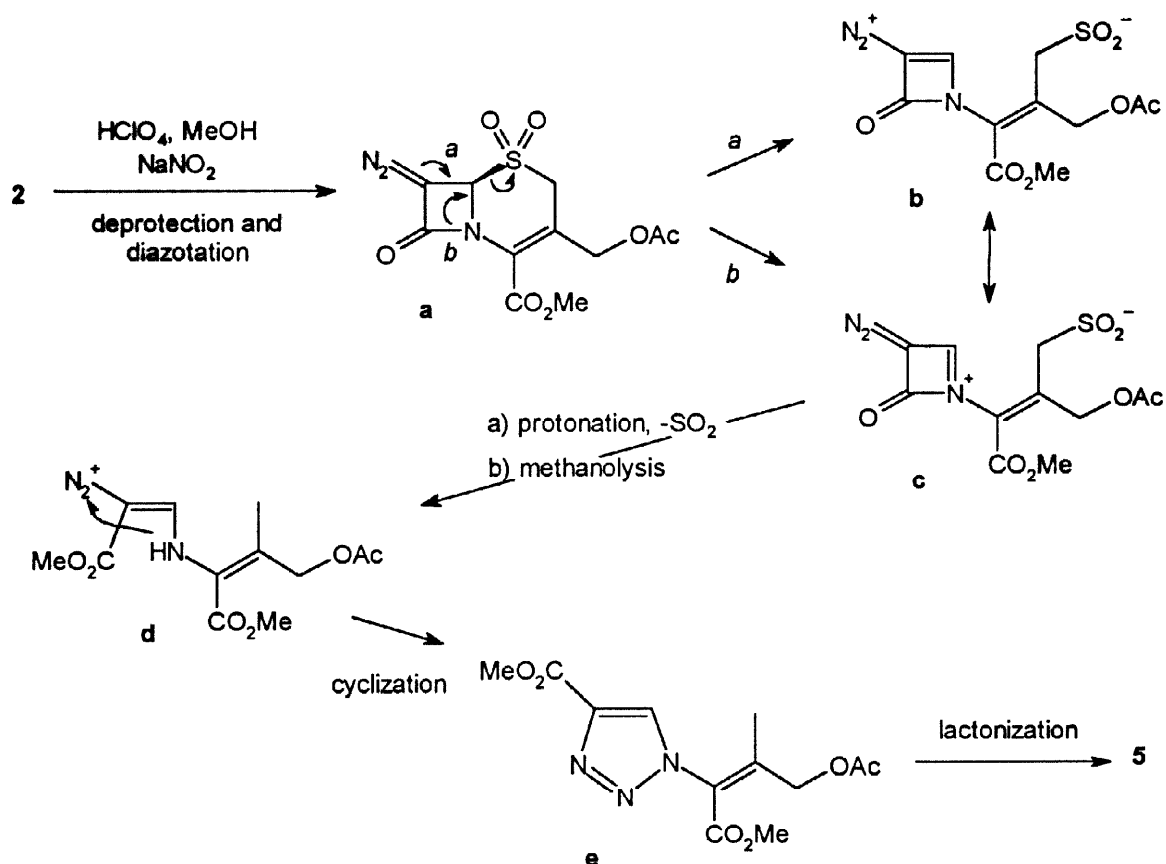


i) HClO<sub>4</sub>/MeOH, NaNO<sub>2</sub>; ii) Boc<sub>2</sub>O; iii) CH<sub>2</sub>N<sub>2</sub> or pBr-C<sub>6</sub>H<sub>4</sub>COCH<sub>2</sub>Br; iv) H<sub>2</sub>O<sub>2</sub>/NaWO<sub>4</sub>; v) TFA, anisole; vi) i-amyl nitrite, cat. TFA; vii) MeOH, Rh<sub>2</sub>(OAc)<sub>4</sub>

<sup>†</sup> Present address: Biogal Pharmaceutical Works, Debrecen, Hungary

reaction. Our original supposition was that these three steps could be performed in a one-pot operation with a mixture of aq. perchloric acid, methanol and sodium nitrite, because **1** or the corresponding tBoc-sulphide gave the desired 7 $\alpha$ -methoxy derivative (**3**) under these conditions, albeit in low overall yield (~10%) together with several unidentified resinous products. Remarkably, under similar conditions **2a** was *in toto* converted to a non- $\beta$ -lactam product.<sup>6,7</sup> According to preliminary analyses it contained no sulphur, but it exhibited a high nitrogen content. With an X-ray diffraction structure elucidation in mind we aimed at the preparation of the corresponding 4-bromophenacyl ester, but when **2b** was subjected to the same reaction conditions, chromatographic work-up yielded to the same **5** and 1-(4-bromophenyl)-2-hydroxyethanone. Thus, finally **5** was used for X-ray diffraction structure elucidation.

The formation of **5** is the result of several steps of a debatable sequence. First, the tBoc protecting

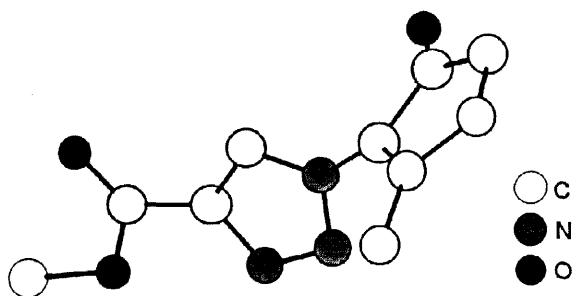
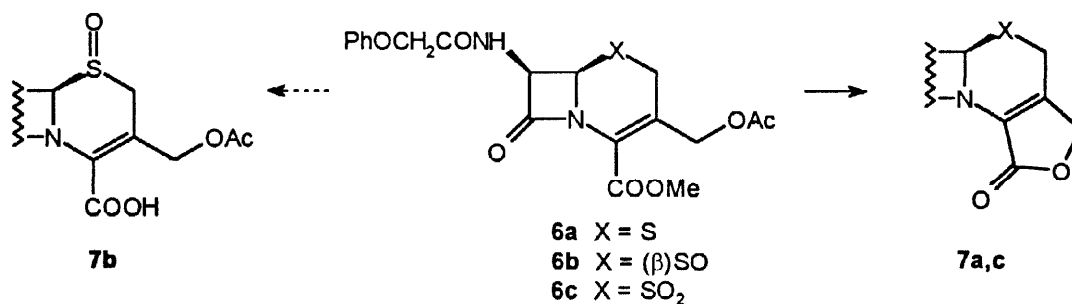


group leaves quickly in the strong acidic milieu and diazotisation occurs (a). Most probably the good leaving character of the sulphone is responsible for that instead of the analogous **2**  $\rightarrow$  **4** process the intermediates **b** or **c** are formed. In the penicillin and cephalosporin chemistry several other more or less similar sulphone-related ring opening reactions are known.<sup>4</sup> The ring opening of **a** may formally proceed in two ways: C-6-C-5 elimination leads to the **b** diazonium intermediate, whereas a N-C-5 elimination results in the formation of the **c** immonium intermediate; as **b** and **c** are mutual resonance forms the pathways are indistinguishable. Elimination of  $\text{SO}_2$  may happen in this or a later stage.

The reaction of diazonium or diazo compounds with amines, a well known old reaction producing triazenes, is used mostly for obtaining aliphatic triazenes, although cyclic compounds, like benzotriazoles from *o*-phenylenediamines are available this way too. In the reviews (5a-b) a couple of examples can be found for

the triazole formation of this type. In our case during the  $c \rightarrow d$  step formation of the new  $N-N=N$  bond and the opening of the  $\beta$ -lactam ring are very probably unseparable processes.

One of the steps of the formation of **5** is the acid-catalysed hydrolysis of the 3-acetoxy and the 4-methyl ester groups. A subsequent lactonization is not surprising, as this is usually a quick process among the 3-hydroxymethyl-cephem-4-carboxylic acids. When the analogue **6c** is subjected to the same reaction conditions (without  $\text{NaNO}_2$ ), formation of the lactone derivative **7c** is practically quantitative. However, the oxidation state of the sulphur clearly influences the rate of hydrolysis of the two esters attached to the  $\gamma$ -positions relative to the sulphur: whereas a complete lactone formation took place in the case of the sulphide and sulphone,<sup>9</sup> only the partial hydrolysis of the sulfoxide **6a** occurred giving rise to a mixture of products:



Chem3D representation of the X-ray structure of **5**.  
The dihedral angle of the two rings is  $72^\circ$ .

### Acknowledgement

This work was partly funded by the grant of the Hungarian National Science Fund OTKA T 23592. The authors are indebted for Dr Attila Bényei for the X-ray analysis.

### References

- Reviews: a) Mascaretti, O. A.; Roveri, O. A. and Danelon, G. O. "Recent Advances in the Chemistry and Biochemistry of  $\beta$ -Lactams as  $\beta$ -Lactamase Inhibitors" in *Recent Progress in the Synthesis of Antibiotics*, (ed. Lukacs, G.), pp. 677-749, Springer Verl., Berlin, 1993; b) Southgate, R.; Branch, C.; Coulton, S. and Hunt, E. "Chemistry and Synthesis of Some Novel  $\beta$ -Lactam Antibiotics and  $\beta$ -Lactamase Inhibitors" *ibid*, pp. 621-675
- Review: Edwards, P. B. and Bernstein: "Synthetic Inhibitors of Elastase" *Medicinal Res. Rev.* 1994, 14, 127

3. Sályi, S.; Tamás, L.; Gunda, T. E. and Sztaricskai, F. *Synth. Commun.* 1996 26, 445
4. a) Cheu, W. L.; Chang, C. W. and Hedbergh, K. *Tetrahedron Lett.* 1986 27, 3449; b) Haginaka, J.; Wakai, J.; Yasuda, H.; Uno, T. and Nagakawa, T. *Chem. Pharm. Bull.* 1985 33, 2035; c) Alpegiani, M.; Bissolino, P.; Borghi, D.; Rizzo, V. and Perrone E. *Bioorg. Med. Chem. Lett.* 1993 3, 2259; d) Pant, C. M. and Stoodley, R. J. *J. Chem. Soc. Chem. Commun.* 1977 57
5. a) Wulfman, D. S., in "The Chemistry of diazonium and diazo groups" (Patai, S. ed.) Part I., p. 247, Wiley, 1978; b) Dehne, H. "1,2,3-Triazole". In "Methoden der Organischen Chemie" (Schaumann, E. ed), Band E8d, p. 305, Thieme, 1994
6. Starting materials: *Methyl 7 $\beta$ -tert.-butoxycarbonyl-cephalosporanic acid 1,1-dioxide (2a)*: m.p. 179-80 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 1.42 (s, 9H), 2.15 (s, 3H), 3.81 (s, 3H), 4.18, 4.40 (ABq, 2H, J = 18 Hz), 4.52, 4.98 (ABq, 2H, J = 13.2 Hz), 5.33 (d, H, J = 4.4 Hz), 5.81 (dd, H, J = 4.4, 9.4 Hz), 7.25 (d, H, J = 9.4 Hz); *2-[(4-Bromophenyl)-2-oxo-]ethyl 7 $\beta$ -tert.-butoxycarbonyl-cephalosporanic acid 1,1-dioxide (2b)*: m.p. 170-1 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 1.42 (s, 9H), 2.09 (s, 3H), 4.23, 4.44 (ABq, 2H, J = 18.4 Hz), 4.84, 4.96 (ABq, 2H, J = 13.0 Hz), 5.40 (d, H, J = 4.6 Hz), 5.84 (dd, H, J = 4.6, 9.4 Hz), 5.70, 5.87, (ABq, 2H, J = 17 Hz), 7.35 (d, H, J = 9.4 Hz), 7.77-7.97 (aromatic, 4H).
7. *Methyl 1-(4-Methyl-2-oxo-2.5-dihydro-furan-3-yl)-1H-[1.2.3]triazole-4-carboxylic acid (5)*: 1 g of 2a was dissolved in a mixture of 60 ml methanol and 20 ml 70% aq. HClO<sub>4</sub>, and the solution was cooled 0-5 °C. 0.66 g of NaNO<sub>2</sub>, dissolved in 5 ml of H<sub>2</sub>O was added dropwise while stirring the mixture. It was allowed to stand for 3 hours in the cold, then it was poured into 200 ml of 10% NaHCO<sub>3</sub> solution and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was separated, washed with 10% NaHCO<sub>3</sub> and water, dried, evaporated, and the residue was recrystallized twice from EtOAc-Et<sub>2</sub>O, yielding to 0.27 g of 5, m.p. 126-8 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 2.32 (s, 3H), 3.90 (s, 3H), 5.20 (s, 2H), 9.07 (s, H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 12.5 (CH<sub>3</sub>), 52.0 (OCH<sub>3</sub>), 72.1 (CH<sub>2</sub>), 121.5 (C), 128.6 (CH), 138.9 (C), 158.1 (C), 160.2 (CO), 167.1 (CO).  
Crystal data: C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>O<sub>4</sub>, M = 223.19, monocline C2/c, a = 25,805(6), b = 5,722(3), c = 13,194(3) Å,  $\beta$  = 93,91(1)°, V = 1943(1) Å<sup>3</sup>, Z = 8, T = 293 K,  $\mu$  = 0,123 mm<sup>-1</sup>; wR(F<sup>2</sup>) = 0.2449 (145 parameters); the data collection was performed with an Enraf-Nonius Mach3 diffractometer, the collection, calculation and refinement of the data were made by the programs CAD-4 Express, SIR-92 and SHELXL93.<sup>8</sup>
8. a) Cusy, G. and Taylor, J. K. *Tetrahedron* 1989 45, 455; b) Kaltemberg, J.; de Waard, E. R. and Huisman, H. O. *Tetrahedron Lett.* 1973 1482
9. 7a: m.p.: 157-8 °C (EtOH); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 3.50, 3.75 (ABq, 2H, J = 18.1 Hz), 4.54 (s, 2H), 4.92 (s, 2H), 5.09 (H, d, J = 5.2 Hz), 6.04 (H, dd, J = 5.2, 9.2 Hz), 6.89-7.41 (6H, m). 7c: m.p.: 244-5 °C (acetone-EtOH); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 4.62 (2H, s), 4.64, 4.74 (2H, ABq, J = 14 Hz), 4.99, 5.08 (2H, ABq, J = 14.5 Hz), 5.35 (H, d, J = 5.1 Hz), 6.24 (H, dd, J = 5.1, 8.8 Hz), 6.89-7.35 (5H, m), 8.70 (H, d, J = 8.8 Hz)